Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Bone, Reproductive and Urologic Drugs Advisory Committee Meeting January 9, 2018

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 new drug application (NDA) 206089, oral testosterone undecanoate capsules, submitted by Clarus Therapeutics, for the proposed indication of testosterone replacement in males for conditions associated with a deficiency or absence of endogenous testosterone: primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired).

These summary minutes for the January 9, 2018, meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee of the Food and Drug Administration were approved on February 28, 2018.

I certify that I attended the Janaury 9, 2018, 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
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
January 9, 2018

The following is a final report of the Bone, Reproductive and Urologic Drugs Advisory Committee meeting held on January 9, 2018. A verbatim transcript will be available in approximately six weeks, sent to the Division of Bone, Reproductive and Urologic Products and posted on the FDA website at:
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/ucm585826.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 January 9, 2018, at the College Park Marriott Hotel and Conference Center, General Vessey Ballroom, 3501 University Blvd. East Hyattsville, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Clarus Therapeutics. The meeting was called to order by Vivian Lewis, MD (Chairperson). The conflict of interest statement was read into the record by Kalyani Bhatt, PharmD (Designated Federal Officer). There were approximately 100 people in attendance. There were ten (10) Open Public Hearing speaker presentations.

Issue: The committee discussed new drug application (NDA) 206089, oral testosterone undecanoate capsules, submitted by Clarus Therapeutics, for the proposed indication of testosterone replacement in males for conditions associated with a deficiency or absence of endogenous testosterone: primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired).

Attendance:

Bone, Reproductive and Urologic Drugs Advisory Committee Members Present (Voting): Douglas C. Bauer, MD; Roger T. Dmochowski, MD (attended via phone); Matthew T. Drake, MD, PhD; Beatrice Edwards, MD, MPH, FACP; Margery Gass, MD; Vivian Lewis, MD (Chairperson); Pamela A. Shaw, PhD; Sarah E. Sorscher, JD, MPH (Consumer Representative)

Bone, Reproductive and Urologic Drugs Advisory Committee Members Not Present (Voting): Anne E. Burke, MD, MPH; 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; George Bishopric (Patient Representative); Robert Brannigan, MD; Glenn D. Braunstein MD; Tobias Gerhard, PhD, RPh;

Stuart S. Howards, MD; Ziya Kirkali, MD; A. Michael Lincoff, MD; Donald E. Mager, PharmD, PhD; Robert Rej, PhD; Peter W.F. Wilson, MD

FDA Participants (Non-Voting): Hylton V. Joffe, MD, MMSc; A. Roger Wiederhorn, MD, DMSci; Dhananjay D. Marathe, PhD; Preston Dunnmon, MD; Chongwoo Yu, PhD

Open Public Hearing Speakers: Jason DallaGrana; Stefan Schwarz; Virginia Cover; Gary Glissman; Sheryl K. Kelly; Ryan Bregante; Randy Scott Lane; Kelsey Maffei; David Davis, Daniel Shapiro, MD, MPH (National Center for Health Research)

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
INDUSTRY PRESENTATION	**Clarus Therapeutics, Inc.**
Introduction	**Robert Dudley, PhD, DABT** President & CEO, Clarus Therapeutics, Inc.
Medical Landscape	**John K. Amory, MD, MPH, MS** Professor of Medicine University of Washington School of Medicine Seattle, Washington
Efficacy	**Ronald S. Swerdloff, MD** Distinguished Professor of Medicine David Geffen School of Medicine at UCLA Chief, Division of Endocrinology Harbor-UCLA Medical Center
Non-Cardiovascular Safety	**Theodore Danoff, MD, PhD** Chief Medical Officer, Clarus Therapeutics, Inc.
Cardiovascular Safety Assessment	**William B. White, MD** Professor of Medicine and Chief Hypertension and Clinical Pharmacology Division University of Connecticut Health

INDUSTRY PRESENTATION (CONT.)

Safety Conclusions and Risk Management

Clinical Practice Perspective	**Theodore Danoff, MD, PhD**
	Jed Kaminetsky, MD Clinical Assistant Professor, Department of Urology NYU Langone Health Medical Director, Manhattan Medical Research
Closing Comments	**Robert Dudley, PhD, DABT**

Clarifying Questions to Industry

BREAK

FDA PRESENTATIONS

Ambulatory Blood Pressure Analysis	**Preston Dunnmon, MD** Medical Officer Division of Cardiovascular and Renal Products (DCRP) ODE I, OND, CDER, FDA
Additional Clinical Effects	**A. Roger Wiederhorn, MD, DMSci** Medical Officer DBRUP, ODE III, OND, CDER, FDA
Dose Titration Algorithm	**Dhananjay D. Marathe, PhD** Pharmacometrics Reviewer Division of Pharmacometrics (DPM) Office of Clinical Pharmacology (OCP) Office of Translational Sciences (OTS), CDER, FDA
Bioanalysis	**Chongwoo Yu, PhD** Clinical Pharmacology Reviewer Division of Clinical Pharmacology-III (DCP-III) OCP, OTS, CDER, FDA

