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
May 11-12, 2022

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.

Topic: On May 11, 2022, the subcommittee discussed the development of a conceptual framework that will inform the decision-making of the FDA on sponsor plans and requests for waivers of early pediatric investigations of molecularly-targeted cancer drugs and biologics when multiple same-in-class products are approved and/or in development, recognizing that the rarity of pediatric cancers may preclude the feasibility of investigations of multiple products. Investigation of more than one product may be appropriate when specific product characteristics predict an improved benefit-risk assessment that warrants clinical investigation.

On May 12, 2022, the subcommittee considered and discussed the potential utility and steps to validation of an intermediate clinical endpoint, response to induction therapy, in the development of new drugs for the first-line treatment of patients with high-risk neuroblastoma. The European Medicines Agency (EMA) was invited and presented on both days.

These summary minutes for the May 11-12, 2022 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC) of the Food and Drug Administration were approved on June 6, 2022.

I certify that I attended the May 11-12, 2022 meeting of the pedsODAC of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Joyce Yu, PharmD	Alberto S. Pappo, MD
Acting Designated Federal Officer, pedsODAC	Chairperson, pedsODAC

Final Summary Minutes of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Meeting
May 11-12, 2022

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 May 11-12, 2022. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary members were provided the briefing materials from the FDA. The meeting was called to order by Alberto S. Pappo, MD (Chairperson). The conflict of interest statement was read into the record by Joyce Yu, PharmD (Acting Designated Federal Officer). There were approximately 303 people online on May 11th and approximately 213 people online on May 12th. There was one Open Public Hearing (OPH) speaker presentation on May 11th and one OPH speaker presentation on May 12th.

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

Agenda: On May 11, 2022, the subcommittee discussed the development of a conceptual framework that will inform the decision-making of the FDA on sponsor plans and requests for waivers of early pediatric investigations of molecularly-targeted cancer drugs and biologics when multiple same-in-class products are approved and/or in development, recognizing that the rarity of pediatric cancers may preclude the feasibility of investigations of multiple products. Investigation of more than one product may be appropriate when specific product characteristics predict an improved benefit-risk assessment that warrants clinical investigation.

On May 12, 2022, the subcommittee considered and discussed the potential utility and steps to validation of an intermediate clinical endpoint, response to induction therapy, in the development of new drugs for the first-line treatment of patients with high-risk neuroblastoma. The European Medicines Agency (EMA) was invited and presented on both days.

Attendance:
ODAC Members Present: Mark R. Conaway, PhD (Participation in Day 2 Only); David E. Mitchell (Consumer Representative); Alberto S. Pappo, MD (pedsODAC Chairperson)

ODAC Members Not Present: Ranjana H. Advani, MD; Jaffer A. Ajani, MD; Massimo Cristofanilli, MD, FACP; Jorge A. Garcia, MD, FACP; Pamela L. Kunz, MD; Christopher H. Lieu, MD; Ravi A. Madan, MD; Jorge J. Nieva, MD; Ashley Rosko, MD; Anthony D. Sung, MD

ODAC Member Not Present (Non-Voting): Jonathan D. Cheng, MD (Industry Representative)

Acting Industry Representative to the Committee (Non-Voting): Albert L. Kraus, PhD

Temporary Members: Rochelle Bagatell, MD; Steven G. DuBois, MD; Ira J. Dunkel, MD; Julia Glade Bender, MD; Richard Gorlick, MD; AeRang Kim, MD, PhD; E. Anders Kolb, MD; Theodore W. Laetsch, MD; Donna Ludwinski, BSChE (Patient Representative, Participation in

Day 1 Only); Gianna McMillan, D.Be (Patient Representative, Participation in Day 2 Only); D. Williams (Will) Parsons, MD, PhD; Nita Seibel, MD (Participation in Day 2 Only)

FDA Participants (Non-Voting): Gregory H. Reaman, MD; Martha Donoghue, MD; Haleh Saber, PhD, MS (Participation in Day 1 Only); Stacy S. Shord, PharmD, BCOP, FCCP (Participation in Day 1 Only); Diana Bradford, MD (Participation in Day 2 Only); Elizabeth S. Duke, MD (Participation in Day 1 Only); Margaret Merino, MD (Participation in Day 1 Only); Anup Amatya, PhD (Participation in Day 2 Only)

Acting Designated Federal Officer (Non-Voting): Joyce Yu, PharmD

Open Public Hearing Speakers: Day 1: Diana Zuckerman, PhD (National Center for Health Research); Day 2: Nina Zeldes, PhD (National Center for Health Research)

The agenda was as follows:

