CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218944Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 142693

MEETING MINUTES

Syndax Pharmaceuticals, Inc.
Attention: Allie Palazzi-Leahy
Manager, Regulatory Affairs
35 Gatehouse Drive, Building D, Floor 3
Waltham, MA 02451

Dear Allie Palazzi-Leahy:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Revumenib (SNDX-5613).

We also refer to the video conference between representatives of your firm and the FDA on October 20, 2023. The purpose of the meeting was to discuss the acceptability of the topline safety and efficacy data from study SNDX-5613-0700 to support an NDA submission for Agency review.

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Rachel McMullen, Senior Regulatory Project Manager at 240-402-4574.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Clinical Team Lead
Division of Hematologic Malignancies I Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	October 20, 2023, 11:00am – 12:00pm EST
Meeting Location:	Videoconference
Application Number:	IND 142693
Product Name:	Revumenib (SNDX-5613)
Indication:	Treatment of adult and pediatric patients with relapsed or refractory acute leukemia with a KMT2A rearrangement
Sponsor Name:	Syndax Pharmaceuticals, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic
Meeting Chair:	Donna Przepiorka, MD, PhD
Meeting Recorder:	Rachel McMullen, MPH, MHA

FDA ATTENDEES

Office of Oncologic Diseases (OOD)/Division of Hematologic Malignancies I (DHM1)
R. Angelo de Claro, MD, Division Director
Kelly Norsworthy, MD, Deputy Division Director
Donna Przepiorka, MD, PhD, Clinical Team Leader
Chatchada Karanes, MD, Clinical Reviewer
Joseph Wynne, MD, PhD, Clinical Reviewer
Ashley Woods, MD, Clinical Reviewer
Cara Rabik, MD, PhD, Clinical Reviewer
Yanxia Li, RN, MSN, ACNP-BC, CCRN, Clinical Reviewer

Office of Oncologic Diseases (OOD)/Division of Hematology, Oncology, Toxicology (DHOT)
Brenda Gehrke, PhD, Nonclinical Supervisor

Office of Clinical Pharmacology/Division of Cancer Pharmacology I
Nan Zheng, PhD, Clinical Pharmacology Team Leader
Miao Zhao, PhD, Clinical Pharmacology Reviewer
Javier Blanco, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics IX
Jonathon Vallejo, PhD, Biometrics Team Leader
Xin Wang, PhD, Biometrics Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products I, Branch II
Shalini Anand, PhD, Senior Pharmaceutical Quality Assessor
Rajiv Agarwal, PhD, Product Quality Reviewer
Dahlia A. Walters, M.S., PMP, FAC-P/PM, Sr. Regulatory Business Process Manager

Office of Pharmaceutical Quality (OPQ)/Office of Pharmaceutical Manufacturing Assessment
Diane Goll, PhD, Chemistry Reviewer

Office of Regulatory Operations (ORO)/Division of Regulatory Operations for Oncologic Diseases/Hematologic Malignancies I
Rachel McMullen, MPH, MHA, Senior Regulatory Health Project Manager
Saumya Nathan, MSc, MS, Senior Regulatory Health Project Manager

SPONSOR ATTENDEES

Syndax Pharmaceuticals, Inc.
Shaliny Kushwaha, VP, Regulatory Affairs, Syndax
Kate Madigan, Chief Medical Officer, Syndax
Neil Gallagher, President, Head of Research and Development, Syndax
Nicole McNeer, Clinical Leader and Medical Director, Menin, Syndax
Rachel Ghiraldi, Director, Regulatory Affairs, Syndax
Soujanya Sunkaraneni, Senior Director, Clinical Pharmacology, Syndax
Ariane Marolewski, VP, Pharmaceutical Development and Manufacturing, Syndax
Christopher Murphy, Senior Director, Regulatory Affairs CMC, Syndax
Peter Ordentlich, Chief Scientific Officer, Syndax
Dennis O'Brien, VP, Drug Safety and Pharmacovigilance, Syndax
Rob Nordness, VP, Drug Safety and Pharmacovigilance, Syndax
Yifan Huang, VP, Biometrics, Syndax
Yu Gu, Senior Director, Biometrics, Syndax

1.0 BACKGROUND

Revumenib, a small molecule inhibitor of the menin-MLL1 interaction, is being developed by Syndax Pharmaceuticals, Inc., (Sponsor) for the treatment of relapsed or refractory acute leukemias harboring a KMT2Ar or mNPM1 mutation. On April 20, 2020, revumenib was granted Orphan Drug Designation for the treatment of acute myeloid leukemia. Fast Track Designation was granted on June 24, 2021, for the investigation of revumenib for the treatment of adult and pediatric patients with relapsed or refractory acute leukemias

harboring a KMT2Ar or NPM1 mutation. Breakthrough Designation for the treatment of adult and pediatric patients with relapsed or refractory acute leukemia harboring a KMT2A rearrangement was granted on November 30, 2022.

The Agency has provided guidance on the clinical development program in eleven meetings or written responses only. Additionally, the clinical development program was also discussed at the June 18, 2020, meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee. On August 25, 2023, the Sponsor requested a Type B pre-NDA meeting. The Agency previously provided feedback on the content and format of the proposed NDA at a Type B meeting on March 23, 2023, and in written response issued on May 19, 2023.

Clinical Development Program

Proposed Indication: For the treatment of adult and pediatric patients with relapsed or refractory acute leukemia with a KMT2A rearrangement.

Supporting Clinical Trials

Study	Study Design and Population	Revumenib Dosing Regimen	Efficacy Endpoint
SNDX-5613-0700 (AUGMENT-101)	Phase 1-2, open-label, single-arm, dose-escalation and dose-expansion study in patients ≥ 30 days old with R/R acute leukemia with KMT2Ar or NPM1c with food effect substudy	Ph 1: starting 113 mg (65 mg/m^2) at q 12 hr n=131 Ph 2: 276 mg q 12 hr (or BSA-based) or 163 mg q 12 hr on strong CYP3A4i n=119	Ph 2: CR+CRh
SNDX-5613-0702	Open-label, dose-escalation combination trial in patients ≥ 30 days old with R/R acute leukemia with KMT2Ar or NPM1c	Starting 226 mg q 12 hr + chemotherapy - 113 mg q 12 hr on strong CYP3A4i	
SNDX-5613-0705	Mass balance, PK, and metabolism study in patients ≥ 18 years old with R/R acute leukemia	276 mg q 12 hr	
SNDX-5613-0706	Phase 1-2 open-label study in patients ≥ 18 years old with R/R solid tumors	Ph 1: 50-276 mg Ph 2: TBD	
SNDX-5613-0707	EAP using capsule (tablet) in patients ≥ 30 days old with R/R acute leukemia with HOXA pathway overexpression	276 (270) mg q 12 hr (or BSA-based) or 163 (160) mg q 12 hr on strong CYP3A4i	
Expanded access	Single-patient protocols (n=~48)	variable	

Study SNDX-5613-0700 Top-Line Results (Cohorts 2A and 2B)

	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 Median (95% CI)	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, 12.3)	(1.9, 45.4)	(1.1, 14.6)

Source: Sponsor's Meeting Package Table 10

FDA sent Preliminary Comments to Syndax on October 16, 2023.

