CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206089Orig1s000

SUMMARY REVIEW
1. Executive Summary

1.1 Overall Recommendation

Jatenzo is an oral soft capsule containing either 158 mg, 198 mg or 237 mg of testosterone undecanoate (TU) for use as chronic testosterone replacement therapy (TRT) by men with a deficiency or absence of endogenous testosterone (T) due to genetic or structural conditions. The starting dose is 237 mg twice daily, and the dose may be adjusted up or down based on serum T concentrations from blood drawn at 6 hours after the morning dose at least 7 days after starting therapy. The principal benefit of Jatenzo over other testosterone products is the convenience of oral dosing.

Testosterone replacement therapy (TRT) is the current standard of care for hypogonadal adult male patients with primary or secondary hypogonadism due to structural or genetic conditions. However, TRT products are widely prescribed to older men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”). There are a host of FDA-approved testosterone products, including a variety of formulation types. Jatenzo represents a new oral therapeutic option in TRT.

This is the second re-submission for this NDA, and this submission consists largely of: 1) focused clinical pharmacology and bioanalytical study data to link plasma T concentrations measured in NaF/EDTA-containing tubes in the Phase 3 study CLAR-15012 to serum T concentrations measured in plain tubes as proposed for dose titration decision-making in labeling, and 2) specific labeling revisions to address the remaining clinical safety concerns (elaborated below).

In short, the Sponsor has submitted acceptable evidence to support safe and effective use of 6-hour post-dose serum T concentrations from plain test tubes for dose titration decisions in...
labeling, and has acceptably addressed the remaining clinical safety issues with appropriate labeling.

Therefore, I recommend Approval of this application.

1.2 Background

The application for approval of Jatenzo (referred to hereafter as “Jatenzo” or “Oral TU”), is supported by results from three, Phase 3 studies; however, the most recent study, CLAR-15102 is the only Phase 3 study that employed the to-be-marketed dose-titration regimen. For this reason, the efficacy and safety results from CLAR-15102 are the focus of this memo. For information on the previously completed phase 3 studies CLAR-09007 and CLAR-12011, the reader is referred to my previous CDTL memos for this application. In brief:

- CLAR-15012 was a randomized (3:1), open-label, active comparator (for safety), efficacy and safety phase 3 study conducted in 222 adult hypogonadal men who were treated with Oral TU or Topical Axiron for approximately 4 months

Consistent with the Division’s expectations for testosterone products, and acknowledging several protocol modifications that were made during the trial, CLAR-15012 was designed to test: 1) the efficacy of Oral TU using FDA’s standard TRT benefit parameters (essentially, testosterone pharmacokinetic [PK] data), 2) the effect of food on systemic T exposure from Oral TU, 3) the safety of Oral TU unto itself, and 4) the safety of Oral TU in comparison to Topical Axiron for two safety issues: effects on blood pressure (BP) and on the adrenal response to adrenocorticotropin (Cosyntropin) stimulation testing.

In brief, the Efficacy data from the Phase 3 pivotal study CLAR-15012 confirms that Jatenzo provides acceptable testosterone replacement in adult men with hypogonadism.

For Safety, the overall phase 3 NDA safety database consists of:

- 166 hypogonadal adult males who received between 20 and 30 weeks of Oral TU using the to-be-marketed doses and dose regimen in CLAR-15012.
- Another 144 hypogonadal adult males who received approximately 16 weeks of treatment with Oral TU, by a slightly different dose regimen, in study CLAR-12011, and
- Another 161 hypogonadal adult males who received approximately 15 weeks of treatment with Oral TU in study CLAR-09007, but at doses higher than used in CLAR-15012 and CLAR-12011.

Thus, in total, 471 hypogonadal adult men received 15-30 weeks of Oral TU in Clarus’ three, phase 3 studies. A total of 86 subjects received Oral TU for approximately 52 weeks in CLAR-12010, the Long-Term Extension to study CLAR-09007, but again, the doses and dose regimen in those studies were different that those used in the other phase 3 studies, resulting in higher systemic T exposures. Nonetheless, these data support the long-term safety of the lower systemic T exposures achieved with the to-be-marketed regimen.
An additional 96 subjects received treatment with Oral TU for 3 to 32 days in six (6), shorter-term phase 2 studies, including Studies CLAR-07004, CLAR-08005, CLAR-09008, CLAR-09009, CLAR-15013 and CLAR-16015. However, most of these Phase 2 data are not useful for assessment due to differences in the Phase 2 and Phase 3 formulations.

In Study CLAR-15012, the overall mean age in the Oral TU group was 51.6 years. Patients older than 65 years of age were excluded from participating in the study. The mean body weight and body mass index (BMI) in the Oral TU group were 101.4 kg and 31.8 kg/m$^2$, respectively. A total of 95.2% of Oral TU subjects were categorized as being overweight or obese. 80.1% of Oral TU subjects were White and 17.5% were Black or African American.

In general, the safety profile for Jatenzo in CLAR-15012 was consistent with the known safety profile for testosterone products, except for one serious safety concern, as follows:

- Jatenzo was shown to raise average BP by a clinically meaningful amount in CLAR-15012. Data from ambulatory blood pressure monitoring (ABPM) show that treatment with Jatenzo was associated with mean 24-hour average systolic/diastolic BP increases of 4.9/2.6 mmHg compared to minimal increases (0.2/0.4 mmHg) with Topical Axiron. In subjects with treated hypertension at baseline, the Jatenzo-related mean BP increases were larger than the increases in the overall group: Oral TU +5.5/+3.3 mmHg vs. Topical Axiron -0.3/-0.8 mmHg. Changes in average daytime and nighttime BP were consistent with the 24-hour (full-day) average. Further, in the Safety Population in CLAR-15012, in the Oral TU group, 7.2% of subjects either started antihypertensive medications after baseline or required a dose increase after baseline, compared to 1.8% of subjects in the Topical Axiron group. It is notable that the observed increases in blood pressure did not appear to plateau at the End-of-Treatment visit, but instead, appeared to be still rising at that point. Based on a plethora of epidemiology data, the magnitude of these observed increases in BP, when chronically sustained, are anticipated to confer an increased risk of heart attack, stroke and cardiovascular death.

Additionally, a nonclinical signal of adrenocortical atrophy and hypoadrenalism in animals was evaluated by adrenocorticotropin (Cosyntropin) stimulation testing in a sub-study of CLAR-15012; however, that Cosyntropin sub-study was marred by serious flaws in design and procedures, rendering the data uninterpretable.

In this second NDA re-submission, the Sponsor proposed:

- New labeling to address the increased BP-related safety concern. With final full agreement on labeling, this issue is resolved. To be clear, I now agree with FDA’s REMS Oversight Committee (ROC) that a REMS is not necessary.

- A repeat clinical study of the effect of Jatenzo on adrenal function, as a required postmarketing study. This proposal is acceptable and this issue is resolved.

In addition to these two Clinical concerns for the original and 1st re-submissions, there was one remaining concern each for two other review disciplines, as follows:
Clinical Pharmacology expressed a concern that in CLAR-15012, the Sponsor had measured total T concentrations from plasma in NaF/EDTA-containing test tubes instead of measuring T concentrations from serum in plain test tubes with the intent of preventing ex vivo conversion of TU to T in the tubes themselves. However, based on data limitations, the extent to which NaF/EDTA tubes prevented possible TU to T ex vivo conversion was unknown. Clinical Pharmacology advised (and the Division agreed) that an investigation to determine the rate and extent of the TU to T ex vivo conversion during the time course of plasma sample preparation was warranted. Clinical Pharmacology also requested (and the Division agreed) that the Sponsor conduct an additional in vivo study to compare the total T concentrations measured from serum in plain tubes and plasma in NaF/EDTA tubes at different time points (e.g., 0, 15, 30, 60, 90, and 120-minutes post-sample collection) using different temperature conditions (e.g., room temperature or on ice) to determine the rate and extent of the TU to T ex vivo conversion during the time course of plasma sample preparation.

In this 2nd re-submission, the Sponsor provided results from the requested bioanalytical studies as well as additional results from related studies. These new results were reviewed by the FDA team and were determined to be appropriate and sufficient to support the Sponsor’s proposed labeling that prescribers use a 6-hour post-dose serum T concentration in plain test tubes to adjust dose in patients on Jatenzo therapy. The concern is resolved.

Pharmacology/Toxicology had previously expressed the concern that the submitted nonclinical studies were not acceptable to support approval of the NDA through a 505(b)(1) pathway because the doses of Oral TU used in those studies were inadequate to characterize the chronic effects of Oral TU on male fertility and carcinogenicity. In the fertility study, the tested doses did not produce the anticipated effects on spermatogenesis and fertility. With regards to the 6-month mouse carcinogenicity study, the maximally tolerated dose (MTD), maximum feasible dose or dose-limiting dose were not identified in the 28-day dose range finding study nor in the 6-month study itself. To resolve this concern, Pharmacology/Toxicology requested (and the Division agreed) that the Sponsor provide justification for dose selection for the fertility study and conduct a new, adequately designed carcinogenicity study, or re-classify their NDA as a 505(b)(2) application without submitting additional nonclinical studies as long as appropriate nonclinical published literature references were submitted.

In this 2nd re-submission, the Sponsor classified their NDA as a 505(b)(2) application and submitted acceptable published nonclinical literature references. This concern is resolved.

Based on resolution of these final Clinical, Clinical Pharmacology, and Pharmacology/Toxicology concerns, I find that this application may be Approved.

2. **Background**

2.1 **DESCRIPTION OF PRODUCT**
Testosterone undecanoate (TU) capsules, containing 158 mg, 198 mg and 237 mg TU, are immediate release soft gelatin capsules. They are manufactured at the commercial manufacturing facilities of [redacted].

In the original application, the Sponsor sought approval of two dosage strengths (158 mg and 237 mg). Since that time, the Sponsor added the request for a third strength capsule, 198 mg. Information for all dosage strengths is provided in my previous CDTL memos. Details for the 198 mg capsule are provided here to elucidate the components of the Jatenzo product.

The 198 mg capsules are manufactured from [redacted]. The total fill material weight for the 198 mg capsules is 1000 mg. The 198 mg capsules are opaque white in color with “198” printed in red ink.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (mg) per 198 mg capsule</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone Undecanoate</td>
<td>197.9</td>
<td>Active Ingredient (b)(4)</td>
</tr>
<tr>
<td>Oleic Acid NF, EP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borage Seed Oil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butylated Hydroxytoluene NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peppermint Oil NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyoxyl 40 Hydrogenated Castor Oil NF (Cremophor RH40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Fill Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft Gelatin Capsule Shell</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelatin (b)(4), NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorbitol (b)(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purified Water USP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Titanium Dioxide USP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsule Imprinting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red Ink (b)(4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Module 2.3 Quality Overall Summary, Table 2.3.P.1-3, page 2
2.2 REGULATORY HISTORY

On June 29, 2007, new IND#78,104 for oral TU capsules was submitted.

On March 23, 2009, a Type C Guidance Meeting was held with the Sponsor to discuss data from their completed Phase 2 studies and their plan for Phase 3 studies.

On February 1, 2010, another Type C meeting was held with the Sponsor to discuss issues related to Phase 3 study design as well as FDA concerns related to potentially high serum DHT:T concentration ratios in the completed Phase 2 studies.

On October 8, 2013, a Pre-NDA meeting was held with the Sponsor.

Prior to this first Pre-NDA meeting, there are at least 6 notable Advice/Information Request letters conveyed to the Sponsor during the IND phase, briefly summarized here:

- March 7, 2008: Division provides comments on a proposed Phase 2 study protocol (Study CLAR-07004)
- March 26, 2010: Division provides comments on long-term safety risks related to potentially high DHT concentrations and DHT/T ratios
- May 28, 2010: Division provides comments on the proposed Androgel-controlled, Phase 3 “pivotal” study protocol for Study CLAR-09007
- August 2, 2010: Division provides comments on the time for a single serum T concentration sample for use in titrating the dose in the proposed Phase 3 study CLAR-09007
- September 11, 2012: Division provides comments on the 1 year, open-label extension study (Study CLAR-12010) to Study CLAR-09007
- May 8, 2013: Division provides comments on the second proposed “pivotal” Phase 3 study protocol (Study CLAR-12011)

On January 3, 2014, the original NDA was submitted.

On September 18, 2015, a joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management Advisory Committee (DSARM) was held to discuss the Oral TU NDA. The majority of panel members concluded that efficacy and safety had not yet been adequately established for the product. The voting questions posed to the AC, and their results, were:

- Is there sufficient evidence to conclude that oral testosterone undecanoate is effective as testosterone replacement therapy? Result: 8 Yes, 12 No, and 1 Abstain.
- Is the overall benefit/risk profile of oral testosterone undecanoate acceptable to support approval of this product for testosterone replacement therapy? Result: Yes 4, No 17, and Abstain 0.

On November 3, 2014, a Complete Response action for NDA 206089 was issued.
On April 3, 2015, Clarus submitted a formal Request for Dispute Resolution. This request appealed the need to conduct additional clinical investigations to demonstrate the efficacy and safety of oral TU and the effect of food on T exposure related to oral TU.

On April 28, 2015, a meeting was held with Sponsor to discuss the issues raised in the Request for Dispute Resolution.

On July 17, 2015, the formal Dispute Resolution Request was denied.

On October 28, 2015, a Type C Guidance was held with Sponsor. In brief, the following clinical issues were discussed relating to the requested third Phase 3 study:

- Sponsor was advised to conduct a food effect study prior to the next Phase 3 study.
- New elements of the proposed next Phase 3 study design (e.g., a lower starting dose, \( C_{\text{avg}} \) thresholds of 350 and 800 ng/dL for titration, and 24-hour \( C_{\text{avg}} \)-based titrations) suggested an increased likelihood of achieving the pre-defined targets for efficacy.
- The protocol as proposed would exclude patients with “poorly controlled” hypertension. (>150/90 mmHg).
- A well-conducted ambulatory blood pressure monitoring (ABPM) sub-study comparing Oral TU to an active comparator, supplemented by rigorous cuff blood pressure measurements on all subjects seemed reasonable to the Division. Isolated periodic assessments of SBP would be insufficient.
- \( T C_{\text{avg}} \) can be used to guide dose titration decisions in CLAR-15012; however, Sponsor should submit a pre-specified analysis plan that describes their proposal for model-based bridging utilizing data from CLAR-15012 to justify the time window for a single PK measurement and titration thresholds for labeling that best correlates with results from CLAR-15012.
- An adequate clinical approach was needed to evaluate the observed nonclinical effect on the adrenal gland. The Division recommended using the Cosyntropin (ACTH) stimulation test in a subset of Phase 3 subjects.
- If the Sponsor’s product is not used in the shared Cardiovascular Outcomes Trial (CVOT) postmarketing study for testosterone products, the Sponsor may eventually receive a request to conduct a required post marketing CVOT using oral TU.

