Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the of the
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
December 6, 2016

Location: Tommy Douglas Conference Center, Building 9, Ballroom C&D, 10000 New Hampshire Avenue, Silver Spring, Maryland.

Topic: The committee discussed appropriate clinical trial design features, including acceptable endpoints for demonstrating clinical benefit, for drugs intended to treat secondary hypogonadism while preserving or improving testicular function, including spermatogenesis.

These summary minutes for the December 6, 2016, meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee of the Food and Drug Administration were approved on _January 30, 2017_.

I certify that I attended the December 6, 2016, 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/
LaToya Bonner, PharmD
Acting Designated Federal Officer, BRUDAC

/s/
Vivian Lewis, MD
Chairperson, BRUDAC

Summary Minutes of the
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
December 6, 2016

The following is ther final report of the Bone, Reproductive and Urologic Drugs Advisory Committee meeting held on December 6, 2016. A verbatim transcript will be available in approximately two weeks, sent to the Division of Bone, Reproductive and Urologic Products and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/ucm507639.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 of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 6, 2016, at the Tommy Douglas Conference Center, Building 9, Ballroom C&D, 10000 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 Applicants (Repros Therapeutics Inc., Veru Healthcare and MHB Labs, Inc.). The meeting was called to order by Vivian Lewis, MD (Chairperson). The conflict of interest statement was read into the record by LaToya Bonner, PharmD (Acting Designated Federal Officer). There were approximately 100 people in attendance. There were three (3) Open Public Hearing speaker presentations.

Issue: The committee discussed appropriate clinical trial design features, including acceptable endpoints for demonstrating clinical benefit, for drugs intended to treat secondary hypogonadism while preserving or improving testicular function, including spermatogenesis.

Attendance:

Bone, Reproductive and Urologic Drugs Advisory Committee Members Present (Voting): Douglas C. Bauer, MD; Toby Chai MD; Kathryn M. Curtis, PhD; Roger T. Dmochowski, MD; Matthew T. Drake, MD, PhD; Vivian Lewis, MD (Chairperson); Stuart S. Howards, MD; Sarah E. Sorscher, JD, MPH (Consumer Representative)

Bone, Reproductive and Urologic Drugs Advisory Committee Members Not Present (Voting): Anne E. Burke, MD, MPH; Amy D Herring, ScD

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; George A. Bishopric, MD (Patient Representative); Diane M. Biskobing, MD; Robert E. Brannigan, MD; Glenn D. Braunstein, MD; Kenneth Burman, MD; Daniel Gillen, PhD; Philip Hanno, MD, MPH; Kurt McCammon,

MD; Jay Sandlow, MD; Peter Schlegel, MD; Abraham Thomas, MD, MPH; Kevin Weinfurt, PhD

FDA Participants (Non-Voting): Hylton V. Joffe, MD, MMSc; Audrey Gassman, MD; Olivia Easley, MD; Selena Daniels, PharmD, MS; Suresh Kaul, MD, MPH

Open Public Hearing Speakers: JohnTeal, MD; Wayne Hellstrom, MD (International Society of Sexual Medicine and Sexual Medicine Society of North America); Leila Rahimi (American Urology Association)

The agenda was as follows:

Call to Order and Introduction of Committee	**Vivian Lewis, MD** (Chairperson), BRUDAC
Conflict of Interest Statement	**CDR LaToya Bonner, PharmD, NCPS** Acting Designated Federal Officer, BRUDAC
FDA Introductory 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 SPEAKER PRESENTATION	
Treatment of Secondary Hypogonadism	**Sergio Oehninger, MD, PhD** Director, Division of Reproductive Endocrinology The Jones Institute for Reproductive Medicine Eastern Virginia Medical School
Clarifying Questions to the Guest Speaker	
INDUSTRY PRESENTATIONS	
Introduction	**Michael Wyllie, PhD** Managing Director, Global Pharma Consulting, Ltd. Introduction
Treatment Considerations for Secondary Hypogonadism	**Mohit Khera, MD** Associate Professor of Urology Baylor College of Medicine

INDUSTRY PRESENTATIONS (CONT.)