2.0 DISCUSSION

2.1. Regulatory

Question 1: *Does the Agency agree that the results from SNDX-5613-0700 support submission of an NDA for the treatment of adult and pediatric patients with relapsed or refractory acute leukemia with a KMT2A rearrangement?*

FDA Response to Question 1:
In general, positive results from at least two adequate and well-controlled trials or one adequate and well-controlled trial with supporting evidence would be sufficient efficacy data to support submission of a marketing application. There is insufficient information in your meeting package to ensure that your proposed efficacy data are adequate to support a marketing application. We have the following comments:

a. In your 10/12/2023 response to our information request, you indicated that 19 subjects were enrolled on Cohort 2A and 87 on Cohort 2B (total 106 subjects), and that these two cohorts were now closed to accrual. You also indicate in Section 12.3.1 of the meeting package that the interim analysis conducted in the first 57 patients in Cohorts 2A and 2B will be the final analysis. We recommend that you revise the protocol to prespecify the timing of additional efficacy analyses for all subjects enrolled, even if descriptive only, through the end of the study.

b. Please clarify what is the median (range) of follow-up for the 57 patients included in the interim analysis.

c. For the purposes of regulatory decision-making, the efficacy analysis of a single-arm trial of a targeted agent is expected to be conducted in the subjects confirmed by the companion diagnostic to have the cognate mutation. You report in Section 12.4.1 of the meeting package that 5 of 78 subjects in SNDX-5613-0700 were not confirmed to have a KMT2Ar by the clinical trial assay (CTA). How many of the 57 subjects in the pivotal cohort had a KMT2Ar confirmed by the CTA? Please provide efficacy results for the subjects in the pivotal cohort with confirmed KMT2Ar.

d. In your 10/12/2023 response to our information request, you indicated that 281 subjects were enrolled in various arms and cohorts in SNDX-5613-0700. The efficacy results for subjects 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. What are the efficacy results for such patients?

e. You proposed to base an efficacy claim using 10% as the null rate. The acceptability of the 10% null rate will be a review issue. Ensure that your submission includes data to justify the meaningfulness of results based on the proposed null rate, especially in the context of the safety profile of your drug.

f. We note some discrepancies in the timing of the submitted interim analysis and the definition of efficacy-evaluable patients between SAP (final version 4.0 dated 14 August 2023) and the meeting document.

    i. According to SAP, the analysis of the pooled MLLr population is the same time as the analysis timepoints for Cohort 2B, and the interim analysis for Cohort 2B occurs when the first 38 adult efficacy-evaluable patients (i.e., treated patients who are centrally confirmed for mutational status, and have at least 5% blasts in bone marrow at baseline) have had the opportunity to complete a minimum of 4 cycles of therapy or have discontinued therapy.

    However, according to the meeting document, it appears that the timing of this interim analysis was delayed to the time point when the first 38 adult efficacy-evaluable patients are followed for of 6 months. Furthermore, one more condition, “had the opportunity to be followed for 6 months”, is being added to the definition of efficacy-evaluable patients. Please clarify this discrepancy.

    ii. Note that all the analyses should be performed according to SAP and otherwise would be considered as ad hoc and exploratory.

iii. In addition, clarify how the primary analysis handles efficacy-evaluable patients who did not have the opportunity to be followed for 6 months, e.g., who discontinued study or lost to follow up before 6 months.

g. The calculation of the efficacy boundary for the pooled MLLr population in SAP is unclear. Given the problems outlined below, we find it challenging to claim statistical significance based on the proposed efficacy boundary for the pooled population. Please provide sensitivity analyses which derive this boundary based on the maximum and minimum sample sizes possible under the planned design. For example, a conservative boundary uses the maximum target sample size, which is 64 2A adult + 64 2B adult + 40 pediatrics = 168, as the denominator.

i. First, this boundary is derived using group sequential design with information fraction based on the pooled population; however, this information fraction is not clearly defined because its denominator (i.e., the number of efficacy-evaluable patients in the pooled population at the Cohort 2B final analysis) is unknown given that all the cohorts and pediatric and adult patients are enrolled independently.

ii. We also note the SAP lacks important details regarding the methods of calculating this boundary, e.g., alpha spending function. The SAP only says one R package "gsDesign" is used but does not mention what parameters are fed into the relevant code, for example, is OBF or Pocock method or other alpha spending function employed?

iii. Furthermore, an alternative way, such as allocating a fixed alpha for this interim analysis, is not specified in the SAP either.

Discussion:

1(a): The Sponsor proposed to revise the protocol to prespecify the timing of additional descriptive efficacy analyses for all subjects enrolled through the end of study. They indicated that descriptive efficacy analyses will be performed when all enrolled subjects in Cohort 2A and Cohort 2B have had a minimum of 4 cycles of therapy or have discontinued therapy. FDA had no objection to the proposed plan for Cohorts 2A and 2B but reminded the Sponsor that in order for the results to be considered unbiased, the prespecified plan for additional efficacy analyses should address all subjects in all arms in Part 1 and all cohorts in Part 2. FDA confirmed that additional analyses were not required to be submitted in the original NDA.

1(f): FDA recommended that the Sponsor update the protocol and SAP to reflect a minimum of 6 months of follow up for this interim analysis and to also clarify this in future documents such as the CSR.

1(g): FDA recommended that the Sponsor add the clarification of boundary calculations in the SAP. The Sponsor can copy and paste the R code into an appendix of the SAP or clarify the code and parameters to feed to the corresponding code, so that FDA can reproduce and verify the sponsor's numbers.

2.2. Clinical Pharmacology

Question 2: *The results from Study SNDX-5613-0705 have identified M1 as the major metabolite of revumenib. Furthermore, in vitro and clinical data both support CYP3A4 metabolism as the primary elimination pathway for revumenib. Study SNDX-5613-0705 is ongoing, and additional data may be available at the time of the 90-day update. Does the Agency agree that the currently available data is sufficient for characterization of metabolites and excretion pathways for the NDA submission?*

FDA Response to Question 2:
No, we do not agree. Currently available data is not adequate for the characterization of the metabolism and excretion pathways, or to support your conclusion that the major pathway of revumenib clearance is via hepatic metabolism, primarily through CYP3A4. Potential issues for preliminary data from the mass balance study include but are not limited to the following:

- Only 47% of the total dose was recovered in the mass balance study. Ideally, total recovery of radioactivity in urine and feces should be at least 90%. Provide justification for the low recovery rate and assess the impact on the characterization of metabolism and excretion pathways.

- Metabolite profiling in the excreta (e.g., urine and feces) are unclear.

Refer to FDA guidance "Clinical Pharmacology Considerations for Human Radiolabeled Mass Balance Studies" for greater details (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-pharmacology-considerations-human-radiolabeled-mass-balance-studies).

Please note that the NDA should be complete at the time of submission, and an update to the analysis of mass balance study results provided 90 days after submission that was not requested in an Information Request from FDA may be considered a major amendment of the NDA.

Discussion:
The Sponsor provided the number of plasma, urine, and feces samples planned and collected in each patient on study and committed to assess the impact of the low recovery of radioactivity on characterization of metabolism and excretion pathways.

FDA acknowledged the incomplete sample collection, especially for urine and fecal samples. FDA reiterated that the current available preliminary data (e.g., low recovery of total radioactivity and lack of metabolite identification and profiling in urine and fecal samples) preclude adequate characterization of the metabolism and excretion pathways.

FDA also advised that there should be at least 6 evaluable patients with adequate recovery to support the mass balance evaluation.

FDA indicated that the NDA can be submitted with the available data and an assessment on the impact of low recovery on the characterization of metabolism and excretion pathways. Adequacy of the data to support characterization of the metabolism and excretion pathways of revumenib will be a review issue. The Sponsor acknowledged that submission of new data during the review cycle may be considered a major amendment.