Subsequent to the submission of the final protocol for the third phase 3 study CLAR-15012, and initiation of the study, the Sponsor submitted several protocol amendments, the details of which are described in the Clinical review of the 1st re-submission. With the stipulated protocol changes, the Sponsor chose to continue the ongoing study. The Sponsor stated that subjects who had progressed beyond Visit 5 would have their treatment durations extended by approximately 70 days, for a total of approximately 6 months of treatment. That proposal was acceptable to the Division.

On September 28, 2016, at a Type C Guidance Meeting, the Division conveyed the following comments and recommendations to the Sponsor:

- Changing the testosterone assay while the Phase 3 trial was underway will require in-depth analysis once the NDA re-submission is received by FDA. The Sponsor was asked...
to consider washing subjects out, confirming that they are hypogonadal on the new assay, then re-starting subjects from the beginning of the treatment period.

- The titration scheme and food effect are important factors that may affect approvability.
- Titration decisions made in the Phase 3 trial should be shown to align with decisions made in clinical practice using a single blood draw.
- Blood pressure safety results may be impacted in patients who were initially erroneously titrated.
- The primary analysis population should include all randomized subjects who took at least one dose of study drug regardless of whether there is on-treatment pharmacokinetic data.
- Additional comments pertaining to the ABPM analyses were offered.

On April 27, 2017, a Pre-NDA meeting for the planned (1st) re-submission was held.

On June 22, 2017, the (1st) NDA resubmission was submitted. Major amendments submitted during the review added 3-month review extension time.

On January 18, 2018, another meeting of the BRUDAC was held to discuss the Oral TU NDA re-submission.

For the Clinical issues, the Committee’s general perspectives were:

- Members agreed that potential CV risks associated with Jatenzo were of significant concern. The observed BP increases, for a chronically administered drug, were expected to increase the risk for serious CV events. This could have a large population impact given that the group likely to use the drug includes older men who are already at increased CV risk due to advanced age and co-morbid conditions such as diabetes, obesity, hyperlipidemia and hypertension. These men often receive testosterone for uses that are not FDA-approved, such as “age-related hypogonadism”. Most panelists were less concerned about the CV risks in the small population of men who are otherwise at low CV risk and have “classical” hypogonadism, for example, men with Klinefelter’s Syndrome.

- Members stated that the effects of Jatenzo on serum lipids and hematocrit did not raise concerns beyond what is generally known about testosterone therapies.

- Members stated that although the significance of transient elevations in DHT was not known, these findings did not raise specific safety concerns. None of the committee members felt this issue needed additional study.

- Members stated that the adrenal effects observed on animals could be further assessed in humans in the postmarketing period.

For the use of plasma testosterone concentrations from NaF/EDTA-containing tubes on which to base dosing decisions, the Committee’s general perspectives were:

- 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-containing...
tubes instead of from serum in the more commonly used plain tubes. It was noted that although the NaF/EDTA-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.

- A specific recommendation was to assess the rate and extent of testosterone undecanote to testosterone ex vivo conversion during the time course of plasma sample preparation collected from patients dosed with Jatenzo.
- There was also interest in learning more about the potential cross-reactivity of testosterone undecanote with the testosterone immunoassays that are commonly used to monitor patients on TRT.

The following voting question was posed to the Committee: Is the overall benefit/risk profile of Jatenzo acceptable to support approval as a testosterone replacement therapy? Result: 9 Yes, 10 No, and 0 Abstain.

Committee members largely viewed the product as a potentially beneficial new treatment option for men who needed TRT. However, members advised that the risk of increased BP would need to be mitigated, either through a REMS, product labeling, or prescriber education.

### 2.3 PRIMARY MEDICAL REVIEWER’S RECOMMENDATION FOR APPROVABILITY

The primary Clinical reviewer, Debuene Chang, stated in her final review, dated March 15, 2019:

“Risk Benefit Assessment: The Clinical review team concludes that Jatenzo is safe and effective under the condition that the Sponsor makes labeling revisions which address the prior Clinical safety deficiencies. The risk/benefit for Jatenzo for TRT in men with hypogonadism will then be considered acceptable for approval of this NDA.”

More specifically, the Clinical review stated:

“In the prior review cycle, the Clinical review team had recommended a Complete Response (CR) action based on the BP-related Clinical safety deficiency. However, the Clinical review team now recommends that the Sponsor make substantive labeling revisions, including changes to the Boxed Warning, a new Contraindication, and a comprehensive Medication Guide, as well as a PMR study that will assess patients’ comprehension of the Med Guide, and that these changes address the safety deficiencies identified in the original submission and Sponsor’s 1st resubmission response to 1st CR Letter...Thus, if the Sponsor address all these changes to fully resolve the Clinical safety deficiency, then the Clinical review team finds that Jatenzo is safe and effective as labeled, and that the risk/benefit ratio for Jatenzo for TRT in men with hypogonadism is acceptable for NDA approval”.

Finally, the Clinical review stated:
“The Clinical review team recommended and the Sponsor was requested to conduct two PMR studies:

- Medication Guide comprehension study: The Sponsor committed to conduct the required postmarketing study and the Sponsor provided acceptable milestone dates for protocol submission, study completion and study report submission.
- Cosyntropin stimulation test study to assess the potential for hypoadrenalism: The Sponsor committed to conduct the required postmarketing study and the Sponsor provided acceptable milestone dates for protocol submission, study completion and study report submission”.

The Clinical review team had no other requests for postmarketing risk management strategies or postmarketing requirements, with the exception of a possible pediatric trial to satisfy the Pediatric Research Equity Act (PREA) as discussed in Section 10 of this memorandum.

_CDTL Comment:_ In a March 26, 2019, labeling Addendum memo, the Clinical team stated that all Clinical labeling issues had been resolved and the NDA could now be approved from a Clinical perspective.

3. **CMC**

The Chemistry review team, led by Mark Seggel, had the following recommendation in their final review dated March 18, 2019:

“In its present form, Clarus Therapeutics’ second resubmission of their 505(b)(2) New Drug Application #206089, for Jatenzo (testosterone undecanoate capsules), 158 mg, 198 mg, and 237 mg, is not ready for approval. Labeling (package insert) negotiations have not been completed, and in its present form, the labeling does not comply with 21 CFR 201.

(However) Sufficient information and supporting data have been provide in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status.”

_CDTL Comment:_ In their March 25, 2019, labeling Addendum review (CMC review #3), CMC stated that all labeling issues had been resolved and the NDA could be approved from the CMC perspective.

4. **Nonclinical Pharmacology/Toxicology**

In their final review dated March 1, 2019, the Pharmacology/Toxicology (PharmTox) review team of Yangmee Shin and Mukesh Summan had the following Recommendation:

“Approvability: From a Pharmacology and Toxicology (perspective), the current submission, along with the original NDA submission, contains adequate information to support approval of NDA 206089 via a 505(b)(2) pathway.”

PharmTox noted specifically that as part of this third cycle review, the label was updated
appropriately to meet the requirements of the Pregnancy and Labeling Lactation Rule (PLLR).

From the prior PharmTox studies, it is relevant to note findings from the 13-week subchronic toxicity in dogs. Observations in that study included: marked testicular atrophy /degeneration with reduced testicular weight and reduction in epididymal sperm, marked prostate hypertrophy, cholesterol reduction by >45%, and marked atrophy of the adrenal cortex with reduced adrenal weight. The reduced adrenal weight did not reverse upon drug discontinuation. The Sponsor suggested that adrenal cortical atrophy was a result of feedback suppression of androgen synthesis in the adrenals. Dogs in the high-dose group were exposed to roughly 2 to 8 times the testosterone AUC exposure at “worst case” in human males, assuming a single dose of 475 mg taken in conjunction with a high fat meal. Exposure to the prodrug TU in dogs was only 2 times the worst-case TU exposure in human males.

In the 1st re-submission, the Sponsor included two repeat-dose oral toxicity studies of TU (same formulation used in Phase 3 clinical studies and intended for commercial use) conducted in male dogs. In the 90-day dog toxicity study, in which the testosterone exposure was approximately 12-fold higher than that observed in the Phase 3 clinical trials, reductions in cortisol levels and adrenal changes were observed again. The Sponsor re-asserted that these results reflected the expected pharmacological effect of supraphysiological levels of testosterone on the adrenal gland.

A 9-month chronic toxicity dog study was also conducted at oral TU doses up to 8-fold higher than the maximum anticipated human daily oral TU dose. In this study, despite a reduction in adrenal weights, and aside from moderate adrenal vacuolation in one high-dose dog, there was no histopathological evidence of toxicity in the adrenal gland nor was TU exposure (with average circulating TU concentration on Day 270 of 500 ng/dL) associated with a decrease in circulating levels of cortisol.

To address potential clinical relevance of the nonclinical finding of adrenocortical atrophy and hypoadrenalism, at the request of the FDA, the Sponsor conducted a Cosyntropin stimulation testing sub-study in CLAR-15102; however, results from this sub-study were marred by procedural flaws and design deficiencies. The issue was raised at a January 2018, meeting of the FDA BRUDAC, who, based on the available clinical and nonclinical evidence, concluded that the nonclinical adrenal results were unlikely to be clinically relevant and advised doing a well-conducted, repeat Cosyntropin stimulation study in the postmarketing period. The Division made such a request and the Sponsor has agreed to carry out a 1-year, Cosyntropin stimulation study as a PMR.

5. Clinical Pharmacology/Biopharmaceutics

In their final review dated February 27, 2018, the Clinical Pharmacology review team of Chongwoo Yu, Donny Tran and Shirly Seo had the following Recommendation:

“The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology III has reviewed NDA 206089 submitted on September 27, 2018 and January 7, 2019. The overall Clinical Pharmacology information submitted to support this NDA is acceptable and JATENZO is recommended for approval from a Clinical Pharmacology standpoint”.

Reference ID: 4409369
Clinical Pharmacology had one request for a postmarketing study, to which the Sponsor agreed:

Conduct in vitro studies to assess the potential of testosterone undecanoate (Note: which may be considered a “pro-drug” of testosterone for Jatenzo therapy) to inhibit or induce drug metabolizing enzymes and transporters. If in vitro studies suggest a potential for interaction, additional in vivo studies may be required.

Clinical Pharmacology outlined the prior Clinical Pharmacology Deficiency and the new scientific information that resolved that Deficiency, summarized here:

In the “pivotal” Phase 3 study, CLAR-15012, dose-titration was based on T concentrations measured in plasma from NaF/EDTA-containing tubes kept on ice for 30 minutes prior to centrifugation. A T concentration dose-titration boundary range of 350 ng/dL to 800 ng/dL was used to guide dose adjustment in the study. For labeling, the Sponsor proposed to base the dose-titration decision on the 6-hour post-dose sample because, as discussed with the Division, in Study CLAR-15012, the T concentration at 6 hours post-dose had the highest concordance with $C_{avg}$. After applying the Sponsor’s proposed correction factor of 1.214 (1/0.824), the lower boundary of 350 ng/dL was changed to 425 ng/dL (350 × 1.214) and the upper boundary of 800 ng/dL to 970 ng/dL (800 × 1.214). Thus, for labeling, the Sponsor proposed the new titration boundary range of 425 ng/dL to 970 ng/dL based on T concentrations measured from serum in plain tubes (containing no additives). The table that follows (Table A) shows the dose adjustment scheme proposed for labeling based on serum T concentration from a sample drawn 6 hours after the morning dose.

<table>
<thead>
<tr>
<th>Testosterone Concentration in Serum From Plain Tubes Drawn 6 Hours After Dose</th>
<th>Current JATENZO Dose (mg, BID)</th>
<th>New JATENZO Dose (mg, BID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 425 ng/dL</td>
<td>158</td>
<td>198</td>
</tr>
<tr>
<td></td>
<td>198</td>
<td>237</td>
</tr>
<tr>
<td></td>
<td>237</td>
<td>316</td>
</tr>
<tr>
<td></td>
<td>316</td>
<td>396</td>
</tr>
<tr>
<td>425 – 970 ng/dL</td>
<td>No Dose Change</td>
<td></td>
</tr>
<tr>
<td>&gt; 970 ng/dL</td>
<td>396</td>
<td>316</td>
</tr>
<tr>
<td></td>
<td>316</td>
<td>237</td>
</tr>
<tr>
<td></td>
<td>237</td>
<td>198</td>
</tr>
<tr>
<td></td>
<td>198</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td>158</td>
<td>Discontinue Treatment</td>
</tr>
</tbody>
</table>

BID = twice daily

The Clinical Pharmacology reviews then stated that the Sponsor’s proposed dose titration scheme based on 6-hour post-dose samples using serum T concentration was reasonable because:

- T concentration at 6 hours post-dose ($C_6$) had the highest concordance with $T_{avg}$, which is the most clinically relevant single PK parameter, and
The TU concentrations at 6 hours post-dose were lower compared to at 4 hours post-dose, which results in lower variability in T concentrations due to TU to T ex vivo conversion, and

The Sponsor successfully established the validity of their proposed conversion factor that enables the correlation between T serum concentrations at 6 hours post-dose using plain tubes (as proposed for labeling) to T plasma concentrations from blood collected in NaF/EDTA-containing tubes at 6 hours post-dose (as used in the “pivotal” Phase 3 study, CLAR-15012).