Day 1: May 11, 2022

Call to Order	**Alberto S. Pappo, MD** Chairperson, pedsODAC
Introduction of Subcommittee and Conflict of Interest Statement	**Joyce Yu, PharmD** Acting Designated Federal Officer, pedsODAC
FDA PRESENTATIONS	
Developing a Consistent Conceptual Framework to Address Waivers of Pediatric Studies Required by the RACE for Children Act	**Gregory Reaman, MD** Associate Director for Pediatric Oncology Oncology Center of Excellence (OCE) Office of the Commissioner (OC) Associate Director for Pediatric Oncology Office of Oncologic Diseases (OOD) Office of New Drugs (OND), CDER, FDA
Scope of the Current Problem: Examples of Multiple Same in Class Products for Hematologic Malignancies	**Margret Merino, MD** Medical Officer Division of Hematologic Malignancies 2 OOD, OND, CDER, FDA

GUEST SPEAKER PRESENTATION

European Medicines Agency (EMA)/Paediatric Committee (PDCO) - General Considerations on Waiving Requirements for Pediatric Investigations of Same in Class Products	**Dominik Karres, MD** Scientific Officer Paediatric Medicines Office Scientific Evidence Generation Department Human Medicines Division European Medicines Agency (EMA)

FDA PRESENTATION

Non-Clinical Studies in Decision-Making Related to Pediatric Investigations: FDA Perspective	**Haleh Saber, PhD, MS** Deputy Director Division of Hematology Oncology Toxicology OOD, OND, CDER, FDA

GUEST SPEAKER PRESENTATION

EMA/PDCO - Non-Clinical Considerations in Decision-Making Related to Waiving Requirements for Paediatric Investigations	**Karen Van Malderen, MSc** Non-Clinical Assessor Federal Agency for Medicines and Health Products PDCO Member, EMA Chair of the Non-Clinical Working Group, EMA

FDA PRESENTATIONS

Clinical Pharmacology Considerations for Same-in-Class Products	**Stacy S. Shord, PharmD, BCOP, FCCP** Deputy Division Director Division of Cancer Pharmacology II Office of Clinical Pharmacology Office of Translational Sciences, CDER, FDA
Central Nervous System Penetration and Pediatric Brain Tumor Considerations for Same-In-Class Products	**Elizabeth S. Duke, MD** Medical Officer Division of Oncology 2 OOD, OND, CDER, FDA

Clarifying Questions

LUNCH

GUEST SPEAKER PRESENTATIONS

Product Quality and Formulation Considerations in Decisions Related to Pediatric Investigation of Same in Class Agents	**Siri Wang, PhD** Scientific Director Norwegian Medicines Agency, Oslo, Norway PDCO of the EMA, Netherlands

GUEST SPEAKER PRESENTATIONS (CONT.)

An Industry Perspective on Waiving Requirements for Pediatric Investigations of Same in Class Products	**Scott J. Diede, MD, PhD** Executive Director Global Clinical Development Merck Research Laboratories
Clarifying Questions	

OPEN PUBLIC HEARING

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

ADJOURNMENT

Day 2: May 12, 2022

Call to Order	**Alberto S. Pappo, MD** Chairperson, pedsODAC
Introduction of Subcommittee and Conflict of Interest Statement	**Joyce Yu, PharmD** Acting Designated Federal Officer, pedsODAC
Introductory Remarks	**Martha Donoghue, MD** Acting Associate Director for Pediatric and Rare Cancer Drug Development Oncology Center of Excellence (OCE) Office of the Commissioner (OC) Deputy Director, Division of Oncology 2 (DO2) Office of Oncologic Diseases (OOD) Office of New Drugs (OND), CDER, FDA

FDA AND GUEST SPEAKER PRESENTATIONS

High-Risk Neuroblastoma: Current Treatment and Regulatory Insights	**Diana Bradford, MD** Cross-Discipline Team Leader DO2, OOD, OND, CDER, FDA
Current Treatment and Regulatory Insights – EMA and FDA Part II	**Dominik Karres, MD** Scientific Officer Paediatric Medicines Office Scientific Evidence Generation Department Human Medicines Division European Medicines Agency (EMA)
Clarifying Questions	

GUEST SPEAKER PRESENTATIONS

Accelerating Cure for High-Risk Neuroblastoma	**Leona Knox** Advocate Head of Research, Solving Kids' Cancer UK London, United Kingdom
Improving Access to Novel Therapies in High-Risk Neuroblastoma	**Navin Pinto, MD** Associate Professor of Pediatrics University of Washington School of Medicine Attending Physician Cancer and Blood Disorders Center Seattle Children's Hospital
Multi-stakeholder Perspective on Current and Potential Future Use of End-Induction Response in Patient Care and Drug Development	**Maja Beck Popovic, MD** Professor of Pediatric Hematology Oncology Head of the Pediatric Hematology Oncology Unit University Hospital in Lausanne, Switzerland
Clarifying Questions	