Question 3: *In characterizing the effect of formulation on the PK of revumenib, results from a relative bioavailability (RBA) assessment and PopPK analysis have demonstrated that formulation has no effect on revumenib exposure. Does the Agency agree that the overall approach to evaluate the impact of formulation on revumenib PK is adequate?*

FDA Response to Question 3:
The currently available data appears to support that revumenib PK is comparable between the capsule and tablet formulation. However, in the NDA submission:

a. Provide data to support the characterization the PK and safety of revumenib (b) (4) [redacted]

b. Provide data to support that PK of the major metabolite M1 is comparable between the different formulations.

c. Conduct exploratory E-R efficacy/safety analysis using formulations as a covariate.

Whether the data support approval of the proposed monocitrate monohydrate tablet (b) (4) [redacted] will be a review issue when the NDA is submitted. Factors that may impact the adequacy of the data include the number of patients treated with the proposed formulations, the quantity and quality of PK data available for each studied formulation, and the results of the analyses.

Question 3a: *The RBA assessment was conducted in 9 patients who received both the*

capsule and tablet formulations of revumenib in a crossover format. These data show similar PK between the capsule and tablet (Section 13.2.3.1). In addition, the effect of formulation (capsule [N=214], tablet [N=11], and oral solution [N=46]) ion the PK of revumenib is being evaluated through a PopPK analysis. Preliminary data analysis as part of a PopPK analysis and preliminary PopPK analysis showed that revumenib PK between the capsules, oral solution, and tablets were similar (Section 13.2.3.2 and Figure 8). Does the Agency agree that the current data and analysis are consistent with comparability of the formulations?

FDA Response to 3a:
Refer to FDA Response to Question 3 above.

Discussion: There was no discussion.

Question 3b: *Further, in vitro studies show that the capsule and tablet formulations dissolve rapidly in aqueous media (Section 13.2.1). The dose strengths of the capsule and tablet formulations are slightly different (eg, 113 mg capsules and 100 mg tablets); however, these small differences are unlikely to affect any assessment of PK, safety, or efficacy, and are therefore considered equivalent. Does the Agency agree with the equivalence of the capsule and tablet dose strengths?*

FDA Response to 3b:
The currently available data appears to support that revumenib PK is comparable between the capsule and tablet formulations.

Discussion: There was no discussion.

Question 3c: *Based on the corroborating results of the dedicated crossover sub-study and the preliminary data analysis showing similar PK of the capsule, tablet, and solution formulations, the Sponsor is not planning to include formulation as a covariate in the ER efficacy/safety model. Does the Agency agree?*

FDA Response to 3c:
The currently available data is not adequate to support that revumenib PK and safety is comparable among all the formulations used in clinical trials. Refer to FDA Response to Question 3 above for additional information to support the evaluation. We recommend that you conduct exploratory E-R efficacy/safety analysis using formulations as a covariate.

Discussion: There was no discussion.

Question 4: *The results from Study SNDX-5613-0700 have demonstrated that food has no effect on revumenib exposure. Does the Agency agree that the available food effect data is sufficient to recommend administering revumenib with or without food?*

FDA Response to Question 4:
No, available data are not adequate to support the administration of revumenib with or without food for the following reasons:

- You have not completed a food effect study for the planned commercial formulations (tablet (b) (4) with monocitrate monohydrate). For the planned food effect substudy with high fat meal in study SNDX-5613-0706, you should ensure that a sufficient number of patients will receive the planned commercial formulations.

- It is unclear if sufficient number of patients who received the commercial formulations have been included in the Population PK analysis. Also, if you plan to use PopPK analysis to support the lack of food effect, you should demonstrate that adequate information on the dose, timing of administration, timing of food intake and food composition, and PK sampling in the absorption phase is available to support the analysis.

Discussion: There was no discussion.

Question 5: *The Sponsor plans to evaluate the effect of renal impairment on the PK of revumenib by utilizing a PopPK analysis. Preliminary analysis concluded no effect of mild and moderate renal impairment on revumenib exposures. Does the Agency agree that the Sponsor's plan to characterize the effect of renal impairment on the PK of revumenib is adequate, and that no dedicated renal impairment study is required for the NDA?*

FDA Response to Question 5:
No, we do not agree. We have the following comments:

a. A dedicated renal impairment study may not be needed if renal excretion plays a minor role for the overall drug elimination, based on the mass balance study. However, the mass balance study has not been completed and the currently available data from the mass balance study are not adequate to characterize the elimination pathways of revumenib and its major metabolite. Refer to the Agency's response to Question 2.

b. If you plan to use PopPK analyses to characterize the impact of renal function on drug exposure, you should demonstrate that there is adequate representation of patients with varying degrees of renal function as well as sufficient data to support the PopPK analyses. However, there is no information about the number of patients with severe renal impairment or the quality of data in the PopPK analyses.

Note that PK characterization of revumenib in patients with severe renal impairment is required, as impaired renal function has also been associated with changes in the absorption, plasma protein binding, and/or tissue distribution of a drug and these changes can be particularly prominent in patients with severely impaired renal function. A reduced pharmacokinetic study design can be considered for evaluation in patients with severe renal impairment.

Discussion: There was no discussion.

Question 6: *The Sponsor plans to evaluate the effect of hepatic impairment on the PK of revumenib utilizing a PopPK analysis. Preliminary analysis concluded little or no effect of mild or moderate hepatic impairment on revumenib exposures. Does the Agency agree that the Sponsor's plan to characterize the effect of hepatic impairment on the PK of revumenib is adequate, and no dedicated hepatic impairment study is required for the NDA?*

FDA Response to Question 6:
A dedicated hepatic impairment study may not be needed if the Population PK analysis is considered adequate for determination of PK in patients with mild and moderate hepatic impairment at the NDA review.

However, PK characterization of revumenib in patient with severe hepatic impairment is required and a reduced pharmacokinetic study design can be considered.

Discussion: There was no discussion.

2.3. Safety

Question 7: *At the 90-day update, the Sponsor will submit additional safety data, using a 02 Oct 2023 data cutoff. Does the Agency agree with this proposed plan?*

FDA Response to Question 7:
We have no objection to your plan to submit a safety update report (SUR) with the 10/2/2023 cutoff date at 90 days after the submission of the NDA. We also have no objection to your plan to include updated datasets, updated tables, figures and listings (TFLs), and updated narratives from Studies SNDX-5613-0700, SNDX-5613-0705, SNDX-5613-0706, SNDX-5613-0702. We also agree that any new safety information from the expanded access protocols can be described in the SUR without adding the data to the datasets. Note, however, as indicated at the Type B meeting on 3/23/2023, the 90-Day SUR is a stand-alone document that should be submitted in the ISS folder of Module 5.3.5.3. Do not submit a new or revised Summary of Clinical Safety.

Discussion: There was no discussion.