Clinical Pharmacology then described the results from additional scientific investigations that support this conclusion, including the specific additional investigations that explored the rate and extent of TU to T ex vivo conversion, including the effects of time, temperature and matrix. In summary, the 3 factors that support translation of a T concentration measured under one set of tube type/incubation temperature/time conditions (serum from blood collected in a plain tube held at room temperature for 30 minutes) to an alternative set of tube type/incubation temperature/time conditions (plasma collected in a NaF/EDTA tube and kept for 30 minutes on ice) are:

- Extent of TU to T ex vivo conversion occurring in serum plain tubes at the incubation temperature over the processing time between sample collection and centrifuging,
- Extent of TU to T ex vivo conversion occurring in NaF/EDTA-containing plasma tubes at the incubation temperature over the processing time between sample collection and centrifuging, and
- Matrix effect associated with the pair of tube type/incubation temperature combinations.

Taking these key factors into consideration, an overall conversion factor was derived to be 0.824 (0.959 × 0.858 × 1.001) for a sample collected 6 hours post-dose. This conversion factor allows for the conversion of a serum T concentration to a NaF/EDTA-containing plasma T concentration. When converting T concentrations from plasma in NaF/EDTA-containing tubes to T concentrations for serum in plain tubes, the conversion factor is (1/0.959) x (1/0.858) x (1/1.001) = 1.214.

When the overall correction factor was applied to actual clinical data from the “pivotal” phase 3 study, CLAR-15012, at Visit 7, matched pairs (contemporaneously collected) of samples were collected into plain and NaF/EDTA-containing tubes, which were incubated for 30 minutes at room temperature or on ice, respectively, before centrifugation. The differences between the measured serum T concentration and the derived serum T concentration (derived from measured NaF/EDTA plasma T concentration and relevant conversion factor) were 1.3% to 3.1%, with 95% CI range ±6%. This close comparison of actual clinical phase 3 data from matched pairs provides robust support that the determined conversion factor is appropriate.

Finally, to bolster this analysis, Clinical Pharmacology analyzed results from sensitivity analyses, including analyses of effects of different processing times (e.g., 60, 90 and 120 minutes post-collection) and different TU concentrations. The results of these sensitivity
analyses were supportive of the overall conclusion. For example, a clinically meaningful difference was not observed with prolongation of the clotting time from 30 minutes to 120 minutes, and no significant differences were observed between the upper and lower bounds of the 95% CI for TU concentrations.

The reader is referred to the Clinical Pharmacology review for additional details.

6. Microbiology

The final Microbiology determination by Bryan Riley was that the information in the application was acceptable from the product quality microbiology perspective, and in this regard, in a final review of the 1st resubmission, the Chemistry review stated:

“The NDA is recommended for Approval from the product quality microbiology perspective (see Dr. Bryan Riley’s January 13, 2014 review). No changes have been made that would impact this previous assessment.”

7. Clinical/Statistical – Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

The clinical development program for Jatenzo consisted of ten (10) clinical studies, including three Phase 3 studies (CLAR-09007, CLAR-12011 and CLAR-15012), one long-term extension safety study (CLAR-12010), and six (6) Phase 2 studies (CLAR-07004, CLAR-08005, CLAR-09008, CLAR-09009, CLAR-15013 and CLAR-16015).

In the three Phase 3 studies, a total of 471 hypogonadal adult males received treatment with Oral TU. In addition, a total of 86 hypogonadal adult males received treatment for approximately 52 weeks in CLAR-12010, the long-term extension to Study CLAR-09007.

The only Phase 3 study that used the final to-be-marketed dose regimen was CLAR-15012. CLAR-15012 was a randomized (3:1), open-label, active comparator (for safety), efficacy and safety “pivotal” phase 3 study conducted in 222 adult hypogonadal men who received Oral TU or Topical Axiron for approximately 4 months. In this study, 166 hypogonadal adult males received between 20 and 30 weeks of Oral TU using the to-be-marketed doses and dose regimen.

An additional 96 subjects received treatment with Oral TU for 3 to 32 days in six (6), shorter-term Phase 2 studies, including Studies CLAR-07004, CLAR-08005, CLAR-09008, CLAR-09009, CLAR-15013 and CLAR-16015. However, most of the phase 2 data is not useful for assessment due to differences in phase 2 and phase 3 formulations and a lack of adequate scientific bridging to those phase 2 data.

Because CLAR-15102 is the only Phase 3 study that used the to-be-marketed doses and dose titration regimen and because CLAR-12011, CLAR-09007 and CLAR-12010 employed doses and dose regimens that either achieved supraphysiological T exposures (as in CLAR-09007) or did not meet the pre-defined efficacy criteria (as in CLAR-12011), the results from CLAR-15012 are the focus of the next sections of this CDTL memo (specifically, the sections entitled Demographics, Disposition of Subjects, Efficacy Results and Safety Results). For information...
concerning CLAR-09007, CLAR-12011 or CLAR-12010, the reader is referred to my previous CDTL memo and to the medical officers’ current and past Clinical reviews.

7.2 DEMOGRAPHICS

The study subjects in CLAR-15012 were adult hypogonadal males with serum total T concentration at the screening visit <300 ng/dL by two repeated morning blood draws and symptoms suggestive of hypogonadism. The mean testosterone concentrations at Screen Visit 1 and Screen Visit 2 were 190.2 ng/dL and 194.9 ng/dL, respectively in the Oral TU group and 183.9 ng/dL and 174.4 ng/dL in the Topical Axiron group, respectively. All but 1 subject in both treatment groups reported at least 1 hypogonadal symptom at Baseline. The most common symptoms of hypogonadism across both treatment groups were reduced sexual desire and activity (80.6%), decreased energy or self-confidence (78.4%) and decreased spontaneous erections (60.4%). The median duration of hypogonadism was 4.2 years in the Oral TU group and 4.1 years in the Topical Axiron group.

The mean ages of the study subjects in the Oral TU and Topical Axiron groups were 51.6 years and 53.4 years, respectively. The BMIs for the Oral TU group and the Topical Axiron groups were 31.8 kg/m\(^2\) and 30.9 kg/m\(^2\) respectively. 80.1% of Oral TU and 75.0% of Topical Axiron subjects were White and 17.5% of Oral TU and 19.6% of Topical Axiron subjects were Black or African American.

Similar proportions of subjects in both treatment groups were categorized at Baseline as prediabetic or diabetic (60.2% for Oral TU and 60.7% for Topical Axiron). A history of hypertension was reported for a slightly greater proportion of subjects in the Oral TU group (52.4%) compared with the Topical Axiron group (46.4%).

7.3 DISPOSITION OF SUBJECTS

In CLAR-15012, 12 of 166 (7.2%) subjects who received at least one dose of Oral TU discontinued versus 7 of 56 (12.5%) Topical Axiron subjects who discontinued. Therefore, 92.8% of Oral TU subjects versus 87.5% of Topical Axiron subjects completed the study. The most common reason for early discontinuation from the study was subject request in the Oral TU group (3.0%) and subject request and “Other” in the Topical Axiron group (5.4% each). Adverse events led to early discontinuation from the study in 4 (2.4%) Oral TU subjects and 1 (1.8%) Topical Axiron subject.

Table 2 shows disposition of subjects in CLAR-15012 with reasons for study discontinuation.
Table 2: Overall Subject Disposition by Treatment Group in CLAR-15012

<table>
<thead>
<tr>
<th>Number of Subjects (%)</th>
<th>Oral TU</th>
<th>Topical Axiron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects Randomized</td>
<td>166</td>
<td>56</td>
</tr>
<tr>
<td>Subjects Treated (Modified ITT)</td>
<td>166</td>
<td>55</td>
</tr>
<tr>
<td>Subjects Who Completed Study</td>
<td>154 (92.8)</td>
<td>49 (87.5)</td>
</tr>
<tr>
<td>Subjects Who Discontinued Early from the Study</td>
<td>12 (7.2)</td>
<td>7 (12.5)</td>
</tr>
<tr>
<td>Reasons for Early Discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject Request</td>
<td>5 (3.0)</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>Subject no longer able to commit to study procedures</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Subject moved out of state</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Subject felt he was under dosed</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Spouse requested subject withdrawal due to his general health problems</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>4 (2.4)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Non-compliance with Study Drug or Procedure</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Other a</td>
<td>0</td>
<td>3 (5.4)</td>
</tr>
</tbody>
</table>

Source: Table: Table 9 CLAR-15012 Clinical Study Report, page 83

Abbreviations: ITT = intention-to-treat; PSA = prostate-specific antigen; TU = testosterone undecanoate

aOther reasons (n=3) included: subject had high PSA prior to starting the study, was not eligible, and subsequently withdrew; subject withdrew consent after realizing he was randomized to Topical Axiron instead of Oral TU; and site closure not related to study conduct.

Note: Percentages were calculated from the total number of randomized subjects per treatment group.

7.4 EFFICACY RESULTS

7.4.1 Assessment of Efficacy

The assessment of efficacy in this NDA was consistent with efficacy assessments conducted for TRT products in prior NDAs as well as with the Division’s expectations and requirements for efficacy assessments in TRT studies.

In Study CLAR-15012, the need for dose titration was based on a subject’s total testosterone C_avg determined from serial pharmacokinetic (PK) samples obtained over a 24-hour period. According to the Sponsor, using the C_avg from samples obtained over a 24-hour period as the determinant for titration ensured a more complete characterization of the subject’s testosterone concentration. The final Oral TU dose could remain at the 237 mg BID starting dose or be up-titrated to 316 mg BID or to 396 mg BID, or down-titrated to 158 mg BID or to 198 mg BID. Topical Axiron was dosed as per its approved labeling.

Therefore, in CLAR-15012, the dose and dosing regimens were:
- Initial fixed starting doses:
  - Oral TU: 237 mg BID, immediately prior to meals in the morning (breakfast) and evening (dinner), approximately 12 hours apart.
  - Topical Axiron: 60 mg once daily every morning to clean, dry axillary skin.
- Titration boundaries
  - The dose titration boundaries for Oral TU were $C_{avg} < 350$ and $> 800$ ng/dL total testosterone.
  - The dose titration boundaries for Topical Axiron were $C_{avg} < 300$ ng/dL and $> 1000$ ng/dL.

Subjects underwent 24-hour pharmacokinetic samples over 24 hours at Visit 2, and at Visit 4 or 4b. The need for dose titration was based upon the $C_{avg}$ that had been determined at Visits 2 and at Visits 4 or 4b. Dose changes, if necessary, were enacted at Visits 3 or 5. Subsequent to study protocol amendment 2.0 (related to a change in central laboratory), the titration opportunities occurred at Visits 3b and 5b.

The dose titration regimen for Oral TU is shown schematically in Figure 1 below. For additional details, the reader is referred to the medical officer’s Clinical review.

**Figure 1: Oral Testosterone Undecanoate Titration Scheme**

*Source: Figure 3 CLAR-15012 Clinical Study Report page 30*

*Abbreviations: BID = twice daily; $C_{avg}$ = average concentration PK = pharmacokinetic; $T$ = testosterone; TU = testosterone undecanoate*

Following the final titration dose adjustments, subjects were maintained on drug dose until the final PK endpoint testing at Visit 7.
7.4.1.1 Primary Efficacy Analysis

Consistent with FDA requirements for Phase 3 TRT studies, the primary efficacy endpoint was an estimate of the proportion of Oral TU-treated subjects with a T $C_{avg}$ within the normal range after dose titration was complete, and in CLAR-15012, that 24-hour PK sampling occurred on Visit 7.

The primary efficacy analysis was conducted treating all missing data as if the subject failed to achieve a Visit 7 plasma sample measurement in the eugonadal range unless the data were missing due to a cause not related to study drug (e.g., the subject moved from study center area). For missing values not attributed to a study drug-related causes, the Visit 7 $C_{avg}$ was imputed by last observation carried forward (LOCF), and then it was determined whether the $C_{avg}$ was within the eugonadal range. Success required that at least 75% of subjects’ $C_{avg}$ to fall within the eugonadal range, with the lower limit of a 95% CI not below 65%.

Due to the novel bioanalytical method in this study, a new testosterone $C_{avg}$ eugonadal range was required for adult men when their blood was collected in NaF/EDTA-containing test tubes. The Sponsor determined this new eugonadal range based in part on results for Study CLAR-16014. Briefly, in CLAR-16014, blood was collected from 97 healthy young men, and T concentrations were measured from the subjects’ plasma in NaF/EDTA-containing tubes. The mean T concentration, calculated using natural-log transformed T concentrations, was 478 ng/dL; and the eugonadal range was determined as the exponential of this mean $\pm$ 2 SDs of the population, namely 252 to 907 ng/dL. Therefore, the efficacy results shown in this section are presented based on T concentrations derived from the plasma NaF-EDTA-containing tubes and the plasma NaF/EDTA-related eugonadal range.

Overall, 145 of 166 (87.3%) Oral TU subjects and 48 of 55 (87.3%) of Topical Axiron subjects had T $C_{avg}$ values within the defined range (252 ng/dL − 907 ng/dL) at Visit 7.

Table 3 shows the number and percentage of patients who achieved eugonadal T $C_{avg}$ at Visit 7 using the primary efficacy analysis in the modified ITT population. Table 3 also shows the mean $C_{avg}$ for the treatment groups.

