FDA Briefing Document

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)

June 17 and 18, 2020

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office.

We have brought the following issues to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package will not include issues relevant to any final regulatory recommendation. It is intended to focus on issues identified by the Agency for discussion by the Advisory Committee.

Information will be presented to gauge investigator and sponsor interest in exploring potential pediatric development plans for products in early stages of development for cancer indications. The subcommittee will consider and discuss issues concerning possible diseases to be studied, patient populations to be included, and possible study designs in the development of these products for pediatric use. The discussion will also provide information to the Agency pertinent to the formulation of Written Requests for pediatric studies, if appropriate. The products under consideration are for June 17, 2020 are: (1) SP 2577, presentation by Salarius Pharmaceuticals, Inc.; Pharmaceuticals, Inc.; and (2) Marizomib, presentation by Celgene International II Sàrl, a wholly owned subsidiary of Bristol-Myers Squibb. The products under consideration for June 18, 2020 are: (1) CD30.CAR-T, presentation by Tessa Therapeutics and (2) SNDX-5613, presentation by Syndax.

The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

Memorandum

Date: May 22, 2020

To: Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) Members, Consultants, and Guests

From: Gregory Reaman, MD
Associate Director Pediatric Oncology
Oncology Center of Excellence, Office of the Commissioner
Associate Director Pediatric Oncology,
OOD, OND, CDER, FDA

Subject: FDA Background Package for June 17 and 18, 2020 Meeting

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Thank you for agreeing to participate in the upcoming Pediatric Oncology Subcommittee of the ODAC. The Subcommittee will hear about pediatric development plans for four products that are under development for one or more oncology indications. We believe that this focused discussion will utilize the expertise of the Pediatric Oncology Subcommittee in guiding the Agency's decisions related to the issuance of Written Requests in accordance with current legislative initiatives enacted to accelerate drug development in the pediatric population. The Subcommittee will consider and discuss issues relating to the development of these products for potential pediatric use and provide guidance to facilitate the formulation of Written Requests for pediatric studies, when appropriate. The products under consideration for June 17, 2020 are: (1) SP 2577, presentation by Salarius Pharmaceuticals, Inc.; Pharmaceuticals, Inc.; and (2) Marizomib, presentation by Celgene International II Sàrl, a wholly owned subsidiary of Bristol-Myers Squibb. The products under consideration for June 18, 2020 are: (1) CD30.CAR-T, presentation by Tessa Therapeutics and (2) SNDX-5613, presentation by Syndax.

As always, we appreciate your time and commitment and look forward to an informative meeting on June 17 and 18, 2020.

REFERENCE:

1. **Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)**: Title V – Pediatric Drugs and Devices (pages 47-58).

   FDASIA legislation is available at: http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf

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Pediatric Legislative Initiatives

Pediatric legislation that provides a combination of incentives and requirements, has significantly increased pediatric drug research and development and led to a substantial increase in products with new pediatric information in labeling.

Relevant pediatric legislative initiatives are listed below:

- 1997 The Pediatric Exclusivity provision - created in the Food and Drug Administration Modernization Act (FDAMA)
- 2002 Best Pharmaceuticals for Children Act (BPCA) – reauthorization of the Pediatric Exclusivity provision
- 2003 The Pediatric Research Equity Act (PREA) - a requirement which allows the FDA to require pediatric studies in drugs and biologics for certain applications
- 2007 Re-authorization of BPCA and PREA in the Food and Drug Administration Amendments Act (FDAAA)
- 2010 The Biologics Price Competition and Innovation Act of 2009 (BPCI) was included in the Patient Protection and Affordable Care Act – created a framework for the approval of follow-on biologics and made biologics, including follow-on biologics, eligible for Pediatric Exclusivity through amendment of section 351 of the Public Health Services Act. BPCI sunsets in March 2015
- 2012 BPCA and PREA made permanent in the Food and Drug Administration Safety and Innovation Act (FDASIA)
- 2017 Title V of the Food and Drug Administration Reauthorization Act (FDARA) (FD&C Act Sec. 505B (a)(3), 21 USC 355c (a)(3), Public Law 115-52) RACE for Children Act