Sperm Concentration is an Acceptable Endpoint for Demonstrating Clinical Benefit in Men who Have Hypogonadotropic Hypogonadism and Oligozoospermia (Impaired Spermatogenesis) as a Cause of Male Infertility	**Edward Kim, MD** Professor of Surgery University of Tennessee Graduate School of Medicine
Human Chorionic Gonadotropin	**Mohit Khera, MD**
Diagnostic Categories of Hypogonadism and Secondary Hypogonadal Population	**Frederick Wu, MD** Professor of Medicine and Endocrinology University of Manchester
Weight Associated, Secondary Hypogonadism: An acquired Estrogen-Dependent Disorder	**Andrew McCullough, MD** Director of Male Sexual Health, Urology Department Lahey Health and Medical Center
Summary and Conclusions	**Michael Wyllie, PhD**

Clarifying Questions to Industry

BREAK

FDA PRESENTATIONS

FDA Clinical Perspective on Development of Non-Testosterone Products to Treat Male Secondary Hypogonadism	**Olivia Easley, MD** Medical Officer DBRUP, ODE III, OND, CDER, FDA
Regulatory Approach to Clinical Outcome Assessment Review for Drug Development	**Selena Daniels, PharmD, MS** Team Leader, Clinical Outcome Assessments Staff OND, CDER, FDA

Clarifying Questions to FDA

LUNCH

Open Public Hearing

Clarifying Questions to the Guest Speaker, Industry or FDA

BREAK

Questions to the Committee/Committee Discussion and Voting

ADJOURN

Questions to the Committee:

1. **DISCUSSION:** For drugs intended to treat secondary hypogonadism while preserving existing testicular function (e.g., maintenance of sperm parameters or demonstration of continued fertility), discuss:

    a. The patient population that should be enrolled in clinical trials
    b. How preservation of testicular function should be defined and assessed
    c. Acceptable endpoints for demonstrating clinical benefit for men with classic hypogonadism and for those who do not have classic hypogonadism
    d. Other trial design features that should be considered

    Committee Discussion:
    Committee members stated that the patient population enrolled in clinical trials should have symptom(s) of hypogonadism with confirmed low serum testosterone measurements at baseline. Several members stated that, for men who do not have "classical" hypogonadism, the trials should be designed to show improvement in hypogonadal symptom(s) or sign(s).

    Regarding the assessment of preservation of testicular function, different viewpoints were expressed, with recommendations ranging from only assessing sperm concentration and quality to demonstating pregnancy outcomes. Rationale for relying on pregnancy outcomes included the intent of these therapies to preserve the ability to father a child and prior studies where this outcome had been successfully evaluated. Rationale for relying on sperm parameters included challenges with using a pregnancy outcome, for example, some patients may not be actively seeking pregnancy but may want to maintain fertility for the future.

    Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** For drugs intended to treat secondary hypogonadism while improving testicular function (e.g., improved sperm parameters or amelioration of infertility), discuss:

    a. The patient population that should be enrolled in clinical trials
    b. How improvement in testicular function should be defined and assessed
    c. Acceptable endpoints for demonstrating clinical benefit for men with classic hypogonadism and for those who do not have classic hypogonadism
    d. Other trial design features that should be considered

    Committee Discussion*: The committee suggested that the patient population that should be enrolled should have the following characteristics:*

    - *At least one abnormal semen parameter (based on more than one semen analysis)*
    - *Normal or low serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations*
    - *Seeking treatment for infertility*
    - *Female partner has been evaluated by a reproductive endocrinologist and the cause of the couple's infertility is not considered due to the female partner*

With regard to acceptable endpoints for demonstrating clinical benefit, again, various viewpoints were expressed, including:

- *Using semen parameters for patients who have azoospermia at baseline*
- *Using semen parameters regardless of whether there is azoospermia or oligospermia at baseline; although several members noted that the extent to which increases in sperm parameters would impact fertility is not well-known*
- *Showing that the treatment reduces the burden of infertility treatment for a couple desiring fertility, such as changing the intervention from needing IVF (in vitro fertilization)to needing IUI (intrauterine insemination)*
- *Using fertility outcomes if the intent is to father a child*

Some committee members recommended a pregnancy registry if the patients involved are actively seeking fertility.

Please see the transcript for details of the committee discussion.

3. **VOTE:** For products intended to treat men with hypogonadism attributed to obesity, is raising serum testosterone concentrations into the normal range for young, healthy eugonadal men and preservation of spermatogenesis, as assessed by maintenance of sperm concentrations, sufficient for establishing evidence of clinical benefit?

   If you voted "no," describe what endpoints would be needed to provide sufficient evidence of clinical benefit for such products. If you voted "yes," specify how preservation of spermatogenesis should be defined based on sperm concentrations, and provide an explanation for your definition.