<table>
<thead>
<tr>
<th>Testosterone $C_{avg}$ Range, n (%)</th>
<th>FDA Target</th>
<th>Oral TU (N=166)</th>
<th>Topical Axiron (N=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>252 ng/dL $\leq C_{avg} \leq$ 907 ng/dL</td>
<td>$\geq 75%$</td>
<td>145 (87.3%)</td>
<td>48 (87.3%)</td>
</tr>
<tr>
<td>Lower bound 95% CI</td>
<td>$\geq 65%$</td>
<td>81.3%</td>
<td>75.5%</td>
</tr>
<tr>
<td>Upper bound 95% CI</td>
<td></td>
<td>92.0%</td>
<td>75.5%</td>
</tr>
<tr>
<td>Cavg mean(SD) ng/dL 95% CI</td>
<td>401.2 (140.2)</td>
<td>379.7, 422.7</td>
<td>390.6 (139.9)</td>
</tr>
<tr>
<td>CI=confidence interval, SD=standard deviation</td>
<td></td>
<td>352.8, 428.5</td>
<td></td>
</tr>
</tbody>
</table>

Source: CLAR-Study 15012 report, Table 15, page 94.
A total of 22 subjects (15 Oral TU, 7 Topical Axiron) had missing values for testosterone C\text{avg} at Visit 7. To evaluate the effect of this missing data on the results of the primary efficacy analysis, three (3) sensitivity analyses, including LOCF, multiple imputation, and imputation from baseline, were performed. All 3 sensitivity analyses provided an imputed testosterone C\text{avg} value for all subjects with missing Visit 7 values, regardless of reasons for discontinuation. For the Oral TU group, all 3 sensitivity analyses resulted in estimates of the percentage of subjects in the eugonadal range of 86.1% to 89.6%. Thus, the primary analysis and all three sensitivity analyses met the efficacy target of \geq 75% of subjects with a testosterone C\text{avg} in the eugonadal range and the lower bound of the 95% CI \geq 65%.

**7.4.1.2 Secondary Efficacy Analysis**

The “key” secondary efficacy endpoints (sometimes referred to as “safety” endpoints in these studies) in CLAR-15012 were the same as for all prior TRT studies - except that the Sponsor conducted a “supplemental analysis” that accounted for the modification in range values due to T plasma concentrations from NaF/EDTA-containing tubes, and included:

- Percentage of patients with T C\text{max} <1500 ng/dL. This endpoint would be considered to have been met if \geq 85% of patients had T C\text{max} in this range at Visit 7;
- Percentage of patients with T C\text{max} 1800 to 2500 ng/dL, inclusive. This endpoint would be considered to have been met if <5% of patients had T C\text{max} in this range at Visit 7;
- Number of patients with T C\text{max} >2500 ng/dL. This endpoint would be considered to have been met if no patients had T C\text{max} in this range at Visit 7;

In the supplemental analysis, the usual C\text{max} thresholds (as above) were adjusted for the upper limit of the plasma T concentration from NaF/EDTA-containing tubes eugonadal range, namely 907 ng/dL. The adjustment factor was the ratio of 907 ng/dL to the typical eugonadal upper limit of 1000 ng/dL (e.g., 907/1000 = 0.907). Thus, T C\text{max} criteria were evaluated by estimating the proportions of Oral TU-treated subjects at Visit 7 according to the following categories: < 1361 ng/dL (e.g., 1500 × 0.907), > 1633 to \leq 2268 ng/dL, and > 2268 ng/dL. This post hoc analysis was performed to understand how the revised upper limits of normal, based on plasma T concentrations in NaF/EDTA-containing tubes might affect the C\text{max} outlier results.

For the traditional C\text{max} outlier criteria:
- 137 of 151 (90.7%) of Oral TU subjects and 47 of 48 (97.9%) of Topical Axiron subjects had T C\text{max} \leq 1500 ng/dL at Visit 7;
- 3 of 151 (2.0%) of Oral TU subjects and 1 of 48 (2.1%) of Topical Axiron subjects had T C\text{max} >1800-2500 ng/dL at Visit 7;
- 3 of 151 (2.0%) of Oral TU subjects and 0 of 48 (0%) of Topical Axiron subjects had T C\text{max} >2500 ng/dL at Visit 7;

For the adjusted C\text{max} outlier criteria:
- 125 of 151 (82.8%) of Oral TU subjects and 47 of 48 (97.9%) of Topical Axiron subjects had T C\text{max} \leq 1361 ng/dL at Visit 7;
- 5 of 151 (3.3%) of Oral TU subjects and 1 of 48 (2.1%) of Topical Axiron subjects had T
C\textsubscript{max} >1633-2268 ng/dL at Visit 7;

- 4 of 151 (2.6%) of Oral TU subjects and 0 of 48 (0%) of Topical Axiron subjects had T

C\textsubscript{max} >226 ng/dL at Visit 7;

Tables 4 and 5 provide these same results in tabular format:

**Table 4: Percentage of Subjects with Testosterone C\textsubscript{max} Values in Protocol Specific Ranges**

<table>
<thead>
<tr>
<th>Testosterone C\textsubscript{max} at Visit 7</th>
<th>FDA Target</th>
<th>Oral TU (N=151)</th>
<th>Topical Axiron (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1500 ng/dL</td>
<td>≥85%</td>
<td>137 (90.7%)</td>
<td>47 (97.9%)</td>
</tr>
<tr>
<td>&gt;1800-2500 ng/dL</td>
<td>≤5%</td>
<td>3 (2.0%)</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>&gt;2500 ng/dL</td>
<td>0</td>
<td>3 (2.0%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: CLAR-15012 study report, Table 18, page 98

**Figure 5: Percentage of Subjects with Testosterone C\textsubscript{max} Values in Selected Ranges at Visit 7 Based on Adjusted C\textsubscript{avg} Upper Limit**

<table>
<thead>
<tr>
<th>Testosterone C\textsubscript{max} Adjusted at Visit 7</th>
<th>FDA Target</th>
<th>Oral TU (N=151)</th>
<th>Topical Axiron (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1361 ng/dL</td>
<td>≥85%</td>
<td>125 (82.8%)</td>
<td>47 (97.9%)</td>
</tr>
<tr>
<td>&gt;1633-2268 ng/dL</td>
<td>≤5%</td>
<td>5 (3.3%)</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>&gt;2268 ng/dL</td>
<td>0</td>
<td>4 (2.6%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: CLAR-15012 CSR: Table 20, page 102

We conducted a detailed analysis of the 3 outliers (or 4 outliers, if using the adjusted range value), with C\textsubscript{max} > 2500 ng/dL. For the original 3 patients with C\textsubscript{max} >2500 ng/dL:

- The dihydrotestosterone/testosterone (DHT/T) molar ratios were all between 0.0439 and 0.0602 values that are less than half the DHT/T ratio (0.1484) of the other Oral TU-treated subjects in the 2-hour post dose sample. Contamination with testosterone would be expected to increase the testosterone concentration but not affect the DHT concentration.

- In these 3 subjects, the C\textsubscript{max} values were >2500 ng/dL after the AM dose, but their C\textsubscript{max} values were substantially below 2500 ng/dL after the PM dose.

- The increase in the C\textsubscript{max} was not associated with the fat content of the preceding meal.

Based on this evidence, we agreed with the Sponsor’s conclusion that the 3 original C\textsubscript{max} outliers were likely spurious, perhaps related to T contamination that may have occurred at the clinical investigative site. Based on the results from the supplemental analysis, one additional C\textsubscript{max} > 2268 ng/dL outlier was identified and a narrative for that subject (Subject ) is provided in the 2nd resubmission Clinical review. In this single subject, with one single outlier value >2268 ng/dL at a single timepoint, an alternative reason for his outlier value was not discernible from the available evidence, although contamination might have been a potential issue in this subject too.
In summary, the observed distribution of $C_{\text{max}}$ values at Visit 7 for subjects treated with Oral TU was within or was very close to the targeted distribution that is accepted by FDA for TRT products.

Table 6 and Figure 2 summarize the mean T PK parameters obtained at Visit 7. For Oral TU, these PK parameters are compiled separately for the morning and evening dosing intervals, and for the combined 24-hour interval as $C_{\text{max-am}}$, $C_{\text{max-pm}}$, $C_{\text{max24}}$, $T_{\text{max-am}}$, $T_{\text{max-pm}}$, $AUC_{\text{am}}$, $AUC_{\text{pm}}$, $AUC_{24}$, $C_{\text{avg-am}}$, $C_{\text{avg-pm}}$, and $C_{\text{avg24}}$.

Table 6: Summary of Oral TU and Topical Axiron Total T PK Parameters at Visit 7, by Treatment, for all Doses Combined in CLAR-15012 (from NaF-EDTA Plasma)

<table>
<thead>
<tr>
<th>Visit</th>
<th>PK Parameter</th>
<th>Units</th>
<th>Oral TU Subjects</th>
<th>Topical Axiron Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Visit 7</td>
<td>$C_{\text{max-am}}$</td>
<td>ng/dL</td>
<td>155</td>
<td>773.3</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max-pm}}$</td>
<td>ng/dL</td>
<td>151</td>
<td>838.4</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max24}}$</td>
<td>ng/dL</td>
<td>151</td>
<td>1008.3</td>
</tr>
<tr>
<td></td>
<td>$T_{\text{max-am}}$</td>
<td>h</td>
<td>155</td>
<td>3.87</td>
</tr>
<tr>
<td></td>
<td>$T_{\text{max-pm}}$</td>
<td>h</td>
<td>151</td>
<td>16.00</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{min-am}}$</td>
<td>ng/dL</td>
<td>155</td>
<td>141.8</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{min-pm}}$</td>
<td>ng/dL</td>
<td>151</td>
<td>145.9</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{min24}}$</td>
<td>ng/dL</td>
<td>151</td>
<td>131.3</td>
</tr>
<tr>
<td></td>
<td>$AUC_{\text{am}}$</td>
<td>ng*h/dL</td>
<td>155</td>
<td>4566.6</td>
</tr>
<tr>
<td></td>
<td>$AUC_{\text{pm}}$</td>
<td>ng*h/dL</td>
<td>151</td>
<td>5083.3</td>
</tr>
<tr>
<td></td>
<td>$AUC_{24}$</td>
<td>ng*h/dL</td>
<td>151</td>
<td>9635.1</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{avg-am}}$</td>
<td>ng/dL</td>
<td>155</td>
<td>379.9</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{avg-pm}}$</td>
<td>ng/dL</td>
<td>151</td>
<td>424.6</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{avg24}}$</td>
<td>ng/dL</td>
<td>151</td>
<td>402.5</td>
</tr>
</tbody>
</table>

* $T_{\text{max}}$ values shown are median (range);  
* Axiron $T_{\text{max}}$ is relative to the AM dose since Axiron was applied just once daily, in the morning, $T_{\text{max-am}}$ and $T_{\text{max24}}$ are interchangeable for Axiron  
* $C_{\text{avg24}}$ calculated after study completion using actual sample collection times  
* $C_{\text{avg24}}$ calculated for titration decisions as study was conducted, using nominal sample collection times (not done for Visit 7)  

Source: Appendix B, Table B-1

Figure 2 shows mean concentration-time profiles for total T for each of the 3 PK visits in the CLAR-15012 for subjects administered Oral TU. The mean concentrations include all study subjects at each visit; the results are not stratified by dose.
In regard to the T metabolites dihydrotestosterone (DHT) and estradiol (E2):

For DHT, mean peak exposures ($C_{\text{max24}}$) and total exposures ($AUC_{24}$) for plasma DHT concentrations in the Oral TU-and Topical Axiron-treated subjects were very similar between groups at all 3 pharmacokinetic visits. At Visit 7, the plasma DHT $C_{\text{max}}$, $AUC$, and $C_{\text{avg}}$ values were very similar between the Oral TU and Topical Axiron groups. For example, the mean 24-hour plasma DHT $C_{\text{avg}}$ values were 73.3 ng/dL and 73.8 ng/dL for Oral TU and Topical Axiron, respectively. The CLAR-15012 study report states that these values are not more than 13% above the upper limit of the normal range for DHT $C_{\text{avg}}$ concentrations in eugonadal men. The mean DHT/T ratios for Oral TU and Topical Axiron were 0.18 and 0.19, respectively. A DHT/T ratio of 0.10 has been cited by some authors as normal for eugonadal men.

**CDTL Comment:** Normal range DHT $C_{\text{avg}}$ values and DHT/T ratios vary in the medical literature reports. Comparisons of Oral TU and Topical Axiron DHT $C_{\text{avg}}$ concentrations and DHT/T ratios to normal euogonadal ranges therefore should be approached with caution.

For E2, mean peak exposures and total exposures for serum E2 in the Oral TU-and Topical Axiron-treated subjects were also very similar at Visit 7. At Visit 7, the E2 $C_{\text{max}}$, $AUC$, and $C_{\text{avg}}$ values were very similar between the Oral TU and Topical Axiron groups. For example, the mean 24-hour E2 $C_{\text{avg}}$ values were 32.3 pg/mL and 33.0 pg/mL, for Oral TU and Topical Axiron, respectively,
**Statistician’s Conclusion**

In their final review of the 1st resubmission, dated February 13, 2018, the Statistical review team of Sonia Castillo and Mahboob Sobhan had the following overall conclusion:

“The one submitted study provides evidence demonstrating the efficacy of oral testosterone undecanoate capsules for the treatment of adult male hypogonadism. The evidence is based on achieving plasma total testosterone levels within the normal range at study end in at least 75% of men with the lower bound of the 95% confidence interval for the estimate of the proportion of men achieving the plasma total testosterone levels within the normal range no less than 65%. The normal range of plasma total testosterone level for this product is defined as ≥252 ng/dL and ≤907 ng/dL. The percentage of men with a plasma total testosterone level within the normal range at study end was 87.3% (145 of 166 subjects) with 95% confidence interval of 81.3% to 92.0%”.

There was one comment of note from the Statistical review:

- The Applicant changed the laboratory used to assay the plasma total testosterone concentrations after they discovered that the original laboratory produced unreliable concentration values. These concentration values are used to determine the plasma total testosterone $C_{avg}$ used in the primary efficacy evaluation. Based on information provided in this NDA submission, the Clinical Pharmacology review team concluded that changing the assay laboratory was not an issue and that the plasma T data from the new laboratory was acceptable.

While the new laboratory was re-assaying the ongoing subjects’ stored Visit 2 blood samples, subjects continued taking their current study product dose until new re-assay values were available to re-evaluate their titration outcome. Subjects were considered to have “restarted” the study based on the Visit 2 blood sample new re-assay results and were evaluated for a titration decision at their new “Visit 3”. The Applicant submitted protocol Amendment 2 on July 14, 2016 under IND 78,104, to describe this study conduct change, and redefined the upcoming subject clinic visits as Visit 3b, Visit 4b, and Visit 5b in protocol Amendment 3 submitted on March 24, 2017 under IND 78,104.

