NDA MULTIDISCIPLINARY REVIEW AND EVALUATION

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Application Number	**NDA 218944**
Application Type	Type 1 Original
Priority or Standard	Priority
Submit Date	1/26/2024
Received Date	1/26/2024
PDUFA Goal Date	12/26/2024
Office/Division	OOD/DHM1
Review Completion Date	11/14/2024
Applicant	Syndax Pharmaceuticals, Inc.
Established Name	Revumenib
(Proposed) Trade Name	Revuforj
Pharmacologic Class	Menin inhibitor
Formulations	Tablets (25 mg, 110 mg, 160 mg)
Applicant Proposed Indication/Population	For the treatment of adult and pediatric patients with relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene rearrangement (KMT2Ar)
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	For the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older.
SNOMED CT for the Recommended Indication/Population	91861009 91857003 1187123005

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REVIEWERS OF THE MULTIDISCIPLINARY REVIEW AND EVALUATION

Nonclinical Reviewer	Daniela Torres, PhD
Nonclinical Team Leader	Brenda Gehrke, PhD
Office of Clinical Pharmacology Reviewers	Ritu Chadda, PhD, Hongshan Li, PhD, Ying-Hong Wang, PhD, Javier G. Blanco, PhD
Office of Clinical Pharmacology Team Leaders	Ruby Leong, PharmD., Jiang Liu, PhD, Yuching Yang, PhD, Sarah Dorff, PhD
Clinical Reviewer	Chatchada Karanes
Clinical Team Leader	Donna Przepiorka, MD, PhD
Statistical Reviewer	Xin Wang, PhD
Statistical Team Leader	Jonathan Vallejo, PhD
Associate Director for Labeling (OOD)	Elizabeth Everhart, MSN, RN, ACNP
Cross-Discipline Team Leader	Donna Przepiorka, MD, PhD
Division Director (DHOT) (or designee)	Tiffany Ricks, PhD
Division Director (OCP)	Brian Booth, PhD
Division Director (OB)	Yuan Li Shen, DrPH
Division Director (DHM1) (or designee)	Kelly Norsworthy, MD
Office Director (or designee)	Marc Theoret, MD

Additional Reviewers of the Application

Regulatory Project Manager (DHM1)	Rachel McMullen, MPH, MHA
Associate Director for Safety (OCE)	Shan Pradhan, MD
Safety Data Analyst (OCE)	Zhongjun Luo, PhD
Oncology RWE (OCE)	Catherine Lerro, PhD, MPH; Donna Rivera, PharmD, MSc
CDRH	Deblina Banerjee, PhD; Christopher Trindade, MD
DMPP	Maria Nguyen, MSHS, BSN;
DPMH	Ethan D. Hausman, MD
IRT	Yanyan Ji, PhD; Anna Sun, PhD; Jing Sun, PhD; Justin S Collazo, PharmD; Eliford N Kitabi, PhD; Michael Y Li, MS; Christine E Garnett, PharmD
OPDP	Valeri Guerrier, PharmD
OPQ	ATL: Shalini Anand, PhD DS: Rajan Pragani, , PhD; Haripada Sarker, PhD DP: Rajiv Agarwal, PhD; Shalini Anand, PhD Manufacturing: Diane Goll, PhD; Zhaoyang Meng, PhD Biopharm: Gerlie Geiser, PhD; Anitha Govada, PhD RBPM: Dahlia Walters, MS
OSE/DMEPA	Sue Black, PharmD; Nicole Iverson, PharmD, BCPS
OSE/DRM	Till Olickal, PhD, PharmD; Naomi Boston, PharmD
OSI	Anthony Orencia, MD, PhD; Min Lu, MD, MPH

GLOSSARY

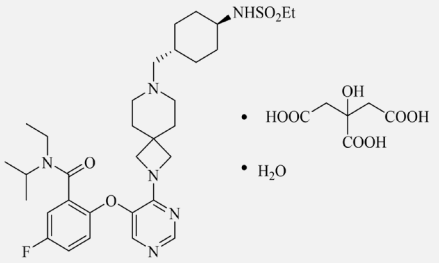
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
A/G	albumin globulin ratio
ALL	acute lymphoblastic leukemia
AML	Acute myeloid leukemia
AUC0-last	area under the concentration-time curve from time zero (0) until the last measurable concentration
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CNS	Central nervous system
CR	Complete response
CRh	CR with partial hematologic recovery
CSR	clinical study report
DOR	Duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
FDA	Food and Drug Administration
GCP	good clinical practice
GLP	good laboratory practice
HLM	human liver microsomes
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISS	integrated summary of safety
ITT	intent to treat
Meddra	Medical Dictionary for Regulatory Activities
MLFS	morphological leukemia-free state
MRD	minimal residual disease
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OSE	Office of Surveillance and Epidemiology
OS	overall survival
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PRO	patient reported outcome
QTc	corrected QT interval
RDI	relative dose intensity
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
RIR	response to information request
SAE	serious adverse event
SAP	statistical analysis plan
STD10	severely toxic dose in 10% of animals
Tmax	time to maximum plasma drug concentration
TEAE	Treatment-emergent adverse event
TI-56	Transfusion independence 56 days
TK	toxicokinetic
TTR	Time to response

1 EXECUTIVE SUMMARY

1.1. Product Introduction

Proposed Trade Name:	Revuforj
Established Name:	Revumenib
Also Known As:	SNDX-5613, SNDX-50613, VTP-50613
Chemical Name:	Benzamide, N-ethyl-2-[[4-[7-[[trans-4-[(ethylsulfonyl)amino] cyclohexyl]methyl]-2,7-diazaspiro[3.5]non-2-yl]-5-pyrimidinyl] oxy]-5-fluoro-N-[1-methylethyl]-, 2-hydroxypropane-1,2,3-tricarboxylic acid, hydrate
Molecular Formula:	$C_{32}H_{47}FN_6O_4S \bullet C_6H_8O_7 \bullet H_2O$
Molecular Weight:	840.96 g/mol
Dosage Forms:	Tablet (25, 110, and 160 mg)
Therapeutic Class:	Antineoplastic
Chemical Class:	Small molecule
Pharmacologic Class:	Menin inhibitor
Mechanism of Action:	Inhibits the interaction of both wild type KMT2A and KMT2A fusion proteins with menin. The binding of KMT2A fusion proteins with menin is involved activation of a leukemogenic transcriptional pathway in acute leukemias with KMT2A translocations.

Chemical Structure:



Revumenib is a new molecular entity. NDA 218944 for the oral tablets was submitted under the 505(b)(1) pathway for the proposed indication of treatment of adult and pediatric patients with relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene rearrangement (KMT2Ar) using a dose of 270 mg (160 mg/m^2 for those weighing < 40 kg) twice daily.

The review team recommends approval of revumenib for "treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older using a dose of 270 mg (160 mg/m^2 if weighing less than 40 kg) orally BID without strong CYP3A4i or 160 mg (95 mg/m^2 if weighing less than 40 kg) orally BID with strong CYP3A4i given until disease progression or unacceptable toxicity.
The recommendation is based on the findings in Study SNDX-5613-0700 of a 21.2% CR/CRh rate, median duration of CR/CRh of 6.4 months, and 14% rate of conversion to transfusion independence. Additional studies are warranted to confirm safety with long-term use, to establish the appropriate dosages in patients with organ impairment, and to assess for potential drug interactions.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Study SNDX-5613-0700 (AUGMENT-101, NCT04065399), was an open-label, Phase 1-2, multiple-cohort, multicenter trial of revumenib monotherapy in adult and pediatric patients at least 30 days old with relapsed or refractory (R/R) acute leukemia having a genetic variant associated with HOXA overexpression, including KMT2A translocations (KMT2At). Patients with an 11q23 partial tandem duplication (PTD) were excluded. Eligibility required a QTcF < 450 msec at study baseline. Treatment consisted of revumenib at a dose approximately equivalent to 160 mg in adults orally twice daily with a strong CYP3A4i until disease progression, unacceptable toxicity, failure to achieve morphological leukemia-free state by 4 cycles (112 days) of treatment, or hematopoietic stem cell transplantation (HSCT).

The Phase 1 portion was an open-label, dose-escalation study with seven single-arm cohorts (1A through 1G) based on concurrent CYP3A4i use, treatment schedule, and/or formulation. The Phase 2 portion included three single-arm disease-based cohorts (2A with KMT2Ar acute lymphoblastic leukemia (ALL) or mixed-phenotype acute leukemia (MPAL), 2B with KMT2Ar acute myeloid leukemia (AML), and 2C with NPM1c AML). Local testing was used for diagnosis and enrollment, and a central clinical trial assay (CTA) was used to confirm the KMT2Ar for Cohorts 2A and 2B. The primary objective of Phase 2 was to assess the rate of complete remission (CR) or CR with partial hematological recovery (CRh). Each Phase 2 cohort had a Simon 2-stage design to target a 25% CR/CRh rate and exclude a 10% rate. The primary analysis was to be conducted after completion of the first stage in Cohort 2B, and the analysis set was a pool of participants from Cohorts 2A+2B (Pivotal Cohort) with KMT2Ar by the CTA. Using the adjudicated endpoints, FDA calculated that the CR/CRh rate was 21% (95% CI 11%, 34%) for the 57 participants in the Pivotal Cohort. Because the lower 95% CI exceeded the prespecified lower bound of 10%, the trial was considered positive.

Because there was not sufficient information to confirm that the CTA could be considered reliable for selection of patients representative of the intended population, FDA conducted an ad hoc analysis that included all Phase 1 and Phase 2 participants with acute leukemia having an 11q23 translocation by local assay and baseline marrow blasts at least 5%, who were treated with at least one dose of revumenib at the recommended Phase 2 dosage (RP2D), and who completed the Cycle 7 Day 1 visit or discontinued earlier or responded earlier (Efficacy Cohort). The Efficacy Cohort included 104 participants (79 adults and 25 children) of median age 37 years (range, 1-79 years) predominantly with AML (83%). The median number of relapses was only 1, but 80% of the relapses were refractory to the last treatment.

In this population, the CR/CRh rate was 21% (95% CI 13.8, 30.3), the median duration of CR/CRh was 6.4 months (95% CI 2.7, NE), and the rate of conversion to 56-day transfusion independence (TI-56) was 14% (95% CI 8, 24). Of concern, the point estimates for CR/CRh and TI-56 with revumenib were quite low, and the consistency between CR/CRh and other measures of benefit, such as severe infection or bleeding, was not very robust. This was explained in part

by the short duration of treatment. The median duration of treatment was only 71 days (range 3-619 days). As remissions may be delayed in onset for nonmyelosuppressive drugs, there may not have been sufficient time for remissions to have occurred. The short duration of treatment was not clearly due to lack of efficacy, since approximately half of the participants who achieved CR, CRh, or at least cleared blasts from the marrow also ended treatment prematurely (median 84 days) and went on to HSCT, precluding ascertainment of TI-56 or TI-112. Nonetheless, remissions were seen in participants with refractory disease, the remissions were durable, the results were consistent across subpopulations, and the endpoints that were analyzed are used commonly in regulatory decision-making to denote effectiveness for nonmyelosuppressive treatments for acute leukemias.

Additional confirmatory evidence includes data showing the activity of revumenib in nonclinical in vitro and in vivo proof-of-concept studies, the observation of activity (albeit not substantial evidence of effectiveness) in a population with other gene variants associated with HOXA overexpression, and lack of efficacy in participants with acute leukemias not having genetic variants associated with HOXA overexpression. The results from the Efficacy Cohort of Study SNDX-5613-0700 and the additional confirmatory data are considered substantial evidence of effectiveness of revumenib for treatment of R/R acute leukemia with a KMT2At. As there was not sufficient pharmacokinetic (PK) information to establish an appropriate dosage for patients less than 1 year old, and there are no clinical efficacy data that could be used to overcome this deficiency, the evidence of effectiveness from SNDX-5613-0700 would be applicable only to patients 1 year and older.

1.3. Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The expected survival is weeks for patients with relapsed or refractory acute leukemia.	R/R acute leukemia with a KMT2At is a fatal disease.
Current Treatment Options	• There are no drugs approved specifically for R/R acute leukemias with KMT2At. • The standard of care for R/R acute leukemias is intensive cytotoxic chemotherapy followed by HSCT; 5-year OS is about 10%. There is substantial toxicity with chemotherapy. • The experience with targeted therapies (e.g., inotuzumab, blinatumomab, gemtuzumab) for R/R acute leukemias with KMT2At is limited to small subset analyses and case series. No conclusions can be made from this limited experience.	New treatments are needed to improve survival of patients with R/R acute leukemias with a KMT2At.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• SNDX-5613-0700 was a multiple-cohort, dose-escalation, dose-expansion trial that included 104 participants treated with revumenib equivalent to 160 mg in adults BID with a strong CYP3A4i for R/R acute leukemias having a KMT2At. • The CR/CRh rate was 21% (95% CI 13.8, 30.3). • The median DOCR/CRh was 6.4 months (95% CI 2.7, NE). • The rate of TI-56 was 14% (95% CI 8, 24). The duration of treatment was too short to calculate TI-112. • The leukemias observed in the clinical trial included < 10% of the known KMT2A translocation partners.	Revumenib at a dose equivalent to 160 mg BID with a strong CYP3A4i is active in the treatment of R/R acute leukemias having a KMT2At. Additional studies are needed to confirm activity in leukemias with rare translocation partners.
Risk and Risk Management	• Fatal adverse reactions included differentiation syndrome (DS), hemorrhage, and sudden death. • DS occurred in 29% and QTc prolongation in 29%. • Adverse reactions resulted in dose reduction in 10% and treatment discontinuation in 12%. • The most common adverse reactions (≥ 20%) included hemorrhage, nausea, phosphate increased, musculoskeletal pain, infection, aspartate aminotransferase increased, febrile neutropenia, alanine aminotransferase increased, parathyroid hormone intact increased, bacterial infection, diarrhea, differentiation syndrome, electrocardiogram QT prolonged, phosphate decreased, triglycerides increased, potassium decreased, decreased appetite, constipation, edema, viral infection, fatigue, and alkaline phosphatase increased. • The safety of long-term use has not been established. • There is insufficient information regarding toxicities of revumenib with potential drug-drug interactions and in patients with severe renal or hepatic impairment. • The clinical trials included specific monitoring to mitigate serious toxicities.	The safety profile of revumenib at the recommended dosage appears tolerable in the short term as administered in the clinical trials, and serious risks should be mitigated with appropriate labeling, but additional studies are needed to establish safe dosing in special populations.

R/R acute leukemia with a KMT2At is a fatal disease. Current available therapy has limited efficacy and considerable toxicity, especially the cytotoxic chemotherapy agents. Study SNDX-5613-0700 was a multiple-cohort, dose-escalation, dose-expansion trial that included 104 participants with R/R acute leukemia with a KMT2At treated with revumenib at the recommended dosage. The CR/CRh rate was 21% (95% CI 13.8, 30.3), the median DOCR/CRh

was 6.4 months (95% CI 2.7, NE), and the rate of TI-56 was 14% (95% CI 8, 24). The CR/CRh and TI-56 rates are somewhat low, and this was attributed in part to the short duration of treatment (median 2.3 months) with a substantial proportion of participants, even those who achieved a remission, coming off treatment prematurely to proceed to HSCT or alternative therapy. Nonetheless, durable responses were seen in patients with refractory disease. Thus, the results of the efficacy analysis, taken together with the additional confirmatory data, were considered substantial evidence of effectiveness of revumenib for treatment of R/R acute leukemia with KMT2A translocation in patients 1 year and older. The low CR/CRh rate and the low rate of conversion to transfusion independence warrant careful consideration of the risk-benefit assessment.

The ISS database included 337 treatments in 324 unique participants on four clinical trials and 50 single-patient protocols. The clinically important adverse reactions identified included DS and prolonged QTc. Due to the severity and potential mortality, DS warrants a boxed warning and Medication Guide, and prolonged QTc warrants a warning. Additional safety signals identified included cataracts, elevated transaminases, elevated parathyroid hormone, paraesthesia, taste disorder, and drug hypersensitivity. As signaling through menin is associated with tumor suppressor functions, secondary malignancy due to inhibition of menin function was an adverse event of special interest. Follow-up was too short to ascertain for this event.

The representative safety population included 135 participants (104 adults and 31 children) with R/R acute leukemia, having a KMT2A translocation treated with revumenib at the RP2D. The median duration of exposure to revumenib was 2.3 months (range < 1 to 23 months), and only 3% of patients were exposed for more than 6 months.

Fatal adverse reactions occurred in 4 (3%) participants, including 2 with DS, 1 with hemorrhage, and 1 with sudden death. Adverse reactions leading to dose reduction occurred in 10%, and adverse reactions leading to permanent discontinuation occurred in 12%. The Applicant's analysis of dose intensity (DI) showed that over 75% of participants in the Phase 2 portion of the trial maintained at least 80% DI for the first 3 cycles (there were too few participants continuing treatment thereafter). Thus, it appears that the recommended dosage of revumenib is tolerable, albeit with a clear need for strategies to mitigate fatal events.

The most common adverse reactions (≥ 20%) included hemorrhage, nausea, phosphate increased, musculoskeletal pain, infection, aspartate aminotransferase increased, febrile neutropenia, alanine aminotransferase increased, parathyroid hormone intact increased, bacterial infection, diarrhea, differentiation syndrome, electrocardiogram QT prolonged, phosphate decreased, triglycerides increased, potassium decreased, decreased appetite, constipation, edema, viral infection, fatigue, and alkaline phosphatase increased. Additional clinically relevant adverse reactions in less than 20% of patients included cardiac failure, pericardial effusion, ventricular tachycardia, cardiac arrest, hyperparathyroidism, cataract, abdominal pain, sudden death, drug hypersensitivity, taste disorder, syncope, headache, paraesthesia, renal impairment, and rash.

Temporally, the median time to onset of most adverse reactions was within the first cycle, so monitoring should be most intensive during the first 4 weeks of treatment. Overall, the safety profile of revumenib at the recommended dosage would be considered acceptable for a relapsed or refractory population where alternative therapies are not available or have limited effectiveness.

The Division determined that given the observed response rate with durability, and with the mitigation strategies in place in labeling, the clinical benefit of revumenib at this time appears to outweigh the risks of treatment of R/R acute leukemias with a KMT2At in adult and pediatric patients 1 year and older. Additional studies are warranted to confirm safety with long-term use, to establish appropriate dosages in patients with organ impairment, and to assess for potential drug interactions. The Applicant also committed to develop an in vitro diagnostic device for identifying KMT2A translocations, develop an oral solution dose form, and conduct an in vitro study to assess activity of revumenib with additional KMT2A translocation partners.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application			
□	The patient experience data that was submitted as part of the application, include:		Section where discussed
	□	Clinical outcome assessment (COA) data	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	Natural history studies	
	□	Patient preference studies (e.g., submitted studies or scientific publications)	
	□	Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.		
	□	Input informed from participation in meetings with patient stakeholders	
	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	Other: (Please specify):	
X	Patient experience data was not submitted as part of this application.		

2 THERAPEUTIC CONTEXT

2.1. Analysis of Condition

The Applicant's Position:

Acute leukemia is a life-threatening condition with poor long-term outcomes, and is rapidly fatal without treatment. KMT2A rearrangement is the genetic driver in approximately 10% of acute leukemias including acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and mixed phenotype acute leukemia (MPAL), presenting in all ages from infants to older adults, and confers poor prognosis. The binding of KMT2A fusion proteins with menin is the key driver of KMT2A-rearranged (*KMT2A*r) acute leukemias through activation of a leukemogenic transcriptional program. In nonclinical in vitro and in vivo studies using models harboring KMT2A fusions, revumenib demonstrated anti-tumor activity through disruption of the *KMT2A*r-menin interaction (Caslini 2007).

Progression free survival for newly diagnosed *KMT2A*r leukemia remains poor, regardless of whether chemotherapy or venetoclax/azacitidine regimens are used (Cherry 2021). Remission rates after relapse (5% CR in 2nd salvage) and overall survival (2.4 months in 2nd salvage) in *KMT2A*r AML patients remain low (Issa 2021). Outcomes of ALL with *KMT2A*r are also poor, with 5 year OS and relapse-free survival (RFS) of 17% and 15% (Richard-Carpentier 2021). In addition, AML patients with post-transplant relapse have poor overall survival (Bazarbachi 2020), and those who have relapsed following front-line treatment with venetoclax have a low probability of responding to subsequent therapy (CR ~4%) and poor overall survival as well (median 2.4 months) (Maiti 2021).

The FDA's Assessment:

KMT2A translocation (KMT2At) products are leukemogenesis drivers in multipotent progenitors.[1] The resulting acute leukemia (also known as MLLr leukemia) can appear phenotypically as acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or mixed-phenotype acute leukemia (MPAL), depending on fusion partner and clonal epigenetic changes.[2,3,4] Relapse with a lineage switch may occur.[3,5]

[1] Armstrong SA et al. MLL translocations specify a distinct gene expression profile that distinguishes a unique leukemia. Nat Genet 2002;30:41.
[2] Khoury JD et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022;36:1703.
[3] Iacobucci I et al. KMT2A-rearranged leukemia: the shapeshifter. Blood 2022;140:1833.
[4] Tertakasuma R et al. Epigenetic regulator genes direct lineage switching in MLL/AF4 leukemia. Blood 2022;140:1875.
[5] Liao W et al. Does lineage plasticity enable escape from CAR-T cell therapy? Lessons from MLL-r leukemia. Exp Hematol 2021;100:1.

KMT2At acute leukemia accounts for > 70% of infant ALL, 35-50% of infant AML, and 10% of acute leukemias in older children and adults.[6] The demographics of patients with KMT2At acute leukemia diagnosed 2010 - 2020 as reported to SEER[7] are shown in Table 1. The ALL cases predominated in the pediatric population, while the AML cases predominated in adults.

FDA Table 1. Demographics of Patients with KMT2At Acute Leukemia in SEER 22 Registries 2010 - 2020

	N	%
Age		
Less than 1 year	118	11.3%
1 to 5 years	84	8.0%
6 to 11 years	42	4.0%
12 to 16 years	30	2.9%
17 to 40 years	190	18.2%
41 to 64 years	268	25.7%
65 to 74 years	143	13.7%
75 years and older	169	16.2%
Sex		
Female	525	50.3%
Male	519	49.7%
Race and Ethnicity		
White	624	59.8%
Hispanic	214	20.5%
Black or African American	101	9.7%
Asian or Pacific Islander	99	9.5%
American Indian/Alaska Native	5	0.5%
Unknown	1	0.1%
Histologic Type		
Acute myeloid leukemia with t(9;11)(p21.3;q23.3); KMT2A-MLLT3	730	69.9%
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); KMT2A-rearranged	269	25.8%
Mixed-phenotype acute leukemia with t(v;11q23.3); KMT2A-rearranged	45	4.3%

Source: FDA analysis[7]

[6] Winters AC et al. MLL-rearranged leukemias-An update on science and clinical approaches. Front Pediatr 2017;5:4

[7] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Limited-Field Data, 22 Registries, Nov 2021 Sub (2000-2019) - Linked to County Attributes - Time Dependent (1990-2019) Income/Rurality, 1969-2020 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2023, based on the November 2022 submission. Includes ICD-O-3 codes 9807, 9813, and 9897 within years of diagnosis 2010-2020.

KMT2A is an adverse prognostic factor for newly diagnosed acute leukemias, with 5-yr OS 35-50%.[6,8,9] The FDA agrees that patients with relapsed KMT2At leukemia have a poor prognosis.

2.2. Analysis of Current Treatment Options

There is currently no established standard of care in the R/R *KMT2A*r acute leukemia population. Guidelines recommend salvage chemotherapy or investigational trials, and transplant if eligible (Majhail 2015; Pollyea 2023). Historically, < 5% of the R/R *KMT2A*r population has been able to proceed to transplant in remission (Issa 2021). Salvage fludarabine/cytarabine combinations are associated with significant toxicity, with approximately 10% treatment-related mortality, and rates of neutropenia, thrombocytopenia, and febrile neutropenia of 50% to 100% (Kaspers 2013, McLaughlin 2012, Zhang 2014, Lee 2009). Mortality during re-induction remains high even with newer regimens such as venetoclax/hypomethylating agents (HMAs), especially in patients who relapse post-transplant; in these patients, mortality rates are 23% within 60 days (Du 2023; Gao 2021). Options are even more limited for patients who have relapsed after transplant, or for older patients who cannot tolerate chemotherapy and have relapsed after venetoclax.

The Applicant's Position:

Although genomic characterization of acute leukemias has led to development of targeted therapies that have improved clinical outcomes for patients with some genetically defined leukemias, none are yet approved for *KMT2A*r leukemia, and specifically there are no menin inhibitors approved for the treatment of acute leukemias. Patients with R/R *KMT2A*r acute leukemia therefore lack a viable treatment option to target the underlying disease driver and have a significant unmet medical need.

The FDA's Assessment:

The FDA agrees that there is no treatment approved specifically KMT2At leukemias. The standard of care for treatment of relapse or refractory (R/R) acute leukemias with or without KMT2At is intensive cytotoxic chemotherapy followed by allogeneic HSCT; median survival of patients with R/R KMT2At acute leukemia is less than 1 year, and 5-year OS is less than 10%.[8,9] There are no prospective trials for treatment of R/R KMT2At acute leukemia. CR rates for patients treated with salvage chemotherapy depends on age, number of prior relapses, and refractoriness to last line of therapy. In a retrospective analysis of 222 adult patients with KMT2At AML, Issa et al reported CR in 66% after 1st line therapy, 34% after 2nd line therapy,

[8] Issa GC et al. Predictors of outcomes in adults with acute myeloid leukemia and KMT2A rearrangements. Blood Cancer J 2021:11:162.
[9] Richard-Carpenter G et al. Outcome of acute lymphoblastic leukemia with KMT2A (MLL) rearrangement: the MD Anderson experience. Blood Adv. 2021;5:5415.

and 5% after 3rd or later line of therapy.[8] There are no published data on outcomes for patients with R/R KMT2At ALL or MPAL.

3 REGULATORY BACKGROUND

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Revumenib is not currently registered or approved in the United States or any other part of the world.

The FDA's Assessment:

The FDA agrees that revumenib is not yet approved in the United States or any other part of the world.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
The development of revumenib was initiated under IND 142,693. Key interactions between the FDA and the Sponsor are detailed in Table 2.

Table 2: Applicant – Summary of Regulatory History

Date	IND 142,693 Submission/Activity
31 May 2019	Initial IND application submitted for Study SNDX-5613-0700.
21 Apr 2020	Revumenib granted orphan drug designation.
26 Jun 2020	Type A Teleconference Meeting (Ref ID: 4634874) to discuss Phase 2 adult and pediatric trial. Agency agreed to enrollment of pediatric patients ≥ 30 days old and a rolling 6 design for the dose escalation portion of Study SNDX-5613-0700.
24 Jun 2021	Revumenib granted Fast Track Designation (Reference ID: 4815990)
15 Jul 2021	Type C Written Responses (Ref ID: 4826163) where the Agency agreed with the salt formulation change (b) (4) to monocitrate monohydrate.
29 Jul 2021	Type A Teleconference Meeting (Ref ID: 4834459) where Agency agreed to a null hypothesis of 10% for the Phase 2 *KMT2A*r AML and ALL cohorts in Study SNDX-5613-0700.
20 Sep 2021	Type A Teleconference Meeting (Ref ID: 4861899) where Agency agreed to the proposed Arm B, revumenib RP2D of 163 mg q12h in combination with a strong CYP3A4i.
01 Nov 2021	Type A Meeting Preliminary Comments (Ref ID: 4881870) where the Agency requested additional data to support an RP2D for patients receiving a moderate CYP3A4i (fluconazole and isavuconazole) and patients on no CYP3A4i.

24 May 2022	Type C Written Responses (Ref ID: 4988982) where Agency agreed with the regulatory starting materials for the manufacturing of revumenib monocitrate monohydrate drug substance in support of marketing approval.
06 Jun 2022	Type C Written Responses (Ref ID: 4994946) where Agency provided recommendations in response to proposed clinical pharmacology plans to support a marketing application for revumenib.
30 Nov 2022	Revumenib Breakthrough Therapy Designation granted for the treatment of adult and pediatric patients with R/R acute leukemia harboring a *KMT2A*r.
20 Jan 2023	Study SNDX-5613-0700, Amendment 14.1 (Version 15.1) amended the primary endpoint to be age and leukemia agnostic and added an efficacy boundary for testing to the planned interim analysis for Cohort 2B.
23 Mar 2023	Type B Multidisciplinary Meeting (Ref ID: 5153948) where overall Agency agreement was reached on the NDA communication plan for SNDX-5613-0700. The Agency also agreed to the proposed revumenib RP2D of 276 mg q12h without a strong CYP3A4i.
19 May 2023	Type B Content Meeting Written Responses (Ref ID: 5177161) where Agency provided overall agreement on the proposed NDA content plan.
27 Jun 2023	Revumenib Race and Ethnicity Diversity Plan submitted to IND 142,693.
15 Aug 2023	Study SNDX-5613-0700, Amendment 15 (Version 16) amended the hypothesis testing procedure to test the pooled *KMT2A*r population as the Primary Analysis #1 and the adult *KMT2A*r AML population as the Primary Analysis #2, with the test of the pooled *KMT2A*r population conducted at both the Cohort 2B IA and final analysis.
20 Oct 2023	Pre-NDA Meeting (Ref ID: 5265866) where Agency accepted the Sponsor's plan to submit an initial NDA filing for revumenib utilizing RTOR and an Assessment Aid. The Agency also agreed to accept an updated CMC stability package within 30 days after completion of the initial NDA.

The FDA's Assessment:

The Agency provided advice on the drug development program in 14 formal meetings or Written Responses Only (WRO) as listed by the Applicant above and in FDA's table below in addition to numerous informal communications. The clinical development program was also discussed at the June 18, 2020, meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee.

FDA Table 3. Additional Key US Presubmission/Submission Regulatory Activities

Date	Regulatory Activity
4/8/2019	Type B Pre-IND WRO
5/20/2020	Advised to include pediatric patients in the Phase 1 study
6/18/2020	Pediatric Subcommittee of the Oncologic Drugs Advisory Committee
12/15/2020	Type C meeting regarding QTc criteria in the DLT definition
7/14/2021	Type C WRO advising Applicant to data needed to support new salts of the tablet (b) (4)

FDA Table 3. Additional Key US Presubmission/Submission Regulatory Activities

Date	Regulatory Activity
2/9/2023	Advised Applicant that efficacy should be based on the population identified by the CDx or a clinical trial assay bridged to the CDx
3/28/2023	Intermediate size expanded access protocol received
3/31/2023	Type B responses regarding the CMC package for the NDA
9/26/2023	FDA declined to agree with stopping enrollment of 2A and 2B at the interim analysis
10/16/2023	Accepted RTOR submission timeline
10/31/2023	First RTOR submission received
12/22/2023	Advised the Applicant of systematic errors in the data sets for Study SNDX-5613-0700 and that the NDA submission would not be considered complete until the revised data sets are submitted
1/26/2024	NDA application submission completed
2/2/2024	Application Orientation Meeting
2/15/2024	iPSP agreed upon
5/17/2024	Midcycle Communication
7/3/2024	Clinical Pharmacology Discipline Review Letter issued
7/11/2024	Orphan Drug Designation for treatment of acute lymphocytic leukemia
7/18/2024	Late-Cycle Meeting
7/26/2024	Review clock extended for major amendment received 7/24/2024
8/1/2024	Orphan Drug Designation for treatment of acute leukemias of ambiguous lineage
9/30/2024	Informal teleconference to discuss deficiencies in the data to support the (b) (4) plan to market the 25 mg tablet.
(b) (4)	

Source: FDA analysis

FDA provided the following key advice to the Applicant during drug development:

- A biowaiver for the tablets is not possible. Plan to provide PK and safety data to support the tablet (b) (4) (Pre-IND 4/8/2019; Type A 6/26/2020; Type C 7/14/2021; Type C 6/6/2022; Type B 3/23/23; Type B 5/19/2023; Type B 10/20/2023)
- Identify in the submission the formulation used by each study participant. Include PK data from the single-patient protocols. (Type B 3/23/23; Type B 5/19/2023)

- A food effects study with the to-be-marketed formulation will be needed. (Type C 6/6/2022; Type B 3/23/23; Type B 10/20/2023)
- Agreed that the available data appear to support RP2Ds of 163 mg q 12 hours with strong CYP3A4 inhibitor and 276 mg q 12 hours without a CYP3A4i. (Type B meeting 3/23/2023)
- Submit (b) (4) for tablet formulations (b) (4) (Type B 5/19/2023; Type B 10/20/2023)
- A companion diagnostic (CDx) will be needed for safe use of this drug. (Pre-IND 4/8/2019; Type B 3/23/23; Pre-NDA 10/24/23)
- The clinical trial assay used to identify patients for the pivotal cohort should be analytically valid. Obtain advice from CDRH. (Advice 5/6/2022; Type B 10/20/2023)
- One adequate and well-controlled trial and independent supporting information may be appropriate to support a marketing application. (Type B 10/20/2023)
- Include adult and pediatric patients in the pivotal cohort. (Type A 6/26/2020)
- Use of CR+CRh may be applicable as the primary efficacy endpoint if revumenib is not myelosuppressive. The acceptability of a -7 to +15 day window for CBC and marrow for the efficacy assessment is a review issue (Type A 7/29/2021; Type B 3/23/23)
- When CR+ CRh is used as the primary endpoint, supporting information on duration of response and transfusion independence is needed. (Type A 7/29/2021)
- The acceptability of 10% as the null rate for CR+CRh will be a review issue. Provide references to support the proposed null rate. The proposed RWE study should provide adequate information for the null rate. (Pre-IND 4/8/2019; Type A 6/26/2020; Type A 7/29/2021; Type B 3/23/23; Type B 10/20/2023)
- Provide the estimands for the primary analysis of the primary endpoint, the duration of response for the primary endpoint, and the transfusion independence endpoint. (Advice 9/30/2022; Advice 10/20/2022; Type B 5/19/2023)
- Agreed with 2-stage design for hypothesis testing. (Type A 7/29/2021)
- For efficacy analysis, enrolled participants in the pivotal cohort must have a minimum of 4 cycles of therapy and a minimum of 6 months of follow-up or discontinued earlier. (Type A 6/26/2020; Type B 10/20/2023).
- Plan to submit the raw data for the efficacy assessments for all patients. (Type B 10/20/2023)

The last part of the NDA was received on 1/26/2024, and the application was filed on 3/26/2024. (b) (4)

(b) (4)

4 SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted inspections for Study SNDX-5613-0700 at Clinical Sites 01 (New York, NY), 04 (Chicago, IL), 07 (Houston, TX), and 09 (Duarte, CA). The sites were chosen on the basis of enrollment of large numbers of participants, a high proportion of treatment responders, and a high number of protocol deviations per patient. Following inspection, the regulatory classification for these sites was No Action Indicated (NAI). The Applicant (Syndax Pharmaceuticals, Inc.) was also audited; the final classification for the Applicant's inspection was NAI. OSI concluded that study data submitted to the Agency are acceptable for review in support of the proposed indication.

4.2. Product Quality

Revumenib drug product (Revuforj) is presented as a pink (25 mg), beige (110 mg), or purple (160 mg) oval film-coated tablet containing 33.4 mg, 146.5 mg, and 213.2 mg revumenib citrate, respectively. The tablets are debossed with “S” on one side and the strength (25, 110, or 160) on the other side The inactive ingredients include microcrystalline cellulose, dicalcium phosphate, crospovidone, hypromellose, sodium bicarbonate, hydrophobic colloidal silica, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, red iron oxide, yellow iron oxide and/or FD&C blue #2/indigo carmine aluminum lake. No excipient posed additional safety risks, and there were no novel excipients. The drug product is supplied in bottles of 30 tablets with an expiry of 24 months when stored at USP controlled room temperature.

The Applicant proposed instructions for use of crushed tablets for patients unable to swallow whole tablets. The Biopharmaceutics Reviewer concluded that the CMC and nonclinical data submitted supported acceptable compatibility, delivered-dose recovery, and in-use stability (2 hours). The DMEPA Reviewer indicated that the Instructions for Use did not warrant a human factors study.[10]

[10] NDA 218944 Wrap-up Meeting 10/29/2024.

During clinical development, the formulations and dose forms used included the [redacted] (b) (4) salt as capsule, oral solution, and extemporaneous solution from capsule, and the citrate salt as tablet and oral solution. All of the formulations and dose forms, including the to-be-marketed forms, were used in Study SNDX-5613-0700. The Clinical Pharmacology Reviewer concluded that there was no clinically meaningful difference in revumenib and M1 pharmacokinetics by capsule or tablet (Section 6.1.1). The paucity of PK data with the 25 mg tablet left some uncertainty, but a biowaiver was granted on the basis that the 25 mg tablet is [redacted] (b) (4) as the 110 mg and 160 mg strengths, and the 25 mg tablet is also very rapidly dissolving.

There were no outstanding safety issues identified for the manufacturing process or from the facilities inspections. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment under 21 CFR 25.31(b). Approval of the NDA was recommended by the Product Quality review team.

4.3. Devices and Companion Diagnostic Issues

For the participants in the Phase 2 portion of Study SNDX-5613-0700, a clinical trial assay (CTA) was used to confirm the KMT2A rearrangement for the Pivotal Cohort. The CTA was performed at [redacted] (b) (4) by fluorescence in situ hybridization (FISH). Based on the information provided in the NDA, the CDRH reviewers concluded that there was not sufficient information to establish the adequacy of the CTA for identification of KMT2Ar in patients with acute leukemias.[11] As such, the assay could not be considered reliable for selection of patients for whom the efficacy result would be generalizable to the intended population.

In practice, KMT2A rearrangements are detected in the karyotyping performed in the diagnostic work-up of leukemia. In cases where there is poor cell growth or a need for rapid diagnosis, alternative methods are used. The Division has determined that a companion diagnostic assay (CDx) would be needed for safe use of revumenib in these circumstances, and the Applicant has committed to develop such an assay postmarketing.

5 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

5.1. Executive Summary

The FDA's Assessment:

[11] NDA 218944 CDRH Consult Reviews by Christopher Trindade, MD, dated 4/12/2024, and by Deblina Banerjee, PhD, dated 6/4/2024.

Revumenib is a menin inhibitor, the first in this new established pharmacologic class. Menin is a scaffold protein that interacts with various proteins to regulate gene transcription via chromatin remodeling. Menin binds to the N-terminal of lysine methyltransferase 2a (KMT2A), and this interaction is involved in leukemic transformation in KMT2A rearranged (KMT2Ar) driven leukemia. Revumenib binds to menin at the KMT2A binding site and disrupts the interaction between menin and KMT2A. Revumenib was developed for the treatment of adult and pediatric patients with relapsed or refractory (r/r) acute leukemia with KMT2A rearrangement.

Revumenib inhibited the interaction between recombinant menin and the N-terminal portion of KMT2A (IC50 = 2.4 nM). The N-terminal portion of KMT2A is retained in all KMT2A fusion proteins and is involved in the interaction with menin; therefore, revumenib can inhibit the interaction between menin and KMT2A fusion proteins. Revumenib showed anti-proliferative activity against 4 leukemia cell lines with different KMT2A fusion proteins (IC50 = 12-24 nM). The primary metabolite of revumenib (referred to as SNDX-60165 or M1) showed minimal anti-proliferative activity in the MV4;11 leukemia cell line (IC50 = 978 nM). The anti-tumor activity of revumenib was evaluated using the human AML cell lines MV4;11 and MOLM-13 in rats or immunocompromised mice and with various routes of administration and treatment durations. Overall, revumenib showed dose-dependent antitumor activity in nonclinical models of human AML. The activity of revumenib was not evaluated in nonclinical models of ALL. In binding assays conducted to determine off-target binding, revumenib did not show activity against the targets evaluated, suggesting a low potential for off-target activity.

In vitro, revumenib treatment in cells with KMT2a fusion proteins showed anti-proliferative activity and alterations to menin-KMT2a target genes and differentiation markers[12]. In vivo, revumenib treatment in a patient derived xenograft (PDX) with a KMT2a fusion protein showed anti-tumor activity and alterations to menin-KMT2a target genes[13]. These findings are supportive of the mechanism of action of revumenib as described in the label.

Based on findings from non-GLP and GLP assays, revumenib and its primary metabolite M1 have the potential to block the hERG channel and contribute to QTc prolongation. The IC50 values for hERG inhibition were 4.75 and 3.46 µM for revumenib and M1, respectively, and suggest that M1 contributes to the effects of hERG inhibition. Increased QTc interval duration and premature atrial contractions were seen after repeated dosing with 225 mg/kg/day in dogs. Revumenib and M1 had Torsade de Pointe (TdP) scores of 2.5 and 2 at 3 µM, respectively, supporting the clinical findings indicating that revumenib can cause QT interval prolongation. In the 4-week repeat dose toxicology study in dogs, revumenib induced reversible increases in QTc interval duration of approximately 9% in males and females.

[12] Perner, F. et al. MEN1 mutations mediate clinical resistance to menin inhibition. Nature. 2023 Mar;615(7954):913-919.
[13] Issa, GC. et al. The menin inhibitor revumenib in KMT2A-rearranged or NPM1-mutant leukaemia. Nature. 2023 Mar;615(7954):920-924.

The bioavailability of revumenib ranged from 20% in mice to 70% in dogs. Revumenib distribution was the highest in the eye uveal tract at concentrations that were sustained to 672 hours post-dose. Revumenib showed greater binding to human plasma (~80% bound) compared to mouse, rat, and dog plasma. In toxicology studies in rats and dogs, exposure (area under the curve or Cmax) generally increased with increasing dose with less than dose proportional increases at higher doses.

Toxicology studies with up to 13 weeks of dosing were conducted in rats and dogs. In GLP-compliant repeat dose toxicology studies, animals were dosed daily via oral gavage. In the 4-week and 13-week toxicology studies in rats, animals received revumenib doses of 75, 150 or 300 mg/kg/day. Irreversible lens opacities were seen at doses ≥ 150 mg/kg/day in the 4-week study with progression after dosing cessation and at doses ≥ 75 mg/kg/day in the 13-week study with progression in some animals throughout the study. Ocular toxicity is a potential risk with this product; therefore, the ocular findings in animals were included in the label. In the 4-week rat study, hyperplasia findings were observed in the testes of males (irreversible at ≥ 75 mg/kg/day) and in the mammary gland and uterus in females (≥ 150 mg/kg/day). Effects on female fertility (decreased corpora lutea) and liver toxicity (increased liver enzymes, organ weights, and hypertrophy) were observed at doses ≥ 75 mg/kg/day.

In the 13-week toxicology study in rats, irreversible findings of hyperplasia were seen in multiple organs (mammary gland, uterus/cervix, vagina, testes, pancreas, and kidney) at all revumenib doses. Increased organ weights generally correlated with microscopic findings of hypertrophy in the liver, thyroid/parathyroid gland, pituitary gland, and adrenal gland or hyperplasia in the uterus/cervix and kidney. Enlarged organ size (liver, thyroid/parathyroid, pituitary and adrenal gland) or pale foci (pancreas) correlated with hypertrophy or hyperplasia, respectively. One male (150 mg/kg/day) euthanized on day 63 due to deteriorating condition had a lymphoma present in various organs including the lungs and thymus, and the cause of death was due to the thymic mass. Due to the potential for tumorgenicity with epigenetic modifying drugs and the multi-organ hyperplasia observed in the 13-week rat study, the lymphoma and hyperplasia findings were added to the labeling for this product. Changes including increased organ weights, enlarged organ size, and hyperplasia/hypertrophy in the thyroid gland, pituitary gland, adrenal gland, and pancreas may be due to impaired menin expression as seen in the inherited endocrine tumor syndrome (MEN1) that is driven by a mutation in menin[14]). Irreversible increases in femur growth plate closure were seen at all revumenib doses, and since this study was conducted in rats of 6-7 weeks of age, the findings suggest potential effects on bone development in pediatric patients. Due to the irreversible findings of increased femur growth plate closure and the proposed pediatric indication, suggested monitoring for bone growth and development in pediatric patients was added to the labeling for this product. In rats, decreased corpora lutea in the ovaries suggest potential effects on female fertility. Revumenib

[14] Mohr H, Pellegata NS. Animal models of MEN1. Endocr Relat Cancer. 2017 Oct;24(10):T161-T177.

exposures at 75 mg/kg/day in rats were approximately 2 times the human exposure (AUC) at the recommended dose of 270 mg twice daily.

In the 4-week toxicology study in dogs, animals received revumenib doses of 25, 50, or 100 mg/kg/day. The high dose of 100 mg/kg/day was not tolerated, and animals in this group were terminated early due to toxicity. Reversible increases in the QTc interval were seen throughout the dosing period (at 2 and 4 weeks). Decreased thymus weights correlated with lymphoid atrophy in males and females at all doses. Germ cell depletion/degeneration in the testes and necrosis in the epididymis of males (irreversible at ≥ 50 mg/kg/day) correlated with decreased organ weights and suggest potential effects on male fertility.

In the 13-week toxicology study in dogs, animals received revumenib doses of 12.5, 25, or 40 mg/kg/day. Irreversible findings of nerve fiber degeneration in the brain, sciatic nerve, and spinal cord were seen at all revumenib doses and suggest the potential for revumenib to affect nerve function in patients. Based on these findings, there is a risk for peripheral neuropathy in patients; therefore, nerve fiber degeneration findings in animals were included in the labeling for this product. Reversible findings of decreased corpora lutea in the ovaries, atrophy in female reproductive organs (uterus/cervix, vagina, and mammary gland), decreased sperm in the epididymis, and degeneration/atrophy, depletion of germ cells, and decreased sperm in the testes were seen at all revumenib doses (≥ 12.5 mg/kg/day) in this study. Based on findings in male and female reproductive organs observed across the GLP repeat dose toxicology studies, there is a risk for infertility that has been added to the labeling for this product. Liver toxicity included findings of degeneration/necrosis and mixed cell inflammation. Revumenib exposures at 12.5 mg/kg/day in dogs were approximately 1.3 times the AUC at the recommended dose of 270 mg twice daily.

In the embryo-fetal development study, pregnant rats received revumenib doses of 30, 100, or 300 mg/kg/day for 12 days during gestation. Lower maternal body weights and decreased body weight gains were observed at all doses. Decreased gravid uterine weights correlated with a reduced number of viable fetuses and lower mean fetal weight at all revumenib doses. There was a dose-dependent increase in the number of resorptions (including total litter resorption at 300 mg/kg/day), post-implantation loss, and malformations at all revumenib doses, suggesting potential fetal toxicity at exposures 0.6 times the human exposure (AUC) at the recommended dose of 270 mg twice daily. Based on data from the embryo-fetal development study and revumenib's mechanism of action, a warning for embryo-fetal toxicity is included in the labeling for this product. While revumenib showed no genotoxic potential in standard genetic toxicology studies, based on its activity as an epigenetic modifier, the reversibility of reproductive findings in toxicology studies within 13 weeks, and the assumption that pharmacodynamic effects are reversible, the FDA agreed to the Applicant's proposal of 4 months duration of contraception for males and females.

In the juvenile dose range-finding study in rats, revumenib doses of 6, 15, 60, or 150 mg/kg/day were administered on postnatal day 7 (PND) until PND 28. Mortality was observed at the 150 mg/kg/day dose and clinical observations included cold extremities and swollen forelimbs. Changes in red cell parameters and organ weights were similar to the changes seen in the 4-week and 13-week rat toxicology studies. A juvenile study was not requested by the FDA, and the Applicant conducted this study at their discretion.

This NDA is approvable from a pharmacology/toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

Not applicable, this is an original NDA.

The FDA's Assessment:

The FDA concurs.

5.3. Pharmacology

Primary Pharmacology

The Applicant's Position:

Revumenib demonstrated potent inhibition of KMT2A binding to human menin (IC_{50} of 2.4 nM; K_i of 0.15 nM), and antiproliferative activity of leukemia cell lines with different KMT2A fusion proteins, MV4;11 [t(4;11)(q21;q23)], MOLM-13 [t(9;11)], KOPN-8 [t(11;19)(q23;p13.3)], and RS4;11 [t(4;11)(q21;q23)], with similar IC_{50} values for proliferation (12 to 24 nM), consistent with blockade of the shared menin-KMT2A binding interaction. The primary metabolite of revumenib, SNDX-60165 (M1, desethyl-revumenib) showed minimal antiproliferative activity of *KMT2A*r cell line MV4;11. In rats bearing MV4;11 SC xenograft tumors, revumenib inhibited tumor growth (1) when administered continuously by infusion over 4 days at solution strengths of 1, 5, and 25 mg/mL (approximately 1.5, 7.5, and 37.5 mg/kg/day) and (2) when administered orally over 29 days at doses of 5, 15, and 50 mg/kg BID. Tumor regression was also observed with oral revumenib in rats bearing MOLM-13 tumors at 15 and 50 mg/kg BID for 28 days. Revumenib administration to mice bearing MV4;11 tumors at oral doses of up to 100 mg/kg BID for 28 days increased survival (lifespan > 71 days; > 97.2%), and decreased leukemic burden in bone marrow, with nearly undetectable levels at the highest tested dose. Increased survival was also observed in mice bearing MOLM-13 tumors with revumenib administered orally at doses of 25, 50, or 100 mg/kg BID or in the diet at concentrations of 0.025%, 0.05%, 0.1%, 0.2% (approximately 43.75, 87.5, 175, and 350 mg/kg/day) for 28 days.

In multiple *KMT2A*r PDX models, encompassing ALL and AML forms of *KMT2A*r leukemias, the close analog VTP-50469 (equipotent in binding/cell-based activity to revumenib) showed profound single-agent antitumor activity. VTP-50469 administered by oral gavage or in the diet reduced the leukemic burden in peripheral blood, bone marrow, and spleen, and confers a pronounced survival benefit. These results suggest that revumenib, as a menin-KMT2A blocker, may provide clinical benefit in the treatment of ALL and AML as single agent.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment for the primary pharmacology of revumenib; however, the activity of the structural analog of revumenib (VTP-50469) is not relevant for this application. Therefore, studies conducted with VTP-50469 were not reviewed for this application nor used to support the NDA. The Applicant described that VTP-50469 was used in some studies for which revumenib was not yet available. The following information provides additional details not described in the Applicant's assessment.

The binding affinity of revumenib to menin relative to KMT2A was evaluated in a competition assay using recombinant human menin and a KMT2A peptide (N-terminal portion of KMT2A, amino acids 4-43). The ability of revumenib to disrupt menin-KMT2A binding was assessed in the homogenous time resolved fluorescence (HTRF) assay based on fluorescence resonance energy transfer (FRET) from the fluorescein isothiocyanate (FITC)-labeled KMT2A peptide and the terbium-labeled anti-His6 antibody for His6-labeled menin. Revumenib concentrations of 0.316 to 1,000 nM were incubated with His6-menin and with 0.25 nM FITC-KMT2A peptide. Results showed a concentration-dependent loss of FRET signal that reflected the affinity of revumenib to menin relative to the KMT2A peptide. The average IC50 value was 2.4 ± 0.8 nM based on 30 independent measurements.

The ability of revumenib to dissociate the KMT2A-menin interaction (inhibitory constant, Ki) was determined by titrating revumenib at a saturating concentration of the KMT2A peptide (3.2 nM). The average Ki value was 0.15 ± 0.03 nM based on 24 independent experiments.
The primary metabolite of revumenib (SNDX-60165 or M1) showed antiproliferative activity against the MV4;11 leukemia cell line with an IC50 of 978 nM.

MV4;11 and MOLM-13 are human AML cell lines. In Rowett Nude (RNU) rats with MV4;11 tumor xenografts administered revumenib via infusion pumps for 4 days (SP-BIO-014), the expression of the human MEIS1 gene was evaluated by quantitative polymerase chain reaction. Results showed a dose-dependent decrease in MEIS1 gene expression (~100% decrease at 25 mg/mL). In RNU nude rats with subcutaneous MOLM-13 tumor xenografts administered revumenib doses of 5, 15, or 50 mg/kg twice daily, tumor progression occurred at 5 mg/kg and tumor inhibition was seen at doses ≥ 15 mg/kg. Revumenib also showed a dose-dependent decrease in hCD45+ tumor cells in the bone marrow of NOD scid gamma (NSG) mice with

MV4;11 or MOLM-13 disseminated tumors treated with revumenib doses up to 100 mg/kg BID or up to 0.2% in the diet (**FDA Table 4**).

FDA Table 4. Summary of in vivo studies with revumenib

Study #	Species	AML model	Route of administration	Dose	Treatment duration (days)	Summary of Results
SP-BIO-014	RNU rat	MV4;11	Subcutaneous infusion pump	1, 5, or 25 mg/mL (~1.5, 7.5, or 37.5 mg/kg/day)	4	~60% tumor growth inhibition at 25 mg/mL
SP-BIO-010	RNU rat	MV4;11	Oral	5, 15, or 50 mg/kg BID	29	~100% tumor growth inhibition at 50 mg/kg BID
SP-BIO-007	RNU rat	MOLM-13	Oral	5, 15, or 50 mg/kg BID	28	
MI3163	NSG mice	MV4;11	Oral	25, 50, or 100 mg/kg BID	28	Reduced tumor burden (↓ hCD45+ cells)
MI3631	NSG mice	MOLM-13	Oral (in diet)	0.025%, 0.05%, 0.1%, or 0.2%	28	Reduced tumor burden (↓ hCD45+ cells)

Source: FDA analysis

In vitro, treatment with revumenib resulted in a concentration-dependent reduction in relative cell counts, as determined by flow cytometry in MOLM-13 cells. In MV4;11 cells, treatment with revumenib resulted in reduced expression of menin-KMT2a target genes including MEIS1 and homeobox (HOX) genes and increased expression of differentiation genes including CD14 and CD11b[12]. In vivo, revumenib treatment resulted in reduced tumor burden (↓ hCD45+ cells) in a PDX mouse model and reduced expression of menin-KMT2a target genes including MEIS1 and HOX genes. Gene expression was determined by RNA sequencing in both of the publications mentioned.

Secondary Pharmacology

The Applicant's Position:

Revumenib (10 μM) had low off-target activity, showing no significant affinity with any target in a screening panel that included 30 different receptors/transporters (HitProfilingScreen) (Study AB73486), or in the KINOMEscan™ containing 97-kinases (Study VIT016-01).

The FDA's Assessment:

Revumenib (10 μM) was screened against a panel of 30 different receptors, ion channels and transporters and against a panel of 97 kinases in binding assays; no off-target binding was identified.

Safety Pharmacology

The Applicant's Position:

Safety pharmacology studies were conducted to test the effects of SNDX-5613 on the cardiovascular, respiratory, and central nervous systems. Revumenib had no effect on central nervous or respiratory function in rats following oral administration at doses up to 300 mg/kg (highest tested dose). The cardiovascular safety of revumenib and its metabolite M1 was evaluated by assessing the effects of revumenib on different sodium, calcium, and potassium cardiac ion channels with 4 non-GLP studies (161206.WJU, 160322.WJU, A2880, and 201028.TZZ) and 1 GLP study (1018-4298). Revumenib and M1 showed inhibitory potential of hERG current, with the metabolite being a more potent inhibitor (IC_{50} of 4.75 and 3.46 µM for revumenib and M1, respectively, which are approximately 13-fold and 6-fold higher than the steady-state unbound C_{max} [0.4 and 0.6 µM, assuming 9.9% and 63% unbound fraction of revumenib and M1, respectively, in human plasma] at the recommended dose of 270 mg q12h), suggesting a significant contribution of the metabolite M1 to QTc prolongation potential with revumenib treatment. Consistent with margins based on hERG inhibition of each compound, revumenib and M1 reached a Torsade de Pointes score of 2.5 at concentrations ≥ 3 µM in rabbit ventricular wedge preparation, which would translate to an 8-fold and 5-fold margin, respectively, over steady-state unbound C_{max} with the dose of 270 mg q12h. No meaningful effects on other cardiac ion channels were observed with revumenib (hNav1.5, hCav1.2, hCav3.2, hKir2.1, Kv4.3/KChIP2.2, or KvLQT1/minK).

In the cardiovascular safety pharmacology studies and in the 14- and 28-day repeat-dose toxicity studies in dogs (Section 5.5.1), there were increases in QTc interval duration at all doses evaluated, which increased in magnitude and duration with increasing doses, and premature atrial contraction with no adverse arrythmias in the safety pharmacology studies and 14-day toxicity study. QTc prolongation was reversible in the 28-day toxicity study since no findings were present at the recovery period and some reversibility was also observed in the 14-day toxicity study. No increase in QTc interval or any electrocardiology findings were observed in the 13-week dog toxicity study (Section 5.5.1).

The FDA's Assessment:

In the non-GLP human ether-à-go-go-related gene (hERG) assay, revumenib concentrations of 0, 1, 3, 10, 30, and 100 uM and M1 concentrations of 0.3, 1, 3, 10, and 30 uM were evaluated for hERG channel inhibition. The IC50 values for revumenib and the primary metabolite of revumenib (SNDX-60165 or M1) were 10.6 µM and 3.5 µM, respectively. In the GLP hERG assay, revumenib concentrations of 0, 1, 3, 10 and 100 uM were evaluated for hERG channel inhibition. Revumenib inhibited hERG with an IC50= 4.75 µM. The IC50 from the GLP hERG

assay was considered to be the most relevant because the 95% confidence limits encompassed the IC50 values from non-GLP assays (95% confidence limits= 0.84 and 26.99 μM).

In the 14-day repeat dose non-GLP dose range finding study in dogs, doses up to 225 mg/kg/day were administered by oral gavage for 14 days. Electrocardiograms (ECGs) were obtained pre-treatment and on study days 1 and 14 at approximately 2, 4, 8, and 24 hours post-dose. All animals in the 225 mg/kg/day group were dosed up to day 8 and prematurely euthanized on day 9 due to adverse decreased activity and dehydration. Increased QT interval duration was seen at doses ≥ 75 mg/kg (up to 30% relative to control) and premature atrial contractions (PACs) were seen only at 225 mg/kg. To determine the potential risk for Torsade de Pointe (TdP), the Applicant evaluated revumenib and M1 using the isolated rabbit ventricular wedge preparation. Revumenib (up to 30 μM) and M1 (up to 10 μM) were added to rabbit ventricular wedge preparations for ≥ 30 minutes, after which electrophysiological recordings were obtained. Results showed revumenib or M1 did not increase QRS duration. Revumenib and M1 induced concentration dependent QT prolongation (< 35% relative to concurrent controls) and TdP scores of 2.5 and 2 at 3 μM, respectively.

In the 28-day repeat dose GLP toxicology study in dogs, revumenib doses of 25, 50, or 100 mg/kg/day were administered by oral gavage daily for 28 days followed by a 4-week recovery period. ECGs were obtained pre-treatment, 2-4 hours post-dose on week 2 and week 4, and at the end of the recovery period on week 8. Increased QTc interval duration (up to 10%) was seen at all doses evaluated (**FDA Table 5**).

FDA Table 5. QTc (msec) from the 4-week repeat dose dog study (% change relative to pre-treatment values)

	control		25 mg/kg/day		50 mg/kg/day		100 mg/kg/day	
	m	f	m	f	m	f	m	f
Week 2	1.0	1.5	1.7	5.2	5.3	2.5	5.5	10.2
Week 4	0.1	-2.3	6.3	6.5	6.4	7.8	9.5	9.0
Week 8	0.3	-2.2	-	-	-2.5	-8.2	-3.8	-2.7

Source: FDA analysis

5.4. ADME/PK

The Applicant's Position:

Absorption
Single-dose pharmacokinetics in mice (SP-BIO-011 and SP-BIO-017), rats (VP-16-MEN-037 and 2740-006), dogs (2740-002, 2740-005, 2313N-2005PK and 2313N-2106), and minipigs (2740-001).

Revumenib was absorbed and bioavailable in all species tested. In rats and dogs, systemic exposure ($AUC_{0\text{-last}}$ and C_{max}) increased with the increase in dose level, supporting use of these species in toxicity studies of revumenib. Repeat-dose pharmacokinetics in in 7 days oral administration (PO) (Study 2017-0171), 14-day (Study 12540), 28-day GLP (Study 1018-3951), and 13-week GLP (Study 1021-2901) in rats and 14-day (Study 12539), 28-day GLP (Study 1018-2592), and 13-week GLP (Study 1021-2912) in dogs. Exposure was proportional to the dose in rats and dogs, except for high doses where exposures were generally less than proportional. There were no consistent differences between male and female rats or dogs in revumenib exposure, and no significant revumenib accumulation was seen.
Distribution Single PO dose of ^{14}C-labeled revumenib to fasted male Long Evans rats (Study 8459997). The results suggested Approximately equal partitioning to plasma and cellular components of the blood, extensive tissue distribution, low concentrations in brain tissues that suggest impairment crossing of the blood-brain barrier, melanin binding potential, and differential binding to tissues. Protein binding of revumenib was in plasma from CD-1 mice, Sprague Dawley rats, beagle dogs, and humans that was fortified with 1 or 10 μM revumenib (Study 2313D-1801, Study 2313N-2102, Study 2313N-2205, Study 2313N-2104 and Study 2313N-2202). Revumenib was moderately bound to plasma proteins across the species. The binding extent was similar at 1 and 10 μM in mouse plasma but a concentration dependence was observed for other species. The mean percent unbound values ranged from 18.5% to 60.8% across the species. Protein binding was greater in human (≈ 80%) and dog plasma than in rat and mouse plasma. Revumenib (at 1, 3, and 10 μM) binding to alpha-1-acid glycoprotein (AAG) solution was low to negligible at AAG concentrations ≤ 0.5 mg/mL, and the binding increased with increasing AAG concentrations up to 4 mg/mL; M1 (at 0.3, 1, and 3 μM) AAG binding was negligible until 1 mg/mL and slightly binding at 2 and 4 mg/mL AAG. For revumenib and M1, AAG protein binding was generally similar at all concentrations tested for revumenib and M1. Ex vivo protein binding in samples of human plasma collected from a clinical study showed the overall unbound mean of revumenib and M1 were 9.91% and 62.6%, respectively and these results were used to estimate the free fractions of revumenib and M1. The binding extent appeared to be independent of the plasma concentrations ranging from 18.6 to 5,970 ng/mL for revumenib and 0.104 to 867 ng/mL for M1. The blood/plasma partitioning of revumenib spiked at 500 and 5,000 ng/mL into human whole blood showed that distribution was reached quickly and indicated that revumenib partitioned to some extent into blood cells in vitro, but plasma concentrations were higher than blood cell concentrations with a blood-to-plasma concentration ratio of ~ 0.8.
Metabolism Revumenib and M1 stability in CD-1 mouse, Sprague Dawley rat, beagle dog, cynomolgus monkey, Gottingen minipig, human hepatocytes and microsomes, and human liver cytosol

(Study XT184014, Study 2313D-1802, Study 2313N-2007, Study 2313N-1805, Study 2313N-2011, Study 2313N-2109) Revumenib was stable in hepatocytes and less than 50% loss of parent was observed over 120 minutes. Studies with recombinant cytochrome P450 (CYP) isoforms suggested that CYP3A4 was the major CYP enzyme involved in the metabolism of revumenib. The contribution of CYP3A4 to metabolism was confirmed in a CYP reaction typing study using human liver microsomes (HLM) and human liver cytosol (HLC). Human liver cytosolic aldehyde oxidase (AO) and flavin-monooxygenase (FMO) enzymes did not appear to be involved in the metabolism of revumenib. A CYP reaction phenotyping study on M1 did not identify any CYP isoforms involved in its metabolism. Revumanib metabolites identification in mouse and rat hepatocyte (Study XT180047), HLM and human hepatocytes (Study 2313N-1805) and rat, dog, and human plasma samples (Study 2313N-2213). Revumenib and up to 9, 11, and 13 related metabolites were detected in mouse and rat hepatocytes, HLM and human hepatocytes and rat, dog, and human plasma. The N-deethylation metabolite (M1) was the most significant metabolite regardless of the species or dosing regimen Inhibition/Induction of drug-metabolizing enzymes Study 2313N-1803, Study 2313N-2006 and Study 2313N-1804. Revumenib did not show direct inhibitory effect on CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6, or CYP2E1 up to 100 μM (highest concentration studied), however, it showed inhibitory effect on CYP2C9 and CYP3A4/5 with IC_{50} values of 58.3 and 6.82 μM, respectively. No detectable time-dependent inhibition of CYP3A4 was observed. Revumenib did not induce CYP1A2, CYP2B6, or CYP3A4 in human hepatocytes via measurement of messenger RNA (mRNA) levels.
Excretion Revumenib and M1 urinary excretion in rats (Study 2313N-2015) and in dogs (Study 2313N-2016) and M1 urinary excretion in rats (Study SYN-DMPK-2021-R0580 and Study SYN-DMPK-2021-R0622). Revumenib urinary excretion after a single IV dose of 2 mg/kg was 12.9% over 24 hours in rats, and 16.4% in dogs. The urinary excretion of M1 after a single IV dose to rats of 2 mg/kg was 25.0% and 15.2% over 24 hours in 2 separate studies.
Drug interactions Revumenib transporter studies (Study 2313N-1808, Study 2313N-2110, and Study 2313N-2010). Transfected Madin-Darby canine kidney cell line (MDCKII) cells were used to assess revumenib as a substrate or inhibitor of multidrug resistance protein 1 (MDR1/P-gp) and breast cancer resistance protein (BCRP). Results showed that revumenib was not a substrate for human MDR1 or BCRP. A study using revumenib concentrations up to 300 μM showed no concentration-dependent inhibition of P-gp and BCRP substrate transport. Transfected vesicles and human embryonic kidney 293 (HEK293) cells were used to evaluate revumenib as a substrate and inhibitor of 8 solute carrier (SLC) membrane transporters. Uptake analysis

of revumenib indicated that it is not a substrate for OATP1B1, OATP1B3, MATE2-K, or BSEP, but is a potential in vitro substrate for OCT1, OCT2, OAT1, OAT3, and MATE1. Revumenib at 30 μM showed no inhibition on OCT2, OAT1, OAT3, OATP1B1, or OATP1B3, and < 50% inhibition on MATE2-K, BSEP, OCT1. The IC_{50} value for MATE1 towards metformin by revumenib was determined to be 0.53 μM, indicating revumenib is unlikely to inhibit the activity of the major transporters other than MATE1.
M1 transporter studies (Study XT228058 and Study 2313N-2201)
M1 was assessed for a substrate potential of human efflux transporters P-gp and BCRP using transfected MDCKII cells. M1 was not a substrate for P-gp or BCRP. M1 was also evaluated as a substrate and inhibitor of 7 SLC transporters (OCT2, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, and MATE2-K) in transfected HEK293 cells. M1 did not appear to be a substrate for the tested transporters except that it might be potentially a substrate for OATP1B1. Additionally, M1 showed no inhibition on OCT2, OAT1, OAT3, OATP1B1, or OATP1B3. The IC_{50} value for MATE1 towards metformin by revumenib was determined to be 0.836 μM, indicating M1 is unlikely to inhibit the activity of the major transporters other than MATE1.

Summary PK parameters from pharmacokinetic studies

Single dose PK following oral dose administration across different species i.e., Mice, Rats, Dogs, and Minipigs are summarized in Table 4 (Module 2.6.4).

Multiple dose PK following oral dose administration across different species i.e., Rats and Dogs are summarized in Tables 2.6.5.4.1, 2.6.5.4.2 and 2.6.5.4.5 (Module 2.6.5).

- **Integrative summary table of C_{max} and AUC parameters across toxicology studies (general, reproductive, and carcinogenicity, if conducted).**

PK Parameter Summary Following Administration of Revumenib 28 -Day Repeated Doses in Sprague Dawley Rats (1018-3951)						
Sex (M/F)/N	M/9	F/9	M/9	F/9	M/9	F/9
Dose (mg/kg)	75	75	150	150	300	300
PK parameters:	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**
C_{max} (ng/mL)	7,540	10,900	14,500	15,800	17,200	18,800
$AUC_{0\text{-}last}$ (ng*h/mL)	70,100	85,800	146,000	174,000	257,000	299,000
PK parameters:	**Day 28**	**Day 28**	**Day 28**	**Day 28**	**Day 28**	**Day 28**
C_{max} (ng/mL)	5,370	7,900	8,980	12,900	15,600	18,400
$AUC_{0\text{-}last}$ (ng*h/mL)	37,100	61,700	85,500	115,000	172,000	232,000
PK Parameter Summary Following Administration of Revumenib 13-Week Repeated Doses in Sprague Dawley Rats (1021-2901)						
Sex (M/F)/N	M/9	F/9	M/9	F/9	M/9	F/9
Dose (mg/kg)	75	75	150	150	300	300
PK parameters:	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**
C_{max} (ng/mL)	5,920	8,300	11,200	11,400	16,100	18,500
$AUC_{0\text{-}last}$ (ng*h/mL)	32,400	51,800	70,300	79,900	182,000	235,000
PK parameters:	**Day 91**	**Day 91**	**Day 91**	**Day 91**	**Day 91**	**Day 91**
C_{max} (ng/mL)	8,030	7,280	10,300	10,300	13,300	15,700
$AUC_{0\text{-}last}$ (ng*h/mL)	31,300	42,400	55,100	124,000	139,000	161,000
PK Parameter Summary Following Administration of Revumenib 28-Day Repeated Doses in Beagle Dogs (1018-2592)						
Sex (M/F)/N	M/3	F/3	M/6	F/6	M/6	F/6
Dose (mg/kg)	**25**	**25**	**50**	**50**	**100**	**100**
PK parameters:	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**
C_{max} (ng/mL)	11,000	11,800	21,400	19,500	35,800	36,800
$AUC_{0\text{-}last}$ (ng*h/mL)	67,400	82,200	155,000	140,000	261,000	309,000
PK parameters	**Day 28**	**Day 28**	**Day 28**	**Day 28**	**Day 23/24**	**Day 23/24**
C_{max} (ng/mL)	8,720	12,200	18,600	19,200	26,500	30,700

$AUC_{0\text{-last}}$ (ng*h/mL)	73,400	108,000	177,000	174,000	218,000	348,000
PK Parameter Summary Following Administration of Revumenib 13-Week Repeated Doses in Beagle Dogs (1021-2912)						
Sex (M/F)/N	M/6	F/6	M/6	F/6	M/6	F/6
PK parameters:	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**
C_{max} (ng/mL)	5,980	5,580	10,600	9,680	14,800	13,600
$AUC_{0\text{-last}}$ (ng*h/mL)	30,800	25,400	57,000	54,700	107,000	90,200
Dose (mg/kg)	**12.5**	**12.5**	**25**	**25**	**40**	**40**
PK parameters:	**Day 91**	**Day 91**	**Day 91**	**Day 91**	**Day 91**	**Day 91**
C_{max} (ng/mL)	5,810	5,840	8,730	7,870	14,000	13,100
$AUC_{0\text{-last}}$ (ng*h/mL)	41,800	34,500	68,300	60,900	122,000	100,000

Tabulation of any exposure margins (b) (4)

	AUC (ng*h/mL)	Exposure Margin
Clinical Study (Recommended Dose)	21,130a	NA
Rodent Antitumor Efficacy Studies	7,400 - 14,200b	≈ 0.4 - 0.7
13-week Rat Repeat-dose study (STD10)	36,850c	≈ 1.7
13-week Dog Repeat-dose study (HNSTD)	64,600d	≈ 3.1
Rat Embryo-fetal Development Study (LOAEL)	12,200e	≈ 0.6

AUC = area under the curve; AUC0-24h = area under the concentration versus time curve from time 0 to 24 hours; AUC0-last = area under the concentration versus time curve from time 0 to the last quantifiable concentration; GD = gestation day; HNSTD = highest non-severely toxic dose; LOAEL = lowest-observed-adverse-effect-level; NA = not applicable; STD10 = severely toxic dose in 10% of animals.
a Extrapolated steady-state exposure (AUC0-24h) calculated by doubling the AUC0-12h of revumenib at the human recommended dose of 270 mg Q12H (Study SNDX-5613-0700).
b AUC estimated from plasma levels of lowest dose of revumenib that provided complete tumor regression or prolonged survival benefit in rodent anti-tumor studies Study SP-BIO-007, Study MI3393, and Study MI3631.
c Sex combined Day 91 AUC0-last at 75 mg/kg/day (Study 1021-2901).
d Sex-combined Day 91 AUC0-last at 25 mg/kg/day (Study 1021-2912).
e GD17 AUC0-last at 30 mg/kg/day, the lowest dose at which embryo-fetal effects were observed (Study 01319004).

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment.

Absorption

PK parameters were determined following a single intravenous or oral revumenib dose in mice, rats, dogs and minipigs. Revumenib bioavailability ranged from 20% in mice to 70% in dogs. In single-dose PK studies, increases in exposure in rats and dogs were approximately dose-proportional from the low dose to the mid dose and less than dose-proportional from the mid dose to the high dose (**FDA Table 6**).

FDA Table 6. Summary of single dose PK parameters

Study	Species	Route of Administration	Dose (mg/kg)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng*hr/mL)	% bioavailability	$T_{½}$ (hr)
	CD-1 mouse	PO	25	1,708	2,803	20	1.9

Study	Species	Route of Administration	Dose (mg/kg)	C_{max} (ng/mL)	AUC $_{0\text{-last}}$ (ng*hr/mL)	% bioavailability	T ½ (hr)
SP-BIO-011 and SP-BIO-017		IV	5	8,340	2776		6.1
VP-16 MEN-037	Sprague Dawley rat	PO	5	45	110	27	1.8
		IV	1	308	84		2.1
2740-002	Beagle dog	PO	5	2,033	6,852	70	3.3
		IV	2	2,210	4,199		3.3
2740-001	Gottingen minipig	PO	5	151	1,089	44	8.4
		IV	2	1,227	1,021		4.1
2740-006	Sprague Dawley rat	PO	75	5,947	32,223	Not determined	2.1
			150	10,010	83,579		2.8
			300	11,523	139,994		2.9
2740-005	Beagle dog	PO	10	5,793	30,114	Not determined	4.1
			30	12,440	90,471		4.1
			100	26,467	183,074		5.1

Source: FDA analysis

Distribution

Tissue distribution following a single oral dose of 10 mg/kg 14C-labeled revumenib in rats was evaluated for up to 672 hours (Study 8459997). Tissues with the highest radioactivity concentrations were the lymphatic system (bone marrow, lymph nodes, thymus, and spleen), eye uveal tract, kidneys, gastrointestinal system (small and large intestine, stomach, cecum, and rectum wall), lungs, pancreas, pituitary gland, and liver (highest Cmax of 32,200 ng eq/g at 0.5 hours post-dose). The eye uveal tract had a Cmax of 19,500 ng eq/g at 168 hours post-dose at concentrations that were sustained through 672 hours post-dose. In males, the testes reached the highest concentration (Cmax =1640 ng eq/g) at 8 hours post-dose and had detectable levels of 75 ng eq/g at 672 hours post-dose. Revumenib concentrations were low in brain tissues (Cmax < 100 ng eq/g).

Protein binding

Revumenib bound to all species but showed greater binding to human plasma (~80% bound) (**FDA Table 7**).

FDA Table 7. Summary of percent unbound from Study 2313D-1801 (mean +/- standard deviation)

Nominal Concentration (µM)	Mouse plasma	Rat plasma	Dog plasma	Human plasma
1	59.7 +/- 7.6	45.0 +/- 7.9	21.8 +/- 1.1	18.5 +/- 1.7
10	58.9 +/- 5.6	60.8 +/- 4.8	40.9 +/- 6.3	32.3 +/- 3.2

Source: FDA analysis
Mean and standard deviation represent n=3.

Toxicokinetics

In the 7-day and 14-day repeat dose toxicology studies, exposure (Cmax and AUC) increased with increasing dose, but increases were generally less than dose-proportional. Exposure was generally similar across males and females. In the 4-week repeat dose rat toxicology study, exposure was slightly higher in females and lower on day 28 compared to day 1. In the 4-week repeat dose dog toxicology study, exposures increased in an approximately dose-proportional manner from 25 to 50 mg/kg/day and less than dose-proportional from 50 to 100 mg/kg/day. In the 13-week rat and dog studies, there were no consistent differences in exposure between males and females and the exposure increased in an approximately dose-proportional manner with increasing dose.

5.5. Toxicology

5.5.1. General Toxicology

The 13 toxicity studies included 7 repeat-dose oral toxicity study in rats (Study 2017-0171) and of up to 91 days of daily treatment in rats (Study 12540, nonGLP, Study 1018-3951, GLP and Study 1021-2901, GLP) and dogs (Study 12539, nonGLP, Study 1018-2592, GLP and Study 1021-2912, GLP). The toxicology program also included: non-GLP screening, a GLP in vitro bacterial reverse mutation assays, a GLP in vitro micronucleus assay in HPBL, a GLP in vivo rat micronucleus assay, a GLP embryo-fetal development study in rats, a non-GLP DRF juvenile toxicity study in rats, and a GLP in vitro phototoxicity study in BALB/c 3T3 mouse fibroblasts. Toxicokinetic investigations were performed in all toxicity studies except for the in vivo micronucleus assay. Daily dosing regimens were used in the GLP repeat-dose studies in rats and dogs. The pivotal 28-day and 13-week oral toxicity studies with recovery were performed in accordance with OECD Principles of GLP (ENV/MC/CHEM(98)17) as accepted by Regulatory Authorities throughout the European Community, United States of America (FDA) and Japan (Ministry of Health, Labor, and Welfare) and in accordance with ICH guidelines, including ICH M3(R2) and ICH S9. The use of the rat and dog as the rodent and non-rodent species for the pivotal repeat-dose toxicity studies of revumenib is supported by the in vitro metabolism and nonclinical PK data observed.

GLP Pivotal Studies

Study title / study number / eCTD location: A 28-day oral gavage toxicity study in Sprague Dawley Rats followed by a 4-Week recovery period / Study 1018-3951 / Section 3.1.3 of Module 2.6.6 and Section 7.1.1 of Module 2.6.7 Key Drug-related Adverse Findings: There were no deaths or severe dose limiting toxicity, therefore the severely toxic dose in 10% of animals (STD10) is considered to be > 300 mg/kg/day. Conducting Laboratory and Location: (b) (4)

GLP compliance: Yes		
Methods		
Dose and frequency of dosing:		0 (control), 75, 150, or 300 mg/kg/day
Route of administration:		Oral gavage
Formulation/Vehicle:		0.5% (w/v) methylcellulose in reverse osmosis water
Species/Strain:		Sprague Dawley
Number/Sex/Group:		10 males and 10 females per dose group
Age:		7 to 8 weeks
Satellite groups:		Not applicable
Parameters	Major findings	
Mortality	No premature deaths.	
Clinical Signs	Generally transient; consisted of salivation with associated wet fur, and occasional behaviors associated with revumenib palatability. No clinical signs during recovery.	
Body Weights	Reversible decreases in body weight and food consumption gains in males at ≥ 75 mg/kg/day, generally limited to the first 2 weeks. In first 3 weeks of recovery, mean body weight gain in males at all dosage levels was generally higher than controls and was overall comparable across groups during the last week preceding termination. No significant effects on body weights and body weight changes in females at any dose.	
Ophthalmoscopy	In Week 4, ophthalmology examinations included dose-dependent non-reversible anterior cortical radial linear multifocal lens opacities unilaterally or bilaterally in 7/30 animals (3 males, 4 females) administered 150 mg/kg/day and 18/30 animals (9 males, 9 females) administered 300 mg/kg/day. No ophthalmologic findings at 75 mg/kg/day.	
Hematology	Dose-related decreases in hematocrit, hemoglobin (up to -15% in both), decreases in RBC (up to -17% in the 150 mg/kg/day group) in males. Decreases in hematocrit (up to -19% in the 150 mg/kg/day group), in hemoglobin (up to -18% in the 150 and the 300 mg/kg/day groups) and RBC (up to -19% in the 150 and the 300 mg/kg/day groups) in females.	
Clinical Chemistry	Males: albumin -5% for 150 mg/kg/day and 300 mg/kg/day, total protein -7% for 150 mg/kg/day, triglycerides -58% for 150 mg/kg/day, ALT +57% for 300 mg/kg/day, AST +102% for 300 mg/kg/day, urea +34% for 300 mg/kg/day. Females: A/G +93% for 75 mg/kg/day, cholesterol +41% for 150 mg/kg/day, urea +66% for 300 mg/kg/day, dose-related increase in ALT up to +267% for 300 mg/kg/day, AST +110% for 300 mg/kg/day, albumin -17% for 300 mg/kg/day, A/G -27% for 300 mg/kg/day, total protein -9% for 300 mg/kg/day, and triglycerides up to -43% for 75 g/kg/day.	

Organ Weights	End of treatment period (Day 29) organ weight changes were found in liver, pituitary, thyroid/parathyroid gland, thymus, and adrenal glands. The increases in pituitary, thyroid/parathyroid, and adrenal gland weights were often associated with gross enlargement of the organ noted macroscopically but with no microscopic changes. End-of-recovery (Day 57) organ weight changes persisted in the liver, thymus, pituitary gland, thyroid/parathyroid glands, and adrenal gland, with partial recovery of liver, thymus, thyroid/parathyroid. Increases in the mean prostate gland and seminal vesicle weights were observed in males at all dose levels, without a clear dose-related trend. No correlation with any macroscopic or microscopic changes.
Histopathology	Microscopic findings observed in liver, mammary gland, ovary, spleen, testes, uterus, and vagina. Microscopic findings in liver (hepatocellular hypertrophy) were associated with increased liver weights, fibrinogen decreases and elevations in liver enzyme activities. The majority of the findings showed some level of reversibility (partial or full recovery), but the microscopic findings in testes (Leyding cell hyperplasia) did not reverse, with a similar incidence and severity at the main phase and recovery period
TK analysis	Revumenib exposure increased in a slightly less than dose-proportional manner over the dose range tested, and exposure was slightly higher for females than for males. Exposure was slightly lower on Day 28 than on Day 1. The $AUC_{0\text{-last}}$ decreased from Day 1 to Day 28. Peak revumenib concentrations were generally observed at 1 to 8 hours postdose on Day 1, and 1 to 4 hours postdose on Day 28.

