Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Meeting
June 17-18, 2020

Location: Please note that due to the impact of the COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topics:
On June 17, 2020, information was presented regarding pediatric development plans for two products that are in development for an oncology indication. The subcommittee considered and discussed issues relating to the development of each product for pediatric use and provided guidance to facilitate the formulation of written requests for pediatric studies, if appropriate. The two products under consideration were: (1) SP 2577 presentation by Salarius Pharmaceuticals, Inc. and (2) Marizomib, presentation by Celgene International II Sàrl, a wholly owned subsidiary of Bristol-Myers Squibb.

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These summary minutes for the June 17-18, 2020 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC) of the Food and Drug Administration were approved on September 24, 2020.

I certify that I attended the June 17-18, 2020 meeting of the pedsODAC meeting of the Food and Drug Administration and these minutes accurately reflect what transpired.

/s/	**/s/**
LaToya Bonner, PharmD	Alberto Pappo, MD
Acting Designated Federal Officer, pedsODAC	*Chairperson, pedsODAC*

Final Summary Minutes of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Meeting
June 17-18, 2020

The Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on June 17 and 18, 2020. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Industry presenters (Salarius Pharmaceuticals, Inc., Celgene International II Sàrl, a wholly owned subsidiary of Bristol-Myers Squibb, Tessa Therapeutics and Syndax Pharmaceuticals, Inc.). The meeting was called to order by Alberto S. Pappo, MD (Chairperson). The conflict of interest statement was read into the record by CDR LaToya Bonner (Acting Designated Federal Officer). There were approximately 350 people online on June 17, 2020. There were approximately 175 online on June 18, 2020. There was one Open Public Hearing (OPH) speaker presentation for Topic 1 and none for Topic 2 on June 17, 2020. There were no OPH speaker presentations for Topic 1 and three (3) for Topic 2 on June 18, 2020.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda:
On June 17, 2020, information was presented regarding pediatric development plans for two products that are in development for an oncology indication. The subcommittee considered and discussed issues relating to the development of each product for pediatric use and provided guidance to facilitate the formulation of written requests for pediatric studies, if appropriate. The two products under consideration were: (1) SP 2577 presentation by Salarius Pharmaceuticals, Inc. and (2) Marizomib, presentation by Celgene International II Sàrl, a wholly owned subsidiary of Bristol-Myers Squibb.

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Attendance:
ODAC Members Present (Voting): Alberto S. Pappo, MD (pedsODAC Chairperson); David E. Mitchell (Consumer Representative) (Participation in Day 1 Topic 1 and Day 2)

ODAC Members Not Present (Voting): Jaffer A. Ajani, MD; Massimo Cristofanilli, MD, FACP; Jorge A. Garcia, MD; Susan Halabi, PhD; Christian S. Hinrichs, MD; Philip C. Hoffman, MD (ODAC Chairperson); Heidi D. Klepin, MD, MS; Gregory J. Riely, MD, PhD; Anthony D. Sung, MD; Thomas S. Uldrick, MD, MS

ODAC Member Present (Non-Voting): Jonathan D. Cheng, MD (Industry Representative)

Temporary Members (Voting): Catherine Bollard, MBChB, MD; Steven G. DuBois, MD (Participation in Day 1 Topic 2 and Day 2); Ira J. Dunkel, MD; Julia Glade Bender, MD; Richard Gorlick, MD; Katherine A. Janeway, MD, MMSc; Naynesh R. Kamani, MD; E. Andy Kolb, MD; Theodore W. Laetsch, MD; Donna M. Ludwinski, BSChE (Patient Representative); Tobey J. MacDonald, MD; Leo Mascarenhas, MD, MS; D. Williams (Will) Parsons, MD, PhD; Elizabeth Raetz, MD; Nita Seibel, MD; Malcolm Smith, MD, PhD

FDA Participants (Non-Voting): Denise Casey, MD; Leslie Doros, MD; Gregory Reamen, MD; Megan Zimmerman, MD

Designated Federal Officer (Non-Voting): CDR LaToya Bonner, PharmD (Acting)

Open Public Hearing Speakers: Day 1 Topic 1: Nina Zeldes, MS (National Center of Health Research) (NCHR); Day 1 Topic 2: None; Day 2 Topic 1: None; Day 2 Topic 2: Lia Gore, MD; Eytan M. Stein, MD; Patrick Brown, MD

The agenda was as follows:

June 17 – 18, 2020 PedsODAC Meeting – Day 1 (June 17, 2020)

Call to Order and Introduction of Committee	**Alberto S. Pappo, MD** Chairperson, (Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC)
Introductory Remarks	**Gregory Reaman, MD** Associate Director for Pediatric Oncology Center of Excellence Office of the Commissioner Associate Director for Oncology Sciences Office of Oncologic Diseases Office of New Drugs, CDER, FDA

Topic 1: SP-2577 – Salarius Pharmaceuticals, Inc.