Each one of these pediatric milestones has expanded and improved consistency and transparency of the pediatric information available for product use. For example, FDAAA requires that study data, both positive and negative, conducted under BPCA and PREA be described in product labeling. Also, a labeling statement of the FDA's determination whether or not the studies demonstrate safety or efficacy or if the studies were inconclusive in pediatric populations must also be included. Another important milestone with the recent passage of FDASIA was the permanent reauthorization of BPCA and PREA. Other important changes to pediatric drug development were included in this legislation. One such change was the requirement for sponsors to submit more detailed plans to perform pediatric studies earlier during drug development. Traditionally, sponsors were not required to provide plans for pediatric studies until relatively late the development of a product. FDASIA now requires that sponsors submit plans for pediatric drug development earlier during the development of the product (i.e., at the end of phase 2). The intent of this legislation is to promote earlier development of products for pediatric use.

Best Pharmaceuticals for Children Act

The intent of BPCA is to provide an incentive to drug developers to perform pediatric studies in order to improve the efficacy and safety data available for products used in children and infants. This incentive allows sponsors to qualify for an additional six months of marketing exclusivity for the entire moiety (molecule responsible for the pharmacological action of the drug), if specific studies addressing relevant pediatric indications are completed and submitted to FDA. A Written Request is a document issued by the FDA which outlines the type of studies to be conducted, study design and objectives, and the age groups to be studied. Because the pediatric exclusivity provision is voluntary, the sponsor may decline a Written Request. Thus, FDA has the ability to request that the sponsor perform pediatric studies under a Written Request that can lead to additional marketing exclusivity for the product.

This process can be initiated by either the sponsor or the FDA. A sponsor may submit a Proposed Pediatric Study Request to the FDA to conduct pediatric studies. If the FDA determines there is a public health need, the Agency may issue a Written Request for pediatric studies. These studies may or may not include the studies proposed by the sponsor. FDA may issue a Written Request on its own initiative when it identifies a need for pediatric data.

Of note, prior to 2010, the Written Request process only applied to drugs, and not to biological products. However, under BPCI, biological products became eligible for additional marketing exclusivity through the Written Request process.

Currently, BPCA and the Written Request Process is the only legislative initiative relevant to the pediatric oncology population. Therefore, we attempt to maximize regulatory authority through BPCA to accelerate the development of potentially effective new therapies for children with cancer.

June 17, 2020: First Session

PRODUCT: SP 2577
COMPANY: Salarius Pharmaceuticals, Inc.

I. Regulatory history

Ewing sarcoma is characterized by the fusion protein EWSR1/FLI1 which acts as a driver for tumor development. Developing treatments to directly target EWS-FLI transcriptional activity have been difficult making transcriptional co-regulators of EWS/FLI, which modulate gene expression, a more viable target. SP-2577 is a selective and reversible lysine-specific histone demethylase 1A (LSD1) inhibitor. LSD1 is required for EWS/FLI mediated oncogenesis and inhibition of this target may prevent EWS/FLI transcriptional activity. LSD1 inhibitors have been shown to deplete LSD1 stability, reverse gene expression patterns, and reduce tumor cell viability. Ewing sarcoma, like other sarcomas, exhibit some of the highest LSD1 protein expression levels out of any cancers. In addition, over-expression of LSD1 has been demonstrated in synovial sarcomas, rhabdomyosarcomas, desmoplastic small round cell tumors, chondrosarcoma, osteosarcoma, and malignant peripheral nerve sheath tumors, as well as hematologic malignancies including acute myeloid leukemia and myelodysplastic syndrome.

LSD-1 has been studied in combination with epigenetic and chemotherapeutic agents in vitro and in vivo. Synergy was demonstrated when combined with HDAC inhibitors and second-line chemotherapeutic agents, cell viability was reduced. Salarius has investigated the effect of SP-2577-mediated LSD1 inhibition in rhabdomyosarcoma, osteosarcoma, and clear cell sarcoma. Prolonged time to event was demonstrated in alveolar rhabdomyosarcoma and osteosarcoma mice models. In melanoma mouse models, single-agent efficacy was observed with SP-2577 and additive efficacy was demonstrated in combination arms when compared to anti-PD-1 treatment alone.