2.4. CDx

Question 8: *The Sponsor plans to submit the NDA for revumenib using local site KMT2Ar testing for enrollment, with subsequent central confirmation of KMT2Ar status for efficacy eligibility in Study SNDX-5613-0700. Would the FDA approve revumenib on this basis and allow for a CDx Premarket Approval (PMA) submission after the NDA filing as a post-marketing commitment?*

FDA Response to Question 8:
No, we do not agree that local testing would be sufficient to confirm appropriate selection of the pivotal cohort for the purposes of labeling. Ideally, the efficacy analysis population is confirmed by the CDx or by a CTA bridged to the CDx. If you wish to propose to use the CTA-confirmed population for regulatory decision-making, include in the submission your justification for that proposal and identify the FDA-approved or -cleared assay used as the CTA. If the assay is not FDA-cleared or -approved for the matrices used for testing, provide the following information:

a. A statement of intended use.

b. The specific test method (including instruments, reagents, and specimen handling).

c. Confirmation that the lab has a process in place for reagent control.

d. A brief discussion of how the test method was validated analytically for each specimen type (marrow, peripheral blood, etc.).

e. A statement of the performance obtained for accuracy and analytical sensitivity.

Whether the CTA is adequate for regulatory purposes will be a review issue. We recommend also that you continue to work with your device collaborator to facilitate the PMA submissions according to the milestones that you described in the meeting package.

Discussion: There was no discussion.

2.5. Quality (Chemistry, Manufacturing and Controls)

Question 9: *Does the Agency agree* (b) (4)

FDA Response to Question 9:
Yes, based on the information you have provided, revising the acceptance criterion for

[redacted] (b) (4)
is acceptable.

Discussion: There was no discussion.

Question 10: *Due to delays in the drug substance PPQ campaign, the tablet* [redacted] (b) (4) *drug product PPQ batches and reports are now expected to be completed in May 2024. This could be late in the overall NDA review process. Accordingly, the Sponsor proposes the tablet* [redacted] (b) (4) *are used for commercial launch* [redacted] (b) (4) *Does the Agency agree that the tablet* [redacted] (b) (4)

FDA Response to Question 10:
Your proposal to use tablet [redacted] (b) (4) for commercial launch is not justified and therefore not acceptable. In most cases, the PPQ study needs to be completed successfully and a high degree of assurance in the process achieved before commercial distribution of a product. In special situations, the PPQ protocol can be designed to release a PPQ batch for distribution before complete execution of the protocol steps and activities, i.e., concurrent release. FDA expects that concurrent release will be used rarely. The Guidance for Industry, Process Validation: General Principles and Practices, provides clarity on concurrent release.

There is no correlation between PPQ batches and PAI's for non-sterile drug products. Pre-approval Inspections, if necessary, occur in parallel with the ongoing review of the application. Syndax is reminded that upon submission of the NDA all Drug Product and Drug Substance commercial manufacturing sites are required to be ready for inspection by FDA authorized investigators. Approval of the NDA requires continuing compliance of the sites in meeting cGMP criteria, and a pre-approval inspection may be required with a satisfactory outcome. To facilitate our inspectional process, we request that you clearly identify all manufacturing facilities on the Form FDA 356h associated with your application. Please see FDA Guidance Document Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers for more information on what facilities to include on the 356h form.

Discussion: There was no discussion.

ADDITIONAL CMC COMMENT

1. Refer to the ICH Q1A (R2) for section on selection of drug product stability batches. Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied

to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches, and the third one can be smaller if justified. Where possible, batches of the drug product should be manufactured by using different batches of the drug substance.

ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS

1. The type of KMT2A gene rearrangement may impact disease characteristics including prognosis and drug response. Include plans to examine the impact of KMT2A gene translocations with specific partners and KMT2A partial tandem duplications on the clinical efficacy of revumenib. Provide: 1) individual level datasets describing, at a minimum, the type of KMT2A gene translocation or tandem duplication, identity of fusion partner, and location of chromosomal breakpoints, and 2) analysis of key primary and secondary clinical efficacy endpoints based on KMT2A rearrangements.

2. The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "*Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format*" (available at: https://www.fda.gov/media/74346/download). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

3. Address the following questions in the Summary of Clinical Pharmacology:

    a. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
    b. What are the exposure-response relationships for efficacy, safety and biomarkers?
    c. What is the effect of revumenib and major metabolites on the QT/QTc interval?
    d. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
    e. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
    f. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

4. Apply the following advice in preparing the clinical pharmacology sections of the original submission:

    a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
    b. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.

    c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

        - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
        - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

5. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population. Refer to Guidance for Industry for population PK, exposure-response relationships, and pharmacometric data and models submission guidelines.

6. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.

7. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.

Discussion: There was no discussion.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  A multidiscipline pre-submission meeting was held on March 23, 2023, and additional advice regarding the proposed submission was provided in written response issued on May 19, 2023. The Agency refers the Sponsor to the minutes of those meetings for any additional agreements that may have been reached.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan.
  - It was concluded that a determination regarding the need for the REMS will be made during the review of the application.
  - There are no anticipated changes in the schedule of meetings specified under the Program for this NDA.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. It was agreed that the following minor application component may be submitted within 30 calendar days after the submission of the original application: A stability update is expected within 30 days of the application submission.

- No late submissions are anticipated other than the issues itemized in pre-submission meetings with the Sponsor.

  Prominently identify each submission containing your agreed-upon late component(s) with the following wording in bold capital letters at the top of the first page of the submission and the discipline name:

  NDA/BLA NUMBER: LATE COMPONENT - QUALITY

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new

indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[1]

[1] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov.

For further guidance on pediatric product development, please refer to FDA.gov.[2]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of

[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

reproductive potential.

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information, please visit FDA.gov.[5]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via

[5] http://www.fda.gov/ectd

the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[6]

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

[6] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[7] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[8]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[9]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to

[7] https://www.fda.gov/media/84223/download
[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[9] https://www.fda.gov/media/85061/download

participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[10]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[11]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

A copy of the Sponsor's response document is attached for reference.

18 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

[10] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[11] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DONNA PRZEPIORKA
10/24/2023 11:53:18 AM

IND 142693

MEETING REQUEST-
WRITTEN RESPONSES

Syndax Pharmaceuticals, Inc.
Attention: Allie Palazzi-Leahy
Senior Associate, Regulatory Affairs
35 Gatehouse Drive, Building D, Floor 3
Waltham, MA 02451

Dear Ms. Palazzi-Leahy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SNDX-5613.

We also refer to your March 24, 2023, correspondence containing a meeting request. The purpose of the requested meeting was to discuss and gain Agency agreement on the content and format of the proposed NDA for SNDX-5613.

Further reference is made to our Meeting Granted letter dated March 28, 2023, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your April 20, 2023, background package.

If you have any questions, contact Rachel McMullen, Senior Regulatory Project Manager, at 240-402-4574.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Clinical Team Lead
Division of Hematologic Malignancies I
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type:	B
Meeting Category:	Pre-NDA (content and format)
Application Number:	IND 142693
Product Name:	SNDX-5613
Indication:	Treatment of adult and pediatric patients with relapsed or refractory acute leukemias harboring a KMT2A rearrangement.
Sponsor Name:	Syndax Pharmaceuticals, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

SNDX-5613 is a small molecule inhibitor of the menin-MLL1 interaction. Syndax Pharmaceuticals, Inc., (Sponsor) is developing SNDX-5613 for the treatment of relapsed or refractory leukemias harboring a KMT2Ar or mNPM1 mutation. On April 20, 2020, SNDX-5613 was granted Orphan Drug Designation for the treatment of acute myeloid leukemia. Fast Track Designation was granted on June 24, 2021, for the investigation of SNDX-5613 for the treatment of adult and pediatric patients with relapsed or refractory acute leukemias harboring a KMT2Ar or NPM1 mutation. Breakthrough Designation for the treatment of adult and pediatric patients with relapsed or refractory acute leukemia harboring a KMT2A rearrangement was granted on November 30, 2022.

