Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee
March 24-25, 2021

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

Topic: The committees discussed biologics license application (BLA) 761130, tanezumab subcutaneous injection, submitted by Pfizer Inc., for the proposed indication of relief of signs and symptoms of moderate to severe osteoarthritis in adult patients for whom use of other analgesics is ineffective or not appropriate.

These summary minutes for the March 24-25, 2021 joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration were approved on June 3, 2021.

I certify that I attended the March 24-25, 2021 joint meeting of the Arthritis Advisory Committee (AAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Moon Hee V. Choi, PharmD	Maria Suarez-Almazor, MD, PhD
Acting Designated Federal Officer, AAC	Acting Chairperson, AAC

Final Minutes of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee Joint Meeting
March 24-25, 2021

The Arthritis Advisory Committee (AAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) of the Food and Drug Administration, Center for Drug Evaluation and Research, met jointly on March 24-25, 2021. 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 Pfizer Inc. The meeting was called to order by Maria Suarez-Almazor, MD, PhD (Acting Chairperson). The conflict of interest statement was read into the record by Moon Hee V. Choi, PharmD (Acting Designated Federal Officer). There were approximately 592 people online on March 24, 2021 and 600 people online on March 25, 2021. There were a total of 17 Open Public Hearing (OPH) speaker presentations.

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

Agenda:

The committees discussed biologics license application (BLA) 761130, tanezumab subcutaneous injection, submitted by Pfizer Inc., for the proposed indication of relief of signs and symptoms of moderate to severe osteoarthritis in adult patients for whom use of other analgesics is ineffective or not appropriate.

Attendance:
Arthritis Advisory Committee Members Present (Voting): Hetlena J. Johnson, EdS (*Consumer Representative*); Martha C. Nason, PhD; Alyce M. Oliver, MD, PhD; David S. Pisetsky, MD, PhD; J. Steuart Richards, MD; Jasvinder Singh, MD, MPH

Arthritis Advisory Committee Members Not Present (Voting): Mara L. Becker, MD, MSCE**;** John M. Davis III, MD, MS**;** Paul F. Dellaripa, MD**;** Michael H. Weisman, MD**;** Margrit Wiesendanger, MD, PhD

Arthritis Advisory Committee Member Present (Non-Voting): Marek J. Honczarenko, MD, PhD (*Industry Representative*)

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Karim Anton Calis, PharmD, MPH, FASHP, FCCP; Marie R. Griffin, MD, MPH; Laurel A. Habel, MPH, PhD; Sonia Hernandez-Diaz, MD, MPH, DrPH; Collin A. Hovinga, PharmD, MS, FCCP; Martin Kulldorff, PhD; Steven B. Meisel, PharmD, CPPS; Lewis S. Nelson, MD; Suzanne B. Robotti (*Consumer Representative)*

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Denise M. Boudreau, PhD, RPh; Soko Setoguchi, MD, DrPh

Drug Safety and Risk Management Advisory Committee Member Not Present (Non-Voting): Reema J. Mehta, PharmD, MPH (*Industry Representative*)

Temporary Members (Voting): Edward Y. Cheng, MD; Daniel B. Horton, MD, MSCE; Lee D. Katz, MD, MBA; Joseph P. O'Brien, MBA *(Patient Representative);* Maria E. Suarez-Almazor, MD, PhD (*Acting Chairperson*)

FDA Participants (Non-Voting): Billy Dunn, MD**;** Eric Bastings, MD; Rigoberto Roca, MD; Silvana Borges, MD; Cynthia LaCivita, PharmD; Martin Ho, MD

Acting Designated Federal Officer (Non-Voting): Moon Hee V. Choi, PharmD

Open Public Hearing Speakers Present: Meg Seymour, PhD (National Center for Health Research); Raimy R. Amasha, MD; Michael A. Carome, MD (Public Citizen); Arif Khan, MD (Northwest Clinical Research Center); Susan Peschin, MHS (Alliance for Aging Research); Denise Marksberry (Global Healthy Living Foundation); Gary A. Puckrein, PhD (National Minority Quality Forum); Bruce Nicholson, MD (Pennsylvania Pain Society); Madeline Reinert (Mental Health America); Maged Mina, MD; Bill McCarberg, MD; Adriane Fugh-Berman, MD (PharmedOut), Sophia Phillips and Kelvin Blade (Health and the Public Interest); Lilly Stairs (American Autoimmune Related Diseases Association); Monica Mallampalli, PhD (HealthyWomen); Ezekiel Fink, MD (Houston Methodist Hospital); Michele I. Andwele (The Arthritis Foundation); Tonya Horton, EdD