Study title / study number / eCTD location**:** A 13-Week Oral Gavage Toxicity Study in the Sprague Dawley Rat Followed by a 13-Week Recovery / Study 1021-2901 / Section 3.1.4 of Module 2.6.6 and Section 7.1.2 of Module 2.6.7 Key Drug-related Adverse Findings: Once daily administration of revumenib by oral gavage was generally tolerated and did not result in any adverse clinical signs or deaths. Clinical signs included a dose-dependent increase in salivation with associated lower jaw wet fur. Based on the overall results and the irreversible adverse microscopic findings in the kidneys, ovaries, uterus/cervix, and vagina in ≥ 10% of animals in the study, the STD10 was considered to be > 75 mg/kg/day. Conducting Laboratory and Location: (b) (4) GLP compliance: Yes	
Methods	
Dose and frequency of dosing:	0 (control), 75, 150, or 300 mg/kg/day
Route of administration:	Oral gavage

Formulation/Vehicle:	0.5% (w/v) methylcellulose in reverse osmosis water
Species/Strain:	Sprague Dawley
Number/Sex/Group:	10 males and 10 females per dose group
Age:	6 to 7 weeks
Satellite groups:	Not applicable

Parameters	Major findings
Mortality	No premature deaths
Clinical Signs	Dose-dependent increase in salivation with associated lower jaw wet fur
Body Weights	Increases in body weight gains and body weights were seen at ≥ 75 mg/kg/day, with greater differences in females, with increases in food consumption in males and females.
Ophthalmoscopy	Increase in frequency of lens opacities in treated animals at Weeks 6 and 13, and on the last dosing day (Day 92). Incidence of the findings increased at the end of the recovery period. Mostly focal opacities with minimal effect on vision at the stage observed.
Hematology	Dose-related decrease in RBC (up to -22% in the 300 mg/kg/day group), hemoglobin (up to -20% in the 300 mg/kg/day group) and hematocrit (up to -19% in the 300 mg/kg/day group), decreases in WBC (up to -32% in the 75 mg/kg/day) and lymphocytes (-37% in the 75 mg/kg/day) and dose-related increase in platelets (+47% in the 300 mg/kg/day) in males. Decrease in RBC (-25% in the 150 mg/kg/day), hemoglobin (-21% in the 300 mg/kg/day) and hematocrit (-21% in the 300 mg/kg/day) and increases in platelets (+34% in the 75 mg/kg/day) in females.
Clinical Chemistry	Males: AST +77% for 300 mg/kg/day, ALT +118% for 300 mg/kg/day, ALP +31% for 300 mg/kg/day, creatine kinase +143% for 300 mg/kg/day, urea +61% for 300 mg/kg/day, A/G +14% for 75 mg/kg/day, increased calcium, potassium up to 14% for 300 mg/kg/day, dose-related increases in phosphorus up to +36% for 300 mg/kg/day, decreases in glucose -22% for 300 mg/kg/day, triglycerides up to -63% for 300 mg/kg/day, total protein up to -10% for 300 mg/kg/day group, and albumin up to -10% for 300 mg/kg/day group. Females: AST +133% for 300 mg/kg/day, ALT +480% for 300 mg/kg/day, ALP +111% for 300 mg/kg/day, GGT +420% for 300 mg/kg/day, creatine kinase +92% for 300 mg/kg/day, urea +56% for 300 mg/kg/day group, dose-related increases in potassium up to +14% for 300 mg/kg/day and in phosphorus up to +43% for 300 mg/kg/day and decreases in glucose -15% for 300 mg/kg/day, total protein up to -15% for 300 mg/kg/day, albumin -26% for 300 mg/kg/day, A/G -36% for 300 mg/kg/day
Urinalysis	Dose-related increase in urine volume (up to 226% in males and 440% in females)

Gross Pathology	Enlarged liver in males and females at 300 mg/kg/day, and in 1 female at 75 mg/kg/day, that correlated microscopically with minimal to mild hepatocellular hypertrophy, considered related to revumenib. Following recovery (Day 183), liver findings partially recovered. Thyroid/parathyroid gland and the pituitary gland were also enlarged in males at ≥ 150 mg/kg/day and in females at all doses with a dose-related increased incidence. These macroscopic findings often correlated with microscopic findings of minimal to mild hypertrophy of the thyroid epithelium microscopically and of the pars intermedia/distalis. Majority of the animals in the 300 mg/kg/day dose had pale foci in the pancreas correlated with minimal hyperplasia of the Islets of Langerhans.
Organ Weights	At the end of dosing (Day 92), there was dose-related increase in several organ weights including the liver, thyroid/parathyroid glands, pituitary glands, adrenal glands, heart, kidney, thymus, and spleen in males and females (at all doses). Uterus weight increased at 300 mg/kg/day. Spleen weights were increased in males and females. Following recovery (Day 183), there was increased weight of thyroid/parathyroid gland, pituitary gland, adrenal gland, kidney, heart, thymus, liver, and spleen in males and females at all dose levels. Liver, kidney, heart, and thymus weights had partially recovered. Thyroid/parathyroid, pituitary, and adrenal gland weights had not recovered.
Histopathology	Dose-related decreased corpora lutea, follicular cysts and hypertrophy of the corpora lutea in the ovaries, increased mucification and/or single cell necrosis in the vagina, and mammary hyperplasia in females at all doses, endometrial hyperplasia in females at doses ≥ 150 mg/kg/day, and closure of the growth plate in the femur in males and females at all doses. Effects were considered revumenib-related and adverse as they suggest that there could be a negative impact on the fertility. Mammary gland hyperplasia was not considered adverse and considered secondary to ovarian changes. Other revumenib-related microscopic observations with a dose-related increase in incidence and/or severity were hyperplasia of the interstitial cells and degeneration/atrophy of the seminiferous tubules in the testes in males (non-adverse), hyperplasia of the Islets of Langerhans in the pancreas in males and females at all doses (non-adverse), decreased corpora lutea, follicular cysts and hypertrophy of the corpora lutea in the ovaries, increased mucification and/or single cell necrosis in the vagina, and mammary hyperplasia in females at all doses, endometrial hyperplasia in females at doses ≥ 150 mg/kg/day, and closure of the growth plate in the femur in males and females at all doses. Decreased cellularity of the hematopoietic compartment of the bone marrow and/or spleen was noted with a dose-related incidence and/or

	severity. These changes were considered revumenib-related and adverse due to the correlated hematology effects. Hyperplasia of the urothelium of the renal pelvis was noted with a higher incidence in females at doses ≥ 150 mg/kg/day. Mild to marked degeneration/necrosis of renal tubules and minimal to mild interstitial fibrosis at doses ≥ 75 mg/kg/day, and mild to moderate interstitial inflammation at doses ≥ 150 mg/kg/day were observed. These changes were considered revumenib-related and adverse.
TK analysis	On dosing Day 1, revumenib plasma concentrations were quantifiable by the first blood sample collection (0.5 hours) at all dose levels in male and female. Peak plasma concentrations in male and female were achieved between 2 to 4 hours postdose. Plasma concentrations were quantifiable through 8 or 24 hours. No consistent differences in systemic exposure between males and females on Days 1 and 91, with male/female ratios of C_{max} and $AUC_{0\text{-}last}$ ranging from 0.44 to 1.1. No significant accumulation of revumenib in males and females on Day 91. Accumulation ratios (sex combined) ranged from 0.72 to 1.4 over the dose range. The systemic exposure on Days 1 and 91 increased in an approximately dose proportional manner with increasing dose.

Study title / study number / eCTD location**:** A 28-Day Oral Gavage Toxicity Study in Beagle Dogs Followed by a 4-Week Recovery Period / Study 1018-2592 / Section 3.2.2 of Module 2.6.6 and Section 7.2.1 of Module 2.6.7 Key Drug-related Adverse Findings: Early termination of the high dose group in Week 4 due to dose dependent poor body condition associated with decreased bodyweight and decreased food consumption. There were no mortalities related to the administration of revumenib in all the treated groups at the terminal phase and recovery period of the study. There was evidence of recovery in both body weight and food consumption. The oral administration of 100 mg/kg/day revumenib was considered a severely toxic dose in the dog in this 28-day study. The highest non-severely toxic dose (HNSTD) was 50 mg/kg/day. Conducting Laboratory and Location: (b) (4) GLP compliance: Yes	
Methods	
Dose and frequency of dosing:	0 (control), 25, 50, 100 mg/kg/day (100 mg/kg/day group terminated early at 24/25 day)
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose in reverse osmosis water
Species/Strain:	Dog, Beagle
Number/Sex/Group:	6 males and 6 females per dose group, except by the 25 mg/kg/day that only included 3 males and 3 females
Age:	11 to 14 months

Satellite groups:	Not applicable
Parameters	Major findings
Mortality	There was no revumenib-related mortality at any dosage level
Clinical Signs	Emesis, retching, salivation, in males and females at all dosage levels as early as Week 1. Slight to severe weakness in males and females as early as Day 7, resulting in early sacrifice of 1 female on Day 22, and 1 male on Days 24 and 26, slight to severe thinness in males and females at all dose levels beginning as early as Day 7, slight to severe decreased activity in males and females beginning as early as Day 7, slight to moderate tremors in males and females, toe walking in 1 male on Days 24 and 26, warm to touch in 2 females on Day 22 or 23, eyes partly closed in 1 female on Day 23, slight to severe slow skin turgor in males and females at 50 and 100 mg/kg/day as early as Day 1. There was recovery for all clinical signs.
Body Weights	Decreases in body weights were noted at all dose levels. Variations from control relatively stable in males and females at ≤ 50 mg/kg/day. Differences were more marked at 100 mg/kg/day. Decreases in body weight were associated with decreases in food consumption at all dosage levels. with marked decrease of body weight and food consumption in the 100 mg/kg/day group. There was recovery for revumenib-related decreases in body weight at all dosage levels and food consumption at 100 mg/kg/day during the 28-day recovery period.
Ophthalmoscopy	There were no revumenib-related ophthalmic findings in Week 4.
ECG	In Weeks 2 and 4, mild increases in the QTc interval were found at all dosage levels. The effect on QTc was not observed in all dogs but appeared to increase with dose level. In Week 4, the greatest increase from pretreatment values were noted at the highest dose level of revumenib, where group means increased 9.6% in males and 8.9% in the females. The magnitude of the QTc prolongation was similar in Weeks 2 and 4. No dysrhythmias were observed in association with this effect on the QTc. The QTc increases were reversible; there were no ECG changes at the end of the recovery period.
Hematology	Increases in neutrophils (+95% for 100 mg/kg/day), and decreases in lymphocytes (-23% for 100 mg/kg/day) and eosinophils (-80% for 100 mg/kg/day) in males. Increases in WBC (+53% for 100 mg/kg/day) and neutrophils (+81% for 100 mg/kg/day), and decreases in eosinophils (-75% for 100 mg/kg/day) in females. At the end of recovery, the changes in WBC parameters showed evidence of reversal or had resolved. There was complete recovery for the increases in red cell mass and decreases in reticulocytes. Changes in coagulation parameters were limited to fibrinogen increases in males and females for 100 mg/kg/day on Day 24/25 (up to 5.10g/L in males and up to 3.87g/L in females).

Clinical Chemistry	Albumin decreased up to -15% for 100 mg/kg/day and calcium -8% for 100 mg/kg/day in males. Increase in ALP (+316% for 100 mg/kg/day) in females.
Urinalysis	There were no revumenib-related urinalysis findings.
Gross Pathology	Increased incidence of small thymus at 100 mg/kg/day (4/5 animals) and 50 mg/kg/day (4/6 animals) compared to controls (1/6 animals). Small thymus correlated with lymphoid atrophy, microscopically. Pale discoloration in all liver lobes in 1 female at 100 mg/kg/day with moderate hepatocellular vacuolation, microscopically. At recovery necropsy, macroscopic findings were limited to the epididymis of 1 male at 100 mg/kg/day with regions of the left epididymis considered small, with marked oligospermia, microscopically.
Organ Weights	At end of treatment, organ weight changes were noted in thymus, adrenal gland, and spleen of males at 25 and ≥ 50 mg/kg/day and females at ≥ 50 mg/kg/day. Animals treated with 100 mg/kg/day were necropsied early (Day 24/25), and percent changes in mean organ weights were not calculated. No correlative histopathology findings in adrenal gland and spleen. Increases in adrenal weight were considered possibly related to stress. At the recovery necropsy (Day 57), decreased weight of testes, thymus and epididymides were found.
Histopathology	Microscopic observations at Main necropsy observed in the testis (germ cell depletion/degeneration at all dose levels), epididymis (single cell necrosis at all dose levels, oligospermia at 100 mg/kg/day, and increased cellular debris at 25 and 100 mg/kg/day), bone marrow (decreased hematopoietic or erythroid cellularity at 100 mg/kg/day) and thymus (lymphoid atrophy in males at all dose levels and females at ≥ 50 mg/kg/day). One female at 100 mg/kg/day euthanized on Day 24 had findings in liver (hepatocellular vacuolation), stomach (vacuolation of parietal cells), spleen and mandibular lymph node (vacuolation of histiocytes), ileum, cecum, and rectum (lymphoid atrophy). These changes were similar to those in the preterminal female euthanized on Day 22.
Other evaluations	Not applicable
TK analysis	Exposure increased in a dose-proportional manner, but the increase was less than proportional following repeated dosing. No apparent sex difference in exposure. The $AUC_{0\text{-last}}$ was similar between Days 1 and the end of the study. Peak concentrations were observed at 0.25 to 1 hour post-dose on Day 1, and 0.25 to 2 hours post-dose on Day 23/24/28. Mean terminal elimination half-life values was 3.84 to 6.56 hours for females and between 3.58 to 6.57 hours for males after single or repeated doses, consistent with the lack of accumulation observed. No obvious difference

	in plasma TK in dogs after oral dosing at dosage levels of 25, 50, and 100 mg/kg/day based upon either sex or dosing occasion.

Study title / study number / eCTD location: A 13-Week Study of SNDX-5613 by Oral Gavage in the Beagle Dog with a 13-Week Recovery Period / Study 1021-2912 / Section 3.2.3 of Module 2.6.6 and Section 7.2.2 of Module 2.6.7 Key Drug-related Adverse Findings: The administration of revumenib by oral gavage for 13 weeks to beagle dogs at dose levels of 12.5, 25, and 40 mg/kg/day was clinically well tolerated. There were no revumenib-related effects on ophthalmology, electrocardiology or urinalysis parameters, and there were no revumenib-related macroscopic findings. No revumenib-related macroscopic findings. There were no mortalities related to the administration of revumenib in all the treated groups at the terminal phase and recovery period of the study. Based on the overall results and the adverse effects noted as dose-related revumenib effects in the spinal cord and sciatic nerve of all animals, it is considered that the HNSTD for revumenib in beagle dogs is > 25 mg/kg/day. Conducting Laboratory and Location: (b) (4) GLP compliance: Yes		
Methods		
Dose and frequency of dosing:		0 (control), 12.5, 25, and 40 mg/kg/day
Route of administration:		Oral gavage
Formulation/Vehicle:		0.5% (w/v) methylcellulose in reverse osmosis water
Species/Strain:		Dog, Beagle
Number/Sex/Group:		6 males and 6 females per dose group
Age:		16 to 18 months
Satellite groups:		Not applicable
Parameters	Major findings	
Mortality	No premature deaths	
Clinical Signs	The administration of revumenib at ≥ 12.5 mg/kg/day was clinically tolerated but was associated with non-adverse sporadic thinness.	
Body Weights	Transient lower body weight gains or losses in males and females at ≥ 12.5 mg/kg/day with a greater severity in females resulting in decreased body weights that were not dose-related but more severe in females at 40 mg/kg/day. The effects on body weights correlated with transient decreases in food consumption which were similarly more severe in females.	
Ophthalmoscopy	No adverse effects	
ECG	No electrocardiology adverse effects.	
Hematology	Non statistically significant increases in WBC in males and females given ≥ 12.5 mg/kg/day at Weeks 6 and 13. Non statistically significant increases	

	in basophil and large unstained cells counts in both males and females 12.5 to 40 mg/kg/day during the 13-week recovery period. When compared to controls, dose-related increases in fibrinogen concentration were noted at Week 6 at ≥ 25 and 12.5 mg/kg/day in males and females, respectively, with associated dose-related decrease in APTT. These effects persisted during Week 13 with a greater severity (APTT of up to +16.55 sec in males and +17.50 sec in females). At Week 26, there were no notable effects in APTT, prothrombin, and fibrinogen concentrations.
Clinical Chemistry	Decreases in triglyceride and cholesterol concentrations in males at ≥ 25 mg/kg/day and females at ≥ 12.5 mg/kg/day, with statistical significance at ≥ 12.5 mg/kg/day (cholesterol) and at ≥ 25 mg/kg/day (triglycerides) at Week 6 (Day 36). Minor decreases in total protein with associated minor decreases in globulin in females at ≥ 12.5 mg/kg/day, with statistical significance at 12.5 and 40 mg/kg/day and resulting in a dose dependent increase in albumin to globulin ratio in females at ≥ 12.5 mg/kg/day at Week 6 (Day 36). Minor decreases in cholesterol in males and females at ≥ 12.5 mg/kg/day and triglycerides in males at ≥ 12.5 mg/kg/day, in males only, there were decreases in total protein at ≥ 12.5 mg/kg/day with associated decreases in albumin and globulin at Week 13 (Day 85). An increase in cholesterol was noted in females given ≥ 12.5 mg/kg/day at Week 26 (Day 179).
Urinalysis	No adverse effects
Gross Pathology	No revumenib-related macroscopic findings
Organ Weights	Increases in adrenal gland weights and decreases in spleen, testes, epididymides, prostate gland and thymus weights in males, and in the spleen, and ovaries of females at all dose levels. No changes in organ weights observed at the end of the Recovery period.
Histopathology	Microscopic findings were observed in the testes, and epididymides of male animals at all dose levels. Findings in testes consisted of seminiferous tubular degeneration and atrophy characterized by depletion of germ cells and decreased sperm. Atrophy of epididymides was noted with severely decreased sperm numbers. Changes were also noted in the mammary gland, ovaries, uterus/cervix, and vagina of females at all dose levels.
Other evaluations	Dose-related incidence of spinal cord and sciatic nerve lesions were observed. Nerve fiber degeneration with microglial cells in the cuneate fasciculus (dorsal funiculus) of the anterior cervical spinal cord and the dorsal funiculus in all the spinal cord segments (cervical, thoracic, and lumbar) was noted in multiple male and female animals that received ≥ 12.5 mg/kg/day. Nerve fiber degeneration was observed in the sciatic nerves of multiple animals treated with ≥ 12.5 mg/kg/day with increased severity noted at 40 mg/kg/day.

TK analysis	Plasma concentrations were quantifiable after oral dosing at the first sample collection time (0.25 hours) at all dose levels in both male and female dogs. Peak plasma concentrations were achieved at median T_{max} of 0.5-1 hours postdose, and plasma concentrations were generally quantifiable through 24 hours. No consistent differences in systemic exposure between males and females on Days 1 and 91 with no significant accumulation on Day 91. The systemic exposure on Days 1 and 91 increased in an approximately dose-proportional manner with increasing dose.

The nonclinical safety of revumenib was well characterized. Toxicity target organs common to rats and dogs were the liver, bone marrow, lymphoid tissues, and reproductive system, with the majority of the findings partially or fully recovered following the 4- or 13-week recovery period, except for some effects in the male and female reproductive system. In rats, the eyes and femur growth plate were also a target based on the lens opacities noted that did not reverse but had a minimal impact on vision, and the increased closure of the femoral growth plate in female rats. In dogs, additional target organs include the heart and the sciatic nerve and spinal cord. Increases of QTc interval duration were observed in dog studies (consistent with inhibition of the hERG channel noted in in vitro studies), and the effect appears to be reversible and to increase with dose. A dose-related incidence of spinal cord and sciatic nerve lesions along with minimal to moderate increase in microglial cells were noted in dogs at all doses and did not reverse. Revumenib caused embryo-fetal effects in rats with litter resorption, higher proportions of post-implantation loss, and lower mean numbers of live fetuses. In a juvenile rat DRF study, revumenib-related toxicities were seen in both males and females at 150 mg/kg/day. Revumenib showed no genotoxic or phototoxic potential. The results of the non-clinical studies are consistent with the proposed mechanism of action of revumenib and support a marketing application for revumenib in the treatment of relapsed or refractory acute leukemia harboring a *KMT2A* rearrangement in adult and pediatric patients.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment. Additional findings not described in the Applicant's assessment are described below.

In the 4-week rat toxicology study, animals were dosed daily at doses of 0, 75, 150, or 300 mg/kg/day for 4 weeks followed by a 4-week recovery period. Irreversible lens opacities were seen at doses of ≥150 mg/kg/day. At the end of the dosing period (week 4), unilateral or bilateral lens opacities were observed in 7/30 animals (23%) at 150 mg/kg/day and 18/30 animals (60%) at 300 mg/kg/day. At the end of the recovery period (week 8), lens opacities were observed in 4/10 (40%) at 150 mg/kg/day and in 6/10 (60%) at 300 mg/kg/day (**FDA Table 8**). Some of the lens opacities had progressed or were novel on week 8.

FDA Table 8. Summary of ophthalmology findings in the 4-week repeat dose rat study (number of animals with finding)

Dose	0 (Control)		75 mg/kg/day		150 mg/kg/day		300 mg/kg/day	
Number of Animals/ Sex (Week 4)	10 M	10 F	10 M	10 F	10 M	10 F	10 M	10 F
Right Eye LCAM	0	0	0	0	0	1	4	1
Left Eye LCAM	0	0	0	0	2	2	0	5
Both Eyes LCAM	0	0	0	0	1	1	5	3
Right Eye LCAF	0	0	0	0	0	0	0	0
Left Eye LCAF	0	0	0	0	0	0	0	0
Both Eyes LCAF	0	0	0	0	0	0	0	0
Dose	**0 (Control)**		**75 mg/kg**		**150 mg/kg**		**300 mg/kg**	
Number of Animals/ Sex (Week 8)	**5 M**	**5 F**	**5 M**	**5 F**	**5 M**	**5 F**	**5 M**	**5 F**
Right Eye LCAM	0	0	0	0	1	0	0	0
Left Eye LCAM	0	0	0	0	0	1	1	1
Both Eyes LCAM	0	0	0	0	1	0	3	0
Right Eye LCAF	0	0	0	0	0	0	0	1
Left Eye LCAF	0	0	0	0	0	1	0	0
Both Eyes LCAF	0	0	0	0	0	0	0	0

LCAM: lens opacity, cortex, anterior, multifocal
LCAF: lens opacity, cortex, anterior, focal
Source: FDA analysis

Decreased red cell mass parameters and fibrinogen, increased erythrocyte distribution width, and increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were seen on day 29 (**FDA Table 9**). Increased organ weights (liver, adrenal gland, pituitary gland, and thyroid/parathyroid glands) and decreased organ weights (thymus) were seen on day 29. Organ weight changes in the pituitary gland, thyroid/parathyroid gland, and adrenal gland were irreversible (**FDA Table 10**).

FDA Table 9. Summary of laboratory findings in the 4-week repeat dose rat study (% change relative to control)

Test	Study Day	Units	Males			Females		
Dose (mg/kg/day)			**75**	**150**	**300**	**75**	**150**	**300**
Erythrocytes Distribution Width	29	%	7%	18%	17%	6%	13%	12%
	57		-3%	-6%	-16%	-7%	-7%	-3%
Erythrocytes	29	10^12/L	-12%	-17%	-16%	-13%	-19%	-19%
	57		-4%	-4%	-3%	-1%	-1%	-6%
Reticulocytes	29	10^9/L	-1%	14%	1%	-4%	3%	8%
	57		-17%	-24%	-36%	9%	-14%	-22%
Hematocrit	29	L/L	-9%	-13%	-15%	-13%	-19%	-18%
	57		2%	-1%	1%	4%	4%	2%
Fibrinogen	29	g/L	-9%	-15%	-16%	-25%	-21%	-13%

Test	Study Day	Units	Males			Females		
	57		10%	14%	15%	-6%	-14%	-4%
Hemoglobin	29		-9%	-13%	-15%	-13%	-18%	-18%
	57		2%	-2%	2%	2%	0%	0%
Alanine Aminotransferase	29	U/L	15%	59%	58%	60%	230%	267%
	57		-21%	-1%	12%	-20%	47%	28%
Aspartate Aminotransferase	29		9%	50%	102%	42%	94%	120%
	57		-12%	-15%	10%	-24%	16%	2%

Source: FDA analysis

FDA Table 10. Summary of organ weights in the 4-week repeat dose rat study (% change relative to control)

Organ/Tissue	Study Day	Males			Females		
Dose (mg/kg/day)		**75**	**150**	**300**	**75**	**150**	**300**
GLAND, ADRENAL	29	-1%	2%	-4%	9%	14%	19%
	57	21%	23%	20%	23%	38%	37%
GLAND, PITUITARY	29	17%	28%	41%	62%	71%	79%
	57	9%	28%	34%	54%	96%	76%
GLAND, THYROID/GLAND, PARATHYROID	29	15%	17%	44%	23%	46%	53%
	57	10%	38%	35%	5%	43%	37%
LIVER	29	0%	9%	41%	31%	48%	81%
	57	-8%	14%	-4%	9%	20%	24%
THYMUS	29	-11%	-6%	-15%	-1%	-13%	-31%
	57	28%	11%	49%	54%	71%	61%

Source: FDA analysis

Irreversible interstitial cell hyperplasia in the testes and partially reversible decreased number of corpora lutea in the ovaries were seen at doses of ≥75 mg/kg. Partially reversible hyperplasia was seen in the female mammary gland at doses ≥150 mg/kg and in the uterus at 300 mg/kg (**FDA Table 11**, **FDA Table 12**).

FDA Table 11. Summary of histopathology findings on day 28 in the 4-week repeat dose rat study

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
Dose (mg/kg/day)				**0**	**75**	**150**	**300**	**0**	**75**	**150**	**300**
LIVER			**# Animals Examined**	10	10	10	10	10	10	10	10
	Hypertrophy	hepatocellular	1 OF 5				6		4	9	1
			2 OF 5				1				9
			Total				7		4	9	10
SPLEEN			**# Animals Examined**	10	10	10	10	10	10	10	10
	Cellularity, Decreased	hematopoietic	1 OF 5	1	3	5	5	1		2	9
			2 OF 5				5				1
			Total	1	3	5	10	1		2	10
OVARY			**# Animals Examined**	0	0	0	0	10	10	10	10
	Corpora Lutea, Decreased Number	bilateral	1 OF 5						2	2	5
			Total						2	2	5
	Cyst	bilateral; follicular	1 OF 5						3	2	5
			Total						3	2	5
GLAND, MAMMARY			**# Animals Examined**	5	7	4	7	10	10	10	9
	Hyperplasia	mammary gland	1 OF 5							2	2
			2 OF 5								3
			Total							2	5
UTERUS			**# Animals Examined**	0	0	0	0	10	10	10	10
	Hyperplasia	endometrium	1 OF 5								2
			Total								2
VAGINA			**# Animals Examined**	0	0	0	0	10	10	10	10
	Keratin, Increased		1 OF 5								2
			Total								2
TESTIS			**# Animals Examined**	10	10	10	10	0	0	0	0
	Hyperplasia	bilateral; interstitial cell	1 OF 5		10	10	10				
			Total		10	10	10				

1= Minimal, 2= Mild, 3= Moderate, 4= Marked, 5= Severe
Source: FDA analysis

FDA Table 12. Summary of histopathology findings on day 57 in the 4-week repeat dose rat study

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
Dose (mg/kg/day)				**0**	**75**	**150**	**300**	**0**	**75**	**150**	**300**
LIVER			**# Animals Examined**	5	5	5	5	5	5	5	5
	Hypertrophy	hepatocellular	1 OF 5								2
			Total								2
OVARY			**# Animals Examined**	0	0	0	0	5	5	5	5
	Corpora Lutea, Decreased Number	bilateral	2 OF 5							2	1
			Total							2	1
	Cyst	bilateral; follicular	2 OF 5							2	1
			Total							2	1
GLAND, MAMMARY			**# Animals Examined**	4	2	5	3	5	5	5	5
	Hyperplasia	mammary gland	1 OF 5							1	
			2 OF 5							1	1
			Total							2	1
UTERUS			**# Animals Examined**	0	0	0	0	5	5	5	5
	Hyperplasia	endometrium	1 OF 5							1	
			Total							1	
TESTIS			**# Animals Examined**	5	5	5	5	0	0	0	0
	Hyperplasia	bilateral; interstitial cell	1 OF 5		5	5	5				
			Total		5	5	5				

1= Minimal, 2= Mild, 3= Moderate, 4= Marked, 5= Severe
Source: FDA analysis

In the 13-week rat toxicology study, animals were dosed daily at doses of 0, 75, 150, or 300 mg/kg/day for 13 weeks followed by a 13-week recovery period. The last day of dosing was on day 92 and the end of the recovery period was on day 183. There were no revumenib related deaths reported; however, 4 animals (2 males and 1 female at 150 mg/kg/day and 1 female at 300 mg/kg/day) were euthanized prior to the terminal endpoint on day 92 or were found dead. Male # 3004 (150 mg/kg/day) showed clinical signs of labored breathing and was euthanized on day 63 due to deteriorating condition. This animal had a lymphoma present around the aorta and in the

thymus, heart, lungs, and various lymph nodes, which were also enlarged macroscopically; the cause of death was due to the thymic mass that was considered a malignant lymphoma. Male #3004 also had minimal hyperplasia in the testis. Another male (150 mg/kg/day) showed swelling and limited use of the left hind paw and was euthanized on day 82 due to severe swelling of the left hindpaw. Both females were found dead on either day 25 or 33 and the cause of death was not determined.

Ophthalmic examinations were performed at pre-treatment, week 6, and week 13 in terminal animals prior to scheduled necropsy (day 92), and at the end of the recovery period (week 26). Lens opacities were observed at revumenib doses ≥ 75 mg/kg/day throughout the dosing and recovery periods. In some animals, lens opacities progressed to bilateral findings (**FDA Table 13**). Increased femur growth plate closure was observed at doses ≥ 75 mg/kg/day, was more pronounced in females on day 92, and did not recover by day 183 (**FDA Table 14**). Increased adrenal gland, pituitary gland, thyroid/parathyroid gland, and uterus/cervix organ weights correlated with irreversible findings of hypertrophy or hyperplasia (**FDA Table 15**). Irreversible findings of hyperplasia were seen in the female mammary gland, uterus/cervix, vagina, testes, pancreas, and kidney at revumenib doses ≥ 75 mg/kg/day. Although mammary gland and uterus/cervix hyperplasia findings were present in some control animals, there was a higher incidence and increase in severity in revumenib treated groups (**FDA Table 16**, **FDA Table 17**). Macroscopic findings of enlarged parathyroid, thyroid, pituitary, adrenal glands, and pale foci in the pancreas were not recovered by day 183.

FDA Table 13. Ophthalmology findings in the 13-week repeat dose rat study (number of animals with finding)

Lens opacity- Cortex anterior													
Sex	**Dose (mg/kg/day)**	**Week 6**			**Week 13**			**Day 92**			**End of recovery**		
Eyes		Right	Left	Both	Right	Left	Both	Right	Left	Both	Right	Left	Both
Male	0	0	0	1	0	0	1	0	0	0	0	0	0
	75	0	0	0	2	0	0	1	0	0	1	0	0
	150	0	2	0	1	1	1	0	0	4*	0	0	1
	300	0	2	2	0	2	6*	0	0	3	0	1	3*
Female	0	0	0	0	0	0	0	0	0	0	0	0	0
	75	1	2	0	0	2	4	0	1	2*	0	1	2
	150	0	1	0	0	1	1	0	1	1*	0	0	0
	300	1	2	1	2	0	6*	2	0	3	1	0	3

*Groups with animals that showed progression from unilateral to bilateral ocular findings
Source: FDA analysis

FDA Table 14. Femur bone findings in the 13-week repeat dose rat study

Day 92	**Male**				**Female**			
mg/kg/day	**0**	**75**	**150**	**300**	**0**	**75**	**150**	**300**
# Animals Examined	9	10	8	10	10	10	10	10
Bone Femur: Growth plate closure								
Open	0	0	0	1 (10%)	1 (10%)	1 (10%)	0	0
Mostly open	9 (100%)	2 (20%)	2 (25%)	5 (50%)	9 (90%)	2 (20%)	0	1 (10%)

Mostly closed	0	8 (80%)	6 (75%)	4 (40%)	0	6 (60%)	7 (70%)	5 (50%)
Closed	0	0	0	0	0	1 (10%)	3 (30%)	4 (40%)
Day 183	**Male**				**Female**			
mg/kg/day	**0**	**75**	**150**	**300**	**0**	**75**	**150**	**300**
# examined	5	5	5	5	5	5	5	5
Bone Femur: Growth plate closure								
Open	0	0	0	0	2 (40%)	0	0	0
Mostly open	2 (40%)	0	1 (20%)	1 (20%)	3 (60%)	1 (20%)	1 (20%)	1 (20%)
Mostly closed	2 (40%)	2 (40%)	3 (60%)	3 (60%)	0	3 (60%)	1 (20%)	4 (80%)
Closed	1 (20%)	3 (60%)	1 (20%)	1 (20%)	0	1 (20%)	3 (60%)	0

Source: FDA analysis

FDA Table 15. Summary of organ weights in the 13-week repeat dose rat study (% change relative to control)

Organ/Tissue	**Day**	**Male**			**Female**		
Dose (mg/kg/day)		**75**	**150**	**300**	**75**	**150**	**300**
GLAND, ADRENAL	92	35%	55%	78%	50%	31%	82%
	183	31%	38%	56%	25%	37%	46%
GLAND, PITUITARY	92	71%	101%	109%	122%	125%	137%
	183	23%	77%	98%	107%	168%	96%
GLAND, THYROID/GLAND, PARATHYROID	92	33%	57%	108%	88%	118%	196%
	183	52%	48%	98%	87%	87%	115%
LIVER	92	37%	55%	97%	88%	96%	169%
	183	21%	15%	23%	8%	19%	20%
KIDNEY	92	27%	38%	41%	20%	17%	29%
	183	16%	17%	36%	8%	18%	20%
UTERUS/CERVIX	92	-	-	-	12%	10%	43%
	183	-	-	-	4%	8%	-8%

Source: FDA analysis

FDA Table 16. Summary of histopathology findings on day 92 in the 13-week repeat dose rat study

Organ/Tissue	**Finding**	**Finding Modifier**	**Severity**	**Male**				**Female**			
				0	**75**	**150**	**300**	**0**	**75**	**150**	**300**
GLAND, MAMMARY			**# Animals Examined**	10	10	10	10	10	10	10	10
	HYPERPLASIA	mammary	1 OF 5					4	3	5	1
			2 OF 5						5	5	5
			3 OF 5						1		4

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
				0	75	150	300	0	75	150	300
			Total					4	9	10	10
OVARY			**# Animals Examined**	0	0	0	0	10	10	10	10
	CORPORA LUTEA, DECREASED NUMBER	bilateral	1 OF 5					4	3	1	
			2 OF 5							3	6
			Total					4	3	4	6
	CYST	bilateral; follicular; unilateral; follicular	1 OF 5					2	3	6	7
		bilateral; follicular	2 OF 5								1
			Total					2	3	6	8
	HYPERTROPHY	bilateral; corpus luteum; unilateral; corpus luteum	1 OF 5						3	4	1
			Total						3	4	1
UTERUS/CERVIX			**# Animals Examined**	0	0	0	0	10	10	10	10
	HYPERPLASIA	endometrial	1 OF 5					1		3	3
			Total					1		3	3
	METAPLASIA	squamous	1 OF 5								1
			Total								1
VAGINA			**# Animals Examined**	0	0	0	0	10	10	10	10
	HYPERPLASIA	stromal / epithelial	3 OF 5								1
			Total								1
	MUCIFICATION, INCREASED		1 OF 5						2	2	6
			2 OF 5						3	4	1
			Total						5	6	7
	SINGLE CELL NECROSIS		1 OF 5						2	3	3
			2 OF 5						1		2
			Total						3	3	5
TESTIS			**# Animals Examined**	10	10	10	10	0	0	0	0
	DEGENERATION/ ATROPHY	bilateral; seminiferous tubule; unilateral; seminiferous tubule	1 OF 5		2	3	8				
		unilateral; seminiferous tubule	2 OF 5		1						
			Total		3	3	8				
	HYPERPLASIA	bilateral; interstitial cell	1 OF 5		9	10	10				
			Total		9	10	10				
LIVER			**# Animals Examined**	10	10	10	10	10	10	10	10
	HYPERTROPHY	hepatocellular	1 OF 5		9	5			9	5	

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
				0	75	150	300	0	75	150	300
			2 OF 5		1	4	10		1	5	10
			Total		10	9	10		10	10	10
GLAND, THYROID			**# Animals Examined**	10	10	10	10	10	10	10	10
	HYPERTROPHY	bilateral; epithelial	1 OF 5		6	3			4	3	1
		bilateral; epithelial; unilateral; epithelial	2 OF 5			1	9				6
			Total		6	4	9		4	3	7
GLAND, PITUITARY			**# Animals Examined**	10	10	10	10	10	10	10	10
	HYPERTROPHY	pars intermedia / distalis	1 OF 5		5	3	1			1	1
			2 OF 5			7	9		10	9	9
			Total		5	10	10		10	10	10
GLAND, ADRENAL			**# Animals Examined**	10	10	10	10	10	10	10	10
	HYPERTROPHY	bilateral; cortex; unilateral; cortex	1 OF 5		2	5	10		8	4	6
		bilateral; cortex	2 OF 5			1					3
			Total		2	6	10		8	4	9
BONE MARROW			**# Animals Examined**	10	10	10	10	10	10	10	10
	CELLULARITY, DECREASED	hematopoietic	1 OF 5			1	1		1	3	7
			Total			1	1		1	3	7
THYMUS			**# Animals Examined**	10	10	10	10	10	10	10	10
	CELLULARITY, DECREASED	lymphoid	1 OF 5			2			1	1	5
			2 OF 5								1
			Total			2			1	1	6
SPLEEN			**# Animals Examined**	10	10	10	10	10	10	10	10
	CELLULARITY, DECREASED	hematopoietic	1 OF 5	1	5	7	10		2	4	7
			2 OF 5			1				1	
			Total	1	5	8	10		2	5	7
STOMACH			**# Animals Examined**	10	10	9	10	10	10	10	10
	DILATATION	gastric gland	1 OF 5		1	3	9		1	3	9
			Total		1	3	9		1	3	9
PANCREAS			**# Animals Examined**	10	10	10	10	10	10	10	10
	HYPERPLASIA	islet of langerhans	1 OF 5		3	2	4		6	8	8
			Total		3	2	4		6	8	8
KIDNEY			**# Animals Examined**	10	10	10	10	10	10	10	10
	DEGENERATION/ NECROSIS	bilateral; tubular; unilateral; tubular	2 OF 5			1	2		1		
			3 OF 5			1	1				

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
				0	75	150	300	0	75	150	300
		bilateral; tubular	4 OF 5			1					
			Total			3	3		1		
	FIBROSIS	bilateral; interstitial; unilateral; interstitial	1 OF 5		1	2	1				
		unilateral; interstitial	2 OF 5				1				
			Total		1	2	2				
	HYPERPLASIA	bilateral; urothelial; pelvis; unilateral; urothelial; pelvis	1 OF 5				2			1	6
		bilateral; urothelial; pelvis	2 OF 5								2
			Total				2			1	8
	INFLAMMATION	unilateral; interstitial; unilateral; pelvis	1 OF 5			1		1	1		1
		bilateral; interstitial; unilateral; interstitial	2 OF 5			2	1				
		unilateral; interstitial	3 OF 5				1				
			Total			3	2	1	1		1
	MINERALIZATION	bilateral; unilateral	1 OF 5					1	3	7	3
		bilateral	2 OF 5					1	1		
			Total					2	4	7	3

1= Minimal, 2= Mild, 3= Moderate, 4= Marked, 5= Severe
Source: FDA analysis

FDA Table 17. Summary of histopathology findings on day 183 in the 13-week repeat dose rat study

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
				0	75	150	300	0	75	150	300
			# Animals Examined	5	5	5	5	5	5	5	5
GLAND, MAMMARY	HYPERPLASIA	mammary	1 OF 5						3	2	1
			2 OF 5						2	1	2
			3 OF 5								1
			Total						5	3	4
OVARY			**# Animals Examined**	0	0	0	0	5	5	5	4
	CORPORA LUTEA, DECREASED NUMBER	bilateral; unilateral	1 OF 5					3		3	
		bilateral	2 OF 5						3	2	1

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
				0	75	150	300	0	75	150	300
			Total					3	3	5	1
	CYST	bilateral; follicular; unilateral; follicular	1 OF 5						5	4	2
		bilateral; follicular	2 OF 5								
			Total						5	4	2
	HYPERTROPHY	bilateral; corpus luteum; unilateral; corpus luteum	1 OF 5						1		
			Total						1		
UTERUS/CERVIX			**# Animals Examined**	0	0	0	0	5	5	5	5
	HYPERPLASIA	endometrial	1 OF 5						3	1	3
			Total						3	1	3
VAGINA			**# Animals Examined**	0	0	0	0	5	5	4	5
	MUCIFICATION, INCREASED		1 OF 5						3	1	2
			2 OF 5								1
			Total						3	1	3
TESTIS			**# Animals Examined**	5	5	5	5	0	0	0	0
	DEGENERATION/ATROPHY	bilateral; seminiferous tubule; unilateral; seminiferous tubule	1 OF 5		3	2	4				
			Total		3	2	4				
	HYPERPLASIA	bilateral; interstitial cell	1 OF 5		5	4	4				
			Total		5	4	4				
LIVER			**# Animals Examined**	5	5	5	5	5	5	5	5
	HYPERTROPHY	hepatocellular	1 OF 5				1		1	1	2
			Total				1		1	1	2
	NECROSIS	hepatocellular	1 OF 5			1					
			2 OF 5			1					
			Total			2					
GLAND, THYROID			**# Animals Examined**	5	5	5	5	5	5	5	5
	HYPERTROPHY	bilateral; epithelial	1 OF 5		5	2	2		5	5	4
			2 OF 5				3				1
			Total		5	2	5		5	5	5
GLAND, PITUITARY			**# Animals Examined**	5	5	5	5	5	5	5	5
	HYPERTROPHY	pars intermedia / distalis	1 OF 5		1	2	3	1	2	2	1
			2 OF 5			1	2		3	3	4
			Total		1	3	5	1	5	5	5
GLAND, ADRENAL			**# Animals Examined**	5	5	5	5	5	5	5	5

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
				0	75	150	300	0	75	150	300
	DEGENERATION/NECROSIS	unilateral; zona fasciculata,FOCAL; unilateral; zona fasciculata,LOCALLY EXTENSIVE	2 OF 5						1		1
			Total						1		1
	HYPERTROPHY	bilateral; cortex	1 OF 5		1	1	3			2	4
			2 OF 5				1				
			Total		1	1	4			2	4
BONE MARROW			**# Animals Examined**	5	5	5	5	5	5	5	5
	CELLULARITY, DECREASED	hematopoietic	1 OF 5				2			1	2
			2 OF 5								1
			Total				2			1	3
THYMUS			**# Animals Examined**	5	5	5	5	5	5	5	5
	CELLULARITY, DECREASED	lymphoid	1 OF 5	3	1		1	2			
			Total	3	1		1	2			
SPLEEN			**# Animals Examined**	5	5	5	5	5	5	5	5
	PIGMENT, INCREASED		1 OF 5					1		1	1
			Total					1		1	1
STOMACH			**# Animals Examined**	5	5	5	5	5	5	5	5
	DILATATION	gastric gland	1 OF 5	1		2	1	1	1	1	
			Total	1		2	1	1	1	1	
PANCREAS			**# Animals Examined**	5	5	5	5	5	5	5	5
	HYPERPLASIA	islet of langerhans	1 OF 5		1	1	1		2	3	3
			Total		1	1	1		2	3	3
KIDNEY			**# Animals Examined**	5	5	5	5	5	5	5	5
	DEGENERATION/NECROSIS	bilateral; tubular; unilateral; tubular	1 OF 5					1	1	1	1
		bilateral; tubular	2 OF 5								1
			3 OF 5							1	
			Total					1	1	2	2
	FIBROSIS	unilateral; interstitial	1 OF 5					1		1	
			Total					1		1	
	HYPERPLASIA	bilateral; urothelial; pelvis; unilateral; urothelial; pelvis	1 OF 5						1	1	3
			Total						1	1	3
	INFLAMMATION	bilateral; interstitial; bilateral; pelvis; unilateral; interstitial; unilateral; pelvis	1 OF 5	2			1		2	3	2
		bilateral; pelvis	2 OF 5	1							
			Total	3			1		2	3	2
	MINERALIZATION	bilateral; unilateral	1 OF 5					2	3	4	4

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
				0	75	150	300	0	75	150	300
			Total					2	3	4	4

1= Minimal, 2= Mild, 3= Moderate, 4= Marked, 5= Severe
Source: FDA analysis

In the 4-week repeat dose toxicology study in dogs, animals were dosed daily with revumenib at doses of 25, 50, or 100 mg/kg/day for 4 weeks followed by a 4-week recovery period. Due to toxicity in the 100 mg/kg/day group, this group was terminated early on day 24/25 after 23 days of dosing. Reversible increases in QTc interval duration (up to 10% relative to pretreatment values) were seen at all revumenib doses throughout the dosing period (**FDA Table 5**). Significant increases in erythrocytes, hemoglobin, and hematocrit (< 15% relative to control) were seen in females at 100 mg/kg/day. Increases in aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) were seen in males (up to 16%, 94%, and 179%, respectively) and in females (up to 34%, 150%, and 316%, respectively). Organ weight changes (absolute values) included decreased thymus weights in males (-88%) and females (-55%) at 50 mg/kg/day on day 29 and decreased testes and epididymis weights (-38% and -38%) at 100 mg/kg/day on Day 57. Of note, the percent changes in mean organ weights were not calculated for animals in the 100 mg/kg/day group. Germ cell depletion/degeneration in the testes and single cell necrosis in the epididymis of males were observed at all revumenib doses at the end of the dosing period and irreversible at ≥50 mg/kg/day (**FDA Table 18**, **FDA Table 19**).

FDA Table 18. Summary of histopathology findings on day 29 or 24/25 in the 4-week repeat dose dog study

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
Dose (mg/kg/day)				**0**	**25**	**50**	**100**	**0**	**25**	**50**	**100**
TESTIS			**# Animals Examined**	3	3	3	3	0	0	0	0
	Germ Cell Depletion/ Degeneration		2 OF 5		2		2				
			3 OF 5		1	2	1				
			4 OF 5			1					
			Total		3	3	3				
EPIDIDYMIS			**# Animals Examined**	3	3	3	3	0	0	0	0
	Oligospermia		2 OF 5				1				
			Total				1				
	Single Cell Necrosis	epithelium; head	1 OF 5		3		1				
			2 OF 5			3	2				
			Total		3	3	3				

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
BONE MARROW, STERNUM			**# Animals Examined**	3	3	3	3	3	3	3	2
	Cellularity, Decreased	hematopoietic	1 OF 5				1				
		erythroid; hematopoietic	2 OF 5				1				1
			3 OF 5				1				1
			Total				3				2
THYMUS			**# Animals Examined**	3	2	2	3	3	3	3	2
	Atrophy	lymphoid	1 OF 5	3							
			2 OF 5		1			1	1		
			3 OF 5			1		2	2	1	1
			4 OF 5		1	1	3			2	1
			Total	3	2	2	3	3	3	3	2
LIVER			**# Animals Examined**	3	3	3	3	3	3	3	2
	Vacuolation	hepatocellular	1 OF 5	1				2			
			3 OF 5								1
			Total	1				2			1

1= Minimal, 2= Mild, 3= Moderate, 4= Marked, 5= Severe
Source: FDA analysis

FDA Table 19. Summary of histopathology findings on day 57 in the 4-week repeat dose dog study

Organ/Tissue	Finding	Finding Modifier	Severity	Male		
Dose (mg/kg/day)				**0**	**50**	**100**
TESTIS			**# Animals Examined**	3	3	3
	Germ Cell Depletion		3 OF 5		1	2
			4 OF 5		2	1
			Total		3	3
EPIDIDYMIS			**# Animals Examined**	3	3	3
	Oligospermia		3 OF 5		1	
			4 OF 5		2	2
			5 OF 5			1
			Total		3	3
	Single Cell Necrosis	epithelium; head	1 OF 5		1	3
			2 OF 5		2	
			Total		3	3

1= Minimal, 2= Mild, 3= Moderate, 4= Marked, 5= Severe
Source: FDA analysis

In the 13-week dog toxicology study, animals were dosed daily at doses of 0, 12.5, 25, or 40 mg/kg/day for 13 weeks followed by a 13-week recovery period. There were no revumenib-related deaths reported in the 13-week dog toxicology study. Changes in red blood cell parameters (decreased erythrocytes, hematocrit, and hemoglobin), white blood cells (increased neutrophils, lymphocytes, basophils, and large unstained cells), coagulation parameters (decreased activated partial thromboplastin time and increased fibrinogen), and clinical chemistry (decreased total protein, albumin, globulin, cholesterol, and triglycerides) observed at the end of dosing were generally recovered by week 26 (**FDA Table 20**).

Changes in organ weights were generally recovered, except for increased thymus weights (+69% in males and +206% in females) during week 26 (**FDA Table 21**). Reversible histopathological changes included decreased corpora lutea in the ovaries and atrophy in the uterus/cervix, vagina, and mammary gland. Nerve fiber degeneration, gliosis, and positive microglia staining were present in the brain, all segments of the spinal cord, and the sciatic nerve at doses ≥ 12.5 mg/kg/day. Degeneration/atrophy, depletion of germ cells, and decreased sperm in the testes, and decreased sperm and atrophy in the epididymis were seen at doses ≥ 12.5 mg/kg/day. Testicular atrophy was partially recovered at doses of ≥ 25 mg/kg/day, and nerve fiber degeneration was not recovered at any dose (**FDA Table 22**, **FDA Table 23**).

FDA Table 20. Summary of laboratory findings in the 13-week repeat dose dog study (% change relative to controls)

Week 13		**Males**			**Females**		
Dose (mg/kg/day)	**Unit**	**12.5**	**25**	**40**	**12.5**	**25**	**40**
Hematology							
Erythrocytes	10^12/L	-15%	-14%	-15%	-9%	-6%	-10%
Hematocrit	L/L	-14%	-12%	-15%	-8%	-7%	-10%
Hemoglobin	g/L	-14%	-14%	-17%	-10%	-8%	-12%
Reticulocytes	10^9/L	52%	31%	67%	0%	43%	37%
Leukocytes		43%	14%	32%	23%	49%	38%
Basophils		184%	172%	284%	145%	179%	157%
Large Unstained cells		320%	347%	540%	295%	330%	314%
Neutrophils		54%	16%	28%	23%	46%	48%
Lymphocytes		16%	10%	40%	16%	53%	18%
Coagulation							
Fibrinogen	g/L	18%	11%	75%	5%	40%	66%
Activated Partial Thromboplastin Time	sec	-7%	-12%	-18%	-5%	-13%	-19%
Clinical Chemistry							

Week 13		Males			Females		
Dose (mg/kg/day)	**Unit**	**12.5**	**25**	**40**	**12.5**	**25**	**40**
Albumin	g/L	-6%	-7%	-12%	-7%	-4%	-4%
Globulin		-15%	-16%	-2%	-13%	-8%	-11%
Total protein		-9%	-10%	-8%	-9%	-5%	-6%
Cholesterol	mmol/L	-13%	-17%	-19%	-20%	-13%	-27%
Triglycerides		-12%	-15%	-26%	5%	-5%	-30%

Source: FDA analysis

FDA Table 21. Summary of organ weights in the 13-week repeat dose dog study (% change relative to control)

Week 13	Males			Females		
Dose (mg/kg/day)	**12.5**	**25**	**40**	**12.5**	**25**	**40**
Epididymis	0%	-21%	-18%	-	-	-
Testes	-27%	-46%	-48%	-	-	-
Prostate gland	-7%	-25%	-25%	-	-	-
Adrenal gland	38%	24%	40%	13%	20%	5%
Spleen	-27%	-36%	-23%	-50%	-51%	-45%
Thymus	10%	-14%	-44%	-34%	34%	-11%
Ovary	-	-	-	-53%	32%	-34%

Source: FDA analysis

FDA Table 22. Summary of histopathology findings on day 92 in the 13-week repeat dose dog study

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
				0	**12.5**	**25**	**40**	**0**	**12.5**	**25**	**40**
NERVE, SCIATIC			**# Animals Examined**	3	3	3	3	3	3	3	3
	DEGENERATION	Nerve fiber, MULTIFOCAL	1 OF 5	1	3	2		1	3	2	
			2 OF 5			1	2			1	3
			Total	1	3	3	2	1	3	3	3
SPINAL CORD, THORACIC			**# Animals Examined**	3	3	3	3	3	3	3	3
	DEGENERATION	nerve fiber; dorsal funiculus, MULTIFOCAL	1 OF 5	1		1	1				2
			2 OF 5			1				1	1
			3 OF 5			1	1				
			Total	1		3	2			1	3
	GLIOSIS	dorsal funiculus, FOCAL	1 OF 5			2					1
			Total			2					1

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
				0	12.5	25	40	0	12.5	25	40
	POSITIVE	increased; microglial cell; white matter, MULTIFOCAL	1 OF 5	2	2	1	1	1	2	2	
			2 OF 5			2	2			1	2
			Total	2	2	3	3	1	2	3	2
SPINAL CORD, CERVICAL			**# Animals Examined**	3	3	3	3	3	3	3	3
	DEGENERATION	nerve fiber; dorsal funiculus, MULTIFOCAL	1 OF 5		1	1	1			1	
			2 OF 5				1				2
			3 OF 5				1				1
			Total		1	1	3			1	3
	GLIOSIS	dorsal funiculus, FOCAL	1 OF 5						1		
			Total						1		
	POSITIVE	increased; microglial cell; white matter, MULTIFOCAL	1 OF 5		2	1	1	1	1		
			2 OF 5			2	1			2	2
			3 OF 5				1				1
			Total		2	3	3	1	1	2	3
	RENAUT BODY	MULTIFOCAL	2 OF 5				1				
			Total				1				
SPINAL CORD, LUMBAR			**# Animals Examined**	3	3	3	3	3	3	3	3
	DEGENERATION	nerve fiber; dorsal funiculus, MULTIFOCAL	1 OF 5		1	1	2		1		1
			2 OF 5			2	1			1	2
			3 OF 5							1	
			Total		1	3	3		1	2	3
	GLIOSIS	dorsal funiculus, FOCAL	1 OF 5			1	1		1	1	
			Total			1	1		1	1	
	POSITIVE	increased; microglial cell; white matter, MULTIFOCAL	1 OF 5		3	1	1	1	2	1	
			2 OF 5			2	1			2	2
			3 OF 5				1				1
			Total		3	3	3	1	2	3	3
BRAIN			**# Animals Examined**	3	3	3	3	3	3	3	3
	DEGENERATION	nerve fiber; anterior cervical spinal cord, MULTIFOCAL	1 OF 5	1	1	1			1	1	
			2 OF 5			1	2			2	3
			3 OF 5			1	1				
			Total	1	1	3	3		1	3	3
	GLIOSIS		1 OF 5								1
			Total								1

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
				0	12.5	25	40	0	12.5	25	40
	positive	increased; microglial cell; anterior cervical spinal cord, MULTIFOCAL	3 OF 5				1				1
			Total	3	2	3	3	3	2	3	3
TESTIS			**# Animals Examined**	3	3	3	3	0	0	0	0
	DEGENERATION/ ATROPHY	bilateral; seminiferous tubule	4 OF 5		3						
			5 OF 5			3	3				
			Total		3	3	3				
	HYPERTROPHY	bilateral; leydig cell	1 OF 5			1	1				
			Total			1	1				
EPIDIDYMIS			**# Animals Examined**	3	3	3	3	0	0	0	0
	ATROPHY	bilateral, DIFFUSE	1 OF 5		3						
			2 OF 5			3	3				
			Total		3	3	3				
	SPERM, DECREASED	bilateral, DIFFUSE	5 OF 5		3	3	3				
			Total		3	3	3				
OVARY			**# Animals Examined**	0	0	0	0	3	3	3	3
	CORPORA LUTEA, DECREASED NUMBER	bilateral	2 OF 5								1
			4 OF 5						3	1	1
			Total						3	1	2
GLAND, MAMMARY			**# Animals Examined**	3	3	3	3	3	3	3	3
	ATROPHY	glandular, DIFFUSE	2 OF 5						3	2	3
			Total						3	2	3
UTERUS/CERVIX			**# Animals Examined**	0	0	0	0	3	3	3	3
	ATROPHY	endometrial, DIFFUSE	1 OF 5								1
			2 OF 5						3		1
			Total						3		2
VAGINA			**# Animals Examined**	0	0	0	0	3	3	3	3
	ATROPHY	epithelial, DIFFUSE	1 OF 5						3		2
			Total						3		2
LIVER			**# Animals Examined**	3	3	3	3	3	3	3	3
	DEGENERATION/ NECROSIS	hepatocellular	1 OF 5			1					
			2 OF 5				2				
			Total			1	2				
	EXTRAMEDULLARY HEMATOPOIESIS		1 OF 5		3	3	2				
			Total		3	3	2				

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
				0	12.5	25	40	0	12.5	25	40
	INFLAMMATION	mixed cell; centrilobular; midzonal; periportal, MULTIFOCAL	1 OF 5			3				3	
			2 OF 5				2				
			Total			3	2			3	

1= Minimal, 2= Mild, 3= Moderate, 4= Marked, 5= Severe
Source: FDA analysis

FDA Table 23. Summary of histopathology findings on day 183 in the 13-week repeat dose dog study

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
				0	12.5	25	40	0	12.5	25	40
NERVE, SCIATIC			**# Animals Examined**	3	3	3	3	3	3	3	3
	DEGENERATION	nerve fiber, MULTIFOCAL	1 OF 5		2	2			1	2	3
			2 OF 5				1				
			Total		2	2	1		1	2	3
	RENAUT BODY		1 OF 5		1	1			1	3	1
			Total		1	1			1	3	1
SPINAL CORD, THORACIC			**# Animals Examined**	3	3	3	3	3	3	3	3
	DEGENERATION	nerve fiber, MULTIFOCAL; nerve fiber; dorsal funiculus, MULTIFOCAL	1 OF 5		3	3			1	3	2
		nerve fiber; dorsal funiculus, MULTIFOCAL	2 OF 5				3				
			Total		3	3	3		1	3	2
	GLIOSIS	dorsal funiculus, FOCAL	1 OF 5						1		
			Total						1		
	POSITIVE	increased; microglial cell; white matter, MULTIFOCAL	1 OF 5		2	2				1	1
			2 OF 5				3				2
			Total		2	2	3			1	3
SPINAL CORD, CERVICAL			**# Animals Examined**	3	3	3	3	3	3	3	3
	DEGENERATION	nerve fiber; dorsal funiculus, MULTIFOCAL	1 OF 5	1	2	3		1	2	2	1
			2 OF 5		1		1			1	2
			3 OF 5				2				
			Total	1	3	3	3	1	2	3	3
	GLIOSIS	dorsal funiculus, FOCAL	1 OF 5			2					2
			Total			2					2

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
				0	12.5	25	40	0	12.5	25	40
	POSITIVE	increased; microglial cell; white matter, MULTIFOCAL	1 OF 5						2	1	
		increased; microglial cell; white matter, FOCAL; increased; microglial cell; white matter, MULTIFOCAL	2 OF 5		2	3	1	1		2	3
		increased; microglial cell; white matter, MULTIFOCAL	3 OF 5				2				
			Total		2	3	3	1	2	3	3
SPINAL CORD, LUMBAR			**# Animals Examined**	3	3	3	3	3	3	3	3
	DEGENERATION	nerve fiber; dorsal funiculus, MULTIFOCAL	1 OF 5		1	2			1		2
			2 OF 5		1	1				3	1
			3 OF 5				3				
			Total		2	3	3		1	3	3
	GLIOSIS	dorsal funiculus, FOCAL	1 OF 5				1				1
			Total				1				1
	POSITIVE	increased; microglial cell; white matter, MULTIFOCAL	1 OF 5	1	2	2	2			1	
			2 OF 5		1	1				2	3
			3 OF 5				1				
			Total	1	3	3	3			3	3
BRAIN			**# Animals Examined**	3	3	3	3	3	3	3	3
	DEGENERATION	nerve fiber; anterior cervical spinal cord, MULTIFOCAL; nerve fiber; medulla oblongata, MULTIFOCAL	1 OF 5	1	2	3			2	2	1
		nerve fiber; anterior cervical spinal cord, MULTIFOCAL	2 OF 5		1		1			1	1
			3 OF 5				2				
			Total	1	3	3	3		2	3	2
	GLIOSIS	FOCAL	1 OF 5	2				1			1
			Total	2				1			1

Organ/Tissue	Finding	Finding Modifier	Severity	Male				Female			
				0	12.5	25	40	0	12.5	25	40
TESTIS			# Animals Examined	3	3	3	3	0	0	0	0
	ATROPHY	bilateral; seminiferous tubule	1 OF 5			2	1				
			2 OF 5				1				
			Total			2	2				

1= Minimal, 2= Mild, 3= Moderate, 4= Marked, 5= Severe
Source: FDA analysis

5.5.2. Genetic Toxicology

The Applicant's Position:

Revumenib was tested in GLP in vitro bacterial reverse mutation and mammalian cell micronucleus assays and an in vivo micronucleus assay in Sprague Dawley rats. There were no revumenib-related genotoxic effects in vitro or in vivo.

Study title / study number / eCTD location Bacterial Reverse Mutation Assay / Study AF95US.502ICH.BTL / Section 4.1.1 of Module 2.6.6 and Section 8.1 Module 2.6.7. **Key findings:** No toxicity or precipitate was observed, and no positive mutagenic responses were observed in any tester strains with or without S9 mix.	
Study type	In Vitro Reverse Mutation Assay in Bacterial Cells
GLP compliance	Yes
Test system	In vitro micronucleus assay. *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537, and at the tryptophan locus in the *Escheria coli* strain WP2 *uvr*A. Revumenib (b) (4) dose levels tested in the preliminary toxicity study were 6.67, 10.0, 33.3, 66.7, 100, 333, 667, 1,000, 3,333, and 5,000 µg/plate

Study title / study number / eCTD location In Vitro Mammalian Cell Micronucleus Assay in HPBL / Study AF95US-348ICH-BTL / Section 4.1.2 of Module 2.6.6 and Section 8.2 Module 2.6.7. **Key findings:** In the micronucleus assay (B1), cytotoxicity (50 ± 5% CBPI relative to the vehicle control) was not observed at any dose in any of the 3 treatment groups. No genotoxicity effects were observed.	
Study type	In Vitro Assays in Mammalian Cells
GLP compliance	Yes
Test system	Human peripheral blood lymphocytes (HPBL).The study was conducted in 2 phases: a 2-part preliminary toxicity assay (A1 and A2) and the

	micronucleus assay (B1). Doses tested in A1 and A2 ranged from 0.05 to 500 µg/mL and in B1 from 62.5 to 500 µg/mL.

Study title / study number / eCTD location An In Vivo Micronucleus Assay of SNDX-5613 by Oral Gavage in Sprague Dawley Rats / Study 1319005 / Section 4.2.1 of Module 2.6.6 and Section 9.1 Module 2.6.7. **Key findings:** Administration of revumenib by once daily oral gavage to Sprague Dawley rats at dose levels of 100, 200, and 400 mg/kg/day for 2 consecutive days resulted in a negative response for induction of micronuclei in young erythrocytes (ie, reticulocytes) in peripheral blood in males and females at all dose levels.	
Study type	In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
GLP compliance	Yes
Test system	Micronuclei in young peripheral blood erythrocytes (ie, reticulocytes). Once daily dose at dose levels of 100, 200, and 400 mg/kg/day for 2 consecutive days.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment of genotoxicity.

5.5.3. Carcinogenicity

The Applicant's Position:

No carcinogenicity studies have been performed.

The FDA's Assessment:

The FDA concurs. Carcinogenicity studies were not warranted for the proposed indication.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Fertility and early embryonic development: As discussed in ICH S9, studies to evaluate the potential effects of revumenib on fertility and early embryonic development were not warranted and therefore not performed.

Embryo-fetal development: In a GLP-compliant study the effects of revumenib on embryo-fetal development with TK were assessed by administering revumenib at 0, 30, 100, or 300 mg/kg/day daily via oral gavage during gestation day (GD) 6-17 (Study 01319004). There were no effects

on maternal survival at any dose level. Clear evidence of embryo-fetal effects was noted. Revumenib-related effects included decreased maternal body weight and food consumption, post-implantation loss, and lower mean numbers of live fetuses at all doses. As revumenib caused clear evidence of embryo-fetal effects, further embryo-fetal studies were not conducted.
Pre- and postnatal development: As discussed in ICH S9 and in FDA Draft Guidance Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry (September 2017), a pre- and post-natal toxicology study is generally not warranted for marketing of pharmaceuticals for the treatment of patients with advanced cancer.

Effect on reproductive organs

Study title / study number / eCTD location:
An Oral (Gavage) preliminary embryo/fetal development study of SNDX-5613 in rats / Study 01319004 / Section 6.1.1 of Module 2.6.6 and Section 11.1 of Module 2.6.7
Key Drug-related Adverse Findings: There were no effects on maternal survival at any dose level. Lower mean maternal body weight gains and reduced food consumption were observed in all dose levels compared to the control group. At 300 mg/kg/day, 3 of 7 pregnant females had total litter resorption, and 2 fetuses from 2 litters had absent eyes. Higher proportions of post-implantation loss and lower mean numbers of live fetuses were noted at and above 30 mg/kg/day. Effects were considered attributable to test article administration.
Conducting Laboratory and Location: (b) (4)
GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 (control), 30, 100, 300 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose (400 cp) in deionized reverse osmosis water
Species/Strain:	Pregnant female Sprague Dawley rats
Number/Sex/Group:	8 females in each dose group
Age:	Approximately 10 to 13 weeks old
Satellite groups:	Not applicable
Study design:	Assessment of embryofetal development and TK analysis. Daily dose during Gestation Days 6 to 17

Parameters	Major findings
Mortality	No premature mortality
Clinical Signs	No abnormal clinical observations were documented during daily observations nor 1 to 2 hour postdose observations
Body Weights	Lower mean body weight gains and lower food consumption were noted in the 30, 100, and 300 mg/kg/day groups compared to the control group during the dosing period that persisted after the end of the dosing period and resulted in lower mean body weights overall.

Reproductive and developmental findings	Higher mean litter proportions of postimplantation loss and lower mean live fetuses were observed in all dose levels compared to the control group. In the 300 mg/kg/day group, 3 of 7 gravid females had entirely resorbed litters. Mean fetal weights were lower in treatment vs. control groups. External and visceral malformations were noted in 0(0), 1(1), 1(1), and 2(2) fetuses (litters) in the control, 30, 100, and 300 mg/kg/day groups, respectively. One and 2 fetuses in the 30 and 300 mg/kg/day groups, respectively, were noted with eye-related malformations (small or absent eye and eye bulge). No remarkable developmental variations were observed in fetuses in this study.
Other relevant evaluations	The peak plasma concentrations of SNDX-5613 were achieved between 1-4 h post-dose. There was no accumulation of SNDX-5613 on GD 17. The systemic exposure (C_{max} and AUC_{last}) of pregnant rats to SNDX-5613 on GDs 6 and 17 increased in an approximately dose-proportional to greater than dose-proportional manner from 30 to 100 mg/kg/day. The systemic exposure to SNDX-5613 on GDs 6 and 17 for C_{max} increased in a less than dose-proportional manner and for AUC_{last} increased in a greater than dose-proportional manner from 100 to 300 mg/kg/day.

Study title / study number / eCTD location: An Oral (Gavage) Range-Finding Juvenile Toxicity Study of Revumenib in Sprague Dawley Rats, with a Toxicokinetic Phase / 01319001 / Section 6.2.1 of Module 2.6.6 and Section 12.1 of Module 2.6.7 **Key Drug-related Adverse Findings**: Treatment-related mortality and moribundity were noted following the initiation of dosing at 150 mg/kg/day and mortality in the 60 mg/kg/day. Conducting Laboratory and Location: (b) (4) GLP compliance: No	
Methods	
Dose and frequency of dosing:	0 (control), 6, 15, 60, 150 mg/kg/day.
Route of administration:	Oral gavage.
Formulation/Vehicle:	Revumenib (b) (4) in 0.5% (w/v) methylcellulose (400 cp) in reverse osmosis water.
Species/Strain:	Sprague Dawley Rat of 7 days old at initial dose.
Number/Sex/Group:	33 males and 33 females per dose group.
Age:	7 days
Satellite groups:	Not applicable
Study design:	Range-Finding Juvenile Toxicity Study of Revumenib in Sprague Dawley Rats

Parameters	Major findings
Mortality	Treatment-related mortality in 1 female in the 60 mg/kg/day group of the TK phase and 19 males and 8 females in the 150 mg/kg/day group of the TK phase and 3 males and 2 females in the 150 mg/kg/day group of the main study.
Clinical Signs	The female with treatment-related premature mortality in 60 mg/kg/day showed hypoactivity, cool and pale body, decreased respiration rate, and was alienated from the nest prior to death. In the 150 mg/kg/day group swollen forelimbs for 2 males and cool extremities for 1 female were noted. At necropsy, the swollen paws were noted for 2 of the males with corresponding antemortem findings.
Body Weights	Slightly lower mean body weight gains were noted in the 150 mg/kg/day group males and females sporadically throughout the treatment period compared to the control group; differences were more severe for males but were generally not statistically significant in either sex. Mean absolute body weights for males and females in this group were lower (up to 18.1% and 10.7%, respectively) than the control group from postnatal day 10-29 and 16-21, respectively.
Reproductive and developmental findings	Not applicable.
Other relevant evaluations	Exposure, in terms of AUC_{tlast} and C_{max}, increased greater than dose-proportionally over the 6 to 150 mg/kg/day dosing range in males and females on all evaluation days. Exposure to SNDX-5613, in terms of AUC_{tlast}, was similar between sexes for most groups. Peak plasma concentrations were observed over a range from 0.5 to 4 hours postdose. On PND 7 and PND 21, where reportable, $t_{1/2}$ ranged from approximately 3 to 10 hours, with longer half-life on PND 7 than on PND 21 due to measurable concentrations at later time points. Exposure to SNDX-5613, in terms of AUC_{tlast}, was up to 10-fold lower on PND 21 and PND 28 than on PND 7. Exposure was generally similar between PND 21 and PND 28.

The FDA's Assessment:

The FDA agrees with the Applicant that fertility and early embryonic developmental studies were not warranted for the proposed indication. We agree with the Applicant's assessment of the embryo-fetal toxicity. The following assessment provides additional information to support the statements regarding the data in the label.

In the embryo-fetal development study in rats, pregnant females received revumenib doses of 30, 100, or 300 mg/kg/day on gestation days 6-17, and the dosing period was followed by a period of no dosing on gestation days 18-21. Lower maternal body weights and decreased body weight gain were seen at doses ≥ 30 mg/kg/day compared to controls throughout the study (**FDA Table 24**). Increased post-implantation loss due to early resorptions was observed at all revumenib doses. Resorptions were seen in 4/8, 6/8, 7/8, and 7/7 gravid females at 0, 30, 100, and 300 mg/kg/day, respectively. Entirely resorbed litters (total resorptions) were only seen at 300 mg/kg/day in 3 of 7 gravid females. These findings resulted in a decreased number of live fetuses and decreased fetal weight at doses ≥ 30 mg/kg/day (**FDA Table 25**). External malformations included small eye bulge, cleft palate, and absent eye bulge(s) in the 30, 100, and 300 mg/kg/day groups, respectively. Visceral malformations included small eye and absent eye in the 30 and 300 mg/kg/day dose groups, respectively (**FDA Table 26**). The AUC at 30 mg/kg on GD17 was 12,200 ng*h/mL and the clinical AUC at the recommended dose of 270 mg twice daily (540 mg/day) was 21,130 ng*h/mL, resulting in an exposure multiple of 0.6.

FDA Table 24. Summary of maternal body weight findings (% change relative to control)

mg/kg/day	30	100	300
Body weight (GD 18)	-3%	-7%	-15%
Body weight (GD 21)	-5%	-11%	-25%
Body weight gain (GD 6-18)	-18%	-28%	-61%
Body weight gain (GD 18-21)	-19%	-38%	-95%
Gravid uterus weight	-23%	-33%	-85%
Adjusted body weight	1%	-4%	-5%
Adjusted body weight gain	-1%	-17%	-23%

adjusted body weight=body weight (GD21)- gravid uterus weight
adjusted body weight gain=0-adjusted body weight
Source: FDA analysis

FDA Table 25. Summary of cesarean section findings (% change relative to control)

mg/kg/day	30	100	300
Number of pregnant females	8	8	7
Female with live fetuses	8	8	4
Total number of resorptions	200%	540%	1729%
Early resorptions	180%	440%	1683%
Late resorptions	-	-	-
Total number of fetuses	-16%	-24%	-73%
Number of live fetuses	-16%	-24%	-85%
Post-implantation loss	241%	552%	1706%

Source: FDA analysis

FDA Table 26. Summary of fetal findings

mg/kg/day	0	30	100	300
Mean fetal weight (% change vs. control)	-	-9%	-22%	-38%
External Malformations (fetuses (litters))				
Total evaluated	106(8)	89(8)	81(8)	14(4)
Small eye bulge	-	1(1)	-	-
Cleft palate	-	-	1(1)	-
Absent eye bulge	-	-	-	2(2)
Visceral malformations (fetuses (litters))				
Total evaluated	106(8)	89(8)	81(8)	14(4)
Absent eye (s)	-	-	-	2(2)
Small eye	-	1(1)	-	-

Source: FDA analysis

In the dose range-finding juvenile toxicity study in rats, revumenib doses of 6, 15, 60, or 150 mg/kg/day were administered orally via gavage starting on postnatal day 7 (PND) until PND 28. At the high dose of 150 mg/kg/day, 22 males and 10 females (including toxicokinetic and main phase animals) were found dead on PND 7 or 8. Clinical observations for these animals included swollen forelimbs and cool extremities. One female in the 60 mg/kg/day group was found dead on PND 8. Clinical observations noted in this female included hypoactivity, cool body, decreased respiration, and pale body. Lower body weights were seen throughout the dosing period in males (up to -18%, relative to control) and females (up to -11%, relative to control) at the 150 mg/kg/day dose.

Minimally dose-dependent decreases in erythrocyte counts, hemoglobin, and hematocrit (up to -24%, relative to stock animals) and increased red cell distribution (up to 48%, relative to stock animals) were observed in males and females at all revumenib doses. Increased adrenal gland weights were seen at ≥ 15 mg/kg/day in males (up to 37% at 15 mg/kg/day, relative to control) and ≥ 60 mg/kg/day in females (up to 52% at 150 mg/kg/day, relative to control). Systemic exposure was evaluated on PND 7, 21 and 28. Exposure increased greater than dose-proportionally and was generally similar between males and females. Exposure was 10-fold lower on PND 21 and PND 28 compared to PND 7.

Other Toxicology Studies

Study title / study number / eCTD location Neutral Red Uptake Phototoxicity Assay of SNDX-5613in BALB/c 3T3 Mouse Fibroblasts / 20345936 / Section 8.1 of Module 2.6.6 and Section 14 of Module 2.6.7. **Key findings**: Revumenib did not demonstrate phototoxic potential in this assay.	
Study type	Photosafety testing with BALB/c 3T3 mouse fibroblasts
GLP compliance	Yes
Test system	Fibroblasts exposed to revumenib and ultraviolet radiation (+UVR), and fibroblasts exposed to revumenib in the absence of ultraviolet radiation (-

	UVR). Promethazine used as the positive control. Formulations administered to the cells for a total of approximately 60 minutes. UVR exposure times were 40:20 to 42:15 (minutes:seconds). Dose levels 1.77, 3.15, 5.60, 9.96, 17.7, 31.6, 56.2, 100 µg/mL.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

(b) (4)

6 CLINICAL PHARMACOLOGY

6.1. Executive Summary

The FDA's Assessment:

Revumenib is an orally available small molecule that inhibits the interaction between menin and histone-lysine N-methyltransferase 2A enzyme (KMT2A) fusion proteins. The Applicant is seeking approval of revumenib for the treatment of adult and pediatric patients with relapsed or refractory (R/R) acute leukemia with KMT2A rearrangements (KMT2Ar). The proposed revumenib dosage without and with strong CYP3A4 inhibitors is 270 mg or 160 mg twice daily (BID) respectively for patients weighing ≥40 kg. Similarly, the proposed dosage is 160 mg/m^2 or 95 mg/m^2 BID without and with CYP3A4 inhibitors, respectively, for patients weighing < 40 kg. Revumenib is proposed to be taken fasted or with a low-fat meal.

The clinical pharmacology section of the NDA is supported by the PK, safety and efficacy data from the registrational Phase 1/2 study SNDX-5613-0700 (Phase 1: n=132, Phase 2: n=125). There is an ongoing mass balance study (SNDX-5613-0705) and ongoing food effect study with a high-fat meal (SNDX-5613-0706).

The clinical pharmacology review focused on acceptability of the proposed revumenib dosages, administration with regards to food, the BA/BE assessment to bridge the proposed to-be-marketed tablet formulation to the clinical trial capsule formulation and relative bioavailability (RBA) of other formulations (various oral solutions), alternative dosages or management strategy for DDI, hepatic and renal impairment, and the type of KMT2A translocation influencing response to revumenib.

Recommendations:

The Office of Clinical Pharmacology has reviewed the information contained in NDA 218944 and concluded that this NDA for the tablet formulation is approvable from a clinical pharmacology perspective. However, given that there is insufficient PK, safety, or efficacy data available for pediatric patients below 1 year of age, this approval is limited to pediatric patients 1 year and older. The key review issues with specific recommendations and comments are summarized below.

<table>
<tr><th>Review Issues</th><th>Recommendations and Comments</th></tr>
<tr><td>Evidence of effectiveness</td><td>The primary evidence of effectiveness comes from Phase 2 of the pivotal Study SNDX-5613-700. Refer to Section 8.2.2 Integrated Assessment of Effectiveness for details.</td></tr>
<tr><td>General Dosing instructions</td><td>The recommended dosage to be administered fasted or with a low-fat meal (e.g., meals with approximately 400 calories, 25% or less fat) in adult and pediatric patients 1 year and older according to the following table:

FDA Table 27. Recommended revumenib dosages
<table>
<tr><th></th><th>Without Strong CYP3A4 Inhibitors</th><th>With Strong CYP3A4 Inhibitors</th></tr>
<tr><td>Patients Weighing 40 kg or more</td><td>270 mg orally twice daily</td><td>160 mg orally twice daily</td></tr>
<tr><td>Patients Weighing < 40 kg</td><td>160 mg/m^2 orally twice daily</td><td>95 mg/m^2 orally twice daily</td></tr>
</table>
For patients who weigh less than 40 kg, these body surface area (BSA)-based dosages should be rounded to nearest achievable dose with the 25 mg, 110 mg and 160 mg tablets according to the following table:</td></tr>
</table>

<table>
<tr><th>Review Issues</th><th>Recommendations and Comments</th></tr>
<tr><td></td><td>FDA Table 28. Revumenib BSA-based dosing using tablets in patients weighing < 40 kg
<table>
<tr><th>BSA (m^2)</th><th>160 mg/m^2
Dose in mg (twice daily)</th><th>95 mg/m^2
Dose in mg (twice daily)</th><th>(b) (4)</th></tr>
<tr><td>1.4</td><td>220</td><td>135</td><td rowspan="12"></td></tr>
<tr><td>1.3</td><td>220</td><td>135</td></tr>
<tr><td>1.2</td><td>185</td><td>110</td></tr>
<tr><td>1.1</td><td>185</td><td>110</td></tr>
<tr><td>1.0</td><td>160</td><td>100</td></tr>
<tr><td>0.9</td><td>135</td><td>75</td></tr>
<tr><td>0.8</td><td>135</td><td>75</td></tr>
<tr><td>0.7</td><td>110</td><td>50</td></tr>
<tr><td>0.6</td><td>100</td><td>50</td></tr>
<tr><td>0.5</td><td>75</td><td>50</td></tr>
<tr><td>0.4</td><td>50</td><td>25</td></tr>
</table>
*Source: modified based on the BSA table proposed by the Applicant</td></tr>
<tr><td>Dosing in patient subgroups (intrinsic and extrinsic factors)</td><td>Organ Impairment:
Based on popPK analyses, mild or moderate renal impairment (RI) or hepatic impairment (HI) did not impact revumenib exposure, and no dosage adjustments are recommended. The effect of severe RI or HI on the PK of revumenib is unknown. Clinical trials to evaluate revumenib and the M1 metabolite PK in patients with severe hepatic impairment or severe renal impairment are necessary to assess the potential risk of increased drug toxicities in patients with severe hepatic or renal impairment.

Age:
Based on popPK analyses, age (1 to 82 years) did not impact revumenib exposure.

Race/Ethnicity:
Race (8% Asian, 8% Black, 71% White) was not identified as a significant covariate per the popPK analysis, however, there appeared to be higher risk of QT prolongation in the Asian population (refer to Section 8.3.6).

Body weight:
Body weight has a significant effect on the PK of revumenib, with higher revumenib exposures in patients with lower body weight. This supports the recommended BSA dosage in patients weighing less than 40 kg.</td></tr>
</table>

Review Issues	Recommendations and Comments
	DDI: • **Strong CYP3A4 inhibitors:** The revumenib dosage of 160 mg or 95 mg/m^2 BID with strong CYP3A4 inhibitors (e.g., voriconazole, posaconazole, itraconazole in Arm B and cobicistat in Arm C) was supported by the PK, safety and efficacy data from 12 patients (n=10 with weight ≥ 40kg, n=2 with weight < 40kg) in Arm B and 12 patients (n=11 with weight ≥ 40kg, n=1 with weight < 40kg) in Arm C of Phase 1 of Study SNDX-5613-700. • **Moderate or weak CYP3A4 inhibitors:** The revumenib dosage of 270 mg or 160 mg/m^2 BID with moderate CYP3A4 inhibitors (e.g., fluconazole, isavuconazole) or weak CYP3A4 inhibitors was supported by the available PK, safety and efficacy data from 7 patients (n=5 with weight ≥ 40kg, n=2 with weight < 40kg) patients in Arm D, or 13 patients (n=11 with weight ≥ 40kg, n=2 with weight < 40kg) in Arm A of Phase 1 of Study SNDX-5613-700. • **Strong or moderate CYP3A4 inducers:** There were no clinical DDI studies conducted. Given the expected decrease in revumenib exposure that can impact efficacy and the expected increase in the M1 metabolite that can impact safety (e.g., QT prolongation), concomitant use of strong or moderate CYP3A4 inducers should be avoided. • **OATP1B1 inhibitors:** According to in vitro data, M1 is a substrate of OATP1B1. According to exposure-response analysis, there was a positive relationship between M1 exposure and prolonged QTc interval (Grade ≥ 2), differentiation syndrome (any grade), neutropenia (Grade ≥ 4), thrombocytopenia (Grade ≥ 4), TEAEs leading to dose reduction, TEAEs leading to dose modification, and any Grade ≥ 3 TEAE. According to the concentration-QT analysis, the M1 metabolite appeared to be a stronger driver of QTc increases than parent revumenib. A clinical trial to evaluate the effect of OATP1B1 inhibitors on the pharmacokinetics of revumenib and M1 is necessary to assess the serious potential risk of drug toxicity. • **CYP3A4 substrates:** According to in vitro data, revumenib is a potential inhibitor of CYP3A4/5. A physiologically-based pharmacokinetic (PBPK) modeling and clinical pharmacokinetic trial, if the FDA determines that the PBPK modeling study results are insufficient, is necessary to evaluate the effect of revumenib and M1 on the PK of CYP3A4 substrates and assess the serious potential risk of increased drug toxicities with sensitive CYP3A4 substrates.