The Agency has provided guidance on the clinical development program in ten meetings or written responses only. Additionally, the clinical development program was also discussed at the June 18, 2020, meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee.

On March 24, 2023, Syndax requested a Type B meeting to discuss and obtain Agency feedback on the content and format of the proposed NDA for SNDX-5613. A pre-NDA meeting is anticipated in Fall 2023.

2.0 SPONSOR QUESTIONS AND FDA RESPONSES

Question 1 (Analysis of Prolonged Thrombocytopenia and Neutropenia)

The potential risk of prolonged neutropenia and thrombocytopenia will be analyzed in patients enrolled in Study SNDX-5613-0700 and presented in Module 2.7.4. Does the

Agency agree with the Sponsor's approach for analyses and presentation of prolonged thrombocytopenia and neutropenia observed in Study SNDX-5613-0700?

FDA Response to Question 1: Although we have no objection to the approach you propose to take, we have the following comments to ensure that the information submitted is reviewable:

a. In general, prolonged thrombocytopenia and neutropenia are concerns with myelosuppressive therapies, such as cytotoxic drugs, but we do acknowledge that targeted agents may cause periods of cytopenia. However, given that you have not previously characterized the incidence, time to onset, duration, interventions, and dose-relationships for cytopenias due to SNDX-5613, nor discussed a potential mechanism, we can provide only general advice to answer your question. We recommend that you provide more details about the characterization of cytopenias at the pre-NDA meeting.

b. A listing of results would not be reviewable. We recommend that you plan to submit the information from Table 2 in xpt format instead.

c. To ensure that you capture cases with elimination of blasts but continued cytopenia that may be due to SNDX-5613, we recommend that you include all patients who achieved at least MLFS in the analyses.

d. For unscheduled visits, the cycle number and cycle day will be needed for the analysis. Include in Table 2 the date, cycle number, and cycle day for each event listed.

Question 2 (Proposed BIMO Plan)
As per the Center for Drug Evaluation and Research's (CDER's) Guidance for Industry, "Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications: Revision 7" (Feb 2020), the FDA Draft Guidance for Industry, "Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions" (Feb 2018), and the "Bioresearch Monitoring Technical Conformance Guide" (Aug 2022), the Sponsor proposes the following plan for the content of the BIMO section of the NDA. Is the proposed plan acceptable?

FDA Response to Question 2: Your proposal appears acceptable.

Question 3 (Proposed Expedited Review Timeline)
Revumenib has received Breakthrough Therapy Designation (BTD) and is therefore eligible for rolling submission and priority review. The Sponsor also intends to apply for Real-Time Oncology Review (RTOR) upon receipt of topline results from

Study SNDX-5613-0700. Does the Agency agree that the general timing and approach proposed in the briefing package would be acceptable, if either RTOR or a rolling submission is granted?

FDA Response to Question 3: You propose to submit 3 portions (nonclinical module, CMC module, and remainder of the NDA) serially. This schedule would be consistent with a plan for rolling review. If you wish to proceed with rolling review, please submit to the IND a request for rolling review with the proposed schedule.

RTOR allows for submission of parts of a module and is used most frequently to submit the cleaned and locked study datasets early for review while the sponsor is writing the clinical study reports using those datasets. If you will have cleaned and locked datasets available prior to December 2023, we recommend that you consider requesting participation in the RTOR program.[1]

Question 4 (Table of Contents):
Does the Agency agree that the Sponsor's plan for the electronic Common Technical Document (eCTD) format of the submission as detailed in the proposed Table of Contents constitutes a complete marketing application for the proposed indication?

FDA Response to Question 4: No. We have the following comments about the table of contents for the tablets NDA:

a. Include a letter of authorization for review of IND 142693.
b. Include in Module 1.6 a copy of all IND meeting correspondence relevant to the development program for the proposed indication.
c. Ensure that Module 1.7 includes all correspondence regarding the Fast Track and Breakthrough Therapy Designations.
d. Include the iPSP in Module 1.9.1.
e. Include in Module 1.12 copies of all other IND correspondence relevant to the development program for the proposed indication.
f. Include a copy of the draft USPI in Word in Module 1.14.1.3.
g. Include a proprietary name request.
h. You may include reports of biomarkers, variant allele frequency, minimal residual disease, etc., in the study report body subfolder in Module 5.3.2.3.
i. We request that you include the study folders for SNDX-5613-0702 and SNDX-5613-0707 in Module 5.3.5 Reports of Efficacy and Safety Studies [Acute Leukemia] in addition to the study folder for SNDX-5613-0700.
j. We would have no objection to grouping the single-patient protocols in one substudy folder in this Module as you have done in the IND.
k. Ensure that there is a mapping document for the ISE in Module 5.3.5.3.

[1] [1] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program

(b) (4)

Question 5 (Proposed Presentation of Drug Substance Information)
The Sponsor intends to submit (b) (4) *revumenib tablets,* (b) (4) *Does the Agency agree with the Sponsor's plan to submit a full Module 2.3 and 3.2.S in the revumenib tablet NDA (1)* (b) (4) *(2) NDA Module 3.2.S? Full revumenib drug product sections will be provided for tablets* (b) (4)

FDA Response to Question 5: Yes, we agree. (b) (4)

Your proposal to submit full SNDX-5613 drug product sections for tablets (b) (4) is acceptable.

Question 6 (Primary Endpoint Data Presentation)
Does the Agency agree with the Sponsor's proposed presentation of the disease response and duration of response (DOR) data and supporting variables for these efficacy endpoints in the NDA?

FDA Response to Question 6: We have the following comments:

a. We have no objection to conducting the primary analysis and sensitivity analyses using the investigator-reported responses. Note, however, that FDA will use the raw data to assess response, and the adjudicated outcome will be used for labeling.

b. There is insufficient information to confirm the acceptability of the endpoint definitions. We recommend that you review prior correspondence regarding estimands.

c. Whether the proposed window of -7 to +15 days between the marrow sampling and the CBC is acceptable will be a review issue.

Question 7 (Format of the Clinical Datasets)
Does the Agency agree with the Sponsor's plan regarding format of the clinical datasets?

FDA Response to Question 7: Yes, the proposed specifications for the clinical dataset as listed in Table 6 are acceptable.

Question 8 (Composition of Annotated Case Report Form [CRF] Supporting Clinical Datasets)

Does the Agency agree with the Sponsor's plan to append the Phase 1 and Phase 2 annotated CRFs to generate one set of Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets for Study SNDX-5613-0700 that has two separate databases for the Phase 1 and Phase 2 parts of the study?

FDA Response to Question 8: We acknowledge that you utilized different CRFs for the Phase 1 and Phase 2 portions of SNDX-5613-0700, and we have no objection to your plan to submit both CRFs with annotations in a single document. Ensure that the document is searchable and has adequate bookmarks to navigate within each CRF individually.

FDA notes that the use of different CRFs may result in inconsistencies which impact interpretation and/or creation of a single dataset which integrates information across the two parts of the trial. FDA recommends the define file explicitly note entries in the datasets that are affected by differences between the CRFs. This may include but is not limited to data elements captured in one CRF but not another and data elements which are captured differently in one CRF vs another. We recommend that for the ADaM dataset, such discrepancies should be resolved in the derivation of the analysis variables rather than being carried over from the SDTM dataset.