Salarius is currently evaluating single-agent SP-2577 in two ongoing clinical studies. Study SALA-002-EW16 is a first-in-human, dose escalation and expansion study of SP-2577 in patients ≥12 years of age with relapsed or refractory Ewing sarcoma to determine the maximum tolerated dose (MTD) and anti-tumor activity. This study is currently enrolling (b) (4) at 1200 mg twice daily (BID) dose level (b) (4) . SP-2577 is also being studied in an ongoing, open-label, dose-finding study to assess safety, pharmacokinetics, and preliminary anti-tumor activity in patients ≥12 years of age with advanced solid tumors (SALA-003-AC19). SALA-003-AC19 is continuing to enroll at the 600 mg BID dose level (b) (4) . There have been no deaths nor study treatment

discontinuations due to a treatment-related adverse event in either study. Of the 16 patients enrolled on each study, six and nine patients remain on study for SALA-002-EW16 and SALA-003-AC19, respectively. Following the dose escalation and declaration of an MTD and recommended Phase 2 dose (RP2D), the SALA-002-EW16 study will expand for an additional 14 Ewing sarcoma patients to complete treatment of 20 patients at that dose.

Salarius proposes the following as the future pediatric development program for SP-2577. Upon completion of the dose expansion portion of study SALA-002-EW16, if SP-2577 demonstrates a modest and durable overall response rate (ORR) and/or a 6-month event-free survival (EFS) rate >12.7% with a tolerable safety profile in the 20 patients treated at the MTD/RP2D, Salarius may design a single-arm, single-agent study in patienst with previously treated Ewing sarcoma age ≥12 years as a potential registration path. If the ORR is 10-15% and the median progression-free survival is three months, Salarius would propose combining SP-2577 with one of the chemotherapies identified from the two remaining arms of the rEECur Phase 2/3 study to assess safety and preliminary efficacy of the combination.

II. Discussion Issues Relating to the Development of SP 2577 in Pediatrics

1. Given that SP-2577 targets LSD1 and studies have demonstrated increased expression of LSD1 in other tumor types in additional to Ewing sarcoma, address other pediatric solid tumors and hematologic malignancies in which there is a biologic rationale for evaluation of its activity.

2. Given the non-clinical results of synergistic effect and increased antitumor activity of SP-2577 in combination with chemotherapeutic and epigenetic agents, and checkpoint inhibitors, consider its use as a combination treatment in pediatric tumors.

3. Please discuss the use of SP-2577 in patients <12 years of age given the range of tumor types that appear to be susceptible to the anti-tumor effects of SP-2577 based on non-clinical data.

June 17, 2020: Second Session

PRODUCT: Marizomib
COMPANY: Celgene International II Sàrl, a wholly owned subsidiary of Bristol-Myers Squibb

I. Regulatory history

Marizomib (MRZ, CC-92763, NPI-0052, salinosporamide A) is a second-generation, irreversible proteasome inhibitor (PI) with a unique β-lactone γ–lactam bicyclic ring structure designed to interfere with altered protein homeostasis regulated by cancer cell proteasome pathways. Preclinical studies have suggested that proteasome inhibitors may have antitumor activity in various adult and pediatric brain tumors[1]. MRZ specifically has been shown to exhibit antitumor activity in glioma cell lines and to have the ability to cross the blood brain barrier (BBB) in animal studies. MRZ has also demonstrated improved survival in a mouse intracranial model of malignant glioma2.

The first in human study of MRZ began in 2006 in adult patients with advanced solid tumors or relapsed/refractory multiple myeloma. Early in development, MRZ was observed to cause central nervous system (CNS) adverse events (AEs) including ataxia and gait disorders, hallucinations, dizziness and cognitive dysfunctioning, some of which were dose-limiting. These observations supported that MRZ was able to cross the BBB in humans.