No subjects had reached the initial Visit 6 at the time of the laboratory change, so all clinical visits after Visit 5b were kept as Visits 6 and 7 (endpoint). Visit 7 is termed “Study End” because all subjects no longer had the original end of study time point of 105 days.

**7.4.2 Overall Assessment of Efficacy**

The efficacy data from the “pivotal” Phase 3 study CLAR-15012 support the Sponsor’s contention that Jatenzo (Oral TU) provides adequate testosterone replacement in adult men with hypogonadism.

**6. Safety**

**8.1 SAFETY RESULTS**

This Clinical Safety review focuses on the safety results from CLAR-15012, the “pivotal” Phase 3 study that employed the to-be-marketed doses and dose-titration
regimen. For details related to the safety results from the prior Phase 3 clinical studies CLAR-09007 and CLAR-12011, and the safety extension study CLAR-12010, the reader is referred to my previous CDTL memos as well as to the current and prior medical officers’ Clinical reviews.

The reader should be aware that while this part of the memo mainly concerns the results from CLAR-15012, the prior safety results from CLAR-09007, CLAR-12011 and CLAR-12010 have all been reviewed and have been taken into consideration as part of the overall Clinical safety assessment.

To reiterate, the overall phase 3 NDA safety database consists of
- 166 hypogonadal adult males who received between 20 and 30 weeks of treatment (using the to-be-marketed doses and dose regimen) with Oral TU in CLAR-15012.
- another 144 hypogonadal adult males who received approximately 16 weeks of treatment with Oral TU, by a slightly different dose regimen than the regimen used in CLAR-15012, in CLAR-12011, and
- another 161 hypogonadal adult males who received up to approximately 52 weeks of treatment with Oral TU, at higher doses and a different dose regimen than used in CLAR-15012 and CLAR-12011, resulting in higher systemic T exposures than in those studies, in the Phase 3 safety Study CLAR-09007.

Thus, a total of 471 patients received treatment with Oral TU in Clarus’ three phase 3 studies. A total of 86 subjects received treatment for approximately 52 weeks in the Long-Term Extension Study to Study CLAR-09007, CLAR-12010. Again, the doses and dose regimen in that study were different that those used in the other phase 3 studies, resulting in higher systemic T exposures than the T exposures achieved in the other phase 3 studies that used lower doses and different dose regimens.

The following sections provide an overview of the CLAR-15012 safety results. For additional details, the reader is referred to the medical officer’s Clinical review.

### 8.1.1 Deaths, Serious Adverse Events and Discontinuations Due to Adverse Events

**Deaths**

There were no deaths in CLAR-15012.

**Serious Adverse Events (SAEs)**

Two subjects in the Oral TU group experienced serious treatment-emergent adverse events (TEAEs) during CLAR-15012:

- **Subject** was a 63-year-old White male with a 12-year history of Crohn’s disease who experienced a serious TEAE of small intestinal obstruction. The event began on Day 89 while receiving the 396 mg BID of Oral TU. The event required hospitalization, and was considered moderate in intensity and not related to study drug. Study drug was interrupted and the subject was treated with 14 days of oral prednisone; the event was
noted as resolved on Day 92, the study drug was restarted, and the subject completed the study without further incident.

- Subject [redacted] was a 53-year-old White male with a 1-year history of umbilical hernia who experienced a serious TEAE of periumbilical abscess. The event began on Day 90 while receiving the 316 mg BID of Oral TU. The event required hospitalization, and was considered severe in intensity and not related to study drug. No action was taken with respect to study drug and the subject was treated with intravenous antibiotics. The event was noted as resolved on Day 95 and the subject completed the study without further incident.

One subject in the Topical Axiron group experienced a serious AE prior to dosing in CLAR-15012. Subject [redacted] experienced a serious AE of perforated appendicitis 13 days prior to randomization in the study. The event was considered severe in intensity and required hospitalization.

There is one additional SAE that was reported to occur 2 weeks after dosing had completed: Subject [redacted] experienced a myocardial infarction 2 weeks after receiving his last dose of Oral TU. The case is described here despite it being reported in a timeframe longer than the 7-day follow-up after study completion per the protocol-specified AE reporting criteria.

- Subject [redacted] was a 53 year-old male with a prior history of hypertension, hyperlipidemia, coronary artery disease status post 2 cardiac catheterizations (last of which was in [redacted] but without stent placement. He also has a history of undescended testicle for which he underwent orchiectomy in [redacted]. He has a urologic history of azoospermia diagnosed in [redacted], infertility diagnosed in [redacted] and erectile dysfunction diagnosed in [redacted]. His hypogonadism was diagnosed in [redacted] The Sponsor narrative did not contain information concerning prior TRT. Concomitant medications at the time of the event included metoprolol, simvastatin and omeprazole.

On [redacted] 14 days after his last dose of study medication, the subject was hospitalized with the diagnosis of myocardial infarction. During hospitalization, two cardiac stents were deployed. This event occurred 7 days after the protocol defined post-completion period of 7 days. The subject had taken Oral TU for 179 days.

The subject’s hematocrit (Hct) values during the study were within normal limits. At screening Visit 2, the Hct was 45.7%. Immediately prior to the first dose of study drug his Hct was 44.8%. At Visit 7, on Day 180, his Hct was 46.2%. The subject’s blood pressures were 138/84 at Visit 1, 142/82 at Visit 4 (Day 21), 136/83 at Visit 4 (Day 57), 137/83 at Visit 4b (Day 130) and 138/80 at Visit 7 (Day 179, [redacted] The subject’s serum lipid concentrations showed no clinically meaningful changes from baseline while on treatment.

The subject’s two serum testosterone levels collected during screening were 142 ng/dL and 83 ng/dL. His Visit 1 pre-dose plasma testosterone level was 112 ng/dL. During the study, the subject’s testosterone levels were (shown in Table 16):
Table 7: CLAR 15012 Subject Testosterone Concentrations

<table>
<thead>
<tr>
<th>Visit</th>
<th>Study Day</th>
<th>TC avg-24hr (ng/dL)</th>
<th>TC max (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 2</td>
<td>21</td>
<td>262</td>
<td>587.3</td>
</tr>
<tr>
<td>Visit 4b</td>
<td>130</td>
<td>598</td>
<td>1426.9</td>
</tr>
<tr>
<td>Visit 7</td>
<td>179</td>
<td>384</td>
<td>778.2</td>
</tr>
</tbody>
</table>

Source: Unlabeled Table in SDN 34

**CDTL Comment:** The subject had hyperlipidemia, hypertension, and serious coronary artery disease at baseline. While he had undergone angioplasty twice, he had not had stents placed. There were no clinically meaningful changes in his BP, hematocrit, or serum lipids while on treatment, and he had no particularly notable T levels. Definitive conclusions about drug causality and this SAE are precluded by the subject’s background medical condition and timing of the event.

**Discontinuations Due to Adverse Events (AEs)**

Four (2.4%) subjects in the Oral TU group and 1 (1.8%) subject in the Topical Axiron group experienced TEAEs that led to premature discontinuation from the study. For Oral TU:

- Subject was a 39-year-old White male who was prematurely discontinued from the study due to the occurrence of rash (bilateral axillary rash with no involvement of eyes or mouth). The event began on Day 62 while receiving 316 mg BID of Oral TU. The rash was treated with an oral antibiotic starting on Day 63. A second rash event occurred on Day 83 in the groin area. Both events were considered mild in intensity and not related to study drug. The subject was withdrawn from the study (last dose received on Day 62); and the events were noted as ongoing.

- Subject was a 56-year-old White male who was prematurely discontinued from the study due to headache. Prior to enrollment, this subject was receiving treatment for Type 1 hypertension. His average blood pressures at Screening were systolic 132 mm Hg (133, 148, and 126 mmHg) and diastolic 83 mmHg diastolic (87, 82, and 80 mmHg). The headache AE began on Day 135 while the subject was receiving 396 mg BID of Oral TU. The patient’s blood pressures on Day 139 (the nearest time to the headache AE) were 148/85 and 143/84 mm Hg. The event was considered moderate in intensity, related to study drug, and did not require any treatment. The event was noted as resolved on Day 138, on the day prior to the subject receiving his last dose of study drug and being withdrawn from the study on Day 139; the subject also experienced TEAEs of moderate flushing, hyperhidrosis, and hypoaesthesia beginning on Day 104, and moderate BP increased and mild hematocrit increased beginning on Day 118, all while taking 316 mg BID of Oral TU. Events of moderate dyspepsia on Day 134 and moderate...
nausea on Day 137 were also reported while he was taking 396 mg BID of Oral TU dose. Each of these TEAEs was considered related to study drug administration.

- Subject (b) was a 44-year-old White male who was prematurely discontinued from the study due to headache. At screening, the subject’s average blood pressure was 133/86 mmHg. The subject’s BPs during the study were 126/90 mmHg (Day 1), 129/81 mmHg (Day 24), 118/83 mmHg (Day 59) and 134/88 mmHg (Day 86). The headache AE began on Day 3 while the subject was receiving 237 mg BID of Oral TU. The event was considered mild in intensity, related to study drug, and required no treatment. The subject was withdrawn from the study (he received his last dose on Day 81); the event was noted as ongoing.

- Oral TU subject (b) discontinued from the study due to an AE, however no specific TEAE was indicated as having led to premature discontinuation. The subject had a severe panic reaction event reported as an AE on Day 125 during blood drawing for PK at Visit 7 and couldn’t complete all procedures for that visit. At the time of discontinuation his oral TU dose was 396 mg BID.

Based on the headache AE reported for Subject (b), as part of the review of the 1st resubmission, the Clinical review team conducted an analysis of reported headache AEs in CLAR-15012 and changes in BP in subjects who reported headaches. A total of 8 Oral TU subjects and 1 Topical Axiron subject reported the AE of headache in CLAR-15012. None of these AEs were classified as SAEs. Four of the Oral TU subjects who reported a TEAE of headache showed small increases from baseline in BP (e.g., Subject (described above) and Subjects (b) [described above] and Subjects (b)). The single Topical Axiron subject who reported a headache AE did not appear to have any increase in BP while on treatment.

**CDTL Comment:** The available data are too sparse to draw conclusions about a relationship between headache and increased BP in CLAR-15012, although such a relationship is possible.

### 8.1.2 Other Adverse Events

#### Commonly Reported Adverse Events

In CLAR-15102, the overall incidence of treatment-emergent adverse events (TEAEs) was higher in the Oral TU group (47.0%) compared with the Topical Axiron group (36.4%), and the difference between groups was driven largely by Gastrointestinal Disorders. Notable results in the System Organ Classes (SOCs) included:

- Gastrointestinal Disorders: 12.0% Oral TU versus 0.0% Topical Axiron
- Investigations (including the preferred terms [PTs] “hematocrit increased” and “HDL-decreased”): 13.9% Oral TU versus 3.6% Topical Axiron
- Vascular Disorders (including the PT “hypertension”): 3.6% Oral TU versus 0.0% Topical Axiron

The PT Headache also had a notable result: 4.8% Oral TU versus 1.8% Topical Axiron.
The relationship between headache and increased BP in CLAR-15012 is not entirely clear, and was discussed in the previous section of this memo.

The most commonly reported TEAEs, reported as PTs by at least 2% of subjects in either treatment group in CLAR-15012, were: “hematocrit increased” (Oral TU 4.8%, Topical Axiron 0%), “HDL-cholesterol decreased” (Oral TU 3.0%, Topical Axiron 0%), “upper respiratory tract infection” (Oral TU 3.6%, Topical Axiron 0%), “nausea” (Oral TU 2.4%, Topical Axiron 0%), “headache” (Oral TU 4.8%, Topical Axiron 1.8%), “hypertension” (Oral TU 3.0%, Topical Axiron 0%), rash (Oral TU 1.2%, Topical Axiron 3.6%), and “overdose” (Oral TU 0.6%, Topical Axiron 3.6%).

The following two tables provide listings of all TEAEs reported by at least 2% of subjects in either treatment group (as above, see Table 8), and all TEAEs reported by at least 1% of subjects and assessed by the investigator as related to treatment (see Table 9).

Table 8: TEAEs Occurring in >=2% in Either Treatment Group in CLAR-15012

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Oral TU (N = 166)</th>
<th>Topical Axiron (N = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any TEAE</td>
<td>78 (47.0)</td>
<td>20 (36.4)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematocrit increased</td>
<td>23 (13.9)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>High-density lipoprotein decreased</td>
<td>8 (4.8)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>5 (3.0)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (12.0)</td>
<td>0</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>4 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16 (9.6)</td>
<td>5 (9.1)</td>
</tr>
<tr>
<td>Nervous system Disorders</td>
<td>6 (3.6)</td>
<td>4 (7.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (4.8)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td>6 (3.6)</td>
<td>4 (7.3)</td>
</tr>
<tr>
<td>Overdose</td>
<td>1 (0.6)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>5 (3.0)</td>
<td>6 (10.9)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (1.2)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>6 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (3.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

a=Adverse Events by MedDRA Version 15.1
Source: CLAR-15012 CSR, Table 35 (Snapshot), page 130.
Table 9: TEAEs Considered Drug-Related by the Investigator and Occurring in >=1% of Subjects in Either Group in CLAR-15012

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term, n (%)</th>
<th>Oral TU (N = 166)</th>
<th>Topical Axiron (N = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any related TEAE</td>
<td>31 (18.7)</td>
<td>8 (14.5)</td>
</tr>
<tr>
<td>High-density lipoprotein decreased</td>
<td>5 (3.0)</td>
<td>0</td>
</tr>
<tr>
<td>Hematocrit increased</td>
<td>4 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>3 (1.8)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Eructation</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: Source: CLAR-15012 Study Report, Table 36, page 130

In regard to the incidence of AEs by patient age, conclusions are limited by the small sample size in CLAR-15012, and also due to the exclusion criterion for subjects > 65 years of age.

**CDTL Comment:** With the exception of Gastrointestinal Disorders, there appear to be no new adverse reactions for Oral TU compared to approved TRT. The available data are not sufficient to conclude that headaches reported with Jatenzo are related to increased BP.

