Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Arthritis Advisory Committee Meeting
July 25, 2019

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

Topic: The committee discussed supplemental new drug application (sNDA) 205832 for nintedanib capsules (drug name OFEV), sponsored by Boehringer Ingelheim, for the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD). The focus of the discussion was whether the application provides substantial evidence of efficacy for the proposed indication.

These summary minutes for the July 25, 2019 meeting of the Arthritis Advisory Committee (AAC) of the Food and Drug Administration were approved on August 20, 2019.

I certify that I attended the July 25, 2019 AAC meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/

Yinghua S. Wang, PharmD, MPH, RAC
Designated Federal Officer, AAC

/s/

Daniel H. Solomon, MD, MPH
Chairperson, AAC

Final Summary Minutes of the Arthritis Advisory Committee (AAC) Meeting

July 25, 2019

The Arthritis Advisory Committee (AAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on July 25, 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 Boehringer Ingelheim. The meeting was called to order by Daniel Solomon, MD (Chairperson). The conflict of interest statement was read into the record by Yinghua S. Wang, PharmD, MPH, RAC (Designated Federal Officer). There were approximately 105 people in attendance. There were four Open Public Hearing (OPH) presentations.

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

Agenda: The committee discussed supplemental new drug application (sNDA) 205832 for nintedanib capsules (drug name OFEV), sponsored by Boehringer Ingelheim, for the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD). The focus of the discussion was whether the application provides substantial evidence of efficacy for the proposed indication.

Attendance:

Arthritis Advisory Committee Members Present (Voting): Mara L. Becker, MD, MSCE; Jeffrey Curtis, MD, MS, MPH; Jennifer Horonjeff, PhD (Consumer Representative); Martha C. Nason, PhD; Alyce M. Oliver, MD, PhD; J. Steuart Richards, MD; Daniel H. Solomon, MD, MPH (Chairperson)

Arthritis Advisory Committee Members Not Present (Voting): John M. Davis III, MD, MS; Aryeh Fischer, MD; Veena K. Ranganath, MD, MS; Jose U. Scher, MD

Arthritis Advisory Committee Members Not Present (Non-voting): James B. Chung, MD, PhD (Industry Representative)

Temporary Members (Voting): William Calhoun, MD, FACP, FCCP, FAAAAI, FACAAI; Brian Garibaldi, MD, MEHP; Nancy Gellar, PhD; Todd Gilligan, MA (Patient Representative); James Katz, MD; Gail Kerr, MD, FRCP(Edin); Susanne May, PhD; Carrie Redlich, MD, MPH; James Stoller, MD; Michael Weisman, MD.

Acting Industry Representative to the Committee (Non-voting): Sean Curtis, MD (Acting Industry Representative)

FDA Participants (Non-voting): Sally Seymour, MD; Nikolay Nikolov, MD; Rachel Glaser, MD; Nadia Habel, MD; Yu Wang, PhD

Designated Federal Officer (Non-voting): Yinghua S. Wang, PharmD, MPH, RAC

Open Public Hearing Speakers: Luke Evnin, PhD (Scleroderma Research Foundation); Rosemary Markoff; Stephanie Fox-Rawlings, PhD (National Center for Health Research); Gregory Cosgrove, MD (Pulmonary Fibrosis Foundation)

The agenda was as follows:

Call to Order and Introduction of Committee	**Daniel Solomon, MD** Chairperson, AAC
Conflict of Interest Statement	**Yinghua S. Wang, PharmD, MPH, RAC** Designated Federal Officer, AAC
FDA Opening Remarks	**Rachel Glaser, MD** Clinical Team Leader Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Boehringer Ingelheim**
Introduction	**Kay Teztlaff, MD** Medical Head Therapeutic Area Respiratory Diseases Boehringer Ingelheim
Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD) Background and Unmet Medical Need	**James R. Seibold, MD** Principal Member Scleroderma Research Consultants
Clinical Development Rationale for SSc-ILD	**Susanne Stowasser, MD** Associate Head Medicine Therapeutic Area Respiratory Diseases Boehringer Ingelheim
Efficacy of Nintedanib for SSc-ILD	**Emmanuelle Clerisme-Beaty, MD** Senior Clinical Program Leader Therapeutic Area Respiratory Diseases Boehringer Ingelheim
Safety of Nintedanib for SSc-ILD	**Veronika M. Kohlbrenner, MD** Director Global Pharmacovigilance Boehringer Ingelheim

APPLICANT PRESENTATIONS (CONT.)	
Benefit/Risk of Nintedanib for SSc-ILD	**Kay Teztlaff, MD**
Clinical Perspective	**Kevin K. Brown, MD** Professor of Medicine National Jewish Health
Clarifying Questions	
BREAK	
FDA PRESENTATIONS	
Overview of Clinical Program	**Nadia Habal, MD** Medical Officer DPARP, ODE-II, OND, CDER, FDA
Statistical Review of Efficacy	**Yu Wang, PhD** Statistical Reviewer Division of Biometrics II, Office of Biostatistics Office of Translational Sciences, CDER, FDA
Clinical Review of Safety and Benefit-Risk Assessment	**Nadia Habal, MD**
Clarifying Questions	
LUNCH	
OPEN PUBLIC HEARING	
Charge to the Committee	**Rachel Glaser, MD**
Questions to the Committee/Committee Discussion	
BREAK	
Questions to the Committee/Committee Discussion	
ADJOURNMENT	

Questions to the Committee:

1. **DISCUSSION:** Discuss the efficacy of nintedanib for treatment of patients with systemic sclerosis interstitial lung disease (SSc-ILD).
   a. Discuss the clinical meaningfulness of the changes in forced vital capacity (FVC) with nintedanib treatment in the population studied.

