Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting
September 17, 2014

Location: College Park Marriott Hotel and Conference Center, 3501 University Blvd.
Hyattsville, Maryland

Topic: The committees discussed the appropriate indicated population for testosterone replacement therapy and the potential for adverse cardiovascular outcomes associated with this use.

These summary minutes for the September 17, 2014, joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee were approved on October 5, 2014.

I certify that I attended the September 17, 2014, joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflects what transpired.

_____/Signed/_____
Kalyani Bhatt
Designated Federal Officer, BRUDAC

_____/Signed/_____
Julie Johnson, MD
Chairperson, BRUDAC

Summary Minutes of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting
September 17, 2014

The following is the final report of the joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on September 17, 2014. A verbatim transcript will be available in approximately six weeks, sent to the Division of Bone, Reproductive and Urologic Products and the Office of Surveillance and Epidemiology and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/ucm404895.htm and http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm380883.htm.

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and Drug Safety and Risk Management Advisory Committee (DSaRM) of the Food and Drug Administration, Center for Drug Evaluation and Research, met jointly on September 17, 2014, at the College Park Marriott Hotel and Conference Center, 3501 University Blvd. Hyattsville, Maryland. Prior to the meeting, the committee members and temporary voting members were provided background materials from the FDA and Industry. The meeting was called to order by Julia Johnson, MD (Chairperson). The conflict of interest statement was read into the record by Kalyani Bhatt, BS, MS (Designated Federal Officer). There were approximately 380 people in attendance. There were fifteen (15) Open Public Hearing speakers.

Issue: The committees discussed the appropriate indicated population for testosterone replacement therapy and the potential for adverse cardiovascular outcomes associated with this use.

Attendance:

Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) Members Present (Voting): Toby C. Chai, MD; Kathryn M. Curtis, PhD; Amy H. Herring, ScD; Stuart S. Howards, MD; Julia V. Johnson, MD *(Chairperson)*

BRUDAC Member (Non-Voting): Keith Gordon, PhD *(Industry Representative)*

BRUDAC Members Not Present (Voting): Jennifer Dietrich, MD; Vivian Lewis, MD; Clifford J. Rosen, MD; Amy K. Whitaker, MD, MS

DSaRM Members Present (Voting): Brian L. Erstad, PharmD; Tobias Gerhard, PhD, RPh, Marjorie Shaw Phillips, MS, RPh, FASHP; Linda S. Tyler, PharmD

DSaRM Members Not Present (Voting): Karen M. Hopkins, MD *(Consumer Representative)*; Jeanmarie Perrone, MD, FACMT; Andy S. Sterghais, PhD, RPh; Til Stürmer, MD, MPH, PhD

DSaRM Member Not Present (Non-Voting): Patrizia Cavazzoni, MD *(Industry Representative)*

Temporary Members (Voting): Robert A. Adler, MD; Richard B. Alexander, MD; Robin Boineau, MD, MA; Kenneth D. Burman, MD; Glenn D. Braunstein, MD; Roger Dmochowski, MD; Michael Domanski, MD; Marc Garnick, MD; A. Michael Lincoff, MD; Nadine Shehab, PharmD, MPH; John R. Teerlink, MD; Abraham Thomas, MD, MPH

Temporary Members Not Present (Voting): Craig Lustig, MPA *(Patient Representative)*

Guest Speakers: Mark Sigman, MD; Peter J. Snyder, MD

FDA Participants (Non-Voting):
Julie Beitz, MD; Mark Hirsch, MD; Hylton V. Joffe, MD, MMSc; Christine Nguyen, MD; Solomon Iyasu, MD, MPH; Judy Staffa, PhD, RPh; CDR David Moeny, RPh, MPH, USPHS

Designated Federal Officer: Kalyani Bhatt, BS, MS

Open Public Hearing Speakers: Michael A. Carome, MD (Health Research Group Public Citizen); Paul Brown (National Center for Health Research); Paresh Dandona (American Association of Clinical Endocrinologists); Richard Swerdloff, MD (Endocrine Society); Richard Todd Light, MD; Mark Richards MD; Ajay K. Nangia, MBBS, FACS (The American Urological Association); Abraham Morgentaler, MD (Harvard Medical School); Vikas Vats, MD (Tesvgen, LLC); Brandon Leonard (Men's Health Network); Frederick Wu (Repros Therapeutics); Robert Cripe; Martin T. Wells, PhD (Cornell University); Robert Cunningham; Adriane Fugh-Berman, MD (Georgetown University Medical Center)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Julia Johnson, 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

