Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Oncologic Drugs Advisory Committee Meeting
May 14, 2019

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland

Topic: During the morning session, the committee discussed new drug application (NDA) 211810 for pexidartinib capsule, submitted by Daiichi Sankyo, Inc. The proposed indication (use) for this product is for the treatment of adult patients with symptomatic tenosynovial giant cell tumor also referred to as giant cell tumor of the tendon sheath or pigmented villonodular synovitis, which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.

During the afternoon session, the committee discussed new drug application (NDA) 212166 for quizartinib tablets, submitted by Daiichi Sankyo, Inc. The proposed indication (use) for this product is for the treatment of adults with relapsed or refractory acute myeloid leukemia which is FLT3-ITD positive, as detected by an FDA-approved test.

These summary minutes for the May 14, 2019 Oncologic Drugs Advisory Committee (ODAC) meeting of the Food and Drug Administration were approved on June 5, 2019.

I certify that I attended the May 14, 2019 Oncologic Drugs Advisory Committee meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Jennifer Shepherd, RPh
Acting Designated Federal Officer
ODAC

/s/
Brian I. Rini, MD, FACP
Chairperson
ODAC

Summary Minutes of the Oncologic Drugs Advisory Committee (ODAC) Meeting
May 14, 2019

The Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on May 14, 2019, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Daiichi Sankyo, Inc. The meeting was called to order by Brian I. Rini, MD, FACP (Chairperson). The conflict of interest statement was read into the record by Jennifer Shepherd, RPh (Acting Designated Federal Officer). There were approximately 170 people in attendance during the morning session and approximately 210 people in attendance during the afternoon session. There were four (4) Open Public Hearing (OPH) speaker presentations during the morning session and four (4) OPH speaker presentations during the afternoon session.

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

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During the afternoon session, the committee discussed new drug application (NDA) 212166 for quizartinib tablets, submitted by Daiichi Sankyo, Inc. The proposed indication (use) for this product is for the treatment of adults with relapsed or refractory acute myeloid leukemia which is FLT3-ITD positive, as detected by an FDA-approved test.

Attendance:

Oncologic Drugs Advisory Committee Members Present (Voting): Massimo Cristofanilli, MD, FACP (Morning Session Only); Susan Halabi, PhD; Philip C. Hoffman, MD; Heidi D. Klepin, MD, MS; Grzegorz S. Nowakowski, MD; Courtney J. Preusse, MA (Consumer Representative); Brian I. Rini, MD, FACP (Chairperson); Thomas S. Uldrick, MD, MS

Oncologic Drugs Advisory Committee Member Present (Non-Voting): Phuong Khanh (P.K.) Morrow, MD, FACP (Industry Representative)

Oncologic Drugs Advisory Committee Members Not Present (Voting): Christian S. Hinrichs, MD; Vassilliki A. Papadimitrakopoulou, MD; Alberto S. Pappo, MD; Gregory J. Riely, MD, PhD; Alice T. Shaw, MD, PhD

Temporary Members (Voting): Susan Broyles (Patient Representative; Morning Session Only); Karim Anton Calis, PharmD, MPH, FASHP, FCCP (Morning Session Only); Sally Hunsberger, PhD; Valerae O. Lewis, MD (Morning Session Only); A. Michael Lincoff, MD

(Afternoon Session Only); Doris Strader, MD (Morning Session Only); Anthony D. Sung, MD (Afternoon Session Only); Wayne Taylor, MD (Patient Representative; Afternoon Session Only); Victor M. Villalobos, MD, PhD (Morning Session Only); Kevin Weinfurt, PhD (Morning Session Only)

FDA Participants (Non-Voting): Kunthel By, PhD (Afternoon Session Only); Albert Deisseroth, MD, PhD (Afternoon Session Only); Ann Farrell, MD (Afternoon Session Only); Lola Fashoyin-Aje, MD, MPH (Morning Session Only); Mallorie Fiero, PhD (Morning Session Only); Patricia Keegan, MD (Morning Session Only); Aviva Krauss, MD (Afternoon Session Only); Christy Osgood, MD (Morning Session Only); Richard Pazdur, MD; Donna Przepiorka, MD, PhD (Afternoon Session Only); Ashley Ward, MD (Morning Session Only)