Question 9 (Proposed Drug Product Bridging Plan)

Does the Agency agree with the Sponsor's plan for bridging (b) (4)

FDA Response to Question 9: Your proposed plan for bridging (b) (4) appears reasonable. In the NDA submission, provide a head-to-head qualitative and quantitative comparison table (b) (4) and justifications to support that the difference (e.g., pH) should not impact drug disposition. In relevant clinical datasets with dosing records (such as EX, ADEX, and datafiles for population PK analyses), clearly specify which formulation(s) was administered to each patient in each phase of each clinical study. Explain in the Reviewer's Guide how this was accomplished. The final determination of the adequacy of the bridging plan will be made during the NDA review.

If the relative bioavailability study shows that the SNDX-5613 tablets are not equivalent to the capsules or if the population PK results conclude the formulation as a significant covariate, it may impact the selection of the therapeutic dosages and interpretation of the benefit-risk profile for the to-be-market formulations. Therefore, both exposure-efficacy and exposure-safety analysis need to be updated by the time of NDA submission. In addition, an updated exposure-response analysis provided as part of the 90-Day Safety Update may trigger a major amendment of the proposed NDA depending on the content and magnitude of the updated exposure-response analysis.

Question 10 (Structure and Format of Drug Product Submissions)
The Sponsor intends to submit 1 executed batch record for each revumenib drug product tablet strength (25, 110, and 160 mg free base equivalents) (b) (4) *with the NDA. Does the Agency agree with the proposed approach for submission of drug product batch records in the NDA?*

FDA Response to Question 10: The approach for submission of drug product batch records in the NDA is acceptable; however, include a summary of batch records for additional batches manufactured. Note that FDA may request additional batch records during the NDA review.

Question 11 (Renal/Hepatic Impairment Study[ies])
Depending on the ongoing AME study (Study SNDX-5613-0705) results, a dedicated renal and/or hepatic impairment study(ies) are planned to be conducted after the initial NDA submission. Does the Agency agree with this approach?

FDA Response to Question 11: Provide rationale and a summary with supporting data from the nonclinical studies and Study SNDX-5613-0705 at a future pre-NDA meeting to support discussions on the need and timing of a dedicated renal or hepatic impairment study. In general, we recommend that a dedicated renal or hepatic impairment study is conducted before NDA submission to support dosing recommendations in specific populations.

3.0 OTHER IMPORTANT MEETING INFORMATION

RACE AND ETHNICITY DIVERSITY PLANS

Refer to FDA Draft Guidance "***Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials- Guidance for Industry***" at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve- enrollment-participants-underrepresented-racial-and-ethnic-populations, for recommendations on the approach to develop and submit a Race and Ethnicity Diversity Plan to enroll representative numbers of participants from underrepresented racial and ethnic populations in the United States, in clinical trials during the development of your product. The Diversity Plan should be developed and discussed with FDA early in clinical development, preferably before initiation of any trials intended to support registration.

Although this draft Guidance specifically focusses on race and ethnicity Diversity Plans for the enrollment of members of racial and ethnic populations that have historically been underrepresented in clinical trials, FDA encourages sponsors to consider

expanding the Diversity Plan to also account for other underrepresented populations (e.g., based on other demographic characteristics such as sex, age, gender, etc.).

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*. For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating, "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov.

For further guidance on pediatric product development, please refer to FDA.gov.[3]

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information, please visit FDA.gov.[4]

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[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] http://www.fda.gov/ectd

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification document *Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[5]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[6]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[7] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before

[5] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[6] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.3 eCTD Sample Submission pg. 44) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission. Additional information can be found at FDA.gov.[8]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[9].

[8] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[9] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[10]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[11]

[10] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[11] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DONNA PRZEPIORKA
05/19/2023 05:07:28 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	**IND 142693**
Request Receipt Date	October 7, 2022
Product	SNDX-5613 (revumenib)
Indication	Treatment of adult and pediatric patients with relapsed or refractory acute leukemia harboring a *KMT2A* rearrangement
Drug Class/Mechanism of Action	Small molecule/menin inhibitor
Sponsor	Syndax Pharmaceuticals, Inc
ODE/Division	OOD/DHM1
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	December 6, 2022

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and*** *will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**
   Treatment of adult and pediatric patients with relapsed or refractory acute leukemia harboring a KMT2A rearrangement

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

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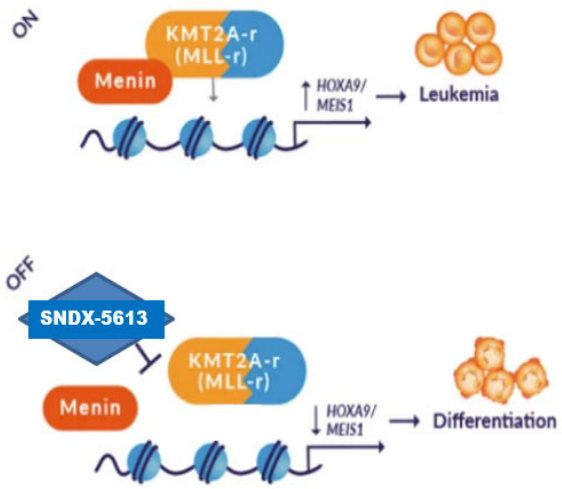
[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

<u>Section II:</u> If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history.

SNDX-5613 is a small molecule that inhibits the binding of menin to wild-type KMT2A and KMT2A fusion proteins (Figure 1). KMT2A (also known as MLL1) is a histone methyltransferase that acts as a transcriptional coactivator with menin. KMT2A rearrangements (KMT2Ar) produce oncogenic fusion proteins that, when combined with menin, bind to DNA and cause transcriptional deregulation of target genes, most notably the homeobox cluster HOXA genes and their cofactor MEIS1, which are key mediators of leukemogenesis, proliferation, and self-renewal.

Figure 1. Targeting menin-KMT2Ar interactions[3]



SNDX-5613 disrupts the interaction between the KMT2A fusion protein and menin, repressing expression of the critical oncogenes that drive proliferation and survival of leukemic cells. In vitro exposure to SNDX-5613 reduced the proliferation of KMT2Ar+ acute leukemia cells lines, and in vivo treatment reduced tumor burden in KMT2Ar+ acute leukemia xenograft models.[4]

KMT2Ar is a leukemogenesis driver mutation in multipotent progenitors.[5] 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 leukaemia (MPAL), depending on fusion partner and clonal epigenetic changes.[6,7,8] Relapse with a lineage switch may occur.[7,9] KMT2Ar acute leukemia accounts for > 70% of infant ALL, 35-50% of infant AML, and 10% of acute leukemias in older children and adults.[10] KMT2A is a adverse prognostic factor for acute leukemias, with 5-yr OS 35-50%.[10,11,12]

SNDX-5613 was granted Orphan Drug Designation on 4/20/2020 for treatment of acute myeloid leukemia, and Fast Track Designation on 6/24/2021 for treatment of adult and pediatric patients with relapsed or refractory acute leukemias harboring a KMT2A gene rearrangement (KMT2Ar) or nucleophosmin 1 (NPM1) mutation.