Review Issues	Recommendations and Comments
	• **MATE1 substrates:** According to in vitro data, revumenib and M1 are potential inhibitors of the multidrug and toxin extrusion protein 1 (MATE-1) transporter. A clinical trial is necessary to evaluate the effect of revumenib and M1 on the PK of MATE1 substrates and to assess the potential risks of increased drug concentrations and toxicities with substrates of MATE1. • **QTc Prolonging Drugs:** Given that revumenib and its M1 metabolite cause concentration dependent QTc interval prolongation, avoid concomitant use of drugs that prolong the QTc interval. If concomitant use is unavoidable, monitor patients more frequently for QTc interval prolongation.
Labeling	The following dosage modifications/management strategy are recommended in the labeling: • **Strong CYP3A4 Inhibitors:** Reduced revumenib dosage of 160 mg BID for patients weighing ≥ 40 kg and 95 mg/m^2 for patients weighing < 40 kg. If the strong CYP3A4 inhibitor is discontinued, increase the dose (after at least 5 half-lives of the strong CYP3A4 inhibitor) to the recommended revumenib dosage without strong CYP3A4 inhibitors. • **Strong or moderate CYP3A4 Inducers:** Avoid concomitant use. • **QTc Prolonging Drugs:** Avoid concomitant use. If concomitant use is unavoidable, monitor patients more frequently for QTc interval prolongation.
Bridge between the to-be-marketed and clinical trial formulations	The development program for revumenib began with the capsule (25 and 113 mg free base equivalents) and 50 mg/mL oral solution (F1, F2) formulations using the (b) (4) salt form. These clinical trial formulations were subsequently transitioned to the proposed to-be-marketed revumenib tablet (25, 110, and 160 mg free base equivalents) (b) (4) using the monocitrate monohydrate salt form. For the tablet formulation, the relative bioavailability assessment conducted in patients was considered adequate for PK bridging to capsules. (b) (4) Pediatric patients or certain adult patients may not be able to swallow the revumenib tablet whole; therefore, appropriate bridging of an oral solution to the clinical trial capsule formulation should be conducted.

There are the following postmarketing requirements (PMR) or postmarketing commitments (PMC) from a clinical pharmacology perspective.

PMR

- Conduct a clinical pharmacokinetic trial to assess the magnitude of change in exposure of revumenib and its metabolite M1 and potential risks of increased drug toxicities to determine an appropriate dosage of revumenib in patients with severe hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."
- Conduct a clinical pharmacokinetic trial to assess the magnitude of change in exposure of revumenib and its metabolite M1 and potential risks of increased drug concentrations to determine an appropriate dosage of revumenib in patients with severe renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing."
- Complete the clinical pharmacokinetic trial to characterize the absorption, distribution, metabolism, and excretion of revumenib and its metabolite M1 and assess the potential risks of increased drug concentrations to determine an appropriate dosage of revumenib. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Pharmacology Considerations for Human Radiolabeled Mass Balance Studies."
- Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of OATP1B1 inhibitors on the pharmacokinetics of revumenib and M1 to assess the serious potential risk of excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."
- Conduct a PBPK modeling study and clinical pharmacokinetic trial if the FDA determines that the PBPK modeling study results are insufficient, to evaluate the effect of repeat doses of revumenib on the single dose pharmacokinetics of a sensitive substrates of CYP3A4 to assess the potential risks of increased drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."
- Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of revumenib on the single dose pharmacokinetics of a substrate of the multidrug and toxin extrusion protein 1 (MATE1) transporter to assess the potential risks of increased drug concentrations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

PMC

- Complete the clinical pharmacokinetic trial to evaluate the effect of a high-fat meal on revumenib exposure, and to determine appropriate administration of revumenib with regard to food. Design and conduct the trial in accordance with the FDA Guidance for Industry: "Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations."
- Conduct a study to assess relative bioavailability between the oral solution and capsule formulations. Design and conduct the trial in accordance with the FDA Guidance for Industry: "Bioavailability Studies Submitted in NDAs or INDs — General Considerations."

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

The clinical pharmacology of revumenib has been studied in 3 ongoing clinical studies in adult and pediatric patients with R/R acute leukemia (SNDX-5613-0700, SNDX-5613-0705) and adult patients with colorectal cancer and other solid tumors (SNDX-5613-0706). The objectives of the clinical studies were to assess the PK including absorption, metabolism, and excretion of revumenib and its primary metabolite M1 (also referred to as N-de ethyl revumenib or SNDX-60165), the effect of intrinsic factors such as age, body weight, renal/hepatic impairment, sex, race, and ethnicity, as well as the effect of extrinsic factors including DDI, food effect, and formulation effect on the PK of revumenib and M1. Validated bioanalytical assays (LC-MS/MS) were developed to measure the concentrations of revumenib in the clinical studies included in this NDA. At the recommended dose of 276 mg q12h without a strong CYP3A4i, the mean (%CV) $C_{max,ss}$ was 2052 (78.9) ng/mL and AUC_{tau} was 10150 (68.5%) ng*h/mL. At 163 mg q12h with a strong CYP3A4i, the mean (%CV) $C_{max,ss}$ was 3220 (33.8%) ng/mL and AUC_{tau} was 22610 (50.1%) ng*h/mL.

Absorption: In vitro, revumenib demonstrated high solubility across the GI pH conditions and tablets were fully dissolved within 15 minutes. Revumenib was classified as having moderate permeability. Following oral administration, revumenib was rapidly absorbed with a median T_{max} of approximately 1 to 2 hours. Revumenib PK was linear and dose-proportional across the dose range (113 mg q12h to 276 mg q12h). Formulation (tablets vs. capsules vs. oral solution) had no clinically meaningful effect on revumenib and M1 PK. Revumenib AUC and C_{max} were lower (approximately 19% and 27%, respectively) when patients were administered a low-fat meal as compared to fasted conditions. The magnitude of these changes in systemic exposures are not considered to be clinically relevant.

Distribution: Revumenib is highly bound to human plasma proteins with unbound fraction for revumenib and M1 9.91% and 62.6%, respectively. The apparent volume of distribution from PopPK analysis was 455 L for a typical patient with a body weight of 69.8 kg.

Metabolism: Revumenib is metabolized primarily by CYP3A4. Metabolite identification profiling of plasma from 5 patients (dosed at 276 mg q12h without any CYP3A4i) given a single dose of [^{14}C]-revumenib showed revumenib was the major component in the plasma, accounting for 48% of the total radioactivity observed. M1 is the only major metabolite with > 10% of total drug-related plasma exposure. No unique or disproportionate metabolites were present.

Elimination: Revumenib plasma concentrations decline rapidly in a monophasic manner with a mean apparent $t_{½}$ ranging from approximately 3 to 5 hours on C1D8 suggesting that steady-state exposures generally were reached by Day 2 to Day 4. The mean accumulation ratio was ~2-fold after repeated dosing. The mean apparent CL/F was 27.2 L/h. The excretory routes of revumenib were investigated in SNDX-5613-0705. Missing samples impacted the ability to quantitatively determine excretory pathways. Results suggested that following a single dose of [^{14}C]-revumenib, 55.3% of the radioactive dose was recovered in urine (25.3%) and feces (30.0%). Due to missing samples, the percent of dose excreted could not be robustly assessed and the actual fraction of dose excreted in urine and feces was likely higher.

Drug-Drug Interactions - Effect of Other Drugs on Revumenib

Use of CYP3A4 Inhibitors: Based on population PK analysis, co-administration of multiple doses of azole antifungals that are strong CYP3A4i (posaconazole, itraconazole, and voriconazole) increased the revumenib AUC and C_{max} by 2-fold and no significant changes in M1 exposure. Based on population PK analysis, co-administration of multiple doses of cobicistat increased the revumenib AUC and C_{max} by 2.5-fold and decreased the M1 exposures by 96%. No clinically significant change in revumenib and M1 exposure (C_{max} and AUC) was observed following co-administration of multiple doses of revumenib with moderate CYP3A4i (fluconazole and isavuconazole). Based on PBPK modeling analysis, no clinically significant change in revumenib and M1 exposure (C_{max} and AUC) was observed following co-administration of multiple doses of revumenib with cimetidine.

Use of Strong & Moderate CYP3A4 Inducers: Based on PBPK analysis, co-administration of moderate and strong CYP3A4 inducers decreased revumenib exposures by 2.5-fold and 5-fold respectively. Co-administration of revumenib with moderate and strong CYP3A4 inducers should be avoided.

Transporter Inhibitors: In vitro, revumenib is not a substrate for P-gp, BCRP, OATP1B1, OATP1B3, MATE2 K, or BSEP but is a substrate of OCT1, OCT2, OAT1, OAT3, and MATE1. M1 is not a substrate for P-gp, BCRP, OCT2, OAT1, OAT3, OATP1B3, MATE1, and MATE2-K, but is a substrate of OATP1B1.

GI-pH modifiers: Based on the physicochemical properties of revumenib, gastric pH modifiers (eg, proton pump inhibitors, H2-receptor antagonists, and antacids) will not affect the solubility, absorption, or PK of revumenib.

Drug-Drug Interactions - Effect of Revumenib on Other Drugs

No dedicated clinical DDI studies were conducted to evaluate the effect of revumenib on other drugs. The potential for revumenib and M1 to be a perpetrator was evaluated in vitro.

Inhibitory Effect on CYP Isozymes: In vitro, revumenib showed no potential clinically significant competitive or time-dependent inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 (testosterone substrate), with values of IC_{50} > 40 μM. Direct (and not time dependent) inhibition of CYP3A4 with midazolam substrate (IC_{50}, 6.82 μM) was observed. The ratio for R1 and the $R1_{gut}$ for CYP3A4 inhibition was above the threshold for a potential clinical drug-drug interaction.

Inducing Effect on CYP Isozymes: In vitro, revumenib did not cause any significant induction of CYP1A2, CYP2B6, or CYP3A4. As revumenib did not induce CYP1A2, CYP2B6, or CYP3A4, revumenib is considered unlikely to induce any other drug-metabolizing pathways. Thus, at clinically relevant doses and exposures in humans, revumenib is unlikely to induce the activity of the major drug-metabolizing enzymes.

Investigation of Uptake Transporters: Revumenib and M1 were evaluated as an inhibitor of efflux and uptake transporters. Revumenib showed no inhibition of P-gp, BCRP, OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, BSEP, and MATE2-K at clinically relevant concentrations. M1 showed no inhibition of OAT1, OAT3, OCT2, OATP1B1, OATP1B3, and MATE2-K at clinically relevant concentrations. However, revumenib and M1 were found to be potent inhibitors of MATE1 with IC_{50} values of 0.53 and 0.84 μM, respectively. A retrospective analysis examining changes in serum creatinine in all patients and glucose levels in patients taking metformin in the SNDX-5613-0700 study was conducted to evaluate the clinical impact of revumenib on MATE1 inhibition. There were no observed clinically relevant changes in these parameters suggesting that revumenib does not cause clinically relevant inhibition of MATE1.

Exposure-response efficacy analysis: Revumenib at a dose of 163 mg q12h with a strong CYP3A4i demonstrated clinically relevant efficacy in patients with R/R *KMT2A*r acute leukemia. There were no meaningful relationships observed in the E-R analyses of various efficacy endpoints. All dose levels led to statistically significant downregulation of leukemogenic or upregulation of myeloid differentiation genes, suggesting that all dose levels explored in this study were at the top of the concentration-response curve. Further, compared with lower doses, 160 mg in the presence of strong CYP3A4i and 270 mg in the absence of strong CYP3A4i is required to adequately maintain the target exposures based on activity in a *KMT2A*r cell-line xenograft model (C_{avg} above *KMT2A*r IC_{90} in at least 90% of patients).

Exposure-response safety analysis: There is no significant changes in continuous safety biomarkers with increase in revumenib or M1 exposures. A statistically significant relationship was observed with revumenib exposure with each of 4 binary safety parameters: neutropenia (Grade ≥ 4), TEAE leading to dose modification, dose discontinuation, and dose delay or interruption. There was a statistically significant relationship with M1 exposure with each of 7 binary safety parameters: prolonged QTc interval (Grade ≥ 2), differentiation syndrome (any grade), neutropenia (Grade ≥ 4), thrombocytopenia (Grade ≥ 4), TEAE leading to dose reduction, TEAE leading to dose modification, and any Grade ≥ 3 TEAE. An increase in age was associated with decreasing incidence of differentiation syndrome.

Potential Effect on Cardiac Repolarization: The increase in QTc interval was concentration dependent with an increase in QTc predicted to be 26.5 msec (upper bound of 90% CI: 30.3 msec) at the mean $C_{max,ss}$ observed in patients after administration of 276 mg BID without a CYP3A4i. In the presence of a moderate or strong CYP3A4i with a dose of 276 mg or 163 mg BID, respectively, the increase in QTc is predicted to be less than 20 msec at the mean $C_{max,ss}$. No effect on HR, cardiac conduction (PR interval and QRS duration) or ECG morphology was observed.

The Applicant's Position:

The clinical pharmacology of revumenib has been well characterized. The data included in the application consists of PK properties of revumenib, PopPK and exposure/response analyses, and results from clinical pharmacology studies, all reflected in the prescribing information.

The FDA's Assessment:

The FDA generally agrees with the Applicant's characterization of revumenib PK in adult and pediatric patients. Additional information regarding the FDA assessment of PK of revumenib when administered with or without a strong CYP3A4 inhibitors are described in Section 6.3.1 FDA Table 31.

According to the exposure-response (E-R) analysis conducted, there was no E-R for efficacy because the exposure for the proposed dosages was on the flat part of the E-R curve. However, there was a positive E-R for safety endpoints including prolonged QTc interval (Grade ≥ 2), differentiation syndrome (any grade), neutropenia (Grade ≥ 4), thrombocytopenia (Grade ≥ 4), TEAE leading to dose reduction, TEAE leading to dose modification, and any Grade ≥ 3 TEAE (refer to section 14.4.3 for details). The positive E-R relationship for safety may have been driven by the higher exposures in patients administered revumenib 160 mg BID with strong CYP3A4 inhibitors as compared to the patients administered revumenib 270 mg BID without strong CYP3A4 inhibitors, shown by the drug exposure versus dose simulated to obtain an average plasma revumenib concentration over IC_{90} (see Figure 18). Refer to the IRT review for the FDA's evaluation of concentration-dependent QT prolongation.

(b) (4)

Based on the in vitro study results, FDA has determined that PBPK modeling and a clinical DDI study if the FDA determines that the PBPK modeling study results are insufficient, is required to evaluate the effect of revumenib and M1 on the PK of sensitive CYP3A4 substrates. A clinical DDI study is also deemed necessary to evaluate the impact of OATP1B1 inhibitors on revumenib and M1.

The FDA determined that the Applicant's retrospective analysis on the impact of revumenib on MATE1 inhibition was inconclusive and a clinical DDI trial to evaluate the effect of revumenib and M1 on the PK of a MATE1 substrate should be conducted.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Data:

The Phase 1 portion of SNDX-5613-0700 was initiated with a starting dose 113 mg q12h and an RP2D of 163 mg q12h administered with a strong CYP3A4i was determined to be an acceptable dose for evaluation in Phase 2. In the Phase 2 portion of the study, revumenib at a dose of 163 mg q12h with a strong CYP3A4i met the primary efficacy endpoint at the IA crossing the pre-specified efficacy boundary. In addition, 276 mg q12h without a strong CYP3A4i was determined to be an acceptable dose based on the preliminary efficacy data, safety profile, and matching the exposures to 163 mg q12h administered with a strong CYP3A4i. The apparent mean $t_{½}$ of revumenib at 276 mg q12h without a strong CYP3A4i ranging from approximately 3 to 5 hours meant that sufficient exposure to ensure efficacy could be obtained with the q12h dosing regimen. Further, model-based simulations indicated there is no significant difference between q12h vs. BID dosing regimen, and no additional benefit with TID dosing regimen. There was no clinically meaningful effect of formulation (tablet versus capsules vs. oral solution) on the PK of revumenib and M1. The dose strengths of the capsule and tablet (eg, 113 mg capsule vs. 110 mg tablet) formulations are considered equivalent, and both the tablet and oral solution may be used interchangeably.

The Applicant's Position:

Based on the totality of the data obtained from the revumenib clinical program, approval is being sought for revumenib 270 mg BID without a strong CYP3A4i for the treatment of R/R acute leukemia in patients with *KMT2A*r. The proposed dose was found to demonstrate efficacy in the indicated population, with a manageable safety profile as shown by TEAEs leading to dose reductions and treatment discontinuation occurring in a minority of patients.

The FDA's Assessment:

The FDA agrees with the Applicant's proposed BID dosages of revumenib (see **FDA Table 25**) with or without strong CYP3A4 inhibitors based on the following data:

- The revumenib dosage of 160 mg or 95 mg/m^2 BID with a strong CYP3A4 inhibitor was supported by the PK, safety and efficacy data from 12 patients (10 patients with weight ≥ 40 kg, and 2 patients with weight < 40kg) co-administered with posaconazole, voriconazole or itraconazole in ARM B and 12 (11 with weight ≥ 40kg, 1 with weight < 40kg) co-administered with cobicistat in Arm C of Phase 1 of Study SNDX-5613-700.
- The revumenib dosage of 276 mg twice daily alone or with a weak or moderate CYP3A4 inhibitor (ARM A, ARM D, ARM F of part 1 from study 700) was then considered safe, with preliminary evidence of activity and slightly lower exposure observed in comparison to the 163 mg BID dosage with a strong CYP3A4 inhibitor.
- Based on the popPK and the exploratory exposure-response (E-R) analyses, there was no significant E-R for the primary efficacy endpoint (CR/CRh) and a positive E-R for safety endpoints including Grade ≥ 2 QTc prolongation, any grade differentiation syndrome (DS), neutropenia, Grade ≥ 4 thrombocytopenia, and Grade ≥ 3 treatment-emergent adverse events (TEAE)s leading to dose modifications.

The FDA agrees that the PK data supports comparability of the to-be-marketed tablet vs. the clinical trial capsule based on the results from the relative bioavailability assessment (RBA) conducted in patients (see FDA Table 29). The upper bound of 90% CI for the geometric mean ratio (GMR) is higher for the PK comparison between tablets and capsules, however, it is not considered clinically meaningful, based on the available safety and efficacy data in these patients (n=9).

FDA Table 29. Relative bioavailability assessment of tablet vs. capsule

Analyte	Dose normalized PK Parameters	Geometric mean (N=20) Tablet (Test)	Geometric mean (N=20) Capsule (Reference)	Geometric Mean Ratio (GMR) Test/Reference (T/R)	90% Confidence Interval (CI)
Revumenib	C_{max} (ng/mL/mg)	14.42 (N=20)	12.15 (N=20)	118.68	100.66-139.92
	AUC_{0-8h} (hr*ng/mL/mg)	71.67 (N=12)	59.32 (N=12)	120.83	100.04-145.94
	AUC_{0-12h} (hr*ng/mL/mg)	72.94 (N=8)	63.64 (N=8)	114.61	87.50-150.12
	AUC_{0-24h} (hr*ng/mL/mg)	184.11 (N=20)	155.63 (N=20)	118.30	102.51-136.53
M1	C_{max} (ng/mL/mg)	3.13 (N=20)	2.89 (N=20)	108.20	96.17-121.74

Analyte	Dose normalized PK Parameters	Geometric mean (N=20) Tablet (Test)	Geometric mean (N=20) Capsule (Reference)	Geometric Mean Ratio (GMR) Test/Reference (T/R)	90% Confidence Interval (CI)
	$AUC_{0\text{-}8h}$ (hr*ng/mL/mg)	20.33 (N=12)	18.48 (N=12)	110.05	91.02-133.05
	$AUC_{0\text{-}12h}$ (hr*ng/mL/mg)	25.51 (N=8)	20.95 (N=8)	121.77	103.67-143.04
	$AUC_{0\text{-}24h}$ (hr*ng/mL/mg)	56.79 (N=20)	49.56 (N=20)	114.60	101.32-129.62

Source: Applicant's response to Clinical Pharmacology Information request dated 06/02/2024

(b) (4)

A clinical trial should be conducted to assess the relative bioavailability between the oral solution and capsule formulations (refer to **Outstanding Issues** below).

FDA Table 30. Exploratory Cross-Study Comparison of (b) (4) vs. patients who received only capsules across Studies SNDX-5613-0700 and SNDX-5613-0702

Analyte	Dose and BSA normalized PK	(b) (4)	Geometric mean (N=228) Capsule	GMR (T/R)	(90% CI)
Revumenib	C_{max} (ng/mL/mg)		31.74 (n=228)	97.07	74.65-126.23
	$AUC_{0\text{-}12h}$ (h*ng/mL/mg)		199.16 (n=183)	72.86	48.18-110.18
	$AUC_{0\text{-}24h}$ (h*ng/mL/mg)		394.25 (n=189)	73.61	48.77-111.11
M1	C_{max} (ng/mL/mg)		3.99 (n=227)	74.42	44.87-123.41
	$AUC_{0\text{-}12h}$ (h*ng/mL/mg)		41.30 (n=182)	50.33	29.77-85.07
	$AUC_{0\text{-}24h}$ (h*ng/mL/mg)		83.14 (n=188)	50.00	29.75-84.03

Source: Applicant's response to Clinical Pharmacology Information request dated 01/02/2024
*Subject (b) (6) was excluded from the comparison because of a dose reduction starting at C1D6 PM due to an AE and was not considered to be at steady state by C1D8.
Capsules were administered either BID or TID. Hence $AUC_{0\text{-}24h}$ was based on either $AUC_{0\text{-}12h}$ or $AUC_{0\text{-}8h}$.

(b) (4)

The F1 and F2 oral solutions were evaluated in 47 and 9 patients (F1+F2: n =56), respectively, across studies SNDX-5613-700 and SNDX-5613-0702 (see Table 29). Exploratory cross-study comparisons indicated that revumenib exposure with the (b) (4) was not comparable to that with the F1 and F2 oral solutions, with a potential higher exposure observed with (b) (4) relative to the F1+F2 solutions. Additionally, similar cross-study comparison between F1+F2 solutions and capsules (see Table 30) indicated these formulations were also not comparable based on lower exposure observed for the F1 and F2 solutions in comparison to the capsules.

FDA Table 31. Exploratory comparison of (b) (4) vs. patients who received F1 or F2 oral solutions across Studies SNDX-5613-0700 and SNDX-5613-0702

Analyte	Dose normalized PK (b) (4) (F1+F2)	(b) (4)	Geometric mean (N=56) F1 + F2 oral solutions	GMR (T/R)	(90% CI)
Parent	C_{max} (ng/mL/mg)		32.02 (n=56)	168.08	94.52-298.89
	AUC_{0-12h} (h*ng/mL/mg)		153.57 (n=53)	165.89	87.63-314.05
	AUC_{0-24h} (h*ng/mL/mg)		307.15 (n=53)	165.89	87.63-314.05
M1	C_{max} (ng/mL/mg)		4.38 (n=54)	118.51	71.05-197.67
	AUC_{0-12h} (h*ng/mL/mg)		32.64 (n=52)	111.81	67.21-185.99
	AUC_{0-24h} (h*ng/mL/mg)		65.28 (n=52)	111.81	67.21-185.99

Source: Applicant's response to Clinical Pharmacology Information request dated 01/02/2024

FDA Table 32. Exploratory comparison of F1+F2 oral solutions vs. patients who received only capsules across Studies SNDX-5613-0700 and SNDX-5613-0702

Analyte	Dose and BSA normalized PK	Geometric mean (N=56) F1+F2 oral solutions	Geometric mean (N=228) Capsule	GMR (T/R)	(90% CI)
Parent	Cmax (ng/mL/mg)	26.39 (N=56)	31.74 (N=228)	83.15	74.09-93.32
	AUC0-12 (h*ng/mL/mg)	123.34 (N=53)	199.16 (N=183)	61.93	52.56-72.97
	AUC0-24 (h*ng/mL/mg)	246.67 (N=53)	394.25 (N=189)	62.57	53.16-73.63
M1	Cmax (ng/mL/mg)	3.50 (N=54)	3.99 (N=227)	87.64	72.25-106.32
	AUC0-12 (h*ng/mL/mg)	25.73 (N=52)	41.30 (N=182)	62.31	51.34-75.62
	AUC0-24 (h*ng/mL/mg)	51.47 (N=52)	83.14 (N=188)	61.90	51.13-74.96

Source: Applicant's response to Clinical Pharmacology Information request dated 01/02/2024
Capsules were administered either q12h or TID. Hence AUC0-24 was based on either AUC0-12 (q12h) or AUC0-8 (TID).

Therapeutic Individualization

Data:

The metabolism of revumenib is predominantly mediated by CYP3A4, so concomitant treatment with drugs that are CYP3A4i or inducers can increase (with inhibitors) or decrease (with inducers) the exposure to revumenib. The PopPK analysis indicated that patients taking a strong CYP3A4i are predicted to have a 2-fold increase in exposure. PBPK analysis concluded that patients taking a moderate CYP3A4 inducer are predicted to have a 3-fold decrease $AUC_{0-\tau,ss}$ and a 2.5-fold decrease in C_{max} and co-administration of a strong CYP3A4 inducer predicted to decrease revumenib AUC and C_{max} by 5.26 and 4-fold, respectively. Based on the biopharmaceutic profile of revumenib, the effect of gastric acid-reducing agents on the bioavailability of revumenib is not expected to be clinically relevant. Covariate analysis of the PopPK model predicted that there is no clinically meaningful effect of age (after accounting for body weight differences), body weight ≥ 40 kg, race, gender, formulation (capsule, tablet, and oral solution), mild to moderate renal and hepatic impairment as well as food effect (low fat meal). Covariate analysis of the PopPK model predicted a clinically meaningful effect on patients < 40 kg. (b) (4)

The Applicant's Position:

The recommended starting dose for revumenib in patients ≥ 40 kg is 270 mg BID and 160 mg/m^2 BID for patients < 40 kg. (b) (4) There is no dose adjustment needed for revumenib in the presence of weak or moderate CYP3A4i. In the presence of strong CYP3A4i, the recommended dose is 160 mg BID orally for patients ≥ 40 kg and 95 mg/m^2 for patients < 40 kg. (b) (4) Co-administration of strong or moderate CYP3A4 inducers with revumenib should be avoided.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment regarding the proposed starting dosages in patients weighing ≥ 40 kg and BSA based starting dosages in patients weighing < 40 kg with or without concomitant use of strong CYP3A4 inhibitors (see **FDA Table 25**). (b) (4) The FDA recommends a higher age cutoff of 1 year for the pediatric patients.

The FDA agrees that no dosage adjustment is needed for revumenib with the concomitant use of weak or moderate CYP3A4 inhibitors. The revumenib dosage of 270 mg or 160 mg/m^2 BID with moderate (e.g., fluconazole, isavuconazole) or weak CYP3A4 inhibitors was supported by the PK, safety and efficacy data from 7 patients (n=5 with weight ≥ 40kg, n=2 with weight < 40kg) patients in Arm D, or 13 patients (n=11 with weight ≥ 40kg, n=2 with weight < 40kg) in Arm A of Phase 1 of Study SNDX-5613-700.

The FDA also agrees that concomitant use of strong or moderate CYP3A4 inducers with revumenib should be avoided.

Outstanding Issues

Data:
N/A

The Applicant's Position:
N/A

The FDA's Assessment:

Organ Impairment

Hepatic
Revumenib is primarily eliminated via hepatic metabolism through CYP3A. The PK of revumenib and the M1 metabolite, which contributes to revumenib's clinically significant effects on QTc prolongation, have not been evaluated in patients with severe hepatic impairment. Patients with severe (total bilirubin >3 x ULN and any AST) hepatic impairment may have higher revumenib and M1 exposures than patients with normal hepatic function, consequently, there is potential for increased toxicity. A PMR for a clinical trial to evaluate revumenib and M1 PK in patients with severe hepatic impairment is necessary to assess the serious potential risk of increased drug toxicities in patients with severe hepatic impairment.

Renal
In the ongoing clinical trial to evaluate the absorption, distribution, metabolism, and excretion (ADME) of revumenib and its metabolites including M1, the overall mean total recovery of radioactivity in urine and feces of 4 patients was 76% (range 70 to 86%) over 240 hours. Forty-nine percent (range 42% to 61%) of the radioactive dose was excreted in feces (7% revumenib, 21% M1) and 27% (range 25% to 30%) in urine (7% revumenib, 13% M1). Furthermore, an impact of severe renal impairment on the PK of drugs predominantly eliminated via the hepatic route cannot always be excluded. The PK of revumenib and M1 have not been evaluated in patients with severe renal impairment. Patients with severe renal impairment (CLcr < 30 mL/min) may have higher revumenib and M1 exposures than patients with normal renal function, consequently, there is potential for increased toxicity. A PMR for a clinical trial to evaluate revumenib and M1 PK in patients with severe renal impairment is necessary to assess the serious potential risk of increased drug toxicities in patients with severe renal impairment.

Mass Balance Study

There is an ongoing clinical trial to evaluate the absorption, distribution, metabolism, and excretion (ADME) of revumenib and its metabolites including M1. An additional PMR will be issued to complete this ADME study.

DDI

OATP1B1 substrate
According to in vitro data, M1 is a substrate of OATP1B1. According to exposure-response analysis, there was a positive relationship between M1 exposure and prolonged QTc interval (Grade ≥ 2), differentiation syndrome (any grade), neutropenia (Grade ≥ 4), thrombocytopenia (Grade ≥ 4), TEAE leading to dose reduction, TEAE leading to dose modification, and any Grade ≥ 3 TEAE. According to the concentration-QT analysis, M1 appeared to be a stronger

driver of QTc increases than the parent revumenib. A PMR for a clinical trial to evaluate the effect of OATP1B1 inhibitors on the pharmacokinetics of revumenib and M1 is necessary to assess the serious potential risk of increased drug toxicity.

MATE-1 inhibitor
According to in vitro data, revumenib and M1 are potential inhibitors of the multidrug and toxin extrusion protein 1 (MATE-1) transporter. A PMR for a clinical trial is necessary to evaluate the effect of revumenib and M1 on the PK and serious potential risk of increased drug toxicities with substrates of MATE1.

CYP3A4 inhibitor
According to in vitro data, revumenib is potential inhibitor of CYP3A4/5. A PMR will be issued to conduct a PBPK modeling study and clinical pharmacokinetic trial if the FDA determines that the PBPK modeling study results are insufficient, to evaluate the effect of repeat doses of revumenib on the single dose pharmacokinetics of a sensitive substrates of CYP3A4 to assess the potential risks of increased drug toxicity.

Food Effects

Revumenib can be administered with or without a low-fat meal. According to the food effect assessment of fed (low-fat meal) vs fasted patients (n=10) in a sub-study of SNDX-5613-0700, revumenib AUC and Cmax were lower (12% and 27%, respectively) when patients were administered a low-fat meal s compared to fasted conditions. Given that the effect of a high-fat meal on revumenib exposure is unknown but is currently being studied, a PMC will be issued to complete the clinical trial to evaluate revumenib PK with a high-fat meal and determine appropriate administration of revumenib with regard to food.

Formulations

The development program for revumenib began with capsules (25 and 113 mg free base equivalents) and 50 mg/mL oral solution (F1, F2) drug formulations using the (b) (4) salt form. Subsequently the proposed to-be-marketed revumenib tablet (25, 110, and 160 mg free base equivalents) (b) (4) using the monocitrate monohydrate salt form were developed. (b) (4) Pediatric patients or certain adult patients may not be able to swallow the revumenib tablet whole; therefore, the Applicant should conduct a relative bioavailability assessment between the oral solution and capsule formulations as a PMC.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:
An overview of the revumenib non-clinical and clinical pharmacology and pharmacokinetics data are presented in Sections 5.3, 5.4, and 6.2.1. Recommended dosing guidelines are presented in Section 6.2.2. Drug-drug interactions are presented in Section 6.2.1.

The Applicant's Position:
The nonclinical and clinical pharmacology of revumenib has been well characterized.

The FDA's Assessment:

The FDA generally agrees with the Applicant's summary of the general pharmacology and PK of revumenib (**FDA Table 33**).

FDA Table 33. Revumenib Pharmacokinetics in patients with relapsed or refractory acute leukemia

Parameter	Dosage	
	163 mg twice daily (with strong CYP3A4 inhibitors) [a]	**276 mg twice daily (without strong CYP3A4 inhibitors) [a]**
General Information		
Exposure[b]		
C_{max} (CV%) ng/mL	3220 (34%)	2052 (79%)
AUC_{0-12} (CV%) ng*h/mL	22,610 (50%)	10,150 (69%)
Dose Proportionality[c]	Dose proportional increases in C_{max} and AUC_{0-12}	
Time to Steady-State	2-3 days	
Accumulation[b]	2-fold	
Absorption		
T_{max} Median (range) hours	2 (0-6)	1 (0.5-4)
Effect of Food		
Low fat meal[d]	No clinically significant differences in revumenib pharmacokinetics observed (Cmax and AUC decreased by 27% and 12% respectively)	
Distribution		
Apparent (Oral) Volume of Distribution[b] (CV%) L	78 (50%)	
Protein Binding[e]	90%	
Blood to plasma ratio	0.8	
Elimination		
Half-Life[b] hours (CV%)	7.5 (57%)	3.6 (36%)
Apparent (oral) Clearance[b] L/hr	7 (51%)	27 (69%)
Metabolism		
Primary Pathway	CYP3A4 in vitro	

Active Metabolite	M1[f]
Excretion[g]	
Feces	Approximately 49% (7% unchanged)
Urine	Approximately 27% (7% unchanged)

Source: FDA analysis
Abbreviations: C_{max} = maximum plasma concentration; AUC= area under the time concentration curve; T_{max} = time to peak concentration
[a]= 1.02 times the highest adult approved recommended dosages
[b]= Steady state
[c]= Dosage range of 113 mg to 339 mg (1.26 times the highest adult approved recommended dosage)
[d]=Approximately 400-500 calories, 25% of calories from fat
[e]= Independent of concentration
[f]= M1 contributes to revumenib's clinically significant effects on QTC but does not contribute to its efficacy at the approved recommended dosage
[g]= A single dose of radiolabeled revumenib 276 mg (1.02 times the highest adult approved recommended dosage) to adult patients with relapsed/refractory acute leukemia.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. All dose levels led to statistically significant downregulation of leukemogenic or upregulation of myeloid differentiation genes (PD), suggesting adequate target coverage can be expected under the proposed dosing regimen. Additionally, results from the E-R analysis for efficacy provide supporting information (Sections 6.2.1 and 0).

The FDA's Assessment:

The FDA generally agrees with the Applicant that revumenib at the proposed dosages induces clinical responses in patients with ALL, MPAL and AML harboring a spectrum of *KMT2A* translocations. The results of the exposure-response analysis for efficacy indicated that there was no relationship between revumenib exposure and response within the exposure range investigated with and without the strong CYP3A4 inhibitor in the study SNDX-5613-0700, suggesting that the exposures achieved with the recommended dosages were on the flat part of the exposure response curve (Refer to Section 14.4.3).

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

The Applicant's Position:
Yes. The proposed dose was found to demonstrate efficacy in the indicated population, with a manageable safety profile as shown by TEAEs leading to dose reductions and treatment

discontinuation occurring in a minority of patients. Data from SNDX-5613-0700 show that CR+CRh responses were rapid and durable, with consistent results obtained across subgroups including leukemia subtypes (AML and ALL) and KMT2A-fusion partners, prior transplant, different races/ethnicities, and irrespective of age, gender, and number of prior lines of therapy. PopPK analyses did not indicate any clinically meaningful effect of age (after accounting for body weight differences), body weight ≥ 40 kg, race, gender, formulation (capsule, tablet, and oral solution), mild to moderate renal and hepatic impairment as well as food effect (low fat meal) in exposure that would warrant does adjustments. Additionally, results from the dosing information and PopPK sections provide supporting information (Sections 6.2.2 and 0).

The FDA's Assessment:

The FDA generally agrees with the Applicant regarding the proposed dosing regimen in adult and pediatric patients aged 1 year and older. The dosage with strong CYP3A4 inhibitor was selected for further expansion based on the results from Phase 1 of study SNDX-5613-700 which evaluated revumenib in the dosage range of 113 mg to 339 mg BID with or without weak, moderate, or strong CYP3A4 inhibitors. The comparable dosage without strong CYP3A4 inhibitor was then selected based on the totality of PK, efficacy and safety data. The selected dosages are also supported by the safety and efficacy observed across the dosage range studied. There was no exposure-response (E-R) observed for efficacy endpoints, including the primary endpoint of CR+CRh rate or other efficacy endpoints of ORR, EFS or OS, suggesting that the exposures achieved with the recommended dosages were on the flat portion of the E-R curve. The CR/CRh rate at the selected dosage of 270 mg BID without strong CYP3A4 inhibitors was 23% (n=3/13) and 22% (n=20/91) at the selected dosage of 160 mg BID with strong CYP3A4 inhibitors. There was positive exposure-response for several binary safety endpoints such as neutropenia (Grade ≥ 4), thrombocytopenia (Grade ≥ 4), QTc prolongation (Grade ≥ 2), differentiation syndrome, and TEAEs leading to dose modification. There was no difference between the selected dosages without and with CYP3A4 inhibitor with respect to safety (i.e., Grade ≥ 3 TEAEs, SAEs, TEAEs leading to dose modification and AESI).

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

The Applicant's Position:

Yes. Based on PopPK analysis, clinically meaningful differences were observed in revumenib and M1 exposures in patients < 40 kg, and dosing is to be adjusted per BSA in these patients. PBPK simulation results suggest similar revumenib exposure in pediatric patients aged 6 to 16 years to adults when dosed on a mg/m^2 basis. (b) (4) Results from the dosing information and PopPK sections provide supporting information (Sections 0 and

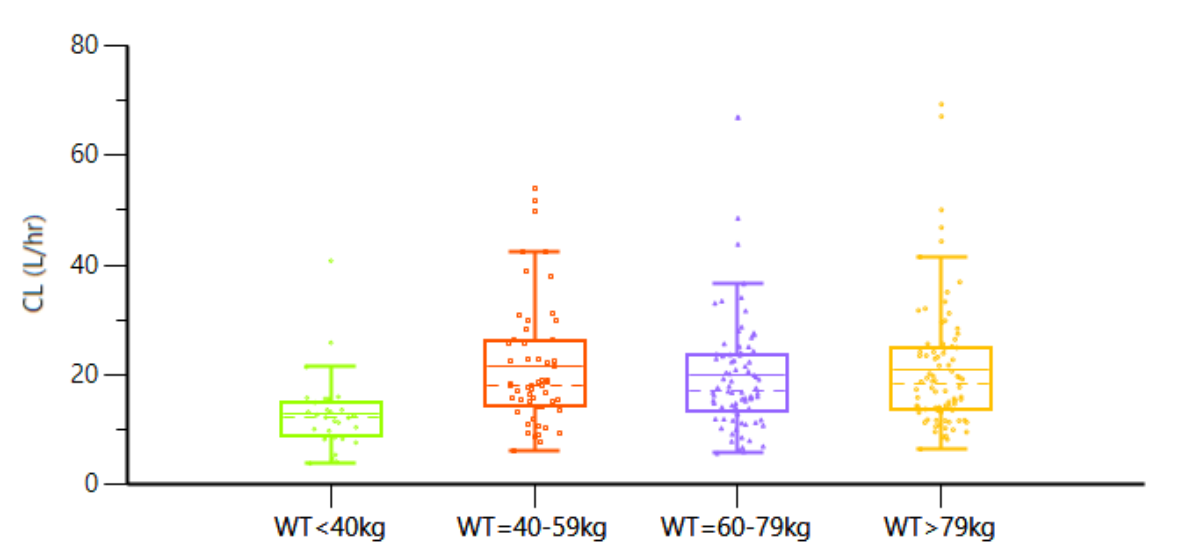
0). The recommended starting dose for revumenib in patients ≥ 40 kg is 270 mg BID and 160 mg/m^2 BID for patients < 40 kg. (b) (4)

The FDA's Assessment:

The covariates evaluated in popPK analysis included body weight, BSA, age, sex, race, mild or moderate hepatic impairment (HI), mild or moderate renal impairment (RI) on revumenib exposure (refer to Section 14.4.2).While, body weight was identified as one of the significant covariates, there was no meaningful impact of age, sex, race, mild or moderate HI and mild or moderate RI on revumenib exposure.

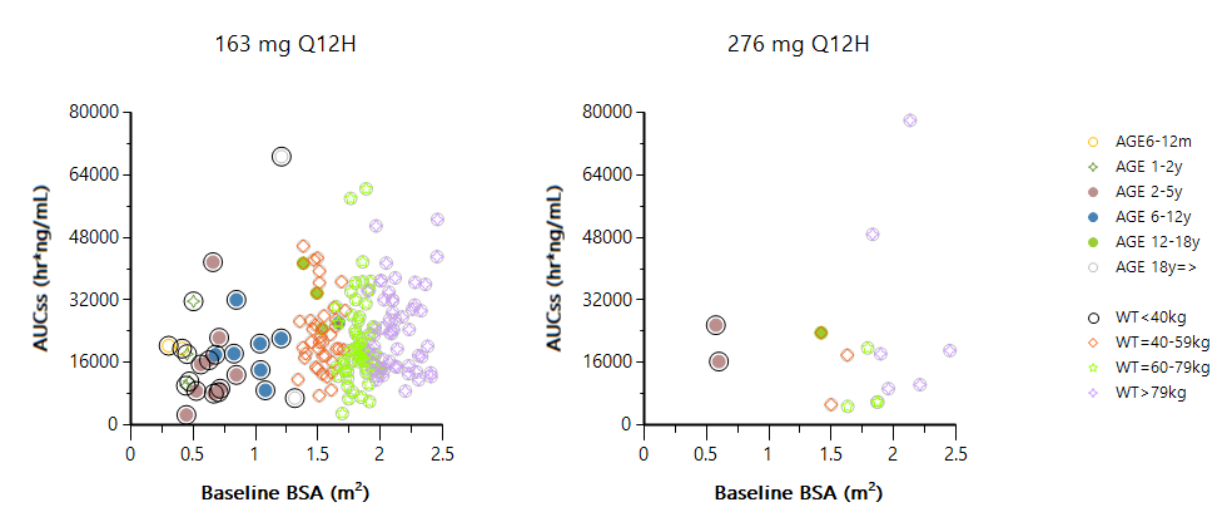
Body weight
Body weight (range 8-146 kg) was identified as a covariate impacting revumenib clearance and volume of distribution. For patients with body weight < 40 kg, the exposure was reported to be approximately 30% higher (see FDA Figure 1) compared to patients with body weight 40 kg or more. The proposed flat dosage (270 mg or 160 mg BID) in adult and pediatric patients with body weight ≥ 40 kg and the proposed BSA-based dosage (160 mg/m^2 or 95 mg/m^2 BID) in adult and pediatric patients 1 year and older with body weight < 40 kg is appropriate based on comparable PK across the age and weight range in adults and pediatrics (see FDA Figure 2, FDA Figure 3).

FDA Figure 1. Clearance vs body weight

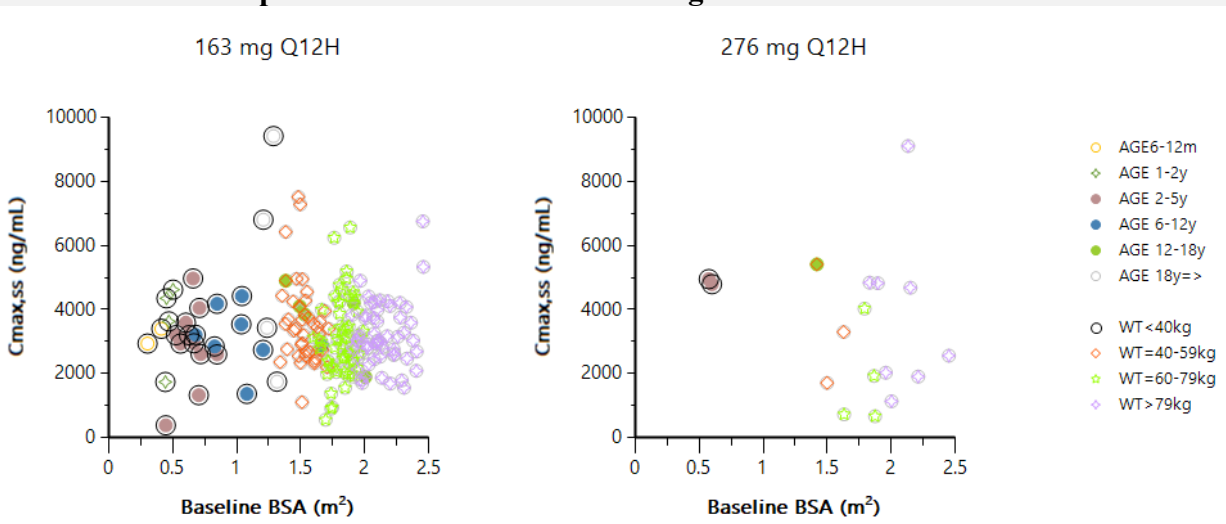


Source: Based on FDA popPK analysis

FDA Figure 2. AUC0-12h at cycle 1, day 7/8 versus baseline body surface area (BSA) in pediatric and adult patients at the recommended dosage with and without strong CYP inhibitor



FDA Figure 3. Cmax at cycle 1, day 7/8 versus baseline body surface area (BSA) in pediatric and adult patients with and without strong CYP inhibitor



Source: FDA analysis based on NCA parameters provided by the applicant

Age

While age (1 to 82 years) did not have an effect on revumenib exposure (see FDA Figure 2,

FDA Figure 3), there is limited information on pediatric patients below 1 year. Although PBPK modeling (Refer to Section 14.4.4 for detail) was conducted to simulate dosages for pediatric patients, there is limited PK, safety, or efficacy data available for pediatric patients below 1 year of age, and therefore this approval is limited to patients 1 year of age and older.

For pediatric patients <17 years of age, revumenib geometric mean (CV%) steady-state C_{max} (n=14) was 3137 (39%) ng/mL and $AUC_{0\text{-}tau}$ (n=13) was 14630 (55%) ng*hr/mL following 95 mg/m^2 BID with strong CYP3A4 inhibitors. Revumenib individual values observed in the two pediatric patients were Cmax (4950 and 4790 ng/mL) and $AUC_{0\text{-}tau}$ (25600 and 16300 ng*hr/mL) following 160 mg/m^2 BID without strong CYP3A4 inhibitors. Revumenib predicted geometric mean (%CV) steady-state Cmax was 1597 (70%) ng/mL and $AUC_{0\text{-}tau}$ was 12570 (56%) ng*hr/mL following 160 mg/m^2 BID without strong CYP3A4 inhibitors.

Organ Impairment
There is no dose adjustment needed for mild or moderate hepatic impairment and mild or moderate renal impairment (see **FDA Table 34**). The assessment for effect of severe renal impairment (CLcr less than 30 mL/min) on revumenib exposure was limited by the number of patients (n=2), with no patients with end-stage renal disease (CLcr less than 15 mL/min). The effect of severe (total bilirubin > 3 × ULN and any AST) hepatic impairment on revumenib pharmacokinetics was not studied. Additionally, based on the ongoing mass balance study, 49% of the drug was excreted in the feces and 27% in urine, both hepatic and renal routes are expected to play a role in revumenib elimination. Therefore, PMRs are requested to evaluate the effect of severe renal and hepatic impairment on revumenib exposure.

FDA Table 34. Impact of mild or moderate hepatic and renal impairment on revumenib PK

	CL ratio estimate Mild vs Normal	CL ratio estimate Moderate vs Normal
Hepatic impairment	0.901	0.816
Renal impairment	0.919	0.834

Source: FDA analysis based on popPK parameters

Race/Ethnicity
A higher risk of QTc prolongation was identified in the Asian patient population with 73% (11/15) of the patients experiencing prolonged QT at the recommended dosage (Refer to section 8.3.6). The biological rationale behind this finding is unknown at this time and given the safety risk finding and the limited number of patients in the Asian subgroup, further investigation of recommended dosage may be needed in this sub-population.

There was no impact of race (8% Asian (n=21), 8% Black (n=20), 71% White (n=178)) on revumenib exposure according to the popPK analysis.

***KMT2A* translocation status**

Patients in SNDX-5613-0700 were enrolled based on local diagnostic testing consisting of karyotyping and FISH for the presence of chromosomal translocations in the *KMT2A* locus. Chromosomal rearrangements in the *KMT2A* locus (11q23.3) are classified in two major categories: 1) translocations that result in fusions with >90 partner genes from various chromosomes, and 2) partial tandem duplications (PTD) and other "cryptic" rearrangements (PMID 37019990). *KMT2A* translocations are detectable by conventional karyotyping and fluorescence in situ hybridization (FISH), whereas PTD are usually not detectable by these techniques (PMID 38730645). Approximately 5-10% of cases of adult AML with *KMT2Ar* have PTD (PMID 37019990). Patients with a *KMT2A* PTD were excluded from the pivotal efficacy and safety cohorts. Therefore, the indication should be updated to reflect the population studied (patients with relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (*KMT2A*) translocation).

Sixty six percent of the patients in SNDX-5613-0700 (n = 170) had a diagnosis of relapsed or refractory ALL, MPAL, or AML with a *KMT2A* translocation at baseline. In this group, the most frequent types of *KMT2A* translocations were: 9:11 (24.1%), 11:19 (17.1%), 6:11 (10.0%), 4:11 (8.8%), 10:11 (7.6%), 1:11 (3.5%), 11:17 (2.4%), and other or unknown fusion partners (26.4%). The distribution of *KMT2A* translocations in both the efficacy cohort (n = 104) and the safety population (SAFPOP, n = 167) were similar. Patients from the pivotal cohorts carried a range of *KMT2A* translocations, and the types and frequencies of *KMT2A* translocations were in general agreement with estimates derived from a large series of pediatric and adult patients with ALL and AML (FDA Table 35; PMID 37019990).

In the efficacy cohort, there were no apparent trends in the distribution of the primary endpoint (CR plus CRh) in response to therapy with revumenib based on the *KMT2A* translocation present at baseline (see FDA Table 36). In the ALL/MPAL subgroups, responses (CR or CRh) were documented in 4 patients carrying the two most common *KMT2A* translocations in ALL (4:11 and 11:19), which account for up to 75% of *KMT2A* translocations in patients with ALL (PMID 37019990). In the AML subgroup, CR plus CRh were documented in 10 patients carrying the four most common *KMT2A* translocations in AML (6:11, 9:11, 10:11, and 11:19), which account for up to 67% of *KMT2A* translocations in patients with AML (PMID 37019990). In the AML subgroup, 33% of responders had *KMT2A* translocations with unknown partners. These results suggest that revumenib induces clinical response across a spectrum of *KMT2A* translocations.

FDA Table 35. FDA adjudicated clinical responses by type of *KMT2A* translocation at baseline (Efficacy cohort)

***KMT2A* translocation**	**Patients with *KMT2A* ALL/MPAL**				**Patients with *KMT2A* AML**				**Total (%) N = 104**
	CR (%)	**CRh (%)**	**NR (%)**	**Total (%)**	**CR (%)**	**CRh (%)**	**NR (%)**	**Total (%)**	
1;11	0	0	0	0	0	0	3 (100)	3 (100)	3 (2.9)
4;11	2 (28.6)	0	5 (71.4)	7 (100)	0	0	0	0	7 (6.7)
6;11	0	0	0	0	1 (10.0)	2 (20.0)	7 (70.0)	10 (100)	10 (9.6)

KMT2A translocation	Patients with *KMT2A* ALL/MPAL CR (%)	CRh (%)	NR (%)	Total (%)	Patients with *KMT2A* AML CR (%)	CRh (%)	NR (%)	Total (%)	Total (%) N = 104
9;11	0	0	0	0	3 (13.0)	1 (4.3)	19 (82.7)	23 (100)	23 (22.1)
10;11	0	0	0	0	2 (20.0)	0	8 (80.0)	10 (100)	10 (9.6)
11;16	0	0	0	0	0	0	1 (100)	1 (100)	1 (1.0)
11;17	0	0	0	0	0	1 (50.0)	1 (50.0)	2 (100)	2 (1.9)
11;18	0	0	0	0	0	0	1 (100)	1 (100)	1 (1.0)
11;19	1 (20.0)	1 (20.0)	3 (60.0)	5 (100)	0	1 (6.7)	14 (93.3)	15 (100)	20 (19.2)
11;22	0	0	0	0	1 (50.0)	0	1 (50.0)	2 (100)	2 (1.9)
Unknown	0	0	6 (100)	6 (100)	3 (15.8)	3 (15.8)	13 (68.4)	19 (100)	25 (24.1)

Source: FDA clinical analysis

Among the 167 patients in the SAFPOP, 39 patients with *KMT2A* translocations (23.4%) experienced at least one DS event (FDA Table 36). DS was documented in patients carrying the most prevalent types of *KMT2A* translocations with the exception of 1:11, 11;18, and 11;22. Approximately 31% of the patients who experienced DS had *KMT2A* translocations with unknown partners (see **FDA Table 36**). There were no apparent trends towards associations between the incidence of DS and the type of *KMT2A* translocation.

FDA Table 36. FDA adjudicated DS by type of *KMT2A* translocation (SAFPOP)

KMT2A translocation	Patients with *KMT2A* ALL/MPAL No DS (%)	DS (%)	Total (%)	Patients with *KMT2A* AML No DS (%)	DS (%)	Total (%)	Total (%) N = 122
1;11	0	0	0	3 (100)	0	3 (100)	3 (2.5)
4;11	6 (75.5)	2 (25.0)	8 (100)	0	0	0	8 (6.6)
6;11	0	0	0	7 (70.0)	3 (30.0)	10 (100)	10 (8.2)
9;11	0	0	0	20 (69.0)	9 (31.0)	29 (100)	29 (23.8)
10;11	1 (100)	0	1 (100)	9 (81.8)	2 (18.2)	11 (100)	12 (9.8)
11;16	0	0	0	0	1 (100)	1 (100)	1 (0.8)
11;17	0	0	0	1 (50.0)	1 (50.0)	2 (100)	2 (1.6)
11;18	0	0	0	1 (100)	0	1 (100)	1 (0.8)
11;19	3 (60.0)	2 (40.0)	5 (100)	12 (63.2)	7 (36.8)	19 (100)	24 (19.7)
11;22	0	0	0	2 (100)	0	2 (100)	2 (1.6)
Unknown	7 (100)	0	7 (100)	11 (47.8)	12 (52.2)	23 (100)	30 (24.6)

Source: FDA clinical analysis

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

The Applicant's Position:

There is no clinically meaningful impact of food effect (low-fat meal) on revumenib and M1 exposure. The PopPK analysis indicated that patients taking a strong CYP3A4i are predicted to have a 2-fold increase in exposure. PBPK analysis concluded that patients taking a moderate CYP3A4 inducer are predicted to have a 3-fold decrease $AUC_{0-\tau,ss}$ and a 2.5-fold decrease in C_{max} and co-administration of a strong CYP3A4 inducer is predicted to decrease revumenib AUC and C_{max} by 5.26 and 4-fold, respectively. In the presence of strong CYP3A4i, the recommended dose is 160 mg BID orally for patients ≥ 40 kg and 95 mg/m^2 for patients < 40 kg; (b) (4) Co-administration of strong or moderate CYP3A4 inducers with revumenib should be avoided.

The FDA's Assessment:

Food Effect

The FDA agrees with the Applicant's proposal to take revumenib fasted or with a low-fat meal. Results from a food effect assessment in 10 patients from Study SNDX-5613-700 showed a decrease in revumenib AUC of 27% and Cmax of 12% (see FDA Table 37) with a low-fat meal that was not considered clinically significant. The observed decrease in exposure observed when administered with food is not considered clinically meaningful, because of the available safety and efficacy data in these patients. However, given the decrease observed in revumenib exposure with the low-fat meal and the unknown effect of a high-fat meal, a PMC is requested to complete the ongoing evaluation of the effect of a high-fat meal on revumenib exposure in Study SNDX-5613-706.

FDA Table 37. Comparison of Fed (Low-Fat Meal) vs. Fasted Conditions

SNDX-5613 (n=10)	**GMR (%)**	**90% Lower CI**	**90% Upper CI**
C_{max} (ng/mL/mg)	72.61	52.37	100.68
AUC_{0-6h} (h*ng/mL/mg)	81.47	60.52	109.67
AUC_{0-24h} (h*ng/mL/mg)	87.69	67.06	114.66

Source: SNDX-5613-0700-other report

Drug-Drug Interactions

Effect of CYP3A4 inhibitors:
Given that most patients with acute leukemia are susceptible to fungal infections, the majority of these patients are administered concomitant azole antifungals, which are strong CYP3A4

inhibitors. For Study SNDX-5613-0700, strong CYP3A4 inhibitors, amongst other CYP3A4 inhibitor types, were most commonly used (see FDA Table 38).

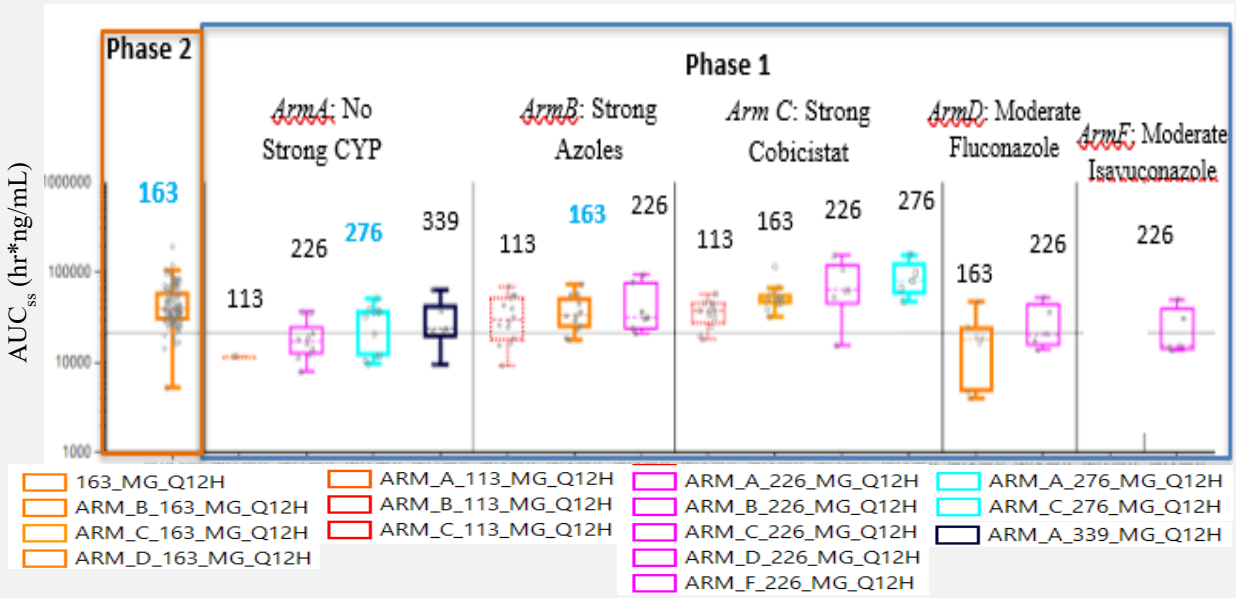
FDA Table 38. % Patients on CYP3A4 inhibitors

CYP Inhibitor Type	%	n=257
Strong	77%	197
Moderate	8%	20
Weak	5%	14
No CYP Inhibitor	10%	26

FDA analysis based on sponsor's popK dataset (n=257 patients).
* Some of the patients received both weak and strong or both weak and moderate inhibitors

Revumenib is a CYP3A4 substrate. Given the interaction between revumenib and the concomitantly administered azoles, Phase 1 dose escalation of SNDX-5613-0700 was conducted without or with weak (Arm A), moderate (Arms D and F) or strong CYP3A4 (Arms B and C) inhibitors across the dosage range of 113-339 mg. The dosage with strong CYP3A4 inhibitor was selected first in the development program from Phase 1 and was moved forward for Phase 2 dose expansion.

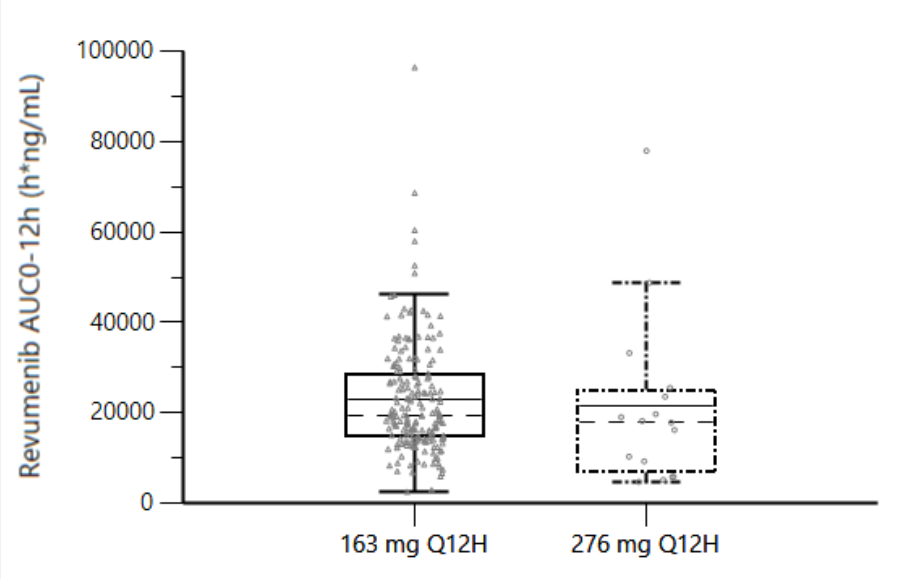
FDA Figure 4. Revumenib AUC_{ss} by Dose Level Across Phase 1 (different arms) and Phase 2



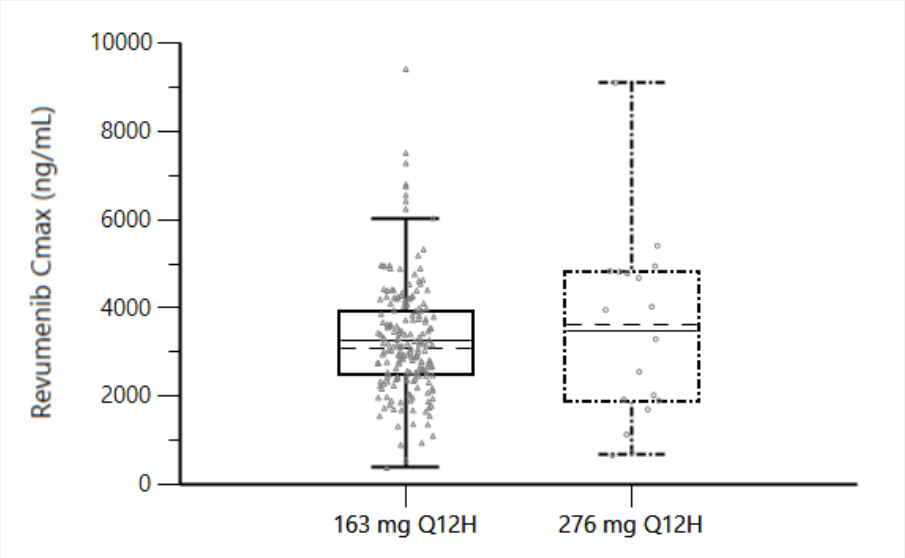
Source: FDA analysis based on the steady state AUC provided by the applicant

The FDA agrees that the proposed dosage of 160 mg or 95 mg/m^2 BID when administered with strong CYP3A4 inhibitors is acceptable based on the available PK (see FDA Figure 4), safety (see Table 84), and efficacy (see FDA Table 62) data in adult and pediatric patients age 1 year and older with R/R acute leukemia. The proposed dosage of 160 mg BID with strong CYP3A4 inhibitor also provides similar exposure (AUC and Cmax at steady state) as the dosage of 276 mg BID without strong CYP3A4 inhibitor (see FDA Figure 5, FDA Figure 6). The proposed dosages with and without strong CYP3A4 inhibitors are also supported by the popPK analysis, according to which strong CYP3A4 inhibitors increased revumenib exposure (AUC) by 110%, along with no E-R for efficacy and positive E-R for safety (refer to section 14.4.2, 14.4.3 for details).

FDA Figure 5. Boxplots of $AUC_{0\text{-}12h}$ at cycle 1, day 7/8 comparing the recommended dosage of revumenib 163 mg BID with strong CYP3A4 inhibitor and 276 mg BID without strong CYP3A4 inhibitor



FDA Figure 6. Boxplots of C_{max} at cycle 1, day 7/8 comparing the recommended dosage of revumenib 163 mg BID with strong CYP3A4 inhibitor and 276 mg BID without strong CYP3A4 inhibitor



*Source: FDA analysis based on the PK parameters provided by the applicant.

Additionally, the FDA agrees with the Applicant that no dosage adjustment is required with moderate or weak CYP3A4 inhibitors based on minimal impact of moderate CYP3A4 inhibitors on revumenib exposure and supported by popPK and E-R analyses for safety and efficacy (refer to section 14.4.2, 14.4.3 for details).

Effect of CYP3A4 inducers:
CYP3A4 inducers are expected to decrease revumenib exposure, which may impact efficacy, and at the same time increase M1, which can increase the risk for toxicities (e.g., QT prolongation). There was no clinical DDI study conducted with concomitant CYP3A4 inducers. While PBPK modeling was performed for both CYP3A4 inhibitors and inducers, generally, the results for CYP3A4 inhibitors were inconsistent compared to the observed data, therefore PBPK model results were not used to inform the effect of CYP3A4 inducers as well (refer to section 14.4.4 for details). Requesting a PMC to study the effect of CYP3A4 inducers on revumenib and M1 exposure was not considered ethical, given the potential increase in safety risk due to higher M1 exposure and the potential negative impact on efficacy due to lower revumenib exposure in the presence of CYP3A4 inducers. Therefore, in the absence of such study, the FDA recommends avoiding co-administration of strong and moderate CYP inducers.

Effect on CYP3A4 substrates:
Revumenib inhibits CYP3A4 as per the in vitro studies. Therefore, a PMR will be issued to conduct a PBPK modeling study and clinical pharmacokinetic trial if the FDA determines that

the PBPK modeling study results are insufficient, to evaluate the effect of repeat doses of revumenib on the single dose pharmacokinetics of a sensitive substrates of CYP3A4 to assess the potential risks of increased drug toxicity. It is unknown if M1 inhibits CYP3A4. According to the M12 Drug Interaction Guidance for Industry, in vitro assessments of metabolites as inhibitors of enzymes or transporters may not be needed if in vitro assessments suggest that the parent drug inhibits major CYP enzymes and transporters and clinical DDI studies are planned. Given that a PMR will be issued to evaluate the effect of revumenib on the PK of a sensitive CYP3A4 substrate, the clinical DDI trial should be designed such that the inhibition potential of metabolites would be implicitly reflected in the clinical DDI study along with the parent drug.

Effect of OCT1, OCT2, OAT1, OAT3, MATE1 and OATP1B1 transporter inhibitors:
As per in vitro studies, revumenib is a substrate of renal transporters including OCT1, OCT2, OAT1, OAT3, and MATE1. However, it was estimated that the overall active renal secretion for revumenib would be less than 25% of the systemic clearance; hence, the renal transporter inhibitors are expected to have minimal effect on revumenib exposure.

Additionally, as per the in vitro studies, M1 is a substrate of the OATP1B1 transporter, and given the known relationship between M1 and QTc prolongation at the recommended dosage, a PMR will be issued to evaluate the effect of OATP1B1 transporter inhibitors on M1 PK.

Effect on MATE1 transporter substrates:
Revumenib and M1 also inhibit MATE1 substrates. Although the inhibition effect of revumenib and M1 was evaluated by the Applicant via a retrospective analysis from patients who received metformin and effects on creatinine and glucose, the available information was too limited to reach a definitive conclusion. Therefore, a PMR will be issued to conduct a dedicated clinical DDI trial to evaluate the inhibitor effect of revumenib and M1 on MATE1 substrates.

7 SOURCES OF CLINICAL DATA

7.1. Table of Clinical Studies

Data:

An overview of clinical studies supporting the efficacy and safety of revumenib is presented in Table 39.

Table 39: Applicant – Clinical Studies Supporting the Efficacy and Safety of Revumenib

Trial Identity	Trial Design Type	Study Population	Regimen / route / schedule	No. of patients enrolled	Primary Endpoint / Objective	No. of Centers and Countries
Studies to Support Efficacy and Safety						
SNDX-5613-0700	Phase 1/2, open-label, dose-exploration and dose-expansion study of revumenib	Aged ≥ 30 days with R/R acute leukemia Patients in the food effect evaluation were ≥ 16 years	Starting dose: Revumenib; 113 mg q12h RP2D: 163 mg q12h and 276 mg q12h with and without strong CYP3A4 inhibitors, respectively. Patients < 40 kg dosed by BSA. Revumenib will be dosed orally q12h or TID (depending on cohort), either with capsules (25 and 113 mg free-base equivalents), tablets (25, 110, and 160 mg), or oral solution. The oral solution may be administered through NG/G-tube.	Phase 1: Estimated: 114 Enrolled: 134 Phase 2: Estimated: 287 adults and pediatric patients (< 18 years) Enrolled: 126 Total Estimated: 401 Enrolled: 260	Phase 1: Primary Endpoints: • Occurrence of DLTs. • Frequency, duration, and severity of TEAEs, TRAEs, and SAEs. • Incidence and shifts of clinically significant clinical laboratory abnormalities. • Change from baseline in other observations related to safety, including ECGs, vital signs, ophthalmologic examination findings, and performance status. • PK parameters: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-24}, CL/F, $V_{z/F}$, and $t_{½}$.	33 sites: Phase 1 - 11 sites in the US Phase 2 - 22 sites in Australia, Canada, France, the Netherlands, and the US

					Primary Objectives • To determine the safety, tolerability, MTD, and RP2D of revumenib in patients with R/R acute leukemia in each of the arms studied • To characterize the PK parameters of revumenib and relevant metabolites in each of the arms studied Phase 2: Primary Endpoints: • CR+CRh rate. • Frequency, duration, and severity of TEAEs, TRAEs, and SAEs. • Incidence and shifts of clinically significant clinical laboratory abnormalities. • Change from baseline in other observations related to safety, including ECGs, vital signs, ophthalmologic examination findings, and performance status. Primary objectives: • To evaluate short- and long-term safety and tolerability of revumenib • To assess the CR + CRh rate	

Studies to Support Only Safety						
SNDX-5613-0702	Phase 1, open-label, dose-escalation study of revumenib in combination with chemotherapy	Aged ≥ 30 days with R/R acute leukemia harboring *KMT2A*r, *NPM1*mut, or *NUP98r*	Revumenib; starting dose: 113 mg q12h; Patients < 40 kg dosed by BSA. Revumenib will be dosed orally q12h either with capsules (25 or 113 mg free base equivalents) or oral solution. The oral solution may be administered through an NG/G-tube if the patient is unable to take orally by self. Regimen 1: Cycle 1: Vincristine, prednisone, pegaspargase/calaspargase pegol-mknL, daunorubicin Cycle 2: Etoposide, cyclophosphamide Regimen 2: Cycle 1 and 2: Fludarabine, cytarabine	Estimated: 54 patients total, 27 in each revumenib + chemotherapy regimen Enrolled: 17	Primary Endpoint: • Occurrence of DLTs • Frequency, duration, and severity of TEAEs, TRAEs and SAEs • Incidence and shifts of clinically significant clinical laboratory abnormalities • Change from baseline in other observations related to safety, including ECG, vital signs, ophthalmologic examination findings and Karnofsky/Lansky performance status Primary Objective: • To determine the safety, tolerability, and RP2D of revumenib in combination with standard chemotherapy in patients with R/R acute leukemia harboring *KMT2Ar*, *NPM1mut*, or *NUP98r*	18 sites in the US and Canada
SNDX-5613-0705	Phase 1, open-label, nonrandomized study	≥ 18 years with R/R acute leukemia (AML, ALL, or MPAL)	Revumenib; single dose (276 mg) of radiolabeled revumenib as an oral solution. Revumenib may continue to be administered thereafter;	Estimated: 8 Enrolled: 5	Primary Endpoints: • Percentage of dose excreted in urine (Feu) • Percentage of dose excreted in feces (Fef)	1 sites in the US

			each dose administered after the first dose will be revumenib nonradiolabeled 276 mg. Doses will be administered q12h in continuous 28-day cycles		• Amount excreted in urine (Aeu) • Amount excreted in feces (Aef) • AUC_{0-t} • AUC_{0-inf} • C_{max} • T_{max} • $t_{1/2}$ Primary Objectives: • To determine the mass balance and routes of elimination of [14C]-revumenib after a single oral dose of [14C]-revumenib • To determine urinary and fecal recovery of total radioactivity after a single oral dose of [14C]-revumenib • To assess the plasma PK of total radioactivity and revumenib after a single oral dose of [14C] revumenib • To characterize and identify metabolites of revumenib in plasma, urine, and feces after a single oral dose of [14C]-revumenib	

SNDX-5613-0706	Phase 1/2, open-label, randomized study (Phase 2)	≥ 18 years with MSS/pMMR, metastatic CRC, or other solid tumors	Phase 1: Starting dose: Revumenib; 163 mg TID capsule or 160 mg TID tablet continuously in 28-day cycles Planned dose levels are 50, 75, 113, 163, 226, 276 mg (capsule) and 50, 75, 110, 160, 220, and 270 mg (tablet) Phase 2 (randomized 2:1) Monotherapy – revumenib TID Investigators Choice – Lonsurf or Stivarga Revumenib dosed orally TID in continuous 28-day cycles either with capsules or tablets	Phase 1: Estimated: 56 Enrolled: 8 Phase 2: Estimated: 102	Primary Endpoints: • Occurrence of DLTs • Frequency, duration, and severity of TEAEs, TRAEs and SAEs • Incidence and shifts of clinically significant clinical laboratory abnormalities. • Change from baseline in other observations related to safety, including ECG and vital signs. • Disease control rate at 6 cycles (DCR6) • ORR Primary Objectives: • To determine the safety, tolerability, MTD, and RP2D of revumenib in patients with CRC and other solid tumors • To assess the anti-tumor effects of revumenib by investigator assessment	3 sites in the US

Note: Study SNDX-5613-0707, an Expanded Access Program study, initiated enrollment in Jul23. There were no SAEs from Study SNDX 5613 0707 reported by the time of the Study SNDX-5613-0700 data cutoff date. Available data from Single Patient Protocols (conducted under IND 142,693) is included in the Integrated Summary of Safety dataset. As of 04Aug23, revumenib has been administered to 50 patients (20 adult and 30 pediatric) under compassionate use single patient protocols, conducted under the commercial IND application.

The Applicant's Position:
The primary evidence of efficacy and safety for revumenib in patients with R/R acute leukemia is based on the ongoing Study SNDX-5613-0700. Efficacy data are derived from an interim analysis (IA) as of a data cutoff date of 24 Jul 2023. The efficacy-evaluable patients in Cohorts 2A+2B at the IA (N=57) were used to analyze the primary and secondary efficacy endpoints. These patients had received at least 1 dose of study drug (163 mg q12 with strong CYP3A4 azole antifungal), been centrally confirmed for mutational status, had at least 5% blasts in bone marrow at baseline (within 28 days prior to start of study treatment), and had been followed for 6months or discontinued earlier. The Phase 1 portion of Study SNDX-5613-0700 provides supportive efficacy data for patients and provides data to support the comparability of 163 mg q12h administered in the capsule formulation, on an empty stomach, to the proposed indicated dose of 276 mg q12h without co-administration of a strong CYP3A4 inhibitor, fasted or with a low-fat meal, in tablet form.

The FDA's Assessment:

FDA agrees with that the above list of clinical studies were included in the submission. Data from the expanded access Study SNDX-5613-0707 were not submitted due to early status of the study (b) (4)

7.2. Review Strategy

The FDA's Assessment:

The key materials used for the review of efficacy and safety included:
- NDA 218944
- Relevant published literature
- Relevant information in the public domain

The Applicant submitted the information from the Phase 1/2 clinical trial SNDX-5613-0700 for the assessment of the efficacy of revumenib monotherapy for relapsed or refractory KMT2Ar acute leukemias. The pooled Cohorts 2A+2B enrolled in SNDX-5613-0700 phase 2 were used by the Applicant as the pivotal cohort. Due to issues with the clinical trial assay (see Section 4.3), FDA chose to not use the clinical trial assay for the selection of the efficacy population (see FDA's Position in Section 8.1.1).

Studies SNDX-5613-0700, SNDX-5613-0702, SNDX-5613-0705, SNDX-5613-0706 and SNDX 5613 single-patient protocols (SPP) will be used for the review of safety.

The clinical reviewers' analyses were performed using JMP 17.0 (SAS Institute, Inc., Cary, NC) and MedDRA Adverse Events Diagnostic (MAED, FDA, Silver Spring, MD), version 4.1.0. The statistical reviewer's analyses were performed using R 4.0.5 (The R Foundation, https://www.r-project.org/).

8 STATISTICAL AND CLINICAL EVALUATION

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. SNDX-5613-0700

Title: A Phase 1/2, Open-label, Dose-Escalation and Dose-Expansion Cohort Study of SNDX-5613 in Patients with Relapsed/Refractory Leukemias, Including Those Harboring an MLL/KMT2A Gene Rearrangement or Nucleophosmin 1 (NPM1) Mutation

INVESTIGATIONAL PLAN

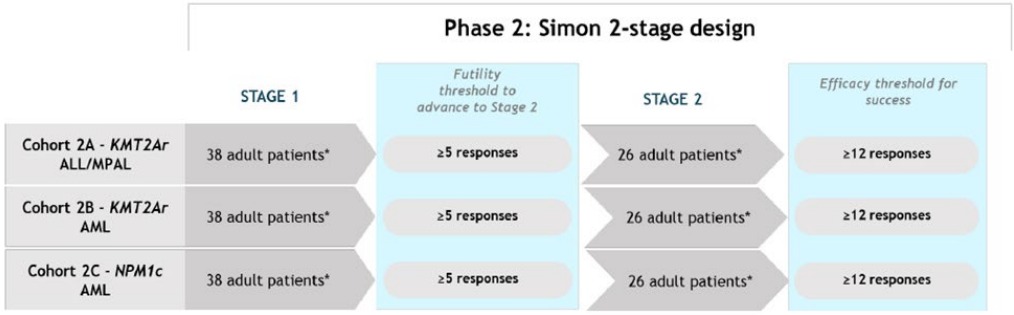
Trial Design

The Applicant's Position:

Basic Study Design
This is an ongoing, multicenter, Phase 1/2, open-label, dose-escalation, and expansion study of revumenib in adult and pediatric patients with R/R acute leukemia. Phase 1 of the study is described in the SNDX-5613-0700 CSR. In Phase 2, each of the cohorts was based on a Simon's 2-stage design (Simon 1989) to test the null hypothesis of CR+CRh rate ≤ 10%. There would be a futility IA and an efficacy final analysis for each of the cohorts.

An IA for superiority/efficacy for primary endpoint (CR+CRh rate) in a pooled population of adult and pediatric patients with *KMT2A*r acute leukemia (Cohorts 2A+2B) was conducted at the time of the pre-planned IA timepoint defined by the Simon's 2-stage design for Cohort B (*KMT2A*r AML).

Figure 7 Applicant – Phase 2 Dose Expansion Study Design Schema



*Up to an additional 20 pediatric patients may be enrolled, giving N = 84 patients per cohort.

Efficacy data included in this application are derived from an interim analysis (IA) as of a data cutoff date of 24 Jul 2023. The efficacy-evaluable patients in Cohorts 2A+2B at the IA were used to analyze the primary and secondary efficacy endpoints. These patients had received at least 1 dose of study drug (163 mg q12h with strong CYP3A4 azole antifungal), been centrally confirmed for mutational status, had at least 5% blasts in bone marrow at baseline (within 28 days prior to start of study treatment; Cohort 2A+2B Efficacy Evaluable Population; N=57). The analysis was performed when patients had been followed for at least 6 months or discontinued earlier. The CR+CRh rate in the pooled *KMT2A*r population (Cohort 2A+2B) was the primary hypothesis which was formally tested in this IA, which is described further in the Statistical Analysis Plan section below.

The Phase 1 portion of SNDX-5613-0700 provides supportive efficacy data for patients and provides data to support the comparability of 163 mg q12h administered in the capsule formulation, on an empty stomach, to the proposed indicated dose of 270 mg BID without co-administration of a strong CYP3A4 inhibitor, with or without food, in tablet form.

Trial Location

The study was sponsored by the Applicant and conducted by qualified investigators in the US only for Phase 1 and in Australia, Canada, France, the Netherlands, and the US for Phase 2. No issues were identified with respect to the applicability of the results from other regions to the US population.

Blinding

This is a single-agent, open-label study; no blinding methods were employed.

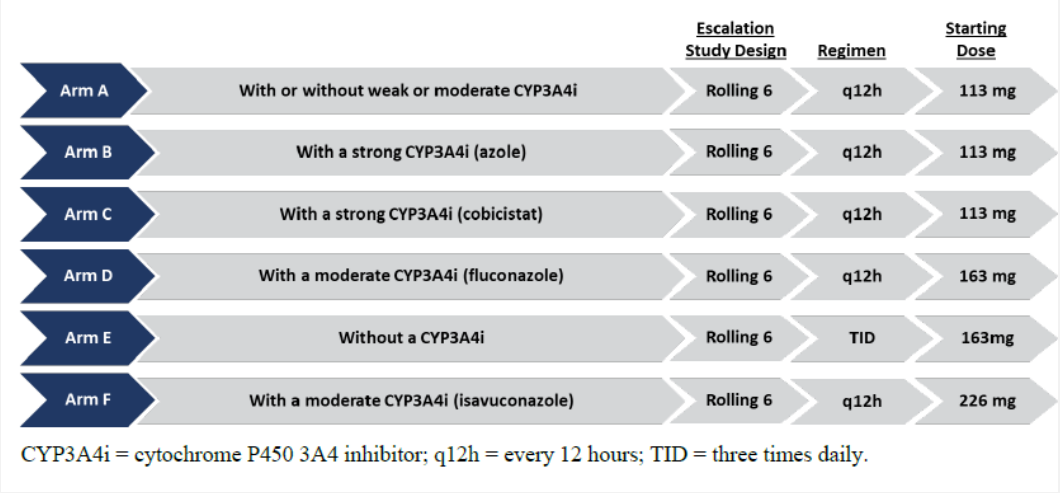
Administrative Structure

Throughout the study, the Safety Review Committee and Independent Data Monitoring Committee monitored safety and efficacy as specified in the respective Charters.

The FDA's Assessment:

FDA confirms the design of the Phase 2 trial as shown in Figure 8. The dose-escalation design schema for the Phase 1 portion is shown below.

FDA Figure 8. Phase 1 Dose Escalation Study Schema



Source: SNDX-5613-0700 Clinical Study Report Figure 1.

New Arm G was added on November 8, 2023, to collect PK and safety data (b) (4) of SNDX-5613 and to characterize excretion pathways and metabolite identification profiling.

	CYP3A4 inhibitor	(b) (4) dosing
ARM G	With a strong CYP3A4 inhibitor	163 mg q12h
	Without strong CYP3A4 inhibitor	276 mg q12h

Source: SNDX-5613-0700 protocol version 17.0.