Celgene sponsors Studies MRZ-108 and MRZ-112, investigating MRZ in patients with recurrent glioblastoma (GBM) and newly-diagnosed GBM respectively. Study MRZ-108 is a completed multicenter, open-label, dose-finding and activity estimating study. Eligible patients were required to have received standard radiation and temozolomide therapy and to not have received prior bevacizumab or other antiangiogenic agents. Parts 1 and 3 evaluated a range of doses of MRZ in combination with bevacizumab while Part 2 investigated single agent MRZ. Study MRZ-112 is an ongoing multicenter, open-label dose-finding and activity estimating study of MRZ given in combination with standard temozolomide and radiation in patients with newly diagnosed GBM. MRZ is administered concomitantly with radiation and temozolomide and then given as an adjuvant agent with temozolomide following radiation. The

1. Zaky W, Manton C, Miller CP, Khatua S, Gopalakrishnan V, Chandra J. The ubiquitin proteasome pathway in adult and pediatric brain tumors: biological insights and therapeutic opportunities. Cancer Metastasis Rev. 2017;36:617–33. https://doi.org/10.1007/s10555-017-9700-2

2. Di K, Lloyd GK, Abraham V, MacLaren A, Burrows FJ, Desjardins A, et al. Marizomib activity as a single agent in malignant gliomas: ability to cross the blood-brain barrier. Neuro Oncol. 2016;18(6):840–8.

recommended dose for MRZ given in combination with radiation and temozolomide in adults was established as 0.8 mg/m2 weekly.

The safety profile of MRZ in patients with CNS tumors is characterized by CNS toxicity including hallucinations in approximately 50% of patients, headache, confusion, gait disturbance, ataxia, dysarthria, seizure, dizziness, dysphonia, and memory impairment. CNS AEs in the adult trials were managed with dose modifications or discontinuation as well as medical management including antipsychotics for hallucinations and steroids during the infusions for headaches and dizziness. Other common AEs observed in adult trials included fatigure, nausea, vomiting, hypertension, and diarrhea. The most common Grade ≥ 3 AEs were fatigue, ataxia, vomiting, hypertension, confusional state, and headache. Six patients died from treatment-emergent AEs that were considered unrelated to MRZ: intracranial hemorrhage (3), disease progression (2) and sudden death (1).

Based on the results of MRZ-108 and MRZ-112, EORTC is sponsoring an ongoing randomized controlled study of MRZ in combination with standard radiation and temozolomide versus standard radiation and temozolomide alone in approximately 750 patients with newly diagnosed GBM (Study EORTC-1709-BTG; NCT03345095). The primary endpoint is overall survival (OS). As of March 2020, the study had enrolled 595 patients. Three patients (2 on the MRZ arm, 1 on the control arm) experienced serious AEs of encephalopathy as of a data cutoff of July 2019. One event was fatal and assessed as related to MRZ, and the other 2 events were considered unrelated. The safety profile has otherwise been consistent with prior studies of MRZ in patients with GBM.

The pediatric development program for MRZ is focused on evaluating combination regimens for pediatric patients with diffuse intrinsic pontine glioma (DIPG). Preclinical studies suggest synergistic antitumor activity in DIPG cell lines treated with MRZ and panobinostat. Studies of single agent MRZ and MRZ in combination with panobinostat in mice xenograft DIPG models also suggest antitumor effects. There is one ongoing clinical study of single agent MRZ and MRZ plus panobinostat in pediatric patients with DIPG who have received prior radiation therapy. The primary endpoint is safety and determination of a recommended phase 2 dose. As of May 1, 2020, no patients have enrolled in this trial.

- On April 30, 2019, FDA and EMA discussed Celgene's proposal for the marizomib pediatric development program during a Pediatric Cluster Call, and a summary of the discussion was shared with Celgene in the form of a Common Commentary released by the FDA Office of Pediatric Therapeutics. Both agencies agreed on the recommendation to Celgene to broaden the pediatric development program to include plans for preclinical and clinical investigation in pediatric HGG. FDA and EMA agreed that a proposed pediatric plan acceptable to both agencies would include pediatric development of marizomib in HGG, including pediatric GBM, as well as

DIPG, in a combinatorial approach informed by ongoing preclinical and clinical studies in these indications.

