Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Bone, Reproductive and Urologic Drugs Advisory Committee Meeting January 16, 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 biologics license application 761062, romosozumab injection, submitted by Amgen, for the proposed indication of treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

These summary minutes for the January 16, 2019, meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee of the Food and Drug Administration were approved on February 11, 2019.

I certify that I attended the January 16, 2019, meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/S/
Kalyani Bhatt, BS, MS
Designated Federal Officer
BRUDAC

/S/
Vivian Lewis, MD
Chairperson
BRUDAC

Summary Minutes of the
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
January 16, 2019

The Bone, Reproductive and Urologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on January 16, 2019, at the FDA White Oak Campus, 10903 New Hampshire Avenue, Building 31 Conference Center The Great Room (Rm. 1503) Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Amgen, Inc. The meeting was called to order by Vivian Lewis, MD (Chairperson). The conflict of interest statement was read into the record by Kalyani Bhatt, BS, MS (Designated Federal Officer). There were approximately 170 people in attendance. There were nine (9) Open Public Hearing speaker presentations.

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

Agenda: The committee discussed biologics license application 761062, romosozumab injection, submitted by Amgen, for the proposed indication of treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

Attendance:
Bone, Reproductive and Urologic Drugs Advisory Committee Members Present (Voting): Douglas C. Bauer, MD; Roger T. Dmochowski, MD; Beatrice Edwards, MD, MPH, FACP (attended via phone); Vivian Lewis, MD (Chairperson); Pamela A. Shaw, PhD

Bone, Reproductive and Urologic Drugs Advisory Committee Members Not Present (Voting): James Q. Clemens, MD, FACS, MSCI**;** Matthew T. Drake, MD, PhD; Margery Gass, MD; Christian P. Pavlovich, MD

Bone, Reproductive and Urologic Drugs Advisory Committee Member Present (Non-Voting): Gerard G. Nahum, MD, FACOG (Industry Representative)

Temporary Members (Voting): Robert A. Adler, MD; Michael Blaha, MD, MPH; Glenn D. Braunstein MD; Kenneth Burman; MD; Natalie Compagni-Portis (Patient Representative); Tobias Gerhard, PhD, RPh; Sundeep Khosla, MD; Frederick G. Kushner, MD, FACC, FAHA, FSCAI, FACP; A. Michael Lincoff, MD; Michele Orza, SCD (Acting Consumer Representative); Clifford J. Rosen, MD; Maria E. Suarez-Almazor, MD, PhD; Thomas J. Wang, MD; Thomas J. Weber, MD

FDA Participants (Non-Voting): Hylton V. Joffe, MD, MMSc; Theresa Kehoe, MD; Jacqueline Karp, MD; Tae Hyun Jung, PhD; Wei Liu, PhD, MSc

Designated Federal Officer (Non-Voting): Kalyani Bhatt, BS, MS

Open Public Hearing Speakers: Elizabeth Thompson (National Osteoporosis Foundation); Judy Black (National Osteoporosis Foundation); Varuna Srinivasan, MBBS MPH (National Center for Health Research); Meena M. Aladdin, PhD (Public Citizen) Andrea J. Singer, MD, FACP, CCD (MedStar Bone Densitometry and Fracture Liaison Service); John Wylam (Aimed Alliance); Kathleen Cody (American Bone Health); Judith Marple (Global Healthy Living Foundation); John Schall (Caregiver Action Network)

The Agenda was as follows:

Call to Order and Introduction of Committee	**Vivian Lewis, MD** Chairperson, BRUDAC
Conflict of Interest Statement	**Kalyani Bhatt, BS, MS** Designated Federal Officer, BRUDAC
FDA Opening Remarks	**Hylton V. Joffe, MD, MMSc** Director, Division of Bone, Reproductive and Urologic Products (DBRUP) Office of Drug Evaluation III (ODE III) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Amgen, Inc.**
Introduction	**Scott Wasserman, MD, FACC** Vice President, Global Development Amgen, Inc.
Osteoporosis: Unmet Medical Need	**Michael McClung, MD, FACP** Founding Director, Oregon Osteoporosis Center
Clinical Efficacy	**Rachel Wagman, MD, FACE** Executive Medical Director, Global Development Amgen. Inc.
Safety – Overall & Cardiovascular	**Scott Wasserman, MD, FACC**
Benefit/Risk	**Scott Wasserman, MD, FACC**
Conclusion	**Steven Galson, MD, MPH** Senior Vice President Global Regulatory Affairs & Safety Amgen, Inc.
Clinical Perspective	**Felicia Cosman, MD** Professor of Medicine Columbia University College of Physician and Surgeons

Clarifying Questions to Applicant

BREAK

FDA PRESENTATIONS

Clinical Efficacy and Safety Assessment	**Jacqueline Karp, MD** Clinical Reviewer DBRUP, ODE III, OND, CDER, FDA
Cardiovascular Safety – Statistical Assessment	**Tae Hyun Jung, PhD** Statistical Reviewer Division of Biometrics VII Office of Biostatistics Office of Translational Sciences, CDER, FDA
Cardiovascular Safety Summary	**Theresa Kehoe, MD** Cross Discipline Team Leader DBRUP, ODE III, OND, CDER, FDA
Feasibility of Using Observational Data to Assess Cardiovascular Risks Associated with Romosozumab	**Wei Liu, PhD, MSc** Reviewer Division of Epidemiology II Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology, CDER, FDA

Clarifying Questions to FDA

LUNCH

OPEN PUBLIC HEARING

Clarifying Questions to Applicant or FDA

BREAK

Questions to the Committee/Committee Discussion and Voting

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss whether the cardiovascular safety of romosozumab has been adequately characterized. If additional safety data are needed, discuss the type(s) of data that are needed and whether these data should be obtained pre-approval or post-approval.