Conflict of Interest Statement	**CDR LaToya Bonner, PharmD** Acting Designated Federal Officer pedsODAC
INDUSTRY PRESENTATIONS	Salarius Pharmaceuticals, Inc.
Introduction	David Arthur Chief Executive Officer (CEO) Salarius Pharmaceuticals, Inc.

INDUSTRY PRESENTATIONS (CONT.)

SP-2577 (Seclidemstat): Mechanism of Action, Design Rationale, Preclinical Data	Bruce McCreedy, PhD Chief Scientific Officer (CSO) Salarius Pharmaceuticals, Inc.
Relapsed Ewing Sarcoma Lacks a Standard of Care	Damon Reed, MD Associate Professor Moffitt Cancer Center Primary Investigator
Seclidemstat Clinical Trials	Margaret Dugan, MD Consulting Sr. Medical Advisor
Clarifying Questions from Subcommittee	

OPEN PUBLIC HEARING

Questions to the Subcommittee and Subcommittee Discussion

LUNCH

Topic 2: Marizomib – Celgene International II Sàrl, a wholly owned subsidiary of Bristol-Myers Squibb

Call to Order Introduction of Subcommittee	**Alberto S. Pappo, MD**
Conflict of Interest Statement	**CDR LaToya Bonner, PharmD**
INDUSTRY PRESENTATIONS	**Celgene International II Sàrl, a wholly owned subsidiary of Bristol-Myers Squibb**
Introduction	Deborah Tady, PharmD, RAC Executive Director Global Regulatory Strategy Celgene, a Bristol-Myers Squibb Company
Pediatric Research Commitment/ Marizomib Development	Sherry A. Leonard, BSc, RAC Director, Global Regulatory Strategy Celgene, a Bristol-Myers Squibb Company
Regulatory History & Key Activities for Pediatric Development	

INDUSTRY PRESENTATIONS (CONT.)

Molecular Mechanism of Action	Mark W. Kieran, MD, PhD Senior Director, Pediatric Oncology Bristol-Myers Squibb
Clinical Trial Experience in Adults	
Ongoing and Planned Clinical Trials in Pediatrics	
Clarifying Questions from Subcommittee	

OPEN PUBLIC HEARING

Questions to the Subcommittee and Subcommittee Discussion	
Closing Remarks	Gregory Reaman, MD

ADJOURNMENT

June 17 – 18, 2020 PedsODAC Meeting – Day 2 (June 18, 2020)

Call to Order Introduction of Subcommittee	**Alberto S. Pappo, MD** Chairperson, Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC)
Introductory Remarks	**Gregory Reaman, MD** Associate Director for Oncology Sciences, Office of Hematology and Oncology Products

Topic 1: CD30.CAR-T – Tessa Therapeutics

Conflict of Interest Statement	CDR LaToya Bonner, PharmD Acting Designated Federal Officer pedsODAC
INDUSTRY PRESENTATIONS	Tessa Therapeutics
CD30.CAR-T for Treatment of Patients with Relapsed or Refractory CD30-positive Classical Hodgkin Lymphoma	Ivan Horak, MD President of Research and Development Tessa Therapeutics

Clarifying Questions from Subcommittee	
OPEN PUBLIC HEARING	
Questions to the Subcommittee and Subcommittee Discussion	
LUNCH	

Topic 2: SNDX-5613 – Syndax Pharmaceuticals, Inc.

Call to Order Introduction of Subcommittee	Alberto S. Pappo, MD
Conflict of Interest Statement	CDR LaToya Bonner, PharmD
INDUSTRY PRESENTATIONS	Syndax Pharmaceuticals, Inc.
SNDX-5613 for the Treatment of Pediatric MLL-r Acute Leukemias	Michael Meyers, MD, PhD Chief Medical Officer Syndax Pharmaceuticals, Inc.
Clarifying Questions from Subcommittee	
OPEN PUBLIC HEARING	
Questions to the Subcommittee and Subcommittee Discussion	
Closing Remarks	Gregory Reaman, MD
ADJOURNMENT	

Questions to the Subcommittee:

Day 1 Topic 1: SP-2577, Salarius Pharmaceuticals, Inc.