II. Discussion Issues Relating to the Development of Marizomib in Pediatrics

1. Please discuss thoughts on trial design and rational combination partners for MRZ investigation in pediatric patients with high grade glioma.

2. Considering the CNS toxicity profile associated with MRZ in the adult clinical experience to date, discuss possible risk mitigation provisions that could be included in pediatric clinical trials. Comment on any developmental or age-related assessments and management guidelines that could potentially mitigate risk in younger children who may experience CNS adverse reactions that have been common and occasionally dose-limiting in the adult MRZ clinical experience.

3. Are there non-CNS pediatric cancers that should be considered for evaluation in the MRZ development program?

June 18, 2020: First Session

PRODUCT: CD30.CAR-T
COMPANY: Tessa Therapeutics

I. Regulatory history

The tumor necrosis factor receptor (TNFR) superfamily coordinates immune response. Within this superfamily, the transmembrane glycoprotein CD30 is important in regulating normal lymphoid cells' function or proliferation. Although not expressed on normal tissues under physiologic conditions, including precursor and mature B and T lymphocytes at rest3, CD30 is a defining marker of classical Hodgkin lymphoma's Reed-Sternberg cells and of anaplastic large cell lymphoma[4]. It is also present to varying degrees on the cell surface of multiple other lymphoma types. CD30 has been identified as an important target for anti-lymphoma therapies. This approach is supported by the established efficacy and safety of the CD30-targeted antibody-drug conjugate brentuximab vedotin, which is approved for indications including patients with classical Hodgkin lymphoma and anaplastic large cell lymphoma (Adcetris® US Package Insert Seattle Genetics 2018).

CD30.CAR-T is the Sponsor's CD30-directed autologous chimeric antigen receptor (CAR) T-cell product. It is produced individually for each patient by collecting peripheral blood mononuclear cells and genetically modifying the cells to express the CD30-specific CAR. After a preparatory regimen of lymphodepleting chemotherapy, the modified cells are then infused back into the patient, where they recognize and attack CD30-expressing cells. Preclinical studies have demonstrated the CD30-specific *in vitro* cytotoxicity of CD30.CAR-T.

The sponsor's overall clinical development plan is summarized in Table 1.

3. Younes, A., and Ansell, S.M. (2016). Novel agents in the treatment of Hodgkin lymphoma: Biological basis and clinical results. Semin Hematol 53, 186-189.

4. Falini B, Pileri S, Pizzolo G, et al. CD30 (Ki-1) Molecule: A New Cytokine Receptor of the Tumor Necrosis Factor Receptor Superfamily as a Tool for Diagnosis and Immunotherapy. Blood 1995; 85(1):1-14.

Table 1 Summary of Existing and Planned CD30.CAR-T Clinical Studies

Study No.	Study Description	Status/Accrual	Number of pediatric patients/Age range
LCCC 1544-ATL Investigator Initiated Trial (University of North Carolina)	Phase 1 Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor for Relapsed CD30+ HL and CD30+ NHL (CART CD30)	Study Completed, Publication available, 9 patients received CD30.CAR-T including 7 HL patients	None
LCCC 1532-ATL Investigator Initiated Trial (University of North Carolina)	Phase 1b/2 Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor (CAR) for Relapsed or Refractory CD30+ HL and CD30+ NHL	Ongoing, 26 cHL patients treated planned 40 CD30+ lymphoma patients	The study population includes CD30 positive pediatric patients. As of 14 Feb 2020, one pediatric patient has been treated.
H-37966 (RELY-30) Investigator Initiated Trial (Baylor College of Medicine)	Phase 1 Study of Relapsed CD30 Expressing Lymphoma Treated with CD30 CAR T Cells	Ongoing, 18 cHL patients treated planned 66 CD30+ lymphoma patients	The study population includes patients aged 12 to 75 for CD30+ Lymphoma. As of 14 Feb 2020, two pediatric patients under 18 have been treated.
TESSCAR01 Tessa Therapeutics	Phase 2, multicenter, single arm study designed to evaluate the efficacy and safety of CD30-directed genetically modified autologous T-cells (CD30.CAR-T) in adult and adolescent patients with relapsed or refractory CD30-positive cHL	Planned to enroll 87 patients for 66 evaluable cHL adult patients and approximately five pediatric patients Expected to initiate in 4Q2020	Planned to enroll approximately five pediatric patients