Clarifying Questions to the FDA

LUNCH

OPEN PUBLIC HEARING

Clarifying Questions to Industry or FDA

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. ***DISCUSSION:*** Discuss whether the safety of Jatenzo 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 whether these data can be obtained post-approval. Specifically cover:

    a. The effects of Jatenzo on cardiovascular risk factors, including blood pressure and lipids, together with effects on hematocrit, and the potential for Jatenzo to increase the risk of adverse cardiovascular outcomes in the population that will likely use the drug, if it is approved.

    b. Supraphysiologic dihydrotestosterone (DHT) concentrations in some subjects.

    c. Subjects with maximal testosterone concentrations (Cmax) exceeding the prespecified targets.

    d. The adrenal-related findings, including adrenocorticotropin (ACTH) stimulation results.

    Committee Discussion: *Committee members agreed that the potential cardiovascular risks associated with Jatenzo were concerning. The observed blood pressure increases, for a chronically administered drug, are expected to increase the risk for serious adverse cardiovascular events, including death. This could have a large population impact given that the group that would likely use the drug predominantly includes a large number of older men who are already at increased cardiovascular risk due to advancing age and co-morbid conditions, such as diabetes, obesity, hyperlipidemia and hypertension. These men are receiving testosterone for uses that are not FDA-approved, such as age-related hypogonadism. Most panelists were less concerned about these risks in the small population of men who are otherwise at low cardiovascular risk and have classical hypogonadism, such as those with Klinefelter's Syndrome.*

    Committee members stated that the effects of Jatenzo on serum lipids and hematocrit did not raise concerns beyond what is generally known about the effects of testosterone therapies on these laboratory parameters.

    The committee members agreed that although the significance of DHT elevations is not known, the DHT findings do not raise specific safety concerns. None of the committee members felt this needed additional study.

Committee members were not particularly concerned that a few subjects had maximal testosterone concentrations exceeding the targets. Some panel members stated that most of these outliers appeared spurious.

Committee members could not definitively exclude a risk for adrenal insufficiency in humans because of deficiencies in the clinical adrenal function testing, and recommended more long-term assessment for adrenal insufficiency in a future clinical study that most thought could be conducted post-approval.

Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Discuss whether the titration regimen proposed for marketing will appropriately identify patients who require titration or discontinuation of Jatenzo.

   Committee Discussion: *The panel agreed that the Applicant's proposed testosterone thresholds assessed 4 to 6 hours after a morning dose was reasonable for titrating Jatenzo in clinical practice. Some panelists expressed reservation about the feasibility of adhering to any specific time window in clinical practice. A committee member stated that additional demographic/metabolic covariates, such as body mass index (BMI), albumin concentrations, and sex hormone binding globulin (SHBG) concentrations could have been used to characterize the variability in testosterone concentrations seen in clinical trial subjects, which may have helped predict the individual concentrations, while another member stated that from a practical perspective, there was adequate bridging between the titration regimen used in the new Phase 3 trial and the titration regimen proposed for marketing.*

   Please s*ee the transcript for details of the committee discussion.*

3. **DISCUSSION:** Discuss whether NaF/EDTA tubes are critical for the safe and effective use of Jatenzo. If you conclude that NaF/EDTA tubes are not critical, discuss how serum tubes will ensure safe and effective use given that the Phase 3 trial used NaF/EDTA tubes.

   Committee Discussion: *Committee members wanted to see more data to be convinced of the need to base Jatenzo dosing decisions on testosterone concentrations from plasma prepared in NaF/EDTA tubes instead of from serum in the more commonly used plain tubes. It was noted that although the NaF-containing tubes are available in most clinical laboratories, it is unclear whether those laboratories would routinely use those tubes for Jatenzo-treated patients instead of the plain tubes currently used for other testosterone therapies. There was interest in learning more about the potential cross-reactivity of testosterone undecanoate with the testosterone immunoassays that are commonly used to monitor patients on testosterone replacement therapies. Another recommendation was to assess the rate and extent of testosterone undecanoate to testosterone ex vivo conversion during the time course of plasma sample preparation collected from patients dosed with Jatenzo.*

Please see the transcript for details of the committee discussion.

4. **VOTE:** Is the overall benefit/risk profile of Jatenzo acceptable to support approval as a testosterone replacement therapy?

   Provide a rationale for your vote.

   Yes: 9 No: 10 Abstain: 0

   Committee Discussion: *Members recognized the potential benefit of a safe and effective oral testosterone replacement therapy as another treatment option for men with classical hypogonadism. There was consensus that Jatenzo would likely be safe and efficacious for such men who are also at low cardiovascular risk but there was substantial concern about its safety if prescribed to large numbers of men with age-related hypogonadism, as was widely anticipated. Committee members who voted for approval generally believed that the risks could be mitigated through measures such as a Risk Evaluation and Mitigation Strategy (REMS), labeling, and mandatory health care provider education. Members who voted "No" were concerned that the scope of use outside of classical hypogonadism could lead to widespread harm in terms of cardiovascular risks.*

   Please see the transcript for details of the committee discussion.

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