8.1.3 Clinical Laboratories, Vital Signs and Electrocardiograms (ECGs)

**Clinical Laboratories**

In CLAR-15012, comprehensive safety laboratory testing was conducted at baseline, periodically while on treatment, and again at end-of-treatment. These tests included: chemistry with liver tests, complete blood count (CBC), lipid profiles, and prostate specific antigen (PSA). The Sponsor provided a summary of routine lab test results at baseline and at all scheduled post-dose visits.

There were no notable changes from baseline in routine chemistry tests, including no notable changes in liver tests.

There were some notable findings in results from complete blood counts, serum lipid profiles and serum PSA. The following subsection summarize these results:

**Increases in Hematocrit/Hemoglobin**

The mean baseline hematocrit values were within the normal range for both treatment groups. At Visit 4b, mean increases in hematocrit were noted in both the Oral TU and Topical Axiron treatment groups (0.028 and 0.019 L/L, respectively), representing a mean percent increase from baseline of 6.4% in the Oral TU group and 4.4% in the Topical Axiron group. Mean increases from baseline in hematocrit were also noted for both treatment groups at their final visit (Visit 7 or Early Termination; Oral TU: 0.026 L/L; Topical Axiron: 0.020 L/L), representing mean percent increases from baseline of 6.0% in the Oral TU group and 4.7% in the Topical Axiron group. Similar results were also observed for hemoglobin and erythrocyte count. Consistent with the increases in mean hematocrit and hemoglobin, 10.2% of all Oral TU
subjects shifted from normal values at baseline to above the normal range at the final visit, compared with 1.9% of Topical Axiron subjects.

There were 8 (4.8%) Oral TU subjects with clinically significant post-baseline hematocrit values (>54%) as compared to 0 (0%) for Topical Axiron per the investigators’ judgement and similarly, there were 8 (4.8%) Oral TU subjects in whom “hematocrit increased” was reported as a TEAE. Among the 8 Oral TU subjects who reported TEAEs of “hematocrit increased”, the events occurred between Day 80 and Day 159. Eight (8) cases occurred at greater than 120 days of exposure to study drug, six of the hematocrit values at or near the time of onset ranged from 54.3% to 57.8%. In these 8 subjects, there was no apparent relationship between Oral TU dose and magnitude of hematocrit increase. One subject was re-tested and no subject required treatment for “hematocrit increased”.

**CDTL Comment:** Oral TU is associated with increases in hematocrit and hemoglobin that appear to be slightly larger than for the approved concurrent active comparator, Topical Axiron.

**Decreases in Serum High Density Lipoprotein (HDL) Cholesterol**

Mean changes from baseline to the final visit (Visit 7 or Early Termination) in total cholesterol concentrations were similar between the treatment groups (Oral TU: -0.252 mmol/L; Topical Axiron: -0.292 mmol/L); however, changes in HDL-cholesterol, LDL-cholesterol, and triglycerides were somewhat different between the treatment groups. Mean decreases from baseline in HDL-cholesterol were noted in both treatment groups at the final visit (Visit 7 or Early Termination); however, the mean decrease observed in the Oral TU group was greater than the mean decrease observed in the Topical Axiron group (-0.18 mmol/L [-6.9 mg/dL] versus -0.05 mmol/L [-2.0 mg/dL]); representing mean percent decreases from baseline of -13.9% in the Oral TU group compared with -3.4% in the Topical Axiron group.

A small mean increase from baseline to the final visit (Visit 7 or Early Termination) in LDL-cholesterol was noted in the Oral TU group (0.09 mmol/L [3.5 mg/dL]), while a small mean decrease from baseline was observed in the Topical Axiron group (-0.10 mmol/L [-4.0 mg/dL]); representing a mean percent increase from baseline of 5.9% in the Oral TU group compared with a decrease of -2.1% in the Topical Axiron group.

Similar results were also observed for triglycerides, with a small mean increase from baseline to the final visit (Visit 7 or Early Termination) observed in the Oral TU group (0.11 mmol/L [9.3 mg/dL]), while a small mean decrease from baseline was observed in the Topical Axiron group (-0.02 mmol/L [-1.4 mg/dL]), representing a median percent increase of 5.5% in the Oral TU group and a median percent decrease of 1.3% in the Topical Axiron group.

A greater proportion of Oral TU subjects shifted from normal HDL-cholesterol at baseline to below the normal range (28.9% for final visit values) compared with Topical Axiron subjects (14.8% for final visit values). Shifts from normal baseline values to above the normal range in total cholesterol and triglycerides were also more common in Oral TU subjects compared with
Topical Axiron subjects (Oral TU: 7.8% and 13.3%, respectively, for final visit values; Topical Axiron: 3.7% and 9.3% for final visit values).

**CDTL Comment:** Oral TU was associated with small increases in total cholesterol, LDL-cholesterol and triglycerides, whereas Topical Axiron was associated with very small decreases in these parameters. Oral TU was associated with decreases in HDL-cholesterol that appear slightly larger than for the approved concurrent active comparator, Topical Axiron.

**Increases in Serum Prostate Specific Antigen (PSA)**
Mean changes in serum PSA (in ng/mL) from baseline to Visit 7 or Early termination were +0.98 for Oral TU subjects and +0.95 for Topical Axiron subjects. PSA values > 4.0 ng/mL occurred in 3 (1.9%) Oral TU patients and in 2 (3.8%) Topical Axiron patients. There were no digital prostate exam abnormalities/changes noted including no nodularity, enlargement, or irregularity. Subject **(b) (6)** had a PSA value of 2.94 ng/mL at Baseline that rose to 5.34 ng/mL at Day 161; the event was considered mild and probably not related to study drug. A follow-up value obtained approximately 2 months later was 3.0 ng/mL.

**CDTL Comment:** TRT has been associated with small increases in serum PSA. Oral TU also appears to be associated with small increases in serum PSA.

**Vital Signs**
Vital signs, including sitting systolic and diastolic blood pressures (SBP/DBP) by blood pressure cuff and resting heart rate (HR), were collected in CLAR-15012, and those data were analyzed at Baseline and at all scheduled post-dose visits.

In addition, based on increases observed in mean blood pressure cuff BPs in the phase 3 study CLAR-12011, ambulatory blood pressure monitoring (ABPM) was requested as an essential component of CLAR-15012 and was performed by the Sponsor at the Baseline and End-of-Treatment Visits in that study. The resulting ABPM data, as collected and analyzed by the Sponsor and Division of Cardiovascular and Renal Products (DCRP) consultants, confirm that Jatenzo increases SBP and DBP by a clinically meaningful amount. On the other hand, Topical Axiron, had no significant effect on SBP or DBP.

In CLAR-15012, by blood pressure cuff measurement, SBP was increased from baseline to Visit 7/Early Termination in both treatment groups (mean ± SD: Oral TU 2.8 ± 11.84 mm Hg, Topical Axiron 1.8 ± 10.76 mm Hg), whereas DBP was essentially unchanged at Visit 7/Early Termination. Based on the Sponsor’s analysis, the change from baseline to the last post-baseline value was statistically significant for SBP (by cuff) and HR for the Oral TU group only.

Figure 3 provides a graphic representation of mean increase from baseline in blood pressure cuff SBP in both groups, Oral TU greater than Topical Axiron, with the rise in BP not appearing to plateau at Visit 7.
Also in CLAR-15012, a total of 135 subjects in the Oral TU group and 45 subjects in the Topical Axiron group had ABPM measurements with interpretable results at both the Pre-Dose Visit (Day -2) and End-of-Treatment Visit (Visit 6) and were included in the ABPM Population for data analysis. Demographic characteristics of the ABPM Population were similar to those for the ITT Population. Among baseline characteristics, a history of hypertension was reported for a slightly greater proportion of subjects in the Oral TU group (53.3%) compared with the Topical Axiron group (46.7%). Baseline hypertension classifications based on BP obtained at Screening showed a larger proportion of subjects in the Oral TU group compared with the Topical Axiron group who were pre-hypertensive (67.4% versus 55.6%), whereas the proportions with Stage 1 hypertension were similar between the treatment groups (9.6% and 8.9%).

The mean increases in daytime average, nighttime average, and 24-hour average SBP from baseline to Visit 6 for the Oral TU group was nominally statistically significantly greater than for the Topical Axiron group with 24-hour average SBP increasing by 4.88 (± 8.75) mm Hg in the Oral TU group and by 0.18 (± 9.38) mm Hg in the Topical Axiron group. Similar results were observed for daytime and nighttime averages, as well as for mean arterial pressure (MAP). Mean increases in daytime average, nighttime average, and 24-hour average DBP from baseline to Visit 6 for DBP were also greater for the Oral TU compared to the Topical Axiron group, but for DBP the differences between groups were not statistically significant. There were no statistically significant differences between groups for changes in HR.

Table 10 below summarizes the ABPM data from CLAR-15012.
Table 10: Systolic and Diastolic Blood Pressure Measured by ABPM at Baseline and Visit 6 by Treatment Group (ABPM Population) in CLAR-15012

<table>
<thead>
<tr>
<th>Vital Sign Measurement</th>
<th>Statistic</th>
<th>Oral TU (N = 135)</th>
<th>Topical Axiron (N = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Change</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime average</td>
<td>Mean (SD)</td>
<td>131.13 (10.149)</td>
<td>131.21 (14.101)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>131.50</td>
<td>131.50</td>
</tr>
<tr>
<td></td>
<td>p-value*</td>
<td>0.008</td>
<td>0.60</td>
</tr>
<tr>
<td>Nighttime average</td>
<td>Mean (SD)</td>
<td>120.05 (11.164)</td>
<td>118.33 (13.102)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>120.10</td>
<td>117.50</td>
</tr>
<tr>
<td></td>
<td>p-value*</td>
<td>0.0309</td>
<td>-0.70</td>
</tr>
<tr>
<td>24-hour average</td>
<td>Mean (SD)</td>
<td>127.52 (9.747)</td>
<td>127.03 (13.243)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>127.80</td>
<td>128.00</td>
</tr>
<tr>
<td></td>
<td>p-value*</td>
<td>0.0013</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Diastolic blood pressure (mm Hg)

| Daytime average        | Mean (SD) | 78.93 (7.819)    | 79.94 (8.547)          |
|                        | Median    | 78.50            | 79.30                  |
|                        | p-value*  | 0.0051           | 0.50                   |
| Nighttime average      | Mean (SD) | 70.07 (7.779)    | 69.40 (8.092)          |
|                        | Median    | 69.60            | 69.00                  |
|                        | p-value*  | 0.0199           | 0.50                   |
| 24-hour average        | Mean (SD) | 76.04 (7.266)    | 76.53 (7.910)          |
|                        | Median    | 75.90            | 75.80                  |
|                        | p-value*  | 0.0653           | -0.20                  |

*a= Versus Topical Axiron for change from baseline, based on analysis of covariance with treatment group as a factor and baseline as covariate.

Source: CLAR-15012 CSR, Table 49, page 164

Figure 4 below reflects the mean changes in 24-hour average SBP and DBP in the ABPM population, shown as subpopulations with and without a baseline history of hypertension. In subjects with a history of hypertension, Oral TU-related increases in SBP and DBP were larger than in subjects without a history of hypertension.
Figure 4: Mean Change from Baseline to Visit 6 in 24-Hour Average Systolic and Diastolic Blood Pressure by Treatment Group and History of Hypertension (ABPM Population)

Source: Snapshot Figure 24, Clar-15012 CSR, page 166

Figure 5 below shows the cumulative distribution curves for 24-hour average daytime SBP collected from ABPM performed at Visit 7/Early Termination for subjects in the ABPM Population in CLAR-15012.
**Figure 5: Cumulative Distribution Curves for Daytime Average Systolic Blood Pressure by Treatment Group (ABPM population) in CLAR-15012**

Source: Snapshot Figure 23, Clar-15012 CSR, page 165

**TU = Oral TU; TA = Topical Axiron**

**CDTL Comment:** The ABPM cumulative distribution curves reveal a more pronounced blood pressure increasing effect for Oral TU compared to the Topical Axiron comparator.

It is also notable that in the Oral TU group, 7.2% of subjects started antihypertensive medication after baseline or required an increase in dose of antihypertensive medication compared with 1.8% of subjects in the Topical Axiron group.

A formal consultation was requested from the Division of Cardiovascular and Renal Products (DCRP) to assist in the review of these vital signs data, including the evidence of increased BP for oral TU from both blood pressure cuff and ABPM measurements. The reader is referred to Section 11.6 of this memo for a summary of the DCRP consult. To summarize the consult briefly here:

DCRP concluded that Oral TU raises blood pressure in a clinically and statistically significant manner, particularly in subjects with pre-existing hypertension. DCRP noted that this effect occurred in the setting of a disproportionate escalation of antihypertensive therapy in the Oral TU arm, and that the BP increase was of a larger magnitude than that seen for the comparator.

DCRP also mentioned that Oral TU induced increases in HR, and those increases may amplify the clinical impact of the Oral TU-related elevations in BP with respect to the occurrence rate of future serious CV events.

**CDTL Comment:** Blood pressure cuff BP data showed a blood pressure increasing effect for Oral TU that was larger than that seen for Topical Axiron. ABPM data showed a clear and confirmed, clinically meaningful increase in daytime, nighttime and 24-hour average SBP for Oral TU that was not observed with the concurrent active comparator, Topical Axiron. These findings were consultatively reviewed by DCRP who confirmed the conclusions. See Section 11.6 of this memo for more detail on DCRP’s analyses and conclusions on these data.
**ECGs**

Electrocardiograms were not performed in CLAR-15012.

### 8.2 Postmarketing Safety Findings

According to the Sponsor’s Safety Update provided in this 2\textsuperscript{nd} resubmission, Jatenzo is not available in any country outside of the United States. As part of the original submission (first review cycle), the Sponsor provided a brief review of the publicly available post marketing experience for Andriol, an oral testosterone undeconoate product marketed in 80 countries, including Europe and Canada, for up to 30 years by a different pharmaceutical company. The data are only indirectly relevant because the starting dose for Andriol is 60 mg to 80 mg titrated to 20 mg to 60 mg BID, which is a dose 4-5 times lower than for Jatenzo (starting dose is 237 mg, or 200 mg BID in T equivalents). In the original NDA submission, the Sponsor also conducted and reported a literature search for Andriol clinical studies in their Integrated Summary of Safety. 34 studies published between 1980 and 2013 were included in their analysis. Of these studies, 19 were controlled studies and 13 were open-label and uncontrolled studies.