Source: Sponsor's Pediatric ODAC Briefing Document

Study LCCC 1544-ATL did not include preparatory lymphodepleting chemotherapy. Nine subjects with CD30+ lymphoid malignancies were treated with CD30.CAR-T after failing at least three prior lines of chemotherapy. There were no reports of cytokine release syndrome (CRS) or notable adverse events. Three subjects (30% of those treated) had complete responses (CRs).

LCCC 1532-ATL and H-27966 (RELY-30), are parallel, ongoing Phase 1/2 studies of CD30.CAR-T in the treatment of relapsed/refractory CD30+ lymphomas after at least two prior lines of therapy. The studies include three lymphodepleting chemotherapy regimens—bendamustine alone, bendamustine plus fludarabine, or fludarabine plus cyclophosphamide—and three CD30.CAR-T dose levels. In the event of stable disease or a partial response after

CD30.CAR-T, a second infusion at the highest dose level is allowed. As of 14 February 2020, 59 total subjects with Hodgkin lymphoma were enrolled, and 44 had been treated with CD30.CAR-T. Of the 39 evaluable subjects, 22 (56%) had CRs and three (8%) had partial responses (PRs), comprising an objective response rate (ORR) of 64%. All responses were observed in subjects who had received fludarabine-containing lymphodepletion. Ten subjects (23% of 44 treated) developed CRS; each instance was Grade 1 and none required treatment with tocilizumab or steroids. Eighteen subjects (41%), most of whom had received fludarabine plus cyclophosphamide lymphodepletion, experienced a spontaneously resolving rash. There have been no dose-limiting toxicities and no neurotoxicity.

TESSCAR001 is an international Phase 2 study of the efficacy and safety of CD30.CAR-T in the treatment of relapsed/refractory CD30-positive classical Hodgkin lymphoma. TESSCAR001 will enroll about five pediatric patients at least 12 years of age, along with as many adult patients as needed to reach 66 evaluable adults. The study's primary objective is to assess the anti-tumor effect of CD30.CAR-T with the primary endpoint of ORR as assessed by an Independent Radiology Review Committee applying the Revised Criteria for Response Assessment: The Lugano Classification (Cheson, et al., 2014). Subjects will receive lymphodepletion with fludarabine and bendamustine prior to infusion of CD30.CAR-T at the highest studied dose, 2×10^8 cells/m^2. Subjects who respond with stable disease or better and subsequently experience disease progression may be eligible for a second dose of CD30.CAR-T. TESSCAR001 is planned to open enrollment in the fourth quarter of 2020.

Across all studies, a total of three pediatric subjects, ages 15, 15, and 17 years, have received CD30.CAR-T. None developed CRS. One experienced continued disease progression, while the other two responded with CRs.

Discussion Issues Relating to the Development of CD30.CAR-T in Pediatrics

1. Pediatric age groups include:

    a. Neonates (birth to age less than one month)
    b. Infants (ages one month to less than two years)
    c. Children (ages two years to less than 12 years)
    d. Adolescents (ages 12 years to less than 17 years)

    Please discuss which pediatric age groups are candidates for study with CD30.CAR-T and which can reasonably be excluded.

2. Please discuss the variability of the preparatory lymphodepletion therapies and their potential applicability to the pediatric population.Please discuss CD30-positive malignancies other than classical Hodgkin lymphoma which could be studied in pediatric patients.

3. Please comment on manufacturing issues related to autologous CAR T cell products in pediatric populations, including collection of leukapheresis material and pediatric sites' ability to contribute to or complete the manufacturing process.

June 18, 2020: Second Session

PRODUCT: SNDX-5613

COMPANY: Syndax Pharmaceuticals Inc.