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[3] Adapted from https://www.onclive.com/view/mll-fusion-proteins-emerge-as-a-promising-target-in-aml
[4] Fiskus W et al. Effective Menin inhibitor-based combinations against AML with MLL rearrangement or NPM1 mutation (NPM1c). Blood Cancer J. 2022;12:5.
[5] Armstrong SA et al. MLL translocations specify a distinct gene expression profile that distinguishes a unique leukemia. Nat Genet 2002;30:41.
[6] 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.
[7] Iacobucci I et al. KMT2A-rearranged leukemia: the shapeshifter. Blood 2022;140:1833.
[8] Tertakasuma R et al. Epigenetic regulator genes direct lineage switching in MLL/AF4 leukemia. Blood 2022;140:1875.
[9] Liao W et al. Does lineage plasticity enable escape from CAR-T cell therapy? Lessons from MLL-r leukemia. Exp Hematol 2021;100:1.
[10] Winters AC et al. MLL-rearranged leukemias-An update on science and clinical approaches. Front Pediatr 2017;5:4.
[11] Issa GC et al. Predictors of outcomes in adults with acute myeloid leukemia and KMT2A rearrangements. Blood Cancer J 2021:11:162.
[12] Richard-Carpenter G. et al. Outcome of acute lymphoblastic leukemia with KMT2A (MLL) rearrangement: the MD Anderson experience. Blood Adv. 2021;5:5415.

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The efficacy endpoints presented by the sponsor were complete remission (CR), CR with partial hematologic recovery (CRh), and duration of remission (DOR), defined as the time from the date of first documented CR or CRh to the first documented relapse or death. These endpoints were prespecified to address an exploratory objective of the Phase 1 portion of the study to evaluate the efficacy of SNDX-5613.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.

For treatments of AML, overall survival (OS) and event-free survival (EFS) are endpoints considered direct measures of clinical benefits and have been used for regular approval. Durable CR is considered reasonably likely to predict long-term clinical benefit. CR+CRh with durability has been used for regular approval in the palliative setting for drugs that are nonmyelosuppressive and reasonably nontoxic.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

The Division would also consider a minimal residual disease-based endpoint such as "MRD-negative CR" as reasonably likely to predict clinical benefit when the assay used is analytically valid and the level of MRD used to define "negative" is justified.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.

There are no approved drugs targeting the KMT2Ar. The standard of care for treatment of relapse or refractory (R/R) acute leukemias with or without KMT2Ar is intensive cytotoxic chemotherapy followed by allogeneic hematopoietic stem cell transplantation; median survival of patients with R/R KMT2Ar acute leukemia is less than 1 year, and 5-year OS is less than 10%.[11,12] There are no prospective trials for treatment of R/R KMT2Ar 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 KMT2Ar AML treated at MD Anderson Cancer Center between January 1990 and December 2019, Issa et al reported CR in 66% after 1st line therapy, 34% after 2nd line therapy, and 5% after 3rd or later line of therapy.[11]

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[13].

There are no drugs for treatment of KMT2Ar + acute leukemias that have been considered for Breakthrough Therapy Designation.

[13] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR

The BTDR is based on the preliminary results from Study SNDX-5613-0700 "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" (Table 1).

Study SNDX-5613-0700 is on-going. Only Arms A and B have completed accrual. The analysis cohort for this BTDR was limited to patients in Arms A and B who have a KMT2A rearrangement and were treated with SNDX-5613 226 mg or 276 mg in Arm A or with 113 mg or 163 mg in Arm B (doses giving exposures consistent with the RP2D).

Table 1: Study SNDX-5613-0700

DESIGN		
Design	Open-label, single-arm, multiple cohort, dose-escalation/dose-expansion first-in-human study of SNDX-5613 as monotherapy	
Eligible population	Adult and pediatric patients at least 30 days old who have a relapsed or refractory acute leukemia with a KMT2A gene rearrangement or an NPM1c gene mutation.	
Treatment schedule	Oral SNDX-5613 (capsule) every 12 hour in 28-day cycles until progression or unacceptable toxicity	
Cohorts	Phase 1 ARM A: No strong CYP3A4 inhibitor/inducers or fluconazole ARM B: With strong CYP3A4 inhibitors ARM C: With cobicistat ARM D: With fluconazole ARM E: SNDX-5613 TID schedule ARM F: With isavuconazole Phase 2 COHORT 2A: Patients with MLLr ALL or MPAL COHORT 2B: Patients with MLLr AML. COHORT 2C: Patients with NPM1c AML	
Sample size	Phase 1 - Up to 30 subjects in each arm Phase 2 - Up to 84 subjects in each cohort (64 adult and 20 pediatric)	
Primary efficacy endpoint	CR+CRh	
Efficacy analysis plan	A single proportion binomial test with at least 90% power and 1-sided significance level of 2.5% to exclude CR+CRh rate of 10%.	
SUBJECTS		
Number of subjects enrolled	Overall study enrollment not stated Enrolled in Arms A or B: n=68 Enrolled in Arms A or B, has KMT2A rearrangement, and treated with SNDX-5613 dose at the target exposure: n=37	
Subject characteristics	**Demographics**	**Disease characteristics**
	Median age 34 yrs (range, 0.8-79) Male/Female 35% / 65% Race White 60% Black 14% Asian 11% Other 15%	AML/ALL/MPAL 78%/22%/0 Primary refractory 11% Relapse refractory/untreated 62% / 27% Median prior therapies 3 (range, 1-9) Prior HSCT 57%

Table 1: Study SNDX-5613-0700

RESULTS	
CR rate **(95% CI)**	5/37 (14%) (5, 29)
CR+CRh rate **(95% CI)**	10/37 (27%) (14, 44)
DOR (CR/CRh) **Median** **95% CI** **Range**	 7.0 months 1.9, NR 0.03, 14.16

The CR+CRh rate of 27% with the 95% CI excluding rates less than 14%, in addition to the median duration of responses being 7 months, was considered preliminary evidence of activity of SNDX-5613 for treatment of R/R KMT2A acute leukemia.

b. Include any additional relevant information. Consider the following in your response:

Subgroup Analyses

Table 2: Subgroup Analysis of CR/CRh of Pooled Analysis Population

Subgroup	**N**	**CR/CRh**	
		n	**% (95% CI)**
All	**37**	**10**	**27% (14, 44)**
Age Group[a]			
>= 18 years	29		31% (15, 51)
< 18 years	8		13% (0.3, 53)
Diagnosis[a]			
AML	29		31% (15, 51)
ALL	8		13% (0.3, 53)
Disease Status at Study Baseline[b]			
Primary refractory	4	1	25% (1, 81)
Refractory relapse	23	5	22% (7, 44)
Untreated early first relapse	7	1	14% (0, 58)
Untreated late first relapse	1	1	100% (3, 100)
Untreated second or greater relapse	2	2	100% (16, 100)
Line of Therapy[b]			
2	6	1	17% (0, 64)
3	8	3	38% (9, 76)
4	23	6	26% (10, 48)

[a] Provided by sponsor
[b] Calculated by reviewer

The study population was heterogeneous with regard to age and various disease characteristics. Responses were observed across all subgroups assessed. The estimate of the CR/CRh rate was not quantatitively consistent across subgroups, but the samples sizes were quite small, and the 95% CI was wide.

Comparison to Available Therapy

The current standard of care for treatment of R/R KMT2Ar acute leukemia is conventional cytotoxic chemotherapy. There are no clinical trials of conventional therapy for treatment of R/R KMT2Ar acute leukemia specifically; additionally, no trials of chemotherapy for R/R acute leukemia in general provided outcomes by specific mutation that would allow for a reliable estimate of response for the KMT2Ar subpopulation. The Division chose to use the retrospective analysis published by Issa et al[11] for the efficacy benchmark. It should be noted that the population in this publication was limited to patients with the AML phenotype, while those treated with SNDX-5613 included both the AML and ALL phenotypes. Use of the publication was considered acceptable, since phenotype is not a known prognostic factor for R/R KMT2Ar acute leukemia, and as shown in the subgroup analysis in Table 2 above, the CR/CRh rate was lower in patients with the ALL phenotype than with the AML phenotype, so the comparison would disavantage the SNDX-5613 clinical trial.