Acting Designated Federal Officer (Non-Voting): Jennifer Shepherd, RPh

Open Public Hearing Speakers for the Morning Session: Peter Tesler, MD, MPH; Varuna Srinivasan, MBBS, MPH (National Center for Health Research); Angie Rowe (Global Genes); Rhoda Mercado

Open Public Hearing Speakers for the Afternoon Session: Dorothy Schilder; Patricia Lewis; Varuna Srinivasan, MBBS, MPH (National Center for Health Research); Justin Oh and Chung Oh

The morning session agenda proceeded as follows:

Call to Order and Introduction of Committee	**Brian I. Rini, MD, FACP** Chairperson, ODAC
Conflict of Interest Statement	**Jennifer Shepherd, RPh** Acting Designated Federal Officer, ODAC
Introductory Comments	**Lola Fashoyin-Aje, MD, MPH** Cross-Discipline Team Leader Division of Oncology Products 2 (DOP2) Office of Hematology & Oncology Products (OHOP) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS Introduction	**Daiichi Sankyo, Inc.** **Eric Richards, MS, MPH** Vice President Global Head Regulatory Affairs, Oncology Daiichi Sankyo, Inc.
TGCT Disease Background and Treatment Landscape	**Nicholas Bernthal, MD** Chief, Division of Musculoskeletal Oncology Department of Orthopaedic Surgery David Geffen School of Medicine at UCLA

APPLICANT PRESENTATIONS (CONT.)

Development Program and Efficacy	**William D. Tap, MD** Sarcoma Medical Oncology Service Chief Memorial Sloan Kettering Cancer Center
General Safety Assessment of Pexidartinib	**Antoine Yver, MD, MSc** Executive Vice President and Global Head Oncology R&D Daiichi Sankyo, Inc.
Hepatic Safety	**Laurie DeLeve, MD, PhD** Professor of Medicine University of Southern California Keck School of Medicine Division of Gastrointestinal and Liver Diseases
Risk Evaluation and Mitigation Strategy (REMS)	**Eric Richards, MS, MPH**
Clinical Perspective	**William D. Tap, MD**

FDA PRESENTATIONS

Background & Safety Results and Issues	**Christy Osgood, MD** Clinical Reviewer DOP2, OHOP, OND, CDER, FDA
Efficacy Results and Issues	**Mallorie Fiero, PhD** Statistics Reviewer Division of Biometrics V (DBV) Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA

Clarifying Questions

BREAK

OPEN PUBLIC HEARING

Questions to the Committee/Committee Discussion

LUNCH

The afternoon session agenda proceeded as follows:

Call to Order and Introduction of Committee	**Brian I. Rini, MD, FACP** Chairperson, ODAC
Conflict of Interest Statement	**Jennifer Shepherd, RPh** Acting Designated Federal Officer, ODAC
Introductory Comments	**Donna Przepiorka, MD, PhD** Cross-Discipline Team Leader Division of Hematology Products (DHP) OHOP, OND, CDER, FDA
APPLICANT PRESENTATIONS	**Daiichi Sankyo, Inc.**
Introduction	**Eric Richards, MS, MPH** Vice President Global Head Regulatory Affairs, Oncology Daiichi Sankyo, Inc.
Disease Background/Unmet Need	**Mark Levis, MD, PhD** Program Co-Leader, Hematologic Malignancies and Bone Marrow Transplant Program Director, Adult Leukemia Service Johns Hopkins Sidney Kimmel Comprehensive Cancer Center
Clinical Development and Efficacy	**Jorge Cortes, MD** Deputy Chair and Professor of Medicine Department of Leukemia MD Anderson Cancer Center
Safety	**Youngsook Choi, MD** Executive Director, Clinical Safety Daiichi Sankyo, Inc.
Clinical Perspective	**Jorge Cortes, MD**
FDA PRESENTATIONS	
Introduction and Efficacy Review	**Kunthel By, PhD** Statistical Reviewer DBV, OB, OTS, CDER, FDA
Safety Review and Summary	**Aviva Krauss, MD** Clinical Reviewer DHP, OHOP, OND, CDER, FDA
Clarifying Questions	

BREAK

OPEN PUBLIC HEARING

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

Morning Session: NDA 211810; Pexidartinib

1. **DISCUSSION:** Discuss whether the benefits of pexidartinib, as characterized by a clinically meaningful reduction in tumor burden and an improvement in range of motion, outweigh its risk of hepatoxicity.