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

   Committee Discussion: Some of the subcommittee members noted that it was unclear whether increased protein expression of lysine specific demethylase 1 (LSD1) was predictive of response and recommended that additional studies, including functional genomics, be conducted. The subcommittee further agreed that more studies are needed to be conducted to explore larger data associated with other tumor types and to explore combination therapy with the LSD1 inhibitor to study its synergistic effects.

   Some subcommittee members noted uncertainty to whether this product should be used in additional studies for brain tumors since SP-2577 showed a low (3%) blood brain barrier (BBB) penetration. On the other hand, one member, a CNS expert, commented that the product may show activity at 3%, as there is evidence in trials that demonstrated other chemotherapies with efficacy at similar BBB penetration percentage of 2 to 4%. The subcommittee noted the need for further clinical studies to capture other biomarkers that could reveal predictable responses. Please see the transcript for details of the subcommittee discussion.

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

   Committee Discussion: Collectively, the subcommittee agreed that the points considered in this question were addressed in the previous discussion, except for data demonstrating single agent activity. The majority of the subcommittee agreed that it would be difficult to jusifty combination studies with the product at issue without evidence of robust single agent activity. However, one member noted that combination therapy should not rely soley on the evidence of single agent activity and gave the example of tacrolimus that lacked single agent activity, but demonstrated synergistic activity in combined with other chemotherapies in relpased rhabdomyosarcoma. Please see the transcript for details of the subcommittee discussion.

3. **DISCUSSION:** 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.

   Committee Discussion: Most of the subcommittee members commented that the data should include patients over 12 years of age, because the vast majority of patients with Ewing Sarcoma falls in that age group. The members also agreed that there should be a better undertstanding in dose tolerability and weight distribution before expanding the enrollment to patients under the age of 12. In contrats, some of the subcommmittee members supported enrollment of patients under the age of 12 specifically for other histologies including relapsed rhabdomyosarcoma. These members emphasized that enrolling groups under the age of 12 would allow investigators the opportunity to examine pharmacokinetics safety and formulations for this population. A few of the panel members suggested that with the expansion of enrollment, there should be other formulations planned for patient under 12 years of age for agressive disease. To improve the rate of enrollment for younger patients, the subcommittee members suggested for Salarius to investigate the rate of enrollment of younger patients in other current ongoing trials. The members noted that the accrual is low possibly due to the number of institutions with opened trials, the age of patients with Ewing Sarcoma at the time of relapse, and some of these patients may have improved outcomes on one of the therapies prior to going to experimental therapies. Please see the transcript for details of the subcommittee discussion.

Day 1 Topic 2: Marizomib (MRZ), Celgene International II Sàrl

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

   Committee Discussion: The subcommittee noted that after the first cyle, the regimen could proceed to a combination therapy trial, however, this should be done cautiously to prevent loss of a potentially valuable product because it had to be abandoned due to significant toxicity (i.e., cardiac toxicity).

   Some members suggested genomic modifiers as a prominent candidate for combination therapy with MRZ. One member commented on the tolerability of combination therapy in this population, whether the data retrieved would provide guidance to the phase 2 dosing. Another member suggested radiotherapy as previously executed in other clinical trials addressing the same or similar disease. Please see the transcript for details of the subommittee discussion.

2. **DISCUSSION:** 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.

Committee Discussion: The members acknowledged that the targeted population shown in the data already had advanced diffuse intrinsic pontine glioma (DIPG), therefore attribution of some of the neurotoxicity would be difficult to establish. The members also commented that recognizing visual hallucinations in very young children would be difficult to identify as well.

Another concern was the the ability for the investigators to designate attributions of toxicity vs. progression of the disease. The subcommittee advised that there should be specific guidelines on how to mitigate the side effects, how to make attributions of the drugs to the side effects, and how to identify side effects of MRZ (safety profile) in the younger population. Please see the transcript for details of the subcommittee discussion.

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

Committee Discussion: The overall consensus of the subcommittee did not favor further studies incorporating the use of MRZ to the population of interest due to the raised concerns of neurotoxicity. The subcommittee acknowledged that the drug class of MRZ, proteasome inhibitors, is well studied for leukemias and lymphomas, and do not see this agent superceding its predecessors in this population. One of the panel members emphazied the need to approach these studies non traditionally, by studying the content with a written request versus a trial. Please see the transcript for details of the subcommittee discussion.

Day 2 Topic 1: CD30.CAR-T, Tessa Therapeutics

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1. **DISCUSSION:** 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.

