Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
January 10, 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) 208088, oral testosterone undecanoate capsules, submitted by Lipocine Inc. 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 10, 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 10, 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 10, 2018

The following is a final report of the Bone, Reproductive and Urologic Drugs Advisory Committee meeting held on January 10, 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 10, 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 Lipocine, 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 90 people in attendance. There were five (5) Open Public Hearing speaker presentations.

Issue: The committee discussed new drug application (NDA) 208088, oral testosterone undecanoate capsules, submitted by Lipocine Inc. 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; Martin Kaufman, DPM, MBA; Suresh Kaul, MD; LaiMing Lee, PhD

Open Public Hearing Speakers: Sidney M. Wolfe, MD (Health Research Group at Public Citizen); Jay A. Motola, MD FACS (Icahn School of Medicine at Mount Sinai); Michael Bardzil; Megan Polanin (National Center for Health Research); Martin Miner, MD (The Miriam Hospital and Brown University)

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	**Lipocine Inc.**
Introduction	**Mahesh Patel, PhD** President and CEO Lipocine, Inc.
TRT Overview	**Adrian Dobs, MD, MHS** Professor of Medicine Director, Johns Hopkins Clinical Research Network
Efficacy	**Gary Hoel, RPh, PhD** Clinical Consultant, Lipocine Inc.
Safety	**Anthony DelConte, MD** Chief Medical Director, Lipocine Inc.
CV Safety	**Peter A. McCullough, MD, MPH** Vice Chief of Medicine and Cardiologist Baylor University Medical Center

TLANDO in Clinical Practice	**Adrian Dobs, MD, MHS**
Summary	**Anthony DelConte, MD**

Clarifying Questions to Industry

BREAK

FDA PRESENTATIONS

Clinical Assessment	**Martin Kaufman**, **DPM, MBA** Clinical Analyst DBRUP, ODE III, OND, CDER, FDA
Ex Vivo Testosterone Undecanoate To Testosterone Conversion and Stopping Criteria	**LaiMing Lee, PhD** Clinical Pharmacology Reviewer Division of Clinical Pharmacology III Office of Clinical Pharmacology (OCP) Office of Translational Sciences (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 and Voting

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss whether the safety of Tlando 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 Tlando on cardiovascular risk factors, including blood pressure and lipids, together with effects on hematocrit, and the potential for Tlando to increase the risk of adverse cardiovascular outcomes in the population that will likely use the drug if it is approved. Specifically comment on whether ambulatory blood pressure monitoring is needed pre-approval.

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

c. Subjects with maximal testosterone concentrations (C_{max}) exceeding the prespecified targets.

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

Committee Discussion: *Several panel members recommended that a well-designed ambulatory blood pressure monitoring study be performed pre-approval. Based on comments made at the meeting, this recommendation took into account the mean 4 mmHg increase in systolic blood pressure seen with the three times daily dosing regimen that used the same total daily dose as the to-be-marketed regimen, the use of only cuff pressure measurements across all studies, and findings in the public domain showing a clinically meaningful increase in blood pressure with ambulatory blood pressure monitoring for another oral testosterone undecanoate product.*

The lipid and hematocrit findings were largely noted to be a general feature of testosterone use and not a concern to most of the panel members.

The elevated dihydrotestosterone (DHT) concentrations were judged to be a class effect and not known to be associated with any specific clinical risk. It was noted that European studies involving administration of DHT have not raised safety concerns.

There were differences of opinion regarding the clinical relevance of the testosterone Cmax findings. One comment was that the short duration of exposure to this maximal testosterone concentration should be less problematic. Another view was that having these peaks twice daily on a chronic basis could be of potential concern. Since there were no data that tied this exposure to adverse effects, the impact of the Cmax outliers was hard to judge for the panel members.

With regard to the adrenal findings, there was not a high level of concern although it was noted that technical problems with the testing made it difficult to interpret the findings (e.g., some subjects do not appear to have received Cosyntropin for their test).

Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Discuss whether the stopping criteria for use in clinical practice will appropriately identify patients who require discontinuation of Tlando.

Committee Discussion: *Some members raised concerns with the adequacy of the proposed stopping criteria, such as whether the criteria would appropriately capture patients with supratherapeutic testosterone Cavg. Some members also expressed concerns that health care providers would up titrate the dose if the measured testosterone was low, even though the Applicant is seeking approval of only one dose, and that this could raise safety concerns. A recommendation was to use modeling and simulation approaches to refine the accuracy of the prediction.*

Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** Discuss whether testosterone concentrations measured in serum tubes are reliable in patients treated with Tlando.

Committee Discussion: *Several committee members noted the conflicting data on the extent of ex vivo conversion of testosterone undecanoate to testosterone, and stated this is an important issue to resolve before the drug could be approved. Some committee members stated that if there is ex vivo conversion this should not be a safety concern because this conversion will overestimate testosterone concentrations. However, it was noted that ex vivo conversion could call into question the reliability of the data from the Phase 3 trial.*

Please see the transcript for details of the committee discussion

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

Provide a rationale for your vote.

Yes: 6 No: 13 Abstain: 0

Committee Discussion: *Most committee members voted "No,"stating that the existing uncertainties should be resolved before approval. Recommendations included a pre-approval ambulatory blood pressure monitoring study and further assessment of the potential for ex vivo conversion of testosterone undecanoate to testosterone.*

Committee members who favored approval were willing to resolve the uncertainties after approval, citing an unmet need for an oral testosterone product.

Please see the transcript for details of the committee discussion.

The meeting adjourned at 4:30 p.m.