Key Eligibility Criteria

The Applicant's Description:

Patients who were 30 days or older with R/R acute leukemia were eligible for inclusion in the study. Patients with active diagnosis of acute promyelocytic leukemia, or active central nervous system (CNS) disease were excluded. After Protocol Amendment 12 (14 Apr 2022), all patients were required to have a white blood cell (WBC) count below 25,000/µL at the time of enrollment. For the pivotal Phase 2 Cohorts (Cohort 2A + 2B), patients were required to have documented R/R acute leukemia with *KMT2A*r, defined by presence of ≥ 5% blasts in the bone marrow and/or persistence or reappearance of blasts in peripheral blood.

The FDA's Assessment:

The key inclusion criteria are listed below:

- Relapsed or refractory AML, ALL, or MPAL with a KMT2Ar by local testing
- Documented ≥ 5% marrow blasts
- WBC < 25 Gi/L
- No active CNS disease or extramedullary disease
- Age 30 days and older
- ECOG performance 0-2 for individuals 18 and older, Karnofsky performance > 50 for individuals 16 to < 18 years old, and Lansky performance score of > 50 for individuals < 16 years old
- Adequate organ function (GFR ≥ 60 mL/min/1.73 m^2, bilirubin < 1.5x ULN, aminotransferases < 3x ULN, LVEF ≥ 50%)
- QTcF < 450 msec

Treatment Plan

The Applicant's Description:
Revumenib was administered orally (PO) in 28-day cycles via capsule, tablet, or oral solution, with the first study drug dose administered on C1D1. In Phase 2, patients received the RP2D of 163 mg q12h taken with a strong CYP3A4 inhibitor (systemic itraconazole, ketoconazole, posaconazole, or voriconazole), as determined from Arm B of Phase 1. Dose adjustments were allowed for patients who stop taking a strong CYP3A4 inhibitor.

The FDA's Assessment:

FDA agrees in general with the Applicant's description of the treatment plan. Additional dose modifications were made for treatment-emergent adverse events. The table below shows the planned dose reduction levels with or without a strong CYP3A4 inhibitor.

Revumenib Dose Reduction Levels

	SNDX-5613 with a strong CYP3A4i		**SNDX-5613 without a strong CYP3A4i**	
	Capsule, ≥40 kg	*Tablet, ≥40 kg*	*Capsule, ≥40 kg*	*Tablet, ≥40 kg*
Starting Dose	163 mg q12h	160 mg q12h	276 mg q12h	270 mg q12h
Dose Reduction 1	113 mg q12h	110 mg q12h	163 mg q12h	160 mg q12h
Dose Reduction 2	113 mg QD	110 mg QD	113 mg q12h	110 mg q12h
	SNDX-5613 with a strong CYP3A4i		**SNDX-5613 without a strong CYP3A4i**	
	Oral Solution, <40 kg		*Oral Solution, <40 kg*	
Starting Dose	95 mg/m^2 q12h		160 mg/m^2 q12h	
Dose Reduction 1	65 mg/m^2 q12h		95 mg/m^2 q12h	
Dose Reduction 2	65 mg/m^2 QD		65 mg/m^2 q12h	

Source: SNDX-5613-0700 protocol version 17 Table 10

Schedule of Assessments

The Applicant's Description:

A list of all assessments and visits is provided in the SNDX-5613-0700 Protocol.

The FDA's Assessment:

Refer to Appendix 14.6 for the detailed Schedule of Activities.

Key efficacy assessments:

- Bone marrow aspirate and biopsy at screening, first day of each cycle (+ 7 days) through at least C5D1, continuing on the first day of each cycle for those who do not achieve CR or CRh, and as indicated clinically for those who do achieve CR or CRh.
- BM aspirate and biopsy will be repeated at anytime peripheral blood shows evidence of progressive disease.
- CBC at screening, every 3-4 days during Cycle 1, Days 1, 8, and 15 of Cycle 2, and Day 1 of each cycle thereafter.
- Hematology lab results used to determine the response assessment should be within a window of -7 to + 15 days of bone marrow examination date.
- CSF evaluation at screening for high-risk cases and as indicated clinically thereafter.
- Directed physical exam at each study visit.

Special safety assessments:

- Holter monitoring was to be performed for all patients in Phase 1 continuously from 30 minutes (±10 minutes) before the first study drug dose through 48 hours thereafter.
- EKGs at baseline, Days 2, 3/4, 7/8, 10/11, 14/15, 17/18, 21/22 of Cycle 1, Cycle 2 Day 15, Day 1 of subsequent cycles, and prior to and after initiation of any concomitant medication known to prolong the QTcF interval.
- Magnesium, potassium, calcium should be obtained if a patient experiences Grade ≥ 2 QTcF prolongation.
- Ophthalmologic examination (including slit lamp examination) are performed at baseline, C4D1 (-3/+5 days) and every 3 cycles thereafter or more frequently if clinically indicated and at the end of treatment or safety follow-up visit.

Study Endpoints

The Applicant's Description:

The primary endpoints for Phase 2 were CR+CRh rate; frequency, duration, and severity of TEAEs, TRAEs, and SAEs; incidence and shifts of clinically significant clinical laboratory abnormalities; and change from baseline in other observations related to safety, including ECGs,

vital signs, ophthalmologic examination findings, and performance status. Phase 2 also included other measures of efficacy (endpoints of transfusion independence, composite definition of CRc [CR+CRh+Cri+CRp], ORR, TTR, duration of response [DOR] and EFS, OS), and PK and PD characteristics.

The FDA's Assessment:

The primary efficacy endpoint for Phase 2 was CR/CRh using the following definition:

- **Complete remission (CR)**: Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 × 10^9/L (1000/μL) and platelet count ≥100 × 10^9/L (100 000/μL).
- **CR with partial hematologic recovery (CRh)**: Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; residual neutropenia (>0.5 × 10^9/L [500/μL]) and thrombocytopenia (>50 × 10^9/L [50 000/μL]).

Source: SNDX-5613-0700 protocol version 17 Section 8.1.2

The secondary endpoints included:

- Transfusion independence defined as any transfusion-free period lasting for 56 consecutive days during which the patient is either on revumenib or following withdrawal from revumenib but before start of new therapy.
- Duration of response defined as the date of first documented CR/CRh (corresponding to the date of bone marrow sampling) to the first documented relapse or death.

No estimands were included in the protocol or statistical analysis plan (SAP).

Statistical Analysis Plan and Amendments

The Applicant's Description:

In Phase 2, each of the cohorts was based on a Simon's 2-stage design to test the null hypothesis of CR+CRh rate ≤ 10%, which is considered the lower bound for antileukemic activity in patients with R/R acute leukemia with *KMT2A*r and who have no available therapeutic options (DiNardo 2020; Issa 2021a; Roboz 2014; Stahl 2018; Stahl 2021). This lower bound is supported by outcomes in *KMT2A*r patients, where a CR+CRi rate of only 9% is observed at ≥ 3 lines of conventional treatment (Issa 2021a). CR rate in this publication was 5%. CR+CRh rate was not reported. A superiority/efficacy IA for primary endpoint (CR+CRh rate) in the pooled *KMT2A*r population (Cohort 2A +2B adults and pediatrics) was conducted at the time of the pre-planned IA timepoint defined by the Simon's 2-stage design for Cohort 2B (*KMT2A*r AML). The first stage of the Simon's 2-stage design consisted of the first 38 adult efficacy evaluable patients. When the 38 adult efficacy evaluable patients in Cohort 2B were enrolled,

there were 57 patients in the Efficacy Evaluable Population for IA: Cohorts 2A + 2B. The efficacy boundary of ≥ 12 CR+CRh responders was determined based on the actual number of efficacy evaluable patients available for the IA (N=57) using fixed alpha spend at the IA by controlling the overall alpha under 0.025. If this boundary was met, enrollment into Cohorts 2A and 2B was to be stopped early for efficacy. In response to Agency feedback, the protocol and SAP were updated post-database freeze to clarify the timing of the IA. Protocol version 17 amendment 16 (08 Nov 2023) and SAP version 5 (10 Nov 2023) were developed to specify that the futility interim analysis would be performed when the first 38 adult efficacy evaluable patients have had 6 months of follow-up or have discontinued therapy. Additional descriptions of statistical methods are summarized in the SNDX-5613-0700 CSR, Section 3.7.

The FDA's Assessment:

The major design change of pooling across disease types and age groups was made in protocol version 15.0 dated 30 September 2022. FDA did not object to this change with the rationale of the mechanism of action being age and leukemia agnostic. The definition of primary efficacy analysis population was further clarified in protocol version 16.0 dated 11 August 2023 to include all the KMT2Ar patients with confirmed mutation and treated at RP2D, regardless of age and disease type. An efficacy interim analysis based on such a pooled population was added in protocol version 17.0 dated 8 November 2023 was to be triggered by only enrollment of Cohort 2B adult patients. Given Simon 2-stage was employed to enroll Cohort 2B adult patients, the timing of interim and final analysis for the pooled population were determined at the end of Stage 1 and 2 of Cohort 2B. These amendments are summarized in Table 40.

With the above protocol amendments, the enrollment of adult patients was conducted according to a Simon 2-stage design within each disease cohort, and additional pediatric patients were enrolled, but the overall efficacy analysis was pooled across age and disease types. Given these amendments, the sponsor proposed an efficacy boundary determined by the exact binomial boundary from a group sequential trial. For this calculation, the sample size of the pooled population was projected to be 102 at final analysis, and the efficacy boundary with the observed 57 patients was estimated to be 0.0097 (1-sided).

As the prespecified efficacy analysis population required the central confirmation of mutation status, whose data was determined as invalid by FDA (see Section 4.3), FDA concluded that a cohort identified by conventional testing locally may be a better representation of patients with KMT2A translocations (see Section 4.3). In the following sections under "FDA's position", FDA refers to the prespecified efficacy analysis set as the *Pivotal Cohort* and defined an additional analysis set, the *Efficacy Cohort*, which included acute leukemia patients in Phase 1 and 2 with an 11q23 translocation by local assay and baseline blasts at least 5%, treated with at least one dose of study drug at the recommended dosage, and completed the Cycle 7 Day 1 visit, or discontinued earlier, or responded earlier.

Protocol Amendments

The Applicant's Description:

The first patient was enrolled under SNDX-5613-0700 protocol version 3, amendment 2 (26 Jun 2019) and the conduct of the study has been modified by 15 amendments and other country-specific amendments as of the data cutoff of 24 Jul 2023. Key changes and rationale under each substantial amendment prior to the data cutoff are summarized in SNDX-5613-0700 Protocol, Appendix 16.1.1. Changes to the study conduct were made prior to database freeze for the interim analysis, thus are not considered to impact the interpretation of the study results presented in this report. Protocol version 17 amendment 16 (08 Nov 2023) dated after the data freeze was developed in response to Agency feedback and corresponded to the SAP version 5 (10 Nov 2023).

The FDA's Assessment:

FDA Table 40. Protocol Amendments for Study SNDX-5613-0700

Protocol version	Date	Key Changes
Original version	May 29, 2019	Initial version
Version 2.0	June 21, 2019	• Require WBC below 50,000/µL at enrollment • Clarify assays and central laboratories confirming KMT2Ar and NPM1 mutation • Modify exclusion criteria for QTc prolongation to be gender specific, transplant patients have to be off calcineurin inhibitor for at least 4 weeks. • Add criteria that subjects will discontinue treatment after 4 cycles if a PR is not achieved. • Revise safety stopping rule to include: o any non-hematologic TEAE not resulting directly from active leukemia that leads to permanent discontinuation, results in a patient receiving less than 80% dose intensity in the first two cycles, or requires more than one dose interruption o any hematologic TEAE resulting in more than one dose reduction in the absence of residual leukemia
Version 3.0	June 26, 2019	• Revise the stopping rule to include specific bounds to be used to pause the study for toxicity in Phase 2.
Version 4.0	October 8, 2019	• Add MRD to be included in the local assessment.
Version 5.0	January 14, 2020	• Clarify washout window of 14 days for all anti-leukemia therapy including targeted therapies • Permit concomitant use of hydroxyurea with SNDX-5613 for cytoreduction
Version 6.0	February 15, 2020	• Dose escalation was divided into two arms, Arm A and Arm B, to distinguish between patients receiving or not receiving a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer as antifungal prophylaxis at the start of SNDX-5613 • Modify primary endpoints to specify Arm A and Arm B will be assessed independently.

FDA Table 40. Protocol Amendments for Study SNDX-5613-0700

Protocol version	Date	Key Changes
		• Revised the exclusion criteria to reflect that concurrent use of strong inhibitors or inducers of CYP3A4 are not allowed in Phase 1 Arm A or Phase 2. • Increased the sample size for Phase 1 from 30 to 54 patients with up to 30 patients in Arm A and up to 24 patients in Arm B. This increased the overall sample size for the study from 132 to 156 patients.
Version 7.0	March 31, 2020	• Reduced the frequency of ophthalmologic examinations based on inability to obtain such non-essential exams during COVID-19 pandemic • Increased the threshold for a QTc prolongation that would be considered a DLT from any Grade 2 to any Grade 3 QTc prolongation. • Dose modification during the DLT period was modified as "Withhold treatment for any Grade 2 QTc prolongation ≥ 481 msec. SNDX-5613 should be resumed without dose modification as soon as the QTc has returned to Grade 1. Any ≥Grade 3 QTc prolongation is defined as a DLT (see Section 6.1.2)."
Version 8.0	April 27, 2020	• Adjusted the design of the dose escalation phase to allow up to 6 patients per Arm and dose level if at least 1 patient experiences a response CRc in order to gain additional safety data and explore efficacy information in more patients before starting Phase 2 of the study.
Version 9.0	July 15, 2020	• The age was changed from > 18 years to > 30 days • Change inclusion criteria to include only R/R acute leukemia harboring an MLL rearrangement or NPM1c mutation to be enrolled in phase 1. Previous language included only agnostic genetic mutation status. • Add that the study will include a food effect evaluation in 12 patients who enroll into either the Phase 1 or Phase 2 portion of the study. • Add BSA-based dosing for patients < 40 kg. • Changed the dose escalation design from accelerated titration leading to a 3+3 to a Rolling 6 escalation design • Increased the expansion of dose levels from "6 patients" to "up to 12 patients" and added "after the cohort has been cleared by the SRC" • Clarified that only adult patients (≥ 18 years) would contribute to the primary Phase 2 efficacy study objective. • Clarified that adult and pediatric patients would contribute to the secondary Phase 2 efficacy study objective. • Add to assess post base-line transfusion independence to secondary objectives. • Allow use of G-CSF in pediatrics and adults. • Add dose modification of SNDX-5613 when a strong CYP3A4 inhibitor was discontinued.
Version 9.1	July 22, 2020	

FDA Table 40. Protocol Amendments for Study SNDX-5613-0700

Protocol version	Date	Key Changes
Version 10.0	September 25, 2020	• Adjusted the exclusion criteria and dosages for the Phase 2 portion of the study to allow for patients who are receiving the strong CYP3A4 inhibitors
Version 11.0	January 29, 2021	• To add a dose-escalation arm to the Phase 1 portion of the protocol to evaluate SNDX-5613 in combination with cobicistat
Version 12.0	September 24, 2021	• Clarified the patients who will be included in the dose intensity evaluation in Cycle 1 and Cycle 2, for the definition of the RP2D. • Clarified that patients enrolled into Arm B back-fill cohorts at 163 mg q12h after 23 September 2021 will prospectively be included in Phase 2 • Updated the Simon's 2-stage design for the adult evaluable population using the null hypothesis of 10%, target CR rate of 25% and power of 90%. The sample was correspondingly updated • Clarify that patients post-transplant should be followed for survival. • Add the option for patients to remain on study during HSCT and resume SNDX-5613 treatment post-transplant. • Adjusted the dose modifications for hematologic toxicities to reduce the time prior to holding the dose and lengthening the time for a patient's counts to return to within a normal range.
Version 13.0	April 14, 2022	• Added dose modification directions for ≥Grade 3 peripheral neuropathy • Provided further clarification on the identification and treatment of the AESI of differentiation syndrome. • Reduced the WBC count inclusion criterion from < 50,000/μL to < 25,000/μL.
Version 14.0	June 27, 2022	• Patients with the NUP98 genotype can be enrolled in Phase 1. • Arm E was added to characterize SNDX-5613 TID dosing without CYP3A4 inhibitor, and to determine the dose needed to match the exposure of SDNX-5613 when given with a strong CYP3A4 inhibitor at the RP2D. • Arm F was added to characterize SNDX-5613 dosing with a moderate CYP3A4 inhibitor, isavuconazole, and to determine the dose needed to match the exposure of SDNX-5613 when given with a strong CYP3A4 inhibitor at the RP2D, based on Phase 1 PK data suggesting effects of isavuconazole on SNDX-5613 exposure. • Added details of the Phase 1 Capsule versus Tablet Evaluation in Phase 1. • Added details of the food effect evaluation • Added option for 35 additional patients to enroll in the study to ensure large enough sample size to collect adequate data on each drug formulation to assess safety, efficacy, and PK as needed. • Added text to allow for prophylactic intrathecal chemotherapy in phase 1 and for phase 2 backfill patients. • For consistency across SNDX-5613 protocols, Grade 4 differentiation syndrome will not be considered a DLT if it resolves within 7 days.

FDA Table 40. Protocol Amendments for Study SNDX-5613-0700

Protocol version	Date	Key Changes
		• Additional guidance added around the use of hematopoietic growth factors in patients who have achieved remissions but have yet to recover counts. • New text to provide additional guidance to Investigators on resumption of SNDX- 5613 dose after HSCT with respect to CNIs and strong CYP3A4 inhibitors. • Defined criteria for "No response" as an additional disease response assessment • Updated based on 3 dose levels for Arm E (up to 276 TID) and 2 dose levels for Arm F (up to 276 q12h).
Version 15.0	September 30, 2022	• The primary endpoint analysis was updated to include a pooled analysis of all MLLr patients • An efficacy boundary for testing the primary hypothesis in adult AML was added to the interim analysis for Cohort 2B as measured by CR/CRh rate (lower bound of 95% CI >13%). • Pediatric Phase 2 cohort size amended to allow for up to 20 patients < 18 years of age to enroll in each cohort.
Version 15.1	January 18, 2023	• In secondary objectives, changed BORR to ORR and added MLFS to CRc+PR • Update the use of a 56-day period to define transfusion independence. • Expanded window for baseline ophthalmologic exams to up to 28 days prior to Cycle 1 Day 1 through Cycle 1 Day 4 • Added Next Generation Sequencing (NGS) as an additional central confirmation method • Provide additional clarification on steroid dosing for differentiation syndrome management
Version 15.2	June 27, 2023	• Switched the order of the hierarchical testing procedure to test the pooled MLLr population (AML, ALL/MPAL, adults and pediatrics) as the Primary Analysis #1 and the adult MLLr AML population as the Primary Analysis #2
Version 16.0	August 11, 2023	• Specify that patients who have not achieved at least MLFS by 4 cycles should be taken off therapy • Updated definition of efficacy evaluable population: • Update CBC to within 7 to +15 days of the bone marrow collection for the response assessment, and require repeat bone marrow collection through at least Cycle 5 • Removed Next Generation Sequencing (NGS) as a central confirmation method for MLLr or NPM1 mutational status
Version 17.0	November 8, 2023	• Added new arm G in phase 1 to collect PK and safety data for the (b) (4) formulation of SNDX-5613, and to characterize excretion pathways and metabolite identification profiling. • Updated total sample size up to 413 patients • Added justification of the RP2D of 276 mg SNDX-5613 without a strong CYP3A4 inhibitor. • Added that patients with NPM1m acute leukemia are not eligible to enroll in Arm G.

FDA Table 40. Protocol Amendments for Study SNDX-5613-0700

Protocol version	Date	Key Changes
		• Update timing of interim analysis for Cohorts 2A and 2B will have at least 6 months follow-up. • Timing of descriptive efficacy analysis for Phase 1 and Phase 2 Cohorts 2A and 2B (at least 4 months follow-up), and timing of interim and final analyses of Phase 2 Cohort 2C (at least 4 months follow-up).

Source: Adapted from Study SNDX-5613-0700 Clinical Study Report Appendix 16.1.1

STUDY RESULTS - APPLICANT'S POSITION

Compliance with Good Clinical Practices

Data:

The protocol for this study was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The conduct of all aspects of the study, including methods of obtaining informed consent, were also in accordance with principles enunciated in the declaration, the ICH GCP, and applicable regional regulations/guidelines.

The Applicant's Position:

No significant GCP compliance deficiencies were identified during investigator site audits conducted by the Applicant.

Financial Disclosure

Data:

A financial disclosure review of SNDX-5613-0700 has been conducted and disclosure of financial interests and/or arrangements, including statements of due diligence for the investigators who conducted the study are described in FDA forms 3454, 3455 and Module 1.3.4.

The Applicant's Position:

The integrity of the data in SNDX-5613-0700 was not affected by the financial interests of the investigators.

Data Quality and Integrity

Data:

No issues were identified with the data quality or integrity from SNDX-5613-0700 which could affect the efficacy results. Study centers were monitored by (b) (4) Centers were visited in person at regular intervals prior to COVID-19 restrictions (March 2020) and a Visit Log was maintained. During the pandemic, remote visits were utilized to continue with oversight of study conduct and data collection and integrity. Following the pandemic, a combination of remote and in person visits were conducted, depending on restrictions to site access. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data. Direct access to patient medical and laboratory records was permitted to verify entries on the study-specific electronic case report forms.

The Applicant's Position:

No data integrity concerns reported during the study impacted evaluation.

Patient Disposition

Data:

A total of 57 adult and pediatric patients were included in the Efficacy Evaluable Population for the IA (pooled population). The most frequent reasons for discontinuation from study treatment in the pooled population were PD (26 patients [45.6%]), achieved remission and underwent HSCT (14 patients [24.6%]), and adverse events (AE) (9 patients [15.8%]). Of the 14 patients who proceeded to transplant, 7 patients resumed revumenib after transplant. The patient status was collected until death or until the patient was lost to follow-up. Discontinuation from the study overall was mainly due to the death of the patient (35/36 patients who discontinued from the study). Patient's disposition and reasons for discontinuation of study treatment were consistent for adult and pediatric patients in patients with *KMT2A*r AML (Cohort 2B) and *KMT2A*r ALL/MPAL (Cohort 2A) versus the overall population (SNDX-5613-0700 CSR, Table 14.1.2.2.4)

The Applicant's Position:

The most frequent reasons for treatment discontinuation were PD, achieved remission, underwent HSCT, and an AE.

Protocol Violations/Deviations

Data:

Major protocol deviations were reported for a total of 38 patients (30.4%) in the Phase 2 Safety Population, and were most frequently related to procedures / tests (12 patients [9.6%]), the study drug (9 patients [7.2%]), and other reasons (15 patients [12.0%]) (SNDX-5613-0700 CSR, Table 12). No COVID-19-related major protocol deviations were reported.

The Applicant's Position:

Major protocol deviations were assessed as not having a significant impact to the safety of patients or study conduct, and the patients involved were continued on study. These deviations are unlikely to impact the overall interpretation of the data.

Table of Demographic Characteristics

Data:

Summary of demographics characteristics are presented in Table 41.

Table 41 Applicant - Summary of Demographics (Efficacy Evaluable Population for the Interim Analysis)

Characteristic Subgroup/Statistic	Cohort 2A (N=8)	Cohort 2B (N=49)	Cohort 2A+2B (N=57)
Age (years)			
n	8	49	57
Mean (SD)	30.19 (21.679)	35.71 (20.956)	34.93 (20.951)
Median (Range: Min, Max)	30.50 (1.5, 68.0)	35.00 (1.3, 75.0)	34.00 (1.3, 75.0)
Age Group (years)			
Pediatric, n (%)			
0 < Age < 2	1 (12.5)	2 (4.1)	3 (5.3)
2 ≤ Age < 12	1 (12.5)	6 (12.2)	7 (12.3)
12 ≤ Age < 18	0	3 (6.1)	3 (5.3)
Adult, n (%)			
18 ≤ Age < 65	5 (62.5)	32 (65.3)	37 (64.9)
65 ≤ Age < 75	1 (12.5)	5 (10.2)	6 (10.5)
Age ≥ 75	0	1 (2.0)	1 (1.8)
Race			
Black or African American	1 (12.5)	3 (6.1)	4 (7.0)
Asian	0	6 (12.2)	6 (10.5)
White	6 (75.0)	37 (75.5)	43 (75.4)
Unknown	1 (12.5)	3 (6.1)	4 (7.0)
Race Group			
White	6 (75.0)	37 (75.5)	43 (75.4)
Non-white	1 (12.5)	9 (18.4)	10 (17.5)
Unknown	1 (12.5)	3 (6.1)	4 (7.0)
Sex			
Male	3 (37.5)	21 (42.9)	24 (42.1)
Female	5 (62.5)	28 (57.1)	33 (57.9)

Source: SNDX-5613-0700 CSR, Table 14.1.2.4.2.4

The Applicant's Position:

Patients in this study were represented across a broad age range, with balanced representation of male and female patients, and inclusion across races/ethnicities, and thus representative of the US patient population with this disease.

Other Baseline Characteristics

Data:

Overall, 49 patients (86.0%) in Cohorts 2A+2B (pooled population) had a primary diagnosis of AML, and 7 patients (12.3%) had a primary diagnosis of ALL (SNDX-5613-0700 CSR, Table 14.1.2.5.2.4.1). The most common baseline disease status in the pooled population was refractory relapse (32 patients [56.1%]), whilst 14 patients (24.6%) were primary refractory (SNDX-5613-0700 CSR, Table 14.1.2.5.2.4.3). Reflecting the aggressive course of *KMT2A*r acute leukemia, the median time from initial diagnosis to enrolment for adult and pediatric patients in the pooled population was less than 1 year (9.69 months; range: 1 to 89.5 months) (SNDX-5613-0700 CSR, Table 14.1.2.5.2.4.1).

The population was heavily pre-treated, with a median of 2 prior lines of therapy (range: 1 to 11) and 26 patients (45.6%) having received ≥ 3 prior lines. Most patients were previously treated with venetoclax (41 patients [71.9%]). A total of 26 patients (45.6%) in the pooled population had prior HSCT and 4 patients (7.0%) had more than 1 prior transplant (HSCT) (SNDX-5613-0700 CSR, Table 14.1.2.5.2.4.3).

The Applicant's Position:

This study enrolled a notably heavily pretreated population of R/R adult and pediatric patients with *KMT2A*r leukemia. Patients were represented with multiple leukemia subtypes (AML, ALL/MPAL, and range of *KMT2A* fusion partners). Patients' prior treatment was reflective of their aggressive disease.

Treatment Compliance

Data:

In Phase 2, a total of 4 patients had protocol deviations related to non-compliance with study medication. Two patients received an incorrect dose on at least 1 occasion. Despite individual missed doses, the mean (SD) and median RDIs were 90.13 (15.364) and 98.02, respectively (range: 35.0 to 101.1) in the Phase 2 Safety Population (SNDX-5613-0700 CSR Table 14.1.3.1.2.1).

The Applicant's Position:

Treatment compliance was well maintained with high median RDIs.

Concomitant Medications, and Rescue Medication Use

Data:

All 57 patients reported a concomitant medication, which were similar to those reported for the Phase 2 Safety Population. The most common concomitant medications by ATC level 2 were antimycotics for systemic use (per protocol) (100%), antibacterials for systemic use (96.5%), and antivirals for systemic use (93.0%). The most common concomitant medications by PT were paracetamol (47 patients [82.5%]), aciclovir (44 patients [77.2%]), and ondansetron and allopurinol (39 patients [68.4%] each) (SNDX-5613-0700 CSR, Table 14.1.2.7.2.2).

The Applicant's Position:

Concomitant medication use was representative of this patient population.

Efficacy Results – Primary Endpoint

Data:

The study met the primary efficacy endpoint at the IA crossing the pre-specified efficacy boundary for the Cohort 2A+2B Efficacy Evaluable Population for the IA (Table 42).

Table 42: Applicant - Summary of Response (Cohort 2A+2B Efficacy Evaluable Population for the Interim Analysis)

	Adults	Peds	Adult+Peds
	N = 44 n (%)	N = 13 n (%)	N = 57 n (%)
CR+CRh rate	**10 (22.7)**	**3 (23.1)**	**13 (22.8)**
95% CI	(11.5, 37.8)	(5.0, 53.8)	(12.7, 35.8)
p-value			0.0036
DOR for CR/CRh: Median (95% CI); months	4.3 (1.0, NR)	NR (NR, NR)	6.4 (3.4, NR)
CR rate	**9 (20.5)**	**1 (7.7)**	**10 (17.5)**
95% CI	(9.8, 35.3)	(0.2, 36.0)	(8.7, 29.9)
CRh rate	**1 (2.3)**	**2 (15.4)**	**3 (5.3)**
95% CI	(0.1, 12.0)	(1.9, 45.4)	(1.1, 14.6)
CRc rate (CR+CRh+CRp+Cri)	**20 (45.5)**	**5 (38.5)**	**25 (43.9)**
95% CI	(30.4, 61.2)	(13.9, 68.4)	(30.7, 57.6)
MRD Status			
CR/CRh with MRD Status Available	7	3	10
Negative	5 (71.4)	2 (66.7)	7 (70.0)
CRc with MRD Status Available	17	5	22
Negative in CR/CRh/CRp/CRi	12 (70.6)	3 (60.0)	15 (68.2)

Source: SNDX-5613-0700 CSR, Table 14.2.1.2.2 and Table 14.2.2.1.2.2.

The primary endpoint of CR+CRh rate was analyzed by various subgroups (

Figure 9). Patients achieved responses of CR+CRh across the various pre-specified subgroups including both AML and ALL and pediatric and adult patients (Table 43), and across the represented KMT2A fusion partners based on ad hoc analysis requested by the FDA (Table 44). The youngest responder was aged 1 year (CR), and oldest was aged 75 years (CR) (SNDX-5613-0700 CSR, Listing 16.2.6.1.1.2).

Table 43: Applicant – Summary of CR+CRh Rate by Leukemia Type and by Age (Efficacy Evaluable Population for Interim Analysis: Cohort 2A +2B)

	Leukemia Type		Age	
Endpoint	**AML** N=49	**ALL/MPAL** N=8	**< 18 Years** N=13	**≥ 18 Years** N=44
CR+CRh n (%)	12 (24.5)	1 (12.5)	3 (23.1)	10 (22.7)
95% CI	(13.3, 38.9)	(0.3, 52.7)	(5.0, 53.8)	(11.5, 37.8)
Median DOCR+CRh (months)	6.4	NR	NR	4.3
95% CI	(3.4, NR)	(NR, NR)	(NR, NR)	(1.0, NR)

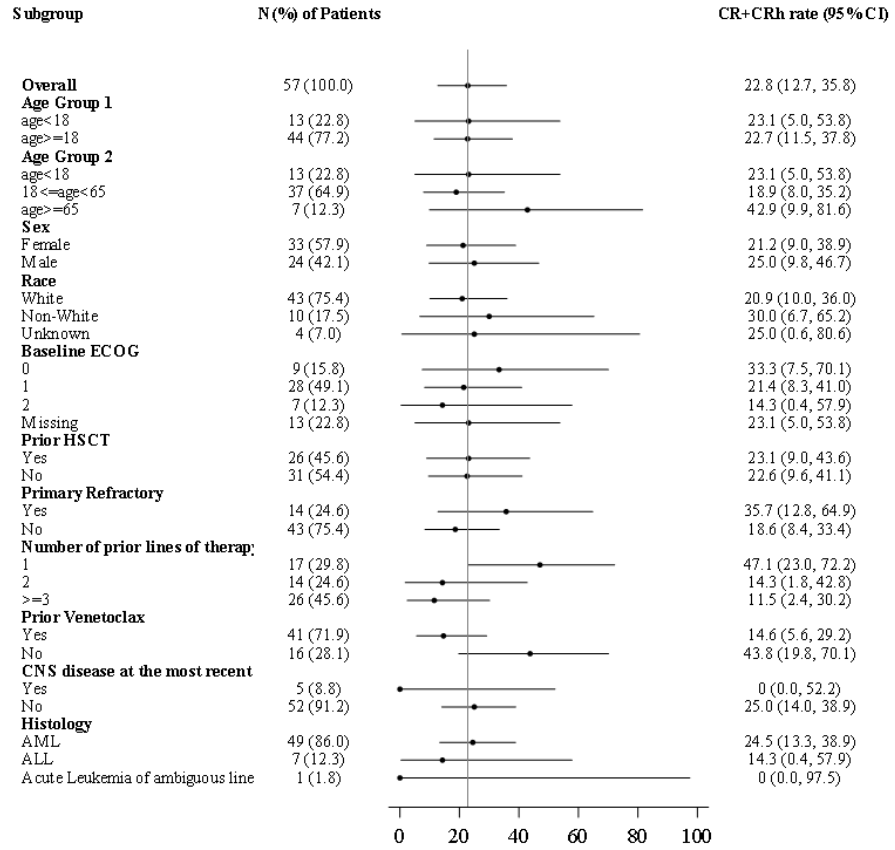
Source: SNDX-5613-0700 CSR, Table 14.2.1.2.3 and Table 14.2.2.1.2.3 (Cohort 2A) and Table 14.2.1.2.1 and Table 14.2.2.1.2.1 (Cohort 2B), Table 14.2.1.2.2 and Table 14.2.2.1.2.2

Table 44: Applicant - Summary of CR+CRh Rate Across *KMT2A*r Subgroups (Efficacy Evaluable Population for Interim Analysis: Cohort 2A +2B)

	Number of Patients with CR+CRh n/N	**CR+CRh rate % (95% CI)**
Overall	13/57	22.8 (12.7, 35.8)
KMT2A rearrangement/translocation		
4;11	0/2	0 (0.0, 84.2)
9;11	2/11	18.2 (2.3, 51.8)
11;19	2/13	15.4 (1.9, 45.4)
10;11	2/7	28.6 (3.7, 71.0)
6;11	2/7	28.6 (3.7, 71.0)
1;11	0/2	0 (0.0, 84.2)
KMT2A fusion partner unknown	4/13	30.8 (9.1, 61.4)
Other translocations	1/2	50.0 (1.3, 98.7)

Source: SNDX-5613-0700 CSR, Table 14.2.9.2.2.1

Figure 9: Applicant – Forest plot for CR+CRh rate (Efficacy Evaluable Population for Interim Analysis: Cohort 2A + 2B)



Source: SNDX-5613-0700 CSR, Figure 14.2.9.2.2

The Applicant's Position:

In a heavily pre-treated population including younger patients relapsed post-transplant and older patients relapsed after venetoclax, the SNDX-5613-0700 Phase 2 study in *KMT2A*r leukemia met the primary efficacy endpoint for CR+CRh at the IA. CR+CRh responses were rapid, durable, and observed across leukemia subtypes (AML and ALL) and *KMT2A*-fusion partners, across patients with varied number and types of prior therapies including those with prior transplant, across different races/ethnicities, and irrespective of age, gender, confirming that *KMT2A*r is the common driver and sensitive to menin inhibition. Subgroup results should be interpreted with caution as the interim analysis was not powered to test statistical significance in these groups.

Efficacy Results – Secondary Endpoints

Duration of CR+CRh and Time to CR+CRh

Duration and time to CR+CRh are summarized in Table 45.

Table 45: Applicant – Summary of Duration of CR+CRh and Time to First CR+CRh in Responders (Cohort 2A+2B Efficacy Evaluable Population for the Interim Analysis)

Characteristic	Adults (N=10) n (%)	Peds (N=3) n (%)	Adult+Peds (N=13) n (%)
DOR (months)			
Median (95% CI)	4.3 (1.0, NR)	NR (NR, NR)	6.4 (3.4, NR)
Estimated DoR Rate (95% CI)			
Month 3	90.0 (47.3, 98.5)	100.0 (100.0, 100.0)	91.7 (53.9, 98.8)
Month 6	47.3 (11.7, 77.0)	100.0 (100.0, 100.0)	58.9 (23.1, 82.6)
Time to Response (months)			
n	10	3	13
Mean (SD)	1.99 (1.092)	2.38 (1.481)	2.08 (1.135)
Median (Range: Min, Max)	1.87 (0.9, 4.6)	2.27 (1.0, 3.9)	1.87 (0.9, 4.6)
DOR for CR (months)			
Median (95% CI)	5.0 (1.0, NR)	NR (NR, NR)	5.0 (1.0, NR)
DOR for CRh (months)			
Median (95% CI)	3.4 (NR, NR)	NR (NR, NR)	NR (3.4, NR)

Source: SNDX-5613-0700 CSR, Table 14.2.2.1.2.2

Overall Response Rate and CRc Rate

The ORR (CRc+MLFS+PR rate) in adult and pediatric *KMT2A*r patients in Cohorts 2A and 2B was 63.2% (36/57 patients, 95% CI: 49.3, 75.6), with a median DOR of 4.3 months (95% CI: 1.9, NR) (Table 46). Responses were observed across fusion partner subtypes (SNDX-5613-0700 CSR, Table 14.2.9.2.2.2).

Overall response was based on the best pre-transplant response. Amongst the 36 patients in the pooled population who achieved a response, 14 patients (38.9%) (10 adult and 4 pediatric) proceeded to transplant (SNDX-5613-0700 CSR, Table 14.2.1.2.2.1). All 14 patients were in Cohort 2B (with *KMT2A*r AML) and included 8 patients who proceeded to transplant before achieving CR+CRh; 4 patients with a best pre-transplant response of CRp and 4 patients with a best response of MLFS. The remaining 6/14 patients who proceeded to transplant had a best pre-transplant response of CR+CRh (SNDX-5613-0700 CSR, Table 14.2.1.2.1.1). Eleven (11)/14 of the patients proceeding to transplant did so within 56 days of their best overall response (SNDX-5613-0700 CSR, Listing 16.2.6.1.2.2). Of the patients who proceeded to transplant, 6 patients with responses of CR+CRh pre-transplant also achieved CR+CRh post-transplant, and 5 patients with lesser responses (CRp/MLFS) pre-transplant achieved CR+CRh post-transplant (SNDX-5613-0700 CSR, Listing 16.2.6.1.1.2.1).

Table 46: Applicant - Overall Response Rate (Cohort 2A+2B Efficacy Evaluable Population for the Interim Analysis)

	Cohorts 2A+2B		
	Adults	**Peds**	**Adult++Peds**
	(N=44) n (%)	(N=13) n (%)	(N=57) n (%)
Overall response rate (CRc+MLFS+PR), n (%)	30 (68.2)	6 (46.2)	36 (63.2)
95% CI	(52.4, 81.4)	(19.2, 74.9)	(49.3, 75.6)
DOR: Median (95% CI) (months)	4.0 (1.9, 6.4)	NR (0.5, NR)	4.3 (1.9, NR)
Best Overall Response, n (%)			
Reponses contributing to ORR			
Complete remission (CR)	9 (20.5)	1 (7.7)	10 (17.5)
CR with partial hematologic recovery (CRh)	1 (2.3)	2 (15.4)	3 (5.3)
CR with incomplete platelet recovery (CRp)	10 (22.7)	1 (7.7)	11 (19.3)
CR with incomplete hematologic recovery (CRi)	0	1 (7.7)	1 (1.8)
Morphologic Leukemia-free state (MLFS)	9 (20.5)	1 (7.7)	10 (17.5)
Partial remission (PR)	1 (2.3)	0	1 (1.8)

Source: SNDX-5613-0700 CSR, Table 14.2.1.2.2 and Table 14.2.4.2.2

The CRc rate (CR+CRh+CRi+CRp rate) in adult and pediatric *KMT2A*r patients in Cohorts 2A+2B (pooled population) (N=57) was 43.9% (95% CI: 30.7, 57.6), with a median DOR of 5.2 months (95% CI: 3.1, NR), and median TTR of 1.05 months (range: 0.9 to 3.9 months). CRc rate was similar between adult and pediatric patients (SNDX-5613-0700 CSR, Table 14.2.3.2.2).

Event-Free Survival

The median EFS in adult and pediatric *KMT2A*r patients in Cohorts 2A+2B was 2.8 months (95% CI: 2.3, 5.6) (N=57). The estimated 3-month EFS rate was 46.3% (95% CI: 32.6, 59.0) (SNDX-5613-0700 CSR, Table 14.2.5.2.2).

Overall Survival

The median OS in adult and pediatric patients combined in Cohorts 2A+2B was 8.0 months (95% CI: 4.1, 10.9) (N=57). Median OS in adult patients was 8.0 months (95% CI: 4.1, 10.9) and pediatric patients was 6.9 months (95% CI: 2.3, NR) (SNDX-5613-0700 CSR, Table 14.2.6.2.2).

Transfusion Independence

A total of 46 patients (80.7%) in Cohorts 2A+2B Efficacy Population were RBC and platelet transfusion dependent at baseline (SNDX-5613-0700 CSR, Table 14.1.2.5.2.4.4). Eight (8) out of 46 patients (17.4%) who were transfusion dependent at baseline were independent of RBC and platelet transfusions for at least 56 days post-baseline (Table 47). Five out of 11 patients (45.5%) who were independent of RBC and platelet transfusions at baseline remained transfusion-independent for at least 56 days post-baseline.

Table 47: Applicant – Summary of Transfusion Independence Status (Cohort 2A+2B Efficacy Evaluable Population for the Interim Analysis)

	Post-baseline Transfusion Status		
Baseline Transfusion Status	**Dependent n (%)**	**Independent n (%)**	**NE n (%)**
Red Blood Cells and Platelets			
Dependent (n = 46)	38 (82.6)	8 (17.4)	0
Independent (n = 11)	5 (45.5)	5 (45.5)	1 (9.1)
Total (n = 57)	43 (75.4)	13 (22.8)	1 (1.8)

Source: SNDX-5613-0700 CSR, Table 14.2.11.2.2.

Generally, a greater proportion of adult and pediatric patients in Cohorts 2A+2B with responses of CR+CRh achieved (57.1%) or maintained (50.0%) both platelet and RBC transfusion independence compared to those with lesser or no responses (SNDX-5613-0700 CSR, Table 14.2.12.2.2).

The Applicant's Position:

Measures supporting clinical benefit in this otherwise palliative population included durability of CR+CRh, overall survival, ORR, transfusion independence and the ability of nearly a quarter of patients to proceed to potentially curative transplant.

Efficacy Results - Exploratory Efficacy Endpoints

In Phase 1 of SNDX-5613-0700, 77 patients with R/R *KMT2A*r leukemia were enrolled, including 17 *KMT2A*r leukemia patients who were treated at the RP2D; 13 patients at 276 mg q12h without a strong CYP3A4i (Arm A) and 4 patients at 163 mg q12h with a strong CYP3A4i (Arm B) (SNDX-5613-0700 CSR, Table 14.1.2.1.2). Patients treated at the RP2D in Arms A+B in Phase 1 were comparable to Cohorts 2A+2B in Phase 2 and population was heavily pre-treated, with a median of 3 prior lines of therapy (range: 1 to 9) and 11 patients (64.7%) having received ≥ 3 prior lines (SNDX-5613-0700 CSR, Table 14.1.2.5.1.2.3).

Investigator-reported CR+CRh rate, median duration of CR+CRh, ORR, and median duration of overall response were similar between these patients in the Phase 1 and Phase 2 studies (Table 11). Similar to Phase 2 Cohorts 2A+2B, responses were observed across a broad age range (1 to 82 years) (SNDX-5613-0700 CSR, Listing 16.2.6.1.1.1), and in both AML and ALL (SNDX-5613-0700 CSR, Listing 16.2.4.2.1.1). Five (5) out of 12 responders proceeded to transplant in remission (SNDX-5613-0700 CSR, Listing 16.2.6.1.2.1).

Table 11 Applicant – Summary of Response in *KMT2A*r Patients in Phase 1 and Phase 2 Treated at the RP2D

	Phase 1	Phase 2
Endpoint	Pooled *KMT2A*r patients treated at the RP2D (Arms A+B) (N=17)	Pooled *KMT2A*r patients (Cohorts 2A+2B) (N=57)

CR+CRh rate (95% CI)	29.4% (10.3, 56.0)	22.8% (12.7, 35.8)
DOR for CR+CRh: Median (95% CI) (months)	6.3 (2.7, NR)	6.4 (3.4, NR)
ORR (95% CI)	70.6% (44.0, 89.7)	63.2% (49.3, 75.6)
DOR for overall response: Median (95% CI) (months)	7.3 (1. 9, NR)	4.3 (1.9, NR)
CRc rate (95% CI)	47.1% (23.0, 72.2)	43.9% (30.7, 57.6)
MRD Status		
CR/CRh with MRD status available	5	10
Negative	4 (80.0)	7 (70.0)
CRc with MRD status available	8	22
Negative	7 (87.5)	15 (68.2)

Source: SNDX-5613-0700
CSR, Table 14.2.1.1.2, Table 14.2.2.1.1.2, Table 14.2.1.2.2, Table 14.2.2.1.2.2, Table 14.2.4.1.2, and Table 14.2.4.2.2

The Applicant's Position:

Exploratory efficacy endpoints in the Phase 1 study, including remission rates and durability of remission in the patients treated at the subsequently identified RP2D, were similar to results seen in the Phase 2 study at the IA, providing supportive evidence of efficacy in a comparable population.

Dose/Dose Response

Data:

There was no significant E-R efficacy relationship between the primary clinical efficacy endpoint (CR+CRh rate) and $C_{max,ss}$, $C_{avg,ss}$, $C_{min,ss}$. There was a statistically significant inverse relationship between TAE and CR+CRh (p=0.016); however, the TAE metric is confounded in this analysis. There was no significant E-R efficacy relationship between the other secondary efficacy endpoints (ORR, EFS or OS) for any of the 4 revumenib exposure metrics. Consistent with primary endpoint analysis, exploratory data analysis from Phase 1 and Phase 2 showed that all dose levels led to statistically significant downregulation of leukemogenic, and upregulation of myeloid differentiation genes, with no clear correlations between exposures and expression, suggesting that all dose levels explored in this study were at the top of the concentration-response curve. Simulations indicated that doses below the proposed dose would not achieve the targeted preclinical IC_{90}.

The Applicant's Position:

At the proposed indicated dose (163 mg q12h with a strong CYP3A4i), the Phase 2 study met the primary efficacy endpoint for the indicated population. The proposed dose met all requirements for an optimal dose, including target engagement, safety, and efficacy.

Durability of Response

Data:
Patients achieved CR or CRh as early as 1 month, with median time to response (TTR) for *KMT2A*r patients in Cohorts 2A + 2B of 1.87 months (range: 0.9 to 4.6 months). The median duration of CR/CRh was 6.4 months (95% CI: 3.4, NR). Estimated DOR rate at Month 6 was 58.9% (95% CI: 23.1, 82.6).

The Applicant's Position:
Durable CR + CRh responses represent a substantial improvement over historic controls, in an otherwise palliative population in whom historic OS is 2 to 3 months.

Persistence of Effect

Data:

This application includes 57 patients in the Efficacy Evaluable Population for IA in Phase 2, with a median duration of treatment of 10.4 weeks (range: 1 to 36 weeks). The median duration of CR+CRh was 6.4 months (95% CI: 3.4, NR), and median duration of overall response was 4.3 months (95% CI: 1.9, NR). *KMT2A*r leukemia patients at the RP2D in Phase 1 (N=17), had a median treatment duration of 10.0 weeks (range: 1 to 89 weeks). The median duration of CR+CRh in these patients was 6.3 months (95% CI: 2.7, NR), and median duration of overall response was 7.3 months (95% CI: 1. 9, NR). Responses as long as 1.4 years (521 days, CRc) in a *KMT2A*r AML patient in Phase 2 (Cohort 2B) and 1.3 years (480 days, CRh) in a *KMT2A*r AML patient in Phase 1 (treated at the RP2D of 276 mg q12h in Arm A) have been observed.

The Applicant's Position:

There are limited data on long-term disease control.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:
N/A

The Applicant's Position:
N/A

Additional Analyses Conducted on the Individual Trial

Data:
N/A

The Applicant's Position:
N/A

STUDY RESULTS - FDA'S POSITION

Compliance with Good Clinical Practices

The Clinical Study Report indicated that the trial was conducted in compliance with Good Clinical Practice (GCP). The Applicant provided certificates for 12 vendor audits and 3 clinical site audits (Sites 01, 09, and 10).

In the 2/15/2024 RIR, the Applicant identified 13 foreign clinical sites where Study SNDX-5613-0700 was conducted not under IND. One site (28) did not enroll any patients. All documentation for the other 12 sites as required under 21 CFR 312.120 was submitted in Appendix 16.1.3 of the Clinical Study Report.

Financial Disclosure

The Applicant disclosed a financial arrangement for one investigator at Clinical Site (b) (6) see Appendix 14.2 for details). (b) (6) The clinical site inspection revealed no actionable issues. Sensitivity analyses of the primary endpoint are conducted to ensure no bias in the study conclusions from this site. The Applicant provided attestation of no financial conflict of interest for remainder of the Investigators (Form 3454).

Data Quality and Integrity

A number of data quality and integrity issues were identified:

The data set for Study SNDX-5613-0700 was received in SDN 3. FDA questioned the accuracy of the marrow blast percentages reported in ADCUS1, and whether the source was aspirate or biopsy was not clear. In the 12/1/2023 RIR and tcon on 12/22/2023, the Applicant confirmed that the reported results may not reflect morphological examination and could be either aspirate or biopsy. Revised versions of PR, SUPPPR, ADPR, and ADCUS1 were submitted in SDN 12. Due to continued issues with data entry errors and data mapping issues, corrected versions were submitted in SDN 20. The Applicant subsequently indicated in the 3/1/2024 and 3/15/2024 RIRs that the data in PR were still incorrect as the CRFs were not corrected, but the actual results for blasts by biopsy vs aspirate from the pathology reports were accurate in SUPPPR in SDN 20. Therefore, PR could not be used for efficacy analyses, so data from SUPPPR was used instead.

Results of spinal fluid examinations were submitted for only some of the study participants. In the 12/1/2023 RIR, the Applicant confirmed that CSF examinations were not always recorded in the database and clarified that investigator conclusions for the CNS disease assessments were entered in RS for all study participants.

FDA utilized the available raw data to adjudicate responses and dates of next systemic therapy, including HSCT and CAR T cell therapy, for all study participants. There were 7 participants in the Efficacy Cohort for whom FDA assessed the remission or date of remission to differ from that reported by the Applicant. These discrepancies are summarized in Table 48. The final adjudicated responses and dates are in FADJ0700.xpt submitted in SDN 41, and the derived time-to-event endpoints using the adjudicated dates are in ADPOOL.xpt submitted in SDN 61.

FDA Table 48. Discrepancy in Best Overall Response Between Investigator's and FDA's assessments (Efficacy Cohort)

Subject ID	Investigator's assessment	FDA's adjudication	Reason for discrepancy and summary of supporting data
(b) (6)	CR	CRh	BM and counts consistent with CRh on (b) (6)
	CR	No response	BM blasts 5% on (b) (6) CR required < 5%. marrow blasts.
	CR	No response	No BM done at the time of counts reached CR
	CR	No response	No BM done at the time of counts reached CR
	CR	CRh	Marrow and counts were consistent with CRh on (b) (6)
	CRh	CR	Counts and BM consistent with CRh on (b) (6) and CR on (b) (6)
	No response	CRh	BM bx and Counts meet CRh on (b) (6)

Source: FDA analysis

Lastly, the Applicant submitted in SDN 71 an update of the SNDX-5613-0700 data set with a data cut date of 7/5/2024. There was no Reviewer's Guide for this data set. In the 7/29/2024 RIR, the Applicant indicated that this was a snapshot from the database for the on-going trial. As such, the data in this version of the data set are not used for labeling purposes.

Patient Disposition

FDA's efficacy analysis used the dataset with a data cut-off of 7/24/2023. There were 409 individuals screened for Study SNDX-5613-0700 between 10/30/2019 and 7/20/2023, 260 were enrolled, and 257 were treated.

Table 49 shows the treated population by Phase and Arm. For the purposes of selection of the analysis sets, the recommended dosage (RD) was a starting dose of revumenib 160/163 mg q 12 hr with a strong CYP3Ai or 270 mg/276 mg q 12 hr without a strong CYP3Ai.

FDA Table 49. Participants Enrolled and Treated

Phase and Arm	Population	Total	11q23 Translocation Locally	11q23 and Treated at RD	KMT2At by CTA	Pivotal Cohort[a]	Efficacy Cohort[b]
1A	No strong CYP3A4i	37	28	13	-	-	13
1B	With strong CYP3A4i	31	17	4	-	-	4
1C	Cobicistat	39	22	9	-	-	7
1D	Mod CYP3A4i	13	5	0	-	-	-
1E	No CYP3A4i at all	6	3	3	-	-	-
1F	Mod CYP3A4i	6	2	0	-	-	-
1G	(b) (4) PK/mass balance	0	0	0	-	-	-
2A	MLLr ALL/MPAL	16	16	16	14	8	14
2B	MLLr AML	78	78	78	66	49	66
2C	NPM1c AML	31	0	0	0	-	-

Source: FDA Analysis
Abbreviations: CTA, clinical trial assay; RD, recommended dosage
[a] Requires KMT2Ar by CTA, baseline blasts at least 5%, and treated with at least one dose of study drug at the recommended dosage in Cohorts 2A or 2B
[b] Requires acute leukemia with 11q23 translocation by local assay, baseline blasts at least 5%, treated with at least one dose of study drug at the recommended dosage, and at least 6 months of follow-up or withdrew earlier.

The *Pivotal Cohort* was comprised of the first 57 enrolled participants in Cohorts 2A or 2B who had a KMT2Ar by CTA and baseline blasts at least 5%, and who were treated with at least one dose of study drug at the recommended dosage.

Because it was determined that the CTA was not analytically valid, it was concluded that a cohort identified by conventional testing locally may be a better representation of patients with KMT2A translocations (see Section 4.3). The criteria for the *Efficacy Cohort* used for FDA's analyses therefore included acute leukemia having an 11q23 translocation by local assay and baseline blasts at least 5%, treated with at least one dose of study drug at the recommended dosage, and completed the Cycle 7 Day 1 visit, or discontinued earlier, or responded earlier. The 104 study participants who met these criteria are listed in ADPOOL.xpt submitted in SDN 61.

The disposition of all screened individuals as reported by the Applicant is shown in Appendix 14.6.2. FDA recoded the disposition events to aggregate similar reasons. Table 50 shows the FDA-recoded dispositions for the pivotal and efficacy cohorts at data cut-off.

FDA Table 50. Participants Disposition

	Pivotal Cohort N=57		Efficacy Cohort N=104	
On Treatment	1	2%	2	2%
Reasons for Treatment Discontinuation				
Lack of Efficacy	27	47%	53	51%
HSCT	14	25%	24	23%
Adverse Event	9	16%	15	14%
Subject Withdrew Consent	4	7%	7	7%

FDA Table 50. Participants Disposition

	Pivotal Cohort N=57		Efficacy Cohort N=104	
Noncompliance	1	2%	1	1%
Prohibited Concomitant Medication	1	2%	1	1%
Investigator Decision	0	0%	1	1%
On Study	21	37%	32	31%
Reasons for Study Discontinuation				
Death	35	61%	67	64%
Subject Withdrew Consent	1	2%	4	4%
Lost To Follow-up	0	0%	1	1%

Source: FDA Analysis

Protocol Violations

The Applicant reported 2,198 protocol violations of which 1,142 were considered key. Table 51 shows the incidence of key protocol violations in the pivotal and efficacy cohorts. The majority of key protocol violations involved testing and procedures.

FDA Table 51. Incidence of Key Protocol Violations

Category	Pivotal Cohort N=57		Efficacy Cohort N=104	
Procedures / Tests	43	75%	70	67%
Laboratory	34	60%	59	57%
Other	11	19%	22	21%
Visit Schedule	11	19%	20	19%
CCMEDS	6	11%	14	13%
Study Drug	8	14%	13	13%
ICF Issues	7	12%	11	11%
Inclusion / Exclusion	2	4%	3	3%

Source: FDA analysis

Protocol violations due to the COVID-19 pandemic were reported for no participants in the pivotal cohort and for 3 participants in the efficacy cohort. The 2 key COVID-related protocol violations in the efficacy cohort included one participant with end-of-treatment testing not done and one participant with Cycle 1 Day 10/11 visit not done. These two protocol violations would not impact the efficacy results substantially.

Demographic and Baseline Characteristics

The baseline demographic characteristics are shown in Table 52. Adults comprised 79% of the pivotal cohort and 76% of the efficacy cohort. Most participants (83-84%) had a performance status of 0-1.

FDA Table 52. Demographic Characteristics

Demographic	Pivotal Cohort N= 57		Efficacy Cohort N = 104	
Median Age (Range)	34 years (1.3-75)		37 years (1.3-79)	
Age Group				
< 2 years	3	5%	4	4%
2 to < 12 years	7	12%	17	16%
12 to < 17 years	2	4%	4	4%
17 to < 65 years	38	67%	65	63%
65 to < 75years	6	11%	12	12%
75 years and older	1	2%	2	2%
Sex				
Female	33	58%	67	64%
Male	24	42%	37	36%
Race Group				
White	43	75%	75	72%
Asian	6	11%	10	10%
Unknown	4	7%	10	10%
Black or African American	4	7%	8	8%
Multiple	0	0%	1	1%
Ethnicity				
Not Hispanic or Latino	44	77%	76	73%
Hispanic or Latino	9	16%	23	22%
Unknown	4	7%	5	5%
Performance Status*				
0	16	28%	29	28%
1	32	56%	57	55%
2	9	16%	18	17%
Region				
United States	54	95%	98	94%
Ex-United States	3	5%	6	6%

Source: FDA Analysis
*0=ECOG 0, KPS 90-100, LPS 90-100; 1=ECOG 1, KPS 70-80, LPS 70-80; 2=ECOG 2, KPS 50-60, LPS 50-60

Table 53 shows the disease characteristics at baseline. Most participants had AML, although two participants had AML as a lineage switch from ALL at initial diagnosis. The median blast percentage was 70% (range 6-98%) in the pivotal cohort and 69% (range, 5-98%) in the efficacy cohort. The median number of prior regimens was 2 (range 1-11) in both the pivotal and efficacy cohorts. Most participants (80-81%) were transfusion-dependent at baseline.

FDA Table 53. Baseline Disease Characteristics

	Pivotal Cohort N= 57		Efficacy Cohort N = 104	
Disease				
AML	49	86%	86	83%
ALL	7	12%	16	15%
MPAL	1	2%	2	2%
KMT2At by central assay				
Yes	57	100%	71	68%
Translocation				
KMT2A fusion partner unknown	13	23%	26	25%
t(9;11)	11	19%	23	22%
t(11;19)	13	23%	20	19%
t(6;11)	7	12%	10	10%
t(10;11)	7	12%	10	10%
t(4;11)	2	4%	7	7%
t(1;11)	2	4%	3	3%
t(11;17)	0	0%	2	2%
t(11;22)	1	2%	2	2%
t(11;16)	1	2%	1	1%
Disease status				
Primary refractory	14	25%	22	21%
Untreated relapse	11	19%	21	20%
Refractory relapse	32	56%	61	59%
Number of prior relapses				
0	14	25%	22	21%
1	28	49%	55	53%
2	14	25%	20	19%
>=3	1	2%	7	7%
Prior HSCT				
Yes	28	49%	46	44%
Prior CAR T cells				
Yes	1	2%	3	3%
Transfusion status				
Dependent	46	81%	83	80%
Independent	11	19%	21	20%

Source: FDA Analysis

Treatment Compliance

Per protocol, participants could be treated until unacceptable toxicity, progression of leukemia, or if at least MLFS was not achieved by completion of 4 cycles (112 days) of the therapy. For all 104 participants in the Efficacy Cohort, the median duration of Treatment Period 1 was 71 days (range 3-619 days). Table 54 shows the duration of Treatment Period 1 by post study HSCT and best response. Approximately half of the participants who achieved CR, CRh, or at least cleared blasts from the marrow ended Treatment Period 1 and went on the HSCT. The participants who went on to HSCT had a median duration of Treatment Period 1 of 84 days.

For the 35 participants who cleared blasts from the marrow without achieving CR or CRh, the median duration of Treatment Period 1 was 86 days (range, 41-253 days).

FDA Table 54. Efficacy Cohort - Duration of Treatment

Post Study HSCT	Best Response	Treatment Period 1 Duration (days)		
		N	Median (range)	
No	CR	7	110	(82 - 619)
	CRh	4	138	(86 - 178)
	MBF	20	99	(42 - 253)
	NR	44	45	(3 - 115)
Yes	CR	6	85	(48 - 125)
	CRh	5	86	(67 - 172)
	MBF	15	84	(41 - 109)
	NR	3	59	(50 - 89)

Source: FDA analysis
Abbreviations: CR, complete remission, CRh; CR with partial hematological recovery; MBF, marrow blasts < 5% without CR and CRh; NR, no documentation of marrow blasts < 5%

For the Efficacy Cohort, the median relative dose intensity was 99% (range, 38-100%). The relative dose intensity was < 80% for only 15% of the participants. Table 55 shows the relative dose intensity by cycle for the 125 participants treated in the Phase 2 portion of the trial. A substantial proportion of participants had < 80% relative dose intensity from Cycle 4 onwards. FDA could not assess the relative dose intensity by cycle in the Efficacy Cohort, since EX reported only dosing on visit days and changes in dose; actual dose over time was not recorded (Applicant's 12/1/2023 RIR).

FDA Table 55. Phase 2 - Treatment Compliance

	Relative Dose Intensity Per Cycle n (%)		
	< 80% Dose	80-100% Dose	> 100% Dose
Cycle 1 (N=125)	17 (13.6)	107 (85.6)	1 (0.8)
Cycle 2 (N=101)	15 (14.9)	86 (85.1)	0
Cycle 3 (N=72)	16 (22.2)	55 (76.4)	1 (1.4)
Cycle 4 (N=42)	14 (33.3)	28 (66.7)	0
Cycle 5 (N=22)	7 (31.8)	15 (68.2)	0
Cycle 6 (N=12)	7 (58.3)	5 (41.7)	0
Cycle 7 (N=10)	6 (60.0)	4 (40.0)	0
Cycle 8 (N=5)	3 (60.0)	2 (40.0)	0
Cycle 9 (N=5)	2 (40.0)	3 (60.0)	0
Cycle 10 (N=1)	0	1 (100.0)	0

Source: Applicant RIR received 1/24/2024

Concomitant Medications and Rescue Medication Use

The cell therapies and first subsequent systemic therapies used for the efficacy analyses were adjudicated by FDA. The other results of anti-leukemia therapies in this section were analyzed as reported without adjudication.

Prephase Anti-Leukemia Therapy

There were 33 (32%) participants in the Efficacy Cohort who received systemic anti-leukemia therapy on Days -28 to Day-1. Treatments included hydroxyurea (25%), cytarabine (7%), methotrexate (3%), steroids (3%), an asparaginase class product (2%), vincristine (2%), cyclophosphamide (1%), doxorubicin (1%), and FLAG-Ida (1%).

Concomitant Anti-Leukemia Therapy

There were 39 (38%) participants in the Efficacy Cohort who received systemic anti-leukemia therapy during the period of Day 1 to Day 60. Treatments included hydroxyurea (35%), steroids (3%), and cytarabine (1%).

Anti-Leukemia Cell Therapy

HSCT after start of study treatment was reported for 28% of participants in the Efficacy Cohort, and CAR T-cell therapy was reported for 4% of participants in the Efficacy Cohort.

Subsequent Anti-Leukemia Therapy

Excluding hydroxyurea and steroids, there were 41 (39%) participants in the Efficacy Cohort who received systemic anti-leukemia therapy after start of study treatment. Table 56 shows the distribution of drugs reported. It should be noted that some of the drugs listed may have been used as the preparative regimen for HSCT or for the lymphodepleting regimen for CAR T cells, but it is not clear that these were flagged accurately in ADCM.

FDA Table 56. Subsequent Therapies in the Efficacy Cohort

Therapy	Number*
Venetoclax	17
Cytarabine	16
Fludarabine	13
Cyclophosphamide	9
Busulfan	8
Revumenib	7
Decitabine	6
Methotrexate	6
Azacitidine	5
Gemtuzumab Ozogamicin	5

FDA Table 56. Subsequent Therapies in the Efficacy Cohort

Therapy	Number*
Gilteritinib	5
Melphalan	5
Cladribine	4
Idarubicin	4
Blinatumomab	2
Clofarabine	2
Etoposide	2
Inotuzumab Ozogamicin	2
Investigational Drugs	2
Thiotepa	2
Vincristine	2
Cytarabine/Daunorubicin	1
Decitabine/Venetoclax	1
Hyper-CVAD	1
Mercaptopurine	1
Tagraxofusp	1

Source: FDA analysis
*Some participants may have received more than one drug.

Efficacy Results – Primary Endpoint

The results of response rate based on FDA's adjudicated responses are summarized in FDA Table 57 for the Pivotal Cohort and Efficacy Cohort. The CR/CRh rates were similar between two cohorts, and both lower bounds of 95% CIs excluded the proposed benchmark of 10%. These adjudicated results are generally consistent with the Applicant's results.

FDA Table 57. Summary of Response Rates

	Pivotal Cohort (N = 57)	Efficacy Cohort (N = 104)
CR/CRh: n (% [95% CI])	12 (21% [11%, 34%])	22 (21% [14%, 30%])
CR: n (% [95% CI])	7 (12% [5%, 24%])	13 (13% [7%, 20%])
CRh: n (% [95% CI])	5 (9% [3%, 19%])	9 (9% [4%, 16%])

Source: FDA Analysis

The results of response rate for the Pivotal Cohort are summarized by disease type (AML versus ALL/MPAL) and age groups (age < 17 versus age ≥ 17 years old) in FDA Table 58. Regarding disease type, the data were driven by 49 AML patients whereas there was only one responder out of 8 ALL/MPAL patients. Regarding age group, response rate appeared similar between those aged <17 versus ≥17 years old. Similar results were observed when a different age threshold of 18 years old was used.

FDA Table 58. Summary of Response by Disease Type and Age Group (Pivotal Cohort)

	Disease Type		Age Group	
	ALL/MPAL (N = 8)	**AML (N = 49)**	**Age < 17 years (N = 12)**	**Age ≥17 years (N = 45)**
CR/CRh: n (%[95% CI])	1 (13% [0, 53%])	11 (22% [12%, 37%])	3 (25% [5%, 57%])	9 (20% [10%, 35%])
CR: n (% [95% CI])	0	7 (14% [6%, 27%])	1 (8% [0%, 38%])	6 (13% [5%, 27%])
CRh: n (% [95% CI])	1 (13% [0, 53%])	4 (8% [2%, 20%])	2 (17% [2%, 48%])	3 (7% [1%, 18%])

Source: FDA Analysis

The results of response rate and durability for the Efficacy Cohort are summarized by disease type (AML versus ALL/MPAL) and age groups (age <17 versus age ≥17 years old) in FDA Table 59. Results from this larger analysis set confirms the similar findings conveyed above in FDA Table 58 for the Pivotal Cohort.

FDA Table 59. Summary of Response by Disease Type and Age Group (Efficacy Cohort)

	Disease Type		Age Group	
	ALL/MPAL (N = 18)	**AML (N = 86)**	**Age < 17 years (N = 25)**	**Age ≥17 years (N = 79)**
CR/CRh: n (% [95% CI])	4 (22% [6%, 48%])	18 (21% [13%, 31%])	7 (28% [12%, 49%])	15 (19% [11%, 29%])
CR: n (% [95% CI])	3 (17% [4%, 41%])	10 (12% [6%, 20%])	3 (12% [3%, 31%])	10 (13% [6%, 22%])
CRh: n (% [95% CI])	1 (6% [0, 27%])	8 (9% [4%, 18%])	4 (16% [5%, 36%])	5 (6% [2%, 14%])
Source: FDA Analysis				

Efficacy Results – Secondary and Other Relevant Endpoints

Duration of Response

Results of duration of response are summarized in FDA Table 57 for the Pivotal Cohort and Efficacy Cohort, respectively. The median duration of response was 6.4 months, and its 95% CI varied between two cohorts due to relatively small numbers of responders: (4.3, NE) months in the Pivotal Cohort and (2.7, NE) months in the Efficacy Cohort, where NE stands for not estimable.

FDA Table 60. Summary of Duration of Response

	Pivotal Cohort (N = 57)	**Efficacy Cohort (N = 104)**
Median time to response, range, months	1.9, 0.9~3.9	1.9, 0.9~5.6
Median DOR[1] (95% CI), months	6.4 (4.3, NE)	6.4 (2.7, NE)
Median duration of CR[2] (95% CI), months	NE (4.3, NE)	4.3 (1.0, NE)
Median duration of CRh[3] (95% CI), months	6.4 (2.7, NE)	6.4 (2.7, NE)

Source: FDA Analysis

1. Duration of response (DOR) is defined as the time from first CR or CRh to the first documented relapse or death, whichever occurs first.
2. Duration of CR is defined as the time from first CR to the first documented relapse or death, whichever occurs first, among CR responders.
3. Duration of CRh is defined as the time from first CRh to the first documented relapse or death, whichever occurs first, among CRh responders.

Time to response

The median time to response was 1.9 months in both Pivotal Cohort and Efficacy Cohort. The time to response ranged from 0.9 to 3.9 months in the Pivotal Cohort and to 5.6 months in the Efficacy Cohort.

Transfusion Independence

The transfusion dependence data are summarized in FDA Table 61 for the Pivotal Cohort and Efficacy Cohort. The two cohorts demonstrated similar results. Among the patients who were dependent on RBC and/or platelet transfusions at baseline, 14~17% became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the patients who were independent of both RBC and platelet transfusions at baseline, 46~48% remained transfusion independent during any 56-day post-baseline period.

FDA Table 61. Transfusion Dependence at Baseline and Post Baseline

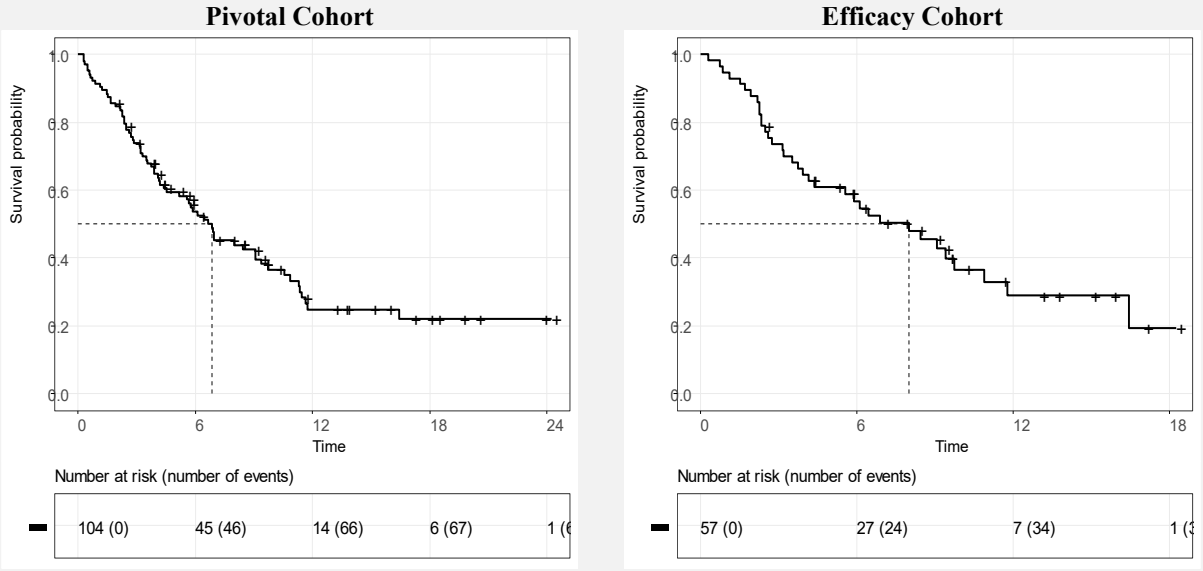
	Post-baseline Transfusion Status	
Baseline Transfusion Status	**Dependent n (%)**	**Independent n (%)**
Pivotal Cohort (N = 57)		
Dependent (n = 46)	38 (83)	8 (17)
Independent (n = 11)	6 (55)	5 (46)
Total (n = 57)	43 (77)	13 (23)
Efficacy Cohort (N = 104)		
Dependent (n = 83)	71 (86)	12 (14)
Independent (n = 21)	11 (52)	10 (48)
Total (n = 104)	82 (79)	22 (21)

Source: FDA Analysis

Overall Survival

The median OS was estimated similarly in two cohorts: 8 (95% CI: 4.4, 11.8) and 6.9 (95% CI: 5.2, 9.4) months in the Pivotal Cohort and Efficacy Cohort, respectively.

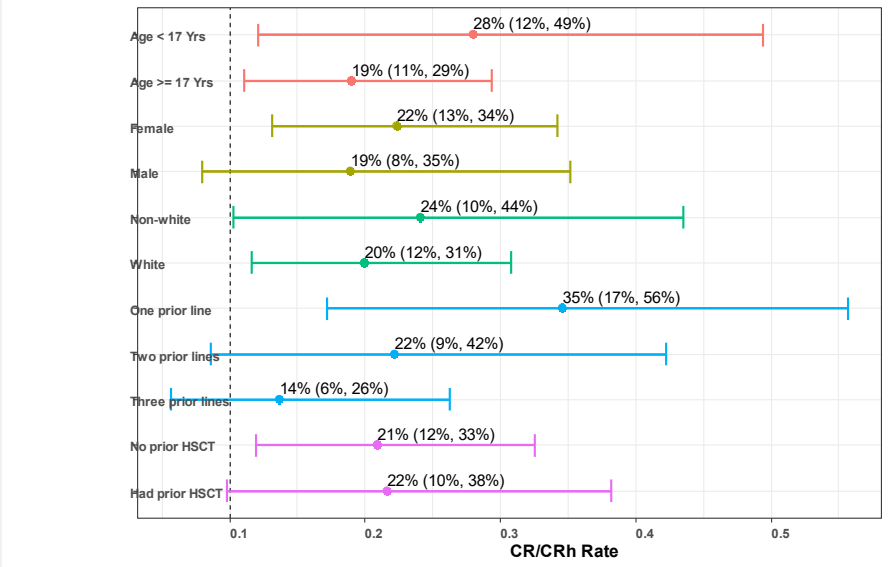
FDA Figure 10. Kaplan-Meier Estimates of Overall Survival



Source: FDA Analysis

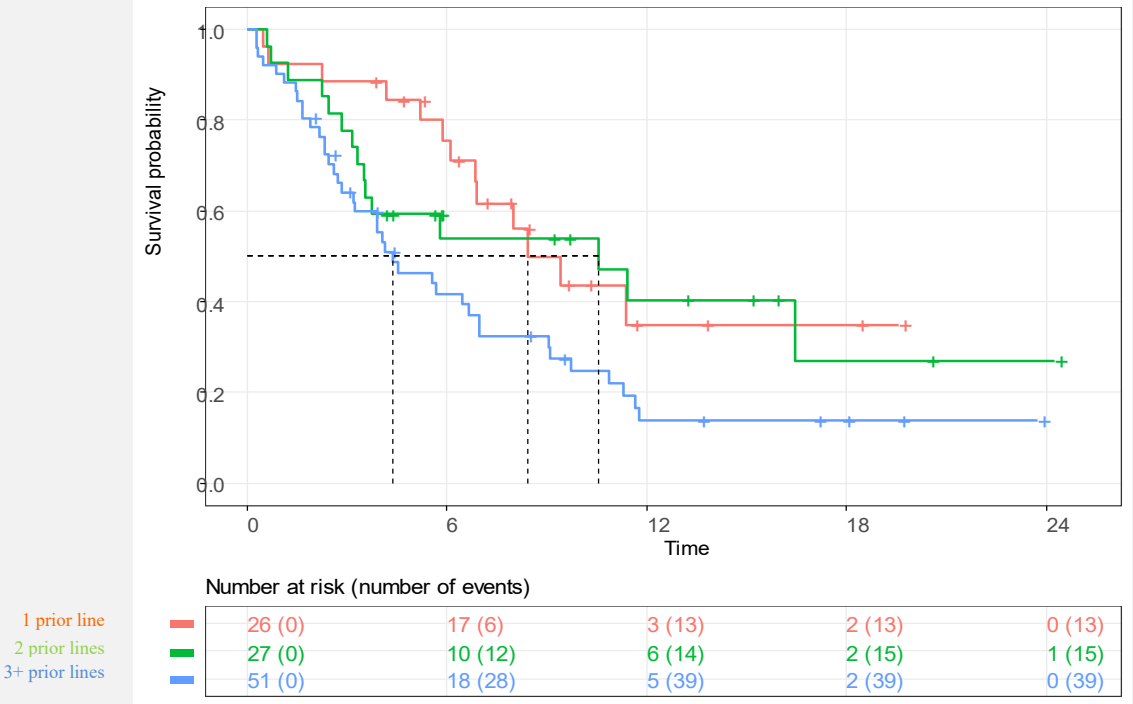
Subpopulations

The results of response rates by age, gender, race, prior line of therapy and use of HSCT are depicted in Figure 11 for the Efficacy Cohort. The response rates deteriorated as the number of prior lines increased, which is expected. All the other subgroups demonstrated similar trend as the overall study population. Similar results were observed when the Pivotal Cohort was used for these subgroup analyses.



FDA Figure 11. Subgroup analysis of response rate (Efficacy Cohort)
Source: FDA Analysis

In addition, the reviewer evaluated the overall survival by number of prior lines and confirmed the above finding that the treatment effect increased as the number of prior lines increased.



FDA Figure 12. Kaplan-Meier Estimates of Overall Survival by Number of Prior Lines (Efficacy Cohort)
Source: FDA Analysis

Efficacy Results – Exploratory and COA (PRO) Endpoints

FDA agrees with the sponsor's summary of exploratory analyses. In addition, FDA conducted sensitivity analysis of response rates and durability using the Efficacy Cohort with FDA's adjudicated responses, which yielded similar results as the primary analysis results.

Additional Analyses Conducted on the Individual Trial

Response by dose level

Table 62 shows the proportion of participants who achieved CR or CRh by dose level using BID dosing. The analysis included participants with acute leukemia, a KMT2A translocation, at least 5% blasts at baseline, and follow-up through the Cycle 7 Day 1 visit or discontinued earlier. See Table 67 for the dose level criteria.

FDA Table 62. Patients with KMT2At Acute Leukemias - CR/CRh by Dose Level

	Achieved CR or CRh /Number (%) at Dose Level*									
	L-2 N=1		L-1 N=29		RP2D N=104		L+1 N=9		L+2 N=1	
	n	%	n	%	n	%	n	%	n	%
All Participants										
Total	1/1	100.0%	7/29	24.1%	22/104	21.2%	5/9	55.6%	0/1	0.0%
By Disease										
AML	1/1	100.0%	6/24	25.0%	18/86	20.9%	4/6	66.7%		
ALL			1/4	25.0%	3/16	18.8%	0/2	0.0%	0/1	0.0%
MPAL			0/1	0.0%	1/2	50.0%	1/1	100.0%		

Source: FDA analysis
* See Table 67 for the dose level criteria.

Clinical TL Comment: Although it appears that the CR/CRh rate was higher with doses above the RP2D, the number of patients studied was small, and the 95% CI wide (21-86%).

Additional subgroup analyses of CR/CRh

Table 63 shows additional subpopulation analyses by baseline demographic characteristics in the efficacy cohort.

FDA Table 63. Efficacy Cohort - Subgroup Analysis by Demographic Characteristics

			Achieved CR/CRh	
Grouping	**Subpopulation**	**N**	**n (%)**	
Age	< 17 years	25	7	28%
	>= 17 years	79	15	19%
Age subgroup	< 2 years	4	1	25%
	2 to < 12 years	17	4	24%
	12 to < 17 years	4	2	50%
	17 to < 65 years	65	9	14%
	65 to < 75 years	12	4	33%
	>= 75 years	2	2	100%
Sex	Female	67	15	22%
	Male	37	7	19%
Race	White	75	15	20%
	Asian	10	4	40%
	Unknown	10	2	20%
	Black or African American	8	1	13%
	Multiple	1	0	0%

FDA Table 63. Efficacy Cohort - Subgroup Analysis by Demographic Characteristics

			Achieved CR/CRh	
Ethnicity	Not Hispanic or Latino	76	16	21%
	Hispanic or Latino	23	6	26%
	Unknown	5	0	0%
Region	United States	98	20	20%
	Ex-United States	6	2	33%
Site 07	No	74	17	23%
	Site 07	30	5	17%

Source: FDA analysis

Clinical TL Comment: Notwithstanding the small numbers in many of the subgroups, there was a treatment effect across all subpopulations. This analysis also determined that the remission rate for Site 07 would not bias the results for the study overall.

Table 64 shows additional subpopulation analyses by disease characteristics in the efficacy cohort. To further assess whether disease severity or burden impacted the response rate, additional subgroupings included baseline transfusion dependence, baseline marrow blast count, use of prephase chemotherapy, and use of low-dose chemotherapy during Cycles 1 and 2.

FDA Table 64. Efficacy Cohort - Subgroup Analysis by Disease Characteristics

			Achieved CR/CRh	
Grouping	**Subpopulation**	**N**	**n (%)**	
Diagnosis	AML	86	18	21%
	ALL	16	3	19%
	MPAL	2	1	50%
Translocation	KMT2A fusion partner unknown	26	6	23%
	t(9;11)	23	4	17%
	t(11;19)	20	3	15%
	t(6;11)	10	3	30%
	t(10;11)	10	2	20%
	t(4;11)	7	2	29%
	t(1;11)	3	0	0%
	t(11;17)	2	1	50%
	t(11;22)	2	1	50%
	t(11;16)	1	0	0%
Baseline disease status	Refractory relapse	61	9	15%
	Primary refractory	22	6	27%
	Untreated relapse	21	7	33%

FDA Table 64. Efficacy Cohort - Subgroup Analysis by Disease Characteristics

			Achieved CR/CRh	
Grouping	**Subpopulation**	**N**	**n (%)**	
Number of prior relapses	0	22	6	27%
	1	55	10	18%
	2	20	4	20%
	>=3	7	2	29%
Prior HSCT	No	58	13	22%
	Yes	46	9	20%
Baseline transfusion dependence	Dependent	83	13	16%
	Independent	21	9	43%
Baseline marrow blasts	>= 30%	77	11	14%
	< 30%	27	11	41%
Prephase chemotherapy	No	71	17	24%
	Yes	33	5	15%
Cycle 1-2 low-dose chemotherapy	No	65	18	28%
	Yes	39	4	10%

Source: FDA analysis

Clinical TL Comment: Notwithstanding the small numbers in many of the subgroups, the treatment effect appeared independent of disease characteristic. It is noted, however, that the identified translocations cover only 10% of the known KMT2A translocations. With regard to measures of disease burden, the results are consistent with the expectation that patients would have a lower response rate with higher disease burden, especially if they had disease severe enough to require additional cytoreduction either just prior to study baseline or during the initial cycles of treatment.

Response in the marker-negative population

In the Applicant's 9/19/2024 RIR, they identified 26 participants with no documented gene variants associated with HOXA overexpression. A CR or CRh was identified for only 1 (4%) of those 26 participants. The responder (Subject (b) (6)) had ANC 2.5 Gi/L and platelets 175 Gi/L at baseline with marrow blast count of 5% on biopsy and 1% on the aspirate.