GUEST PRESENTATIONS

Male Hypogonadism	**Peter J. Snyder, MD** Professor of Medicine Division of Endocrinology, Diabetes, and Metabolism University of Pennsylvania
Male Hypogonadism	**Mark Sigman, MD** Krishnamurthi Family Professor and Chief of Urology Warren Alpert Medical School of Brown University Chief of Urology Rhode Island Hospital and The Miriam Hospital
Clarifying Questions to the Guest Presenters	

INDUSTRY PRESENTATIONS

Introduction	**Dr. Kraig Kinchen, MD, MSc** Senior Medical Director, Global Urology Team Eli Lilly and Company
Hypogonadism and Clinical Benefits of Testosterone Replacement Therapy	**Dr. Adrian Dobs, MD** Director Clinical Research Network Johns Hopkins University School of Medicine
Cardiovascular Events and Testosterone Replacement Therapy	**Dr. Shalender Bhasin, MD** Director, Research Program in Men's Health: Aging and Metabolism and Director Boston Claude D. Pepper Older Americans Independence Center Brigham and Women's Hospital Harvard Medical School
Drug Utilization, Industry Recommendations and Conclusions	**Dr. Rita Jain, MD** Vice President, Clinical Development, Men & Women's Health & Metabolics, AbbVie Inc.
Clarifying Questions to Industry	

FDA PRESENTATIONS

Testosterone Replacement Therapy and Drug Utilization Patterns	**Mohamed Mohamoud, PharmD, MPH, BCPS** Drug use Analyst Division of Epidemiology II Office of Surveillance and Epidemiology (OSE) CDER, FDA

Prescription Drug Promotion - Testosterone Replacement Therapy	**Trung-Hieu Brian Tran, PharmD, MBA** Regulatory Review Officer Division of Consumer Drug Promotion (DCDP) Office of Prescription Drug Promotion (OPDP) Office of Medical Policy (OMP), CDER, FDA
Current Issues in Drug Development and Indicated Population	**Mark S. Hirsch, MD** Medical Team Leader in Urology DBRUP, ODE III, OND, CDER, FDA
Testosterone Therapy and Cardiovascular Risk: Surveillance, Observational and RCT Data	**Monique Falconer, MD, MS** Epidemiologist Division of Epidemiology II OSE, CDER, FDA

Clarifying Questions to FDA

Open Public Hearing

Clarifying Questions

Questions to the Committee/Committee Discussion

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. The current approach to establishing the efficacy and safety of testosterone products for marketing approval is based upon pharmacokinetic assessments of serum testosterone concentrations and an acceptable safety profile. The product must be able to reliably raise low serum testosterone concentrations into the normal range for healthy, eugonadal men. FDA does not require a demonstration that testosterone products ameliorate or improve any specific hypogonadal sign or symptom.

    a. **DISCUSSION:** Describe the specific patient populations for which approval is supported based on data generated from this current approach.

Committee Discussion: *The joint committees agreed that the use of testosterone replacement products in men with inherited or acquired loss of testosterone production in conjunction with a recognized disease condition ("classical" hypogonadism") was supported by data. There was general consensus that the current paradigm for drug development is not capable of generating data in support of testosterone replacement therapy for "age-related hypogonadism". Committee members agreed that the current information supports an indication only for classical hypogonadism and not for age-related hypogonadism. There was consensus that the labeling for testosterone needs to be revised accordingly to reflect the*

appropriate indicated population. Some committee members expressed a concern that age-related hypogonadism had not yet been established as a disease condition. Two members opined that testosterone therapy may be justified in selected older men with significant hypogonadal signs/symptoms and documented 'very low' serum testosterone concentrations (e.g., less than 100 ng/dL). However, even these two committee members recognized the need for additional research to assess the effectiveness of testosterone therapy for this patient population. The joint committees agreed that the use of testosterone therapy for symptomatic men without documented low testosterone levels was not appropriate. Please see the transcript for details of the committees' discussion.

b. **DISCUSSION:** Discuss changes that would be needed in the current development paradigm to support an indication for testosterone replacement therapy in men with "age-related" hypogonadism.