Taken together, the pre- and postmarketing safety information provided for Andriol appears to show an overall AE profile, including laboratory results, that is consistent with the TRT class, except for some non-specific Gastrointestinal Disorders. However, it should be reiterated that the doses used in the studies for Andriol were mostly 40 mg to 80 mg TU, which are lower than the proposed Jatenzo doses.

### 8.3 Overall Assessment of Safety Findings

In general, the safety profile for Oral TU was consistent with the known safety profile for TRT products, except for mild gastrointestinal disorders, and one serious and clinically important finding: a well-defined, clinically meaningful increase in average systolic BP that was not observed for the concurrent comparator Topical Axiron. The Oral TU-related increases in BP are larger in hypogonadal men with a history of hypertension, including in hypogonadal men with treated hypertension. The mean increase in average daytime SBP for Oral TU is approximately 5 mmHg, with Topical Axiron showing a negligible mean increase (approximately 0.1 mmHg). In the Oral TU group, 7.2% of subjects started antihypertensive medication after baseline or required an increase in dose of antihypertensive medication compared with 1.8% of subjects in the Topical Axiron group. The magnitude of this BP effect, if sustained chronically, is expected to increase the risk of heart attack, stroke and cardiovascular death in the aging male population, who frequently have a history of cardiovascular disease, and are likely to be prescribed the product for reasons other than hypogonadism related to structural or genetic conditions.

### 9. Advisory Committee Meeting

On January 9, 2018, a meeting of the BRUDAC was held to discuss the 1\textsuperscript{st} resubmission of the
Jatenzo NDA. This was the second FDA Advisory Committee meeting convened to discuss Clarus’ Oral TU, and this meeting focused on the evidence provided in the Sponsor’s 1st resubmission.

For the Clinical issues, the Committee’s general perspectives were:

- Members agreed that potential CV risks associated with Jatenzo were of significant concern. The observed BP increases, for a chronically administered drug, were expected to increase the risk for serious CV events. This could have a large population impact given that the group likely to use the drug includes older men who are already at increased CV risk due to advanced age and co-morbid conditions such as diabetes, obesity, hyperlipidemia and hypertension. These men often receive testosterone for uses that are not FDA-approved, such as “age-related hypogonadism”. Most panelists were less concerned about the CV risks in the small population of men who are otherwise at low CV risk and have “classical” hypogonadism, for example, men with Klinefelter’s Syndrome.

- Members stated that the effects of Jatenzo on serum lipids and hematocrit did not raise concerns beyond what is generally known about testosterone therapies.

- Members stated that although the significance of transient elevations in DHT was not known, these findings did not raise specific safety concerns. None of the committee members felt this issue needed additional study.

- Members stated that the adrenal effects observed in animals could be re-assessed in humans in the postmarketing period.

For the use of plasma testosterone concentrations from NaF-EDTA-containing tubes on which to base dosing decisions, the Committee’s general perspectives were:

- 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-containing tubes instead of from serum in the more commonly used plain tubes. It was noted that although the NaF/EDTA-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.

- A specific 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.

- There was also interest in learning more about the potential cross-reactivity of testosterone undecanoate with the testosterone immunoassays that are commonly used to monitor patients on TRT.

The following voting question was posed to the Committee: Is the overall benefit/risk profile of Jatenzo acceptable to support approval as a testosterone replacement therapy? Result: 9 Yes, 10 No, and 0 Abstain.

Committee members largely viewed the product as a potentially beneficial new treatment option for men who needed TRT. However, members advised that the risk of increased BP would need
to be mitigated, either through a REMS, product labeling, or prescriber education.

10. Pediatrics

Recent discussions within FDA have focused on whether FDA should require postmarketing studies of testosterone therapy in pediatric patients with permanent forms of hypogonadism, such as children with Klinefelter’s disease or chemotherapy-induced primary hypogonadism. There have been suggestions from some Divisions, including the Division of Pediatric and Maternal Health (DPMH) and the Division of Metabolism and Endocrinology Products (DMEP) that such studies are feasible and practical, and could ultimately provide useful and necessary information for clinical practitioners concerning TRT in pediatric patients with permanent forms of hypogonadism. Others in FDA believe that the relevant pediatric population is small and that given the complexity of studies that might need to be conducted, PREA requirements should be waived due to lack of feasibility. An FDA Advisory Committee is planned for April 8, 2019 to discuss the issue publicly. In the meantime, because FDA has not determined that such a trial is infeasible and we are otherwise ready to approve this NDA, the Division will request that Clarus satisfy PREA by conducting a required postmarketing trial (PMR) of Jatenzo in male pediatric patients aged 14 years and above with hypogonadism due to structural or genetic etiologies. Should it subsequently be determined that such a trial is infeasible, we will release the applicant from conducting this PMR.

11. Other Regulatory Issues Including Consultations

11.1 Consultation: Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was consulted to conduct inspections of three clinical sites that participated in the Phase 3 study CLAR-15012. The three sites selected were: Laurence Belkoff (Bala Cynwd, PA), Gregory Flippo (Birmingham, AL) and Charles White (Mobile, AL).

No issues of clinical significance were identified at any of these three investigative sites.

In the final conclusion of their Clinical Inspection Summary, Roy Blay and Phillip Kronstein, concluded:

“...based on the results of these inspections, the study (CLAR-15012) appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective application.”

11.2 Consultation: Office of Surveillance and Epidemiology (OSE)/ Division of Medication Errors Prevention and Analysis (DMEPA)

In their final review dated January 18, 2019, Denise Baugh and Lolita White of DMEPA concluded:

“The revised container label and shipping label for ‘Jatenzo’ is acceptable from a medication error perspective. We have no further recommendations at this time.”
CDTL Comment: Two additional changes were made to the container/carton labeling subsequent to this final DMEPA review. First, in JATENZO was removed at the request of OPDP. The Sponsor complied with the request. Second, requests were made to the Sponsor to add bar codes to the container/carton labels and the Sponsor agreed.

Also, in their final review dated January 7, 2019, Celeste Karpow and Loilta White of DMEPA concluded:

‘The proposed proprietary name, Jatenzo, is acceptable.

11.2 Consultation: Office of Surveillance and Epidemiology (OSE)/Division of Medical Policy Programs (DMPP)

In their final memo dated March 22, 2019, Kelly Jackson, Marcia Britt Williams, and LaShawn Griffiths of DMPP (and Jina Kwak of OPDP) described the process that DMPP and OPDP used to propose revisions to the Sponsor’s proposed Medication Guide based on Jatenzo Prescribing Information (PI) provided to DMPP by the Division on March 19, 2019, and had the following conclusion:

“The Medication Guide is acceptable with our recommended changes.”

CDTL Comment: The FDA-revised Medication Guide was returned to Sponsor on March 23, 2019 and all Medication Guide-related labeling issues were resolved on or before March 25, 2019.

11.3 Consultation: Office of Surveillance and Epidemiology (OSE)/Division of Risk Management (DRISK)

In their final March 22, 2018, memo for the 1st resubmission, Courtney Cunningham and Jamie Wilkins Parker of DRISK stated that the unresolved clinical safety and clinical pharmacology issues identified in the 2nd cycle review precluded a final determination by DRISK on the potential need for a REMS. DRISK advised the Sponsor to include a variety of measures in the 2nd resubmission to communicate and reduce risks, with special emphasis on clear and cautionary labeling, including a Medication Guide, to address the Clinical safety issues.

Prior to the 2nd resubmission, the Division and DRISK met with the FDA’s REMS Oversight Committee (ROC) who emphasized the importance of labeling in risk communication and risk management for Jatenzo.

During this 3rd review cycle, DRISK again emphasized the importance of labeling, including a Medication Guide, for risk communication and risk management for Jatenzo. DRISK also concurred with the Division’s request for a postmarketing study to assess patient’s comprehension of the key increased blood pressure risk message in the Medication Guide. DRISK did not advise a REMS for Jatenzo.

11.4 Consultation: Office of Prescription Drug Promotion (OPDP)

In her final memo dated March 13, 2019, Jina Kwak of OPDP had the following conclusion
“OPDP’s comments on the proposed labeling are based on the draft PI received from DBRUP on March 7, 2019 and (these) are provided below….A combined OPDP and DMPP review will be completed and comments on the proposed Medication Guide will be sent under separate cover….OPDP has reviewed the proposed carton and container labeling received on March 12, 2019 and our comments are provided below."

CDTL Comment: OPDP had several recommendations for revisions to the PI, Medication Guide and container/carton labeling, and all of the OPDP recommendations for revision were instituted through successful labeling discussions with Sponsor.

11.5 Financial Disclosure

In compliance with 21 CFR Part 54, the Sponsor submitted a Final Certification/Disclosure Table listing all investigators who participated in the “pivotal” phase 3 study CLAR-15012. All investigators had no disclosable information except for an investigator from Clarus for advisory services. Site (b)(6) was active between (first patient visit) and (last patient visit). A total of (b)(6) patients were enrolled at Site (b)(6) This number represents approximately (b)(6) of the total enrollment in CLAR-15012. (b)(6) enrolled patients at Site (b)(6) were randomized to oral TU (oral TU subjects).

CDTL Comment: Any bias at this site, if it were present, would be expected to have little impact on the overall efficacy results of the study. Only (b)(6) patients were enrolled at Site (b)(6) In addition, the primary endpoint is a pharmacokinetic measurement, a hard endpoint not inherently subject to bias.

11.6 Consultation: Division of Bone, Reproductive and Urologic Products: Endocrinology (DBRUP/Endocrinology)

In their final consult review dated December 6, 2018. Linda Jaffe and Theresa Kehoe of DBRUP provided Endocrinology advice and consultation to the Clinical review team in DBRUP concerning the results of the Cosyntropin stimulation testing sub-study conducted in CLAR-15012. This sub-study was performed to clarify the potential clinical relevance of the adrenal findings observed in toxicology studies in dogs.

The Endocrinology consult contained the following Conclusion and Recommendations:

“Conclusion: In this reviewer’s opinion, the data presented by the Sponsor are insufficient to definitively demonstrate or refute hypoadrenalism associated with TU exposure. First, the number of subjects included in the study was small, and inconsistent with the proposed protocol. The protocol for subject selection for participation in this sub-study is unclear. Concerns for early hypoadrenalism associated with TU include abnormal results seen only in the TU group after a relatively short exposure time of up to 170 days. Mildly abnormal results of a test that is associated with supraphysiologic stimulation of the adrenal glands raises concerns for possible early adrenal dysfunction. The 4 subjects with abnormal results did not demonstrate signs or symptoms of hypoadrenalism, as expected with the cortisol levels they achieved. A decline in CBG could be a potential explanation.
for slightly low stimulated cortisol values in these subjects. If CBG levels were lower, then we would also expect lower pre-stimulated cortisol values on Visit 8, which was not a consistent finding. Variability in the time the test was done is a confounding factor that could affect pre-stimulated cortisol values. On the other hand, many subjects in both groups had low AM cortisol levels at baseline, prior to TU and Axiron treatment. This raises concerns about the performance of the assay itself. Although the time the study was performed was inconsistent, the 4 subjects with abnormal results were studied between 8:15 am and 10:35 am, so time of day cannot sufficiently explain the findings”.

Recommendations:

- A more robust study should be performed to evaluate the possibility of adrenal insufficiency with TU and active comparator Axiron.
- The results of the current study can be used to inform power calculations.
- This reviewer considers the Cosyntropin 0.25 mg intravenous test with cortisol testing pre-injection and 30 and 60 minutes post-injection to be an appropriate screening test.
- The minimum acceptable cut-off of cortisol level ≥18 mcg/dL should be used to evaluate results.
- Testing times should be standardized to 8 AM and a simultaneous pre-Cosyntropin cortisol, ACTH and CBG level should be obtained each time.
- Samples for cortisol, ACTH and CBG should be batched. The assays chosen should have optimal performance.
- Serial tests should be performed at baseline and 6 month intervals for at least 1 year, or sooner if clinically indicated, to determine if progressive adrenal insufficiency occurs with ongoing TU use.
- The Cosyntropin study protocol should describe how subjects are selected for participation.
- The Cosyntropin study protocol should be submitted for review prior to initiation of the study”.

At the January 9, 2018, meeting of the BRUDAC, committee members discussed the study results submitted in the 1st resubmission of the Jatenzo NDA. Committee members were asked to consider the results from the Cosyntropin stimulation test sub-study. Based on the animal data, as well as the available clinical safety information showing no evidence of clinical adrenal insufficiency in any clinical trial subject, the members agreed that potential adrenal effects could be re-assessed in humans in the postmarketing period.

Therefore, the Division requested the Sponsor’s agreement to conduct a 1-year, required, postmarketing clinical trial to determine potential clinical relevance of the adrenocortical atrophy and adrenal insufficiency observed in some dog studies. The study results would hinge on subjects’ response to baseline and periodic Cosyntropin stimulation testing. Linda Jaffe, consultant in Endocrinology, assisted in drafting the PMR request for this second Cosyntropin stimulation test study, to which the Sponsor agreed.
**11.7 Consultation: Division of Cardiovascular and Renal Products (DCRP)**

In their final review dated September 19, 2017, Preston Dunnmon, Shari Targum and Norman Stockbridge of DCRP stated the following conclusions:

- “The Sponsor has now submitted an NDA CR which includes the analyses DCRP requested. A total of 135 subjects in the Oral TU group and 45 subjects in the Topical Axiron (TA) comparator group had ABPM measurements with interpretable results at both the pre-dose visit (Screen 3 Day -2) and at Visit 6 that were included in the ABPM Population. The mean increase in daytime average, nighttime average, and 24-hour average systolic blood pressure from Baseline to Visit 6 for the TU group was greater than for the TA group, with 24-hour average systolic blood pressure increasing by 4.88 (±8.749) mm Hg in the TU group and 0.18 (±0.384) mm Hg in the TA group. Similar results were observed for mean arterial pressure and pulse pressure. With cuff pressure determinations, systolic blood pressure increased from baseline to Visit 7/Early Termination similarly in both treatment groups (mean ± SD: Oral TU 2.8 ± 11.84 mm Hg, Topical Axiron 1.8 ± 10.76 mm Hg), whereas diastolic blood pressure was essentially unchanged at Visit 7/Early Termination”

- “(In our opinion)...the ABPM data more accurately reflects blood pressure changes because of the vastly increased amount of data that is being averaged - averaging multiple values per hour, then multiple hours per analysis time period”.