Clinical TL Comment: Given the discrepancy between the biopsy and aspirate results at baseline, it is possible that the responding participant may not have been in relapse at study baseline. The results for the remaining marker-negative population are consistent with the hypothesis that HOXA overexpression is needed for revumenib to demonstrate an effect, although the small number of marker-negative participants leaves some uncertainty.

Response by dose form

The majority of the efficacy data presented above represents the experience with the capsule or F1/F2 oral solution dose forms. The SNDX-5613-0700 data set version with a data cut date of 7/5/2024 was used to assess activity using tablets (b) (4) the to-be-marketed dose forms. (b) (4)
With regard to the tablet formulation, a comparison of CR/CRh was made for the participants with acute leukemia and a KMT2Ar or NPM1mut who received only capsules or only tablets at the recommended dosage. The response outcomes used were as reported by the Applicant; the remissions were not adjudicated by FDA. A CR or CRh was reported for 22/121 (18.2%) using capsules alone and 5/28 (17.9%) using tablets alone. However, using tablets alone, remissions were observed only in the participants with NPM1mut. For the participants with KMT2Ar, a CR or CRh was reported for 16/83 (18.3%; 95% CI 11-29%) using capsules alone and 0/9 (0%; 95% CI 0-28%) using tablets alone. The Applicant attributed the low response rate to the small number of participants using tablets (Applicant's 9/19/2024 RIR).

Clinical TL Comment: It is a concern that no participants treated with tablets alone achieved CR/CRh, but the 95% CI does not exclude the observed point estimate in the Efficacy Cohort, and the small sample size may preclude a meaningful analysis. Essentially, the data are not sufficient to comment on comparability of the tablet and capsule dose forms with regard to efficacy.

8.2. Integrated Review of Effectiveness

The Applicant's Position:

The SNDX-5613-0700 study met the primary efficacy endpoint at the IA for the Cohort 2A+2B Efficacy Evaluable Population. Both the Phase 1 and Phase 2 portions of SNDX-5613-0700 enrolled a notably heavily pretreated population of R/R adult and pediatric *KMT2A*r leukemia patients, nearly half having had a prior HSCT and more than half categorized as refractory relapse patients. The data from this single arm study show that CR+CRh responses were rapid and durable, with consistent results obtained across subgroups including leukemia subtypes (AML and ALL) and KMT2A-fusion partners, prior transplant, different races/ethnicities, and irrespective of age, gender, and number of prior lines of therapy. Efficacy subgroup analyses demonstrated consistency with the primary analysis and support that the results are applicable to the proposed indication.

Despite extensive prior treatment, a significant proportion of patients achieved a depth of response sufficient to proceed to HSCT. Conversion to transfusion independence was demonstrated in this population that included patients proceeding to transplant within 56 days after achieving their best response, which may have limited the potential to demonstrate transfusion independence during the available follow-up time. The majority of patients responded to treatment (as measured by ORR) and overall survival was longer than historical

reports for R/R *KMT2A*r patients. Similar efficacy results were observed in the Phase 1 study, lending supportive evidence of the robustness of the Phase 2 results. Thus, by multiple measures, revumenib treatment at the indicated dose resulted in a statistically significant, clinically meaningful response in a heavily pretreated patient population with R/R *KMT2A*r leukemia.

8.2.1. Assessment of Efficacy Across Trials

The FDA's Position:

Methods

The Applicant proposed an indication "for the treatment of adult and pediatric patients with relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene rearrangement (KMT2Ar)" using revumenib 270 mg PO BID for patients 40 kg or greater, 160 mg/m^2 PO BID for patients less than 40 kg (b) (4)

Issues with the clinical development program: The clinical development program included one multiple-cohort, single-arm, Phase 1 - 2 trial of revumenib monotherapy (SNDX-5613-0700) in patients at least 30 days old with relapsed or refractory leukemia having a KMT2Ar, NPM1 mutation, or NUP98 mutation by local testing. The Phase 1 portion was an open-label, dose-escalation study with seven single-arm cohorts (1A through 1G) based on concurrent CYP3i use, schedule, and/or formulation. The Phase 2 portion included three single-arm disease-based cohorts (2A - KMT2Ar ALL or MPAL, 2B - KMT2Ar AML, and 2C - NPM1c AML), each with a Simon 2-stage design to target a 25% CR+CRh rate and exclude a 10% rate.

- A weakness in the program is that there is only one adequate and well-controlled trial, and it is a single-arm study. In general, for a single pivotal study to support an NDA, the trial should be well-designed, well-conducted, internally consistent and provide statistically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform, and additional confirmatory evidence should be provided. At the pre-NDA meeting on October 20, 2023, FDA indicated that results for the Phase 1 participants with CTA-confirmed KMT2Ar not in the pivotal cohort but who were treated with revumenib at doses that provide exposure comparable to the proposed recommended dose could be used as supporting evidence of effectiveness in addition to the Phase 2 pivotal cohort.

- The revumenib RP2D from the clinical trials was 163 mg q 12 hr with a strong CYP3Ai or 276 mg q 12 hr without a strong CYP3Ai (95 mg/m^2 q12h or 160 mg/m^2 q12h, respectively, for patients weighing < 40 kg) using revumenib (b) (4) salt in a capsule or liquid formulation. The proposed to-be-marketed drug product is a monocitrate monohydrate salt in a tablet formulation at strengths that differ from those of the drug product used in the clinical trials, such that the proposed recommended dosage in labeling would differ slightly from that used in the pivotal cohort.

Issues with the pivotal trial: The review team identified several issues with the design and conduct of the trial:

- The null CR/CRh rate of 10% was not agreed upon (pre-NDA meeting on October 20, 2023). FDA requested that the Applicant provide data to justify the clinical meaningfulness of such a low CR/CRh rate for the benefit-risk assessment. (b) (4)

- The Applicant proposed a window of -7 to +15 days between the marrow sampling and the CBC for remission assessment (Written Responses issued 5/19/2023). For this application, the proposed window was accepted and used in the remission adjudication process.

- Although the FDA provided advice on the estimand for the primary endpoint (Correspondence dated October 20, 2022), the estimand was not incorporated into the protocol or SAP. FDA applied this advice in the remission adjudication process.

- Per the SAP, the efficacy evaluable population required central confirmation for mutational status. During review of this NDA, CDRH concluded that the CTA was not analytically valid (see Section 4.3). Given that this raised a concern about the generalizability of the results from an arbitrary subset of patients, it was determined that for labeling purposes, the efficacy evaluable population should be based on the assay used for enrollment (local assay) instead. Therefore, the pivotal cohort was analyzed as prespecified to confirm that the trial was positive, and a post hoc analysis was performed using the broader population (Efficacy Cohort) from Phase 1 and Phase 2 based on local assay as described in Section 8.1.1 to be used in labeling.

- For other molecularly targeted agents for treatment of AML, remission is generally delayed in onset, with median time on treatment being 4.2 months and median time to remission being 2.8 months.[15] For the Efficacy Cohort in Study SNDX-5613-0700, the median time on treatment was only 2.3 months (see Table 54). How this short follow-up time affected observation of the efficacy endpoints needs to be considered.

- Anti-leukemia therapy was administered to 32% of the efficacy cohort within 28 days prior to start of study treatment, and anti-leukemia therapy, largely hydroxyurea, was administered to 38% of the efficacy cohort during the first 60 days on treatment. Whether this additional anti-leukemia therapy affected the remission rate required additional analyses.

The primary analysis was to be conducted after completion of the first stage in Cohort 2B, and the analysis set was a pool of participants from Cohorts 2A+2B (Pivotal Cohort). Using the

[15] Le R et al. Complete remission with partial hematological recovery as a palliative endpoint for treatment of acute myeloid leukemia. Blood 2024;144:206-214.

adjudicated endpoints, FDA calculated that the CR/CRh rate was 21% (95% CI 11%, 34%) in the Pivotal Cohort. Because the lower 95% CI exceeded the prespecified lower bound of 10%, the trial was considered positive.

Because of concerns that the CTA used to identify the Pivotal Cohort selected a subgroup that may not be representative of the intended population, FDA included in the analysis set (Efficacy Cohort) all participants enrolled with acute leukemia having an 11q23 translocation by local assay and baseline marrow blasts at least 5%, treated with at least one dose of revumenib starting at the RP2D, and completed the Cycle 7 Day 1 visit or discontinued earlier or responded earlier.

Clinical Benefit Endpoint(s)

For nonmyelosuppressive drugs given in settings without intent to cure, FDA has used durable CR/CRh for regulatory decision-making on the basis of recovery of adequate blood counts to protect against infection and avoid transfusions with corroborating evidence. On the basis of the safety review, FDA has concluded that revumenib is nonmyelosuppressive (see Section 8.3.5). The SNDX-5613-0700 SAP specified CR/CRh rate as the primary efficacy endpoint, and DOR and transfusion-independence were secondary endpoints. Therefore, for this application, efficacy was established on the basis of the rate of CR/CRh, the duration of CR/CRh, and the rate of conversion from transfusion dependence to transfusion independence.

Table 65 shows the Efficacy Cohort results for the endpoints used to demonstrate effectiveness. Of note is the low proportion of patients achieving CR/CRh (21%) and the low rate of conversion to transfusion independence (14%). These observations may be explained in part by the short duration of treatment in this cohort (median 2.3 months). In fact, for participants who achieved only marrow blast clearance, the median time on treatment was also only 2.8 months, and half went on to HSCT; the high rate of premature treatment termination may clearly have precluded the ability to even detect CR/CRh.

FDA Table 65. Efficacy Cohort - Clinical Benefit and Supporting Endpoints

Endpoint	Result
CR/CRh	22/104 (21.2%; 95% CI 13.8, 30.3)
Median time to CR/CRh	1.9 months (range, 0.9, 5.6)
CR	13/104 (12.5%; 95% CI 6.8, 20.4)
CRh	9/104 (8.7%; 95% CI 4.0, 15.8)
Median duration of CR/CRh	6.4 months (95% CI 2.7, NE)
Conversion from TD to TI-56	12/83 (14%; 95% CI 8, 24)
Conversion from TD to TI-112	Not done

Source: FDA analysis

Similarly, with such short time on treatment, participants would not have had the time to demonstrate conversion to transfusion independence. Even for the participants who achieved

CR/CRh, the time on treatment would have been too short to assess for TI-112, so that endpoint was not calculated. Given the proportion of patients who went on to HSCT so rapidly, one may conclude that this was not an appropriate study cohort for use of the CRh palliative endpoint.

As revumenib is first-in-class, FDA also assessed for consistency between response and other measures of clinical benefit (Table 66). Although the outcomes are improved numerically in participants with CR or CRh, the results are clearly not very robust. This also may be explained by the short time on treatment.

FDA Table 66. Assessment of Consistency Between Response and Clinical Outcomes

Outcome	CR (N=13)	CRh (N=9)	NR (N=82)
Grade 3-5 Infection Incidence	46%	22%	43%
Grade 3-5 Hemorrhage Incidence	8%	0%	16%
Grade 3-5 Infection Events/100 Patient-Years	138.6	66.7	227.0
Grade 3-5 Hemorrhage Events/100 Patient-Years	16.4	3.7	64.3
TI-56 Observed Post Baseline	69%	44%	11%
TI-112 Observed Post Baseline	Not done	Not done	Not done

Source: FDA analysis

Subpopulations

See Section 8.1.1 for subgroup analyses by demographic characteristics, baseline disease-related characteristics, and prephase and concurrent treatments. With regard to demographics, a treatment effect was observed across all subgroups, including the entire age range studied and by type of leukemia. Of note, however, is that the leukemias in the study participants had only nine of the over 100 known KMT2A translocation partners, most of which are involved in transcriptional activities. The uncertainty with regard to the rare translocation partners can be addressed in a postmarketing study. KMT2A partial tandem duplications are not known to be susceptible to this therapy, and patients with these rearrangements were excluded from this trial. As such, the indication should be limited to KMT2A translocations specifically rather than KMT2A rearrangements.

A key subgroup was defined by patients who received prephase therapy versus those who did not. This subgroup reflects an additional issue with the design of the pivotal trial, which is the role of prephase therapy. Heterogenous and uncontrolled use of prephase therapy can produce treatment regimens which are difficult to define, thereby impacting a determination of efficacy for the intended regimen. In this case, the subgroup results appear to suggest that prephase therapy did not have an appreciable effect on the efficacy results. In fact, the lowest CR/CRh rates were in participants who received prephase chemotherapy or required low-dose chemotherapy to control counts while on study. By contrast, participants with signs of lesser disease burden (baseline marrow blasts < 30% or transfusion independence at baseline) had the highest CR/CRh rates.

Supporting Endpoints

See Section 8.1.1 for the analyses of supporting endpoints, including time to response, red blood cell and platelet transfusion independence and overall survival (OS). The results for time to response and conversion to transfusion independence are discussed above. OS is not interpretable in a single-arm trial, so OS is not considered further.

Dose/Dose Response

The analysis of CR/CRh by dose (Table 62) is consistent with the Applicant's determination of revumenib 163 mg q 12 hr with a strong CYP3Ai or 276 mg q 12 hr without a strong CYP3Ai as being the RP2D. The CR/CRh rate appeared higher with higher doses, but the numbers of participants at the higher doses are small, and the toxicity rates are higher, so the doses at the RP2D would appear appropriate.

There were not a sufficient number of pediatric participants to allow a dose-efficacy analysis within the pediatric age group. At the dosages studied in children in the Efficacy Cohort (95 mg/m^2 q 12 hr with a strong CYP3Ai or 160 mg/m^2 q 12 hr without a strong CYP3Ai), the incidence of CR/CRh appeared similar to that in adults. There are no data for neonates, an age subgroup not included in the trial. Additionally, the Clinical Pharmacology review team has determined that there is not sufficient PK information to establish an appropriate dosage for patients less than 1 year old, and there are no clinical efficacy data that could be used to overcome this deficiency. Therefore, for labeling, the intended population would be limited to those 1 year and older.

Lastly, although the clinical trials were conducted largely using revumenib capsules as the dose form, the to-be-marketed drug product, a tablet, differs in salt, dose form, and strength. The Applicant proposed to use the 160 mg tablet rather than the 163 mg capsule and to use the 270 mg by tablets instead of 276 mg by capsules. In the assessment of efficacy by dose form, a CR/CRh was achieved by 0 (0%; 95% CI 0-28%) of 9 participants with KMT2At acute leukemias using tablets alone. Due to small numbers of participants evaluable for efficacy using the tablet dose form, the clinical data are not sufficient to allow conclusions regarding comparability. The acceptability of the dosage using the to-be-marketed dose form is based on the relative bioavailability study instead (see Section 6.2).

Additional Efficacy Considerations

Study SNDX5613-0700 allowed patients to resume treatment of revumenib after transplantation if the following conditions were met:

- Patient was between 30 and 180 days post-HSCT.
- Patient had successful hematopoietic recovery as demonstrated by ANC ≥ 0.5 Gi/L and platelets ≥ 50 Gi/L without transfusions.

- Patient must not have had acute or chronic Graft-Versus-Host Disease that required systemic immunosuppression.
- Patient was in CRc.

FDA noted the benefit and risk profile of such posttransplant resumption of treatment was not possible to evaluate with the study design. Therefore, in the absence of such supporting data, instruction that address posttransplant resumption will not be included in dosing instructions in the USPI.

Lastly, although FDA indicated at the pre-NDA meeting on October 20, 2023, that data from the Phase 2 cohort and supporting evidence from the Phase 1 participants could be utilized to establish SEE, due to study conduct issues the Efficacy Cohort included participants from both the Phase 1 and Phase 2. Additional confirmatory evidence would include the observation of activity (albeit not substantial evidence of effectiveness) in a population with other genetic variants associated with HOXA overexpression (Section 8.1.1), lack of efficacy in participants with acute leukemias not having genetic variants associated with HOXA overexpression (Section 8.1.1), the in vitro cytotoxic effect of prolonged revumenib exposure on KMT2At leukemia cell lines (Section 6), and tumor growth inhibition in xenograft models (Section 6).

8.2.2. Integrated Assessment of Effectiveness

The FDA's Position:

The efficacy of revumenib was established based on the results of the Efficacy Cohort from Study SNDX5613-0700 in pediatric and adult participants with R/R acute leukemia with KMT2At. The demographics of the study population were consistent with those of the US population with KMT2At acute leukemias, and the results were considered generalizable to the US population (see Section 8.1.1).

In Study SNDX5613-0700, eligible participants who received revumenib at the recommended dosage had a higher CR/CRh rate than the proposed null, which was not previously agreed upon with FDA. The CR/CRh rate was 21% (95% CI: 11%, 34%) in the Pivotal Cohort and 21% (95% CI: 14%, 30%) in the Efficacy Cohort. Both lower bounds of 95% CI excluded the prespecified benchmark of 10%. The median duration of response was 6.4 (95% CI: 4.3, NE) months in the Pivotal Cohort and 6.4 (95% CI: 2.7, NE) months in the Efficacy Cohort. The median time to response was 1.9 months in both cohorts with all the responders achieving a response by 6 months.

The efficacy of revumenib was supported by transfusion independence data. In the Pivotal and Efficacy cohorts, 14~17% of transfusion dependent patients at baseline became independent of RBC and platelet transfusions during any 56-day post-baseline period; and 46~48% of transfusion independent patients at baseline remained independent during any 56-day post-baseline period.

These data, taken together with the nonclinical proof of concept data, provide substantial evidence of effectiveness of revumenib for treatment of R/R acute leukemia with KMT2A translocation in patients 1 year and older. The low CR/CRh rate and the low rate of conversion to transfusion independence warrant careful consideration of the risk-benefit assessment.

8.2.3. Approach to Substantial Evidence of Effectiveness

The FDA's Position:

1. Verbatim indication: For the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older

2. SEE was established with:
   a. Adequate and well-controlled clinical investigation(s):
      i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations
   OR
   b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence[16,17,18]
   OR
   c. ☐ Evidence that supported SEE from a prior approval *(e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)*[17]

3. Complete response, if applicable
   a. ☐ SEE was established
   b. ☐ SEE was not established *(if checked, omit item 2)*

[16] FDA draft guidance for industry Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (2019)
[17] FDA guidance for industry Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products (1998)
[18] Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)

8.3. Review of Safety

Selection of the Safety Population

Data**:**
The data presented in this NDA includes 287 adult and pediatric patients from 4 studies: 1 pivotal study SNDX-5613-0700, and 3 supportive studies SNDX-5613-0702, SNDX-5613-0705, and SNDX-5613-0706.

The Applicant's Position:
Patients in these studies allowed for the adequate evaluation of the safety profile of revumenib in the intended population. The population of SNDX-5613-0700 was reflective of the intended indication and included patients with both AML and ALL aged 0.8 to 82 years.

Anticipated Safety Issues

Data:
The important identified risks for patients treated with revumenib are DS and QTc prolongation (Section 8.3.5).

The Applicant's Position:
DS is an important identified risk with potentially fatal consequences, mitigated with early recognition, systemic steroid treatment, and dose interruption. As such, a black box warning and medication guide for DS for revumenib is proposed. QTc prolongation is an important identified risk, with events managed with dose interruptions and reductions.

8.3.1. Safety Review Approach

Selection of the Safety Population

Data:

The overall Safety Population comprised 287 patients treated across all clinical trials, including 257 patients treated in SNDX-5613-0700. A total of 149 patients received doses corresponding to the RP2D, across both Phase 1 and Phase 2 of SNDX-5613-0700. The ISS dataset comprises data from both phases of SNDX-5613-0700, 3 supportive studies, and single patient protocols. Analyses of the following sets of data are the focus of this application:

- ISS RP2D Subset - consists of patients in SNDX-5613-0700 (Phase 2 and Phase 1) who were treated at the RP2D (N=149).
- ISS Overall Set - consists of all patients treated in SNDX-5613-0700 (N=257).

The Applicant's Position:

Safety data from the other supportive studies do not directly inform the safety profile of revumenib monotherapy in R/R AML patients as revumenib was given in combination with other therapies or is being investigated for the treatment of other indications.

The FDA's Assessment:

The safety database included data from 337 treatments in 324 unique participants; 13 participants who completed Study SNDX-5613-0700 were subsequently retreated on single-patient protocols and are assessed in these analyses as separate treatment events. The treatments were provided on four clinical trials and 50 single-patient protocols under the Applicant's IND; the four clinical trials are described in Section 7.1. Table 67 shows the numbers of patients by each trial and trial cohort.

FDA Table 67. Safety Database

STUDYID	Disease	Phase	Actual Treatment Cohort	CYP3A Inhibitor	Level	N
SNDX-5613-0700	AL	Phase 1	Arm A: 113 mg Q12H	No strong	L-2	1
SNDX-5613-0700	AL	Phase 1	Arm A: 226 mg Q12H		L-1	12
SNDX-5613-0700	AL	Phase 1	Arm A: 276 mg Q12H		RP2D	16
SNDX-5613-0700	AL	Phase 1	Arm A: 339 mg Q12H		L+1	8
SNDX-5613-0700	AL	Phase 1	Arm B: 113 mg Q12H	Strong	L-1	16
SNDX-5613-0700	AL	Phase 1	Arm B: 163 mg Q12H		RP2D	8
SNDX-5613-0700	AL	Phase 1	Arm B: 226 mg Q12H		L+1	7
SNDX-5613-0700	AL	Phase 1	Arm C: 113 mg Q12H	Cobistat (Strong)	L-1	13
SNDX-5613-0700	AL	Phase 1	Arm C: 163 mg Q12H		RP2D	13
SNDX-5613-0700	AL	Phase 1	Arm C: 226 mg Q12H		L+1	7
SNDX-5613-0700	AL	Phase 1	Arm C: 276 mg Q12H		L+2	6
SNDX-5613-0700	AL	Phase 1	Arm D: 163 mg Q12H	Moderate	L-2	7
SNDX-5613-0700	AL	Phase 1	Arm D: 226 mg Q12H		L-1	6
SNDX-5613-0700	AL	Phase 1	Arm E: 163 mg TID	None	TID	6
SNDX-5613-0700	AL	Phase 1	Arm F: 226 mg Q12H	Isavucon (Moderate)	L-1	6
SNDX-5613-0700	AL	Phase 2	163 mg Q12H or RP2D	RP2D	RP2D	125
SNDX-5613-0702	AL	Combo	Regimen 1	L-1	L-1	3
SNDX-5613-0702	AL	Combo	Regimen 2	L-1	L-1	3
SNDX-5613-0702	AL	Combo	Regimen 2	RP2D	RP2D	11
SNDX-5613-0705	AL		276 mg Q12H	No mod/strong	RP2D	5
SNDX-5613-0706	ST	Phase 1	163 mg Capsule/160 mg Tablet TID		TID	3
SNDX-5613-0706	ST	Phase 1	226 mg Capsule/220 mg Tablet TID		TID	5
SNDX-5613-SPP	AL		Unknown		UNK	50

Source: FDA analysis
Abbreviations: AL, acute leukemia; L, dose level; N, number of subjects; RP2D, recommended Phase 2 dose; ST, solid tumor

Due to the potential for drug interactions, the Phase 1 portion of Study SNDX-5613-0700 included robust evaluation of revumenib dosing with various CYP3Ai. The rows highlighted in green on Table 67 above represent the proposed recommended dosage for revumenib monotherapy for the intended population accounting for concomitant CYP3Ai use.

Based on the review of safety data monitoring (Section 8.3.3), it was concluded that data from SNDX-5613-0700 and SNDX-5613-0705 could be pooled for analysis. Table 68 below delineates the three populations for the safety analyses. All 337 treatments (highlighted in blue) are used for the assessment of fatal adverse reactions and differentiation syndrome, the 167 participants with acute leukemia treated with revumenib at the proposed recommended dosage (highlighted in green) are used for the main safety analyses (SAFPOP), and the 256 participants with acute leukemia treated with twice daily dosing on SNDX-5613-0700 and SNDX-5613-0705 (yellow cells) are used for the dose-toxicity analysis. For the purposes of the safety analyses in subsequent sections, subpopulations identified as KMT1Ar positive were identified based on local testing as reported in the variable ADLOC.MLLREAR.

FDA Table 68. Derivation of the Safety Analysis Sets

Level	Number of Participants by Study and Dose Level					All
	SNDX-5613-0700	SNDX-5613-0705	SNDX-5613-0702	SNDX-5613 SPP	SNDX-5613-0706	
L-2	8	0	0	0	0	8
L-1	53	0	6	0	0	59
RP2D	162*	5*	11	0	0	178
L+1	22	0	0	0	0	22
L+2	6	0	0	0	0	6
UNK	0	0	0	50	0	50
TID	6	0	0	0	8	14
All	257	5	17	50	8	337

Source: FDA analysis
Abbreviations: AL, acute leukemia; L, dose level; N, number of participants; RP2D, recommended Phase 2 dose; SPP, expanded-access single-patient protocols; ST, solid tumor; TID, three times a day; UNK, unknown
*SAFPOP n=167

Lastly, for presentation of data in the USPI, 135 participants were identified in the Safety Update Report (SUR) based on being treated on Studies SNDX-5613-0700 or SNDX-5613-0705, having acute leukemia, having a KMT2A translocation by local assay, and being treated with revumenib at the RP2D.

Anticipated Safety Issues

The Applicant's Position:
To further evaluate the important identified risks of DS and QTc prolongation the following approaches were implemented:

- The Sponsor, with FDA agreement, developed an identification algorithm for potential DS in line with Montesinos (2009) and updated by Norsworthy (2020). All patients enrolled in Cohorts 2A and 2B and patients from Phase 1 with *KMT2A*r treated at the RP2D were included.

- To identify TEAEs potentially associated with QTc prolongation, a search of the clinical database for SNDX-5613-0700 utilizing the SMQ (broad) for Torsade de pointes/QT prolongation was also conducted.

The FDA's Assessment:

Revumenib is a small molecule inhibitor of the KMT2A-menin interaction. The potential risks of revumenib derived from the drug chemistry, mechanism of action, and nonclinical studies, and those emerging during premarket clinical evaluations, are as follows:

- *QT prolongation*: Revumenib inhibited hERG potassium channel in vitro and increased the QTc interval when tested in dogs.
- *Hepatotoxicity*: Elevated transaminases and bilirubin were observed in rats and dogs. Hepatocellular necrosis occurred at high doses. Additionally, hepatocellular vacuolation consistent with lipid accumulation was seen in rats. Hepatocyte-specific deletion of *MEN1* induced liver steatosis in aging mice.[19]
- *Peripheral neuropathy*: Nerve fiber degeneration in the spinal cord and nerve fiber lesions were noted in the sciatic nerves in dogs.
- *Cataract development*: Focal or multifocal anterior lens opacities were seen in studies in rats.
- *Multiple endocrine neoplasms:* The *MEN1* gene is associated with tumor suppressor functions.[20] Patients with inactivating variants of *MEN1* develop tumors of the parathyroid, pancreatic islet, pituitary, and neuroendocrine cells in several organs. In the toxicology studies of revumenib, dose-dependent increases in the weights of the thyroid, parathyroid, and pituitary glands were observed but without corresponding microscopic changes other than hypertrophy (see Section 5.5.2).
- *Anemia and thrombocytopenia*: By mechanism of action, revumenib is not considered to be myelosuppressive. However, in nonclinical toxicology studies, anemia was observed at high doses, and decrease in platelet number was seen inconsistently. In colony-forming unit (CFU) assays, revumenib had no impact on CFU-GM, a small reduction of CFU-E and BFU-E at 6 µM and higher, and an IC50 of 0.12-0.33 µM for CFU-MK (Final Study Reports SNX-01 and SNX-02).
- *Differentiation syndrome (DS):* During the early phase of the trial, DS emerged as a risk that required revisions to the protocol for early management in order to mitigate serious outcomes.

[19] Cao Y, Xue Y, Xue L, et al. Hepatic menin recruits SIRT1 to control liver steatosis through histone deacetylation. J Hepatol. 2013;59:1299-306.
[20] Biancaniello C, D'Argenio A, Giordano D, et al. Investigating the Effects of Amino Acid Variations in Human Menin. Molecules. 2022;27:1747.

8.3.2. Review of the Safety Database

Overall Exposure

Data:

In the ISS RP2D Subset, median treatment duration was 10.0 weeks (range: 0, 89). Twenty-seven patients (18.1%) started 5 or more cycles of treatment. The median RDI was 98.02% (range: 35.0%, 101.1%). In the ISS Overall Set, median treatment duration was 9.7 weeks (range: 0, 89). Forty-nine patients (19.1%) started 5 or more cycles of treatment (SNDX-5613-0700 ISS Analysis, Table 14.1.3.1.1). The median RDI was 98.86% (range: 35.0%, 128.1%).

The Applicant's Position:
Exposure was within the range planned in the study protocols and is adequate to support characterization of the safety profile of revumenib.

The FDA's Assessment:

For all 337 treated participants, the median duration of treatment was 61 days (range, 1 - 620 days). For the 167 participants in the SAFPOP, the median duration of treatment period 1 was 69 days (range, 1 - 620 days). Table 69 shows the maximum duration of treatment for patients in the SAFPOP. Only 6% of the participants were treated for more than 6 months.

FDA Table 69. SAFPOP Duration of Exposure in Treatment Period 1

Treatment Duration	KMT2Ar Positive N=123 n, %		KMT2Ar Negative N=44 n, %		All N=167 n, %	
1 to 91 days	86	70%	28	64%	114	68%
92-182 days	33	27%	11	25%	44	26%
183-273 days	3	2%	5	11%	8	5%
More than 273 days	1	1%	0	0%	1	1%

Source: FDA analysis

Characteristics of the Safety Population

Data:

The majority of patients treated in the ISS RP2D Subset were White (103 [69.1%]) and female (92 [61.7%]), with a median age of 42.0 years (range: 1.3 to 82.0 years). There were 122 (81.9%) adult patients including 90 (60.4%) aged 18 to < 65 years, 22 (14.8%) aged 65 to < 75 years, and 10 (6.7%) aged ≥ 75 years. There were 27 (18.1%) pediatric patients who were aged < 18 years, including 4 (2.7%) aged < 2 years, 19 (12.8%) aged 2 to < 12 years, and 4 (2.7%) aged 12 to < 18 years. Most patients treated in the ISS RP2D Subset had an ECOG score of 1 (80 [53.7%]) with a similar proportion with a score of 0 or 2 (22 [14.8%] and

20 [13.4%], respectively). The median baseline left ventricular ejection fraction was 60.0% (range: 40, 78). The majority of patients were red blood cell or platelet transfusion dependent at baseline (76 [51.0%] and 86 [57.7%], respectively), with 94 (63.1%) being either red blood cell or platelet transfusion dependent.

The Applicant's Position:
The population of SNDX-5613-0700 was reflective of the intended indication in the US.

The FDA's Assessment:

Table 70 shows the demographics of the 337 participants in the safety database and by clinical trial.

FDA Table 70. Safety Database Demographics

	Study					All N=337
	SNDX-5613-0700 N=257	SNDX-5613-0705 N=5	SNDX-5613-0702 N=17	SNDX-5613 SPP N=50	SNDX-5613-0706 N=8	
Median age (range)	42 years (0.75, 82)	59 years (19, 78)	4 years (0.75, 37)	14 years (1, 71)	63.5 years (41, 69)	38 years (0.75, 82)
Age group (n, %)						
< 2 years	7 3%	0 0%	4 24%	3 6%	0 0%	14 4%
2 to < 12 years	25 10%	0 0%	6 35%	19 38%	0 0%	50 15%
12 to < 17 years	11 4%	0 0%	3 18%	6 12%	0 0%	20 6%
17 to < 65 years	157 61%	3 60%	4 24%	19 38%	4 50%	187 55%
65 to < 75 years	37 14%	0 0%	0 0%	3 6%	4 50%	44 13%
>= 75 years	20 8%	2 40%	0 0%	0 0%	0 0%	22 7%
Sex (n, %)						
Female	145 56%	1 20%	6 35%	29 58%	3 38%	184 55%
Male	112 44%	4 80%	11 65%	21 42%	5 63%	153 45%
Race (n, %)						
White	182 71%	3 60%	11 65%	33 66%	7 88%	236 70%
Black Or African American	20 8%	2 40%	1 6%	5 10%	0 0%	28 8%
Asian	22 9%	0 0%	2 12%	3 6%	1 13%	28 8%
American Indian or Alaska Native	1 < 1%	0 0%	0 0%	0 0%	0 0%	1 < 1%
Multiple	4 2%	0 0%	0 0%	0 0%	0 0%	4 1%
Unknown	28 11%	0 0%	3 18%	9 18%	0 0%	40 12%
Ethnicity (n, %)						
Not Hispanic or Latino	187 73%	4 80%	9 53%	33 66%	8 100%	241 72%
Hispanic Or Latino	53 21%	1 20%	6 35%	9 18%	0 0%	69 20%
Unknown	17 7%	0 0%	2 12%	8 16%	0 0%	27 8%
Disease (n, %)						
AML	223 87%	5 100%	13 76%	0 0%	0 0%	241 72%
ALL	28 11%	0 0%	3 18%	0 0%	0 0%	31 9%

FDA Table 70. Safety Database Demographics

	Study					All N=337
	SNDX-5613-0700 N=257	SNDX-5613-0705 N=5	SNDX-5613-0702 N=17	SNDX-5613 SPP N=50	SNDX-5613-0706 N=8	
MPAL	5 2%	0 0%	1 6%	0 0%	0 0%	6 2%
MDS	1 < 1%	0 0%	0 0%	0 0%	0 0%	1 < 1%
Solid tumor	0 0%	0 0%	0 0%	0 0%	8 100%	8 2%
Missing	0 0%	0 0%	0 0%	50 100%	0 0%	50 15%

Source: FDA analysis

Table 71 shows the demographics of the 167 participants in the SAFPOP and by KMT2Ar.

FDA Table 71. SAFPOP Demographics

	KMT2Ar Positive N=123	KMT2Ar Negative N=44	All N=167
Median age (range)	37 years (1.25, 79)	62 years (11, 82)	43 years (1.25, 82)
Age group (n, %)			
< 2 years	4 3%	0 0%	4 2%
2 to < 12 years	20 16%	1 2%	21 13%
12 to < 17 years	4 3%	0 0%	4 2%
17 to < 65 years	78 63%	24 55%	102 61%
65 to < 75 years	14 11%	9 20%	23 14%
>= 75 years	3 2%	10 23%	13 8%
Sex (n, %)			
Female	75 61%	25 57%	100 60%
Male	48 39%	19 43%	67 40%
Race (n, %)			
White	84 68%	33 75%	117 70%
Black or African American	10 8%	4 9%	14 8%
Asian	11 9%	4 9%	15 9%
American Indian or Alaska Native	0 0%	0 0%	0 0%
Multiple	2 2%	0 0%	2 1%
Unknown	16 13%	3 7%	19 11%
Ethnicity (n, %)			
Not Hispanic or Latino	85 69%	37 84%	122 73%
Hispanic Or Latino	27 22%	5 11%	32 19%
Unknown	11 9%	2 5%	13 8%
Disease (n, %)			
AML	102 83%	44 100%	146 87%
ALL	19 15%	0 0%	19 11%
MPAL	2 2%	0 0%	2 1%

Source: FDA analysis

Reviewer's comment: The predominance of KMT2Ar positive population in pediatric age group of 22% compared to 2% in KMT2Ar negative group reflects the increased incidence of KMT2A mutation in pediatric age group. The overall safety database and SAFPOP demographics reflects adequate representation of the target population for subjects with acute leukemia in United States.

Adequacy of the Safety Database:

Data:
The overall Safety Population comprised 287 patients, including 257 patients treated in Study SNDX-5613-0700. This included 149 patients in the ISS RP2D Subset. In the ISS R2PD Subset, median treatment duration overall was 10.0 weeks (range: 0, 89), with 88 patients (59.1%) who started 3 or more cycles of treatment, and 27 patients (18.1%) who started 5 or more cycles of treatment.

The Applicant's Position:
The integrated safety analysis plan and safety database presented herein were agreed upon with the Agency at the NDA Content Meeting in 2023 and confirmed at the pre-NDA meeting in 2023. The treatment duration observed allowed for adequate representation of the safety profile in the indicated population.

The FDA's Assessment:

FDA agrees that the size of the safety database is adequate to identify common AEs. The following issues are noted:

- Due to the relatively small number of patients treated at the recommended dosage (n=167), rare events may be missed.
- The proportion of pediatric patients is less than expected based on the SEER analysis (see Section 2.1).
- The proportion of minorities is consistent with the distribution in the US population based on the SEER analysis (see Section 2.1).
- The duration of treatment is too short to establish the safety profile with long-term use.

Reviewer's comment: Additional data for long-term use may be required in particularly the long-term effect on bone growth in pediatric patients.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The FDA's Assessment:

The data set for the Integrated Summary of Safety (ISS) was received in SDN 9.

The original data set could not be analyzed in MAED, because there were duplications in USUBJID and SUBJID in ADSL. Additionally, the ISS data set included screen failures not treated with revumenib and was missing TE flags, cause of death, flags for death within 30 days, actual dose level, and the data cutoff date for one or more studies other than SNDX-5613-0700. ADLB was missing grades for multiple labs, and the data elements for PARAMCD and AVALC were not standardized in all cases. ADVS had incorrect units for age. Also, diagnosis at study baseline was not collected for a substantial proportion of participants, but by design could be imputed from the initial diagnosis in Studies SNDX-5613-0700, SNDX-5613-0702, and SNDX-5613-0705. FDA conducted the initial safety review below using files in the ISS dataset in SDN 9 supplemented by hand with data from the individual study data sets.

A revised ISS data set was received with the SUR in SDN 35. The ISS data set from the SUR was used in the analyses for Section 6 of the USPI. FDA also corrected missing grades in the ADLB from the SUR for analysis of laboratory abnormalities used in the review below and in the USPI.

The Applicant also submitted an unsolicited revision of the ISS data set in SDN 76. The integrity of this version of the ISS data set is unknown, and as it was unsolicited, it is not used in this review.

Lastly, the Applicant submitted an update of the SNDX-5613-0700 data set in SDN 71. In the 7/29/2024 RIR, the Applicant indicated that this was a snapshot from the database for the on-going trial. As such, it is used solely in the safety analysis for the comparability of formulations.

Categorization of Adverse Event

The Applicant's Position:
Safety was assessed by the surveillance and recording of AEs (including SAEs). TEAEs were defined as AEs that start on or after the first administration of study drug and within 30 days of last dose date. MedDRA v23.0 and CTCAE version 5.0 were used for the safety analysis.

AESI are based on current safety data and known risks, and included DS, prolonged QTc, and peripheral neuropathy (PN). In order to improve the accuracy of estimating the risk of adverse reactions, grouped terms were used for some analyses.

The FDA's Assessment:

Adverse events and severe adverse events were defined according to ICH E2A guidelines.

Adverse events were reported down to the investigator's verbatim term. FDA confirms the external dictionaries used for grading and terminology as well as the definition of treatment-emergent as stated by the Applicant.

The FDA compared the verbatim adverse event term with the coded MedDRA Preferred Term and did not identify systematic irregularities. Terms that referred directly to relapse, persistence of disease, or progression of AML were excluded from the FDA's analyses. TEAEs were summarized by maximum grade per patient. A listing of the Grouped Terms used by FDA can be found in Appendix 14.6.4.

FDA identified differentiation syndrome (DS), QT prolongation, peripheral neuropathy, hepatotoxicity, cataracts, anemia, thrombocytopenia, and endocrine neoplasms as Adverse Events of Special Interest (AESI). Table 72 shows FDA's search strategy for AESIs.

FDA Table 72. Criteria Used to Ascertain AESI

AESI	Search Strategy
Differentiation syndrome	ADAE - PT Differentiation syndrome DS screening algorithm (see Section 8.3.5)
QT prolongation	ADAE - PT Electrocardiogram QT prolonged, HLT Ventricular arrhythmias and cardiac arrest; HLT Death and sudden death ADEG - Outlier analysis, arrythmias
Peripheral neuropathy	ADAE - PT Paraesthesia, Taste disorder, Neuropathy peripheral
Liver enzyme abnormalities	ADAE - HLT Liver function analyses ADLB - ALT, AST, bilirubin, alkaline phosphatase
Cataracts	ADAE - PT Cataract ADOE - Len abnormalities
Cytopenias	ADAE - Anaemia, Thrombocytopenia, Neutropenia, Neutrophil count decreased, Haemoglobin decreased, Platelet count decreased ADLB - Neutrophils, hemoglobin, platelets
Endocrine neoplasms	ADAE - HLGT Endocrine neoplasms benign, HLGT Endocrine neoplasms malignant and unspecified; PT Hyperparathyroidism, Hypercalcaemia, Hypoglycaemia, Abdominal pain, Diarrhoea, Ulcer, Headache, Hyperadrenocorticism, Hyperaldosteronism

Source: FDA analysis

Routine Clinical Tests

Data:

Laboratory assessments were performed at scheduled time points described in the

SNDX-5613-0700 study protocol and included hematology, chemistry, serology, and endocrine parameters. Laboratory results were graded according to CTCAE toxicity grade. Vital signs, ECG, and ECOG performance status were collected as per the protocol.

The Applicant's Position:

Routine clinical assessments and schedule were reasonable and adequate for the population.

The FDA's Assessment:

Table 73 describes the safety reporting instructions by protocol. The instructions were similar enough to allowing pooling for analyses as described in Section 8.3.1. FDA agrees that the safety tests and schedule of testing were adequate for the assessment of safety with the exception of coagulation studies.

FDA Table 73. Safety Data Reporting Instructions by Protocol

STUDYID	Deaths and SAEs	Grade AEs	Labs	AESIs
SNDX-5613-0700	SAEs collected until 30 days after the last SNDX-5613 dose. AEs and SAEs reported during HSCT while off SNDX-5613 as well as before resumption of SNDX-5613 will be summarized and listed separately.	All grade collected until 30 days after the last dose. For HSCT pts, TEAE collected form start of study drug until last dose before HSCT plus 30 days and AEs that begin after resumption of SNDX-5613 post HSCT and within 30 days after the last dose of SNDX-5613.	All lab tests considered significantly abnormal during the study or within 30 days after the last dose should be repeated until the value return to normal or baseline.	-Differentiation syndrome -QTcF prolongation (avg of triplicate EKG) grade 2 or higher -peripheral neuropathy All serious and non-serious AESI are collected and reported.
SNDX-5613-0705	Same as -0700	Same as -0700	Same as -0700	Same as -0700
SNDX-5613-0702	SAEs collected until 30 days after the last SNDX-5613 dose	All grade collected until 30 days after the last dose Collection of AE and SAEs for HSCT patients are the same as -0700	All lab tests considered significantly abnormal during the study or within 30 days after the last dose should be repeated until the value return to normal or baseline	All serious and non-serious AESI are collected and reported. • Differentiation syndrome • -QTcF prolongation (avg of triplicate EKG)grade 2 or higher • -peripheral neuropathy
SNDX-5613-0706	SAEs collected until 30 days after the last SNDX-5613 dose	All grade collected until 30 days after the last dose	All lab tests considered significantly abnormal during the study or within 30 days after the last dose should be repeated until the	All serious and non-serious AESI are collected and reported. • QTcF prolongation (avg of triplicate EKG)grade 2 or higher

FDA Table 73. Safety Data Reporting Instructions by Protocol

STUDYID	Deaths and SAEs	Grade AEs	Labs	AESIs
			value return to normal or baseline	• peripheral neuropathy Does not collect DS
SNDX-5613-SPP	Did not specify timing of data collection or reporting	Did not have specific data collection or time frame of reporting AEs and SAEs	All lab tests considered significantly abnormal during the study or within 30 days after the last dose should be repeated until the value return to normal or baseline	Each protocol mention AESI including • Differentiation syndrome • QTcF prolongation (avg of triplicate EKG)grade 2 or higher • peripheral neuropathy

Source: FDA analysis

8.3.4. Safety Results

Deaths

Data:

There were 151 deaths in the ISS Overall Set that were adjudicated by the Sponsor in addition to the Investigator-reported cause. Deaths occurring due to PD or occurring > 30 days (unless a related SAE) after the last dose were not to be reported as TEAEs leading to death. One hundred and eight deaths were adjudicated as being due to either of these situations and were not reported as TEAEs leading to death. There was 1 exception where the patient died 26 days after the last dose due to unknown cause; however, the patient was assessed as having disease progression before discontinuation of revumenib.

There were 43 TEAEs leading to death; the investigator-reported event terms and causalities are listed in Table 74. A summary of deaths for Study SNDX-5613-0700 is presented in Table 75. Of the 149 patients in the ISS RP2D Subset, 25 patients (16.8%) experienced TEAEs leading to death. Events occurring in > 1 patient in the ISS RP2D Subset were septic shock (5 patients [3.4%]), respiratory failure (4 patients [2.7%]), pneumonia (3 patients [2.0%]), haemorrhage intracranial (2 patients [1.3%]), and sudden death (2 patients [1.3%]) (SNDX-5613-0700 ISS Analysis, Table 14.3.19.1.1).

In the ISS Overall Set, TRAEs leading to death were observed in 4 patients (1.6%), with 1 patient (0.4%) each for the PTs of hemorrhage intracranial, myocardial ischemia, pneumonia, and respiratory failure (SNDX-5613-0700 ISS Analysis, Table 14.3.20.1.1). These are the same events reported in the ISS RP2D Subset.

Table 74 Applicant – Grade 5 Adverse Events within 30 days of Last Dose of Study Drug (Safety Population From SNDX-5613-0700)

Study Arm	Age/Gender	Study Day of Death	TEAE Leading to Death	Relationship to Study Drug
Phase 1 Arm A: 276 mg q12h	60.0/M	45	COVID-19 pneumonia	Not related
Phase 1 Arm B: 113 mg q12h	21.0/M	78	Haemorrhage intracranial	Unlikely related
Phase 1 Arm C: 113 mg q12h	34.0/F	112	Cardiac arrest	Not related
Phase 1 Arm B: 226 mg q12h	61.0/F	72	Sepsis	Not related
Phase 1 Arm C: 113 mg q12h	28.0/F	50	Respiratory failure	Not related
Phase 1 Arm B: 226 mg q12h	78.0/M	52	COVID-19	Not related
Phase 1 Arm C: 226 mg q12h	15.0/F	25	Sepsis	Not related
Phase 1 Arm A: 339 mg q12h	45.0/M	27	Septic shock	Not related
Phase 1 Arm C: 276 mg q12h	51.0/M	48	Sepsis	Not related
Phase 1 Arm A: 276 mg q12h	3.0/M	87	Septic shock	Not related
Phase 1 Arm D: 163 mg q12h	37.0M	18	Septic shock	Not related
Phase 1 Arm C: 113 mg q12h	22.0/F	87	Respiratory failure	Not related
Phase 1 Arm B: 163 mg q12h	64.0/F	93	Pneumonia	Unlikely related
Phase 1 Arm B: 113 mg q12h	56.0/F	85	Multiple organ dysfunction syndrome	Unlikely related
Phase 1 Arm B: 113 mg q12h	51.0/M	37	Sinusitis fungal	Not related
Phase 1 Arm D: 163 mg q12h	23.0/M	70	Haemorrhage intracranial	Not related
Phase 1 Arm C: 113 mg Q12h	36.0/M	47	Septic shock	Not related
Phase 1 Arm A: 226 mg q12h	31.0/M	82	Respiratory failure	Not related
Phase 1 Arm B: 113 mg q12h	40.0/F	88	Cardiac arrest	Not related
Phase 1 Arm C: 163 mg q12h	59.0/M	86	Central nervous system lesion	Not related
Phase 1 Arm C: 163 mg q12h	56.0/F	59	Sepsis	Not related
Phase 2 Cohort 2C: Patients with NPM1c AML	63/F	116	Cardio-respiratory arrest	Unlikely Related
Phase 2 Cohort 2B: Patients with *KMT2A*r AML	5/M	97	Hypoxia	Not Related
Phase 2 Cohort 2B: Patients with *KMT2A*r AML	45/M	9	Respiratory failure	Not Related
Phase 2 Cohort 2B: Patients with *KMT2A*r AML	74/M	99	Enterocolitis, Respiratory failure, Septic shock	Not Related
Phase 2 Cohort 2B: Patients with *KMT2A*r AML	55/F	68	Sudden death	Not Related
Phase 2 Cohort 2C: Patients with NPM1c AML	57/M	5	Upper gastrointestinal haemorrhage	Not Related
Phase 2 Cohort 2C: Patients with NPM1c AML	59/F	34	Sudden death	Not Related

Study Arm	Age/Gender	Study Day of Death	TEAE Leading to Death	Relationship to Study Drug
Phase 2 Cohort 2B: Patients with *KMT2A*r AML	57/F	51	Septic shock	Not Related
Phase 2 Cohort 2B: Patients with *KMT2A*r AML	18/F	71	Acute myeloid leukaemia	Not Related
Phase 2 Cohort 2B: Patients with *KMT2A*r AML	55/F	19	Haemorrhage intracranial	Probably Related
Phase 2 Cohort 2B: Patients with *KMT2A*r AML	38/F	34	Myocardial ischaemia	Possibly Related
Phase 2 Cohort 2C: Patients with NPM1c AML	80/F	3	Cardiac arrest	Not Related
Phase 2 Cohort 2B: Patients with *KMT2A*r AML	69/M	15	Respiratory failure	Possibly Related
Phase 2 Cohort 2C: Patients with NPM1c AML	60/M	45	Septic shock	Unlikely Related
Phase 2 Cohort 2B: Patients with *KMT2A*r AML	59/M	186	Respiratory failure, Septic shock	Not Related
Phase 2 Cohort 2B: Patients with *KMT2A*r AML	65/F	46	Fall	Not Related
Phase 2 Cohort 2C: Patients with NPM1c AML	63/F	66	Pneumonia	Not Related
Phase 2 Cohort 2A: Patients with *KMT2A*r ALL/MPAL	1.50/F	26	Pulmonary haemorrhage	Not Related
Phase 2 Cohort 2C: Patients with NPM1c AML	68/M	19	Haemorrhage intracranial	Not Related
Phase 2 Cohort 2B: Patients with *KMT2A*r AML	29/F	58	Pneumonia	Possibly Related
Phase 2 Cohort 2B: Patients with *KMT2A*r AML	36/M	127	Death	Not Related
Phase 2 Cohort 2C: Patients with NPM1c AML	71/M	54	Sepsis	Not Related

Note: There was 1 patient with an event (multiple organ dysfunction syndrome) not categorized as a TEAE due to start of new antileukemic therapy, which is not included in this table.
Source: SNDX-5613-0700 CSR Listing 16.3.2.1.1 and Listing 16.3.2.1.2

Table 75 Applicant – Summary of Deaths (Safety Population from SNDX-5613-0700)

	Ph1 N=132 n (%)	Ph2 N=125 n (%)
Total Deaths	82 (62.1)	69 (55.2)
Due to progressive disease	38 (28.8)	28 (22.4)
Due to adverse event	22* (16.7)	23 (18.4)
Other	12 (9.1)	6 (4.8)
Unknown	10 (7.6)	12 (9.6)
Deaths within 30 days after last dose	36 (27.3)	40 (32.0)
Due to progressive disease	11 (8.3)	12 (9.6)
Due to adverse event	22* (16.7)	22 (17.6)
Other	1 (0.8)	2 (1.6)
Unknown	2 (1.5)	4 (3.2)

	Ph1 N=132 n (%)	Ph2 N=125 n (%)
Deaths beyond 30 days after last dose	46 (34.8)	29 (23.2)
Due to progressive disease	27 (20.5)	16 (12.8)
Due to adverse event	0	1 (0.8)
Other	11 (8.3)	4 (3.2)
Unknown	8 (6.1)	8 (6.4)

*There was one patient with an event (multiple organ dysfunction syndrome) not categorized as a TEAE due to start of new antileukemic therapy.
Source: SNDX-5613-0700 CSR Listing 16.3.2.1.1 and Listing 16.3.2.1.2

The Applicant's Position:

R/R *KMT2A*r leukemia is a rapidly progressive disease with a high fatality rate and on-treatment deaths were expected in this population. In the ISS RP2D Subset, TEAEs leading to death were reported in 16.8% of patients and TRAEs leading to death in 2.7% of patients. The majority of deaths were related to complications of underlying disease.

The FDA's Assessment:

Deaths

There were 162 deaths reported in the safety database, including 151 on SNDX-5613-0700, 1 on SNDX-5613-0705, 4 on SNDX-5613-0702, and 6 on the single-patient protocols. (The ISS data set reflects 163 deaths, but in the 5/23/2024 RIR, the Applicant clarified that the report of death of Subject (b) (6) was an error.) Table 76 shows the numbers of deaths and numbers of deaths within 30 days of the last dose of revumenib in the SAFPOP and in the safety database.

FDA Table 76. SAFPOP and Safety Database Deaths

	SAFPOP						Safety Database N=337 n, %	
	KMT2Ar Positive N=123 n, %		KMT2Ar Negative N=44 n, %		All N=167 n, %			
Deaths	72	59%	23	52%	95	57%	162	48%
Deaths within 30 days of last dose of revumenib	32	26%	17	39%	49	29%	81	24%

Source: FDA analysis

Fatal Adverse Events

There were 60 fatal treatment-emergent adverse events reported in the safety database, including 47 on SNDX-5613-0700 and 13 on the single-patient protocols. Table 77 shows the numbers of

participants with fatal treatment-emergent adverse events in the SAFPOP and in the safety database. The most common TEAEs reported as fatal were Infection (5%), Respiratory failure (2%), Haemorrhage (2%), and terms related to death (2%).

FDA Table 77. SAFPOP and Safety Database Fatal TEAEs

TEAE*	SAFPOP						Safety Database N=337 n, %	
	KMT2Ar Positive N=123 n, %		KMT2Ar Negative N=44 n, %		All N=167 n, %			
Infection	5	4%	5	11%	10	6%	18	5%
Respiratory failure	4	3%	0	0%	4	2%	8	2%
Haemorrhage	2	2%	2	5%	4	2%	7	2%
Sudden death	1	1%	1	2%	2	1%	2	1%
Cardiac arrest	0	0%	1	2%	1	1%	3	1%
Viral infection	1	1%	0	0%	1	1%	2	1%
Central nervous system lesion	1	1%	0	0%	1	1%	1	< 1%
Death	1	1%	0	0%	1	1%	1	< 1%
Enterocolitis	1	1%	0	0%	1	1%	1	< 1%
Fall	1	1%	0	0%	1	1%	1	< 1%
Hypoxia	1	1%	0	0%	1	1%	1	< 1%
Myocardial ischaemia	1	1%	0	0%	1	1%	1	< 1%
Cardio-respiratory arrest	0	0%	1	2%	1	1%	1	< 1%
Multiple organ dysfunction syndrome	0	0%	0	0%	0	0%	2	1%
Abdominal pain	0	0%	0	0%	0	0%	1	< 1%
Bacterial infection	0	0%	0	0%	0	0%	1	< 1%
Decreased appetite	0	0%	0	0%	0	0%	1	< 1%
Fungal infection	0	0%	0	0%	0	0%	1	< 1%
Insomnia	0	0%	0	0%	0	0%	1	< 1%
Nausea	0	0%	0	0%	0	0%	1	< 1%

Source: FDA analysis
*Includes grouped terms

Fatal Adverse Reactions

FDA reviewed all deaths within 30 days of last dose of revumenib to determine whether the root cause of death was a fatal adverse reaction. For the purposes of adjudication, FDA assigned the root cause of death as the underlying malignancy in patients with malignancy that was active and nonresponsive. For 63% of the deaths, FDA and the Applicant agreed that the root cause was the underlying malignancy. Table 78 shows the FDA adjudication for the remainder of the deaths.

FDA Table 78. FDA-Adjudicated Root Causes of Death

USUBJID	Dose Level*	Applicant's Reason for Treatment Discontinuation	Applicant's Cause of Death	FDA-Adjudicated Cause of Death
(b) (6)	L-1	Other	Respiratory failure	Leukemia
	L-1	Adverse event	Multi-organ failure	AE-Infection
	L-1	Adverse event	Cardiac arrest.	Leukemia
	L+1	Other	Septic shock	AE-Infection
	RP2D	Adverse event	Other causes-cardiac arrest	Leukemia
	RP2D	Progressive disease	Cancer related	**AR-DS**
	L+1	Adverse event	Sepsis	Leukemia
	RP2D	Adverse event	Covid-19 pneumonia	AE-COVID
	RP2D	Adverse event	Grade 5 respiratory failure and septic shock	AE-Infection
	RP2D	Adverse event	Respiratory failure	Leukemia
	RP2D	Adverse event	Septic shock	AE-Infection
	L-2	Investigator decision	Septic shock	Leukemia
	L-2	Other	Unknown	Leukemia
	L+2	Adverse event	Septic shock	Leukemia
	RP2D	Adverse event	Septic shock	AE-Infection
	RP2D	Adverse event	Lung infection	AE-Infection
	RP2D	Adverse event	Upper gastrointestinal hemorrhage	Leukemia
	L+1	Adverse event	Septic shock	AE-Infection
	L-1	Adverse event	Cardiac arrest	**AR-Cardiac Arrest**
	L-2	Other	Intercranial hemorrhage	Leukemia
	RP2D	Progressive disease	Progression	**AR-Sudden Death**
	RP2D	Adverse event	Sudden death	**AR-Sudden Death**
	RP2D	Adverse event	Cardiac arrest, intracranial hemorrhage	**AR-Hemorrhage**
	RP2D	Adverse event	Cause of death currently unknown	**AR-Sudden Death**
	RP2D	Adverse event	Intracranial hemorrhage	**AR-Hemorrhage**
	RP2D	Adverse event	Septic shock	Leukemia
	RP2D	Adverse event	Cardiac ischemia	**AR-DS**
	RP2D	Adverse event	Respiratory failure	Leukemia
	UNK	Death	Missing	Leukemia
	UNK	Death	Missing	Leukemia

Source: FDA analysis
Abbreviations: AR, adverse reaction; UNK, unknown.
*See Table 67 for the explanation of the dose levels

FDA identified eight fatal adverse reactions. The following are narrative descriptions of the fatal adverse reactions:

(b) (6) A 1.5-year-old female with relapsed refractory KMT2Ar ALL-B lymphoblastic leukemia who was enrolled in a phase 2/cohort 2A and received revumenib 95 mg/M2 started on (b) (6) Her course was complicated by grade 3 differentiation syndrome on day 3, associated with fever, tachycardia, hypoxemia associated with bacteremia and small left-sided pleural effusion. She responded to dexamethasone which was discontinued on Day 9. She also developed pneumatosis intestinalis on day 13 and was treated with cefepime, metronidazole and total parenteral nutrition.
By day 17, the patient had increased abdominal distention with tachypnea associated with WBC of 11,000 and 31% monocytes. This progressed to respiratory failure associated with bilateral lung opacities, pleural effusion, edema, increased creatinine, and required ventilatory support and continuous hemofiltration by Day 20. Her symptoms were compatible with grade 4 DS and was restarted on dexamethasone on day 24 but no improvement. By day 26, she suddenly became more hypoxemic with blood in endotracheal tube and expired from pulmonary hemorrhage. DS was active at the time of death. FDA concluded that recurrence of differentiation syndrome was due to revumenib.

(b) (6) A 34-year-old Asian female with relapsed KMT2A AML treated on a phase 1/Arm C of revumenib at 113 mg Q12H with cobicistat 150 mg daily. She had prior menin inhibitor (JNJ 75276617) without response and investigational TMLI radiotherapy as conditioning regimen for haploidentical HSCT in (b) (6) There was no prior cardiac history noted at screening or during treatment. She achieved MLFS with 0% marrow blasts on Day 85 of revumenib. The patient was last seen on Day 111 for RBC and platelet transfusion. The site was notified of the patient death at home on Day 112. No outside records were available at the time of reporting. We concluded that cause of death was cardiac arrest. FDA could not exclude a possible relation to revumenib.

(b) (6) A 63-year-old white female with NPM1 mutated AML was treated on a Phase2/cohort 2C of revumenib at 163 mg Q12H. On Day 108, the patient was found unconscious at home. An emergency medical service initiated advanced cardiovascular life support for hypotension respiratory failure. She was subsequently transferred to an intensive care unit but remained unresponsive and was unable to wean off from ventilator. On Day 116, she was terminally extubated. An autopsy was not performed. The cause of death was adjudicated as sudden death. FDA could not exclude a possible relation to revumenib.

(b) (6) A 59-year-old female with NPM1 mutated AML with myelodysplastic related changes was treated on a phase 2/ cohort 2C of revumenib at 163 mg Q12H. Her treatment course was complicated by grade 4 differentiation syndrome on day 4 and resolved by Day 7 after treatment with steroids and hydroxyurea. She then developed Staphylococcal epidermidis bacteremia on day 22 and resolved by Day 27 after treatment with cefepime and vancomycin. CT scan showed decreasing liver lesions. On Day 33, she developed

syncope resulted in a fall and hit the left forehead at the end of CT scan. Neurological examination was normal. A chest CT showed resolved scattered ground glass/tree-in-bud opacities, decreased size of small pericardial effusion, and unchanged 4 mm left upper lobe pulmonary nodule. The patient was sent home on the same day. She was found dead in bed next day on Day 34. An autopsy showed scalp hematoma, no intracranial injury. Liver showed lymphoplasmacytic granulomatous inflammation with infiltration by fungal branching hyphae. Silver stain was positive for fungal organism. The cause of death was adjudicated as sudden death. FDA could not exclude a possible relation to revumenib.

(b) (6) A 55-year-old female with relapsed KMT2Ar AML was treated on a phase 2/Cohort 2B of revumenib at 163 mg Q12H. On Day 17, she was found unresponsive at home, an emergency medical service was called. She was resuscitated and taken to emergency department when she was intubated and hospitalized. CT head on the next day, Day 18 showed a large intracerebral hemorrhage with mass effect and herniation. Her platelet count was 1×10^9/L which increased to 56×10^9/L after platelet transfusion. The patient died from intracranial hemorrhage on Day 19 of study. The cause of death was adjudicated as hemorrhage. FDA concluded that hemorrhage was due to severe thrombocytopenia and could not exclude a possible relation to revumenib.

(b) (6) A 55-year-old white female with relapsed KMT2Ar AML was treated on a phase 2/cohort 2B of revumenib at 163 mg Q12H. On Day29, the patient was found on the floor at home, unable to speak but responsive and was taken to the hospital. He was diagnosed with intracranial hemorrhage based on brain CT scan and underwent craniectomy and was treated with levetiracetam, mannitol, cefazolin and posaconazole prophylaxis. He was discharged home on Day 38. On Day 67, the patient received platelet transfusion and had no problem before going to bed. On Day 68, he was found dead at home, confirmed by paramedics. No autopsy was performed. Cause of death was adjudicated as sudden death. FDA could not exclude a possible relation to revumenib.

(b) (6) A 68-year-old white male with relapsed NPM1 mutated AML was treated on a phase2/cohort 2C of revumenib at 163 mf Q12H**.** On Day 13**,** he was admitted for intracranial hemorrhage with platelet count of 13,000/µL and was treated with aminocaproic acid, levetiracetam, furosemide, Vitamin K and transfusion support. He expired from intracranial hemorrhage on Day 19. The cause of death was adjudicated as hemorrhage. FDA could not exclude a possible relation to revumenib.

(b) (6) A 32-year-old white female with KMT2Ar AML was treated on a phase 2/cohort 2B of revumenib at 163 mg Q12h. The patient had history of grade 2 differentiation syndrome (DS) on Day 15 and initially resolved after therapy with dexamethasone and hydroxyurea. The DS symptoms worsened after discontinuation of steroids and dexamethasone and hydroxyurea was restarted on Day 29 when WBC rose to 73.7 × 109/L with ANC at 73.0%. On Day 34, she presented to emergency room with blurred vision, chest pain and poor oral intake for 2 days. WBC count decreased to 36.4 K/mm3 with ANC was 33860/µL.

Potassium, lactic acid and liver enzymes were elevated, with normal bilirubin. Electrocardiogram (ECG) showed new right bundle branch block and left anterior fascicular block (RBBB/LAFB) and possibly a T wave inversion in lead I and AVL. The patient went unresponsive while in the waiting room and found to have no pulse or spontaneous respirations. Cardiopulmonary resuscitation was unsuccessful, and she expired that day. The DS was ongoing at the time of death of grade 5 myocardial infarction. Therefore, we concluded that cause of death was due to differentiation syndrome and led to myocardial infarction. FDA concluded that differentiation syndrome was related to revumenib.

Clinical TL Comment: A fatal adverse reaction was observed in 7/178 (4%) of participants treated at the RP2D, including 2 (1%) deaths due to DS. This warrants a boxed warning for DS. The etiology of the sudden deaths is not clear and requires further evaluation.

Serious Adverse Events

Data:

SAEs occurring in ≥ 3% of patients in the ISS RP2D Subset are presented in Table 79. The SAE of ECG QT prolonged was reported in 2.7% of patients (SNDX-5613-0700 ISS Analysis, Table 14.3.5.1.1).

Table 79: Applicant – SAEs in ≥ 3% Patients in the ISS RP2D Subset by PT (ISS Overall Set in Safety Population)

Preferred Term	163 mg q12h with strong CYP3A4 inhibitor (N=133) n(%)	276 mg q12h without strong CYP3A4 inhibitor (N=16) n(%)	ISS RP2D Subset (N=149) n(%)	ISS Overall Set (N=257) n(%)
Any serious TEAE	105 (78.9)	14 (87.5)	119 (79.9)	187 (72.8)
Febrile neutropenia	33 (24.8)	3 (18.8)	36 (24.2)	58 (22.6)
Differentiation syndrome	20 (15.0)	0	20 (13.4)	25 (9.7)
Pneumonia	9 (6.8)	2 (12.5)	11 (7.4)	14 (5.4)
Sepsis	9 (6.8)	0	9 (6.0)	22 (8.6)
Septic shock	7 (5.3)	1 (6.3)	8 (5.4)	12 (4.7)
Respiratory failure	6 (4.5)	2 (12.5)	8 (5.4)	12 (4.7)
Bacteremia	8 (6.0)	0	8 (5.4)	9 (3.5)
Nausea	5 (3.8)	0	5 (3.4)	6 (2.3)

Source: SNDX-5613-0700 ISS Analysis, Table 14.3.5.1.1

The Applicant's Position:

AML is a life-threatening disease, and SAEs occurred in 79.9% of patients in the ISS RP2D Subset. The most common SAEs were febrile neutropenia, DS, pneumonia, sepsis, bacteremia, respiratory failure, and septic shock.

The FDA's Assessment:

An SAE was reported for 79% of participants in the SAFPOP. Table 80 shows the incidence of SAEs by SOC in the SAFPOP. The SOCs with the highest incidences of SAEs were Infections and infestations, Blood and lymphatic system disorders, and Vascular disorders.

FDA Table 80. SAFPOP - SAEs by SOC

SOC	SAFPOP N=167	
	n	(%)
Infections and infestations	65	38.9
Blood and lymphatic system disorders	44	26.3
Vascular disorders	31	18.6
Gastrointestinal disorders	22	13.2
Neoplasms benign, malignant and unspecified	21	12.6
Respiratory, thoracic and mediastinal disorders	16	9.6
Cardiac disorders	12	7.2
General disorders and administration site conditions	11	6.6
Metabolism and nutrition disorders	10	6.0
Investigations	8	4.8
Musculoskeletal and connective tissue disorders	8	4.8
Nervous system disorders	7	4.2
Injury, poisoning and procedural complications	5	3.0
Psychiatric disorders	2	1.2
Endocrine disorders	1	0.6
Skin and subcutaneous tissue disorders	1	0.6

Source: FDA analysis

Table 81 shows the SAEs with an incidence of at least 2% reported for the SAFPOP. The most common events reported as SAEs were Infection, Febrile neutropenia, Bacterial infection, Haemorrhage, and Differentiation syndrome.

FDA Table 81. SAFPOP - SAEs

SAE*	SAFPOP N=167	
	n	(%)
Infection	45	27
Febrile neutropenia	38	23
Bacterial infection	29	17
Haemorrhage	21	13
Differentiation syndrome	20	12
Thrombosis	9	5
Respiratory failure	8	5
Viral infection	7	4
Musculoskeletal pain	6	4
Depressed level of consciousness	5	3
Electrocardiogram QT prolonged	5	3
Fungal infection	5	3
Nausea	5	3
Diarrhoea	4	2

Source: FDA analysis
*Includes grouped terms

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

TEAEs leading to treatment discontinuations occurred were reported for 22 patients (14.8%) in the ISS RP2D Subset. All TEAEs that led to discontinuation were reported for single patients apart from septic shock (4 patients [2.7%]), hemorrhage intracranial (2 patients [1.3%]), respiratory failure (2 patients [1.3%]), and sudden death (2 patients [1.3%]) (SNDX-5613-0700 ISS Analysis, Table 14.3.15.1.1). Other TEAEs leading to discontinuation were AML, arthralgia, atrioventricular block second degree, back pain, COVID-19 pneumonia, cardiac arrest, cardiac failure, febrile neutropenia, myocardial ischemia, nausea, neck pain, pneumonia, sepsis, upper gastrointestinal hemorrhage, and vomiting (SNDX-5613-0700 ISS Analysis, Table 1.3.15.1.1).

The Applicant's Position:

TEAEs leading to discontinuation occurred in a minority of patients. The important identified risks of DS or QTc prolongation were manageable and did not lead to discontinuation in Study SNDX-5613-0700.

The FDA's Assessment:

TEAEs resulted in permanent discontinuation for 14% of participants in the SAFPOP. Table 82 shows the TEAEs that resulted in permanent discontinuation in the SAFPOP. The most common events reported were infections.

FDA Table 82. SAFPOP - TEAEs Resulting in Withdrawal

TEAE*	SAFPOP N=167	
	n	(%)
Infection	6	3.6
Haemorrhage	3	1.8
Respiratory failure	2	1.2
Sudden death	2	1.2
Atrioventricular block second degree	1	0.6
Cardiac arrest	1	0.6
Cardiac failure	1	0.6
Central nervous system lesion	1	0.6
Electrocardiogram QT prolonged	1	0.6
Febrile neutropenia	1	0.6
Musculoskeletal pain	1	0.6
Myocardial ischaemia	1	0.6
Nausea	1	0.6
Viral infection	1	0.6

Source: FDA analysis
*Includes grouped terms

Dose Interruption/Reduction Due to Adverse Effects

Data:

A total of 75 patients (50.3%) in the ISS RP2D Subset required a dose interruption (ie, dose delayed or dose skipped) due to a TEAE (SNDX-5613-0700 ISS Analysis, Table 14.3.13.1.1). This included patients who had interruptions and restarted treatment on the same day as directed by protocol for electrolyte management and/or QTc prolongation. The most commonly reported TEAEs (≥ 4%) that led to dose interruptions in the ISS RP2D Subset were ECG QT prolonged (23 patients [15.4%]), hypokalaemia (12 patients [8.1%]), febrile neutropenia (11 patients [7.4%]), vomiting (10 patients [6.7%]), DS (8 patients [5.4%]), ALT increased (7 patients [4.7%]), and AST increased (6 patients [4.0%]).

TEAEs leading to dose reductions occurred in 20 patients (13.4%) in the ISS RP2D Subset (SNDX-5613-0700 ISS Analysis, Table 14.3.14.1.1). These all were reported for single patients apart from ECG QT prolonged (12 patients [8.1%]), thrombocytopenia (4 patients [2.7%]), neutropenia (3 patients [2.0%]), and nausea (2 patients [1.3%]).

The Applicant's Position:

Guidance for dose interruption and dose reduction were provided in the SNDX-5613-0700 study protocol. The incidence of TEAEs leading to reduction was low. Most events of DS were managed by dose interruption and administration of steroids and most events of QTc prolonged were managed by dose interruption or reduction.

The FDA's Assessment:

TEAEs resulted in dose reduction for 13% and in dose interruption for 50% of participants in the SAFPOP. Table 83 shows all TEAEs that resulted in dose reduction and TEAEs that resulted in dose interruption in at least 2% of the SAFPOP. QT prolongation was the most common event associated with dose reductions or dose interruptions.

FDA Table 83. SAFPOP - TEAEs Resulting in Dose Reduction or Dose Interruption

	SAFPOP N=167	
TEAE*	**n**	**(%)**
For Dose Reductions		
Electrocardiogram QT prolonged	13	7.8
Thrombocytopenia	4	2.4
Neutropenia	3	1.8
Nausea	2	1.2
Anaemia	1	0.6
Decreased appetite	1	0.6
Infection	1	0.6
Transaminases increased	1	0.6
Weight decreased	1	0.6
White blood cell count decreased	1	0.6
For Dose Interruptions*		
Electrocardiogram QT prolonged	25	15
Febrile neutropenia	14	8.4
Infection	14	8.4
Nausea	13	7.8
Hypokalaemia	12	7.2
Transaminases increased	9	5.4

FDA Table 83. SAFPOP - TEAEs Resulting in Dose Reduction or Dose Interruption

TEAE*	SAFPOP N=167	
	n	(%)
Differentiation syndrome	8	4.8
Haemorrhage	6	3.6
Bacterial infection	4	2.4
Diarrhoea	4	2.4
Respiratory failure	4	2.4

Source: FDA analysis
*Includes grouped terms; **In at least 2% of the SAFPOP

Clinical TL Comment: Sudden death, QT prolongation, infection, bleeding, and DS were the events identified most frequently as serious and requiring intervention. Infection and bleeding may have resulted from leukemia-related cytopenias, but the cardiac events and DS would be considered ARs.

Reviewer's comment: the most common reasons for dose interruptions and dose reduction of revumenib were due to QTc prolongation in both RDMLLr and RDNMLL.

Significant Adverse Events

Data:

There were 136 patients (91.3%) in the ISS RP2D Subset with a TEAE Grade ≥ 3 (Table 84).

Table 84: Applicant – Study Drug TEAEs Grade ≥ 3 Reported for ≥ 10% Patients in the ISS RP2D Subset by PT (ISS Overall Set in Safety Population)

Preferred Term	Maximum CTCAE grade	163 mg q12h with strong CYP3A4 inhibitor (N=133) n(%)	276 mg q12h without strong CYP3A4 inhibitor (N=16) n(%)	ISS RP2D Subset (N=149) n(%)	ISS Overall Set (N=257) n(%)
Any ≥ Grade 3 TEAEs	Grade 3-5	122 (91.7)	14 (87.5)	136 (91.3)	222 (86.4)
	Grade 3	46 (34.6)	8 (50.0)	54 (36.2)	91 (35.4)
	Grade 4	53 (39.8)	4 (25.0)	57 (38.3)	88 (34.2)
	Grade 5	23 (17.3)	2 (12.5)	25 (16.8)	43 (16.7)
Febrile neutropenia	Grade 3-5	53 (39.8)	4 (25.0)	57 (38.3)	90 (35.0)
	Grade 3	53 (39.8)	4 (25.0)	57 (38.3)	89 (34.6)
	Grade 4	0	0	0	1 (0.4)
Electrocardiogram QT prolonged	Grade 3-5	23 (17.3)	3 (18.8)	26 (17.4)	34 (13.2)
	Grade 3	22 (16.5)	3 (18.8)	25 (16.8)	33 (12.8)
	Grade 4	1 (0.8)	0	1 (0.7)	1 (0.4)
Anaemia	Grade 3-5	27 (20.3)	2 (12.5)	29 (19.5)	42 (16.3)

Preferred Term	Maximum CTCAE grade	163 mg q12h with strong CYP3A4 inhibitor (N=133) n(%)	276 mg q12h without strong CYP3A4 inhibitor (N=16) n(%)	ISS RP2D Subset (N=149) n(%)	ISS Overall Set (N=257) n(%)
	Grade 3	24 (18.0)	2 (12.5)	26 (17.4)	39 (15.2)
	Grade 4	3 (2.3)	0	3 (2.0)	3 (1.2)
Neutrophil count decreased	Grade 3-5	20 (15.0)	2 (12.5)	22 (14.8)	34 (13.2)
	Grade 3	4 (3.0)	0	4 (2.7)	5 (1.9)
	Grade 4	16 (12.0)	2 (12.5)	18 (12.1)	29 (11.3)
Platelet count decreased	Grade 3-5	20 (15.0)	2 (12.5)	22 (14.8)	39 (15.2)
	Grade 3	1 (0.8)	0	1 (0.7)	5 (1.9)
	Grade 4	19 (14.3)	2 (12.5)	21 (14.1)	34 (13.2)
Differentiation syndrome	Grade 3-5	20 (15.0)	0	20 (13.4)	23 (8.9)
	Grade 3	18 (13.5)	0	18 (12.1)	21 (8.2)
	Grade 4	2 (1.5)	0	2 (1.3)	2 (0.8)
White blood cell count decreased	Grade 3-5	19 (14.3)	1 (6.3)	20 (13.4)	34 (13.2)
	Grade 3	6 (4.5)	1 (6.3)	7 (4.7)	12 (4.7)
	Grade 4	13 (9.8)	0	13 (8.7)	22 (8.6)
Pneumonia	Grade 3-5	14 (10.5)	2 (12.5)	16 (10.7)	20 (7.8)
	Grade 3	10 (7.5)	2 (12.5)	12 (8.1)	15 (5.8)
	Grade 4	1 (0.8)	0	1 (0.7)	2 (0.8)
	Grade 5	3 (2.3)	0	3 (2.0)	3 (1.2)

Source: SNDX-5613-0700 ISS Analysis, Table 14.3.8.1.1.

The Applicant's Position:

Most patients experienced Grade 3 or Grade 4 TEAEs primarily related to underlying disease. The most common Grade ≥ 3 TEAE was febrile neutropenia.

The FDA's Assessment:

See Sections 8.3.5 and 8.3.8.

Treatment-Emergent Adverse Events and Adverse Reactions

Data:

A summary of TEAEs is provided in Table 85.

Table 85: Applicant – Summary of TEAEs (ISS Overall Set in Safety Population)

	163 mg q12h with strong CYP3A4 inhibitor (N=133) n(%)	276 mg q12h without strong CYP3A4 inhibitor (N=16) n(%)	ISS RP2D Subset (N=149) n(%)	ISS Overall Set (N=257) n(%)
Any grade TEAE	131 (98.5)	15 (93.8)	146 (98.0)	251 (97.7)

	163 mg q12h with strong CYP3A4 inhibitor (N=133) n(%)	276 mg q12h without strong CYP3A4 inhibitor (N=16) n(%)	ISS RP2D Subset (N=149) n(%)	ISS Overall Set (N=257) n(%)
Grade ≥ 3 TEAE	122 (91.7)	14 (87.5)	136 (91.3)	222 (86.4)
SAE	105 (78.9)	14 (87.5)	119 (79.9)	187 (72.8)
TEAEs leading to death	23 (17.3)	2 (12.5)	25 (16.8)	43 (16.7)
TRAEs leading to death	4 (3.0)	0	4 (2.7)	4 (1.6)
TEAEs leading to Dose Modification	71 (53.4)	7 (43.8)	78 (52.3)	123 (47.9)
TEAE leading to Dose Reduction	17 (12.8)	3 (18.8)	20 (13.4)	30 (11.7)
TEAE leading to Dose Interruption	69 (51.9)	6 (37.5)	75 (50.3)	116 (45.1)
TEAEs leading to study drug discontinuation	19 (14.3)	3 (18.8)	22 (14.8)	33 (12.8)
AESI	67 (50.4)	9 (56.3)	76 (51.0)	116 (45.1)
Differentiation syndrome	33 (24.8)	5 (31.3)	38 (25.5)	48 (18.7)
Prolonged QTc of CTCAE Grade 2 or higher	37 (27.8)	6 (37.5)	43 (28.9)	64 (24.9)
Peripheral Neuropathy	5 (3.8)	0	5 (3.4)	19 (17.4)

Source: SNDX-5613-0700 ISS Analysis, Table 14.3.1.1.1

TEAEs that occurred in ≥ 10% of patients in the ISS RP2D Subset are summarized in Table 86.

Table 86: Applicant – TEAEs Occurring in ≥ 10% Patients in the ISS RP2D Subset by PT (ISS Overall Set in Safety Population)

Preferred Term	163 mg q12h with strong CYP3A4 inhibitor (N=133) n(%)	276 mg q12h without CYP3A4 inhibitor (N=16) n(%)	ISS RP2D Subset (N=149) n(%)	ISS Overall Set (N=257) n(%)
Any TEAEs	131 (98.5)	15 (93.8)	146 (98.0)	251 (97.7)
Nausea	54 (40.6)	7 (43.8)	61 (40.9)	113 (44.0)
Febrile neutropenia	55 (41.4)	4 (25.0)	59 (39.6)	93 (36.2)
Electrocardiogram QT prolonged	44 (33.1)	8 (50.0)	52 (34.9)	88 (34.2)
Diarrhoea	43 (32.3)	7 (43.8)	50 (33.6)	76 (29.6)
Vomiting	43 (32.3)	6 (37.5)	49 (32.9)	88 (34.2)
Hypokalaemia	40 (30.1)	2 (12.5)	42 (28.2)	59 (23.0)
Epistaxis	41 (30.8)	0	41 (27.5)	62 (24.1)
Differentiation syndrome	33 (24.8)	5 (31.3)	38 (25.5)	48 (18.7)
Fatigue	33 (24.8)	3 (18.8)	36 (24.2)	67 (26.1)
Oedema peripheral	33 (24.8)	2 (12.5)	35 (23.5)	57 (22.2)
Anaemia	32 (24.1)	2 (12.5)	34 (22.8)	54 (21.0)
Constipation	30 (22.6)	4 (25.0)	34 (22.8)	52 (20.2)

Preferred Term	163 mg q12h with strong CYP3A4 inhibitor (N=133) n(%)	276 mg q12h without CYP3A4 inhibitor (N=16) n(%)	ISS RP2D Subset (N=149) n(%)	ISS Overall Set (N=257) n(%)
Decreased appetite	27 (20.3)	3 (18.8)	30 (20.1)	50 (19.5)
Aspartate aminotransferase increased	29 (21.8)	0	29 (19.5)	50 (19.5)
Hyponatraemia	21 (15.8)	7 (43.8)	28 (18.8)	43 (16.7)
Alanine aminotransferase increased	26 (19.5)	1 (6.3)	27 (18.1)	51 (19.8)
Dyspnoea	25 (18.8)	2 (12.5)	27 (18.1)	44 (17.1)
Abdominal pain	21 (15.8)	3 (18.8)	24 (16.1)	43 (16.7)
Arthralgia	19 (14.3)	5 (31.3)	24 (16.1)	44 (17.1)
Back pain	20 (15.0)	3 (18.8)	23 (15.4)	41 (16.0)
Platelet count decreased	21 (15.8)	2 (12.5)	23 (15.4)	43 (16.7)
Cough	20 (15.0)	2 (12.5)	22 (14.8)	37 (14.4)
Headache	21 (15.8)	1 (6.3)	22 (14.8)	48 (18.7)
Neutrophil count decreased	20 (15.0)	2 (12.5)	22 (14.8)	36 (14.0)
White blood cell count decreased	21 (15.8)	1 (6.3)	22 (14.8)	36 (14.0)
Hypomagnesaemia	19 (14.3)	2 (12.5)	21 (14.1)	28 (10.9)
Pain in extremity	20 (15.0)	1 (6.3)	21 (14.1)	32 (12.5)
Pyrexia	17 (12.8)	3 (18.8)	20 (13.4)	42 (16.3)
Stomatitis	18 (13.5)	2 (12.5)	20 (13.4)	29 (11.3)
Pneumonia	16 (12.0)	2 (12.5)	18 (12.1)	23 (8.9)
Dysgeusia	16 (12.0)	1 (6.3)	17 (11.4)	35 (13.6)
Hyperphosphatasemia	14 (10.5)	3 (18.8)	17 (11.4)	39 (15.2)
Hyperkalaemia	13 (9.8)	3 (18.8)	16 (10.7)	26 (10.1)
Insomnia	15 (11.3)	1 (6.3)	16 (10.7)	21 (8.2)
Thrombocytopenia	15 (11.3)	1 (6.3)	16 10.7)	24 (9.3)
Blood alkaline phosphatase increased	14 (10.5)	1 (6.3)	15 (10.1)	31 (12.1)
Hyperglycaemia	15 (11.3)	0	15 (10.1)	29 (11.3)
Pleural effusion	15 (11.3)	0	15 (10.1)	21 (8.2)

Source: SNDX-5613-0700 ISS Analysis, Table 14.3.3.1.1

The Applicant's Position:

The most common TEAEs (> 20%) were nausea, febrile neutropenia, ECG QT prolonged, diarrhea, vomiting, hypokalemia, epistaxis, DS, fatigue, oedema peripheral, anaemia, and constipation. The AE profile of revumenib is predictable, and TEAEs are primarily related to the underlying disease, mechanism of action, or were expected based on preclinical characterization.

