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FDA Bone, Reproductive and Urologic Drugs Advisory Committee

Testosterone Undecanoate: Tlando

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(I have no financial conflict of interest)

Questions for Advisory Committee and Public Speakers Safety Issues for Discussion

- 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.

FDA/Clarus Previous Agreement on Post FDA Rejection Study for the other Testosterone Undecanoate: Jatanzo

- “The protocol and analytical plans for ambulatory blood pressure monitoring (ABPM) and cuff pressure data were the subject of extensive discussions between the Applicant and FDA prior to the conduct of CLAR-15012. In its final iteration, which was submitted by the Applicant and agreed to by the FDA, that plan incorporated the following”,
- “A well conducted Ambulatory Blood Pressure Monitoring (ABPM) comparing oral TU to an active comparator, supplemented by rigorous cuff pressure measurement on all subjects seemed reasonable. Isolated assessment of systolic blood pressure would not be sufficient.”

FDA Briefing Document for January 9, 2018 meeting, PDF pages 17

Characteristics of the Two Newer Studies on Tlando

Neither (LPCN 1021-16-002 nor LPCN 1021-16-003) has a comparator testosterone product in the study.

“Isolated assessment of systolic blood pressure”, rejected by FDA/Clarus for follow-up studies on Jatanzo as not being sufficient, were the measurement utilized in both of the newer studies on Tlando.

FDA Cardiology Consultation Advice on Tlando

• In all three of these open-label studies, only single morning cuff pressures were acquired. *It is unclear whether the same equipment and/or the same office staff were acquiring these data from visit to visit on each subject, raising the potential for wide variability in the vital sign readings that were recorded.*

• In LPCN 1021-16-002, there was an elevated pulse rate of approximately 4 beats per minute at the end of four weeks of dosing. In LPCN 1021-16-003, there was a 1 beat per minute increase in heart rate and a 4 mmHg increase in SBP after approximately four weeks of dosing.

• The major contributor to defining the non-invasive hemodynamic effects of Tlando come from the 52-week study. *However, the ability to generalize population central tendency data for vital signs from this study is limited by the premature withdrawal of 38% of the Tlando-treated subjects and the 32% of Androgel subjects over the 52 weeks of the study.* From the available data, it appears that there was an approximately 1-2 beats per minute increase in heart rate for both Tlando and Androgel-treated subjects over the 52 weeks of therapy, without demonstrable increases in the central tendencies for SBP or DBP in either group. In contrast, “hypertension/blood pressure increased” was among the most common vital sign-related adverse events.

FDA Cardiology Consultation Conclusions on Tlando (cont'd)

- "Based on the available data, it appears that both Tlando and AndroGel raise heart rate, and LPCN 1021-16-003 demonstrates a mean 4 mmHg increase in SBP with Tlando. The 52-week study does not exonerate Tlando from blood pressure effects because its cuff blood pressure data acquisition was methodologically non-duplicative (single morning cuff pressures) in the setting of an open-label trial design with a 38% dropout rate in the experimental treatment arm. *Therefore, a "no blood pressure effect" conclusion from that study is speculative and could be incorrect*.
- The cardiology consultants recommend that the Applicant perform *a well-designed, adequately sized, and appropriately controlled ambulatory blood pressure monitoring study* to further assess the effects of Tlando on blood pressure and heart rate".

FDA Briefing Document, January 10, 2018, PDF pages 16-17

- **Cmax outliers:** As noted previously, trials for testosterone therapies have three standard secondary *endpoints to assess for unacceptably high maximal exposures to testosterone that could potentially raise safety concerns*. *In the new trial that tested 225 mg twice daily, none of these three targets were met.*

Table 22. Proportion of Subjects for the T Cmax Secondary Endpoint on Efficacy Day – Safety Set

Measure	Target	T Cmax (0-24)
Number of Subjects		95
T Cmax < 1500 ng/dL, %	≥ 85%	74%
1800 - 2500 ng/dL, %	≤ 5%	14%
T Cmax > 2500 ng/dL (n)	No subject	One subject

- 11% more (10 out of 95) patients above FDA's specified maximum T Cmax target of < 1500 ng/dl
- 9% more (8 more patients out of 95) than FDA's maximum 5% percent target had elevated T Cmax levels in 1800 to 2500 range
- 1 patient (versus specified none) had T Cmax over 2500

Concerning Testosterone Metabolites

- **Testosterone Metabolites**: *The goal of testosterone replacement therapy is to restore testosterone and its major metabolites (DHT and estradiol) to the normal range.* The Applicant's data show that Tlando leads to supratherapeutic DHT and estradiol concentrations in some subjects:

• In the 225 mg twice daily trial, the maximal concentration for DHT was above the upper limit of the reference range in 97% of Tlando-treated subjects. About 67% of subjects had a maximal DHT more than twice the upper limit of the reference range. About 79% of subjects had DHT Cavg above the upper limit of the reference range, and about 19% had DHT Cavg more than twice the upper limit of the reference range.

• The maximal concentration for estradiol was above the upper limit of the reference range in 46% of Tlando-treated subjects, with 3.3% of subjects more than twice the upper limit of the reference range. About 16% had estradiol Cavg above the upper limit of the reference range, all of which were less than twice the upper limit of the reference range.

FDA Briefing document, January 10, 2018, PDF page 7

Possible Adrenal Insufficiency

- Testosterone undecanoate caused adrenal cortical vacuolation in male rats and adrenal atrophy in dogs. The Applicant conducted ACTH stimulation testing in the 150 mg three times daily and 225 mg twice daily clinical trials.

FDA's endocrinology consultant stated that

- "that the four-week treatment period may be insufficient to assess whether Tlando, a drug that is expected to be taken chronically, causes adrenal dysfunction. The consultant concluded that the data are insufficient to rule out a risk of adrenal insufficiency, and recommended further assessment of adrenal function over a longer study duration."

FDA Briefing package, PDF page 31

Is the overall benefit/risk profile of Tlando acceptable to support approval as a testosterone replacement therapy?

Clearly no, for the following reasons:

- Concerning the important cardiovascular risk question of drug-induced hypertension, Tlando might superficially appear safer than Jatanzo. This conclusion is highly challengeable since Lipocine neither used a comparator drug in these two latest trials nor used ambulatory blood pressure monitoring, both done by Clarus for Jatanzo and now recommended by FDA's cardiology consultants for Tlando.
- Combined with the unacceptable pharmacokinetics, other serious questions of its safety, and the availability of many other more predictable versions of testosterone, neither the advisory committee nor the FDA should consider its approval. The question FDA is asking you, whether such studies could be done after approval, is not acceptable in the context of a then-to-be-mass-marketed, but yet unproven drug.