Committee Discussion: *The committee members agreed that nintedanib's place in therapy is not clear with regards to disease course and in the sequence of treatment with other agents. The members also agreed that the study's primary efficacy endpoint was met but noted that the study data is not robust to answer questions on long-term use. The committee members had mixed opinions on forced vital capacity (FVC) as an indicator of disease progression and lung function; some members commented that FVC is an important key component of pulmonary function tests while others weighed in on additional indicators (such as high-resolution CT scans to guide decision-making). Several committee members noted that changes in FVC are meaningful, especially in the context of a chronic, progressive disease. Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** Discuss the FVC data from the following subgroups and the implications for use of nintedanib in patients in the US.
   a. US and Canada subgroup compared to the overall study population
   b. Patients on background mycophenolate versus no background mycophenolate treatment

Committee Discussion: *The committee members agreed that while the subgroup analysis is underpowered, there were interesting trends in the data. One member noted that overall positive results were driven by data from the non-US and Canada subgroup and no background mycophenolate subgroup. Other members expressed dissatisfaction with the relatively sparse dataset for these subgroups. Please see the transcript for details of the Committee's discussion.*

3. **VOTE:** Do the data provide substantial evidence of the efficacy of nintedanib for the treatment of systemic sclerosis interstitial lung disease?
   a. If no, what further data are needed?

Vote Result: Yes: 10 No: 7 Abstain: 0

Committee Discussion: *The majority of committee members voted "Yes", that the data provide substantial evidence of the efficacy of nintedanib for the treatment of systemic sclerosis interstitial lung disease. These members noted that the primary endpoint was met, there are no alternative treatment options for fibrotic disease, and SSc-ILD is a rare disease with tremendous unmet need. Several members who voted "Yes" expressed their hesitation in voting the way they did because of the lack of robustness of the data but recognized that there are challenges in conducting trials in this population. The committee members who voted "No" argued that it is worrisome that FVC was used as a surrogate marker, that there was no benefit seen in the secondary outcomes, and the data do not provide "substantial" evidence of efficacy. Some committee members recommended additional trials to assess effects of long-term use and to evaluate more patient-oriented outcomes. Please see the transcript for details of the Committee's discussion.*

4. **VOTE:** Is the safety profile of nintedanib adequate to support approval of nintedanib for the treatment of systemic sclerosis interstitial lung disease?
   a. If no, what further data are needed?

   Vote Result: Yes: 14 No: 2 Abstain: 1

   Committee Discussion: *The majority of committee members voted "Yes", that the safety profile of nintedanib is adequate to support approval of nintedanib for the treatment of SSc-ILD. These members noted that the safety profile is known and in line with what's on the current approved label. Some committee members expressed concern at the extent of gastrointestinal side effects seen, and agreed that it may be difficult to piece out the underlying cause in these patients who already have significant gastrointestinal disruption from their disease state and are on other drugs that may cause similar adverse events. It was also noted that the risk of pneumonia may be hard to interpret given that many patients were on concomitant immunosuppressants. Some members commented that the discussion on acceptable or tolerated level of adverse events should be held between physicians and patients. The committee members who voted "No" noted that the adverse events may precipitate other issues and the magnitude of side effects seems to offset the benefit. The committee member who abstained noted that the safety profile of nintedanib may not be as manageable as discussed. Please see the transcript for details of the Committee's discussion.*

5. **VOTE:** Is the benefit-risk profile adequate to support approval of nintedanib at the proposed dose of 150 mg twice daily for the treatment of systemic sclerosis interstitial lung disease?
   a. If no, what further data are needed?

   Vote Result: Yes: 10 No: 7 Abstain: 0

   Committee Discussion: *The majority of committee members voted "Yes", that the benefit-risk profile is adequate to support approval of nintedanib at the proposed dose of 150 mg twice daily for the treatment of systemic sclerosis interstitial lung disease. They agreed that nintedanib provides a viable option for a disease that has a great unmet need and poor outlook. The committee members who voted "No" noted that the benefit-risk profile is not adequate to support approval of nintedanib because the magnitude and level of evidence for efficacy were small and the side effect profile remains concerning. The committee members noted the need for trials with longer term follow-up and more information on which subgroups of patients will benefit from use of this medication. There was also a recommendation for a trial using a lower dose, such as 100 mg twice daily. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 4:30 p.m.