LUNCH

SPEAKER AND FDA PRESENTATIONS

Steps to Validation of Early Endpoints to Support Drug Development in Neuroblastoma: Key Concepts	**Lisa M. McShane, PhD** Chief, Biometric Research Program Associate Director, Division of Cancer Treatment and Diagnosis National Cancer Institute National Institutes of Health
Early Endpoint Validation	**Anup Amatya, PhD** Acting Lead Mathematical Statistician Division of Biometrics V Office of Biostatistics Office of Translational Sciences, CDER, FDA
Clarifying Questions	

OPEN PUBLIC HEARING

Questions to the Subcommittee and Subcommittee Discussion	
Closing Remarks	**Martha Donoghue, MD**

ADJOURNMENT

Questions to the Subcommittee:

Day 1: May 11, 2022

Topics Related to Considerations for Evaluating Planned Waivers of Pediatric Investigations of Same in Class Agents

1. **DISCUSSION:** Consider the degree of unmet clinical need in a specific disease context that should influence decisions related to planned waiver requests for pediatric studies of multiple same-in-class novel agents.

   Subcommittee Discussion: *The Subcommittee members generally agreed that unmet clinical need should not significantly influence decisions to grant waiver requests for pediatric studies of multiple same-in-class novel agents. Several Subcommittee members mentioned other factors that should be balanced with unmet clinical need, including: 1) rarity of the disease and the feasibility of investigations, 2) toxicity profile of the agent, 3) disease prognosis, and 4) degree of efficacy. Please see the transcript for details of the Subcommittee's discussion.*

2. **DISCUSSION:** Consider the importance of any comparative efficacy results of same in class agents in one or more adult cancers as well as comparative toxicity data (type, magnitude, and frequency) that could contribute to a decision where evaluation of more than one same in class product in children might be warranted.

   Subcommittee Discussion: *The majority of Subcommittee members agreed that, when available, both comparative efficacy and comparative toxicity data results of same in class agents in adults are important when evaluating more than one same in class agent in children. Some Subcommittee members commented that the decision to evaluate more than one same in class product in children may be limited by the availability of such data. One Subcommittee member mentioned anaplastic lymphoma kinase (ALK) inhibitors as an example of the importance of comparative efficacy results in adults and children. Another Subcommittee member noted that understanding the biological similarities and differences between adult and childhood malignancies is also helpful, and may provide clinicians with a reasonable expectation that, in certain diseases, the relative efficacy is likely to be similar. With regards to comparative toxicity data, a few Subcommittee members stated that clinicians should additionally consider the relevance of certain toxicities typically seen in children, such as myelosuppression. Please see the transcript for details of the Subcommittee's discussion.*

3. **DISCUSSION:** Consider whether differences in specific product quality indicators, dosage forms, route of administration, impact clinical benefit considerations and influence a decision to investigate multiple same in class products.

   Subcommittee Discussion: *The majority of Subcommittee members agreed that product quality indicators, dosage forms, and route of administration, are all important with regard*

to clinical benefit considerations and decisions to investigate multiple same in class products. Some Subcommittee members mentioned additional factors such as: 1) drug-drug interactions, 2) CNS penetration, 3) dosing schedule and frequency of administration, 4) palatability, and 5) the potential for agents to be administered in combination with other therapies. Please see the transcript for details of the Subcommittee's discussion.

4. **DISCUSSION:** Consider the importance of non-clinical efficacy data on whether pediatric investigations of more than one same-in-class products are warranted in children and if/when pre-clinical studies in pediatric-specific models might be required.

   Subcommittee Discussion: *One Subcommittee member commented that clinical data is significantly more important than pre-clinical data in determining whether pediatric investigation of more than one same in class product is warranted in children. This Subcommittee member also noted the relevance of pediatric-specific pre-clinical models to assess differences in efficacy or toxicity. Another Subcommittee member also agreed that clinical data is more important than pre-clinical data, however, non-clinical data can be helpful in rare pediatric tumors. Please see the transcript for details of the Subcommittee's discussion.*

5. **DISCUSSION:** Consider the specific pharmacological parameters that should be considered and the importance of central nervous system (CNS) penetration when primary CNS tumors may be key target tumors of interest when evaluating the need for pediatric investigation of more than one same in class agent.

   Subcommittee Discussion: *Some Subcommittee members stated that CNS penetration is important and should be considered when evaluating the need for pediatric investigation of more than one same in class agent. One Subcommittee member commented that CNS penetration could also be considered more broadly with any available clinical data in regards to drug efficacy. Please see the transcript for details of the Subcommittee's discussion.*

6. **DISCUSSION:** Discuss the extent to which sponsors should include sufficient data to address the features discussed in initial Pediatric Study Plans (iPSPs) to inform assessment and decision-making and whether other features should be considered in decision-making about waiving requirements to investigate multiple same in class drugs.