I. Regulatory History and Background

Mixed lineage leukemia (MLL) gene rearrangements occur in 5–10% of acute leukemias and are especially prevalent in infant acute leukemias, both acute lymphobastic leukemia (ALL) and acute myeloid leukemia (AML)(up to 80% of cases). The MLL-rearranged (MLLr) leukemia subtype is characterized by resistance to therapy and high frequency of early relapse, even after initial complete remission. MLLr in pediatric ALL is a significant predictor of adverse outcome and new therapeutic approaches are urgently needed to improve outcomes for children with poor prognosis MLLr acute leukemia. Acute leukemias in both adult and pediatric patients may arise because of rearrangements involving the MLL gene, located on chromosome 11q23. Depending on the progenitor cell of origin, MLLr can appear phenotypically as ALL, AML, or in a minority of cases MPAL.The MLL gene encodes a large histone methyltransferase that directly binds DNA and positively regulates gene transcription, including homeobox (HOX)genes. MLL is involved in chromosomal translocations, partial tandem duplication, and amplifications, all of which result in hematopoietic malignancies due to sustained HOX expression and stalled differentiation.

SNDX-5613 is a small molecule inhibitor of the binding of wild-type MLL1 and MLL1 fusion proteins to menin. The interaction of MLL1 fusion proteins with menin is the key driver in MLLr acute leukemias. SNDX-5613 bears the IUPAC chemical name of trans N-ethyl-2-((4-(7-((4-(ethylsulfonamido) cyclohexyl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)pyrimidin-5-yl)oxy)-5-fluoro-N-isopropylbenzamide sesquifumarate salt.

SNDX-5613 binds with high affinity to the MLL1 binding pocket on menin (Ki=0.15$\pm$0.03 nM) and displays activity across a range of cells harboring MLLr fusions. SNDX-5613 disrupts the interaction between menin and the MLL1 fusion proteins which is required for leukemogenic activity, thus impairing expression of critical oncogenes, causing growth arrest and the inhibition of cellular proliferation. SNDX-5613 and close analogues have demonstrated single agent activity in multiple leukemic xenograft models and provided survival benefit after oral dosing in nonclinical models. Pharmacologic inhibition of the menin-MLL interaction represents a potential targeted strategy for the treatment MLLr acute leukemia.

The toxicology program for SNDX-5613 has been conducted in Sprague Dawley rats and beagle dogs. Based on the in vitro metabolism and PK data observed in the rat and dog, they were selected as the rodent and non-rodent species for the pivotal repeat-dose toxicity studies of SNDX-5613. Off-target screening assays as reported by the sponsor showed no cross reactivity of SNDX-5613 against >125 molecular targets. Therefore, treatment-related adverse events are expected to be due to mechanism-based target effects. Potential main targeted organs of toxicity identified in the 28-day rat and dog toxicology studies were the heart (electrocardiogram changes in dogs), eyes (cataracts in rats only), liver, bone marrow,

lymphoid tissues, male reproductive system, and female reproductive system. The observed dose limiting toxicity for SNDX-5613 was weight loss/appetite suppression.

Syndax is currently conducting clinical studies under one active Investigational New Drug application. SNDX-5613 has received orphan drug designation in the US for the treatment of patients with MLLr AML, including adult and pediatric patients. SNDX-5613 is manufactured in two oral formulations, capsules, and liquid. SNDX-5613 capsules are provided in three immediate release strengths: 25, 113 and 156 mg expressed as free base equivalents. SNDX-5613 liquid drug product consists of a 50 mg/mL SNDX-5613 solution (reported as free base equivalents).

Study SNDX-5613-0700 is a Phase 1/2, open-label, dose-escalation and -expansion study of SNDX-5613. Patients aged ≥18 years with relapsed/refractory acute leukemia for whom there is no available therapy are being enrolled. In Phase 1, patients with relapsed/refractory acute leukemia may be enrolled agnostic of genetic mutation status.

SNDX-5613 is being investigated initially on a q12h dose schedule; alternative dose schedules may be explored as guided by emerging data. SNDX-5613 is being administered PO in 28-day cycles, with the first study drug dose administered on Cycle 1, Day 1 (C1D1). Patients will continue SNDX-5613 until progressive disease (PD) or unacceptable toxicity.