The agenda was as follows:

Day 1: March 24, 2021

Call to Order	**Maria Suarez-Almazor, MD, PhD** Acting Chairperson, AAC
Introduction of Committee and Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Acting Designated Federal Officer, AAC
FDA Opening Remarks	**Rigoberto Roca, MD** Director Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP), Office of Neuroscience (ON) Office of New Drugs (OND), CDER, FDA
GUEST SPEAKER PRESENTATION	
Brief Overview of Patient Preference Information (PPI)	**Deborah A. Marshall, PhD** Professor, Cumming School of Medicine Arthur J.E. Child Chair in Rheumatology, Outcomes Research

Clarifying Questions	
APPLICANT PRESENTATIONS	**Pfizer Inc.**
Introduction	**Ken Verburg, PhD** Senior Vice President, Medicine Team Lead Global Product Development, Internal Medicine Pfizer Inc.
Osteoarthritis: Current Therapeutic Context	**Thomas J. Schnitzer, MD, PhD** Professor of Medicine Northwestern University Feinberg School of Medicine Chicago, IL
Efficacy of Tanezumab in Osteoarthritis	**Ken Verburg, PhD**
Safety of Tanezumab in Osteoarthritis	**Christine West, PhD** Senior Director, Global Clinical Lead Global Product Development Pfizer Inc.
Risk Management Plan	**Anne Hickman, DVM, PhD** Senior Director Global Safety and Risk Management Lead Worldwide Research and Development Pfizer Inc.
Utility of Tanezumab in Clinical Practice and Patient Selection and Monitoring Considerations	**Alan Kivitz, MD, FACR** President Altoona Center for Clinical Research & Altoona Arthritis and Osteoporosis Center
Benefit-Risk and Conclusions	**Ken Verburg, PhD**
Clarifying Questions	
LUNCH	
FDA PRESENTATIONS	
Tanezumab: FDA Efficacy Review	**Mary Therese O'Donnell, MD, MPH** Medical Officer DAAP, OND, ON, CDER, FDA

FDA PRESENTATIONS (CONT.)

Tanezumab: FDA Safety Review	**Anjelina Pokrovnichka, MD** Medical Officer DAAP, OND, ON, CDER, FDA
Tanezumab: FDA Patient Preference Study Review	**Martin Ho, MS** Associate Director Office of Biostatistics and Epidemiology Center for Biologics Evaluation and Research, FDA
Risk Management	**Somya Dunn, MD** CDR, U.S. Public Health Service Risk Management Analyst Division of Risk Management Office of Medication Error Prevention and Risk Office of Surveillance and Epidemiology CDER, FDA
Tanezumab: FDA Summary	**Robert Shibuya, MD** Medical Officer DAAP, OND, ON, CDER, FDA

Clarifying Questions

BREAK

OPEN PUBLIC HEARING

ADJOURNMENT

Day 2: March 25, 2021

Call to Order	**Maria Suarez-Almazor, MD, PhD** Acting Chairperson, AAC
Introduction of Committee and Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Acting Designated Federal Officer, AAC
Charge to the Committee	**Rigoberto Roca, MD**

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committees:

1. **DISCUSSION:** Discuss whether the Applicant has adequately characterized the risk of joint-related adverse reactions that may be caused by tanezumab, including:

    a. Characterization of the risk of destructive arthropathy over time (e.g., whether the risk continues to increase with ongoing tanezumab treatment; whether a risk ceiling is reached after a set duration of treatment).

    b. Evaluation of long-term prognosis and outcome in patients who develop a joint-related adverse reaction and subsequently discontinue tanezumab.

    Committee Discussion*: The committee members expressed concerns with the Applicant's characterization of the risk of destructive arthropathy over time, stating that tanezumab could be used for many years and thus, long-term data from a longer study would be needed to determine the cumulative risks of tanezumab on osteoarthritis. One committee member added that it is unknown whether the risk ceiling has been reached because there are no data on the rate of increase in the risk of destructive arthropathy beyond Week 52. Another committee member noted that the Applicant did not adequately characterize the outcome of patients with composite joint safety endpoint events over time, and only addressed if the patient underwent a total joint arthroplasty (TJA). This committee member added that TJA as an outcome metric is unreliable as the threshold for proceeding with a TJA is highly variable depending upon patient, surgeon, and the native culture as noted by the Applicant. Regarding long-term prognosis after tanezumab discontinuation, the committee members generally agreed that the long-term effects of discontinuation of tanezumab on rapidly progressing osteoarthritis or joint adverse reactions remain unknown. Please see the transcript for details of the Committees' discussion.*

2. **DISCUSSION:** Considering the risk mitigation strategies used in the post-2015 studies with tanezumab:

    a. Discuss whether these strategies are effective in mitigating the risk of destructive arthropathy.

    b. Discuss whether the proposed risk mitigation measures are adequate to identify tanezumab-mediated adverse effects on the joint prior to radiographic evidence of joint damage.