The FDA's Assessment:

Common TEAE

TEAEs were reported for 99% of participants in the SAFPOP. Table 87 shows the incidence of TEAEs by SOC in the SAFPOP. The SOCs with the highest incidences of SAEs were

Gastrointestinal disorders, Metabolism and nutrition disorders, Investigations, and Infections and infestations.

FDA Table 87. SAFPOP - TEAEs by SOC

SOC	SAFPOP N=167	
	n	(%)
Gastrointestinal disorders	128	76.6
Metabolism and nutrition disorders	121	72.5
Investigations	117	70.1
Infections and infestations	111	66.5
Blood and lymphatic system disorders	102	61.1
General disorders and administration site conditions	102	61.1
Vascular disorders	97	58.1
Respiratory, thoracic and mediastinal disorders	83	49.7
Musculoskeletal and connective tissue disorders	82	49.1
Nervous system disorders	68	40.7
Skin and subcutaneous tissue disorders	59	35.3
Psychiatric disorders	48	28.7
Cardiac disorders	45	26.9
Neoplasms benign, malignant and unspecified	45	26.9
Renal and urinary disorders	31	18.6
Injury, poisoning and procedural complications	29	17.4
Eye disorders	24	14.4
Ear and labyrinth disorders	12	7.2
Hepatobiliary disorders	12	7.2
Reproductive system and breast disorders	10	6.0
Endocrine disorders	6	3.6
Immune system disorders	6	3.6
Congenital, familial and genetic disorders	1	0.6
Product issues	1	0.6

Source: FDA analysis

Table 88 shows the most common (>= 15%) TEAEs in the SAFPOP. See Appendix 14.6.5 for the list of TEAEs that occurred in at least 2 participants.

FDA Table 88. SAFPOP - Common TEAEs

TEAE*	SAFPOP N=167	
	n	(%)
Haemorrhage	86	51.5
Nausea	85	50.9
Infection	74	44.3
Musculoskeletal pain	70	41.9
Febrile neutropenia	68	40.7
Electrocardiogram QT prolonged	57	34.1
Diarrhoea	53	31.7
Bacterial infection	50	29.9
Oedema	48	28.7
Transaminases increased	43	25.7
Hypokalaemia	42	25.1
Differentiation syndrome	41	24.6
Fatigue	41	24.6
Constipation	39	23.4
Anaemia	37	22.2
Decreased appetite	34	20.4
Viral infection	34	20.4
Dyspnoea	33	19.8
Abdominal pain	29	17.4
Hyponatraemia	29	17.4
Headache	26	15.6
Cough	25	15.0
Platelet count decreased	25	15.0

Source: FDA analysis
*Includes grouped terms

Grades 3-5 TEAE

Grades 3-5 TEAEs were reported for 90% of participants in the SAFPOP. Table 89 shows those that occurred in at least 2% the SAFPOP.

FDA Table 89. SAFPOP - Grades 3-5 TEAEs

TEAE*	SAFPOP N=167	
	n	(%)
Febrile neutropenia	65	38.9
Infection	55	32.9
Anaemia	31	18.6
Bacterial infection	31	18.6
Electrocardiogram QT prolonged	28	16.8
Haemorrhage	25	15.0
Neutrophil count decreased	23	13.8
Platelet count decreased	23	13.8
White blood cell count decreased	21	12.6
Differentiation syndrome	20	12.0
Thrombocytopenia	16	9.6
Hypokalaemia	14	8.4
Transaminases increased	13	7.8
Decreased appetite	12	7.2
Diarrhoea	10	6.0
Fatigue	10	6.0
Respiratory failure	10	6.0
Dyspnoea	9	5.4
Musculoskeletal pain	9	5.4
Neutropenia	9	5.4
Thrombosis	9	5.4
Nausea	8	4.8
Viral infection	8	4.8
Depressed level of consciousness	7	4.2
Hypermagnesaemia	7	4.2
Leukocytosis	7	4.2
Cardiac failure	6	3.6
Hypertension	6	3.6
Fungal infection	5	3.0
Hypotension	5	3.0
Renal impairment	5	3.0
Stomatitis	5	3.0
Bone pain	4	2.4
Hyperbilirubinaemia	4	2.4

FDA Table 89. SAFPOP - Grades 3-5 TEAEs

TEAE*	SAFPOP N=167	
	n	(%)
Hyperglycaemia	4	2.4
Hypoxia	4	2.4

Source: FDA analysis
*Includes grouped terms

Related TEAE

TEAEs were reported by investigators to be at least possibly related to revumenib for 80% of participants in the SAFPOP. Table 90 shows those that occurred in at least 5% the SAFPOP.

FDA Table 90. SAFPOP - Related TEAEs

TEAE*	SAFPOP N=167	
	n	(%)
Electrocardiogram QT prolonged	53	31.7
Nausea	52	31.1
Differentiation syndrome	40	24.0
Haemorrhage	22	13.2
Decreased appetite	21	12.6
Febrile neutropenia	20	12.0
Taste disorder	17	10.2
Anaemia	16	9.6
Platelet count decreased	16	9.6
Fatigue	15	9.0
Transaminases increased	15	9.0
Musculoskeletal pain	14	8.4
Oedema	14	8.4
Neutrophil count decreased	13	7.8
White blood cell count decreased	12	7.2
Hypokalaemia	11	6.6
Diarrhoea	10	6.0
Thrombocytopenia	10	6.0
Dyspnoea	9	5.4
Infection	9	5.4

Source: FDA analysis
*Includes grouped terms

Clinical TL Comment: Cardiac events, cytopenias, differentiation syndrome, edema, electrolyte abnormalities, elevated transaminases, gastrointestinal disorders, infections, musculoskeletal pain, and taste disorders were consistently identified as common TEAE. Additional characterization of edema, gastrointestinal disorders, musculoskeletal pain, and taste disorder will be needed.

Laboratory Findings

Data:

New or worsening laboratory abnormalities for the Cohort 2A+2B safety population (N=94) in SNDX-5613-0700 is provided in Table 91.

Table 91: Applicant – Most Common (≥ 10% [Any Grade]) New or Worsening Laboratory Abnormalities in Patients with R/R Leukemia with *KMT2A*r

	Cohort 2A+2B Safety Population	
Parameter	**All Grades, n (%)**	**Grade ≥ 3, n (%)**
Hematology		
Hemoglobin decrease (n = 94)	54 (57)	49 (52)
Leukocytes decrease (n = 79)	38 (48)	33 (42)
Lymphocytes decrease (n = 83)	42 (51)	32 (39)
Lymphocytes increase (n = 83)	13 (16)	1 (1)
Neutrophils decrease (n = 87)	22 (25)	22 (25)
Platelets decrease (n = 94)	45 (48)	43 (46)
Chemistry		
Alanine aminotransferase increase (n = 94)	30 (32)	4 (4)
Albumin decrease (n = 94)	49 (52)	6 (6)
Aspartate aminotransferase increase (n = 94)	37 (39)	4 (4)
Bilirubin increase (n = 94)	17 (18)	4 (4)
Calcium corrected increase (n = 93)	16 (17)	0
Creatinine increase (n = 94)	20 (21)	2 (2)
Magnesium decrease (n = 94)	10 (11)	0
Magnesium increase (n = 94)	16 (17)	5 (5)
Potassium decrease (n = 94)	28 (30)	5 (5)
Potassium increase (n = 94)	11 (12)	2 (2)
Sodium decrease (n = 94)	36 (38)	0

The denominator used to calculate the rate varied from 79 to 94 and was based on the number of patients with a baseline value and at least one post-treatment value.
Source: SNDX-5613-0700 CSR, Table 14.4.5.2.1 and Table 14.4.6.2.1

The Applicant's Position:

As expected, the majority of patients in this heavily pretreated R/R acute leukemia population had cytopenia at baseline. Hematology and chemistry laboratory values varied throughout the course of treatment, without an identifiable trend. This reflects the clinical course and the

associated complications of the underlying disease such as sepsis, concomitant medications, and platelet transfusions. No patients in the Safety Population fulfilled Hy's law criteria.

The FDA's Assessment:

Table 92 shows the new or worsening nonhematological laboratory abnormalities in the SAFPOP based on data in the SUR (see Section 8.3.3). See Section 8.3.5 for further discussion of the liver test abnormalities and the hematological laboratory abnormalities.

FDA Table 92. SAFPOP - New or Worsening Nonhematological Laboratory Abnormalities

Laboratory Abnormality	N	Grades 1-4		Grades 3-4	
		n	%	n	%
Phosphate increased	166	79	48%	-	-
Albumin decreased	166	76	46%	5	3%
Aspartate aminotransferase increased	165	66	40%	3	2%
Alanine aminotransferase increased	166	62	37%	6	4%
Sodium decreased	166	59	36%	0	0%
Parathyroid hormone, intact increased	87	30	34%	-	-
Potassium decreased	166	44	27%	9	5%
Alkaline phosphatase increased	166	43	26%	0	0%
Triglycerides increased	91	24	26%	2	2%
Lactate dehydrogenase increased	162	39	24%	-	-
Phosphate decreased	166	38	23%	-	-
Creatinine increased	166	36	22%	1	1%
Creatinine clearance or GFR decreased	161	34	21%	2	1%
Carbon dioxide increased	104	22	21%	-	-
Carbon dioxide decreased	104	19	18%	-	-
Cholesterol increased	93	16	17%	0	0%
Magnesium increased	165	24	15%	6	4%
Magnesium decreased	165	23	14%	1	1%
Potassium increased	166	22	13%	3	2%
Thyrotropin increased	94	12	13%	-	-
Calcium corrected increased	160	19	12%	0	0%
Thyroxine free decreased	93	11	12%	-	-
Urate increased	165	19	12%	-	-
Bilirubin increased	166	18	11%	3	2%
Calcium corrected decreased	160	18	11%	3	2%
Sodium increased	166	6	4%	0	0%

Source: FDA analysis

There were also 65 instances of elevated parathyroid hormone, intact, in 51 participants. Concurrent measurement of serum calcium and phosphate were available for 58 cases in 46 participants; urine calcium and phosphate were not provided. For the cases with serum calcium and phosphate data, 74% had normal calcium and phosphate, 19% had normal calcium and elevated phosphate, 3% had normal calcium and low phosphate, 2% had low calcium and normal phosphate, and 2% had high calcium and normal phosphate.

The Applicant also provided an early analysis of laboratory abnormalities from 8 participants in Study SNDX-5613-0706, the on-going study of revumenib for treatment of solid tumors. They reported no trends in laboratory abnormalities in that analysis.

Clinical TL Comment: Based on the available data in the SAFPOP and the Applicant's analysis of laboratory testing in Study SNDX-5613-0706, the incidence of serious laboratory abnormalities appears to be low, and we agree that in many cases the abnormality may be leukemia-related rather than an adverse reaction to revumenib. There is, however, a concern regarding parathyroid dysfunction as might be expected with chronic menin inhibition. Based on the parathyroid hormone, calcium, and phosphate levels, it is not clear whether this may be eucalcemic primary hyperparathyroidism or the alternative of early secondary hyperparathyroidism due to a number of etiologies that may occur in patients with acute leukemia. Longer follow-up would be needed to clarify the issue. See also the comments in Section 8.3.5 below regarding hepatotoxicity and cytopenias.

Vital Signs

Data:

No patients in the Safety Population had vital sign findings that were of clinical significance other than those findings reported as AEs.

The Applicant's Position:

The risk of clinically significant findings is low.

The FDA's Assessment:

FDA performed an outlier analysis of vital signs for 137 adults in the SAFPOP. The results showed systolic blood pressure >= 160 mm Hg in 9%, systolic blood pressure < 90 mm Hg in 5%, diastolic blood pressure >= 100 mm Hg in 3%, temperature >= 40° C in none, pulse >= 120 beats per minute in 10%, and respiratory rate >= 30 breaths per minute in 4%. ADVS did not include normal ranges for pediatric participants, so an outlier analysis could not be performed for the pediatric subgroup.

Clinical TL Comment: The outlier percentages observed do not show the potential for a consistent abnormality in vital signs during treatment with revumenib.

Electrocardiograms (ECGs)/QT

Data:

Revumenib is associated with QTc prolongation, an important identified risk. Consistent with the SNDX-5613-0700 cardiac safety report, revumenib did not have a clinically significant effect on heart rate, PR interval, or QRS duration at the doses studied up to 339 mg q12h. There were 18 patients (12.1%) treated at the RP2D who had a maximum post-baseline QTcF prolongations of ≥ 501 msec and 35 patients (23.5%) with a maximum change from baseline of > 60 msec. A summary of the category result of QTcF and the category result of changes from baseline by visit is presented in SNDX-5613-0700 ISS Analysis, Table 14.6.3.1. TEAEs of QTc prolongation are described in Section 8.3.5 below.

The Applicant's Position:

QT prolongation is an identified risk of revumenib. Although revumenib is not clearly associated with electrolyte abnormalities, these are not uncommon in this late-stage leukemia population and therefore, close monitoring of electrolytes is necessary. TEAEs of QTc prolongation were managed through dose interruption or reduction (for ≥ Grade 3) and did not lead to discontinuation in Study SNDX-5613-0700. Few patients developed new, minor ECG morphology changes during the study.

The FDA's Assessment:

The Applicant provided Study SNDX-PMX-005-CQT, "Cardiac Safety Report for Syndax Study SNDX-5613-0700", as an alternative QT study due to infeasibility of a thorough QT study (NDA Module 5.3.3.5). The data were assessed in detail by the Interdisciplinary Review Team (IRT),[21] who confirmed the high incidence of QTcF prolongation at the recommended dose and no impact of revumenib on heart rate, PR interval, or QRS duration. Because the IRT review was complete, the clinical team did not review the PR interval or QRS duration data further. See Section 8.3.5 for clinical comments on QTc prolongation.

Clinical TL Comment: The results of the analyses of PR interval and QRS duration do not raise any safety concerns.

[21] NDA 218944 Interdisciplinary Review Team for Cardiac Safety Studies QT Study Review dated 4/23/2024.

Table: Revumenib safety population: Maximum QTcF Increase from Baseline and incidence of QTc prolongation.

Maximum QTcF	**Safety population with available ECG data N=163**
QTcF < 450 msec	162 (99.4%)
QTcF 450 to <=480 msec	80 (50%)
QTcF 481 to <=500 msec	32 (19.6%)
QTcF >= 501 msec	20 (12.3%)
Maximum QTcF Change from Baseline	**N =163**
>30 to ≤ 60 msec	94 (57%)
>60 msec	37 (23%)

Source: FDA analysis

Clinical Reviewer comment: Most common ECG changes were QTc prolongation, 70% were grade 2 and 3. The QTc prolongation was manageable by interruption of revumenib.

Immunogenicity

Data:

There were no immunogenicity studies conducted.

The Applicant's Position:
N/A

The FDA's Assessment:

FDA acknowledges that no immunogenicity studies were conducted. As revumenib is a small molecule, there should be little risk of immunogenicity. In the safety population, there were five cases of drug hypersensitivity reported using the grouped term based on the verbatim term not identifying an alternative etiology, all in Study SNDX-5613-0700 (Subjects (b) (6)). Two were Grade 1, two were Grade 2, and one was Grade 3. The events were characterized as urticaria (n=2), allergic reaction (n=2), or drug allergy (n=1). The median time to onset was 11 days (range, 1-26 days). No action was taken with the study drug in any case. Three participants received treatment for the event. Four recovered, and one was on-going at the time of data cut-off.

Clinical TL Comment: As no narratives were provided for the allergic reactions to implicate other etiologies, a relation to study drug cannot be excluded using the available data. As such, these cases are considered ARs. None was fatal or life-threatening, so a Warning is not needed. The incidence is quite low (1.5% (95% CI 0.5-3.4%)). Follow-up with routine pharmacovigilance should be sufficient.

8.3.5. Analysis of Submission-Specific Safety Issues

Differentiation Syndrome

Data:

Events of DS (all grades) occurred in 38 patients (25.5%) in the ISS RP2D Subset. Eighteen patients (12.1%) experienced Grade 2 events and 18 patients (12.1%) experienced Grade 3 events. There were 2 patients (1.3%) with Grade 4. No Grade 5 DS events were reported. There were 2 deaths in patients with signs and symptoms of DS concurrent with other acute medical issues, which were not reported as deaths due to DS. No DS events resulted in discontinuation. The median time to initial onset was 10.0 days (range: 3, 41), and the median duration of the initial event was 10.0 days (range: 3, 31 days).

To determine whether DS had been adequately recognized and treated in the study, the Sponsor, with FDA agreement, developed an identification algorithm in line with Montesino (2009), and updated by Norsworthy (2020). All patients enrolled in Cohort 2A and 2B, and patients from Phase 1 with KMT2Ar treated at the RP2D in Study SNDX-5613-0700 were included. Of the 111 patients in the analysis cohort, 84 potential cases of DS were identified in 72 patients that required adjudication, including 33 cases in 31 patients that had been reported by the investigator as DS. There were an additional 51 cases in 43 patients not reported by investigators as DS, that required adjudication based on signs or symptoms potentially consistent with DS. Of the 33 cases of Investigator reported DS, the Sponsor determined that 25 were clearly DS. The remaining 8 cases were adjudicated as possible cases of DS. Of the 51 non-DS-reported cases, 43 were identified as not DS, and 8 cases were adjudicated as possible DS. Systemic steroids were given in all cases of investigator reported DS. Importantly, of the 8 cases that were not Investigator reported as DS but were adjudicated as possible DS, 6 patients (75.0%) were treated with systemic steroids, suggesting that investigators were considering DS in the differential diagnosis

The Applicant's Position:

Most events of DS were recognized early and managed by systemic steroid treatment with or without hydroxyurea and dose interruption. The adjudicated analysis demonstrates that the investigators are skilled in the early recognition and treatment of DS and are appropriately initiating steroid therapy in patients manifesting signs and symptoms that may be DS.

The FDA's Assessment:

FDA screened for potential DS cases by algorithm (Norsworthy et al., 2020) across protocols using revumenib monotherapy, including the investigator-reported DS cases, and reviewed the narratives and other clinical data as provided by the Applicant in RIRs. Based on this adjudication process, FDA identified 64 DS cases in 59 study participants, including 53 in

Study SNDX-5613-0700, 3 in Study SNDX-5631-0705, 3 in single-patient protocols, and none in Study SNDX-5613-0706. The FDA-adjudicated cases are flagged in ADAEFDA.DFSYFL submitted on 10/3/2024. There were four cases for which FDA did not agree with the investigators' conclusion:

- [redacted] (b) (6) was identified by the investigator as having DS. However, the participant had on-going COVID-19 infection, and FDA considered the signs and symptoms to be related to COVID-19 rather than DS.
- [redacted] (b) (6) was identified by FDA's algorithm as having DS based on pleural effusion and fever.
- [redacted] (b) (6) was identified by FDA's algorithm as having DS based on pericardial effusion and elevated creatinine.
- [redacted] (b) (6) was identified by FDA's algorithm as having DS based on reported respiratory failure and acute kidney injury.

There was no relationship between dose and DS; DS was reported in 13% at dose level L-2, 11% at L-1, 26% at the RP2D (SAFPOP), 9% at L+1, and 0% at L+2 (see Table 67 for the description of the dose levels). Table 93 shows the subpopulation analysis of DS cases in the SAFPOP.

FDA Table 93. SAFPOP - DS Subpopulation Analysis

	N	Participants with DS	
		n	%
Age group			
< 17 years	29	10	34%
>= 17 years	138	34	25%
Sex			
Female	100	26	26%
Male	67	18	27%
Race			
White	117	34	29%
Black or African American	14	7	50%
Asian	15	1	7%
Multiple	2	0	0%
Unknown	19	2	11%
Ethnicity			
Not Hispanic or Latino	122	33	27%

FDA Table 93. SAFPOP - DS Subpopulation Analysis

	N	Participants with DS	
		n	%
Hispanic or Latino	32	10	31%
Unknown	13	1	8%
Disease			
AML	146	41	28%
ALL	19	2	11%
MPAL	2	1	50%
KMT2A rearrangement			
No	45	7	16%
Yes	122	37	30%
Study Site			
07	40	22	55%
Other	127	22	17%

Source: FDA analysis

Of note, there was a substantial difference in the incidence of DS at Clinical Site 07, which had the highest accrual in the trial. Several of the DS narratives described a monocytosis occurring during the DS event, and it was not clear whether the signs and symptoms in these cases represented true DS or resulted from the occlusive effects of hyperleukocytosis in monocytic-type leukemias frequently associated with KMT2A translocations. In the 7/3/2024 RIR, the Applicant indicated that monocyte counts were not routinely assessed in the hematology panels, so monocytosis could not be characterized further in the suspected DS cases. The Applicant also indicated that the protocol allowed use of hydroxyurea at the discretion of the investigator. As such, it would not be possible to determine when hydroxyurea was being used for leukemia-related leukocytosis rather than for differentiation-related leukocytosis.

For the 135 participants in the USPI population, there were 44 DS cases in 39 (29%) participants (32% of participants with AML, 25% of participants with MPAL, and 14% of participants with ALL). The median time to onset was 10 days (range 3-41 days). DS was Grades 3-4 in 18 (13%) participants and fatal in one. DS resulted in treatment withdrawal for 1 (1%) participant and treatment interruption for 9 (7%) participants.

Clinical TL Comment: DS is clearly a risk of treatment with revumenib, independent of leukemia type. The high incidence seems to be driven by a single clinical trial site, and although this may be a falsely high rate due to calling DS when the signs and symptoms are due to leukemia-related leukocytosis rather than differentiation, it is not possible at this point to distinguish these adverse events based on the available data. Therefore, the incidence will be reported in the USPI as

described. The life-threatening and fatal cases necessitate a boxed warning. Because this treatment is generally outpatient, a Medication Guide is also warranted.

Additional 7 cases reported by the Applicant as possible or potential DS that FDA adjudicated as not having DS are listed below:

Subject ID	Applicant Adjudication	FDA Adjudication	FDA rationale
(b) (6)	possible	Not DS	Dyspnea and acute kidney injury on D10 occurred in the setting of pulmonary emboli and pneumonia. In the presence of a strong alternative cause, there is no reason to suggest DS.
	possible	Not DS	Tachycardia, hypoxia and rising WBC on D4, not responding to dexamethasone, hydrea and leukapheresis followed by respiratory failure and death on D9. High blast count due to persistent leukemia was a strong alternative cause. There is no reason to suggest DS.
	possible	Not DS	Day 25 of study the patient experienced knee pain, grade 1 dyspnea and leukocytosis with increased monocytes. Symptoms subsided without treatment. The symptoms are not consistent with DS but are consistent with the underlying leukemia.
	possible	Not DS	Day 8 fever and new left lower lobe pulmonary nodules with multifocal ground glass opacities associated with increasing WBC 14.5 with 84% blasts. The symptoms are consistent with the underlying leukemia.
	possible	Not DS	Hypotension was due to dehydration from nausea/ diarrhea and poor oral intake from stomatitis and are not diagnostic of DS.
	Potential DS	Not DS	Grade 1 edema alone without other symptoms does not meet criteria for DS.
	Possible	Not DS	Mucosal inflammation and elevated creatinine level does not meet criteria for DS.

Prolonged QTc

Data:

QT prolongation is an important identified risk of treatment with revumenib. Nonclinical studies have shown inhibition potential of hERG channel current by revumenib. Specific guidelines were provided to manage QT prolongation in SNDX-5613-0700 protocol Sections 6.1.3 and 10.3.3.2.

In Study SNDX-5613-0700, TEAEs of QTc prolongation (all grades) were reported in 52 patients (34.9%) in the ISS RP2D Subset. Grade 3 TEAEs were reported in 25 patients (16.8%) and 1 patient (0.7%) experienced a Grade 4 TEAE. All but one of the Grade 3 events were observed in adults (> 18 years). QTc prolongation TEAEs were reported in 5 (18.5%) pediatric patients at the RP2D, 1 of whom had a Grade 3 (SNDX-5613-0700 ISS Analysis, Table 14.3.22.1.2).

Dose reduction occurred in 12/52 patients (23.1%), and no patient discontinued revumenib due to the event of QTc prolongation. Regarding the initial event of QTc prolongation, TEAEs occurred within the first 28 days of treatment in 39 (75.0%), in 10 patients (19.2%) occurring between 29 and 56 days, and in 3 patients (5.8%) occurring between 57 and 84 days.

In addition to prolonged QTc AEs and events of syncope, an analysis of the SMQ of Torsade de pointes/QT prolongation identified 5 patients with potentially important cardiac events of sudden death (2 [1.3%]), cardiac arrest (1 [0.7%]), cardio-respiratory arrest (1 [0.7%]), and VT (1 [0.7%]).

The Applicant's Position:

Events of QTc prolongation most commonly occurred during the first cycle and were managed by dose interruption, dose reduction, and close electrolye control. Discontinuation due to the event of QTc prolongation did not occur in Study SNDX-5613-0700. When analyzing the SMQ, important cardiac events such as ventricular arrythmias were low in frequency and observed in patients with confounding factors. In cases where multiple etiologies are present, including the underlying cardiac history and morbidity associated with late-stage leukemia, the ability to draw conclusions of association with revumenib treatment is limited.

The FDA's Assessment:

The QTcF interval data were assessed in detail by FDA's Interdisciplinary Review Team (IRT),[22] who confirmed that revumenib was associated with concentration dependent QTc prolongation with a median 18-22 msec ΔQTcF at the RP2D. A consistent effect was seen as early as 2 hours after dosing. This reviewer also assessed for ventricular arrhythmias observed on ECGs as reported in ADEG. There were 162 participants in the SAFPOP with postdose ECGs; premature ventricular complexes were observed in 15%, and ventricular couplets, ventricular trigeminy, ventricular bigeminy, and nonsustained ventricular tachycardia in 1% each.

Table 94 shows the incidences of relevant cardiac TEAE by dose level. There was a clear relationship between QT prolongation and dose. Additionally, multiple deaths were noted, but these did not appear to be dose-related and as indicated in Section 8.3.4, prior QT prolongation or ventricular arrhythmia was not noted prior to death in any of those cases.

[22] NDA 218944 Interdisciplinary Review Team for Cardiac Safety Studies QT Study Review dated 4/23/2024.

FDA Table 94. QT Prolongation and Associated Events by Dose Level

TEAE*	Incidence by Dose Level**									
	L-2 (N = 8)		L-1 (N = 53)		RP2D (N = 167)		L+1 (N = 22)		L+2 (N = 6)	
	n	%	n	%	n	%	n	%	n	%
Electrocardiogram QT prolonged	0	0	15	28	57	34	17	77	1	17
Ventricular tachycardia	0	0	0	0	2	1	0	0	0	0
Sudden death	0	0	0	0	2	1	0	0	0	0
Cardiac arrest	0	0	2	4	1	1	0	0	0	0
Cardio-respiratory arrest	0	0	0	0	1	1	0	0	0	0
Death	0	0	0	0	1	1	0	0	0	0

Source: FDA analysis
*Includes grouped terms
**Dose levels as defined in Table 67

Table 95 shows the subpopulation analysis of the TEAE Electrocardiogram QT prolonged in the SAFPOP. There was a substantially higher incidence of QT prolongation in Asians (73%). In the 9/19/2024 RIR, the Applicant reported that a literature search identified no biological reason for a higher sensitivity in Asians to QT prolonging drugs; this was confirmed by further evaluation by the IRT.[23] There was, however, a trend for increase in incidence with age, being 17% for participants < 17 years old, 33% for those 17 to < 65 years old, and 50% for those at least 65 years old.

FDA Table 95. SAFPOP - Prolonged QT Subpopulation Analysis

		TEAE Electrocardiogram QT prolonged	
	N	n	%
Age group			
< 17 years	29	5	17%
>= 17 years	138	52	38%
Sex			
Female	100	34	34%
Male	67	23	34%
Race			
White	117	36	31%

[23] NDA 218944 Interdisciplinary Review Team for Cardiac Safety Studies QT Study Review dated 10/2/2024.

FDA Table 95. SAFPOP - Prolonged QT Subpopulation Analysis

		TEAE Electrocardiogram QT prolonged	
	N	**n**	**%**
Black or African American	14	5	36%
Asian	15	11	73%
Multiple	2	0	0%
Unknown	19	5	26%
Ethnicity			
Not Hispanic or Latino	122	44	36%
Hispanic or Latino	32	10	31%
Unknown	13	3	23%
Disease			
AML	146	53	36%
ALL	19	4	21%
MPAL	2	0	0%
KMT2A rearrangement			
No	45	22	49%
Yes	122	35	29%

Source: FDA analysis

For the 135 participants in the USPI safety population, there were 94 TEAEs of QT prolongation reported in 39 (29%) participants. The median time to onset was 7 days (range 1-72 days). Electrocardiogram QT prolonged was Grade 3 in 16 (12%) participants; there were no cases reported as Grade 4 or fatal. On analysis of ECG data in ADEG.xpt, QTcF was greater than 500 msec in 8%, and the increase from baseline QTcF was greater than 60 msec in 18%. Electrocardiogram QT prolonged led to dose reduction for 7 (5%) participants, but none resulted in treatment withdrawal. QTc prolongation occurred in 16% of participants < 17 years old, 33% of those 17 to < 65 years old, and in 50% of those 65 years or older.

Clinical TL Comment: QT prolongation is a risk of treatment with revumenib that will require adequate monitoring to mitigate serious outcomes. As such, a warning is warranted. We agree with the Applicant and IRT that the high incidence in Asians may be by chance, especially in the absence of biological plausibility, and that the mitigation strategies described in labeling should be sufficient to prevent serious outcomes as was demonstrated in the clinical trial.

Among 167 patients receiving revumenib at RP2D dose, QTc prolongation occurred in 57 patients (34.1%), 28 patients (16.8%) developed grade 3 or more QTc prolongation. Following

QTc prolongation, 25 patients (15%) had dose interruptions, 13 patients (7.8%) had dose reduced and 1 patient (0.6%) discontinued revumenib.

FDA Table: Characteristics of QTc prolongation in subjects receiving RP2D dose.

	DOSE LEVEL		
	163 mg Q12H N=137	**276 mg Q12H N=24**	**All N=161**
Age Group			
Age < 17	7 (5.1%)	1 (4.2%)	8 (5%)
Age >=17	130 (94.9%)	23 (95.8%)	153 (95%)
AE TOX Grade			
1	39 (28.5%)	5 (20.8%)	44 (27.3%)
2	56 (40.9%)	12 (50%)	68 (42.3%)
3	40 (29.2%)	7 (29.2%)	47 (29.2%)
4	2 (1.5%)	0 (0)	2 (1.2%)
AE action			
Dose not changed	75 (54.7%)	18 (75%)	93 (57.8%)
Dose reduced	15 (11%)	3 (12.5%)	18 (11.2%)
Dose interrupted	43 (31.31%)	3 (12.55)	46 (28.6%)
Dose withdrawal	2 (1.5%)	0	2 (1.2%)
Not applicable	2 (1.5%)	0	2 (1.2%)

Source: FDA analysis

Median onset of QTc prolongation for patients received RP2D was on study day 15 (range 1-227). Seventy percent of subjects with QTc prolongation were grade 1-2. Duration of QTc prolongation lasted 1 day in 47%, 2 days in 15%, and 3-5 days in 15%. Forty percent of subjects with QTc prolongation required dose reduction or interruption. Only two cases required dose discontinuation.

Clinical Reviewer Comment: Among 61 patients who developed grade 3 and 4 QTc prolongation, 38 (62%) patients received revumenib at 163 mg Q12H compared to other dose level. Median onset of QTc prolongation for each dose level was study day 8, except for those received 163 mg Q12H the median onset of QTc prolongation was study day 22. The duration of QTc prolongation was short 70% recovered within 2 days. Majority of subjects (62.6%) in safety population did not require changes of revumenib dose following QTc prolongation. Dose interruption and dose reduction occurred in 24% and 11 % respectively. The 163 mg Q12H dose group required dose interruption (15%) more than other dose groups.

FDA Table: Cardiac events other than QTc prolongation observed in the safety population

	Safety Population N =167
Cardiac events	45 (26.9%)
Atrioventricular block	1 (0.6%)
Atrioventricular block complete	1 (0.6%)
Atrioventricular block second degree	1 (0.6%)
Arrhythmia	1 (0.6%)
Bradycardia	2 (1.2%)
Tachycardia	21 (12.6%)
Sinus bradycardia	4 (2.4%)
Cardiac arrest	1 (0.6%)
Cardio-respiratory arrest	1 (0.6%)
Cardiac arrest due to Ventricular tachycardia	2 (1.2%)
Palpitations	5 (3%)
Mitral valve disease	1 (0.6%)
Tricuspid valve disease	1 (0.6%)
Angina pectoris	2 (1.2%)
Myocardial ischaemia	1 (0.6%)
Cardiac failure	9 (5.4%)
Pericarditis	2 (1.2%)
Pericardial effusion	7 (4.2%)

Source: FDA Analysis

Clinical Reviewer Comment: Most common cardiac events were tachycardia, cardiac failure, pericardial effusion, palpitation and bradycardia. There were four cases of cardiac arrest, two were related to ventricular tachycardia. Cardiac arrest raised concern for long-term safety use of revumenib. Further clinical study to ensure long-term use in subjects treated with revumenib is recommended.

Embryo-Fetal Toxicity

Data:

Based on animal EFT studies and its mechanism of action, revumenib can cause embryo-fetal harm when administered to a pregnant woman. In animal EFT studies, oral administration of revumenib to pregnant rats during organogenesis was associated with embryo-fetal death and alterations to fetal growth at exposures approximately 0.5 times the human exposure area under the curve (AUC) at the recommended dosage.

The Applicant's Position:

The nonclinical data indicates potential for embryo-fetal harm. Adequate contraception should be recommended for women of reproductive potential and males with female partners of reproductive potential during treatment with revumenib and for at least 4 months after the final dose.

The FDA's Assessment:

See Section 8.3.9.

Peripheral Neuropathy

Data:

Peripheral neuropathy (PN) was identified in a nonclinical study with rats. In clinical trials, events of PN are infrequent and most were Grade ≤ 2. PN occurred in 5 patients (3.4%) in the ISS RP2D Subset. In the ISS Overall Set, 19 patients (7.4%) experienced PN. There was 1 patient (5.3%) with a Grade 3 event of PN (SNDX-5613-0700 ISS Analysis, Table 14.3.23.1.1). No patients in Study SNDX-5613-0700 dose reduced or discontinued due to PN.

The Applicant's Position:

Given PN can be observed in heavily pretreated patients in the R/R leukemia setting, PN remains a potential risk with revumenib.

The FDA's Assessment:

In the SAFPOP, taste disorder was reported in 12.0%, peripheral neuropathy in 4.2%, and paresthesia in 1.8%; none was Grade 3 or higher.

FDA Table 96. Peripheral Neuropathy Events by Dose Level

TEAE*	Incidence by Dose Level**									
	L-2 (N = 8)		L-1 (N = 53)		RP2D (N = 167)		L+1 (N = 22)		L+2 (N = 6)	
	n	%	n	%	n	%	n	%	n	%
Paraesthesia	0	0	4	7.5	3	1.8	3	13.6	1	16.7
Taste disorder	1	12.5	4	7.5	20	12.0	7	31.8	2	33.3
Neuropathy peripheral	1	12.5	3	5.7	7	4.2	2	9.1	0	0

Source: FDA analysis
*Includes grouped terms
**Dose levels as defined in Table 67

Table 96 shows the incidence of select peripheral neuropathy events by dose in participants with acute leukemia treated with revumenib BID dosing (see Section 8.3.1 for definitions of the dose levels). The highest incidences of Paraesthesia and Taste disorder are at the highest doses.

Clinical TL Comment: The dose-toxicity relationship suggests that paraesthesia and taste disorder are ARs. Whether peripheral neuropathy is an AR or related to other causes is not clear, so we agree with the Applicant that it is a potential AR.

The following are the additional potential serious risks identified by FDA:

Hepatotoxicity

The FDA's Assessment:

Table 97 shows the incidences of hepatotoxicity events by dose level. There appears to be a trend for a correlation of incidence with dose for Transaminase increased but not for Blood alkaline phosphatase increased or Hyperbilirubinaemia. For Transaminase increased, the median time to onset was 21 days (range, 1 - 185) (see Section 8.3.8). Additionally, Transaminase increased was also reported for 25% of participants on Study SNDX-5613-0706 (see Section 8.3.8).

FDA Table 97. Hepatotoxicity Events by Dose Level

TEAE*	Incidence by Dose Level**									
	L-2 (N = 8)		L-1 (N = 53)		RP2D (N = 167)		L+1 (N = 22)		L+2 (N = 6)	
	n	%	n	%	n	%	n	%	n	%
Transaminases increased	1	13	14	26	43	26	8	36	2	33
Blood alkaline phosphatase increased	0	0	8	15	16	10	5	23	0	0
Hyperbilirubinaemia	0	0	6	11	10	6	3	14	1	17

Source: FDA analysis
*Includes grouped terms
**Dose levels as defined in Table 67

Table 98 shows the subpopulation analysis of Transaminase increased cases in the SAFPOP. There does not appear to be a correlation between Transaminase increased and any demographic factor taking into account the small size of several of the subgroups.

FDA Table 98. SAFPOP - Transaminase increased Subpopulation Analysis

		TEAE Transaminase increased	
	N	**n**	**%**
Age group			
< 17 years	29	6	21%
>= 17 years	138	37	27%
Sex			
Female	100	28	28%
Male	67	15	22%
Race			
White	117	28	24%
Black or African American	14	0	0%
Asian	15	4	27%
Multiple	2	1	50%
Unknown	19	10	53%
Ethnicity			
Not Hispanic or Latino	122	26	21%
Hispanic or Latino	32	10	31%
Unknown	13	7	54%
Disease			
AML	146	35	24%
ALL	19	7	37%
MPAL	2	1	50%
KMT2A rearrangement			
No	45	13	29%
Yes	122	30	25%

Source: FDA analysis

On review of the laboratory data, new or worsening AST, ALT, and bilirubin were found in 40%, 37%, and 11%, respectively, of participants in the SAFPOP, but increased to Grades 3-4 occurred in only 2%, 4%, and 2%, respectively (see Section 8.3.4). The incidences of these laboratory abnormalities were similar in the USPI safety population. FDA identified two cases ([(b) (6)] and [(b) (6)]) with concurrent results that fulfilled the numerical criteria for Hy's law. In both cases, alternative etiologies were found, and neither was concluded to be a drug-induced liver injury (DILI).

Clinical TL Comment: The dose-response trend and the consistency in observations between the populations with leukemia and solid tumors lead to the conclusion that transaminase elevation is an AR. The incidence of high-grade abnormalities was small, and there were no DILI cases, so it appears that the mitigation strategies in the protocol would be sufficient to prevent severe outcomes. As such routine monitoring should be sufficient.

Cytopenias

The FDA's Assessment:

Table 99 shows the incidences of cytopenia events by dose level. Although there appears to be a trend for a correlation of incidence with dose, the incidences were low and were not consistent across similar terms (i.e., Anaemia vs Haemoglobin decreased).

FDA Table 99. Cytopenia Events by Dose Level

TEAE*	Incidence by Dose Level**									
	L-2 (N = 8)		L-1 (N = 53)		RP2D (N = 167)		L+1 (N = 22)		L+2 (N = 6)	
	n	%	n	%	n	%	n	%	n	%
Anaemia	1	13	10	19	37	22	5	23	0	0
Haemoglobin decreased	0	0	0	0	1	1	0	0	0	0
Thrombocytopenia	0	0	1	2	19	11	3	14	1	17
Platelet count decreased	0	0	9	17	25	15	4	18	2	33
Neutropenia	0	0	1	2	9	5	2	9	1	17
Neutrophil count decreased	0	0	5	9	23	14	3	14	1	17

Source: FDA analysis
*Includes grouped terms
**Dose levels as defined in Table 67

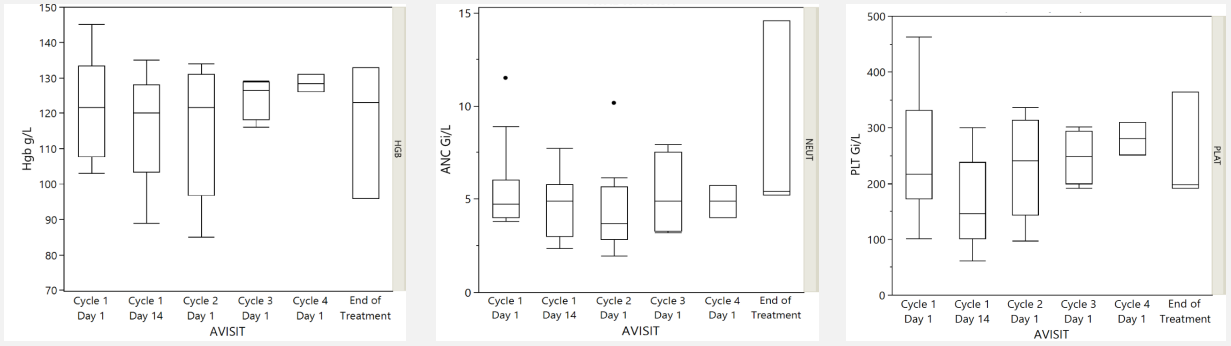
By contrast, on assessment of laboratory data, the Applicant reported maximum post baseline Grades 3-4 neutrophils decreased in 95%, Grades 3-4 platelets decreased in 94%, and Grades 3-4 hemoglobin decreased in 85% (Applicant's 6/28/2024 RIR). There were, however, a large proportion of participants with high-grade cytopenias at study baseline. By FDA's analysis of baseline laboratory data in the SAFPOP, neutrophils were at the Grades 3-4 level in 80%, platelets at Grades 3-4 levels in 77%, and hemoglobin at Grades 3-4 levels in 41%, leaving too few participants with high enough cell counts for credible shift analyses.

As baseline cell counts are generally closer to normal in those without active leukemia, FDA also assessed serial blood count in the 14 participants from Study SNDX-5613-0706. As shown in Figure 13 below, hemoglobin did not change substantially over 4 cycles, and although there were initial dips in neutrophils and platelets at Cycle 1 Day 14, counts were largely unchanged thereafter. On review of TEAE, there was one case each (7%) of Anaemia

(Grade 3), Leukopenia Grade 1, Thrombocytopenia (Grade 1), and Decreased platelets (Grade 2). All resolved without a change in dose of revumenib.

FDA Figure 13. Study SNDX-5613-0706 Serial Blood Counts

a) Hemoglobin b) Neutrophils c) Platelets



Source: FDA Analysis

Clinical TL Comment: The data from Study SNDX-5613-0700 are clearly not adequate to assess for an impact of revumenib on hematopoiesis. Based on participants who achieved remission and continued to have adequate counts, it does not appear that revumenib is myelosuppressive as monotherapy in participants with acute leukemia, and the results from Study SNDX-5613-0706 suggest little or no impact of revumenib on hematopoiesis in participants treated for solid tumors. This is consistent with the Applicant's assertion that revumenib may slow platelet recovery, but it is not myelosuppressive, and it is not expected to cause high grade cytopenias (Applicant's 2/15/2024 RIR). The results may change with longer follow-up, but at the present time, the data are not sufficient to conclude that anemia, neutropenia, and thrombocytopenia are ARs.

Cataracts

The FDA's Assessment:

In Study SNDX-5613-0700, ophthalmologic examinations were to be performed at baseline, on C4D1, every 3 cycles thereafter, and at either EOT or Safety Follow-up. The Applicant reported no ophthalmological examination results of clinical significance and no TEAE Cataract (Study SNDX-5613-0700 Clinical Study Report Section 6.1.11.4).

On review of Study SNDX-5613-0700 ADOE, FDA identified 117 participants with post baseline ophthalmological examinations that included assessment of the lens. Twelve (10%) participants had new lens abnormalities identified postbaseline. These 12 participants had a median age of 51 years (range, 24-79 years). The new lens abnormalities were reported in 17 (7%) of 234 eyes, including 11 cases that were normal at baseline and 6 with worsening lens abnormalities in comparison to baseline.

TEAE Cataract was reported in 1 (0.6%) participant in the SAFPOP with onset on Day 87.

Clinical TL Comment: The results are consistent with cataracts being a potential risk based on the nonclinical data and the observations in the clinical trial. The follow-up is not sufficient to clearly characterize the long-term risk.

Endocrine Neoplasms

The FDA's Assessment:

Table 100 shows the search results for the endocrine neoplasm terms. There were no endocrine neoplasms reported in the ISS database. In the SAFPOP (dose level RP2D), sign and symptom terms consistent with functioning endocrine tumors included Diarrhoea, Abdominal pain, Headache, Hypercalcaemia, Hypoglycaemia, and Hyperparathyroidism. Parathyroid hormone increased (34%) and calcium corrected increased (12%) were also identified in the analysis of laboratory abnormalities in the SAFPOP (see Table 114 in Section 8.3.4).

FDA Table 100. Endocrine Events by Dose Level

HLGT or TEAE*	Incidence by Dose Level**									
	L-2 (N = 8)		L-1 (N = 53)		RP2D (N = 167)		L+1 (N = 22)		L+2 (N = 6)	
	n	%	n	%	n	%	n	%	n	%
HLGT Endocrine neoplasms benign	0	0	0	0	0	0	0	0	0	0
HLGT Endocrine neoplasms malignant	0	0	0	0	0	0	0	0	0	0
Diarrhoea	1	12.5	15	28	53	32	5	23	3	50
Abdominal pain	1	12.5	11	21	29	17	5	23	3	50
Headache	2	25	15	28	26	16	4	18	2	33
Hypercalcaemia	0	0	2	4	6	4	2	9	0	0
Hypoglycaemia	0	0	1	2	2	1	0	0	0	0
Hyperparathyroidism	0	0	1	2	1	1	0	0	0	0
Ulcer	0	0	0	0	0	0	0	0	0	0
Hyperadrenocorticism	0	0	0	0	0	0	0	0	0	0
Hyperaldosteronism	0	0	0	0	0	0	0	0	0	0

Source: FDA analysis
*Includes grouped terms
**Dose levels as defined in Table 67

Clinical TL Comment: The signs and symptoms observed are consistent with functioning endocrine neoplasms, but (with the exception of Hyperparathyroidism) these are not uncommon background events in this patient population, and as such, they are not definitive evidence of

this risk. Additionally, while the absence of reported endocrine neoplasms is reassuring, it is acknowledged that the duration of treatment and follow-up may have been too short to exclude this as a risk. Nonetheless, the benefit-risk analysis is still favorable for short-term use in patients with advanced disease. Additional study to exclude this risk, however, may be needed if, in the future, revumenib is indicated for long-term use in a curative setting. For the current indication, standard pharmacovigilance would likely be sufficient to monitor for endocrine neoplasms.

8.3.6. Safety Analyses by Subgroups

Drug-Demographic Interactions

Data:

Subgroup analyses of TEAEs on the effect of sex, race, ethnicity, body weight, ECOG performance, renal impairment, hepatic impairment, and prior transplant on exposure identified no clear patterns. The subgroup analysis of TEAEs on the effect of age on exposure showed that patients ≥ 65 years of age in the ISS RP2D Subset had an increased incidence of QTc prolongation (17/32 patients [53.1%]) compared to all patients in the ISS RP2D Subset ≥ 18 years of age (47/122 patients [38.5%]) (SNDX-5613-0700 ISS Analysis, Table 14.3.2.1.2).

The Applicant's Position:

There is a higher frequency of QTc prolongation TEAEs observed in patients ≥ 65 years.

The FDA's Assessment:

TEAE by Age

Table 101 shows the TEAE with at least 10% difference in incidence between the pediatric and adult participants. The incidences of Face oedema, DS, and Hypertension were numerically higher in pediatric participants, and those of Headache, Nausea, Oedema, prolonged QT, and Musculoskeletal pain were numerically higher in adult participants. The differences were statistically substantial ($p < 0.01$) only for Hyperkalemia and Hypertriglyceridemia. Within the pediatric age group, there was a trend for increased Face Oedema, Diarrhoea, and Febrile neutropenia with decrease in age (data not shown), but the sizes of the infant and adolescent subgroups were small.

FDA Table 101. SAFPOP - TEAE by Age

TEAE*	Pediatric N = 29		Adult N = 138		Risk Difference
	n	(%)	n	(%)	
Hyperkalaemia	9	31.0	9	6.5	24.5
Hyponatraemia	10	34.5	19	13.8	20.7
Viral infection	10	34.5	24	17.4	17.1
Face oedema	6	20.7	7	5.1	15.6
Differentiation syndrome	10	34.5	31	22.5	12.0
Infusion related reaction	4	13.8	3	2.2	11.6
Hypermagnesaemia	5	17.2	8	5.8	11.4
Hypertriglyceridaemia	3	10.3	0	0	10.3
Hypertension	4	13.8	5	3.6	10.2
Hypoalbuminaemia	4	13.8	5	3.6	10.2
Taste disorder	1	3.4	19	13.8	-10.3
Headache	2	6.9	24	17.4	-10.5
Nausea	12	41.4	73	52.9	-11.5
Cough	1	3.4	24	17.4	-13.9
Dyspnoea	2	6.9	31	22.5	-15.6
Oedema	4	13.8	44	31.9	-18.1
Electrocardiogram QT prolonged	5	17.2	52	37.7	-20.4
Musculoskeletal pain	7	24.1	63	45.7	-21.5

Source: FDA analysis
*Includes grouped terms

Table 102 shows the TEAE with at least 10% difference in incidence between adult participants < 65 years old and those 65 years and older. The elder participants had fewer events of Musculoskeletal pain and Viral infections but a numerically higher incidence of Renal impairment, prolonged QT, and Oedema. The difference was statistically substantial ($p < 0.01$) only for Oedema.

FDA Table 102. SAFPOP - TEAE in Adults

TEAE*	Adults < 65 years old N = 102		Adults 65 years and older N = 36		Risk Difference
	n	(%)	n	(%)	
Musculoskeletal pain	52	51.0	11	30.6	20.4
Viral infection	22	21.6	2	5.6	16
Headache	21	20.6	3	8.3	12.3
Transaminases increased	30	29.4	7	19.4	10

FDA Table 102. SAFPOP - TEAE in Adults

TEAE*	Adults < 65 years old N = 102		Adults 65 years and older N = 36		Risk Difference
	n	(%)	n	(%)	
Neutropenia	4	3.9	5	13.9	-10
Pulmonary oedema	1	1.0	4	11.1	-10.1
Diarrhoea	28	27.5	14	38.9	-11.4
Pleural effusion	8	7.8	7	19.4	-11.6
Renal impairment	7	6.9	7	19.4	-12.6
Electrocardiogram QT prolonged	34	33.3	18	50.0	-16.7
Oedema	25	24.5	19	52.8	-28.3

Source: FDA analysis
*Includes grouped terms

TEAE by Sex

TEAEs with an incidence at least 10% higher in females were Anaemia (28.0% vs 13.4%) and Hypokalemia (31% vs 16.4%). The only TEAE with an incidence at least 10% higher in males was Infection (52.2% vs 39.0%). None of the differences was statistically substantial.

TEAE by Race

Table 103 shows the incidences of potential ARs with substantial differences by race. Specifically, ECG abnormalities and gastrointestinal disorders were highest in participants of Asian descent, thrombocytopenia was lowest in White participants, and transaminase elevations were lowest in Black or African American participants. The difference was statistically substantial ($p < 0.01$) for the ECG abnormalities in Asians.

FDA Table 103. SAFPOP - TEAE by Race

TEAE*	Asian N=15		Black or African American N=14		White N=117	
	n	(%)	n	(%)	n	(%)
Electrocardiogram QT prolonged	11	73.3	5	35.7	36	30.8
Abdominal pain	6	40.0	2	14.3	14	12.0
Abdominal distension	4	26.7	2	14.3	9	7.7
Thrombocytopenia	4	26.7	3	21.4	9	7.7
Transaminases increased	4	26.7	0	0.0	28	23.9
Electrocardiogram T wave abnormal	3	20.0	0	0.0	0	0.0

Source: FDA analysis
*Includes grouped terms

TEAE by Ethnicity

Table 104 shows the TEAE with at least 10% difference in incidence between Hispanic and non-Hispanic participants. Of the potential ARs, participants of Hispanic descent had a numerically higher incidence of Musculoskeletal pain and a lower incidence of Diarrhea.

FDA Table 104. SAFPOP - TEAE by Ethnicity

TEAE*	Hispanic or Latino N = 32		Not Hispanic or Latino N = 122		Risk Difference
	n	(%)	n	(%)	
Musculoskeletal pain	19	59.4	45	36.9	22.5
Constipation	12	37.5	25	20.5	17.0
Confusional state	6	18.8	5	4.1	14.7
Depressed level of consciousness	6	18.8	5	4.1	14.7
Haemorrhage	20	62.5	59	48.4	14.1
Hyperphosphataemia	1	3.1	17	13.9	-10.8
Insomnia	0	0	14	11.5	-11.5
Hyperglycaemia	0	0	16	13.1	-13.1
Diarrhoea	5	15.6	41	33.6	-18.0

Source: FDA analysis
*Includes grouped terms

Clinical TL Comment: The major concerning results are the high incidences of prolonged QT and gastrointestinal disorders in participants of Asian descent (see also the comment in Section 8.3.5) and the high incidences of prolonged QT and Oedema in the elderly. The remainder of the correlations do not appear to have a biological basis and may be random or result from the small subgroups.

Drug-Disease Interactions

Data:

Since *KMT2A*r leukemia can present as myeloid or lymphoid disease, safety was presented both by cohort as well as pooled across cohorts (2A + 2B) in Study SNDX-5613-0700. It is not clear that the leukemia subtype has an impact on the safety profile. Differentiation syndrome occurs as a result of differentiation of myeloid cells thus data is presented for incidence of differentiation syndrome for myeloid vs. non-myeloid disease (see Section 8.3.5). In the ISS RP2D Subset, events of DS (all grades) occurred in 35/130 patients (26.9%) with AML and 3/19 patients (15.8%) with non-AML leukemia (SNDX-5613-0700 ISS Analysis, Table 14.3.21.1.3). In patients with AML, most events were of Grade 2 (17 [48.6%]) or Grade 3 (17 [48.6%]) severity; there was 1 patient (2.9%) who experienced DS of Grade 4. In patients with non-AML leukemia,

there was 1 (33.3%) patient each that experienced Grade 2, Grade 3, and Grade 4 DS. None of these events resulted in study drug discontinuation in patients with AML or non-AML leukemia; 7 (20.0%) and 1 (33.3%) patients, respectively, had dose interruptions due to DS. Most AML patients' events (30 patients [85.7%]) and the events in all patients with non-AML (3 patients [100.0%]) were considered resolved or recovered by the investigator. The median time to onset in patients with AML and patients with non-AML leukemia was 10.0 and 6.0 days, respectively, and the median duration of the event was 10.0 and 7.0 days, respectively. In patients with AML, DS was managed with steroids (35 patients [100.0%]) and hydroxyurea if indicated (11 patients [31.4%]). In non-AML patients, DS was managed with steroids in 3 patients (100.0%) but no patients received hydroxyurea.

The Applicant's Position:
It is not clear that leukemia subtype has an impact on the safety profile of revumenib with the exception of differentiation syndrome which requires myeloid cell differentiation to occur.

The FDA's Assessment:

Table 105 shows the TEAE with at least 10% difference in incidence between ALL and AML in the SAFPOP. None of the differences was statistically substantial. There were too few participants with MPAL for meaningful analyses.

FDA Table 105. SAFPOP - TEAE by Diagnosis

TEAE*	MPAL N=2		ALL N=19		AML N=146		AML-ALL Risk Difference
	n	(%)	n	(%)	n	(%)	
Diarrhoea	0	0	9	47.4	44	30.1	17.2
Stomatitis	1	50	5	26.3	17	11.6	14.7
Decreased appetite	2	100	6	31.6	26	17.8	13.8
Muscular weakness	0	0	4	21.1	11	7.5	13.5
Atelectasis	0	0	3	15.8	4	2.7	13
Transaminases increased	1	50	7	36.8	35	24.0	12.9
Hypertension	0	0	3	15.8	6	4.1	11.7
Hypothermia	0	0	2	10.5	0	0	10.5
Impaired gastric emptying	0	0	2	10.5	0	0	10.5
Oedema	2	100	7	36.8	39	26.7	10.1
Blood alkaline phosphatase increased	0	0	0	0	16	11	-11
Cough	0	0	1	5.3	24	16.4	-11.2
Anaemia	1	50	2	10.5	34	23.3	-12.8
Thrombocytopenia	0	0	0	0	19	13.0	-13
Constipation	2	100	2	10.5	35	24.0	-13.4
Taste disorder	0	0	0	0	20	13.7	-13.7

FDA Table 105. SAFPOP - TEAE by Diagnosis

TEAE*	MPAL N=2		ALL N=19		AML N=146		AML-ALL Risk Difference
	n	(%)	n	(%)	n	(%)	
Fatigue	2	100	2	10.5	37	25.3	-14.8
Electrocardiogram QT prolonged	0	0	4	21.1	53	36.3	-15.2
Differentiation syndrome	1	50	2	10.5	38	26.0	-15.5
Musculoskeletal pain	1	50	4	21.1	65	44.5	-23.5

Source: FDA analysis
*Includes grouped terms

Table 106 shows the TEAE with at least 10% difference in incidence by presence or absence of a KMT2A rearrangement for participants in the SAFPOP. None of the differences was statistically substantial.

FDA Table 106. SAFPOP - TEAE by KMT2Ar

TEAE*	KMT2Ar Positive N=123		KMT2Ar Negative N=44		Risk Difference
	n	(%)	n	(%)	
Differentiation syndrome	34	27.6	7	15.9	11.7
Rash	20	16.3	2	4.5	11.7
Haemorrhage	67	54.5	19	43.2	11.3
Face oedema	13	10.6	0	0	10.6
Tachycardia	12	9.8	9	20.5	-10.7
Infection	51	41.5	23	52.3	-10.8
Fatigue	26	21.1	15	34.1	-13.0
Oedema	31	25.2	17	38.6	-13.4
Febrile neutropenia	45	36.6	23	52.3	-15.7
Electrocardiogram QT prolonged	36	29.3	21	47.7	-18.5

Source: FDA analysis
*Includes grouped terms

Review: As shown in the above tables, revumenib related differentiation syndrome (DS) are unique adverse events observed in higher rate in RDMLLr subgroup compared to RDnMLL (26.8% vs 15.9%). This confirmed the effect of revumenib on menin-KMT2A interaction resulting in cellular differentiation in RDMLLr. The DS is also observed more in AML compared to ALL. Due to small number of ALL, we cannot make conclusion that DS is lower in ALL. QTc prolongation was observed at higher rate in RDnMLL subgroup compared to RDMLLr (45.5% vs 26.8%). However, there were similar rates of grade ≥ 3 QTc prolongation in both groups.

Clinical TL Comment: See Section 8.3.5 for the discussion of DS. For the remainder of the analyses of TEAE by disease, there is not a clear biological basis for correlation, and the differences are not statistically substantial, so the results may be random.

Drug-Drug Interactions

The Applicant's Position:

The dose of revumenib should be reduced when co-administered with strong CYP3A4 inhibitors. No dose adjustment is needed when revumenib is administered with a weak or moderate CYP3A4 inhibitor. Co-administration of revumenib with strong and moderate CYP3A4 inducers should be avoided. See Section 6.2.1 for more information on drug-drug interactions.

The FDA's Assessment:

Table 107 shows the TEAE with at least 10% difference in incidence for participants in the SAFPOP subgrouped by concomitant use of CYP3A4 inhibitors (CYP3A4i). None of the differences for potential ARs was statistically substantial.

FDA Table 107. SAFPOP - TEAE by CYP3A4i Use

TEAE*	CYP3A4i Used N=132		No CYP3A4i Use N=30		Risk Difference
	n	(%)	n	(%)	
Hypokalaemia	39	29.5	3	10.0	19.5
Bacterial infection	43	32.6	5	16.7	15.9
Oedema	41	31.1	5	16.7	14.4
Transaminases increased	38	28.8	5	16.7	12.1
Hyperglycaemia	15	11.4	0	0	11.4
Haemorrhage	72	54.5	13	43.3	11.2
Anaemia	32	24.2	4	13.3	10.9
Cough	22	16.7	2	6.7	10
Hyperkalaemia	12	9.1	6	20.0	-10.9
Pruritus	3	2.3	5	16.7	-14.4
Musculoskeletal pain	51	38.6	16	53.3	-14.7
Hyponatraemia	20	15.2	9	30.0	-14.8

Source: FDA analysis
*Includes grouped terms

Clinical TL Comment: Although there are numerically higher incidences of Oedema and Transaminase increased in participants taking CYP3A4i concurrently with revumenib, the overall safety profile is similar with or without CYP3A4i.

8.3.7. Clinical Outcomes Assessments Informing Tolerability/Safety

Data:

There were no patient-reported outcome assessments collected.

The Applicant's Position:

N/A

The FDA's Assessment:

No patient-reported outcome assessments informing safety were provided.

8.3.8. Specific Safety Studies/Clinical Trials

Data:

No specific safety studies were conducted.

The Applicant's Position:

N/A

The FDA's Assessment:

Dose Dependency for Adverse Events

As indicated in Section 8.3.1, there were 256 participants with acute leukemia treated on Studies SNDX-5613-0700 and SNDX-5613-0705 with revumenib twice daily at various doses with or without CYP3A4i. The dose levels included the recommended dose (RP2D), two lower dose levels (L-1 and L-2), two higher dose levels (L+1 and L+2) (see Table 67 for the dose level criteria). For analysis, TEAEs occurring in 10% or greater at the RP2D or in 5% or greater in L+1 were selected, and TEAEs with a random distribution of incidences across dose levels were excluded. Table 108 shows the remaining TEAE in decreasing order of incidences in the L+1 group.

Notwithstanding the confounding by the small numbers of participants in the L-2 and L+2 groups, there appeared to be correlations with dose for Electrocardiogram QT prolonged, Nausea, Musculoskeletal pain, Oedema, Haemorrhage, Fatigue, Transaminases increased, Taste disorder, Decreased appetite, Hyperkalaemia, Pericardial effusion, and Neutropenia as well as numerical increases in incidence with higher doses for the remaining TEAE.

FDA Table 108. Patients with Acute Leukemias - TEAE by Dose Level

TEAE*	Incidence (%) at Dose Level**				
	L-2 (N = 8)	L-1 (N = 53)	RP2D (N = 167)	L+1 (N = 22)	L+2 (N = 6)
Electrocardiogram QT prolonged	0.0	28.3	34.1	77.3	16.7
Nausea	37.5	49.1	50.9	68.2	83.3
Musculoskeletal pain	37.5	32.1	41.9	54.5	16.7
Oedema	25.0	20.8	28.7	50.0	66.7
Haemorrhage	37.5	45.3	51.5	50.0	66.7
Fatigue	25.0	20.8	24.6	45.5	33.3
Transaminases increased	12.5	26.4	25.7	36.4	33.3
Infection	25.0	35.8	44.3	36.4	33.3
Taste disorder	12.5	7.5	12.0	31.8	33.3
Decreased appetite	12.5	11.3	20.4	27.3	33.3
Viral infection	0.0	15.1	20.4	22.7	16.7
Anaemia	12.5	18.9	22.2	22.7	0.0
White blood cell count decreased	0.0	7.5	13.8	18.2	16.7
Hyperkalaemia	0.0	5.7	10.8	13.6	33.3
Neutrophil count decreased	0.0	9.4	13.8	13.6	16.7
Thrombocytopenia	0.0	1.9	11.4	13.6	16.7
Hypomagnesaemia	0.0	7.5	13.2	13.6	0.0
Pericardial effusion	0.0	1.9	4.2	13.6	0.0
Neutropenia	0.0	1.9	5.4	9.1	16.7
Rash	0.0	5.7	13.2	9.1	0.0
Abdominal distension	0.0	5.7	9.0	9.1	0.0
Face oedema	0.0	3.8	7.8	9.1	0.0
Hypermagnesaemia	0.0	3.8	7.8	9.1	0.0

Source: FDA analysis
*Includes grouped terms
** See Table 67 for the dose level criteria.

Clinical TL Comment: The dose-response analysis confirms the relatedness for numerous TEAEs identified in Section 8.3.4 and highlights additional clinically meaningful risks of pericardial effusion, rash, and face oedema.

Time Dependency for Adverse Events

Table 109 shows the time to onset of key TEAE of any grade and Grades 3-5 in the SAFPOP. The TEAE with the earliest onset was QT prolongation, starting after a median of 8 days of treatment with revumenib, but the range of time to onset was quite wide. In general, most any-grade TEAE had a median onset during the second or third week of treatment. The timing was similar for Grades 3-5 TEAE with the exception of GI-related Grade 3-5 TEAE, which had a median onset after 4-6 weeks of treatment. Cardiac events occurred after several months of treatment.

FDA Table 109. SAFPOP - Time to Onset for Key TEAE

TEAE*	Time to Any Grade TEAE Median (days) (range)		Time to Grades 3-5 TEAE Median (days) (range)	
Electrocardiogram QT prolonged	8	(1 - 84)	22	(1 - 171)
Anaemia	10	(1 - 226)	15	(1 - 226)
Differentiation syndrome	10	(3 - 41)	11	(3 - 35)
Nausea	10	(1 - 155)	28	(1 - 92)
Thrombocytopenia	11	(1 - 148)	11	(1 - 176)
Neuropathy peripheral	12	(2 - 125)	12	(12)
Dyspnoea	13	(1 - 73)	20	(4 - 63)
Diarrhoea	14	(1 - 222)	43	(5 - 222)
Headache	14	(1 - 84)	17	(5 - 28)
Drug hypersensitivity	15	(7 - 26)	7	(7)
Musculoskeletal pain	15	(1 - 127)	9	(4 - 53)
Taste disorder	15	(1 - 98)	-	-
Decreased appetite	17	(1 - 155)	48	(1 - 120)
Fatigue	17	(1 - 155)	31	(5 - 87)
Febrile neutropenia	19	(1 - 129)	19	(1 - 129)
Haemorrhage	20	(1 - 105)	40	(5 - 179)
Face oedema	21	(1 - 162)	26	(26)
Transaminases increased	21	(1 - 185)	26	(6 - 183)
Oedema	22	(2 - 157)	24	(24)
Rash	22	(1 - 347)	-	-
Abdominal pain	26	(5 - 126)	37	(37)
Cardiac failure	65	(4 - 149)	82	(4 - 134)
Pericardial effusion	67	(4 - 144)	68	(4 - 78)
Cataract	87	(87)	-	-

Source: FDA analysis
*Includes grouped terms

Clinical TL Comment: The analysis suggests that monitoring, especially for QT prolongation, should be most intense early in treatment, although vigilance for severe GI toxicity may need to extend for months. The late cardiac events are of great interest, but given the short follow-up for most of the study participants, this may not be characterized sufficiently. Additional study for long-term safety is warranted.

Adverse Events in Other Populations

Study SNDX-5613-0706 was a Phase 1 study for treatment of revumenib tablets or capsules TID in adults with solid tumors. The Applicant submitted safety data for eight participants, including three treated with 163 mg capsule/160 mg tablet TID and five with 226 mg capsule/220 mg tablet TID without CYP3Ai. The median number of treatment cycles was 1 (range, 1-3). The common all-grade TEAE reported were Nausea and Taste disorder (37.5% each), and Transaminases increased, Decreased appetite, Headache, Musculoskeletal pain, Constipation, Hyponatraemia,

Abdominal distension, Hypophosphataemia, and Renal impairment (25.0% each). Prolonged QT was reported for 12.5%.

Safety data were also provided for 50 patients treated on single-patient protocols. Table 110 show the incidence of TEAE occurring in at least 15% of the patients. Prolonged QT was reported in 12.0% and DS in 6.0%.

FDA Table 110. Single-Patient Protocols - Common TEAEs

	N=50	
TEAE*	**n**	**(%)**
Nausea	20	40.0
Infection	18	36.0
Febrile neutropenia	17	34.0
Platelet count decreased	17	34.0
Haemorrhage	15	30.0
White blood cell count decreased	14	28.0
Neutrophil count decreased	12	24.0
Transaminases increased	11	22.0
Bacterial infection	11	22.0
Rash	11	22.0
Anaemia	10	20.0
Decreased appetite	8	16.0
Headache	8	16.0
Musculoskeletal pain	8	16.0
Abdominal pain	8	16.0
Fatigue	8	16.0
Oedema	8	16.0
Diarrhoea	8	16.0
Pyrexia	8	16.0

Source: FDA analysis
*Includes grouped terms

Clinical TL Comment: The safety profile in the other populations is consistent with the experience in the SAFPOP.

Safety by Dose Form

The SNDX-5613-0700 data set version with a data cut date of 7/5/2024 was used to assess activity in the to-be-marketed dose forms. (b) (6) With regard to the tablet formulation, TEAE were evaluated

for the participants with acute leukemia treated at the recommended dose using only capsules or only tablets. Table 111 shows the baseline characteristics of the population included in the analysis.

FDA Table 111. Participant Baseline Characteristics by Dose Form

	Tablets Only N=32		Capsules Only N=132	
Age group				
< 17 years	1	3%	6	5%
>=17 years	31	97%	126	95%
Sex				
Female	16	50%	80	61%
Male	16	50%	52	39%
Race				
White	19	59%	94	71%
Other or Unknown	9	28%	19	14%
Asian	1	3%	11	8%
Black or African American	3	9%	8	6%
Ethnicity				
Not Hispanic or Latino	23	72%	98	74%
Hispanic or Latino	2	6%	19	14%
Not reported or unknown	7	22%	15	11%
Region				
United States	26	81%	94	71%
EX- United States	6	19%	38	29%
Diagnosis				
AML	31	97%	119	90%
ALL	1	3%	10	8%
MPAL	0	0%	3	2%
Mutation				
KMT2Ar	9	28%	83	63%
NPM1mut	20	63%	38	29%
Missing	3	9%	11	8%

Source: FDA analysis

Clinical TL Comment: The cohorts were largely comparable with the exception of the predominance of the NPM1mut in participants on tablets only. This would correspond with Arm C opening later than Arms A and B.

Table 112 shows all-grade and Grades 3 and higher key TEAE by dose form listed in descending order of risk difference. Because the participants on only tablets had a shorter time on treatment (median 57 days, IQR 25-83 days on only tablets and median 68 days, IQR 42-101 days on only capsules), the comparison was limited to events in the first 120 days on treatment.

FDA Table 112. Key TEAE through Study Day 120 by Dose Form

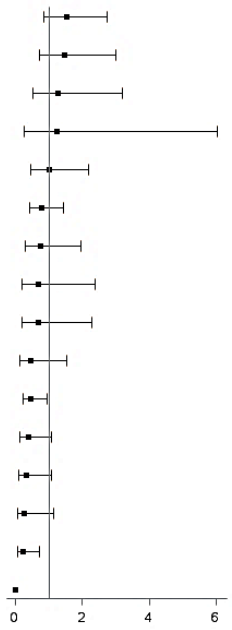
TEAE*	Tablets Only N=32		Capsules Only N=132		Risk Difference
	n	(%)	n	(%)	
All-grade					
Electrocardiogram QT prolonged	15	46.9	45	34.1	12.8
Fatigue	10	31.3	30	22.7	8.5
Taste disorder	6	18.8	20	15.2	3.6
Cataract	1	3.1	1	0.8	2.4
Pericardial effusion	2	6.3	7	5.3	0.9
Anaemia	8	25.0	34	25.8	-0.8
Neuropathy peripheral	0	0.0	4	3.0	-3.0
Thrombocytopenia	3	9.4	18	13.6	-4.3
Differentiation syndrome	5	15.6	27	20.5	-4.8
Abdominal pain	3	9.4	19	14.4	-5.0
Nausea	13	40.6	67	50.8	-10.1
Decreased appetite	3	9.4	26	19.7	-10.3
Transaminases increased	2	6.3	29	22.0	-15.7
Oedema	4	12.5	40	30.3	-17.8
Diarrhoea	3	9.4	36	27.3	-17.9
Haemorrhage	8	25.0	67	50.8	-25.8
Musculoskeletal pain	3	9.4	48	36.4	-27.0
Grade 3 and higher					
Electrocardiogram QT prolonged	6	18.8	19	14.4	4.4
Anaemia	7	21.9	25	18.9	2.9
Fatigue	2	6.3	5	3.8	2.5
Oedema	0	0.0	1	0.8	-0.8
Transaminases increased	2	6.3	10	7.6	-1.3
Pericardial effusion	0	0.0	2	1.5	-1.5
Nausea	1	3.1	7	5.3	-2.2
Decreased appetite	0	0.0	4	3.0	-3.0
Musculoskeletal pain	0	0.0	4	3.0	-3.0
Differentiation syndrome	3	9.4	17	12.9	-3.5
Diarrhoea	0	0.0	5	3.8	-3.8
Thrombocytopenia	2	6.3	16	12.1	-5.9
Haemorrhage	1	3.1	13	9.8	-6.7

Source: FDA analysis
*Includes grouped terms

Figure 14 shows the event rates (events per 100 patient-years (PY)) and hazard ratio (HR) for each all-grade key TEAE.

FDA Figure 14. Event Rates by Dose Form for Key TEAE

TEAE*	n (Events/100 PY) Capsules	Tablets	HR	95% CI
Electrocardiogram QT prolonged	45 (160.01	15 (318.72	1.52	(0.85,2.74)
Fatigue	30 (92.55	10 (172.21	1.47	(0.72,3)
Taste disorder	20 (58.09	6 (84.61	1.28	(0.51,3.2)
Pericardial effusion	7 (17.48	2 (24.66	1.25	(0.26,6.04)
Anaemia	34 (110.82	8 (125.68	1.02	(0.47,2.2)
Nausea	67 (307.59	13 (239.09	0.8	(0.44,1.45)
Differentiation syndrome	27 (78.32	5 (67.29	0.75	(0.29,1.96)
Thrombocytopenia	18 (52.01	3 (39.53	0.7	(0.21,2.39)
Abdominal pain	19 (49.93	3 (38.05	0.68	(0.2,2.3)
Decreased appetite	26 (75.85	3 (44.09	0.47	(0.14,1.55)
Haemorrhage	67 (270.41	8 (120.25	0.46	(0.22,0.96)
Oedema	40 (131.51	4 (55.38	0.39	(0.14,1.09)
Diarrhoea	36 (109.27	3 (39.04	0.33	(0.1,1.08)
Transaminases increased	29 (87.83	2 (25.24	0.27	(0.06,1.13)
Musculoskeletal pain	48 (165.37	3 (41.79	0.23	(0.07,0.72)
Neuropathy peripheral	4 (9.97	0 (0	0.0	(0, .)



Source: FDA analysis
*Includes grouped terms

Clinical TL Comment: Based on the event rate analysis, there is no substantial difference in safety between the two dose forms.

8.3.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

No human carcinogenicity or tumor development studies were conducted.

The Applicant's Position:

N/A

The FDA's Assessment:

Three participants in SNDX-5613-0700 developed a neoplasm other than leukemia, including an oral neoplasm (not otherwise specified), squamous cell carcinoma, and intraepidermal carcinoma (one case each). None occurred in participants treated with revumenib at the recommended dose for acute leukemia having a KMT2A translocation.

Clinical TL Comment: Although the results do not raise a concern for revumenib-induced neoplastic disorders, the follow-up on treatment is too short to exclude the risk.

Human Reproduction and Pregnancy

Data:

There are no clinical data on the use of revumenib during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. The effects on embryogenesis, reproduction, and spermatogenesis in humans are unknown. Based on animal EFT studies and its mechanism of action, revumenib can cause fetal harm when administered to a pregnant woman. There were no confirmed pregnancies reported in SNDX-5613-0700 (SNDX-5613-0700 CSR, Listing 16.2.8.5.1 and 16.2.8.5.2).

The Applicant's Position:

Revumenib can cause fetal harm when administered to pregnant women. Women of reproductive potential and males with a woman partner of reproductive potential should use highly effective contraception during treatment and for at least 4 months after final dose.

The FDA's Assessment:

There was no experience reported for use of revumenib in pregnant patients. Subject (b) (6) was listed as having a positive pregnancy test on Day 270; subsequent blood testing did not confirm that this study participant was pregnant (Applicant's 12/1/2023 RIR).

FDA agrees with the Applicant's statement.

Pediatrics and Assessment of Effects on Growth

Data:

There was a nonclinical finding of an increase in area of the femur growth plate that was closed, relative to control animals. The effect was dose-dependent and more notable in females vs.

males. This effect on femur was interpreted to be a revumenib-related change and was maintained in the recovery phase. This change was not considered adverse, as slightly premature closure of the femoral growth plate did not have any impact on the health of the rats in this study.

The Applicant's Position:

Pediatric assessment of effects on growth have not been performed.

The FDA's Assessment:

FDA agrees with the Applicant's statement.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

In Study SNDX-5613-0700, there were 2 patients who had an overdose. Neither had symptoms, but 1 was hospitalized for observation. There were no overdoses in any supporting studies.

The Applicant's Position:

Potential TEAEs related to overdose are expected to be similar to those in patients that received the RP2D, which include QTc prolongation, nausea, and vomiting. There is no known antidote for revumenib. Treatment of overdose should consist of drug interruption, symptomatic treatment, and ECG monitoring. Re-initiation of revumenib at the correct therapeutic dose may be considered when all toxicities have resolved, but no earlier than 12 hours after the previous dose. No evidence exists that revumenib is addictive or has the potential for illicit or recreational use. The clinical studies in the clinical development program were not designed to study withdrawal/re-initiation of study drug and possible rebound effects.

The FDA's Assessment:

FDA agrees with the Applicant's statement. For clarification, an adverse event of Overdose was reported for two study participants, (b) (6) and (b) (6) Subject (b) (6) took a single dose 1.6x the prescribed dose. The actual dose taken by Subject (b) (6) was not documented.

8.3.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

N/A

The Applicant's Position:

Revumenib has not been approved for commercial use in any country/region worldwide.

The FDA's Assessment:

FDA agrees with the Applicant's statement.

Expectations on Safety in the Postmarket Setting

Data:

N/A

The Applicant's Position:
Similar to the clinical trial experience, the safety profile of revumenib is expected to be acceptable and manageable for the intended patient population in the postmarketing setting with appropriate labeling. The AE profile is characteristic of those symptoms or conditions frequently experienced by patients undergoing treatment for AML or the underlying disease itself and are expected, readily recognized, and managed by the physicians who care for these patients through dose modifications and standard of care measures.

The FDA's Assessment:

We agree that the safety profile of revumenib in the postmarket experience is likely to be similar to that observed in the clinical trials if labeling includes the same mitigation strategies as in the trial protocol, including patient selection, serial safety testing and clinical monitoring, and dose modifications for toxicity. The following are additional labeling considerations to ensure safe use in the postmarket setting:

- Because of the severity and potential mortality, differentiation syndrome warrants special consideration using a boxed warning, and QT prolongation warrants a warning in labeling.

- Revumenib has a narrow therapeutic window. Because pediatric dosing is based on BSA, but tablet is the only dosage form available, (b) (4)

- Whether the size of the tablets presents an unusual hazard for choking or noncompliance in children was also considered. It was the opinion of the DPMH consultant that patients as young as 4-6 years old may be taught to swallow the candidate tablet.[24] Consideration was also given to a lower age limit based on the recent approval of selumetinib capsules for children down to 2 years old. However, the clinical trial of selumetinib included pediatric participants as young as 3 years old to support the safety and effectiveness of the capsules in that age range, while there is no experience with use of the revumenib tablets in that age range. Hence, alternatives, such as tablet crushing (b) (4) would be safer approaches.

- The effectiveness of revumenib in the intended population is thought to rely on inhibition of the interaction of menin with leukemia-promoting KMT2A fusion proteins that arise from translocations and that promote HOXA overexpression. A companion diagnostic device would be necessary to identify patients with the appropriate translocation if conventional cytogenetics was not available. This is clarified in Section 2.1 of labeling, and development of such a device will be a postmarketing commitment.

- Because of the well-characterized mechanism of action, there is an expectation for off-label use in the postmarketing setting for patients with acute leukemia having other genetic variants associated with HOXA overexpression. The integrated safety data set included patients being treated for other diseases, and FDA's analysis did not reveal any new safety issues in those populations. As such, it was concluded that labeling would not require any limitations or additional warnings about use in other disease settings.

Signals for sudden death, hepatotoxicity, endocrine-related disorders, and hypersensitivity reactions were also identified by FDA's safety analyses. Standard pharmacovigilance would likely be sufficient to monitor for these in view of the fact that further characterization of potential safety issues in a clinical trial will be a postmarketing requirement.

Lastly, there are over 100 known KMT2A fusion partners, only nine of which occurred in participants in the clinical trials. Although the broad indication is written based on mechanism of action data as is recommended for rare genetic subtypes, the Applicant has committed to perform additional in vitro testing to confirm the generalizability of these findings to ensure there is no lack of efficacy in the postmarket setting.

[24] NDA 218944 DPHM Consult Review by Ethan D, Hausman, MD, dated 10/23/2024.

8.3.11. Integrated Assessment of Safety

Data:

The overall Safety Population is comprised of 287 patients treated with revumenib across all clinical trials, including 257 treated in Study SNDX-5613-0700. A total of 149 patients (ALL and AML; *NPM1*mut and *KMT2A*r) received revumenib at doses corresponding to the RP2D, across both Phase 1 and Phase 2 of Study SNDX-5613-0700. Sufficient safety data are available to characterize the benefit-risk in the proposed indication (Section 8.3.3).

The important risks for patients treated with revumenib included DS and QTc prolongation via inhibition of hERG channel current:

- DS was most commonly observed during the first cycle. Most events of DS were managed by dose interruption and administration of steroids. Discontinuation of revumenib due to DS did not occur in patients treated at the RP2D (Section 8.3.5).

- Initial events of QTc most commonly occur during the first cycle. Most events of QTc were managed by dose interruption or reduction. In Study SNDX-5613-0700, discontinuation due to the event of QTc prolongation did not occur in patients treated at the RP2D (Section 8.3.5).