Committee Discussion: *The committee members reiterated the need to revise the testosterone labeling to clarify that the efficacy and safety for testosterone therapy in age-related hypogonadism have not been established. Committee members expressed the need to better characterize and clinically define age-related hypogonadism and to conduct additional clinical research to establish the efficacy and safety of testosterone in this population. There was general consensus that clinical studies using meaningful clinical endpoints were needed if a Sponsor were to seek an indication for age-related hypogonadism in the future. The committee stated that more studies on the risk of therapy are needed to assess cardiovascular and other risks associated with short term and long term use of testosterone for age-related hypogonadism. The committees recommended randomized controlled trials be conducted on the use of testosterone to assess the benefits and risks in age-related hypogonadism. Please see the transcript for details of the committee's discussion.*

2. **DISCUSSION:** Discuss whether the totality of the data indicates a cardiovascular safety signal associated with the use of testosterone therapy. Include in your discussion:

   a. The strength of the signal.

   b. Whether you believe the signal is restricted to a certain subset of the population using testosterone products (e.g., older men) or whether it applies to all users.

   c. Whether the current evidence concerning the association of major adverse cardiovascular events and testosterone replacement therapy warrants inclusion in labeling.

Committee Discussion: *The advisory committee panel acknowledged that, in general, the available studies informing the cardiovascular safety signal with testosterone therapy are limited in scope, quality, design, and size. Nonetheless, there was agreement amongst committee members that a weak signal of cardiovascular risk had emerged from results of recent large epidemiologic studies. Given this signal coupled with biologic plausibility for*

cardiovascular-related adverse events with testosterone use, committee members believed that the need for additional studies was critical.

The advisory committee panel concluded that there was not enough evidence to suggest that the potential cardiovascular risk was confined to a certain subset of users of testosterone therapy. The committee commented, however, that safety in higher cardiovascular risk populations, such as older men, those with diabetes, and obese men, had not been adequately studied. Some committee members suggested heightened caution for patients at higher risk for cardiovascular disease.

Overall the committee agreed that the potential signal for cardiovascular risk should be added to the labeling. Most committee members recommended cautionary wording that would reflect the known information regarding potential risk, while a few others suggested a boxed warning.

Please see the transcript for details of the committees' discussion.

3. **VOTE:** The current indication for testosterone replacement therapy is:

"DRUG X is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone

- *Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testes syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.*
- *Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range."*

Should the FDA revise the current indication for testosterone therapies?

Yes: 20 ***No: 1*** ***Abstain: 0***

a. Please provide a rationale for your vote. If you vote to change the indication, describe the specific changes you are recommending to the indication.

Committee Discussion: *There was virtual unanimous agreement that FDA should revise the current indication for the class of testosterone replacement therapy. Committee members stated that the indication should limit testosterone replacement therapy to men with classical hypogonadism. The committees commented that the label should include statements to address the potential cardiovascular risks of testosterone therapy, the importance of proper testing of serum testosterone concentrations to confirm the diagnosis, and that efficacy and*

safety in age-related hypogonadism have not been established. Please see the transcript for details of the committees' discussion.

4. **VOTE:** Should FDA require sponsors of testosterone products to conduct a study (e.g., observational study, controlled clinical trial) to further assess a potential cardiovascular risk with the use of testosterone replacement therapy?

    a. No, a study should not be required
    b. Yes, but only for certain indication(s) for testosterone therapy. When explaining your vote, please specify which indication(s) should prompt the need for a cardiovascular study.
    c. Yes, regardless of the indication for testosterone therapy

    A: 1 B: 16 C: 4 Abstain: 0

    a. Please provide a rationale for your vote. If you voted yes (option B or C), discuss the type of study that should be required (e.g., observational study, controlled clinical trial). Include a discussion of the study population that should be enrolled as well as an acceptable degree of risk that would need to be excluded.

Committee Discussion: *The majority of the committee members agreed that a study is needed only for certain indications for testosterone therapy. These panel members specified a study is needed for age-related hypogonadism. Four committee members stated that a study is needed regardless of indication. These 4 members were concerned that the majority of testosterone therapy will continue to be prescribed for age-related hypogonadism, despite revisions to the indication. The one committee member who voted, "No" explained that he recommended the cardiovascular study be conducted by NIH rather than by industry sponsors. Please see the transcript for details of the committees' discussion.*

The meeting was adjourned at approximately 5:15 pm.