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 18, 2014

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

Topic: The committees discussed new drug application (NDA) 206089, (oral testosterone undecanoate capsules), submitted by Clarus Therapeutics, for the proposed indication of testosterone replacement therapy 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 September 18, 2014, joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee were approved on November 2, 2014.

I certify that I attended the September 18, 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 18, 2014

The following is the final report of the joint meeting 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 18, 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 18, 2014, at the College Park Marriott Hotel and Conference Center, 3501 University Blvd. Hyattsville, Maryland. Prior to the meeting, the members and temporary voting members were provided background materials from the FDA and from the Sponsor, Clarus Therapeutics. 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 75 people in attendance. There were six (6) Open Public Hearing speakers.

Issue: The committees discussed new drug application (NDA) 206089, (oral testosterone undecanoate capsules), submitted by Clarus Therapeutics, for the proposed indication of testosterone replacement therapy 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 (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)*

FDA Participants (Non-Voting):
Julie Beitz, MD; Hylton Joffe, MD, MMSc; Mark Hirsch, MD; Solomon Iyasu, MD MPH; CAPT E. Dennis Bashaw, PharmD; Sayed Al Habet, RPh, PhD

Designated Federal Officer: Kalyani Bhatt, BS, MS

Open Public Hearing Speakers: Stefan D. Schwarz; Steven J. Kulback, MD, FACP (Alabama Internal Medicine, PC); Robert A. Feldman, MD; Paresh Dandona, MD (American Association of Clinical Endocrinologists); Steve Litwitz (statement read by Robert A. Feldman, MD)

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

SPONSOR PRESENTATIONS	**Clarus Therapeutics Inc.**
Introduction	**Robert Dudley, PhD** CEO and President Clarus Therapeutics
Unmet Need	**Glenn Cunningham, MD** Professor of Medicine and Molecular & Cellular Biology Baylor College of Medicine
Effectiveness	**Merrell Magelli, PharmD** Senior Director, Medical Affairs Clarus Therapeutics
Safety	**Theodore Danoff, MD, PhD** Senior Vice President, Clinical and Medical Affairs & CMO Clarus Therapeutics
Benefit-Risk	**Robert Dudley, PhD**
Clarifying Questions to the Sponsor	
FDA PRESENTATIONS	
Overview of Clinical Pharmacology	**Sayed Al Habet, RPh, PhD, ABCP, FCP** Senior Clinical Pharmacologist Office of Clinical Pharmacology (OCP) Office of Translational Sciences (OTS) CDER, FDA
Clinical Efficacy and Safety	**Mark S. Hirsch, MD** Medical Team Leader in Urology DBRUP, ODE III, OND, CDER, FDA
Clarifying Questions to the FDA	
Open Public Hearing	
Additional Clarifying Questions to Sponsor and FDA	
Questions to the Committee/Committee Discussion	
ADJOURNMENT	

Questions to the Committee:

1. **VOTE:** Is there sufficient evidence to conclude that oral testosterone undecanoate is effective as testosterone replacement therapy?

   Please provide a rationale for your vote.

   Yes: 8 No: 12 Abstain: 1

   Committee Discussion: *A majority of the committee voted that the data did not provide sufficient evidence that oral testosterone undecanoate was effective, for reasons that included concerns about the effect of missing data on the results, the failure to meet all the key secondary endpoints in the study, and the small amount of available efficacy data. Other concerns related to a starting dose that was too high and dose titration parameters that forced subsequent exposures to be too low in some patients. The members also cited significant concerns about the effect dietary changes had on systemic absorption, particularly the effect of increased dietary fat content. Some members recommended an additional study that more convincingly demonstrates a more robust outcome for the primary objective and meets the key secondary endpoints.*

   Some committee members stated that there is sufficient evidence of efficacy as the product did meet the primary endpoint in the completer's analysis. These members stated that some of the key secondary endpoints might also fail in studies examining other modes of testosterone delivery. In addition, some panel members raised concerns regarding higher standards for this product as compared to other testosterone products.

   Please see the transcript for details of the committee's discussion

2. **DISCUSSION:** Discuss whether the safety of oral testosterone undecanoate 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.

   Committee Discussion: *The committee agreed that the available safety data were not sufficient to allow for an adequate assessment of safety. In general, the committee agreed that safety had not been well characterized for the product, and that more safety data were needed. The committee further stated that several concerning safety issues had emerged from the available data, including elevated blood pressure and adverse effects of the product on some laboratory parameters (e.g. hs-CRP, cholesterol, and blood pressure). Several panel members voiced safety concerns related to the high variability in exposure with dietary fat content, and some members recommended further investigation of this issue through additional study. Several members of the panel voiced concerns related to high levels of testosterone undecanoate (TU), although the potential risk associated with high TU levels is unclear. Members generally agreed that the long term risks of the product are unknown.*

Please see the transcript for details of the committee's discussion

3. **VOTE:** Is the overall benefit/risk profile of oral testosterone undecanoate acceptable to support approval of this product for testosterone replacement therapy?

   Yes: 4 No: 17 Abstain: 0
   (Please note Drs. Howards and Erstad votes were incorrectly documented into the record. The error was accounted for in the committee's discussion.)

   Committee Discussion: *The majority of the committee agreed that the overall benefit/risk profile was not acceptable to support approval of oral testosterone undecanoate. Some members stated that additional information was needed. The panel commented on the potential risks of the product, including the effect of dietary fat on exposure and the high pharmacokinetic variability. A few members stated the need to assess a lower starting dose and a different dose titration paradigm. Several members stated that the potential risks were currently difficult to label and difficult to manage. The members expressed overall concern regarding effectiveness and safety and encouraged the manufacturer to conduct further studies with the medication. Some members agreed that the whole class of testosterone replacement therapies need further study and this product should not be held to a higher standard.*

   Please see the transcript for details of the committee's discussion.

   The meeting was adjourned at approximately 2:00 pm.