Since SNDX-5613 is not a myelosuppressive drug, the Division could use CR+CRh as the endpoint to assess its clinical activity as a palliative agent; for such drugs, achievement of CR or CRh has been associated with transfusion independence and reduced risks of infection and bleeding while on active treatment. Given that treatment with cytotoxic chemotherapy induces the need for transfusions and increases the risks of infection and bleeding, the palliative benefit of the CRh component of the endpoint would not apply to cytotoxic chemotherapy, so CR is used as the measure of benefit needed to outweigh the toxicities instead. The differences in the applicable endpoints complicates comparisons.

Disease status at baseline is a major prognostic indicator, but due to the retrospective nature of the study, Issa et al[11] used lines of therapy rather than disease status. As Issa et al[11] found differences in outcomes by line of therapy, the evaluation of the activity of SNDX-5613 took line of therapy into account as well (Table 3). For patients treated with SNDX-5613 as 3rd or later line of therapy, the 95% CI for CR+CRh (14-48%) excluded the CR rate with salvage chemotherapy, the CR rate (16%) was numerically higher than with salvage chemotherpay, and the 95% CI rate for CR (5-34%) bordered on excluding the CR rate with salvage chemotherapy. The Division concluded that the results with SNDX-5613 in this subgroup were better than with available therapy. For the patients treated with SNDX-5613 as 2nd line therapy, the point estimates for SNDX-5613 did not exceed those for salvage chemotherapy, but the numbers of patients were small and the 95% CIs were wide, so a detriment in this subgroup could not be concluded.

Table 3: Comparison of SNDX-5613 to Available Therapy for R/R KMT2Ar AML

	2nd Line Treatment		3rd or later Line Treatment	
Response	**SNDX-5613[a]**	**Salvage Chemotherapy[11]**	**SNDX-5613[a]**	**Salvage Chemotherapy[11]**
N	6	91	31	217
CR	0	31 (34%)	5 (16%)	11 (5%)
(95% CI)	(0, 46)		(5, 34)	
CR + CRh	1 (17%)		9 (29%)	
(95% CI)	(0, 64)		(14, 48)	

[a] Includes 8 patients with ALL

Pharmacodynamic Markers

The pharmacodynamic effects of SNDX-5613 on gene expression changes were assessed by RNA-sequencing of bone marrow aspirate samples collected at Screening and at Cycle 2 Day 1 from 21 subjects treated at various dosages across all Arms in Study SNDX-5613-0700. The sponsor showed a down-

regulation of the leukemogenic target genes MEIS1, HOXA9, PBX3, CDK6, FLT3, and RUNX1, the gene expression changes were similar across subjects with AML, ALL, or MPAL, and the changes in gene expression to date were observed independent of clinical response.

Safety Data

The sponsor did not comment on fatal adverse events, but the Division is aware of fatal cases of differentiation syndrome on Study SNDX-5613-0700. The sponsor reported that 26 (38.2%) subjects had adverse events resulting in treatment interruption, 12 (17.6%) had adverse events resulting in dose reduction, and 8 (11.8%) had adverse events resulting in treatment disconinuation.

Adverse events occurring in > 25% were QTc prolongation, nausea, vomiting, febrile neutropenia, diarrhea, increased ALT, and Grades 3-5 adverse events occurring in >5% were febrile neutropenia, QT prolongation, fatigue, and back pain (Table 3). Assuming the febrile neutropenia is related to the underlying leukemia, SNDX-5613 appeared to be less toxic than would be expected for intensive salvage chemotherapy.

Table 3: Common adverse events (≥ 15%) in study SNDX-5613-0700 using monotherapy SNDX-5613.

Preferred Term	All-grade (AE) (N = 68) n (%)	Grade 3 - 5 AE (N = 68) n (%)
Electrocardiogram QT prolonged	38 (55.9)	10 (14.7)
Nausea	34 (50.0)	0
Vomiting	27 (39.7)	1 (1.5)
Febrile neutropenia	21 (30.9)	21 (30.9)
Diarrhoea	20 (29.4)	3 (4.4)
Fatigue	18 (26.5)	4 (5.9)
Alanine aminotransferase increased	17 (25.0)	2 (2.9)
Headache	16 (23.5)	0
Hyperphosphataemia	15 (22.1)	0
Hypokalaemia	15 (22.1)	3 (4.4)
Hyponatraemia	15 (22.1)	1 (1.5)
Epistaxis	14 (20.6)	0
Peripheral edema	14 (20.6)	0
Back pain	13 (19.1)	4 (5.9)
Blood creatinine increased	13 (19.1)	0
Constipation	13 (19.1)	0
Aspartate aminotransferase increased	12 (17.6)	2 (2.9)
Decreased appetite	12 (17.6)	2 (2.9)
Pyrexia	12 (17.6)	2 (2.9)
Cough	11 (16.2)	0
Dyspnea	11 (16.2)	1 (1.5)
Differentiation syndrome	11 (16.2)	0

QTc prolongation and differentiation syndrome (DS) were two adverse events of special interest (AESI). The incidences of these AESI are reported above. The sponsor reported serious adverse events (SAEs) that they considered related to treatment in 3 (4%) subjects for QTc prolongation and in 2 (3%) subjects for DS; the number of treatment-emergent adverse events of these types was not reported. Additionally, QTc prolongation resulted in dose interruption for 12% and in dose reduction for 18%; the sponsor did not comment on the number of withdrawals due to QTc prolongation.

12. Division's recommendation and rationale (pre-MPC review):

☒ **GRANT:**
DHM1 recommends that SNDX-5613 monotherapy be granted Breakthrough Therapy Designation for the treatment of relapsed and refractory KMT2Ar acute leukemia. There is currently no approved targeted therapy for KMT2Ar acute leukemia and available cytotoxic chemotherapy results in low remission rates and overall survival less than 3 months. The results of Study SDNX-5613 showing a CR+CRh rate of 27% with the 95% CI excluding rates less than 14%, in addition to the median duration of responses being 7 months, are preliminary clinical evidence of a substantial improvement over available therapy. Additionally, the safety profile of SNDX-5613 is favorable in comparison to that expected for this population when treated with cytotoxic chemotherapy; adverse events of special interest of SNDX-5613 were QTc prolongation and differentiation syndrome could be managed with dose interruption and/or dose reduction.

☐ **DENY** Provide brief summary of rationale for denial:

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The sponsor proposes to use the results of the single-arm trial to support a marketing application. They expect the top-line results in 2023Q3, and they project submission of the NDA 2023Q4 or 2024Q1. The current study incorporates assessments of QTc effects, drug-drug interactions, food effects, and changes in formulation, including a pediatric formulation. A meeting with CDRH is projected for 2023Q1 to discuss the companion diagnostic currently under development. An expanded access protocol is currently in development.

Since receipt of the IND in 2019, the Division has provided advice to the sponsor in 10 formal meetings, teleconferences, or Written Responses Only. The Division will continue to encourage the sponsor to pursue studies of combination regimens in order to maximize the potential of SNDX-5613.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation.

14. List references, if any:

See footnotes

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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