   Subcommittee Discussion: *One Subcommittee member stated that sponsors should include sufficient data if it is available, to inform assessment and decision-making about waiving requirements to investigate multiple same in class drugs. The Subcommittee members agreed that there should also be flexibility in such decisions if and when new data emerges. One Subcommittee member noted that situations in which a drug lacks activity in pediatric patients, compared to adult patients, could also be an important consideration. Please see the transcript for details of the Subcommittee's discussion.*

Day 2: May 12, 2022

Topics Relating to the End of Induction Response in High-Risk Neuroblastoma

1. **DISCUSSION:** Please discuss the potential benefits and limitations to using an intermediate clinical endpoint in the evaluation of new drugs under development for the first-line treatment of patients with high-risk neuroblastoma.

   Subcommittee Discussion: *Some Subcommittee members identified the following as potential benefits to using an intermediate clinical endpoint in the evaluation of new drugs for the first-line treatment of high-risk neuroblastoma: 1) quicker assessment/evaluation of new therapies, 2) the ability to better identify factors associated with a poor response to induction therapy, and 3) the potential ability to better design successor trials. The Subcommittee members noted that some of the limitations included unclear applicability of the data to newer therapies, given that most of the currently available data are with cytotoxic agents. Another potential limitation voiced by some Subcommittee members was the potential for the intermediate clinical endpoint to inaccurately predict the clinical benefit of a drug. One Subcommittee member further commented that the benefits of using an intermediate clinical endpoint would likely outweigh the limitations. Please see the transcript for details of the Subcommittee's discussion.*

2. **DISCUSSION:** Please discuss the strength of the evidence for using end-of-induction response as a prognostic factor and to assess antitumor activity of investigational treatments during the induction phase of treatment.

   Subcommittee Discussion: *The Subcommittee did not provide any recommendations or consideration for this discussion question as the majority of the members considered this question similar to Question 1. Please see the transcript for details of the Subcommittee's discussion.*

3. **DISCUSSION:** Please discuss how end-of-induction response is used in clinical decision-making and the implications of its use in the design and conduct of clinical trials investigating new treatments for patients with high-risk neuroblastoma.

   Subcommittee Discussion: *Some Subcommittee members commented that using end-of-induction response is important in clinical decision-making and design of clinical trials investigating new treatments for high-risk neuroblastoma. Some Subcommittee members emphasized the importance of allowing patients who have had inadequate end-induction response to remain on-study and continue to be followed in the context of the same trial. Some Subcommittee members also noted that doing so could allow these patients to have the opportunity to receive new therapies. One Subcommittee member mentioned that it is also important to collect information on patients who have an excellent end-of-induction response in a uniform manner to aid in the design of future clinical trials to improve outcomes for this subpopulation. Please see the transcript for details of the Subcommittee's discussion.*

4. **DISCUSSION:** Given the current strength of evidence for using response at the end-of-induction to predict patient outcome and assess antitumor activity, consider the appropriate use of this endpoint in clinical trials.

   Subcommittee Discussion: *Some Subcommittee members stated that end-of-induction response can be used as a surrogate endpoint in clinical trials, but that it will be important to confirm that a good end-of-induction response is predictive of later clinical outcomes. The members also agreed that using end-of-induction response has its limitations and should continue to be assessed as an endpoint. One Subcommittee member thought that disease domain-specific response data could be more informative than induction-response as an overall measure. Another Subcommittee member recommended that when end-of-induction response is used in clinical trials, a breakdown of responses at sites of metastases should be captured, so that an overall assessment of a drug's potential benefit is not skewed by presence of residual disease at the primary tumor site. Please see the transcript for details of the Subcommittee's discussion.*

5. **DISCUSSION:** If there is sufficient evidence to support future efforts, please provide recommendations regarding interest, feasibility and future steps to validation of end-of-induction response as a clinical endpoint in the first-line treatment of patients with high-risk neuroblastoma.

   Subcommittee Discussion: *Some Subcommittee members expressed interest in using end-of-induction response as a clinical endpoint in trials studying the first-line treatment of patients with high-risk neuroblastoma and believe that there is sufficient evidence to support its use and further validation. Other Subcommittee members thought that the data regarding its potential as a surrogate endpoint is still evolving. The Subcommittee members generally agreed that creativity will be important when designing trials to evaluate this as a potential surrogate endpoint. One Subcommittee member highlighted the importance of accurate patient follow-up. Another Subcommittee member voiced the possibility of conducting interim analyses to evaluate this endpoint. Please see the transcript for details of the Subcommittee's discussion.*

The meeting was adjourned at approximately 3:14 p.m. on May 11, 2022 and approximately 2:51 p.m. on May 12, 2022.