Committee Discussion: The members were hesitant to estabish a cut-off age range as an enrollment requirement when a weight base dose criteria is used for enrollment. Most of the members agreed that the study should broaden the spectrum to include younger patients who might benefit from this therapy. On the other hand, some members noted uncertainty of the inclusion of younger patients due to the low mortality rate (2 deaths per year) in this population compared to the mortality rate (7 deaths per year) of patients over the age of 15

years with relapsed or refractory Hodgkin Lymphoma. One member suggested for the study to re-evaulate the idea for CD30.CAR-T as a frontline agent until more information is received from other clinical trials who have incorporated immune checkpoint inhibitors, minimizing radiation exposure and ameliorating long term effects. Some members suggested that histology should be included and used to modify the age-range requirement. Please see the transcript for details of the subcommittee discussion.

2. **DISCUSSION:** 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.

   Committee Discussion: In terms of other potential malignancies that could be included in this trial, the members generally agreed that patients with anaplastic large cell lymphoma should be included in this study. Concerning preparatory lymphodepletion therapies, the members stressed no knowledge of current studies using fludarabine or bendamustine as a single agent or in combination in this population. However, due to the safety profile shown thus far, the members noted that the standardized lympodepletion therapy for this popoulation was extremely reasonable.

   Some of the members noted the challenges of operational issues due to trial's site location. These members urged that a large site which encompasses a robust medicinal pediatric and oncology center would be beneficial in this study. It was further noted that centers with combined adult and pediatric programs are well equipped to facilitate the Institutional Review Board (IRB) procedures. Please see the transcript for details of the subcommittee discussion.

3. **DISCUSSION:** 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.

   Committee Discussion: The members noted the experience from the CD19.CAR-T cell manufacturing program for pediatric patients, in particular with ALL and recently diffuse B-cell lymphoma, provided insight to support procedures proposed for this study. Because these procedures are restricted to patients ≥12 years of age, and now considered standardized practices, the subcommittee members agreed that the manufacturing procedures for assessment and evaluation should not propose any more significant challenges than what was shown in the adult population study. Please see the transcript for details of the subcommittee discussion.

Day 2 Topic 2: SNDX-5613, Syndax Pharmaceuticals, Inc.

1. **DISCUSSION:** 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.

   Committee Discussion: The members agreed that SNDX-5613 demostrated to have a favorable safety profile, it targeted a specific site for mixed lineage rearranged-leukemia (MLLr), and there is a strong preclinical and functional genomics that further validates its activity. The members stressed confidence in the data shown and deemed SNDX-5613 to be the most active component in the reviewed combination regimen. Although it has not been determined on how to issue this agent, either as monotherapy, follow-up with chemotherapy or in combination with chemotherapy, the members agreed that this agent is promising and warrants fast-track evaluation in children with MLLr acute leukemia. Please see the transcript for details of the subcommittee discussion.

2. **DISCUSSION:** 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.

   Committee Discussion: The members agreed that SNDX-5613 was well tolerated in adults and noted the need to simplify the study design to achieve efficacy rapidly for the affected pediatric population. The members raised the issue of realtime pharmacokinetics (PK), recommending to lower the demand for realtime PK data in the study and sort out other statistical means to configure appropriate dosing. Some members recommended to limit the use of azoles, which could address the issues associated with CYP 3A4 interactions. Given the variation of CYP3A pathway maturation in pediatrics, the optimal age cut-off, whether 1 month or greater than 1 year of age, was found to be debatable amongst the members. The members also recommended to consider intra-patient dose escalation to optimize and achieve the dosing level necessary to inhibit mixed-lineage leukemia (MLL) and menin. Please see the transcript for details of the subcommittee discussion.

3. **DISCUSSION:** 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 AMPL.

   Committee Discussion: The members acknowledged the challenges of providing therapy for this subset of rare diseases and argues that a randomized design for this study will only stagnate clinical assessment. The members further commented that sample size, low survival rates, agressive disease adds diffulty to conducting a randomized trial. The members recommended to structure the study as a single arm trial with an effective “backbone”

therapy to control an aggressive disease. One member commented that regardless of reduction (agent activity), that the next step for this population is transplant and it would be imperative to consider post-tranplant administration as well. The members agreed that the survival rate of this small population is the ultimate goal, therefore in this setting, survival rate would be considered a meaningful endpoint. Because SNDX-5613 demonstrated early response in adult studies, the members recommended for this trial to consider a short window for treatment and response and to be escalated quickly to upfront therapy, if efficacious. Please see the transcript for details of the subcommittee discussion.

The meeting was adjourned at approximately 3:30 p.m. on both days.