The proposed USPI is designed to ensure that prescribers are adequately informed about the important identified risks associated with the use of revumenib and the recommended planned actions to ensure safety. The warnings and precautions of the label will include QTc prolongation and embryo-fetal toxicity. In addition, a black box warning is proposed for DS. The product labeling also includes directions to advise patients on identifying and reporting symptoms suggestive of these key safety risks to a healthcare provider for further evaluation. Such evaluations fall within the scope of normal clinical practice and as such, rely on the provider's discretion to balance the risks and benefits for individual patients.

The data provided in Section 6 of the USPI are based on the safety population in SNDX-5613-0700 Phase 2, Cohorts 2A+2B which corresponds to the indicated *KMT2A*r population.

The Applicant's Position:
In Study SNDX-5613-0700, the AE profile of revumenib is acceptable, and TEAEs were primarily related to the underlying disease, mechanism of action, or were expected based on preclinical characterization of revumenib. The AEs are manageable, with low TRAEs leading to dose reduction/discontinuations. The important identified risks for revumenib include QTc prolongation and DS; these are manageable with guidance in the proposed labeling and did not lead to discontinuation of revumenib. Of note, the ISS RP2D population reaffirms the safety data observed in the *KMT2A*r population (SNDX-5613-0700 Cohort 2A+2B). As such, Section 6 of USPI are based on this population and corresponds to the indicated *KMT2A*r population.

The FDA's Assessment:

The integrated safety database in the ISS included 337 treatments in 324 unique participants on four clinical trials and 50 single-patient protocols. Data from 256 participants were available for dose-response analyses. For the main safety analysis population, (SAFPOP), there were 167 participants with relapsed or refractory acute leukemia with KMT2A translocation who were treated with revumenib at the RP2D. For these participants, the median duration of treatment was 10.6 weeks (range 1 to 36 weeks). Only 6% of participants were treated longer than 6 months. Because the safety data come from a single-arm trial, all TEAE reported were considered adverse reactions with the exception of events identified as acute leukemia or those that were clearly biologically implausible.

There were eight fatal adverse reactions in the integrated safety database (4 sudden death or cardiac arrest, 2 DS, and 2 hemorrhage). The clinically important adverse reactions identified in the SAFPOP included DS and prolonged QTc. Due to the severity and potential mortality, DS warrants a boxed warning and Medication Guide, and prolonged QTc warrants a warning. The safety signals identified included cataracts, elevated transaminases, elevated parathyroid hormone, paraesthesia, taste disorder, and drug hypersensitivity. A number of other adverse reactions were observed, but the duration of follow-up is too short to fully character these, so further study will be required postmarketing.

On subpopulation analysis, there was an increase in QT prolongation and edema in participants 65 years and older. Additionally, the incidences of face edema and DS were numerically higher in pediatric participants, while those of headache, nausea, edema, prolonged QT, and musculoskeletal pain were numerically lower than in adult participants, but the numbers of pediatric participants were too small for firm conclusions.

The representative safety population was comprised of 135 participants (104 adults and 31 children) identified in the SUR based on being treated on Studies SNDX-5613-0700 or SNDX-5613-0705, having acute leukemia, having a KMT2A translocation by local assay, and being treated with revumenib at the RP2D. The median duration of exposure to revumenib was 2.3 months (range < 1 to 23 months), and 3% of patients were exposed for more than 6 months.

Fatal adverse reactions occurred in 4 (3%) participants in this population, including 2 with differentiation syndrome, 1 with hemorrhage, and 1 with sudden death. Serious adverse reactions were reported in 73%. The most frequent (≥ 5%) serious adverse reactions were infection (24%), febrile neutropenia (19%), bacterial infection (17%), differentiation syndrome (12%), hemorrhage (9%), and thrombosis (5%).

Adverse reactions leading to dose interruption occurred in 42% of patients; the common (≥ 5%) adverse reactions leading to dose interruption were electrocardiogram QT prolonged (12%), febrile neutropenia (7%), differentiation syndrome (6%), infection (6%), hypokalemia (5%), and

nausea (5%). More than 75% of patients were able to tolerate full dose for the first 3 cycles. Adverse reactions leading to dose reduction occurred in 10%; adverse reactions leading to a dose reduction in > 1% included electrocardiogram QT prolonged (5%). Adverse reactions leading to permanent discontinuation occurred in 12%; adverse reactions resulting in permanent discontinuation in > 1% included infection (4%) and respiratory failure (2%).

The common adverse reactions reported in the USPI Safety Population are shown in Table 113.

FDA Table 113. USPI Safety Population - Common (≥ 20%) Adverse Reactions

	USPI Safety Population N = 135	
Adverse Reaction*	**All Grades %**	**Grade 3 or 4 %**
Vascular Disorders		
Hemorrhage	53	9
Thrombosis	10	5
Gastrointestinal Disorders		
Nausea	51	4
Diarrhea[d]	30	4
Constipation	23	1
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	42	6
Infections and Investigations		
Infection	41	29
Bacterial infection	31	20
Viral infection	23	4
Blood and lymphatic system disorders		
Febrile neutropenia	35	33
Leukocytosis	8	5
Neoplasms benign, malignant and unspecified		
Differentiation syndrome	29	13
Investigations		
Electrocardiogram QT prolonged	29	12
Metabolism and nutrition disorders		
Decreased appetite	24	8
General disorders and administration site conditions		
Edema	23	1
Fatigue	22	5

Source: FDA analysis
*Includes grouped terms

Additional clinically relevant adverse reactions in less than 20% of patients included cardiac failure, pericardial effusion, ventricular tachycardia, cardiac arrest, hyperparathyroidism, cataract, abdominal pain, sudden death, drug hypersensitivity, hyponatremia, hyperkalemia, taste disorder, syncope, headache, paraesthesia, renal impairment, and rash.

Changes in selected postbaseline laboratory values that were observed in the USPI Safety Population are shown in Table 114.

FDA Table 114. USPI Safety Population - Select New or Worsening Laboratory Abnormalities

Laboratory Abnormality	USPI Safety Population N = 135*	
	Grades 1-4 %	Grades 3-4 %
Phosphate increased	50	-
Aspartate aminotransferase increased	37	1
Alanine aminotransferase increased	33	3
Parathyroid hormone, intact, increased	33	-
Phosphate decreased	25	-
Triglycerides increased	25	3
Potassium decreased	24	5
Alkaline phosphatase increased	21	0
Cholesterol increased	19	0
Creatinine increased	19	0
Calcium corrected increased	15	0

Source: FDA analysis
*The denominator used to calculate the rate varied from 73 to 135 based on the number of patients with a baseline value and at least one postbaseline value.

Overall, the safety profile of revumenib at the recommended dosage was considered acceptable for the intended population. Additional data are needed to assess the safety of long-term administration of revumenib.

SUMMARY AND CONCLUSIONS

8.4. Statistical Issues

The FDA's Assessment:

Study SNDX5613-0700 demonstrated a numerically higher than historically reported response rate. The CR/CRh rate was 21% (95% CI: 11%, 34%) in the Pivotal Cohort and 21% (95% CI: 14%, 30%) in the Efficacy Cohort. Both lower bounds of 95% CI excluded the pre-specified benchmark of 10%. The median duration of response was 6.4 (4.3, NE) months in the Pivotal Cohort and 6.4 (2.7, NE) months in the Efficacy Cohort.

The phase 2 portion of Study SNDX5613-0700 was originally designed to enroll adult patients within each disease cohort according to Simon 2-stage design and pediatric patients independently, and there was no efficacy interim. However, as detailed in Section 8.1.1, the

design was amended to pool patients across age and disease types, and add an efficacy interim for the pooled population at a time point triggered by only the enrollment of Cohort 2B. Given these amendments, the sponsor proposed an efficacy boundary determined by the exact binomial boundary from a group sequential trial. The final sample size was not fixed but estimated based on the enrollment across disease cohorts, and the efficacy boundary with the observed 57 patients in Pivotal Cohort at the CSR submission was estimated to be 0.0097 (1-sided), which the primary analysis met by a small margin. Furthermore, as this cohort requires the central confirmation of mutation status and such data was determined as invalid by FDA, FDA concluded that a cohort identified by conventional testing locally may be a better representation of patients with KMT2A translocations (see Section 4.3). Therefore, FDA used an additional analysis set of Efficacy Cohort whose mutation was locally confirmed in the USPI, and all the analysis based on this analysis set were descriptive only with no formal testing.

8.5. Conclusions and Recommendations

The FDA's Assessment:

The clinical benefit of revumenib in this trial was established based on CR/CRh rate of 21% in relapsed or refractory acute leukemia patients with KMT2At identified by local testing with median duration of 6.4 months. However, there is no significant benefit rate of conversion to transfusion independence (14%). The median duration of treatment was short with only 6% in pivotal study received revumenib more than 6 months. Short-term benefits are meaningful. Revumenib was well tolerated with manageable toxicities with dose interruption or dose reduction. Serious risks such as differentiation syndrome, QTc prolongation can be managed with dose adjustments. Safety concerns due to few cases of sudden death, recurrent differentiation syndrome and hepatotoxicity require further postmarketing study requirements. It was determined that there was not sufficient information to inform dosing of patients less than 1 year old. Therefore, the approvable indication is for the treatment of adult and pediatric patients 1 year or older with relapsed or refractory acute leukemia with a KMT2At.

9 ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

This application was not discussed by an Advisory Committee, because review of this application did not raise significant safety or efficacy issues that were unexpected for a drug of this class and for treatment of patients with acute leukemia.

10 PEDIATRICS

Because revumenib is a molecularly targeted drug for treatment of a cancer in adults, this application is subject to the provisions of FDARA in PREA. Under the Agreed iPSP, the (b) (4) The assessment submitted contains adequate data to support the recommended dosage for patients 1 year and older. The estimated incidence rate of KMT2a-translocated acute leukemias in patients < 1 years in the US is approximately 5/1 million per year.[25] Thus, further studies in patients < 1 year old would be impractical due to the small numbers of patients and geographical dispersion. The Division concludes that the data submitted fulfill the requirements under FDARA for the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older and recommends a waiver for patients < 1 year old. The Division's plan was discussed at the OCE-PeRC meeting on 9/25/2024.

11 LABELING RECOMMENDATIONS

FDA modified sections of the USPI and patient labeling; see table below for details on modifications to the USPI. See the approval letter for final approved labeling.

[25] RWE Consult by Catherine Lerro, PhD, MPH dated 3/26/2024.

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

(b) (4)

11.2. Patient Labeling

FDA modified the Medication Guide to align with changes made to the USPI; see the review from the patient labeling team within DMPP archived separately in DARRTS for further details. FDA determined that an Instructions for Use (IFU) would be required to provide details on dispersing a crushed (b) (4) tablet (b) (4) See reviews from DMEPA and DMPP archived separately in DARRTS for further details.

12 RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

Based on this review, a REMS is not necessary to ensure the benefits outweigh the risks of revumenib for the treatment of relapsed or refractory acute leukemia with a KMT2A translocation in adult and pediatric patients 1 year and older. The management of the risks associated with revumenib treatment will be communicated through labeling.

13 POSTMARKETING REQUIREMENTS AND COMMITMENT

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		
X	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	Yes
X	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	Yes
X	Other considerations (e.g., PK/PD), if applicable:	No

Recommended Postmarketing Requirements

PMR #1 - Conduct a clinical trial to assess and further characterize known serious risks related to the use of revumenib of sudden death, QTc prolongation, differentiation syndrome and elevated transaminases, and assess serious potential risks such as elevated parathyroid hormone. The trial will determine whether long-term use of revumenib is associated with increased risk of cardiac deaths, recurrent differentiation syndrome, serious hepatotoxicity, and serious potential risk of endocrine-related disorders due to chronic menin inhibition. All patients should have at least 3 years of treatment or discontinued earlier.

PMR #2 - Conduct a clinical pharmacokinetic trial to assess the magnitude of change in exposure of revumenib and its metabolite M1 and serious potential risk of increased drug toxicities to determine an appropriate dosage of revumenib in patients with severe hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*".

PMR #3 - Conduct a clinical pharmacokinetic trial to assess the magnitude of change in exposure of revumenib and its metabolite M1 and serious potential risk of increased drug toxicities to determine an appropriate dosage of revumenib in patients with severe renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing*".

PMR #4 - Complete the clinical pharmacokinetic trial to characterize the absorption, distribution, metabolism, and excretion of revumenib and its metabolite M1 and assess the serious potential risk of increased drug toxicities to determine an appropriate dosage of revumenib in patients with both hepatic and renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "*Clinical Pharmacology Considerations for Human Radiolabeled Mass Balance Studies*".

PMR #5 - Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of OATP1B1 inhibitors on the pharmacokinetics of revumenib and M1 to assess the serious potential risk of excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "*Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*".

PMR #6 - Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of revumenib on the single dose pharmacokinetics of a substrate of the multidrug and toxin extrusion protein 1 (MATE1) transporter to assess the serious potential risk of excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "*Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*".

PMR #7 - Conduct a physiologically based pharmacokinetic (PBPK) modeling study and a clinical pharmacokinetic trial if the FDA determines that the PBPK modeling study results are insufficient, to evaluate the effect of repeat doses of revumenib on the single dose pharmacokinetics of a sensitive substrate of CYP3A4 to assess the serious potential risk of excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "*Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*".

Recommended Postmarketing Commitments

PMC #1 - Complete the clinical pharmacokinetic trial to evaluate the effect of a high-fat meal on revumenib exposure and to evaluate appropriate administration of revumenib with regard to food. Design and conduct the trial in accordance with the FDA Guidance for Industry: "*Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations*".

PMC #2 - Conduct an in vitro study to clarify the activity of revumenib in acute leukemias with various KMT2A translocations. Include fusion partners that are rare and those that are not involved in the process of transcriptional elongation.

PMC #3 - Conduct a clinical trial to support the availability of an in vitro diagnostic device for identifying KMT2A translocations in patients with acute leukemias for the safe and effective use of revumenib.

PMC #4- Develop an oral solution formulation and conduct a study to assess relative bioavailability between the oral solution and capsule formulations. Design and conduct the trial in accordance with the FDA Guidance for Industry: "*Bioavailability Studies Submitted in NDAs or INDs — General Considerations*".

14 APPENDICES

14.1. References

Applicant's Position:

References available upon request.

14.2. Financial Disclosure

The Applicant's Position:

All Investigators on Study SNDX-5613-0700, SNDX-5613-0702, SNDX-5613-0705, SNDX-5613-0706, were assessed for significant equity or payments, proprietary interest and other compensation. None of the 915 Investigators had financial interests to disclose.

Covered Clinical Study (Name and/or Number):* SNDX-5613-0700

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 915		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: $28,300 Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in study: N/A Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.3. Nonclinical Pharmacology/Toxicology

There are no additional Nonclinical Pharmacology/Toxicology analyses.

14.4. OCP Appendices

14.4.1. Bioanalytical Methods Section

In Studies SNDX-5613-700, SNDX-5613-705 and SNDX-5613-706 included in the clinical pharmacology package, 2 validated HPLC/MS/MS methods ((b) (4) 2313-1806 and (b) (4) 2313-2001) were used to quantitate revumenib and 1 for the M1 metabolite. The validation methods for revumenib and M1 are outlined in FDA Table 115, FDA Table 116 and FDA Table 117, and their cross validation in FDA Table 118.

FDA Table 115. Summary of bioanalytical method validation and in-study performance for measurement of revumenib for method (b) (4) 2313-1806

Bioanalytical method validation report name, amendments, and hyperlinks	Analysis of revumenib in human plasma using high performance LC-MS/MS Bioanalytical Method (b) (4) 2313-1806
Method description	• Human Plasma (K2EDTA), Protein Precipitation with UPLC/MS/MS Analysis
Materials used for standard calibration curve and concentration	• SNDX-50613 (b) (4) (SNDX-5613), powder
Validated assay range	• 0.1 to 100 ng/mL
Material used for quality controls (QCs) and concentration	• SNDX-50613 (b) (4) (SNDX-5613), powder
Source and lot of reagents	• Human Plasma (K2EDTA) from (b) (4) (Lot Nos. BRH1607670, HMN124 HMN30967, HMN79462, HMN316227, and HMN736488, received on 18 Dec 2018, 19 Feb 2019, 16 Apr 2019, 18 Jul 2019, 10 Jan 2020, and 18 Jan 2022, respectively) SNDX-5613 (b) (4) from (b) (4) (Lot Nos. 18AK0359M and 12390-B-R0-01-95-01) [M+4] SNDX-50613 from (b) (4) (Lot No. VRH-A-49-7)

Regression model and weighting	Linear regression model (weighted $1/X^2$)		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative % accuracy from LLOQ to ULOQ	-6.7% to 5.3%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	2.3% to 5.6%	Yes
Performance of QCs during accuracy and precision runs	Cumulative accuracy (% bias) in 5 QCs: LLOQ, LQC, MQC, HQC, DQC	-4.9% to 5.3%	Yes
	Inter-batch %CV	2.7% to 9.9%	Yes
Selectivity & matrix effect	6 lots of individual blank K2EDTA matrix were tested for blank selectivity and specificity and met the acceptance criteria. Selectivity = ≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS Matrix Effect = 1.023 to 1.046 Selectivity: No significant interference in the screened lots of biological matrix. Matrix effect: No suppression or enhancement noted in the 6 blank matrix lots (%CV <15).		Yes
Interference & specificity	Specificity not confirmed in presence of SNDX-60165, bias; -0.6 to 60.1%. Low QC was not within 100±15.0% due to impurity in SNDX-60165. Investigation concluded no impact.		Yes
Hemolysis effect	5 replicates of Low and High QCs in 2% Hemolyzed Plasma. Results met acceptance criteria. % CV 4.3 and 3.4 %Bias 9.7 and -1.9. No interference, suppression, or enhancement noted with hemolyzed matrix.		Yes
Lipemic effect	5 replicates of Low and High QCs in Lipemic Plasma. Results met acceptance criteria. % CV 4.4 and 3.0 %Bias -2.3 and -3.5. No interference, suppression, or enhancement noted with lipemic matrix.		Yes

Dilution linearity & hook effect	200 ng/mL diluted 50-fold and 100-fold, Hook effect-NA	Yes
Bench-top/process stability	In plasma: 17 Hours at ambient temperature In whole blood: 2 Hours in an ice bath	Yes
Freeze-Thaw stability	5 Cycles at -20°C and -70°C	Yes
Long-term storage	1088 Days at -20°C and -70°C	Yes
Carry over	5 accepted runs <20% LLOQ (SNDX-5613) <5% Carryover IS ([M+4] SNDX-50613)	
Method Performance in Study SNDX-5613-0700 (Report Number: 2313-1901)		
Assay passing rate	144 of 146 runs (98.6%) met acceptance criteria, including ISR runs.	Yes
Standard curve performance	Precision %CV: 2.3% to 4.6% Accuracy %RE: -4.0% to 3.0%	Yes
QC performance	%CV: 3.0% to 5.7% %RE: -2.4% to 3.8%	Yes
Method reproducibility	92.1% of 328 samples selected for ISR met acceptance criteria	Yes
Study sample analysis/ stability	All samples were analyzed within established stability of 1088 days	Yes
Standard calibration curve performance during accuracy and precision runs	8 standard calibrators from LLOQ to ULOQ: 0.100, 0.200, 1.00, 3.00, 10.0, 30.0, 90.0, 100 ng/mL	Yes

Source: Method validation reports located in summary of Biopharmaceutics and associated analytical methods report, table 16

FDA Table 116. Summary of bioanalytical method validation and in-study performance for measurement of revumenib for method (b) (4) 2313-2001

Bioanalytical method validation report name, amendments, and hyperlinks	Analysis of revumenib in human plasma using high performance LC-MS/MS Bioanalytical Method (b) (4) 2313-2001
Method description	• Human Plasma (K2EDTA), Protein Precipitation with UPLC/MS/MS Analysis

Materials used for standard calibration curve and concentration	• SNDX-50613 (b) (4) (SNDX-5613), powder		
Validated assay range	• 5 to 2500 ng/mL		
Material used for quality controls (QCs) and concentration	• SNDX-50613 (b) (4) (SNDX-5613), powder; 5 ng/mL (LLOQ), 15 ng/mL (Low), 200 ng/mL (Mid), 2000 ng/mL (High) and 4000 ng/mL (Dilution).		
Source and lot of reagents	• Human Plasma (K2EDTA) from (b) (4) (Lot Nos. HMN363109 and HMN551775, received on 24 Mar 2020 and 11 Feb 2021, respectively) SNDX-5613 (b) (4) from (b) (4) (Lot No 12390-B-R0-01-95-01) [M+4]SNDX-50613 from (b) (4) (Lot No. VRH-A-49-7)		
Regression model and weighting	Linear regression analysis calculations were performed with 1/x2 weighting, where x is the nominal concentration.		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative % accuracy from LLOQ to ULOQ	-7.8% to 4.0%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	2.9% to 5.2%	Yes
Performance of QCs during accuracy and precision runs	Cumulative accuracy (% bias) in 5 QCs: LLOQ, LQC, MQC, HQC, DQC	-6.0% to 4.5%	Yes
	Inter-batch %CV	2.8% to 6.4%	Yes
Selectivity & matrix effect	6 lots of individual blank K2EDTA matrix were tested for blank selectivity and specificity and met the acceptance criteria. Selectivity = ≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS Matrix Effect = 0.993 to 0.994 Selectivity: No significant interference in the screened biological matrix lots.		Yes

	Matrix effect: No suppression or enhancement noted in the 6 blank matrix lots (%CV <15).	
Interference & specificity	Specificity tested in presence of metabolite and co-medication using 5 replicates, no issues observed. SNDX-60165: -2.0 to 2.4% Posaconazole: -4.5 to 3.9%, Ketoconazole: -9.5 to 1.9%, Isavuconazole: -4.1 to 2.4%, Fluconazole: -3.7 to 5.0%, Cobicistat: -4.1 to 1.1%, Rifampicin: -3.2 to -0.7%, Voriconazole and Voriconazole N-Oxide: -0.6 to 4.5, Itraconazole and Hydroxyitraconazole: -2.6 to 5.8%.	Yes
Hemolysis effect	5 replicates of Low and High QCs in 2% Hemolyzed Plasma. Results met acceptance criteria. % CV 3.6 and 3.8 %Bias 1.3 and -9.3	Yes
Lipemic effect	5 replicates of Low and High QCs in Lipemic Plasma. Results met acceptance criteria. % CV 3.3 and 2.8 %Bias -1.3 and -11.3.	Yes
Dilution linearity & hook effect	10000 ng/mL diluted 10-fold, Hook effect- NA	Yes
Bench-top/process stability	In plasma: 72 Hours at Ambient Temperature In whole blood: 18 Hours in an Ice Bath and at ambient temperature	Yes
Freeze-Thaw stability	5 Cycles at -20°C and -70°C (at 0.3 and 80 ng/mL and thawed at ambient temperature) 5 Cycles at -20°C and -70°C (at 4000 ng/mL and thawed at ambient temperature)	Yes
Long-term storage	<20% LLOQ (SNDX-5613) <5% Carryover IS ([M+4]SNDX 50613)	Yes
Carry over	<20% LLOQ (SNDX-5613) <5% Carryover IS ([M+4]SNDX-50613)	
Method Performance in Study SNDX-5613-0700 (Report Number: 2313-1901)		
Assay passing rate	144 of 146 runs (98.6%) met acceptance criteria, including ISR runs.	Yes
Standard curve performance	%CV: 3.6 to 6.1 %RE: -3.8 to 3.0	Yes
QC performance	%CV: 4.9 to 9.4 %RE: -2.8 to 0.8	Yes

Method reproducibility	92.1% of 328 samples selected for ISR met acceptance criteria	Yes
Study sample analysis/ stability	All but 6 samples were analyzed within established stability of 567 days	Yes
Method Performance in Study SNDX-5613-0705 (Report Number: 2313-2111)		
Assay passing rate	4 of 4 runs (100.0%) met acceptance criteria, including ISR runs.	Yes
Standard curve performance	%CV: 2.6 to 8.2 %RE: -3.2 to 2.7	Yes
QC performance	%CV: 5.1 to 8.6 %RE: -12.3 to –2.7	Yes
Method reproducibility	100.0% of 20 samples selected for ISR met acceptance criteria	Yes
Study sample analysis/ stability	All samples were analyzed within established stability of 567 days	Yes
Method Performance in Study SNDX-5613-0706 (Report Number: 2313-2209)		
Assay passing rate	1 of 1 run (100%) met acceptance criteria.	Yes
Standard curve performance	%CV: NA %RE: -6.2 to 5.8	Yes
QC performance	%CV: NA %RE: -7.0 to -1.0	Yes
Method reproducibility	NA	Yes
Study sample analysis/ stability	All samples were analyzed within established stability of 567 days	Yes

Source: Method validation reports located in summary of Biopharmaceutics and associated analytical methods report, table 16

FDA Table 117. Summary of bioanalytical method validation and in-study performance for measurement of M1 for method (b) (4) 2313-2107

Bioanalytical method validation report name, amendments, and hyperlinks	Analysis of M1in human plasma using high performance LC-MS/MS Bioanalytical Method (b) (4) 2313-2107
Method description	• Human Plasma (K2EDTA), Protein Precipitation with UPLC/MS/MS Analysis

Materials used for standard calibration curve and concentration	• SNDX-50613 [redacted] (b) (4) (SNDX-5613), powder		
Validated assay range	• 5 to 2500 ng/mL		
Material used for quality controls (QCs) and concentration	• SNDX-60165 (M1), powder; 5 ng/mL (LLOQ), 15 ng/mL (Low), 100 ng/mL (Mid), 1000 (High), and 2000 ng/mL (Dilution).		
Source and lot of reagents	• Human Plasma (K2EDTA) from [redacted] (b) (4) (Lot Nos. HMN414544, HMN639189, HMN736488, and HMN519229 received on 19 Jun 2020, 08 Jul 2021, 18 Jan 2022, and 16 Dec 2020, respectively) SNDX-60165 (M1) from [redacted] (b) (4) (Lot No. SYE2100694-21) [M+4]SNDX-50613 from [redacted] (b) (4) (Lot No. VRH-A-49-7)		
Regression model and weighting	Linear regression analysis calculations were performed with 1/x2 weighting, where x is the nominal concentration.		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative % accuracy from LLOQ to ULOQ	-6.7% to 8.2%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	2.8% to 6.9%	Yes
Performance of QCs during accuracy and precision runs	Cumulative accuracy (% bias) in 5 QCs: LLOQ, LQC, MQC, HQC, DQC	-5.0% to 0.0%	Yes
	Inter-batch %CV	5.9% to 11.5%	Yes
Selectivity & matrix effect	Selectivity = ≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS Matrix Effect = 0.985 to 0.991 Selectivity: No significant interference in the screened biological matrix lots. Matrix effect: No suppression or enhancement noted in the 6 blank matrix lots (%CV <15).		Yes

Interference & specificity	6 replicates of ULOQ were tested for blank selectivity. The six lots of individual blank matrix met the acceptance criteria.	Yes
Hemolysis effect	5 replicates of Low and High QCs in 2% Hemolyzed Plasma. Results met acceptance criteria. % CV 4.5 and 1.2 %Bias 4.0 and 5.0	Yes
Lipemic effect	5 replicates of Low and High QCs in Lipemic Plasma. Results met acceptance criteria. % CV 2.5 and 3.9 %Bias 7.3 and 1.5	Yes
Dilution linearity & hook effect	5000 ng/mL diluted 20-fold. Hook effect-NA	Yes
Bench-top/process stability	In plasma: 24 Hours at ambient temperature	Yes
Freeze-Thaw stability	5 Cycles at -20°C and -70°C	Yes
Long-term storage	365 Days at -20°C and -70°C	Yes
Carry over	<20% LLOQ (SNDX-5613) <5% Carryover IS ([M+4] SNDX-50613)	
Method Performance in Study SNDX-5613-0700 (Report Number: 2313-1901B)		
Assay passing rate	SNDX-5613: 50 of 54 runs (92.6%) met acceptance criteria, including ISR runs.	Yes
Standard curve performance	%CV: 3.7 to 5.6 %RE: -3.6 to 2.8	Yes
QC performance	%CV: 4.3 to 5.4 %RE: -14.5 to 1.3	Yes
Method reproducibility	96.8% of 347 samples selected for ISR met acceptance criteria	Yes
Study sample analysis/ stability	739 samples were analyzed outside established stability of 365 days. Additional long-term storage stability will be validated.	Yes
Method Performance in Study SNDX-5613-0705 (Report Number: 2313-2111B)		
Assay passing rate	4 of 6 runs (66.7%) met acceptance criteria, including ISR runs.	Yes
Standard curve performance	%CV: 2.3 to 7.2 %RE: -3.6 to 3.0	Yes

QC performance	%CV: 4.5 to 7.5 %RE: -3.0 to 4.0	Yes
Method reproducibility	95.0% of 20 samples selected for ISR met acceptance criteria	Yes
Study sample analysis/ stability	All samples were analyzed within established stability of 365 days	Yes
Method Performance in Study SNDX-5613-0706 (Report Number: 2313-2209B)		
Assay passing rate	1 of 1 run (100%) met acceptance criteria.	Yes
Standard curve performance	%CV: NA %RE: -4.8 to 4.5	Yes
QC performance	%CV: NA %RE: -1.3 to 3.0	Yes
Method reproducibility	NA	Yes
Study sample analysis/ stability	All samples were analyzed within established stability of 365 days	Yes

Source: Method validation reports located in summary of Biopharmaceutics and associated analytical methods report, table 17

FDA Table 118. Summary of method modifications and cross-validation for measurement of revumenib for methods (b) (4) 2313-1806 and (b) (4) 2001

Validation parameters	**Cross-validation bridging performance between (b) (4) and (b) (4) 2001 (Report Number 2313-1901)**		Acceptability
Standard calibration curve performance during accuracy and precision runs (only runs 29 and 30 are for bridging study and reported)	Cumulative accuracy (% bias) in standard calibrators from LLOQ to ULOQ	-13.4% to 6.0%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	4.8% to 6.6%	Yes
Performance of QCs during accuracy and precision runs	Cumulative accuracy (% bias) in 5 QCs: LLOQ, LQC, MQC, HQC, DQC	-5.9% to 8.3%	Yes
	Inter-batch %CV	≤ 9.9%	Yes
	Percent Total error (TE)	≤ -4.4%	Yes

Cross-validation	A bridging test was performed to establish equivalency between the two methods by bridging QC concentrations 5 and 15 ng/mL from the (b) (4) 2313-1806 method and 40 and 80 ng/mL from the (b) (4) 2313-2001 method. The bridging test was considered acceptable if the determined concentration of each bridging QC sample did not deviate from its nominal concentration more than ±15.0%. A minimum of 2/3 (66.67%) of total number of bridging QC samples and at least 50.0% of the replicate QC samples at each concentration level were required.	

Source: Method validation reports located in summary of Biopharmaceutics and associated analytical methods report, table 18

14.4.2. Population PK Analysis

Executive Summary

The FDA's Assessment:

The final revumenib PPK model (run62) comprised a two-compartment model with first- order absorption with Tlag and linear elimination. The model suggests that CL/F, Vc/F, Q/F, and Vp/F increase with increasing body weight; CL/F decreases with decrease in albumin; The applicant used F1 to reflect the exposure change when strong CYP3A4 inhibitors are used concomitantly. F1 increases when revumenib is administered concomitantly with cobicistat or other strong CYP3A4 inhibitors. KA decreases when revumenib is administered with food (or unknown food status). There is no Tlag with the oral solution or tablet formulation; a modest decrease in Tlag was observed in male subjects; a modest decrease in Tlag was observed in Asian subjects; however, the estimated Tlag is not greater than 15 minutes which is not clinically meaningful. The biological rationale behind the impact of sex and race on PK remains unknown. The proposed two-compartmental PK model captured the plasma drug concentration data reasonably well and the estimated covariate effect of strong CYP3A4 inhibitor on bioavailability (F1) supported the dose adjustment for the corresponding concomitant medication usage and the body weight effect on CL supported the BSA based dose definition.

PPK Assessment Summary

The Applicant's Position:

General Information	
Objectives of PPK Analysis	To develop a PopPK model for revumenib and M1, using data from Study SNDX-5613-0700 and to identify and assess the impact of potential covariates that clinically significantly influence revumenib and M1 PK

<table>
<tr><td colspan="2">Study Included</td><td colspan="3">SNDX-5613-0700</td></tr>
<tr><td colspan="2">Dose(s) Included</td><td colspan="3">113 to 339 mg administered with or without CYP3A4 inhibitors.</td></tr>
<tr><td colspan="2">Population Included</td><td colspan="3">Adult and Pediatric Patients with R/R acute leukemia</td></tr>
<tr><td rowspan="3">Population Characteristics (Population PK Report, Table 6 and Table 7)</td><td>General</td><td colspan="3">Age: Median: 42 years (Range: 0.75 to 82 years)
Baseline Weight: Median: 69.8 kg (Range: 8.10, 146 kg)
Sex: Male; 108 (43%)
Race: White, 178 (70.9%); Black or African American, 20 (8.0%); Asian, 21 (8.4%); American Indian/Alaskan Native, 1 (0.4%); Other, 4 (1.6%); Missing, 27 (10.8%)
Ethnicity: Hispanic or Latino, 53 (21.1%); Not Hispanic or Latino, 182 (72.5%); Missing, 16 (6.4%)
Source: Population PK Report, Table 6 and Table 7</td></tr>
<tr><td>Organ Impairment</td><td colspan="3"><table>
<tr><td rowspan="6">Renal function (CrCL)</td><td>Normal renal function</td><td>167 (66.5%)</td></tr>
<tr><td>Mild renal impairment</td><td>68 (27.1%)</td></tr>
<tr><td>Moderate renal impairment</td><td>16 (6.4%)</td></tr>
<tr><td>Severe renal impairment</td><td>0 (0%)</td></tr>
<tr><td>Kidney failure</td><td>0 (0%)</td></tr>
<tr><td>Missing</td><td>0 (0%)</td></tr>
<tr><td rowspan="4">Hepatic function (NCI-ODWG)</td><td>Normal hepatic function</td><td>198 (78.9%)</td></tr>
<tr><td>Mild hepatic impairment</td><td>46 (18.3%)</td></tr>
<tr><td>Moderate hepatic impairment</td><td>7 (2.8%)</td></tr>
<tr><td>Severe hepatic impairment</td><td>0 (0%)</td></tr>
</table>
Source: Population PK Report, Table 6 and Table 7</td></tr>
<tr><td>Pediatrics (if any)</td><td colspan="3">Baseline Age Category: Infants (1 month to < 2 years of age), 7 (2.8%); Children (2 to < 6 years of age), 14 (5.6%); Children (6 to < 12 years of age), 9 (3.6%); Adolescents (12 to < 18 years of age), 13 (5.2%); Adults (≥ 18 years of age), 208 (82.9%)</td></tr>
<tr><td colspan="2">No. of Patients, PK Samples, and BLQ</td><td colspan="3">Therefore, a total of 4869 SNDX-5613 and 4496 SNDX-60165 samples from 251 patients were evaluable in the PopPK analysis. BLQ observations after administration of the first dose (“post-treatment BLQ”) accounted for < 10% of all observations</td></tr>
<tr><td>Sampling Schedule</td><td>Rich Sampling</td><td colspan="3">Patients Weighing ≥ 7 kg: C1D1 (0.25, 0.5, 1, 2, 4, and 6 h postdose), C1D2 (0.25, 0.5, 1, 2, 4 and 6 h postdose), C1D3 or C1D4 (predose), C1D7 or C1D8 (predose, 0.25, 0.5, 1, 2, 4, and 6 h postdose), C1D14 or C1D15 (predose, 0.25, 0.5, 1, 2, 4 and 6 h postdose), C2D8 (predose, 0.25, 0.5, 1, 2, 4 and 6 h postdose), and C5D1 (predose, 0.25, 0.5, 1, 2, 4, and 6 h postdose).
Patients Weighing < 7 kg: C1D1 (0.5, 1, 2 and 4 h postdose), C1D3 or C1D4 (predose), C1D7 or C1D8 (predose, 0.5, 1, and 4</td></tr>
</table>

<table>
<tr><td></td><td></td><td colspan="3">h postdose), C2D15 (predose, 0.5, 1, 2, and 4 h postdose) and C5D1 (predose, 0.5, 1, 2, and 4 h postdose).</td></tr>
<tr><td></td><td>In ITT Population</td><td colspan="3">R/R acute leukemia</td></tr>
<tr><td>Covariates Evaluated</td><td>Static</td><td colspan="3">Summarized in Table 6 and Table 7 of the Population PK Report</td></tr>
<tr><td></td><td>Time-varying</td><td colspan="3"><table>
<tr><th>Covariate</th><th>Statistic/Value</th><th>Study SNDX-5613-0700</th></tr>
<tr><td>Age (years; N=260)</td><td>Mean (SD)</td><td>41.6 (23.6)</td></tr>
<tr><td></td><td>Median [min, max]</td><td>41.5 [1.00, 83.0]</td></tr>
<tr><td>Body weight (kg; N=455)</td><td>Mean (SD)</td><td>66.9 (25.9)</td></tr>
<tr><td></td><td>Median [min, max]</td><td>68.3 [8.10, 146]</td></tr>
<tr><td>Body mass index (kg/m^2; N=442)</td><td>Mean (SD)</td><td>24.9 (7.10)</td></tr>
<tr><td></td><td>Median [min, max]</td><td>24.3 [11.5, 53.7]</td></tr>
<tr><td></td><td>Missing</td><td>6 (1.4%)</td></tr>
<tr><td>Creatinine (µmol/L; N=851)</td><td>Mean (SD)</td><td>67.0 (29.0)</td></tr>
<tr><td></td><td>Median [min, max]</td><td>63.6 [8.84, 336]</td></tr>
<tr><td>Estimated glomerular filtration rate (mL/min/1.73 m^2; N=865)</td><td>Mean (SD)</td><td>115 (49.4)</td></tr>
<tr><td></td><td>Median [min, max]</td><td>105 [21.9, 339]</td></tr>
<tr><td></td><td>Missing</td><td>6 (0.7%)</td></tr>
<tr><td>Creatinine clearance (mL/min; N=896)</td><td>Mean (SD)</td><td>121 (63.4)</td></tr>
<tr><td></td><td>Median [min, max]</td><td>105 [20.5, 466]</td></tr>
<tr><td>Formulation (N=269)</td><td>Capsule</td><td>213 (79.2%)</td></tr>
<tr><td></td><td>Oral solution</td><td>45 (16.7%)</td></tr>
<tr><td></td><td>Tablet</td><td>11 (4.1%)</td></tr>
<tr><td>Food effect (N=395)</td><td>Fasted</td><td>122 (30.9%)</td></tr>
<tr><td></td><td>Fed</td><td>27 (6.8%)</td></tr>
<tr><td></td><td>Unknown</td><td>246 (62.3%)</td></tr>
<tr><td>Concomitant CYP3A4 weak inhibitor (N=271)</td><td>No</td><td>193 (71.2%)</td></tr>
<tr><td></td><td>Yes</td><td>78 (28.8%)</td></tr>
<tr><td>Concomitant CYP3A4 moderate inhibitor (N=261)</td><td>No</td><td>227 (87.0%)</td></tr>
<tr><td></td><td>Yes</td><td>34 (13.0%)</td></tr>
<tr><td>Concomitant cobicistat and other strong CYP3A4 inhibitors (N=300)</td><td>Without a strong CYP3A4 inhibitor[a]</td><td>106 (35.3%)</td></tr>
<tr><td></td><td>With cobicistat</td><td>37 (12.3%)</td></tr>
<tr><td></td><td>With other strong CYP3A4 inhibitors</td><td>154 (51.3%)</td></tr>
<tr><td></td><td>With cobicistat and other strong CYP3A4 inhibitor</td><td>3 (1.0%)</td></tr>
<tr><td>Renal function (N=337)</td><td>Normal renal function</td><td>192 (57.0%)</td></tr>
<tr><td></td><td>Mild impairment</td><td>108 (32.0%)</td></tr>
</table></td></tr>
</table>

		Moderate impairment	35 (10.4%)
		Severe impairment	2 (0.6%)
		Kidney failure	0 (0%)
		Missing	0 (0%)

Source: Population PK Report, Table 8

Final Model	Summary	Acceptability [FDA's comments]
Software and Version	NONMEM® (Version 7.4.3; (b) (4) for PopPK modelling. R (Version 4.0.0 or higher) for simulations, graphs, and data manipulations. Xpose and Perl-speaks-NONMEM (PsN; (b) (4) for model diagnostics and covariate testing.	Acceptable
Model Structure	The PK of revumenib was adequately described by a 2-compartment model with linear elimination, first-order absorption, and an absorption lag time. M1 was adequately described by a 2-compartment model with first-order conversion and linear elimination.	Acceptable
Model Parameter Estimates	Table 119 for revumenib and Table 120 for M1	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Table 119 for revumenib and Table 120 for M1	Acceptable
BLQ for Parameter Accuracy	Concentration samples that were BLQ were kept in the analysis dataset and flagged accordingly. If more than 15% of the data were BLQ, for any 1 analyte, then likelihood-based methods of imputation were considered (eg, M3 likelihood imputation). BLQ observations after administration of the first dose ("post-treatment BLQ") accounted for < 10% of all observations. Hence, exclusion of BLQ samples was deemed defendable.	Acceptable
GOF, VPC	Figure 15 and Figure 16	Acceptable
Significant Covariates and Clinical Relevance	Figure 17	Acceptable

Analysis Based on Simulation (optional)	Model based simulations were conducted for revumenib and M1 to support formulation, dosing regimen, dose recommendations in adults and pediatrics.	Acceptable
Labeling Language	Description	Acceptability
12.3 PK	The PK characteristics of revumenib are summarized in USPI Section 12.3 pharmacokinetics.	Acceptable

The Applicant's Position above provides a summary of PopPK analyses. A summary of descriptive statistics of baseline categorical covariates is in Population PK Report Table 7, and a summary of continuous covariates included in the PK dataset is in Table 6. Parameter Estimates from the Final Population PK Model are summarized in Table 119 (revumenib) and Table 120 (M1).

Table 119 Applicant – Final Revumenib Model Parameter Estimates

Parameters (Unit)	Estimates	RSE%	SIR RSE%	SIR 95% CI	
CL/F (L/hr)	18.3	6.34	4.50	[16.8, 19.9]	
Vc/F (L)	121	6.31	5.11	[110, 134]	
Q/F (L/hr)	12.0	13.6	8.59	[10.2, 14.1]	
Vp/F (L)	334	18	11.0	[274, 415]	
KA (1/hr)	2.06	15.5	13.0	[1.56, 2.61]	
Tlag (hr)	0.227	1.04	0.512	[0.225, 0.229]	
F1 (-)	1.00	FIX	-	-	
Body weight effect on CL/F (-)	0.287	20.8	19.0	[0.178, 0.395]	
Body weight effect on Vc/F (-)	0.716	9.43	9.18	[0.588, 0.848]	
Body weight effect on Q/F (-)	0.826	14.5	10.4	[0.662, 0.999]	
Body weight effect on Vp/F (-)	0.936	25.6	20.0	[0.606, 1.34]	
Cobicistat effect on F1 (-)	1.55	12.5	10.3	[1.22, 1.85]	
Other strong CYP3A4 inhibitor effect on F1 (-)	1.10	15.4	9.21	[0.916, 1.31]	
Fed effect on KA (-)	-0.702	22.1	11.0	[-0.819, -0.517]	
Unknown food effect on KA (-)	-0.511	22.3	14.2	[-0.633, -0.357]	
Solution effect on Tlag (-)	-1.00	FIX	-	-	
Tablet effect on Tlag (-)	-1.00	FIX	-	-	
Albumin effect on CL/F (-)	0.977	24.3	20.9	[0.586, 1.36]	
Male effect on Tlag (-)	-0.131	9.73	4.98	[-0.143, -0.117]	
Asian effect on Tlag (-)	-0.144	9.2	6.97	[-0.163, -0.124]	

Parameters (Unit)	Estimates	RSE%	SIR RSE%	SIR 95% CI	
Random effects	**Estimates**	**RSE%**			**Shrinkage (%)**
IIV on CL/F (CV%)	53.3	5.98	5.23	[47.6, 59.9]	7.89
Covariance (CL/F and Vc/F)	0.107	22.8	22.3	[0.0609, 0.154]	-
Correlation (CL/F and Vc/F)	0.538	-	-	-	-
IIV on Vc/F (CV%)	41.3	16.0	13.7	[27.1, 52]	33.7
IIV on KA (CV%)	237	6.86	6.01	[187, 317]	11.8
Residual error	**Estimates**	**RSE%**			**Shrinkage (%)**
Additive error on the log scale (equivalent to a proportional error on the linear scale)	0.685	2.63	1.17	[0.67, 0.702]	5.03

Source: Population PK Report, Table 12

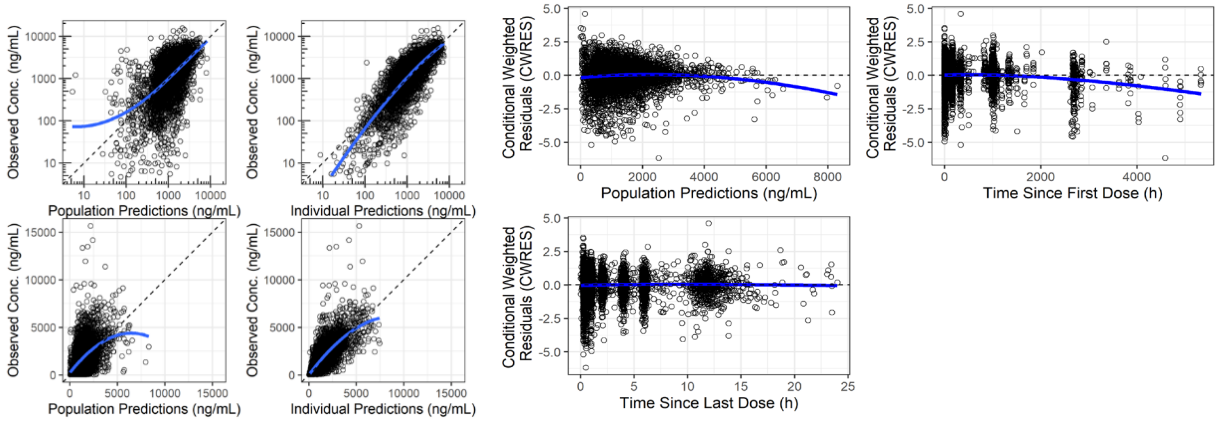
Table 120 Applicant – Final M1 Model Parameter Estimates

Parameters	Estimates	RSE%	SIR RSE%	SIR 95% CI	
CLm/F (L/hr)	6.99	7.80	4.39	[6.41, 7.63]	
Vcm/F (L)	2.23	17.6	15.0	[1.66, 2.94]	
Qm/F (L/hr)	12.3	8.23	4.83	[11.1, 13.5]	
Vpm/F (L)	49.6	10.3	4.81	[44.9, 54.6]	
Fm (-)	0.183	FIX	-	-	
Cobicistat effect on Fm	-0.996	0.095	0.0297	[-0.997, -0.995]	
Other strong CYP3A4 inhibitor effect on Fm	-0.508	9.93	3.82	[-0.545, -0.467]	
Body weight effect on CLm/F	0.31	25.4	20.0	[0.194, 0.434]	
Body weight effect on Qm/F	0.779	12.4	9.82	[0.638, 0.93]	
Cobicistat effect on CLm/F	-0.732	8.30	4.27	[-0.787, -0.66]	
Random effects	**Estimates (CV%)**	**RSE%**			**Shrinkage (%)**
IIV on CLm/F (CV%)	66.1	6.68	5.17	[59.3, 75.1]	3.94
Covariance (CLm/F and Vcm/F)	0.377	23.6	23.0	[0.218, 0.557]	-
Correlation (CLm/F and Vcm/F)	0.328	-	-	-	-
IIV on Vcm/F (CV%)	617	7.1	6.27	[414, 1030]	19.5
Residual error	**Estimates**	**RSE%**			**Shrinkage (%)**
Additive error on the log scale (equivalent to a proportional error on the linear scale)	0.485	3.66	1.12	[0.475, 0.497]	4.41

Source: Population PK Report, Table 16

Goodness of fit plots for the final model of revumenib are shown in Figure 15. Similar plots were generated for M1 and are presented in Figure 17 of the Population PK Report.

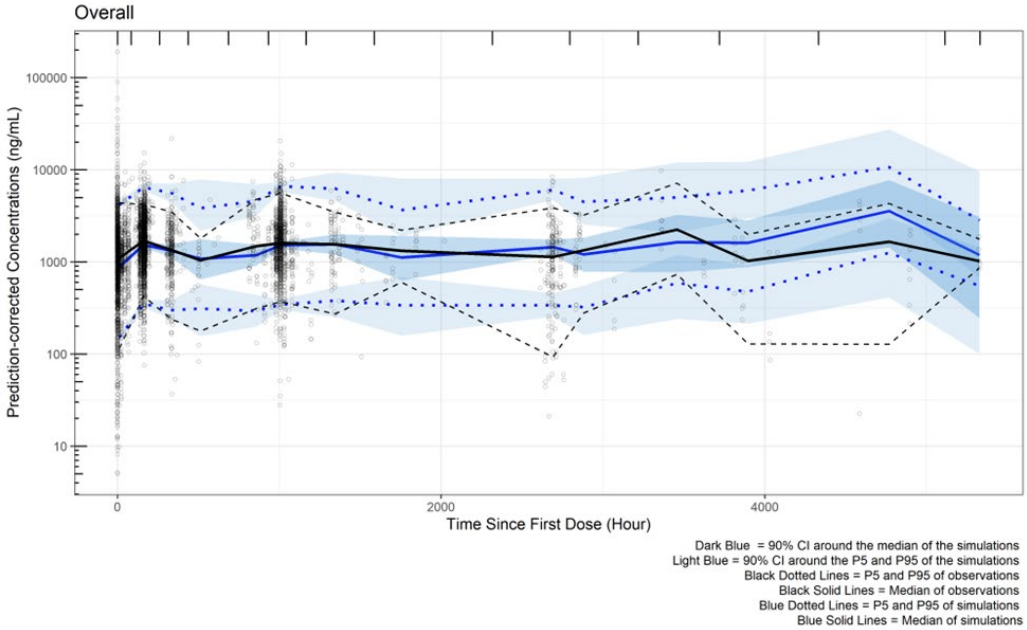
Figure 15 Applicant – Goodness-of fit Plots for the Final Population PK Model for Revumenib



Source: Population PK Report, Figure 10

Visual Predictive Check plots for the final model of revumenib are shown in Figure 16. Similar plots were generated for M1 and are presented in Figure 21 of the Population PK Report.

Figure 16 Applicant – Prediction-Corrected VPC for Revumenib

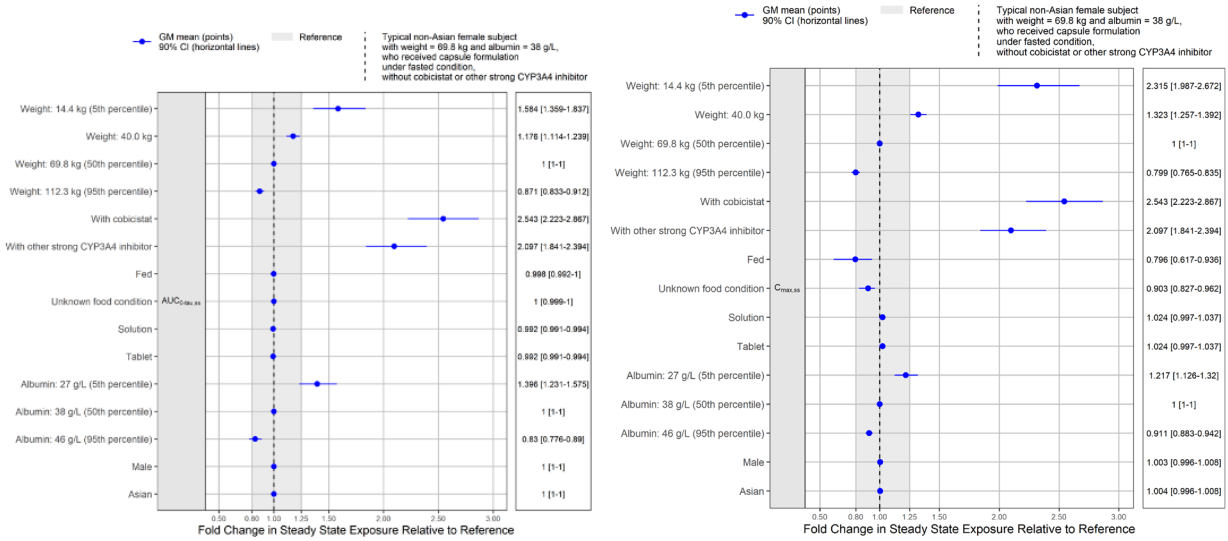


Source: Population PK Report, Figure 14

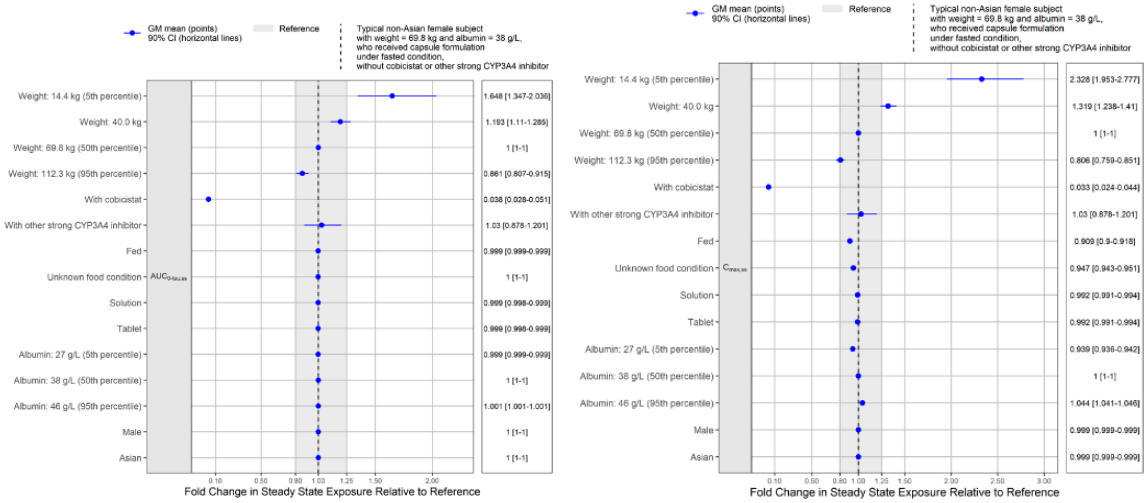
The forest plots of covariate effects for revumenib and M1 exposure are presented in Figure 17.

Figure 17 Applicant – Forest Plot of Covariate Effects on Steady-State Revumenib and M1 Exposure – Univariate Analysis

Revumenib:

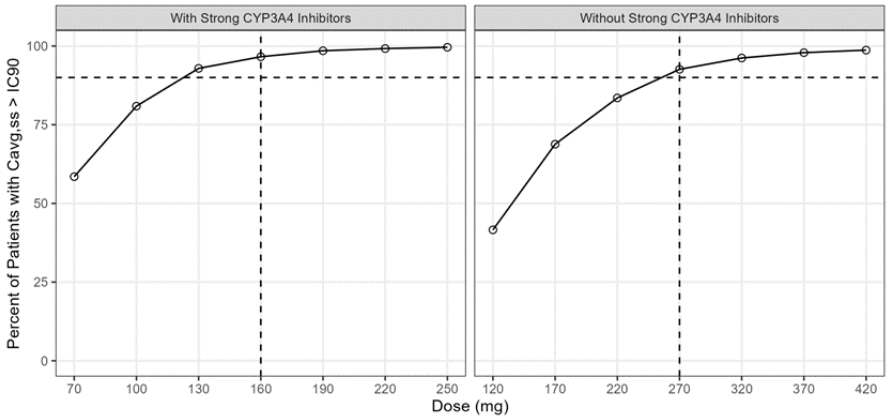


M1:



Source: Population PK Report, Figure 22 and Figure 23

Figure 18 Applicant – Predicted Proportion of Patients Achieving Revumenib Average Concentrations Sufficient for At Least 90% *KMT2A*r Inhibition



Source: Simulation Report, Figure 16

The FDA's Assessment:

The analysis is useful for selecting revumenib dose when strong CYP3A4 inhibitor is co-administered. However, the analysis results could have uncertainties because of the PPK estimated effect of strong CYP3A4 inhibitor on CL/F1 is much smaller than PBPK estimated effect.

14.4.3. Exposure-Response Analysis

ER (efficacy) Executive Summary

The FDA's Assessment:

Efficacy Response Rate: exploratory data analysis (EDA) was conducted on binary efficacy endpoints CR, CRh, CRi, CRp, CR+CRh rate, ORR, CRc rate, and PBTI in CR + CRh and CRc rate responders with respect to exposure metrics maximum concentration at steady state (Cmax,ss), average concentration at steady state (Cavg,ss), minimum concentration at steady state (Cmin,ss) and time averaged exposure (TAE) and categorical and continuous covariates. Linear logistic regression plots were conducted to establish if significant associations existed between efficacy endpoints and exposure metrics and between efficacy endpoints and covariates. For those efficacy endpoints that indicated a significant relationship between exposure metrics through the EDA, multiple logistic regression models were conducted. First, the most significant exposure with endpoint was selected as the base model. Then, covariate searching based on the base model was conducted to develop the final models.

Time-to-Event Endpoints: EDA was conducted on time-to-event (TTE) efficacy endpoints OS, EFS, TTR (CR, ORR, and CRc), and DOR (CR, ORR, and CRc) with respect to exposure

metrics Cmax,ss, Cavg,ss, Cmin,ss, and TAE and categorical and continuous covariates. Kaplan-Meier (KM) plots were conducted to establish if significant associations existed between efficacy endpoints and exposure metrics and between efficacy endpoints and covariates. For those efficacy endpoints that indicated a significant relationship between exposure metrics through the EDA, Cox proportional hazard models were conducted. First, the most significant exposure with endpoint was selected as the base model. Then, covariate searching based on the base model was conducted to develop the final models.

The applicant's exposure-response analysis for efficacy is acceptable in general.

ER (efficacy) Assessment Summary

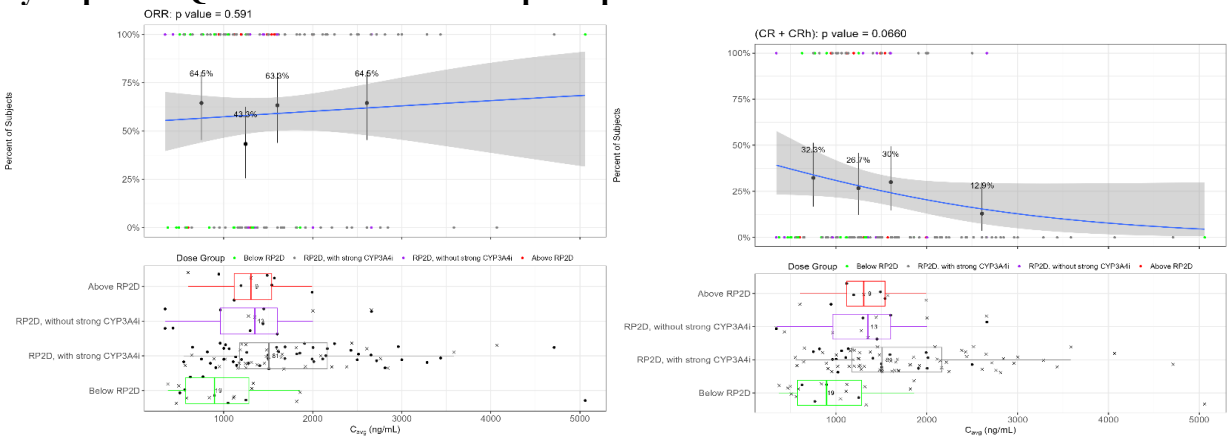
The Applicant's Position:

<table>
<tr><td colspan="3">General Information</td></tr>
<tr><td colspan="2">Goal of ER analysis</td><td>To evaluate the relationships between revumenib exposures and efficacy endpoints based on data from patients with KMT2Ar acute leukemias.</td></tr>
<tr><td colspan="2">Study Included</td><td>Study SNDX-5613-0700</td></tr>
<tr><td colspan="2">Endpoint</td><td>Primary clinical efficacy endpoint: CR + CRh rate
Other key efficacy endpoints: ORR, OS, EFS</td></tr>
<tr><td colspan="2">No. of Patients (total, and with individual PK)</td><td>122</td></tr>
<tr><td>Population Characteristics (E-R Efficacy Report, Table 4)</td><td>General</td><td>
<table>
<tr><th>Covariate</th><th>Overall (N=122)</th></tr>
<tr><td colspan="2">Age (years)</td></tr>
<tr><td>Mean (SD)</td><td>37.5 (21.3)</td></tr>
<tr><td>Median [min, max]</td><td>38.0 [0.750, 79.0]</td></tr>
<tr><td colspan="2">Sex</td></tr>
<tr><td>Male</td><td>46 (37.7%)</td></tr>
<tr><td>Female</td><td>76 (62.3%)</td></tr>
<tr><td colspan="2">Race</td></tr>
<tr><td>White</td><td>85 (69.7%)</td></tr>
<tr><td>Black or African American</td><td>9 (7.4%)</td></tr>
<tr><td>Asian</td><td>13 (10.7%)</td></tr>
<tr><td>American Indian/Alaskan Native</td><td>0 (0%)</td></tr>
<tr><td>Native Hawaiian or Other Pacific Islander</td><td>0 (0%)</td></tr>
<tr><td>Other</td><td>1 (0.8%)</td></tr>
<tr><td>Missing</td><td>14 (11.5%)</td></tr>
</table>
</td></tr>
</table>

	Pediatrics (if any)	There were pediatrics patients in the dataset. The ages of patients in the analyses ranged from 0.75 – 79.0 years. Age was included as a continuous covariate.	
Dose(s) Included		113 to 339 mg mainly administered as q12h dosing regimen.	
Exposure Metrics Explored (range)		C_{avgss}, $C_{max,ss}$, $C_{min,ss}$ and TAE, were explored. Exposure metric distribution is summarized in Figure 4 of the E-R Efficacy Report.	
Covariates Evaluated		Table 4 of the E-R Efficacy Report.	
Final Model Parameters		Summary	Acceptability
Model Structure		Binary efficacy endpoints: Exploratory univariate logistic regression analysis followed by multivariate logistic regression model if exploratory analysis showed a plausible significant relationship. TTE efficacy endpoints: KM plots followed by Cox-PH model if KM plots showed a plausible significant relationship.	**Acceptable**
Model Parameter Estimates		Table 6 and Table 9 in E-R Efficacy Report	Acceptable
Model Evaluation		VPC	Acceptable
Covariates and Clinical Relevance		No covariates of clinical relevance were identified.	Acceptable
Simulation for Specific Population		N/A	Acceptable
Visualization of E-R relationships		Figure 19	Acceptable
Overall Clinical Relevance for ER		There was no clinically plausible E-R efficacy relationships for the primary clinical efficacy endpoint (CR+CRh rate) or other key efficacy endpoints (ORR, EFS, or OS) for most exposure metrics.	Acceptable
Labeling Language		Description	Acceptability
12.2 Pharmacodynamics		No exposure efficacy language was proposed in Section 12.2 of the USPI.	Acceptable

Source: E-R Efficacy Report, Table 4

Figure 19 Applicant – Exposure-Response Curves for ORR and CR+CRh rate Stratified by Exposure Quartile with Dose Group Boxplots



Source: E-R Efficacy Report, Figure 13 (ORR) and Figure 17 (CR+CRh rate)

Reviewer's Comment: We generally agree that the ER for efficacy is flat. The observed reverse ER relationship for CR+CRh is probably confounded by the high exposure outliers in the RP2D, with strong CYP3A4i group where other factors may influence the response.

ER (safety) Executive Summary

The FDA's Assessment:

The applicant conducted exposure-response (E-R) analysis for both continuous safety markers and binary safety endpoints. The applicant's exposure-response analysis for safety is acceptable in general.

For continuous safety markers such as heart rate, a longitudinal analysis relating the time course of biomarker, concentration, and other potential covariates was considered. Constant, linear, or nonlinear functions (e.g., Emax model) were explored to identify the appropriate functions that best described the relationship between observed safety biomarker data and corresponding drug exposure. An indirect response or effect compartment model was evaluated as well where a temporal delay was observed between the measured safety biomarker data and the corresponding drug exposure.

For the binary analysis, all safety endpoints were binary with the E-R safety analysis only conducted for adverse events (AEs) with an overall incidence rate of ≥10% and <90%. Univariate analysis was performed initially to select the appropriate exposure metrics for further modeling. A linear logistic regression analysis was subsequently undertaken for revumenib and its metabolite SNDX-60165 separately. Initially, only revumenib or SNDX-60165 systemic

exposure metrics were considered as an independent variable. If there was no evidence of an exposure dependency (i.e., $p>0.05$), the relationship between exposure and the safety endpoints was not further investigated. However, if a statistically significant E-R relationship was identified, the model with the most statistically significant exposure metric was used as the base model and other candidate covariates of interest were investigated.

Covariate selection was determined for its significance based on the lowest value of the Akaike information criterion (AIC) or the likelihood ratio test at the $p<0.01$ level for forward inclusion and $p<0.001$ level for backward deletion. To evaluate the performance of the E-R safety models, observed and predicted (95% confidence interval [CI]) incidences for each safety endpoint were compared.

ER (safety) Assessment Summary

The Applicant's Position:

<table>
<tr><td colspan="4">General Information</td></tr>
<tr><td colspan="2">Goal of ER analysis</td><td colspan="2">To characterize the relationship between revumenib and M1 exposure with safety endpoints.</td></tr>
<tr><td colspan="2">Study Included</td><td colspan="2">Study SNDX-5613-0700</td></tr>
<tr><td colspan="2">Population Included</td><td colspan="2">Patients with acute leukemia</td></tr>
<tr><td colspan="2">Endpoint</td><td colspan="2">Major common AEs/SAEs, and AEs of special interest (including Prolonged QTc interval [Grade ≥ 2] and Differentiation syndrome [any grade]). All endpoints are presented in Table 2 of the E-R Safety Report.</td></tr>
<tr><td colspan="2">No. of Patients (total, and with individual PK)</td><td colspan="2">251</td></tr>
<tr><td>Population Characteristics (E-R Safety Report, Table 6)</td><td>General</td><td colspan="2">
<table>
<tr><th>Covariate</th><th>Statistic/Value</th><th>Overall (N=251)</th></tr>
<tr><td>Age (years)</td><td>Mean (SD)</td><td>42.6 (22.8)</td></tr>
<tr><td></td><td>Median [min, max]</td><td>42.0 [0.750, 82.0]</td></tr>
<tr><td>Body weight (kg)</td><td>Mean (SD)</td><td>68.4 (26.9)</td></tr>
<tr><td></td><td>Median [min, max]</td><td>69.8 [8.10, 146]</td></tr>
<tr><td>Sex</td><td>Male</td><td>108 (43.0%)</td></tr>
<tr><td></td><td>Female</td><td>143 (57.0%)</td></tr>
<tr><td>Age group</td><td>Adult (≥ 18 years)</td><td>208 (82.9%)</td></tr>
<tr><td></td><td>Pediatric (total)</td><td>43 (17.1%)</td></tr>
<tr><td></td><td>Infants (1 month to < 2 years)</td><td>7 (2.8%)</td></tr>
<tr><td></td><td>Children (2 years to < 6 years)</td><td>14 (5.6%)</td></tr>
<tr><td></td><td>Children (6 years to < 12 years)</td><td>9 (3.6%)</td></tr>
<tr><td></td><td>Adolescents (12 years to < 18 years)</td><td>13 (5.2%)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td></td><td>
<table>
<tr><td rowspan="6">Race</td><td>White</td><td>178 (70.9%)</td></tr>
<tr><td>Black or African American</td><td>20 (8.0%)</td></tr>
<tr><td>Asian</td><td>21 (8.4%)</td></tr>
<tr><td>American Indian/Alaskan Native</td><td>1 (0.4%)</td></tr>
<tr><td>Other</td><td>4 (1.6%)</td></tr>
<tr><td>Missing</td><td>27 (10.8%)</td></tr>
</table>
</td></tr>
<tr><td></td><td>Organ impairment</td><td>Source: Population PK Report, Table 7
<table>
<tr><td rowspan="6">Renal function (CrCL)</td><td>Normal renal function</td><td>167 (66.5%)</td></tr>
<tr><td>Mild renal impairment</td><td>68 (27.1%)</td></tr>
<tr><td>Moderate renal impairment</td><td>16 (6.4%)</td></tr>
<tr><td>Severe renal impairment</td><td>0 (0%)</td></tr>
<tr><td>Kidney failure</td><td>0 (0%)</td></tr>
<tr><td>Missing</td><td>0 (0%)</td></tr>
<tr><td rowspan="4">Hepatic function (NCI-ODWG)</td><td>Normal hepatic function</td><td>198 (78.9%)</td></tr>
<tr><td>Mild hepatic impairment</td><td>46 (18.3%)</td></tr>
<tr><td>Moderate hepatic impairment</td><td>7 (2.8%)</td></tr>
<tr><td>Severe hepatic impairment</td><td>0 (0%)</td></tr>
</table>
</td></tr>
<tr><td></td><td>Pediatrics (if any)</td><td>Source: E-R Safety Report, Table 6
<table>
<tr><td>Infants (1 month to < 2 years)</td><td>7 (2.8%)</td></tr>
<tr><td>Children (2 years to < 6 years)</td><td>14 (5.6%)</td></tr>
<tr><td>Children (6 years to < 12 years)</td><td>9 (3.6%)</td></tr>
</table>
</td></tr>
<tr><td></td><td>Geriatrics (if any)</td><td>There were geriatric patients in the E-R safety analysis. The ages of patients in the dataset ranged from 0.75 to 82.0 years. Age was included as a continuous covariate.</td></tr>
<tr><td colspan="2">Dose(s) Included</td><td>113 to 339 mg mainly administered as q12h dosing regimen</td></tr>
<tr><td colspan="2">Exposure Metrics Explored (range)</td><td>$C_{min,ss}$, $C_{max,ss}$, and $C_{avg,ss}$ of Revumenib and M1.
Figure 3 and Figure 4 in E-R Safety Report.</td></tr>
<tr><td colspan="2">Covariates Evaluated</td><td>Table 6 of the E-R Safety Report.</td></tr>
<tr><td colspan="2">Final Model Parameters</td><td>Summary</td><td>Acceptability [FDA's comments]</td></tr>
<tr><td colspan="2">Model Structure</td><td>The significant E-R relationships were described by logistic regression.</td><td>Acceptable</td></tr>
<tr><td colspan="2">Model Parameter Estimates</td><td>Table 121a (Prolonged QTc Interval)

Table 121b (Differentiation Syndrome [Any Grade])</td><td>Acceptable</td></tr>
<tr><td colspan="2">Model Evaluation</td><td>VPC</td><td>Acceptable</td></tr>
</table>

Covariates and Clinical Relevance	Age is the only covariate that is significant on differentiation syndrome (Table 121b)	Acceptable
Simulation for Specific Population	Exposure-safety simulations were conducted for selected safety endpoints for a range of dosing scenarios to support dosing recommendations.	Acceptable
Visualization of E-R relationships	Figure 20	Acceptable
Overall Clinical Relevance for ER	There were no significant changes in continuous safety biomarkers with increase in revumenib or M1 exposures. A statistically significant relationship was observed with revumenib exposure with each of 4 binary safety parameters: neutropenia (Grade ≥ 4), TEAE leading to dose modification, dose discontinuation, and dose delay or interruption. There was a statistically significant relationship with M1 exposure with each of 7 binary safety parameters: prolonged QTc interval (Grade ≥ 2), differentiation syndrome (any grade), neutropenia (Grade ≥ 4), thrombocytopenia (Grade ≥ 4), TEAE leading to dose reduction, TEAE leading to dose modification, and any Grade ≥ 3 TEAE.	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	No exposure safety language was proposed in Section 12.2 of the USPI.	Acceptable

Table 121 Applicant – Parameter Estimates from Final ER Model of (endpoint) QTc and Differentiation Syndrome

a) Summary of Logistic Regression Model Parameters: Prolonged QTc Interval

Parameter	Estimate	95% Confidence Interval	Standard Error	p-Value
Intercept	-1.69	[-2.24, -1.18]	0.269	< 0.0001
Slope of SNDX-60165 $C_{avg,ss}$	0.00171	[0.000561, 0.00289]	0.000590	0.00383

Source: E-R Safety Report, Table 10

b) Summary of Logistic Regression Model Parameters: Differentiation Syndrome (Any Grade)

Parameter (Unit)	Estimate	95% CI	Standard Error	p-Value
Intercept	-1.08	-1.84, -0.366	0.375	0.00383
Slope of SNDX-60165 $C_{max,ss}$	0.00160	0.000475, 0.00276	0.000579	0.00568
Slope of age	-0.0294	-0.0454, -0.0143	0.00791	0.000204

Source: E-R Safety Report, Table 12

FDA added tables c-j including the footnote from the sponsor's E-R safety Report.

c) Summary of Logistic Regression Model Parameters: Neutropenia (Grade ≥4)

	Parameter (Unit)	Estimate	95% CI	Standard Error	p-Value
SNDX-5613 $C_{max,ss}$	Intercept	-2.34	-3.14, -1.59	0.392	<0.0001
	Slope of SNDX-5613 $C_{max,ss}$	0.000232	0.00000403, 0.000454	0.000114	0.0418
SNDX-60165 $C_{min,ss}$	Intercept	-2.35	-2.98, -1.78	0.305	<0.0001
	Slope of SNDX-60165 $C_{min,ss}$	0.00221	0.000785, 0.00366	0.000727	0.00236

Source: E-R Safety Report, Table 14

d) d) Summary of Logistic Regression Model Parameters: Thrombocytopenia (Grade ≥4)

Parameter (Unit)	Estimate	95% CI	Standard Error	p-Value
Intercept	-1.86	-2.44, -1.32	0.285	<0.0001
Slope of SNDX-60165 $C_{avg,ss}$	0.00149	0.000283, 0.00271	0.000615	0.0155

Source: E-R Safety Report, Table 16

e) Summary of Logistic Regression Model Parameters: TEAE Leading to Dose Discontinuation

Parameter (Unit)	Estimate	95% CI	Standard Error	p-Value
Intercept	-2.55	-3.31, -1.85	0.370	<0.0001
Slope of SNDX-5613 $C_{min,ss}$	0.000960	0.000527, 0.00142	0.000226	<0.0001
Concomitant administration of drug with QT prolongation risk	-1.51	-2.56, -0.604	0.492	0.0022

Source: E-R Safety Report, Table 18

f) Summary of Logistic Regression Model Parameters: TEAE Leading to Dose Delays or Interruptions

Parameter (Unit)	Estimate	95% CI	Standard Error	p-Value
Intercept	-0.897	-1.44, -0.378	0.270	0.000885
Slope of SNDX-5613 $C_{avg,ss}$	0.000467	0.000193, 0.000760	0.000144	0.001170

Source: E-R Safety Report, Table 20

g) Summary of Logistic Regression Model Parameters: TEAE Leading to Dose Modification

	Parameter (Unit)	Estimate	95% CI	Standard Error	p-Value
SNDX-5613	Intercept	-0.574	-1.04, -0.129	0.231	0.0129
	Slope of SNDX-5613 $C_{min,ss}$	0.000919	0.000512, 0.00137	0.000219	0.0000273
SNDX-60165	Intercept	-0.169	-0.583, 0.238	0.209	0.418
	Slope of SNDX-60165 $C_{min,ss}$	0.00169	0.000476, 0.00298	0.000638	0.00807

Source: E-R Safety Report, ***Table 22***

h) Summary of Logistic Regression Model Parameters: TEAE Leading to Dose Reduction

Parameter (Unit)	Estimate	95% CI	Standard Error	p-Value
Intercept	-2.93	-3.73, -2.22	0.384	<0.00001
Slope of SNDX-60165 $C_{avg,ss}$	0.00246	0.00102, 0.00394	0.000738	0.000872

Source: E-R Safety Report, Table 24

i) Summary of Logistic Regression Model Parameters: Grade ≥3 TEAE

Parameter (Unit)	Estimate	95% CI	Standard Error	p-Value
Intercept	1.28	0.728, 1.87	0.290	<0.0001
Slope of SNDX-60165 $C_{min,ss}$	0.00259	0.00057, 0.00493	0.00111	0.0193

Source: E-R Safety Report, Table 26

j) Summary of Binary Endpoints with Overall Incidence of ≥10%

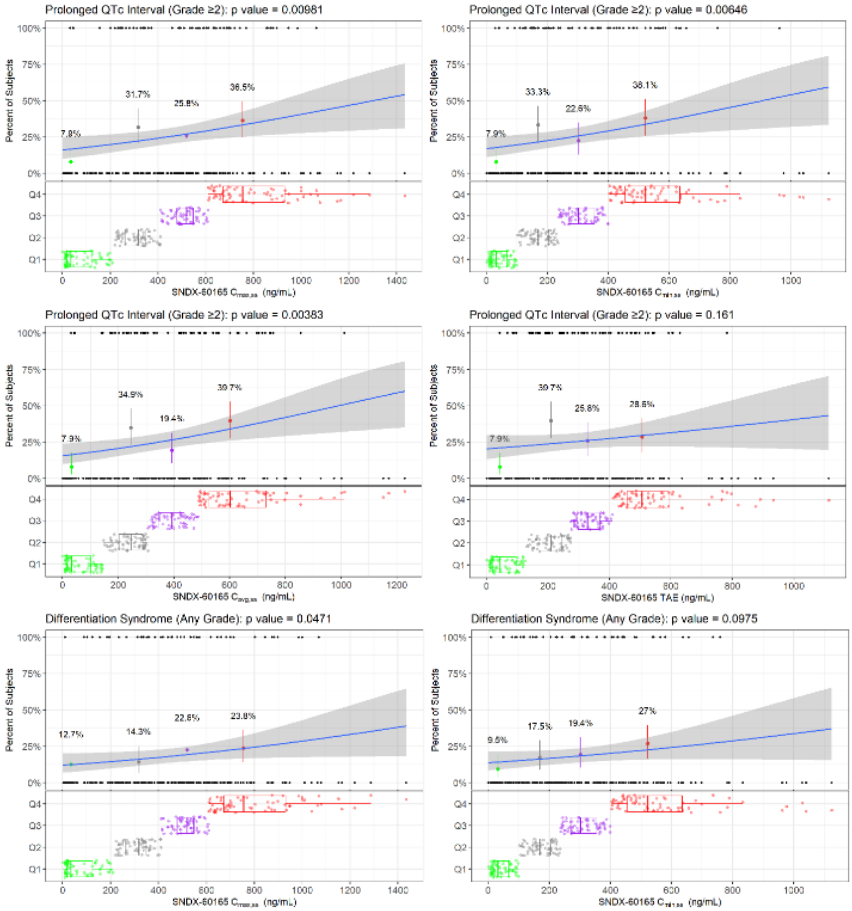
Safety Endpoint	Description	Incidence (%)
1	Prolonged QTc interval (Grade ≥2)	25.5
2	GI toxicities (any grade)	77.7
3	Differentiation syndrome (any grade)	18.3
4	Neutropenia (Grade ≥4)	15.9
5	Thrombocytopenia (Grade ≥4)	21.1
6	Renal toxicity (any grade)	19.1
7	TEAE leading to dose modification	57.0
8	TEAE leading to dose reduction	12.4

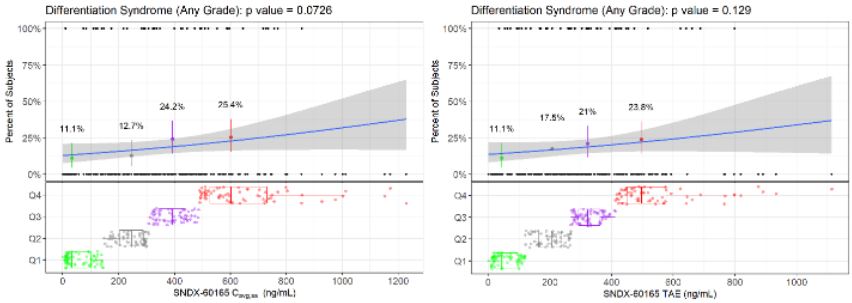
9	TEAE leading to dose delay or interruption	47.0
10	TEAE leading to dose discontinuation	13.1
11	Any TEAE Grade ≥3	86.9
12	Neutrophil count decreased (any grade) derived from lab data	98.8
13	Platelet count decreased (any grade) derived from laboratory data	99.6
14	Hemoglobin decreased (any grade) derived from laboratory data	100
15	Neutrophil count decreased (Grade ≥3) derived from laboratory data	96.8
16	Platelet count decreased (Grade ≥3) derived from laboratory data	95.2
17	Hemoglobin decreased (Grade ≥3) derived from laboratory data	88.4

Source: E-R Safety ***Report, Table 28***

Limitations: The ER for safety is generally exploratory and appears reasonable.

Figure 20 Applicant – ER Curves of Prolonged QTc Interval (Grade ≥ 2) and Differentiation Syndrome (any grade) vs M1 Exposures in R/R acute Leukemia Patients





Source: ER-Safety Report, Figure 32 and Figure 34

The FDA's Assessment:

No outstanding review issue was identified. The reviewer reproduced applicant's analyses. No independent reviewer's analysis was conducted.

Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

The E-R analyses support the overall favorable benefit-risk for revumenib. The proposed dose was found to demonstrate efficacy in the indicated population, with a manageable safety profile as shown by TEAEs leading to dose reductions and treatment discontinuation occurring in a minority of patients. Further, simulations indicated that doses below the proposed dose would not achieve the targeted preclinical IC_{90}. Revumenib prolongs QTcF in a concentration-dependent manner, which was appropriately managed in SNDX-5613-0700 through dose modification and interruption, correction of electrolyte abnormalities, and dose adjustments for concomitant use with strong CYP3Ai. The proposed dose met all requirements for an optimal dose, including target engagement, safety, and efficacy.

The FDA's Assessment:

The proposed dose is acceptable in general, but it is inadequate to claim that the proposed dose met all requirement for an optimal dose considering the limitation of currently available clinical data and the adverse events observed and its association with Cmax. In addition, the true effect of mild or moderate CYP3A4 inhibitor on revumenib exposure remains unclear, and the effect of strong CYP3A4 inhibitor on revumenib is inconsistent between PPK and PBPK estimations.

14.4.4. Physiologically based Pharmacokinetic Modeling Review

Executive Summary

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

- evaluate the drug-drug interaction (DDI) potential of revumenib as a victim of Strong (itraconazole, cobicistat), moderate (fluconazole) and weak (cimetidine) CYP3A inhibitors and strong (rifampin) and moderate (efavirenz) CYP3A inducers on revumenib in adults and pediatrics.