   Committee Discussion: *The committee members agreed that the cardiovascular safety profile of romosozumab has not been adequately characterized. Committee members noted that it is unclear whether there is an increased cardiovascular risk with romosozumab, given the differences between the two trials (337 and 142). All members agreed that additional data are necessary to better characterize the potential cardiovascular risk. Most members agreed that a traditional observational study would not provide reliable data to draw conclusions regarding romosozumab's cardiovascular safety. This concern was based on the likely channeling of the use of the drug to patients with low cardiovascular risk given that a Boxed Warning about cardiovascular risk is contemplated. To mitigate the effect of channeling, baseline randomization would be needed. Some members recommended a dedicated cardiovascular outcomes trial (CVOT) to better characterize the risk. Most members recognized that a dedicated CVOT would provide the most reliable data, although some thought it would not be feasible because it would likely require many thousands of patients and take several years to complete. Some suggested that enriching the population with patients at higher cardiovascular risk would help to overcome this limitation. Proponents of a CVOT agreed that it should be active-controlled rather than placebo-controlled to ensure clinical equipoise in a population at high risk of fracture.*

   Another recommendation was to use a "pragmatic" or "hybrid" trial that randomizes patients at baseline (to either romosozumab or active control) and utilizes existing healthcare systems (e.g., claims databases, electronic health records) to overcome some of the limitations of both traditional observational studies and randomized controlled trials.

   Regarding the timing of an additional study examining cardiovascular safety, all but one member agreed that the study could be conducted post-approval.

   Because the available nonclinical data do not provide evidence of a mechanistic cause to explain a higher risk of cardiovascular events with romosozumab, some members also recommended additional nonclinical studies of sclerostin's effect on the cardiovascular system.

   Please see the transcript for details of the committee discussion.

2. **DISCUSSION**: Amgen is seeking an indication for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

Discuss whether the benefit/risk profile of romosozumab could be improved by further narrowing the indicated population to patients at low cardiovascular risk, and if so, how to define the narrowed population.

Committee Discussion: *The committee members agreed that romosozumab appears to be effective and that there is significant benefit in preventing the morbidity and mortality associated with osteoporosis. However, because of the uncertainties surrounding the cardiovascular risk of romosozumab, some members stated that it may be challenging for physicians and patients to weigh the benefits and risks on an individual basis. Additionally, the panel members noted that withholding the drug from anyone with a single cardiovascular disease risk factor may deny a greatly needed benefit (e.g., prevention of potential morbidity and mortality associated with severe osteoporosis). Several committee members cited data showing that the risk of major adverse cardiac events is highest for patients who have had a myocardial infarction or stroke within the past year. Most members agreed that the best approach would be to warn against romosozumab use in this population.*

In addition, a few committee members recommended more clarity in the definition of "high risk for fracture" in order to help better guide selection of the individual patients for whom the benefits would likely outweigh the risks. One member stated that the phrase "intolerant to other available osteoporosis therapy" was not specific enough.

Several members also noted that it would be useful to have data that would provide greater context for clinical decision making. For example, studies that evaluate romosozumab's effects on quality of life or functional status may provide additional context when discussing the benefits and risks.

Please see the transcript for details of the committee discussion.

3. **VOTE**: Is the overall benefit/risk profile of romosozumab acceptable to support approval?

    A. Yes, for Amgen's proposed indication (treatment of osteoporosis in postmenopausal women at high risk of fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy)

    B. Yes, but for a different indication

    C. No

    Provide a rationale for your vote. If you voted for (B), describe the patient population in whom the benefits outweigh the risks.

    Votes submitted into the system/record

    Vote Result: ***A: 15*** ***B: 3*** ***C: 1***

One panel member who voted "B" meant to vote for A. As a result, A is 16, B is 2 and C is 1.

Most committee members voted "A" in support of approval of Amgen's proposed indication for romosozumab. These panel members agreed that romosozumab is clearly effective for treating severe osteoporosis, a common serious disease for which therapeutic options are limited and that these benefits outweigh the identified and potential risks. However, members recommended that an additional study be conducted post-approval to better characterize romosozumab's potential cardiovascular risk. Additionally, there was wide support among members for including a Boxed Warning recommending against use in patients at highest risk for major adverse cardiac events, particularly those with a recent myocardial infarction or stroke until the cardiovascular risk of romosozumab is better characterized.

One of the members who voted "B" had concerns about the potential safety signal and had suggested the need for a Risk Evaluation and Mitigation Strategy (REMS) or additional pre-approval data. The other member who voted "B" stated that the phrase "intolerant to other available osteoporosis therapy" was too vague.

The one member who voted "C" stated that there is not enough evidence to determine whether or not the benefits outweigh the risks.

Please see the transcript for details of the committee discussion.

The meeting adjourned at approximately 4:00 p.m.