   Vote Result: Yes: 5 No: 16 Abstain: 0

   Committee Discussion: *The majority of the committee voted "No," stating that raising testosterone concentrations and maintaining spermatogenesis is not sufficient evidence of clinical benefit. Most members stated that the treatment would need to show an improvement in symptom(s) or sign(s) of hypogonadism.*

   One committee member hoped that sponsors could build on work done on existing instruments rather than develop an entirely new instrument, which could streamline the drug development process.

   Some of the committee members who voted "Yes," stated they had assumed that the patients noted in the question had symptomatic hypogonadism, in which case raising testosterone concentration and maintaining spermatogenesis could demonstrate clinical benefit.

   Please see the transcript for details of the committee discussion.

4. **VOTE:** For products intended to treat men with classic secondary hypogonadism and azoospermia or oligospermia, is raising sperm concentration above a specific threshold sufficient evidence of clinical benefit?

a. Yes, but only for azoospermia
b. Yes, but only for oligospermia
c. Yes, for azoospermia and oligospermia
d. No

Include rationale for your answer. If you voted "no," describe what endpoint(s) would be needed to provide sufficient evidence of clinical benefit for such products. If you voted "yes," (chose a, b, or c), specify the threshold for sperm concentration that should be exceeded to establish evidence of clinical benefit and explain why you selected that threshold.

Vote Result: A: 2 B: 0 C:13 D:6 No-Voting: 0 Abstain: 0

Committee Discussion: The *majority of the committee voted "C" indicating that raising the sperm concentration above a given threshold is sufficient evidence of clinical benefit for men with classic secondary hypogonadism and azoospermia or oligospermia. While it was acknowledged that achievement of pregnancy and a live birth is the ultimate goal when treating men with azoospermia or oligospermia, several members stated that pregnancy outcomes would be a challenging endpoint because it may require a long duration of follow-up and is also confounded by factors other than oligospermia or azoospermia (such as female factors).*

The two committee members who voted "A," commented that increasing an azoospermic patient's sperm concentration from undetectable to above a threshold that makes them eligible for noninvasive fertility procedures, such as IVF/intra-cytoplasmic sperm injection (ICSI), could provide evidence of clinical benefit.

Committee members who voted "D" (i.e., "No") stated that a pregnancy outcome is the only clinically meaningful endpoint to patients who are infertile.

Note that the vote result reflects the original vote. Two members who voted "C"stated that they intended to vote "D" and one member who voted "D" stated that he had intended to abstain from voting.

Please see the transcript for details of the committee discussion.

5. **VOTE:** For products intended to treat men with secondary hypogonadism and azoospermia or oligospermia, but who do not have classic hypogonadism, is raising sperm concentration above a specific threshold sufficient evidence of clinical benefit?

    a. Yes, but only for azoospermia

b. Yes, but only for oligospermia
c. Yes, for azoospermia and oligospermia
d. No

Include rationale for your answer. If you voted "no," describe what endpoint(s) would be needed to provide sufficient evidence of clinical benefit for such products. If you voted "yes," (chose a, b, or c), specify the threshold for sperm concentrations that should be exceeded to establish evidence of clinical benefit and explain why you selected that threshold.

Vote Result: A: 2 B: 0 C:8 D:10 No-Voting: 0 Abstain: 1

Committee Discussion: *Ten of the 21 committee members voted "D," stating that raising the sperm concentration for men with "non-classic" secondary hypogonadism and azoospermia or oligospermia above a specific threshold would not provide evidence of clinical benefit, and that pregnancy outcomes would be needed. One member noted that men with "non-classical" secondary hypogonadism is a heterogeneous population that is not well-defined.*

Committee members who voted "C," stated that raising sperm concentrations of azoospermic or oligospermic patients above a specific threshold could be evidence of clinical benefit if the patient can then undergo certain infertility treatments (e.g., IVF/ICSI in a patient who was previously azoospermic) or have reduced burden of infertility treatment (e.g., IUI in a patient who would otherwise have needed IVF/ICSI).

Committee members who voted "A," concurred with the rationale that increasing sperm counts from undetectable at baseline to a detectable concentration after treatment could be favorable if patients then become eligible for certain infertility interventions such as IVF/ICSI. However, they stated that it is unclear what sperm concentration threshold in oligospermic patients would provide evidence of clinical benefit.

Note that the vote result reflects the original vote. One member who had originally voted "C," subsequently noted into the record during the explanation of the vote that he meant to vote "A".

Please see the transcript for details of the committee discussion.

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