    Committee Discussion*: With the data provided, the committee members generally agreed that the risk mitigation measures used in the post-2015 studies with tanezumab were not effective in mitigating the risk of destructive arthropathy. These committee members stated that the adverse effects of joint destruction or changes in subchondral structure are irreversible changes and, once these changes occur, a total joint replacement is a likely outcome. Therefore, these committee members concluded that the risk mitigation strategies do not reduce/mitigate the risk of joint destruction and would not prevent further progression of the arthropathy. The committee members noted that addressing the long-term effects on the joints may be accomplished with a long-term study. One committee member noted that one*

minor element of this REMS program that could have risk mitigation success would be to limit the concomitant use of NSAIDS while taking tanezumab but admitted that this would be difficult to achieve in real-world clinical practice. Another committee member stated that being able to identify a specific population that would not be at risk for destructive arthropathy or being able to stop treatment at the first sign or symptoms would help mitigate risks but acknowledged that the available evidence does not support this possibility. Please see the transcript for details of the Committees' discussion.

c. Discuss whether these strategies can successfully be implemented in routine clinical use as part of a REMS.

***Committee Discussion**: Overall, the committee members expressed concern with the ability to implement the proposed risk mitigation strategy in routine clinical use as part of a REMS given the adverse effects observed in the study population and the known limitations of tanezumab use. Some committee members noted other challenges to be considered for the use of tanezumab in routine clinical practice, such as patient education on concomitant use of NSAIDS, as many are available over-the-counter and many patients may not be able to distinguish an NSAID from an analgesic such as acetaminophen. Other committee members noted the importance of appropriate training required for the technologist taking the x-ray as well as the need for the REMS to determine which clinical specialty would be caring for the patient as the practice pattern could vary across different clinical settings (e.g., internists, orthopedic surgeons, general radiologists, musculoskeletal radiologists, rheumatologists). Please see the transcript for details of the Committees' discussion.*

d. Discuss whether there are additional risk mitigation components that could be added to prevent or reduce the incidence of structural joint damage.

***Committee Discussion**: One committee member stated that a MRI, in general, will detect the composite joint safety endpoint more accurately than radiographs as the radiographs are dependent upon positioning of the joint and weight bearing. This committee member also noted that the chondral damage may occur in parts of the joint surface not always visible in radiographic profiles with standard anteroposterior/lateral views, and that identifying such chondral damage may require special views, such as the Rosenberg view (i.e., periapical radiograph with weight-bearing and 45 degrees of knee flexion), that could be more sensitive to demonstrating chondral loss. Other committee members suggested patient selection such as enrolling: 1) patients that have severe osteoarthritis only on a single joint and not on the other weight-bearing joint and monitor those joints to mitigate risks of joint damage or 2) patients that have a contraindication to NSAIDs. Please see the transcript for details of the Committees' discussion.*

3. **VOTE:** Will the REMS proposed by the Applicant ensure that the benefits of tanezumab outweigh its risks?

a. If you voted "No", comment on what other studies or information would be needed to address the risks of tanezumab and/or modify the risk mitigation program.

Vote Result: Yes: 1 No: 19 Abstain: 0

***Committee Discussion**: The committee members in a near-unanimous vote, voted "No", agreeing that the REMS proposed by the Applicant did not ensure that the benefits of tanezumab outweigh its risks. Many of these committee members stressed the need for long-term use data to better design the risk mitigation program. Several committee members noted the need for follow-up data on those participants who had stopped taking tanezumab and the effects of rapidly progressing osteoarthritis in these patients. One committee member stated that it would be helpful to see more patient preference data that incorporates the risk to healthy joints vs. forced choice answers. The one committee member who voted "Yes" stated that there were areas where the REMS proposed by the Applicant could be improved with more time, but overall, the benefits of tanezumab outweighed its risks. Please see the transcript for details of the Committees' discussion.*

The meeting was adjourned at approximately 4:37 p.m. ET on March 24, 2021 and at approximately 12:49 p.m. ET on March 25, 2021