- “TU raises blood pressure in a clinically and statistically significant manner, particularly in subjects with pre-existing hypertension. This effect occurred in the setting of a disproportionate escalation of antihypertensive therapy in the TU arm, and is of a larger magnitude than was seen for the topical comparator. (We believe that the)...TU induced increases in heart rate will amplify the clinical impact of the TU elevations in blood pressure with respect to the occurrence rate of future CV outcome events.”

- “…the current ABPM study has adequately defined the impact of TU on vital signs”.

The following key clinical statements are derived from the DCRP consult:

- ABPM systolic and diastolic mean pressures for Oral TU were elevated in comparison to the Topical Axiron control in all three timeframes assessed (daytime, nighttime, and 24-hour average).

- Oral TU induced elevations were present across the entire SBP/DBP ranges as shown by cumulative function distributions (CDFs).

- As would be expected, blood pressure effects were exaggerated in the subgroup of subjects with hypertension at baseline.

- There was no clear relationship between a particular dose of Oral TU and mean increase from baseline in 24-hour average blood pressure.

- Cuff pressures in the Safety Population showed a more subtle rightward shift of the SBP CDF curve for SBP, especially notable in the higher blood pressure ranges.
The DBP cuff pressures for Visit 7 demonstrate a similar trend for DBP, with Oral TU also demonstrating the most extreme post-baseline shifts.

It is somewhat disconcerting that...the Visit-7/ET blood pressure data suggests that SBP increases had not plateaued at the end of the study.

The clinically and statistically significant changes in SBP and DBP as a function of pre-existing hypertension that was demonstrated for the ABPM data was not as clearly detected by cuff pressures.

Categorical blood pressure grouping classifications based on JNC-7 definitions demonstrated the higher likelihood of drug-induced shifting into higher blood pressure categories with both Oral TU and Topical Axiron, though the percent increases into stage one and stage 2 hypertension were higher for Oral TU.

The Kaplan-Meier analyses of time to shift to Stage I and Stage II hypertension categories demonstrates the ongoing nature of these BP elevations, which again are more prominent in the Oral TU treatment group.

**CDTL Comment:** Prescribers and patients need to be aware of the increases in BP due to Jatenzo, in both ABPM and blood pressure cuff measurements. They also need to be aware of the potential need to start or increase anti-hypertensive medications in some patients and that blood pressure cuff results may not identify small, but clinically meaningful, increases. Finally, prescribers and patients need to be aware that chronically sustained increases in BP can increase the risk of occurrence of myocardial infarction, stroke and CV death, especially in patients with background CV disease.

**11.8 Consultation: Controlled Substances Staff (CSS)**

In their final consult review dated March 6, 2019, Joshua Hunt, Alicja Lerner and Dominic Chiapperino of CSS offered the following Conclusion and Recommendations:

"**Conclusion:** Testosterone undecanoate is a prodrug of testosterone, which is a Schedule III controlled substance as defined under the Anabolic Steroids Control Act (effective 1991). Section 9 (Drug Abuse and Dependence) of the Jatenzo product labeling has been discussed previously with the Sponsor (and the Division) and is consistent with other testosterone products and acceptable for approval

**Recommendations:** We have no additional recommendations for Sponsor at this time.

As part of their consultation for this 2nd resubmission, CSS requested and reviewed narratives for all cases of depression, suicidality, aggression and anger reported in the Oral TU clinical trials. Additionally, CSS requested and reviewed specific information on study drug accountability in the Jatenzo clinical trials.

The Sponsor responded that there were 6 adverse event reports of depression, one event of suicidal ideation, one of aggression, and two of anger. CSS notes that the narratives for the 6 cases of depression indicated that in 4 of these cases, the patient had a history of depression. All depression cases were mild to moderate in severity. The suicidal ideation event was reported in a patient with worsening depression and was described as “mild” in severity. CSS stated that the
evidence from these cases did not justify further changes to the Jatenzo label at this time.

Finally, the study drug accountability did not reveal any findings of note.

12. **Labeling**

Labeling is key for risk communication and risk management for this application, especially as it pertains to increased BP. The clinical safety issues for Jatenzo that require special attention in labeling are: 1) increased BP that can increase the risk of serious CV events, 2) cases of depression and suicidal ideation, 3) increased hematocrit and hemoglobin, and 4) increased heart rate.

For the increased BP issue, key labeling elements include the Boxed Warning, related Contraindication, related Warning & Precaution, related Adverse Reactions subsection, related parts of the Patient Counseling section, and related parts of the Medication Guide. In this section, the labeling language for increased BP issue is summarized. For details and verbatim text the reader is referred to the final agreed-upon Jatenzo labeling.

**Boxed Warning**
- Jatenzo can increase BP
- Increased BP due to Jatenzo can increase the risk of having a myocardial infarction, stroke or CV death, especially in men with a history of, or risk factors for, cardiovascular disease.
- Practitioners need to monitor for and treat new-onset hypertension as well as exacerbations of pre-existing hypertension while patients are on Jatenzo.
- Due to the risk of increased BP that can increase the risk of MACE, JATENZO should not be used to treat men for whom the benefits have not been established, such as those with low testosterone due to a condition that is not associated with a structural or genetic disorder.

**Contraindications:**
- Due to the risk of increased BP that can increase the risk of major CV events, do not use Jatenzo for the treatment of men with low testosterone due to a condition that is not associated with a structural or genetic disorder (such as for the treatment of “age-related” hypogonadism). The Indications section of labeling provides examples of conditions that cause low testosterone and are associated with structural and genetic disorders.

**Warnings & Precautions:**
- “Increased BP” is added as a new first Warning) to convey the following:
  - In clinical trials, by ABPM, Jatenzo was shown to increase systolic BP and diastolic BP in the first 4 months of treatment on average by 4.9 mmHg and 2.5 mmHg, respectively. Such an increase in BP can increase the risk of having a major adverse CV event, especially in patients with established cardiovascular disease or risk factors for cardiovascular disease.
  - In a 4-month study of Jatenzo, 12 of 166 patients (7.2%) were started on antihypertensive medications or required changes to their antihypertensive
medication regimen.

- Prescribers should be counseled to check BP as early as 3 weeks after initiating Jatenzo and periodically thereafter and to treat new-onset hypertension and exacerbations of pre-existing hypertension.
- Very small increases in blood pressure may not be detected but still can increase the risk of having a major adverse CV event.

Adverse Reactions:

- The Adverse Reactions section includes a special subsection that provides additional summary details concerning Jatenzo-related increases in BP.

Patient Counseling:

- The Patient Counseling section informs prescribers to inform patients about the Jatenzo-related risk of increased BP that can increase the risk of MACE, as well as about the need to have blood pressure monitored while on Jatenzo.

Medication Guide:

- The Medication Guide summarizes the key information concerning the risk of increased BP and conveys important recommendations to patients, as follows:
  - Jatenzo can increase your BP which could increase your risk of heart attack, stroke, or cardiac death
  - Inform your Healthcare Providers if you have hypertension
  - If your BP increases while you are on Jatenzo, antihypertensive medications may need to be started, or if you are already taking antihypertensive medications, new antihypertensive medications may need to be added or the dosages of your current antihypertensive medications may need to be adjusted to control your BP
  - Take your antihypertensive medications as instructed
  - If your BP cannot be adequately managed, Jatenzo may need to be discontinued

For labeling language for the other clinical safety issues, including several cases of depression and a case of suicidal ideation, increased hematocrit and hemoglobin, and increased heart rate, the reader is referred to the medical officer’s Clinical review and the final agreed-upon labeling.

13. **Recommendations/Risk Benefit Assessment**

13.1 **Recommended Regulatory Action**

I recommend Approval action of this application.

13.2 **Risk Benefit Assessment**

In brief, the efficacy data from the phase 3 “pivotal” study CLAR-15012 confirms that Jatenzo provides acceptable testosterone replacement in adult men with hypogonadism.

For safety, a total of 471 hypogonadal adult men received 15-30 weeks of Oral TU in three, phase 3 studies. A total of 86 subjects received Oral TU for approximately 52 weeks in the 1-
year, safety extension study CLAR-12010. An additional 96 subjects received treatment with Oral TU for 3 to 32 days in six, short-term phase 2 studies, but most of this data is not useful for assessment due to differences in the Phase 2 and Phase 3 formulations.

In general, the safety profile for Jatenzo appears consistent with the known safety profile for testosterone products, except for one serious safety concern, as follows:

- Data from ambulatory blood pressure monitoring (ABPM) from CLAR-15012 show that Jatenzo therapy is associated with mean 24-hour average systolic/diastolic BP increases of 4.9/2.6 mmHg compared to minimal average BP increases (0.2/0.4 mmHg) with Topical Axiron. In subjects with treated hypertension, the Jatenzo-related increases in SBP/DBP are slightly larger: Oral TU +5.5/+3.3 mmHg vs. Topical Axiron -0.3/-0.8 mmHg. Further, in the Oral TU group in CLAR-15012, 7.2% of subjects either started antihypertensive medications after baseline or required a dose increase after baseline, compared to 1.8% of subjects in the Topical Axiron group. The observed increases in BP did not appear to plateau at the End-of-Treatment visit, but instead, appeared to be still rising at that point. Based on a plethora of epidemiology data, the magnitude of these increases in BP, when chronically sustained, are anticipated to confer an increased risk of heart attack, stroke and cardiovascular death.

Additionally, a nonclinical signal of adrenocortical atrophy and hypoadrenalism in animals was evaluated by adrenocorticotropic (Cosyntropin) stimulation testing in a sub-study of CLAR-15012; however, that Cosyntropin sub-study was marred by serious flaws in its design and procedures, rendering the available clinical data uninterpretable. Still, no subject in any Oral TU clinical trial demonstrated any evidence of overt adrenal insufficiency and the FDA’s BRUDAC advised that this study could be repeated in the postmarketing period.

In this 2nd NDA re-submission, the Sponsor proposed:
- New labeling to address the increased BP-related safety concern. With final full agreement on labeling, this issue is resolved. To be clear, I now agree with FDA’s REMS Oversight Committee (ROC) that a REMS is not necessary.
- A repeat clinical study of the effect of Jatenzo on adrenal function, as a required postmarketing study. This proposal is acceptable and this issue is resolved.

In addition to these two Clinical concerns for the previous submissions, there was one remaining concern each for Clinical Pharmacology and one for Pharmacology/Toxicology, as follows:

- Clinical Pharmacology expressed a concern that in CLAR-15012, the Sponsor had measured total T concentrations from plasma in NaF/EDTA-containing test tubes instead of measuring T concentrations from serum in plain test tubes. The Sponsor’s intent was to prevent ex vivo conversion of TU to T in the tubes themselves. However, based on data limitations, the extent that NaF/EDTA tubes did actually prevent possible TU to T ex vivo conversion was unknown. The Division advised the Sponsor to conduct an investigation to determine the rate and extent of the TU to T ex vivo conversion during the time course of plasma sample preparation. The Division also requested that the Sponsor conduct an additional in vivo study to compare the total T concentrations measured from serum in plain tubes and plasma in NaF/EDTA-containing tubes at different time points (e.g., 0, 15, 30, 60, 90, and 120-minutes post-sample collection).
using different temperature conditions (e.g., room temperature or on ice) to determine the rate and extent of the TU to T ex vivo conversion during the time course of plasma sample preparation. In this 2nd re-submission, the Sponsor provided results from the requested studies as well as additional results from related studies. These new results were determined to be appropriate and sufficient to support the Sponsor’s proposed labeling that informs prescribers to use a 6-hour post-dose serum T concentration in plain test tubes to titrate dose in patients on Jatenzo. The concern is resolved.

- Pharmacology/Toxicology had previously expressed the concern that the submitted nonclinical studies were not acceptable to support approval of the NDA through a 505(b)(1) pathway because the doses of Oral TU used in those studies were inadequate to characterize the chronic effects of Oral TU on male fertility and carcinogenicity. To resolve this concern, the Division requested that the Sponsor provide justification for dose selection for the fertility study and conduct a new, adequately designed carcinogenicity study, or re-classify their NDA as a 505(b)(2) application without submitting additional nonclinical studies as long as appropriate nonclinical published literature references were submitted. In this 2nd re-submission, the Sponsor classified their NDA as a 505(b)(2) application and submitted acceptable published nonclinical literature references. This concern is resolved.

Based on resolution of these final Clinical, Clinical Pharmacology, and Pharmacology/Toxicology concerns, I now find the benefit/risk assessment to be favorable and I recommend that this Application may be Approved.

### 13.2 Recommendation for Postmarketing Risk Management Activities

There are no recommendations for specific additional postmarketing risk management activities.

### 13.4 Recommendation for other Postmarketing Study Requirements and Commitments

The following PMR studies will be requested as part of the Approval:

- A study to determine patient comprehension of the increased BP key risk message in the Medication Guide.
- An efficacy and safety clinical trial in male pediatric patients 14 years of age and older with hypogonadism due to structural or genetic etiologies, such as Klinefelter’s syndrome.
- A 1-year clinical trial evaluating the effect of Jatenzo on adrenal function in humans (e.g., a repeat Cosyntropin stimulation study).
- An in vitro study to assess the drug-drug interaction (DDI) potential of TU as the perpetrator. A clinical DDI study may also be indicated, depending on the results of the in vitro study.

### 13.5 Recommended Additional Comments to Applicant

There are no additional comments for the Sponsor.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARK S HIRSCH  
03/26/2019 10:08:18 AM

HYLTON V JOFFE  
03/26/2019 04:03:00 PM

I concur with approval. This document serves as FDA’s decisional memorandum on the application.