Upon enrollment, patients are assigned to one of two dose-escalation arms as described below based on the effect of CYP 3A-4 inhibitors on SNDZ-5613 activity:

Arm A: Patients must not be receiving a strong cytochrome P450 3A4 (CYP3A4) inhibitor. Patients who were receiving a strong CYP3A4 inhibitor must have discontinued the medication at least 7 days prior to enrollment.

Arm B: Patients must be receiving a strong CYP3A4 inhibitor for at least 7 days prior to enrollment. After identification of the RP2D in Phase 1, the safety and efficacy of SNDX-5613 will be explored in 3 indication-specific Expansion cohorts, as follows:

- Cohort 2A: Patients with MLLr ALL/MPAL
- Cohort 2B: Patients with MLLr AML
- Cohort 2C: Patients with NPM1c AML

Each Expansion Cohort will employ a Simon 2-stage (mini-max) design with up to 34 patients planned in each cohort. Thus, up to 102 patients are planned to be enrolled in Phase 2.

Enrollment in each Expansion Cohort will be conducted independently. Initially, up to

21 patients will be enrolled in Stage 1 of each cohort. If at least 4 of 21 patients in the cohort experience a CR or complete remission with partial hematologic recovery (CRh), based on disease-specific response criteria, then 13 additional patients will be enrolled in Stage 2.

The first patient was enrolled into SNDX-5613-0700 in November 2019. Sponsor reports that as of a data cutoff of 30 April 2020, 6 patients had been had been enrolled into the study, either into Arm A or Arm B and dosed with SNDX-5613 at either Dose Level (DL) 1 or DL2. All patients had reported at least one adverse event regardless of causality and 5 patients had reported at least 1 treatment related adverse event. None of the treatment related events were ≥ Grade 3 or serious adverse events. No DLT events had been reported. No deaths or discontinuations due to a treatment related AE were reported.

Consistent with the nonclinical toxicology findings, Grade 1-2 QTc prolongation events were observed but were asymptomatic and self-resolved or resolved following a dose reduction.

Two of the 4 patients with an MLL mutation at enrollment had an improvement in their disease status at their first response assessment on Cycle 1 Day 28: A patient enrolled into Arm B, DL2 had a CR with incomplete blood count recovery at the first response assessment, which, despite a dose reduction for QTc prolongation, improved to a CR (FISH and flow negative).

A patient enrolled into Arm B, DL1 had a PRi (blast count 40% to 20%) at the first response assessment, the blast count continued to improve.

As the patients in pediatric single-patient protocols were among the first patients to be treated with SNDX-5613 the initial patients' treatment plan used a "ramp-up" dosing regimen starting with approximately 50% of the starting dose that would be given to an adult, and doses were increased to 100% dose after 5 days. The PK profiles of SNDX-5613 in the pediatric patients were according to the sponsor generally similar to those in adults, although the small number of subjects treated and limited PK sampling precludes any definitive pharmacokinetic conclusions. Based on a review of preliminary and interim estimated AUC0-24, adjusted for dose, the sponsor believes that adult and pediatric patients appear to have a similar exposure to SNDX-5613 in the systemic circulation.

II. Discussion Issues Relating to the Development of SNDX-5613 in Pediatrics

1. Please consider the adequacy of evidence of activity and lack of serious acute toxicity, given the timeline of the development of SNDX-5613 in adults to date, to support development of this product in children.

2. Please consider the adequacy of the currently available PK data in children from the compassionate use experience in attempts to model exposure:response after the adult RP2D has been defined and demonstrated to be active. Discuss alternative strategies for efficient RP2D definition in children. Discuss the effect of CYP-3A inhibition on possible activity.

3. Given the adult experience to date and the requirement for extended continuous dosing to achieve a response, consider how the activity of SNDX-5613 might be assessed in a single agent setting in a disease characterized by an aggressive clinical course at relapse. Given the adult experience with added cytoreductive therapy consider a possible development strategy using a relapse therapy backbone that would allow isolation of the effect of SNDX-5613 in MLLr ALL, AML, and acute mixed phenotype leukemia (AMPL).