   Committee Discussion*: Many committee members stated that pexidartinib demonstrated benefit as measured by response rate; however, many felt that although the patient-reported outcomes also represented benefit, there is less certainty in the magnitude of effect due to missing data. The committee members discussed that there is a clear benefit to some individual patients, but that the evidence is less clear regarding benefit at a population level. The committee members discussed that there is concern about hepatotoxicity and that a Risk Evaluation and Mitigation Strategy (REMS) is needed to educate prescribers and further eavluate this risk. The committee members also discussed the number of open questions regarding this drug, given the relatively small sample size due to the rarity of the disease. These questions included whether the optimal dose and duration of therapy had been selected given the risk of hepatotoxicity. Please see the transcript for details of the Committee discussion.*

2. **VOTE:** Does the demonstrated benefit of pexidartinib outweigh the risks of the drug in the proposed indication?

   Vote Result: Yes: 12 No: 3 Abstain: 0

   Committee Discussion*: The majority of the committee agreed that the demonstrated benefit of pexidartinib outweighs the risks of the drug in the proposed indication. Several committee members who voted "Yes" emphasized the lack of treatment options for patients with TGCT as a factor for their vote. Those voting "No" stated concerns over liver toxicity, proper use in clinical practice, and the possibility that pexidartinib may be used in patients for whom surgerical resection is appropriate. Please see the transcript for details of the Committee discussion.*

Afternoon Session: NDA 212166; Quizartinib

1. **DISCUSSION:** Please discuss whether the results of the OS analysis of Study AC220-007 are persuasive evidence of effectiveness of quizartinib and the reasons for your opinion.

   Committee Discussion*: The committee members discussed the uncertainty that remains around the overall survival (OS) analysis and the question of benefit and magnitude of benefit. Several committee members stated that the high drop-out rates and the lack of follow up in those patients are very concerning. The committee also discussed concerns about the uncertainty of clinical benefit of other non-standard endpoints such as increased transplant rates and CRi (complete remission with incomplete hematologic recovery).. Please see the transcript for details of the Committee discussion.*

2. **DISCUSSION:** Please discuss the feasibility and adequacy of a) a contra-indication for use with drugs that prolong QT via the complementary IKr channel and b) a recommendation for administration of beta-blockers to prevent arrythmias as means to reduce the risk of life-threatening and fatal cardiac events resulting from IKs blockade if quizartinib is marketed.

   Committee Discussion*: Committee members voiced the opinion that it would be acceptable to advise prescribers of the risk of using QT prolonging drugs with quizartinib, but a contraindication for use with QT prolonging drugs is not warranted, since in the current era of targeted therapies, oncologists are expereienced with managing patients on drugs with QT prolonging effects. Additionally, the Committee indicated a relatively low concern over the risk of QT prolongation with the administration of quizartinib for patients with relapsed or refractory AML who would have no other treatment options, The committee also discussed advising the administration of beta blockers to prevent arrhythmias was not something that should be blanketly recommended. Please see the transcript for details of the Committee discussion.*

3. **VOTE:** Do the results of Study AC220-007 demonstrate that treatment with quizartinib provides for a benefit that outweighs the safety risks for patients with relapsed or refractory FLT3-ITD-positive AML?

   Vote Result: Yes: 3 No: 8 Abstain: 0

   Committee Discussion*: The majority of the committee members voted "No" that the results of Study AC220-007 did not demonstrate that treatment with quizartinib provides for a benefit that outweighs the safety risk for patients with relapsed or refractory FLT3-ITD-positive AML. Two committee members stated that the type of information from the trial was similar to that typically provided by a Phase II trial and that additional study is needed to demonstrate clinical benefit. Many committee members stated that the difference in patients randomized but not treated in the control arm vs. the quizartinib arm and the potential bias that this presented was very concerning. One member who voted "Yes" stated that there is potential for risk with QT prolongation, but that it wasn't clearly seen. Please see the transcript for details of the Committee discussion.*

   The meeting was adjourned at approximately 4:45 p.m.