The Division of Pharmacometrics has reviewed the PBPK reports (SNDX-PMX-004-pbpk and syx-2-b-PBPK) and related model summary reports, response to FDA PBPK information requests submitted on March 28th, 2024 (seq0030) and April 10th, 2024 (seq0039), May 29th (seq0055), and the modeling supporting files, and concluded that:

- The PBPK analyses are adequate to predict the effects of CYP3A perpetrators on revumenib exposure in patients older than 1 years old. The accuracy of the predicted results is moderate.
  - Strong CYP3A inhibitors were predicted to increase revumenib exposure 3- to 4-fold.
  - Moderate CYP3A inhibitors isavuconazole and fluconazole were predicted to increase revumenib exposure 1.4- to 2-fold.
  - The strong CYP3A inducer rifampin was predicted to reduce revumenib exposure by 81%.
  - The moderate CYP3A inducer efavirenz was predicted to reduce revumenib exposure by 69%

(b) (4)

Methods

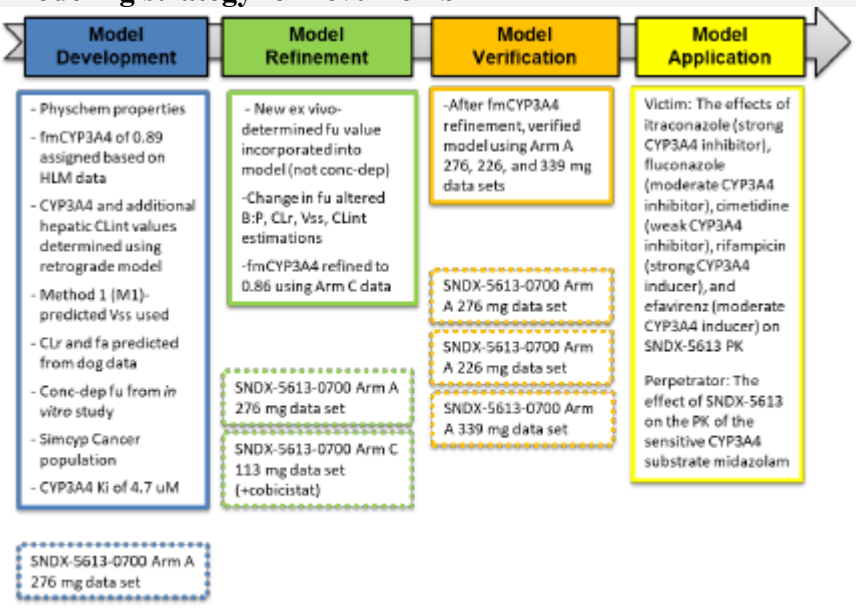
All simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Version 22, Certara, Sheffield, UK) unless noted below. Simulations were performed using the default cancer population (sim-Cancer) model for adult patients and the pediatric population model for patients aged younger than 18 years old. Fixed individual trial design was adopted so that subject demographics (age, sex, weight, height), laboratory values (serum creatinine, human serum albumin, hematocrit) and dosing regimens were matched to each patient in the actual trials. Twenty trials were simulated for each simulation scenario. For pediatric simulations, the ontogeny profile of CYP3A4 reported by Upreti and Wahlstorm was applied (PMID: 26139104) and the sim-pediatric model was used for simulations in pediatric patients. A virtual twin approach with matching demographic and laboratory values, the same as listed above, to each pediatric patient was used in all pediatric simulations.

Schemas of the PBPK modeling and simulation strategy are shown in Figure 21, which summarize the studies used for model development and verification, and model applications of revumenib and its metabolite M1 in predicting DDI of revumenib and M1 as a victim of

CYP3A4 induction or inhibition. The revumenib PBPK model consists of a first-order absorption model, a minimal PBPK model (method 2) for distribution, and an enzyme kinetics model for elimination. This revumenib model was initially built in Simcyp Version 20. Some of the model parameters (e.g. fraction absorbed, V_{ss}, CL_{int}) presented in Figure 21**A** were updated or refined in version 22 based on data from the human ADME and in vitro phenotyping, and PK data in adult cancer patients following 276 mg twice daily (BID) from the study SNDX-5613-0700 when M1 was incorporated in the model. The M1 model consists of a minimal PBPK distribution model, and its elimination was split among metabolic, biliary and renal based on the human ADME data. The final model input parameters were summarized in Table 122**.** Revumenib K_i values for CYP3A4 and CYP2C9 were estimated from IC50 values using the Cheng-Prusoff equation.

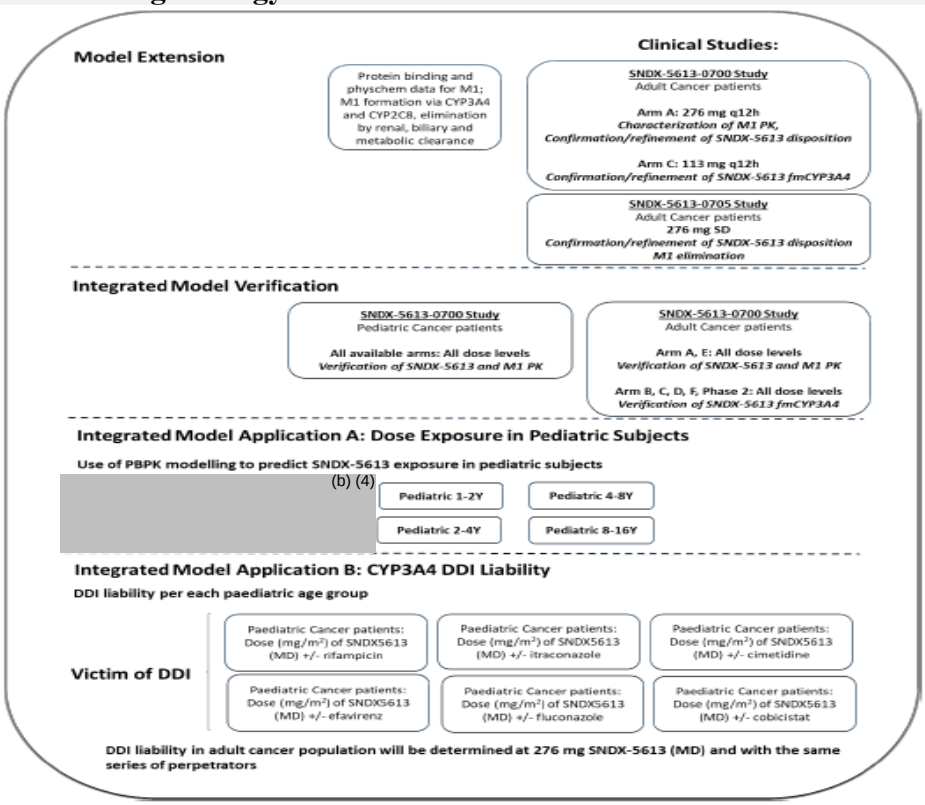
The Simcyp library files cobicistat, itraconazole (SV-itraconazole_fasted Soln), fluconazole, posaconazole, voriconazole, isavuconazole (RES-isavuconazole), rifampin (SV-Rifampicin-MD), efavirenz and cimetidine were used without any modification unless otherwise noted. Metabolites of itraconazole (SV-OH-itraconazole) and voriconazole (SV-voriconazole N-oxide) were also considered in the simulations. For simulations in pediatric patients, the default compound library file for cimetidine was modified prior to use. Specifically, MATE1-mediated transport of cimetidine across the apical side of kidney proximal tubule was added to MATE2-K-mediated transport. This modification was necessary as the current V22 Simcyp Pediatric Simulator does not incorporate ontogeny of MATE1. The change did not impact systemic concentrations of cimetidine and was so not expected to impact the ability of cimetidine to act as a weak CYP3A4 perpetrator.

FDA Figure 21. Modeling and simulation strategy
A. Modeling strategy for revumenib



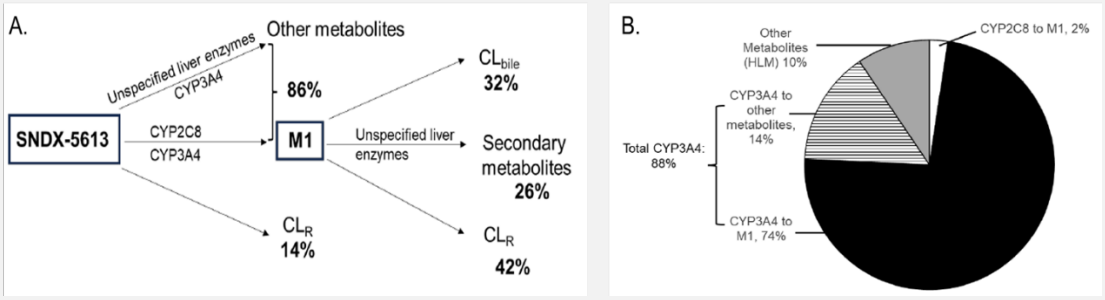
fm: fraction metabolised; CL_{int}: intrinsic clearance; V_{ss}: volume of distribution at steady state; fa: fraction absorbed; K_i: enzyme competitive inhibition constant

B. Modeling strategy for the revumenib metabolite M1



fm: fraction metabolised; MD: multiple dose

C. Summary of revumenib and M1 elimination process



A. SNDX-5613 and M1 elimination processes incorporated within the SNDX-5613 and M1 PBPK models. B. Summary of SNDX-5613 hepatic metabolic elimination.
Source: Figures 1 and 3 in the PBPK reports (SNDX-PMX-004 and syx-2-b)

FDA Table 122. Final input parameters in the PBPK models of revumenib and its metabolite M1

PARAMETER	Value	Reference
Physicochemical and Binding Parameters		
Molecular Weight (g/mol)	630.82	Report PR0351-002A
Log P	2.94	Report Q1805395
Compound type	Monoprotic base	Simcyp data checklist
pKa	9.4	Report Q-4207
B:P	0.70049	Predicted – Simcyp V22
fu	0.085	Entered value to obtain the *ex vivo* measured fu of 0.099 (Report 2313N-2104)
Main binding protein	HSA	Report 2313N-2102
Absorption Model – First Order		
fu_{gut}	0.099	Assumed equal to observed fu
$P_{trans,0}$ ($x10^{-6}$ cm/s)	1100	Adjusted to recover observed fa of 0.92 in adult cancer patients (Clinical Study SNDX-5613-0705)
$P_{eff,man}$ (pred) ($x10^{-4}$ cm/s)	1.4588	Predicted
Q_{gut} (L/h)	6.0897	Estimated from retrograde model
ka (1/h)	1.0813	Predicted
fa	0.92	Metabolite profiling of samples from Clinical Study SNDX-5613-0700
F_G	0.97	Predicted
Distribution Model – Minimal PBPK Model		
V_{SS} (L/kg)	4.1476	Predicted Method 2; rat and dog V_{SS} values 3.07 and 3.57 L/kg respectively
K_p scalar	3	Adjusted to recover PK profiles in model development study (276 mg BID cohort of Arm A – no isavuconazole and no fluconazole)
Elimination Parameters		
CL/F (L/h)	29.07	Clinical Study SNDX-5613-0700 – Geomean clinical CL/F for 276 mg BID cohort of Arm A (no isavuconazole and no fluconazole)
fm_{CYP3A4}	0.88	Clinical Study SNDX-5613-0700 – optimised using parent and metabolite plasma data from Arm C (cobicistat)
fm_{CYP2C8}	0.02	
M1 CYP3A4 CL_{int} (µL/min/pmol)	0.358	Retrograde model. CL/F obtained from Clinical Study SNDX-5613-0700 – Arm A (29.07 L/h)
M1 CYP2C8 CL_{int} (µL/min/pmol)	0.066	
Other metabolites CYP3A4 CL_{int} (µL/min/pmol)	0.068	
Additional HLM CL_{int} (µL/min/mg)	6.268	
fu_{mic}	1	fu_{mic} set to default of 1 when using retrograde model
CL_R (L/h)	2.95	Optimised to recover observed fe of ~14% reported in metabolite profiling of samples from Clinical Study SNDX-5613-0705
Interaction Parameters		
CYP3A4 K_i (µM)	4.7	Report 2313N-1803; midazolam as substrate
CYP2C9 K_i (µM)	36.0	Report 2313N-1803
fu_{mic}	0.956	Predicted; HLM concentration 0.1 mg/mL

Final input Parameters of the M1 model

PARAMETER	Value	Reference
		(b) (4)

Elimination Parameters of the M1 inhibited model

Elimination Parameters
(b) (4)

Source: Tables 1 – 3 in the PBPK report (SNDX-PMX-004-pbpk)

Additional Comments

- The data provided in the compound file summaries of the PBPK models of posaconazole and isavuconazole are insufficient for verifying the ability of these models to predict their inhibitory effects on CYP3A substrates. In addition, revumenib exposure when co-administered with fluconazole were overpredicted, which will be discussed in the Results. The reviewer performed additional simulations to further verify the ability of these azole models to predict their inhibitory effects on CYP3A substrates and the results are presented in Table 123.

- Because the accuracy of the predicted revumenib exposure when co-administered with azoles is dependent on the ability of both revumenib and these inhibitor models to predict their concentrations in different age groups, the reviewer requested the applicant to compare the simulated plasma concentration-time profiles and PK parameters of the azoles, CYP3A inducers rifampin and efavirenz, and the weak CYP3A inhibitor cimetidine with their observed concentrations in pediatric patients in literature (FDA-IR dated March 20th, 2024).

The results showed that the PBPK models of fluconazole, isavuconazole and cimetidine could reasonably capture their steady state PK profiles and PK parameters in patients aged (b) (4) – 15 years old, 1 – 18 years old, and 4- 15 years old, respectively (SYX/2/C). The cobicistat model overpredicted the cobicistat exposure in subjects aged 6 to 12 years old, but the predicted values were within 2-fold of the observed values (SYX/2/C). The default PBPK models of itraconazole, posaconazole, voriconazole, rifampin and efavirenz significantly overpredicted their exposure in pediatric patients (SYX/2/C). Therefore, modifications were made to the default perpetrator files via reducing the fraction absorbed or increasing the clearance or both so that the predicted steady state exposure of these inhibitors were around 2-fold of majority of the observed data of pediatric PK (**Table 124**). Of note, the default fluconazole file was also modified for slight improvement of predictions and a more mechanistic parameterization of its elimination pathway where the IV clearance was converted to undefined human liver microsome intrinsic clearance (CL_{int}). The simulated and observed exposure of these CYP3A inhibitors and inducers using the modified models are shown in **Tables 5 -8**.

FDA Table 123. Predicted and observed drug interactions with azoles

Dosing Regimen		AUC ratio			C_{max} ratio			References
Perpetrators	**Victims**	**Observed**	**Predicted**	**Pred/obs**	**Observed**	**Predicted**	**Pred/obs**	
Fluconazole 400 mg IV SD	**Alfentanil** 20 mg/kg IV SD	2.06	1.89	1.09				PMID 9661572
Fluconazole 400 mg PO SD	**Alfentanil** 15 mg/kg IV SD 3h after	2	1.88	0.94				PMID 1672184
Fluconazole 400 mg PO SD	**Alfentanil** 40 mg/kg PO SD 3h after	4.37	3.44	0.79	1.72	2.02	1.18	PMID 1672184
Posaconazole 300 mg QD 6d	**Ibrutinib** 30 mg SD D5 1h after	9.52	13.19	1.39	8.52	9.44	1.11	PMID 37872104
Posaconazole 300 mg QD 7d	**Ibrutinib** 70 mg SD D6 12h after	10.30	12.09	1.17	8.23	9.00	1.09	PMID 37872104
Posaconazole 300 mg QD 8d D21	**Venetoclax** 400 mg QD D6-D20 50 mg QD D21-D28	8.80	9.57	1.09	7.06	7.54	1.07	PMID 28161120
Isavuconazole 200 mg TID D1 QD D2-D5	**Acalabrutinib** 100 mg SD D5	1.60	1.41	0.88	1.37	1.31	0.95	PMID 35165925

All simulations were performed using Simcyp version 22.
Source: reviewer's analyses

FDA Table 124. Modifications made to the default perpetrator files for pediatric simulations

Perpetrators	Modification made to the default perpetrator files
Itraconazole	fraction absorbed (f_a) in the itraconazole file was reduced from (b) (4) to 0.5 to improve the prediction of its steady-state PK following oral dosing. No change was made to the OH-itraconazole file.
Posaconazole	a relative expression factor (REF) value of 2.5 for UDP-glucoronosyltransferase (UGT) 1A4 was included as an empirical approach to increase the systemic clearance of the drug. No change was made to the f_a value.
Voriconazole	the f_a value was reduced from (b) (4) to 0.50 and additional HLM CL_{int} was increased from (b) (4) to 1.30 μL/min/mg protein. No change was made to the voriconazole N-oxide file.

Perpetrators	Modification made to the default perpetrator files
Efavirenz	the f_a value was reduced from (b) (4) to 0.33. In addition, in order to account for the reduced CYP2B6 abundance and activity associated with the CYP2B6 516GT and 516TT genotypes compared to the CYP2B6 516GG genotype, a reduction in CYP2B6 intrinsic clearance of 0.74-fold and 0.24-fold was applied to pediatric subjects carrying these genetic polymorphisms, respectively relative to the extensive metabolizers (PMID: 37078251).
MD-Rifampicin	the IV clearance (CL) was converted to undefined HLM CL_{int}; the f_a value was reduced from (b) (4) to 0.5. Because the elimination was not assigned to a specific pathway, no ontogeny was applied.

Source: Quantitative prediction of the steady-state exposure of CYP3A perpetrators in the pediatric population (SYX/2/C, seq0039)

FDA Table 125. Simulated and observed itraconazole and hydroxyitraconazole exposure in pediatrics following oral administration of itraconazole solution

	Itraconazole					OH-itraconazole				
	Day 1		Day 14 or 15			Day 1		Day 14 or 15		
	AUC_{tau}	C_{max}	AUC_{tau}	C_{min}	C_{max}	AUC_{tau}	C_{max}	AUC_{tau}	C_{min}	C_{max}
	5 mg/kg QD itraconazole oral solution (PMID: 9527794)									
	Age group : 0.5 – < 2 years									
Simulated	9785	953	17323	338	1306	16040	1168	37697	274	1610
Observed	1340	138	6390	159	571	2340	179	13200	308	690
S/O	7.3	6.91	2.71	2.12	2.29	6.85	6.52	2.86	0.889	2.33
	Age group: 2 – < 5 years									
Simulated	9563	928	16513	314	1253	15491	1132	25305	571	1520
Observed	2740	314	7330	179	534	6730	493	13400	487	687
S/O	3.49	2.96	2.25	1.76	2.35	2.3	2.3	1.89	1.17	2.21
	Age group : 5 – 12 years									
Simulated	10744	1004	19401	395	1412	17467	1229	31354	791	1783
Observed	2010	298	8770	223	631	4920	447	13450	437	699
S/O	5.35	3.37	2.21	1.77	2.24	3.55	2.75	2.33	1.81	2.55
	2.5 mg/kg QD itraconazole oral solution (PMID: 12121932)									
	Age group: 6 -18 years									
Simulated	3648	390	6735	135	530	6310	523	11377	273	728
Observed	1820	226	7050	192	623	3340	197	11180	383	552
S/O	2.00	1.72	0.956	0.702	0.851	1.89	2.65	1.02	0.712	1.32
	2.5 mg/kg BID itraconazole oral solution (PMID: 12121932)									
	Age group: 6 -18 years									
Simulated	3775	399	14496	996	1402	6487	531	20733	1545	1853
Observed	1820	226	11520	782	1340	3340	197	11890	997	1170
S/O	2.07	1.76	1.26	1.27	1.24	1.94	2.69	1.74	1.55	1.58

Source: Tables 3 -7 in Quantitative prediction of the steady-state exposure of CYP3A perpetrators in the pediatric population (SYX/2/C, seq0039)

FDA Table 126. Simulated and observed posaconazole exposure in pediatrics following administration of multiple doses of posaconazole

	Dose 1		Last Dose		
	AUC_t (ng/mL.h)	C_{max} (ng/mL)	AUC_{tau} (ng/mL.h)	CL/F (L/h)	C_{max} (ng/mL)
	6 mg/kg posaconazole IV QD (PMID: 32682946)				
	2 – 7 years old				
Simulated	8087	3233	34463	3.00	7315
Observed			31100	3.27	3060
S/O			1.11	0.916	2.39
	7 – 17 years old				
Simulated	7800	3458	31463	7.49	7661
Observed			44200	4.76	3340
S/O			0.712	1.57	2.29
	6 mg/kg posaconazole PO QD (PMID: 32682946)				
	2 – 7 years old				
Simulated	11358	1096	16195	6.38	1410
Observed			23000	4.60	1510
S/O			0.704	1.39	0.934
	7 – 17 years old				
Simulated	12845	1223	19508	12.1	1622
Observed			25000	8.39	1370
S/O			0.780	1.44	1.18
	6 mg/kg posaconazole PO BID (PMID: 30913226)				
	2 – 7 years old				
Simulated	8863	1204	25576	4.13	2788
Observed	1300	196	6770		726
S/O	6.82	6.14	3.78		3.84
	7 – 18 years old				
Simulated	8714	1213	23228	8.18	2594
Observed	1140	156	11800		1200
S/O	7.64	7.78	1.97		2.16

Source: Tables 16 – 18 in Quantitative prediction of the steady-state exposure of CYP3A perpetrators in the pediatric population (SYX/2/C, seq0039)

FDA Table 127. Simulated and observed voriconazole exposure in immunocompromised children following voriconazole administration

Statistic	AUC_{tau} (µg/mL.h)	C_{max} (µg/mL)	AUC_{tau} (µg/mL.h)	C_{max} (µg/mL)
	2-11 years old (PMID: 20547816)			
	IV 7 mg/kg BID		**IV 5 mg/kg BID**	
Simulated	37.0	7.1	29.9	5.6
Observed	49.3	11.4	26.1	5.8
S/O	0.751	0.622	1.146	0.957
	2 to <12 years old (PMID: 20660687)			
	Cohort 1		**Cohort 2**	
	IV 4 mg/kg Q12h		**IV 6 mg/kg Q12h**	
Simulated	16.78	3.50	31.51	5.10
Observed	11.83	3.21	17.25	4.29
S/O	1.419	1.090	1.827	1.191
	IV 6 mg/kg Q12h		**IV 8 mg/kg Q12h**	
Simulated	34.48	5.43	57.53	7.68
Observed	22.91	4.35	29.78	5.77
S/O	1.505	1.248	1.932	1.331
	Oral 4 mg/kg Q12h		**Oral 6 mg/kg Q12h**	
Simulated	5.16	1.09	10.85	2.00
Observed	5.18	1.18	8.37	1.76
S/O	0.996	0.924	1.296	1.138

Source: Tables 23 – 24 in Quantitative prediction of the steady-state exposure of CYP3A perpetrators in the pediatric population (SYX/2/C, seq0039)

FDA Table 128. Simulated and observed PK parameters of cobicistat following 150 mg cobicistat once daily in pediatric and adult subjects.

Statistic	Last dose AUC_{tau} (µg/mL.h)	Last dose C_{max} (µg/mL)
	6 – 12 years	
Simulated	28204	3247
Observed	15891	2079
S/O	1.77	1.56
	Adults	
Simulated	15126	1504
Observed	9459	1450
S/O	1.60	1.04

Simulated values listed are the arithmetic means. Source observed data: Natukunda et al. (2017); Source simulated data: natukunda-2017-cobi-150mg-qd-6-12years; natukunda-2017-cobi-150mg-qd-adult

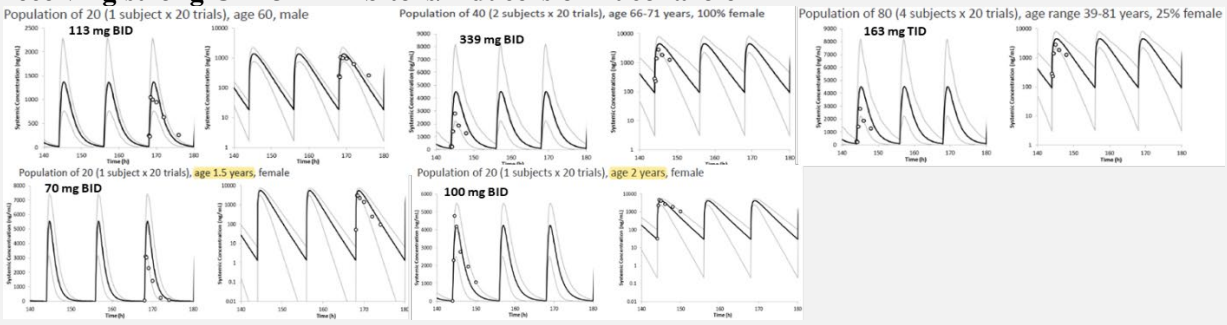
Source: Table 30 in Quantitative prediction of the steady-state exposure of CYP3A perpetrators in the pediatric population (SYX/2/C, seq0039)

Results

1. Verification of the PBPK models of revumenib and its metabolite M1

Clinical PK data that had not been used in model development was used to verify the ability of the PBPK models of revumenib and its metabolite M1 to describe the PK profiles of revumenib and M1. The PK profiles of revumenib from the representative simulations are shown in Figure 22-Figure 28, and the observed and predicted PK parameters of revumenib and M1 were compared and are shown in Figure 29.

FDA Figure 22. Simulated and observed plasma concentrations of revumenib in patients not receiving strong CYP3A inhibitors/inducers or fluconazole

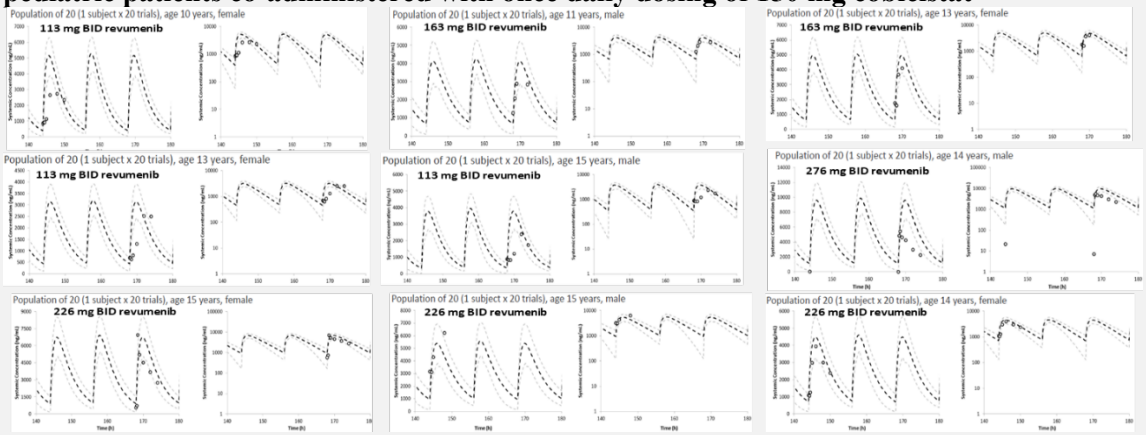


Depicted are simulated (lines) and observed data (circles, SNDX-5613-0700). The grey lines represent the 5th and 95th percentiles and the solid black line the mean data for the simulated population. Linear scale on the left and the Log-linear scale on the right
Source: syx2c-appendix-d of the PBPK report sndx-pmx-004-pbpk

FDA Figure 23. Simulated and observed plasma concentration-time profiles of revumenib in adult patients co-administered with once daily dosing of 150 mg cobicistat

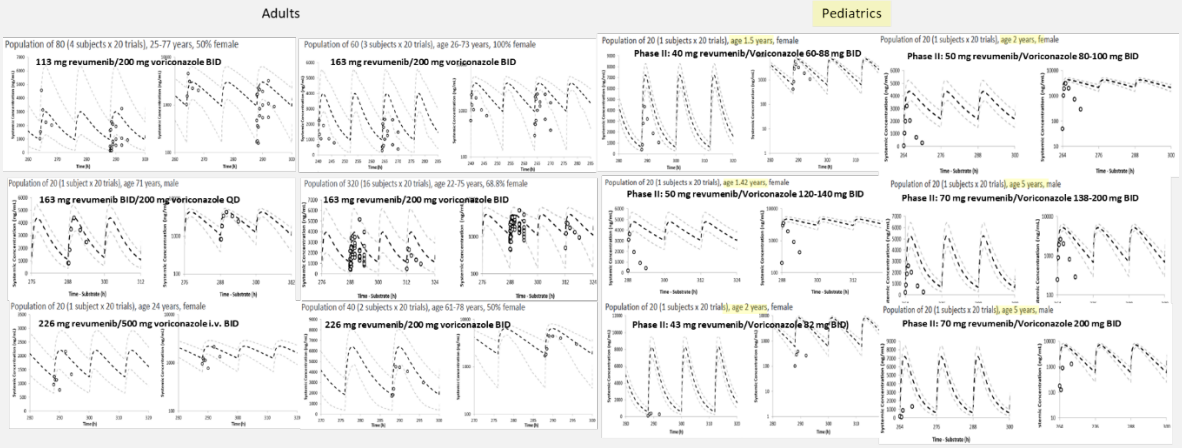
Depicted are simulated (lines) and observed data (circles, SNDX-5613-0700). The dashed grey lines represent the 5th and 95th percentiles and the black line the mean data for the simulated population.
Source: syx2c-appendix-d of the PBPK report sndx-pmx-004-pbpk

FDA Figure 24. Simulated and observed plasma concentration-time profiles of revumenib in pediatric patients co-administered with once daily dosing of 150 mg cobicistat



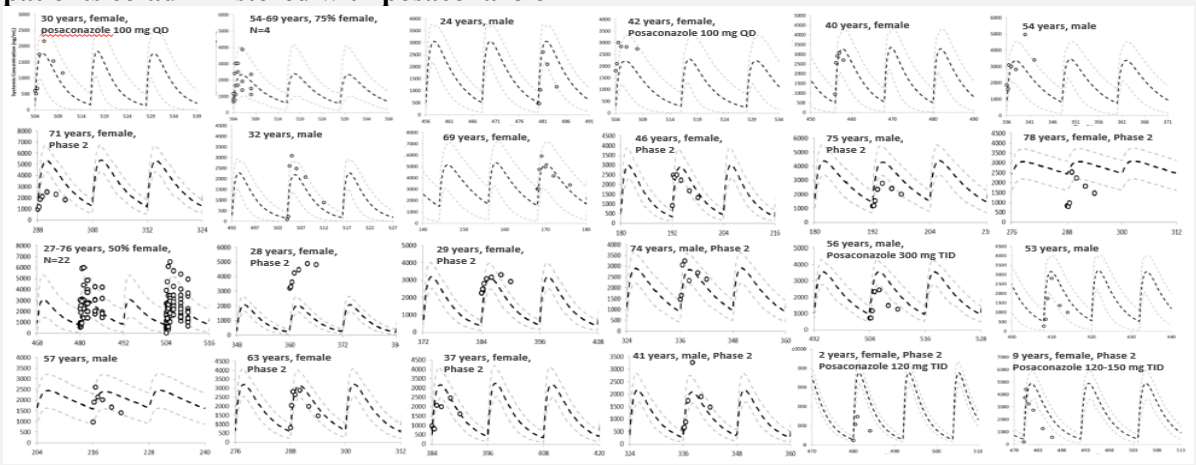
Depicted are simulated (lines) and observed data (circles, SNDX-5613-0700). The dashed grey lines represent the 5th and 95th percentiles and the black line the mean data for the simulated population.
Source: syx2c-appendix-d of the PBPK report sndx-pmx-004-pbpk

FDA Figure 25. Simulated and observed plasma concentration-time profiles of revumenib in patients co-administered with voriconazole



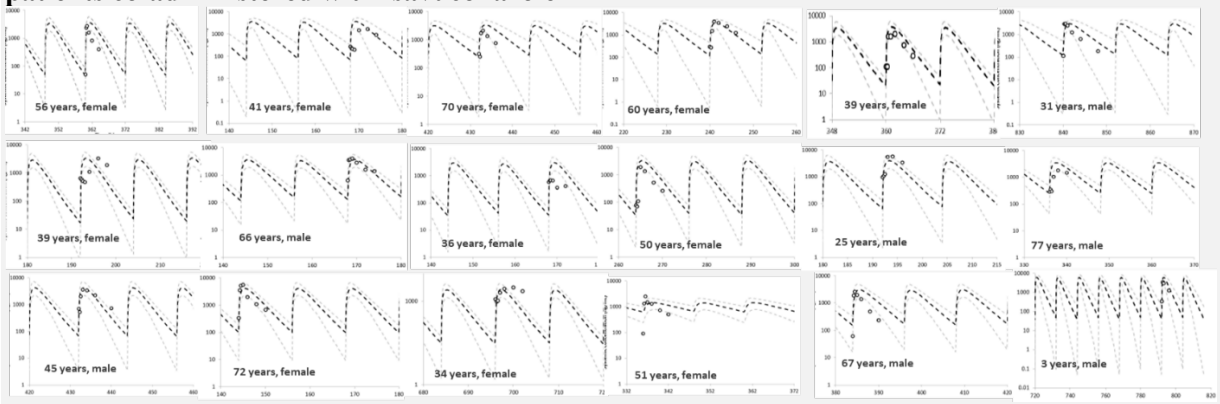
Depicted are simulated (lines) and observed data (circles, SNDX-5613-0700). The dashed grey lines represent the 5th and 95th percentiles and the black line the mean data for the simulated population.
Source: syx2c-appendix-d of the PBPK report sndx-pmx-004-pbpk

FDA Figure 26. Simulated and observed plasma concentration-time profiles of revumenib in patients co-administered with posaconazole



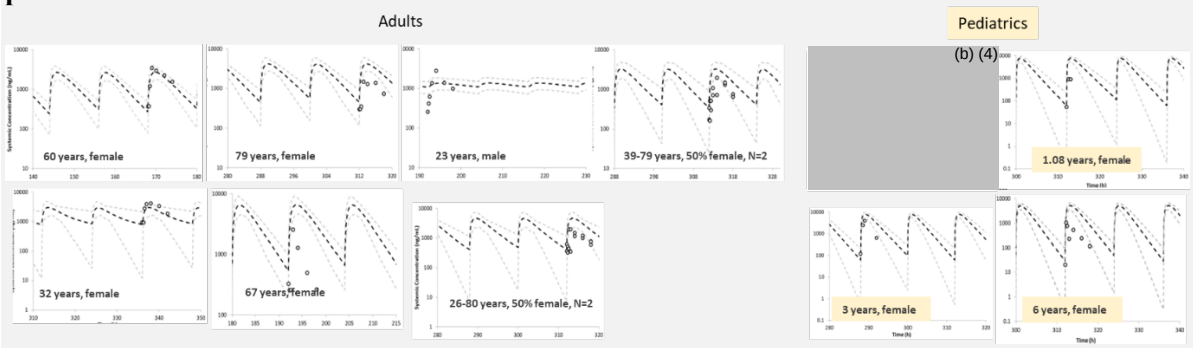
Depicted are simulated (lines) and observed data (circles, SNDX-5613-0700). The dashed grey lines represent the 5th and 95th percentiles and the black line the mean data for the simulated population.
Source: syx2c-appendix-d of the PBPK report sndx-pmx-004-pbpk

FDA Figure 27. Simulated and observed plasma concentration-time profiles of revumenib in patients co-administered with isavuconazole



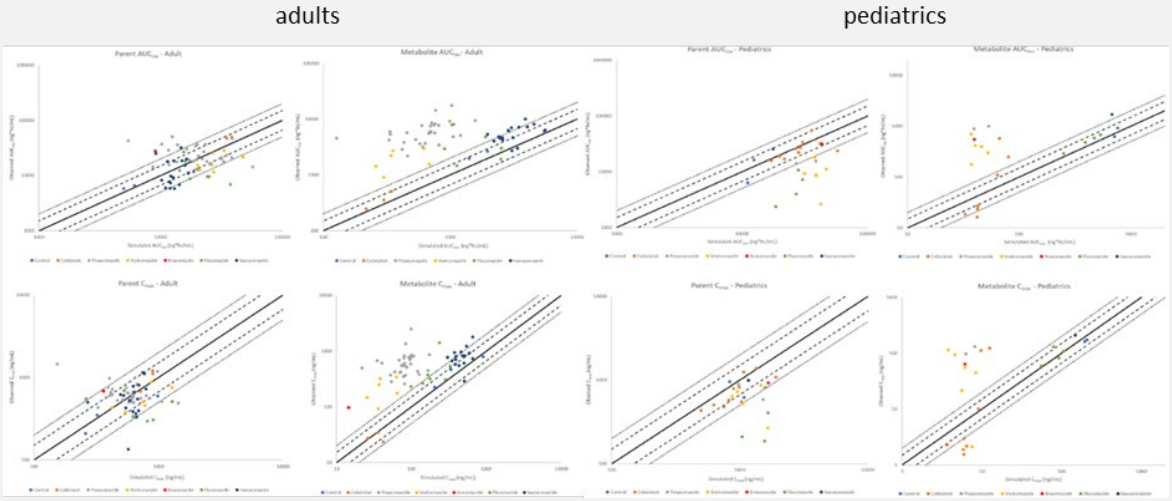
Depicted are simulated (lines) and observed data (circles, SNDX-5613-0700). The dashed grey lines represent the 5th and 95th percentiles and the black line the mean data for the simulated population.
Source: syx2c-appendix-d of the PBPK report sndx-pmx-004-pbpk

FDA Figure 28. Simulated and observed plasma concentration-time profiles of revumenib in patients co-administered with fluconazole



Depicted are simulated (lines) and observed data (circles, SNDX-5613-0700). The dashed grey lines represent the 5th and 95th percentiles and the black line the mean data for the simulated population.
Source: syx2c-appendix-d of the PBPK report sndx-pmx-004-pbpk

FDA Figure 29. Simulated and observed AUC and C_{max} of revumenib and *its metabolite M1* on C1D8 in adult and pediatric patients with cancer receiving revumenib twice daily with or without multiple doses of CYP3A inhibitors



Depicted are circles which represent PBPK model simulation (X-axis) and the corresponding observed PK parameter value (Y-axis) (Clinical Study SNDX-5613-0700). Data for itraconazole AUC not shown –simulated values greater than 10-fold deviation from observed. For pediatrics, simulation uses Upreti and Wahlstrom (2016) CYP3A4 ontogeny. The solid line represents the unity line, dashed lines represent the area that is within 1.5-fold of the unity line, and dotted lines represent the area that is within 2-fold of the unity line.
Source: Figures 7, 8, 11, and 12 (PBPK report sndx-pmx-004-pbpk)

FDA Assessment:

The revumenib model is acceptable for the purpose of DDI potential evaluation as a victim in patients aged older than 18 years old. The plasma concentration-time profile and PK parameters of revumenib were optimized using PK data from patients in Arm A who was taking 276 mg revumenib BID without co-administering with CYP3A inhibitors, and its fraction metabolized by CYP3A (fm, CYP3A) was optimized using data from patients in Arm C who was taking 113 mg revumenib BID together with 150 mg cobicistat QD. The applicant verified that the revumenib model could reasonably well describe the plasma concentration-time profiles of revumenib in patients who were taking revumenib at doses alone or co-administered with cobicistat (Arm C) (Figure 22 and Figure 23).

Majority of the model-estimated AUC and Cmax were within 0.8- and 1.25-fold of the observed values (Figure 29). Revumenib had linear PK from doses ranging from 113 to 276 mg BID and the same cobicistat dosing regimen (150 mg QD) was given to patients in Arm C who were taken revumenib with doses ranging from 163 to 276 mg BID. The data from Arm A and Arm C are similar to that used in the model development. Therefore, these data are insufficient for verifying the performance of the revumenib model in adult patients.

Additional verification was performed by simulating revumenib PK in patients who were taken revumenib together with other CYP3A inhibitors. To determine prediction accuracy, the reviewer

assessed the prediction errors, which compare the predicted to the observed values of PK parameters, the average fold error (AFE), which assesses the bias of the prediction, and the absolute average fold error (AAFE), which assesses the precision of the prediction. As shown in Figure 24-Figure 29 and Table 129, the revumenib model could reasonably well predict the plasma concentration-time profiles and PK parameters of revumenib in patients who were taking revumenib together with posaconazole or isavuconazole; nearly 80% and 90% of revumenib AUC and C_{max} values were predicted within 2-fold of the observed values, respectively (Table 129). The model tended to overpredict the revumenib PK in patients who were taking voriconazole or fluconazole (AFE > 1). The reviewer performed additional verification of the fluconazole model, and the model could reproduce its interactions with alfentanil following both IV and oral administration (Table 123). Therefore, the overprediction may not be due to inability of the fluconazole model to reproduce its inhibitory effect on CYP3A. Similarly, revumenib exposure in patients co-administered with voriconazole was overpredicted by the voriconazole model whose ability to reproduce its inhibitory effect on CYP3A was verified based on the data in the voriconazole file summary provided by the vendor. It was noted that the PK parameters for revumenib were highly variable with CV% values up to 179.4%. However, the variability in the voriconazole and fluconazole groups was comparable to that in posaconazole and isavuconazole groups, respectively. Therefore, the cause of the overprediction by voriconazole and fluconazole is unclear. Considering the limited number of subjects and sparse sampling in some subjects, the high variability, and the ability of the model to simulate revumenib exposure in patients who were co-administered with posaconazole and isavuconazole, the revumenib model is acceptable for the purpose of DDI potential evaluation as a victim in patients aged older than 18 years old. It should be noted that the AAFEs for the predicted AUC and Cmax of revumenib were greater than 1 but less than 2 in patients who were taking revumenib together with posaconazole or isavuconazole, indicating the precision of these predictions are not satisfactory, which could comprise the accuracy of the predictions discussed in the subsequent sections. Applications of the revumenib model in patients younger than 18 years old are discussed in the later sections.

For the revumenib metabolite M1, the M1 model underpredicted the M1 exposure in patients who were taking CYP3A inhibitors other than cobicistat, and in most cases, the prediction errors were greater than 2-fold of the observed values (Table 129 and **Figure 29**). Therefore, this M1 model is inappropriate to be used to predict the effect of CYP3A perpetrators on M1 exposure.

FDA Table 129. Comparison of Simulated and observed PK parameters* of revumenib with or without co-administration with CYP3A inhibitors in patients with cancer

CYP3A inhibitors	Prediction Accuracy	Adults (>18)				Ped 12-18				Ped < 12				Age (years)
		Revumenib		M1		Revumenib		M1		Revumenib		M1		
		AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	
None	N	3	3	3	3					2	2	2	2	
(7/0/2)	% PE within BE	67	67		(b) (4)					0	50		(b) (4)	
	% PE within 1.5	67	67							50	50			2
	% PE within 2	100	100							100	100			1.5
	AFE	1.08	1.24							1.16	1.23			
	AAFE	1.26	1.30							1.51	1.41			
Cobicistat	N	4	4	4	4	7	7	6	7	2	2	1	1	
(13/7/2)	% PE within BE	50	75		(b) (4)	43	71		(b) (4)	50	0	0	0	11
	% PE within 1.5	100	100			71	71			100	50	0	0	10
	% PE within 2	100	100			86	100			100	100	0	0	
	AFE	0.89	0.92			1.15	1.22			1.14	1.64			
	AAFE	1.18	1.20			1.34	1.28			1.14	1.64			
Voriconazole	N	6	6	6	6					6	6	6	6	1.5 -5
(37/0/6)	% PE within BE	17	33	0	0					0	33	0	0	
	% PE within 1.5	33	66	0	0					0	33	0	0	1.42, 2
	% PE within 2	66	100	0	0					17	66	0	0	1.5
	AFE	1.69	1.35							4.07	2.80			
	AAFE	1.69	1.35							4.07	2.80			
Posaconazole	N	31	31	31	31					2	2			2, 9
(55/0/2)	% PE within BE	28	48	0	0					0	50	0	0	
	% PE within 1.5	45	76	0	0					0	50	0	0	
	% PE within 2	86	93	0	0					50	50	0	0	9
	AFE	0.86	0.90							1.91	1.59			
	AAFE	1.71	1.44							1.91	1.59			
Itraconazole	N	1	1	1	1					1	1	1	1	1.4
(1/0/1)	% PE within BE	0	0	0	0					0	0	0	0	
	% PE within 1.5	0	0	0	0					100	0	0	0	
	% PE within 2	0	100	0	0					100	100	0	0	
Fluconazole	N	7	7	7	7					4	4	4	4	0.75, 1.08, 3, 6
(9/0/4)	% PE within BE	29	14		(b) (4)					0	0		(b) (4)	
	% PE within 1.5	29	29							0	0			
	% PE within 2	43	43							0	25			3
	AFE	1.71	1.41							5.18	4.34			
	AAFE	2.07	2.00							5.18	4.34			
Isavuconazole	N	17	17	16	16					1	1	1	1	
(17/0//1)	% PE within BE	29	47		(b) (4)					0	100	0	0	
	% PE within 1.5	41	59							100	100	0	(b) (4)	3
	% PE within 2	76	94							100	100	0		
	AFE	1.12	1.14											
	AAFE	1.60	1.48											
All	N	56	56	56	56					18	18	18	18	
(139/7/18)	% PE within BE	29	45							5.6	17			
	% PE within 1.5	43	69							28	33			
	% PE within 2	75	89							39	61			
	AFE	0.98	0.99							2.67	2.39			
	AAFE	1.7	1.48							2.86	2.43			

BE, bioequivalent bounds (0.8 -1.25); N, number of simulation scenarios. Numbers in the brackets indicate the number of observed subjects in each corresponding age group. Some scenarios had more than one subjects (Figures 3-9); PE, prediction error = | predicted/observed -1 | x 100%. AFE, average fold error; AAFE, absolute average fold error. AFE and AAFE were not calculated for M1 and for revumenib with data only from one subject. Cells highlighted in gray have no data. * Observed PK parameters were estimated from the study SNDX-5613-0700 using the noncompartmental analysis.
Source: reviewer's analysis based on the response provided in fda-response-march26-2024-q1.xlsx

2. Effects of CYP3A perpetrators on the PK of revumenib

The predicted effects of CYP3A inhibitors and inducers on the PK pf revumenib following 160 mg/m^2 orally twice daily are summarized in Table 130.

FDA Table 130. Geometric mean ratios of simulated PK parameters of revumenib in the absence and presence of CYP3A4 perpetrators in patients aged greater than 18 years old

CYP3A DDI Potential	Perpetrators	Dosing regimen	Revumenib		Source
			AUC Ratio	C_{max} Ratio	
Strong inhibitors	Cobicistat	150 mg QD	4.53	3.58	Applicant
	Itraconazole	200 mg QD	4.14	3.31	Applicant
	Posaconazole	400 mg QD	3.87	3.12	Reviewer
		300 mg QD	3.63	2.95	Reviewer
		100 mg QD	2.56	2.2	Reviewer
Moderate inhibitors	Fluconazole	400 mg QD	2.66	2.26	Applicant
	Isavuconazole	200 mg Q8h 2d/BID	1.38	1.33	Reviewer
		100 mg Q8h 2d/BID	1.21	1.18	Reviewer
Weak inhibitor	Cimetidine	400 mg TID	1.16	1.13	Applicant
Strong inducer	Rifampin	600 mg QD	0.19	0.25	Applicant
Moderate inducer	Efavirenz	600 mg QD	0.31	0.4	Applicant
Weak inducer	Rifampin	10 mg QD	0.75	0.78	Reviewer
	Zanubrutinib	160 mg BID	0.84	0.86	Reviewer

QD, once daily; BID, twice daily; TID, three times a day; Q8h, every 8 hours. For zanubrutinib simulation, the zanubrutinib model published at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213217Orig1s000MultidisciplineR.pdf was used. Revumenib 160 mg/m2 BID was given with zanubrutinib 160 mg BID simultaneously for 14 days.
Source: Tables 15 -20 in the PBPK report (sndx-pmx-004-pbpk) and the reviewer's analysis

The FDA's Assessment:

Effects of CYP3A inhibitors:

As discussed earlier, the revumenib model is acceptable for evaluating the DDI potential of revumenib as a victim in patients aged older than 18 years old. However, the results should be interpreted with caution since the predictive performance of the revumenib model is moderate (AAFE >1, Table 129).

Revumenib exposure following coadministration with itraconazole or fluconazole was overpredicted for unknown reasons (Table 129). The accuracy of the revumenib model to predict interactions with posaconazole and isavuconazole was moderate because the AFE values were close to 1 but the AAFE values were close to 2. The reviewer assessed the effects of alternative strong and moderate CYP3A inhibitors posaconazole and isavuconazole on revumenib exposure after verifying the ability of these models to predict clinical interactions with CYP3A substrates (Table 123). Overall, strong CYP3A inhibitors were predicted to increase the AUC and C_{max} of revumenib approximately 4- and 3-fold, respectively, in adult patients (Table 130). The effect of posaconazole was dose dependent. The moderate CYP3A inhibitor isavuconazole had a weak inhibitory effect on revumenib. Table 129 shows that revumenib exposure following

coadministration with fluconazole tended to be overpredicted. To further evaluate the potential interaction between fluconazole and revumenib, the clinically observed interactions of known CYP3A substrates with fluconazole or isavuconazole were compared. 400 mg fluconazole, in general, had greater effects on the CYP3A sensitive substrates compared to 200 mg isavuconazole (Table 130). Because the relatively better performance of the revumenib model to predict its exposure in patients who were co-administered isavuconazole (Table 129), the predicted effect of isavuconazole on revumenib was compared with its effects on other CYP3A substrates in Table 130, and then taken together the effects of fluconazole on CYP3A substrates, the effect of fluconazole on revumenib AUC is expected to be around 2-fold.

FDA Table 131. Comparison of the effects of fluconazole and isavuconazole on CYP3A substrates

CYP3A inhibitors / substrates	Fluconazole 400 mg SD or QD	Pubmed ID	Isavuconazole 200 mg QD	Pubmed ID
midazolam	4.93	16172184	2.03	27273461
acalabrutinib	2.16	35165925	1.6	35165925
cyclosporine	1.75	30912163	1.29	27273343

Source: Certara Drug Interaction Database

For the weak CYP3A inhibitor cimetidine, its PBPK model in Version 22 often underestimated the observed DDI with sensitive CYP3A substrates as shown in Table 4 of the cimetidine file summary provided by platform developer. However, given the predicted effects of moderate CYP3A inhibitors (**Table 130**), the effect of a weak CYP3A inhibitor on revumenib is expected to be minimal.

Effects of CYP3A inducers:
Strong CYP3A inducer rifampin and moderate CYP3A inducer efavirenz were predicted to reduce revumenib AUC by 80% and 70%, respectively, in adult patients (Table 130). Revumenib is not a substrate of P-gp and BCRP, one of the factors that may affect the prediction accuracy of rifampin induction. Therefore, the predicted results are acceptable. Weak CYP3A inducers were predicted to have minimal effects on revumenib exposure (Table 130).

3. Revumenib exposure in pediatrics

Pediatric patients aged 9 to 18 years old

Revumenib exposure was reasonably simulated in pediatric patients aged 9 to 18 years old who were given revumenib concomitantly with cobicistat or posaconazole (Table 129). Considering the large interindividual variability and between study variability, the steady state exposure of cobicistat and posaconazole in this age group simulated by using the default cobicistat model and the modified posaconazole model were acceptable (Table 126 and Table 128). Therefore, the revumenib model was considered verified in this age group and could be used to simulate the effects of CYP3A inhibitors and inducers on revumenib exposure. The simulated effects are shown in Table 132. In general, the predicted extent of interaction of revumenib with CYP3A inhibitors and inducers in patients aged 9 to 18 years old was similar to that predicted in adult patients except for itraconazole. Itraconazole had a weaker effect on revumenib in pediatric

patients compared to adult patients, which was likely due to the lower itraconazole concentration simulated using the itraconazole model modified based on the observed itraconazole concentrations in this age group (SYX/2/C).

Of note, the cobicistat model overpredicted the cobicistat exposure in subjects aged 6 to 12 years old, but the predicted values were within 2-fold of the observed values (SYX/2/C) (Table 129). The cobicistat overprediction didn't lead to significantly overpredicted revumenib exposure. This is likely because the effect of cobicistat reached its maximum at lower concentrations.

FDA Table 132. Geometric mean ratios of simulated PK parameters of revumenib in the absence and presence of CYP3A4 perpetrators in patients aged 9 to 18 years old

CYP3A DDI Potential	Perpetrators	Dosing regimen	Revumenib	
			AUC Ratio	C_{max} Ratio
Strong inhibitors	Cobicistat	2 mg/kg QD	4.31	3.1
	Itraconazole	5 mg/kg QD	3.12	2.5
	Posaconazole	6 mg/kg QD	≤ 2.53	≤ 2.0
Moderate inhibitors	Fluconazole	12mg/kg QD	3.03	2.32
		5 mg/kg QD	2.49	1.99
	Isavuconazole	10 mg/kg QD	≤ 1.48	≤ 1.36
Weak inhibitor	Cimetidine	10 mg/kg TID	1.17	1.12
Strong inducer	Rifampin	15 mg/kg QD	0.19	0.3
Moderate inducer	Efavirenz	600 mg QD	0.36	0.49

Source: Tables 2 -5 in the clin-resp-20mar2024 (seq0039), Tables 18 - 20 in the PBPK report sndx-pmx-004-pbpk, and Tables 3 and 4 in the clin-resp-16may2024 (seg0055).

Pediatric patients aged 1 to < 9 year old

As shown in Table 129, in the study arms in which revumenib was co-administered with azoles, the exposure of revumenib and M1 was significantly overpredicted and in most cases, the prediction errors of revumenib AUC and C_{max} were greater than 2-fold of the observed values. Because the accuracy of the predicted revumenib exposure when co-administered with azoles is dependent on the ability of both revumenib and these inhibitor models to predict their concentrations in different age groups, the reviewer requested the applicant to compare the simulated plasma concentration-time profiles and PK parameters of CYP3A perpetrators with their observed concentrations in pediatric patients in literature (FDA information request dated March 20th, 2024). It was found that the default PBPK models of itraconazole, posaconazole, voriconazole, rifampin and efavirenz significantly overpredicted their exposure in pediatric patients (SYX/2/C). Therefore, modifications were made to the default perpetrator files so that the predicted steady state exposure of these inhibitors were around 2-fold of majority of the observed perpetrator PK in pediatrics (Table 124). Verification simulations shown in Table 129 were updated with these modified models. No significant improvements on predictive performance were observed compared to the simulation results obtained using the default models. Therefore, the cause for overprediction of revumenib exposure when co-administered with CYP3A inhibitors is unclear. It cannot be ruled out that the simulated perpetrator exposure

using the models adjusted based on the published data may not reflect their exposure in pediatric patients taking revumenib due to the high variability in the exposure of CYP3A inhibitors in this age group, or the revumenib model overpredicted its exposure in some patients due to lack of knowledge of drug absorption or other unknown factors in pediatrics.

Of note, revumenib exposure in patients who were not taken any CYP3A inhibitors or who were taken either posaconazole or isavuconazole were reasonably predicted considering the PK variability of revumenib; the model predicted exposure of revumenib were around 2-fold of the observed values. Majority of the overpredictions were observed in patients who were taken voriconazole or fluconazole. The largest differences between the observed and predicted revumenib AUC in these patients were observed in patients having sparse plasma samples. Therefore, at least in some cases, the overprediction (Table 129) may be due to inaccuracy of the observed PK estimates of revumenib. It should be also noted that a similar trend of overprediction was observed in adult patients who were taken voriconazole or fluconazole despite models of both inhibitor and revumenib were considered adequately verified in adult populations.

Considering the large PK variability and that the revumenib model reasonably predicted revumenib exposure in pediatric patients who were not taken any CYP3A inhibitors or who were taken either posaconazole or isavuconazole, it is acceptable to use the revumenib model to predict the DDI with posaconazole or isavuconazole in pediatric patients aged 1 to < 9 years old. The predicted interactions are shown in Table 133. In general, the predicted extent of interaction of revumenib with CYP3A inhibitors and inducers in patients aged 1 to <9 years old was similar to that predicted in adult patients except for itraconazole, which had a weaker effect on revumenib in pediatric patients compared to adult patients. This is likely due to the lower itraconazole concentration simulated using the itraconazole model modified based on the observed itraconazole concentrations in this age group (SYX/2/C).

FDA Table 133. Geometric mean ratios of simulated PK parameters of revumenib in the absence and presence of CYP3A4 perpetrators in patients aged 1 to less than 9 years old

CYP3A DDI Potential	Perpetrators	Dosing regimen	Revumenib	
			AUC Ratio	C_{max} Ratio
Strong inhibitors	Cobicistat	2 mg/kg QD	4.99	2.87
	Itraconazole	5 mg/kg QD	2.86	2.13
	Posaconazole	6 mg/kg QD	≤ 3.39	≤ 2.07
Moderate inhibitors	Fluconazole	12mg/kg QD	3.28	2.13
		5 mg/kg QD	2.45	1.76
	Isavuconazole	10 mg/kg QD	≤ 1.39	≤ 1.27
Weak inhibitor	Cimetidine	10 mg/kg TID	1.17	1.12
Strong inducer	Rifampin	15 mg/kg QD	0.21	0.36
Moderate inducer	Efavirenz	225 -275 mg QD	0.36	0.53

Source: Tables 2 -5 in the clin-resp-20mar2024 (seq0039), Tables 18 - 20 in the PBPK report sndx-pmx-004-pbpk, and Tables 3 and 4 in the clin-resp-16may2024 (seg0055).

(b) (4)

14.5. Additional Clinical Outcomes Assessment Analyses

There were no additional clinical outcomes assessment analyses.

14.6. Additional Clinical Analyses

14.6.1. Study SNDX-5613-0700 Schedule of Activities

Cycle 1 Schedule of Activities

Evaluation	Screening	Cycle 1							
	D -21 to -1	C1D1/BL[1]	D2[2]	D3 or 4	D7 or 8[3]	D10 or 11	D14 or 15	D17 or 18	D21 or 22
Provision of written informed consent	X								
Complete medical history, including cancer and HIV	X								
Prior medications[4]	X								
Echocardiogram/MUGA	X								
Mutation status in tumor cells[5]	X								
Height[6]		X							
Weight		X							
Complete physical examination[7]	X								
Symptom-directed physical examination[7]		X	X	X	X	X	X		
Vital signs[8]	X	X	X	X	X	X	X		
Performance Status score[9]	X	X							
Holter monitoring (Phase 1 only)[10]		X							
Clinic 12-lead ECGs[11] Table 3, Table 4, and Table 5	X[12]	X	X	X	X		X		X
Blood sample collection for:									
Screening serology[13]	X								
Coagulation studies (PT/PTT/Fibrinogen)	X								
Hematology[14]	X	X		X	X	X	X	X	X
Clinical chemistry[15]	X	X	X	X	X	X	X	X	X
Cholesterol panel[16]		X							
Endocrine panel[17]	X								
Serum pregnancy testing[18]	X	X							
PK[19] Table 3, Table 4, and Table 5		X	X	X	X		X[20]		
Biomarkers[21]		X		X					
Coagulation panel[22]	X								
Urinalysis[23]		X							
Cerebrospinal fluid and CNS disease history	X[24]	Cerebrospinal fluid to be submitted for central testing whenever collected for local, clinical purposes (see lab manual)							

Evaluation	Screening	Cycle 1							
	D -21 to -1	C1D1/BL[1]	D2[2]	D3 or 4	D7 or 8[3]	D10 or 11	D14 or 15	D17 or 18	D21 or 22
Ophthalmologic exam (including slit lamp exam)[25]	X								
Bone marrow aspiration and/or biopsy[26]	X								
SNDX-5613 administration[27]		X	X	X	X	X	X	X	X
Cobicistat[28]			X	X	X	X	X	X	X
Low-fat breakfast[29]					X		X		
Food effect data collection[30]					X		X		
Adverse events[31]		X	X	X	X	X	X	X	X
Concomitant medications[31]		X	X	X	X	X	X	X	X

Source: Appendices 16.1.1 protocol and/or amendments

Table Cycle ≥ 2 schedule of activities

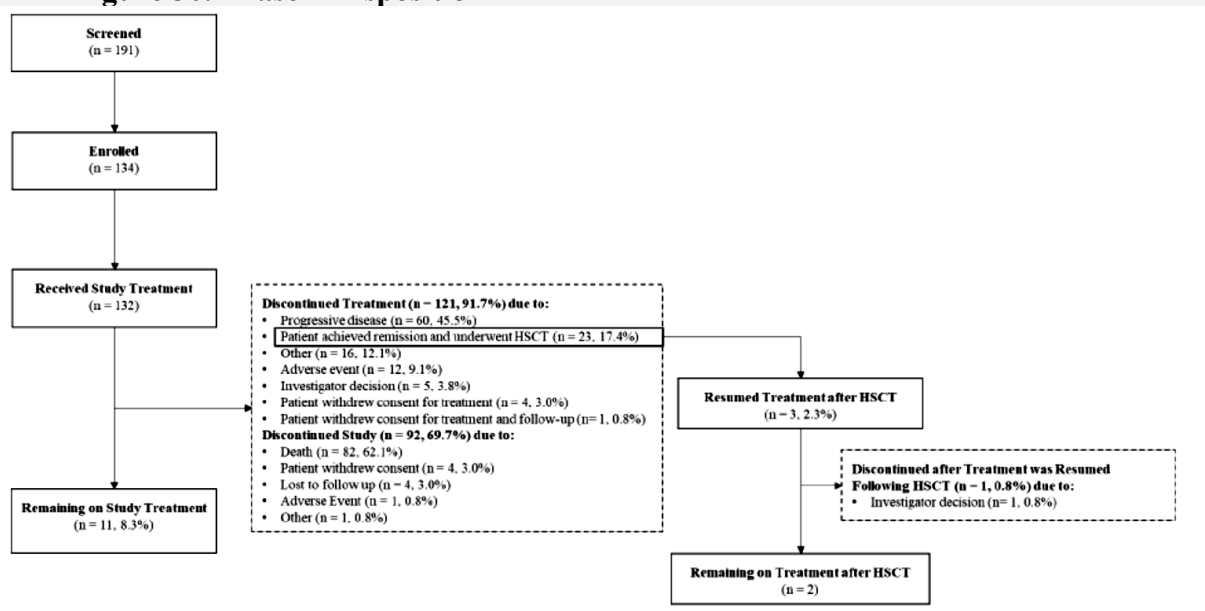
Evaluation		Treatment Period				Follow-up		
		Cycle 2			≥Cycle 3			
	D1 (+/- 1d)	D8[1] (+/- 1d)	D15 (+/- 1d)	D1 (+/- 1d)	EOT (within 7d postdose)	Safety Follow-up (30d postdose [+5d])	Survival FU/Study Termination[24] (Q1M [first 12 months] then Q3M ±7d)
Height[2]	X			X			
Weight	X			X		X	
Complete physical examination[3]						X	
Symptom-directed physical examination[3]	X	X	X	X	X		
Vital signs[4]	X	X	X	X	X	X	
Performance Status score[5]	X			X		X	
12-lead ECGs[6] Table 3, Table 4, and Table 5			X	X		X	
Blood sample collection for:							
Hematology[7]	X	X[7]	X[7]	X	X	X	
Clinical chemistry[8]	X			X	X	X	
Cholesterol panel[9]				X		X	
Endocrine panel[10]				X	X		
Serum pregnancy testing[11]	X			X		X	
PK[12] Table 3 and Table 4		X[1]	X	X[13]			
Biomarkers[14]	X			X			

CNI concentration[15]				X			
Urinalysis[16]	X			X		X	
Cerebrospinal fluid		To be submitted for central testing whenever collected for local, clinical purposes (see lab manual)					
Ophthalmologic exam (inc slit lamp exam)				X[17]	X[17]	X[17]	
Bone marrow aspiration and/or biopsy[7,18]	X			X[19]	X[19]		
SNDX-5613 administration[20]	X	X	X	X			
Cobicistat administration[21]	X		X	X			
Adverse events[22]	X	X	X	X	X	X	
Concomitant medications[22]	X	X	X	X	X	X	
Survival[23]							X

Source: Appendices 16.1.1 protocol and/or amendments

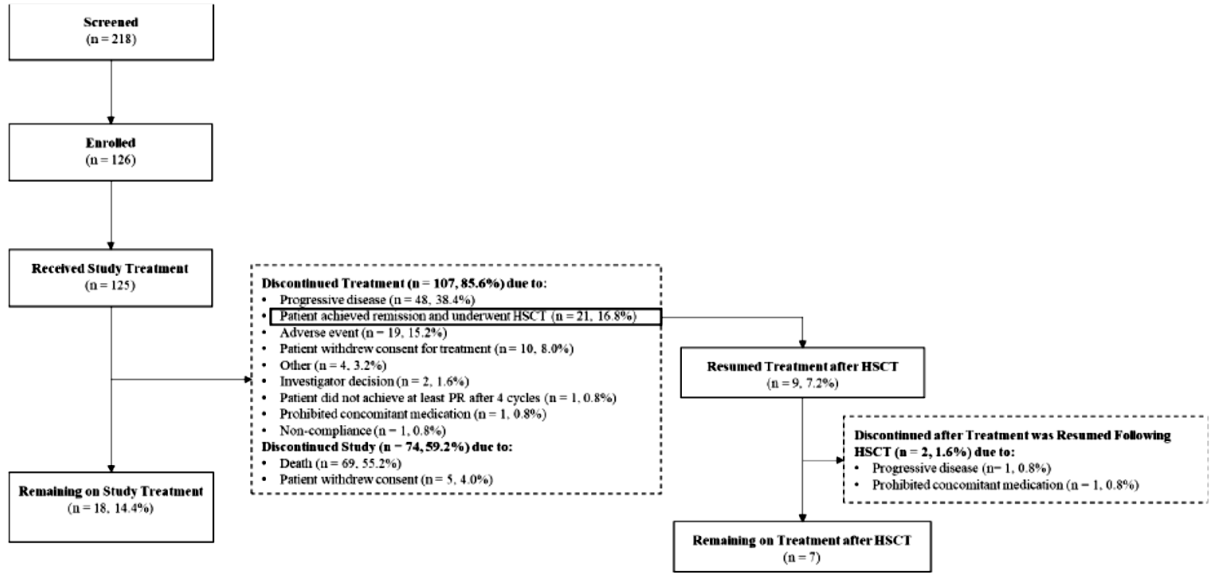
14.6.2. Study SNDX-5613-0700 Disposition of Screened Individuals

FDA Figure 30. Phase 1 Disposition



Source: SNDX-5613-0700 CSR Figure 4

FDA Figure 31. Phase 2 Disposition



Source: SNDX-5613-0700 CSR Figure 6

14.6.3. FDA's Exploratory Analysis of Overall Survival in KMT2Ar AML patients

As the current state of knowledge of OS for the seeking disease population is extremely limited, the reviewer conducted some exploratory analysis to evaluate the survival based on the publications, in particular, Issa 2021a. It was a retrospective study which identified 172 frontline and 50 R/R (aged >= 17 years old) KMT2Ar AML patients treated at MD Anderson Cancer Center between 1990 and 2019. The frontline cohort's subsequent therapy and relapse data were also collected and grouped into the corresponding subgroup of line of therapy. For those with 1 and 2 prior lines in this paper, the median OS was reported to be 6 and 2 months, respectively; the 6-month survival rate were 42% and 18%, respectively; and the 12-month survival rate were 18% and 7%, respectively. No numbers were reported in Issa 2021a for patients with 3 or more prior lines. These estimates for patients with 1 or 2 prior lines were numerically higher in study SNDX5613-0700. For those with 1 and 2 prior lines in the Efficacy Cohort, the median OS was reported to be 8.4 (95% CI: 6.9, NE) and 10.5 (95% CI: 3.5, NE) months, respectively; the 6-month survival rate were 76% (95% CI: 60%, 95%) and 54% (95% CI: 37%, 78%), respectively; and the 12-month survival rate were 35% (95% CI: 18%, 68%) and 40% (95% CI: 24%, 69%), respectively.

The summary above is just for exploratory purpose to provide some context of the disease condition. This trial differs from Study SNDX-5613-0700 in multiple ways. For example, it includes only AML adults, versus Study SNDX-5613-0700 enrolled other diseases (e.g., ALL/MAPL) and pediatric patients. Two study populations also differ in terms of prior use of

transplantation and other therapies. Due to these inherent limitations in cross-trial comparisons, particularly for time-to-event endpoints, such comparisons to historical data would not be considered direct evidence of efficacy. The OS results observed in the pivotal trial cannot be conclusively determined to be an improvement in this setting over historically utilized therapies.

14.6.4. Basis of Grouped Terms Used for the Safety Analyses

FDA Table 134. Group Terms Used for FDA Analyses of Adverse Events

Grouped Term	Basis for Grouped Term
Abdominal pain	HLT Gastrointestinal and abdominal pains (excl oral and throat)
Bacterial infection	HLGT Bacterial infectious disorders, PT Bacteraemia
Cardiac Failure	HLGT Heart failures, HLGT Myocardial disorders, PTs Ejection fraction decreased, Brain natriuretic peptide increased
Cough	HLT Coughing and associated symptoms
Depressed level of consciousness	HLT Disturbances in consciousness NEC
Diarrhoea	HLT Diarrhoea (excl infective), HLT Colitis (excl infective)
Drug hypersensitivity	AETERM
Dyspnoea	HLT Breathing abnormalities
Face oedema	AETERM
Fatigue	HLT Asthenic conditions
Fungal infection	HLGT Fungal infectious disorders, PT Fungaemia
Haemorrhage	Haemorrhage terms (excl laboratory terms) (SMQ)
Headache	HLGT Headaches
Hyperbilirubinaemia	HLT Cholestasis and jaundice, PT Blood bilirubin increased
Hypertension	Hypertension (SMQ)
Hypotension	HLT Vascular hypotensive disorders
Infection	HLGT Infections - pathogen unspecified
Musculoskeletal pain	HLT Muscle pains, HLT Musculoskeletal and connective tissue pain and discomfort, PT Arthralgia
Nausea	HLT Nausea and vomiting symptoms
Neuropathy peripheral	HLGT Peripheral neuropathies, HLT Facial cranial nerve disorders
Oedema	HLT Oedema NEC, PT Peripheral swelling
Paraesthesia	HLT Paraesthesias and dysaesthesias
Rash	HLT Rashes, eruptions and exanthems NEC, HLT Bullous conditions, HLT Exfoliative conditions, HLT Dermatitis ascribed to specific agent
Renal impairment	HLT Renal failure and impairment, HLT Renal function analyses
Stomatitis	HLT Stomatitis and ulceration
Tachycardia	PTs Tachycardia, Atrial tachycardia, Sinus tachycardia, Atrial fibrillation
Taste disorder	PTs Ageusia, Dysgeusia, Hypogeusia, Taste disorder
Thrombosis	Embolic and thrombotic events (SMQ)
Transaminases increased	PTs Hypertransaminasaemia Alanine aminotransferase Alanine aminotransferase increased Aspartate aminotransferase increased Gamma-glutamyltransferase increased Liver function test abnormal Liver function test increased Transaminases increased
Viral infection	HLGT Viral infectious disorders, PT Viraemia
Visual impairment	HLT Visual disorders NEC, HLT Visual impairment and blindness (excl colour blindness)

14.6.5. SAFPOP TEAEs Reported In At Least 2 Participants

TEAE*	SAFPOP N=167	
	n	(%)
Haemorrhage	86	51.5
Nausea	85	50.9
Infection	74	44.3
Musculoskeletal pain	70	41.9
Febrile neutropenia	68	40.7
Electrocardiogram QT prolonged	57	34.1
Diarrhoea	53	31.7
Bacterial infection	50	29.9
Oedema	48	28.7
Transaminases increased	43	25.7
Hypokalaemia	42	25.1
Differentiation syndrome	41	24.6
Fatigue	41	24.6
Constipation	39	23.4
Anaemia	37	22.2
Decreased appetite	34	20.4
Viral infection	34	20.4
Dyspnoea	33	19.8
Abdominal pain	29	17.4
Hyponatraemia	29	17.4
Headache	26	15.6
Cough	25	15
Platelet count decreased	25	15
Neutrophil count decreased	23	13.8
Pyrexia	23	13.8
Stomatitis	23	13.8
White blood cell count decreased	23	13.8
Hypomagnesaemia	22	13.2
Rash	22	13.2
Tachycardia	21	12.6
Taste disorder	20	12
Thrombocytopenia	19	11.4
Hyperkalaemia	18	10.8

Hyperphosphataemia	18	10.8
Thrombosis	18	10.8
Hyperglycaemia	17	10.2
Non-cardiac chest pain	17	10.2
Pleural effusion	17	10.2
Blood alkaline phosphatase increased	16	9.6
Insomnia	16	9.6
Renal impairment	16	9.6
Abdominal distension	15	9
Fungal infection	15	9
Hypophosphataemia	15	9
Muscular weakness	15	9
Fall	14	8.4
Dizziness	13	7.8
Face oedema	13	7.8
Hypermagnesaemia	13	7.8
Weight decreased	13	7.8
Depressed level of consciousness	12	7.2
Hypocalcaemia	12	7.2
Hypotension	12	7.2
Leukocytosis	12	7.2
Anxiety	11	6.6
Blood lactate dehydrogenase increased	11	6.6
Confusional state	11	6.6
Oropharyngeal pain	11	6.6
Rhinorrhoea	11	6.6
Visual impairment	11	6.6
Hyperbilirubinaemia	10	6
Respiratory failure	10	6
Cardiac failure	9	5.4
Depression	9	5.4
Hypertension	9	5.4
Hypoalbuminaemia	9	5.4
Hypoxia	9	5.4
Neutropenia	9	5.4
Bone pain	8	4.8
Dyspepsia	8	4.8

Erythema	8	4.8
Pruritus	8	4.8
Atelectasis	7	4.2
Infusion related reaction	7	4.2
Mental status changes	7	4.2
Nasal congestion	7	4.2
Neuropathy peripheral	7	4.2
Pericardial effusion	7	4.2
Skin abrasion	7	4.2
White blood cell count increased	7	4.2
Alopecia	6	3.6
Dehydration	6	3.6
Dry eye	6	3.6
Dry mouth	6	3.6
Gastrooesophageal reflux disease	6	3.6
Haemorrhoids	6	3.6
Hypercalcaemia	6	3.6
Hyperuricaemia	6	3.6
Pain	6	3.6
Agitation	5	3
Blood fibrinogen decreased	5	3
Chest pain	5	3
Chills	5	3
Dysphagia	5	3
Gait disturbance	5	3
Hiccups	5	3
Hypernatraemia	5	3
Lymphocyte count decreased	5	3
Oral disorder	5	3
Oral pain	5	3
Palpitations	5	3
Pulmonary oedema	5	3
Urinary retention	5	3
Chest discomfort	4	2.4
Drug hypersensitivity	4	2.4
Ear pain	4	2.4
Ingrowing nail	4	2.4

International normalised ratio increased	4	2.4
Lymphadenopathy	4	2.4
Micturition urgency	4	2.4
Muscle spasms	4	2.4
Sinus bradycardia	4	2.4
Skin lesion	4	2.4
Toothache	4	2.4
Urinary incontinence	4	2.4
Acidosis	3	1.8
Activated partial thromboplastin time prolonged	3	1.8
Acute respiratory failure	3	1.8
Catheter site erythema	3	1.8
Catheter site pain	3	1.8
Catheter site rash	3	1.8
Dry skin	3	1.8
Dysuria	3	1.8
Electrocardiogram T wave abnormal	3	1.8
Encephalopathy	3	1.8
Groin pain	3	1.8
Hypertriglyceridaemia	3	1.8
Hypervolaemia	3	1.8
Hypothyroidism	3	1.8
Myositis	3	1.8
Pallor	3	1.8
Paraesthesia	3	1.8
Pleuritic pain	3	1.8
Procedural pain	3	1.8
Proctalgia	3	1.8
Sinus congestion	3	1.8
Skin laceration	3	1.8
Tremor	3	1.8
Tumour lysis syndrome	3	1.8
Abdominal discomfort	2	1.2
Adrenal insufficiency	2	1.2
Alkalosis	2	1.2
Angina pectoris	2	1.2
Aphasia	2	1.2

Bradycardia	2	1.2
Cerumen impaction	2	1.2
Clostridium test positive	2	1.2
Dental caries	2	1.2
Dermatitis diaper	2	1.2
Dysphonia	2	1.2
Ear discomfort	2	1.2
Enterocolitis	2	1.2
Eye pain	2	1.2
Failure to thrive	2	1.2
Gingival pain	2	1.2
Gout	2	1.2
Hot flush	2	1.2
Hyperhidrosis	2	1.2
Hypoglycaemia	2	1.2
Hypothermia	2	1.2
Impaired gastric emptying	2	1.2
Impaired healing	2	1.2
Injection site reaction	2	1.2
Joint effusion	2	1.2
Joint swelling	2	1.2
Lactic acidosis	2	1.2
Lung consolidation	2	1.2
Metabolic acidosis	2	1.2
Nodule	2	1.2
Ocular hyperaemia	2	1.2
Oesophagitis	2	1.2
Pain of skin	2	1.2
Pericarditis	2	1.2
Pneumatosis intestinalis	2	1.2
Pollakiuria	2	1.2
Presyncope	2	1.2
Proctitis	2	1.2
Proteinuria	2	1.2
Pulmonary mass	2	1.2
Restlessness	2	1.2
Rhinalgia	2	1.2

Scrotal mass	2	1.2
Seizure	2	1.2
Serum ferritin increased	2	1.2
Skin hyperpigmentation	2	1.2
Skin irritation	2	1.2
Skin mass	2	1.2
Skin ulcer	2	1.2
Sneezing	2	1.2
Sudden death	2	1.2
Transfusion reaction	2	1.2
Troponin I increased	2	1.2
Ventricular tachycardia	2	1.2
Vitamin D deficiency	2	1.2

Source: FDA analysis
*Includes grouped terms

15 DIVISION DIRECTOR (DHM1)

X
Director, Division of Hematological Malignancies 1 (DHM1)

16 OFFICE DIRECTOR (OR DESIGNEE)

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

NDA Multidisciplinary Review and Evaluation
NDA 218944
Revuforj (revumenib)

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Nonclinical Reviewer	Daniela Torres, PhD	OOD/DHOT	Sections: 5	X Authored Approved
	Signature: Daniela Torres -S Digitally signed by Daniela Torres -S Date: 2024.10.22 11:48:15 -04'00'			
Nonclinical Team Leader	Brenda Gehrke, PhD	OOD/DHOT	Sections: 5	Authored X Approved
	Signature: Brenda Gehrke -S Digitally signed by Brenda Gehrke -S Date: 2024.10.28 10:15:49 -04'00'			
Nonclinical Division Director	Tiffany Ricks, PhD	OOD/DHOT	Sections: 5	Authored X Approved
	Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K. Ricks -S Date: 2024.11.06 13:55:54 -05'00'			
Clinical Pharmacology Reviewer	Ritu Chadda, PhD	OCP/DCPI	Sections: 6, 14	X Authored Approved
	Signature: Ritu Chadda -S Digitally signed by Ritu Chadda -S Date: 2024.10.28 16:34:55 -04'00'			
Clinical Pharmacology Team Leader	Ruby Leong, PharmD	OCP/DCPI	Sections: 6, 14	Authored X Approved
	Signature: Ruby Leong -S Digitally signed by Ruby Leong -S Date: 2024.10.22 14:33:21 -04'00'			
Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections: 6, 14	Authored X Approved
	Signature: Brian P. Booth -S Digitally signed by Brian P. Booth -S Date: 2024.11.07 09:18:16 -05'00'			
Pharmacogenomics Reviewer	Javier Blanco, PhD	OCP/DPM	Sections: 6	X Authored Approved
	Signature: Javier G. Blanco -S Digitally signed by Javier G. Blanco -S Date: 2024.10.22 09:24:59 -04'00'			
Pharmacogenomics Team Leader	Sarah Dorff, PhD	OCP/DPM	Sections: 6	Authored X Approved
	Signature: Sarah E. Dorff -S Digitally signed by Sarah E. Dorff -S Date: 2024.10.22 16:50:53 -04'00'			

NDA Multidisciplinary Review and Evaluation
NDA 218944
Revuforj (revumenib)

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Pharmacometrics Reviewer	Hongshan Li, PhD	OCP/DPM	Sections: 6, 14	X Authored Approved
	Signature: Hongshan Li -S Digitally signed by Hongshan Li -S Date: 2024.10.28 09:17:21 -04'00'			
Pharmacometrics Reviewer	Ying-Hong Wang, PhD	OCP/DPM	Sections: 6, 14	X Authored Approved
	Signature: Yuching Yang -S Digitally signed by Yuching Yang -S Date: 2024.11.07 09:41:16 -05'00'			
Pharmacometrics Team Leader	Yuching Yang, PhD	OCP/DPM	Sections: 6, 14	Authored X Approved
	Signature: Yuching Yang -S Digitally signed by Yuching Yang -S Date: 2024.11.01 15:32:13 -04'00'			
Pharmacometrics Associate Director	Jiang Liu, PhD	OCP/DPM	Sections: 6, 14	Authored X Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2024.10.28 07:50:34 -04'00'			
Statistical Reviewer	Xin Wang, PhD	OOD/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	X Authored Approved
	Signature: Xin Wang -S Digitally signed by Xin Wang -S Date: 2024.10.28 12:15:00 -04'00'			
Statistical Team Leader	Jonathan Vallejo, PhD	OB/DBIX	Sections: 8.1, 8.2, 8.4, 8.5	Authored X Approved
	Signature: Jonathon J. Vallejo -S Digitally signed by Jonathon J. Vallejo -S Date: 2024.10.28 08:28:29 -04'00'			
Division Director (OB) designee	Yuan Li Shen, DrPH	OB/DBIX	Sections: 1, 8.1, 8.2, 8.4, 8.5	Authored X Approved
	Signature: Yuan-li Shen -S Digitally signed by Yuan-li Shen -S Date: 2024.11.01 17:44:03 -04'00'			
Clinical Reviewer	Chatchada Karanes, MD	OOD/DHMI	Sections: 2, 3, 7, 8, 9, 10, 14	X Authored Approved
	Signature: Chatchada Karanes -S Digitally signed by Chatchada Karanes -S Date: 2024.10.28 10:22:47 -04'00'			

NDA Multidisciplinary Review and Evaluation
NDA 218944
Revuforj (revumenib)

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Clinical Team Leader	Donna Przepiorka, MD, PhD	OOD/DHMI	Sections: 2, 3, 7, 8, 9, 10, 14	Authored X Approved
	Signature: Digitally signed by Donna Przepiorka -S Date: 2024.10.18 21:14:57 -04'00'			
Associate Director for Labeling	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	X Authored Approved
	Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S Date: 2024.10.28 09:34:17 -04'00'			
Cross-Discipline Team Leader	Donna Przepiorka, MD, PhD	OOD/DHMI	Sections: 1, 4, 5, 12, 13	X Authored Approved
	Signature: *{See appended electronic signature page}*			
Deputy Division Director (Clinical)	Kelly Norsworthy, MD	OOD/DHMI	Sections: All	Authored X Approved
	Signature: *{See appended electronic signature page}*			
Office Director (or designee)	Marc Theoret, MD	OOD	Sections: All	Authored X Approved
	Signature: *{See appended electronic signature page}*			

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/s/

DONNA PRZEPIORKA
11/14/2024 06:04:48 AM

KELLY J NORSWORTHY
11/15/2024 09:08:46 AM

(b) (4)

MARC R THEORET
11/15/2024 02:45:20 PM
My signature indicates that I have considered the FDA assessments and recommendations included in this Review in determining the regulatory action.