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RESEARCH**

APPLICATION NUMBER:

206089Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW LABELING ADDENDUM

Application Type	NDA
Application Number(s)	206089
Priority or Standard	Standard
Submit Date(s)	September 27, 2018
Received Date(s)	September 27, 2018
PDUFA Goal Date	March 27, 2019
Division / Office	DBRUP/ODE3
Reviewer Name(s)	Debuene Chang MD
Review Completion Date	March 26, 2019
Established Name	Testosterone undecanoate-TU
(Proposed) Trade Name	Jatenzo®
Therapeutic Class	Testosterone replacement therapy (TRT)
Applicant	Clarus Therapeutics
Formulation(s)	158 mg, 198 mg, or 237 mg TU oral soft capsule
Dosing Regimen	237 mg TU twice daily by mouth, with titration to 158, 316 or 396 mg twice daily
Indication(s)	TRT
Intended Population(s)	Adult hypogonadal men

Executive Summary

Updated Recommendation on Regulatory Action

Based on successful completion of labeling and postmarketing requirement (PMR) discussions, the Clinical review team now recommends an Approval action for this new drug application (NDA).

The Clinical review team had previously recommended an Approval action on the condition that the Sponsor resolved the remaining Clinical safety deficiencies for this new drug application (NDA) through specific labeling revisions. Based on the successful completion of labeling and PMR discussions, the remaining Clinical safety deficiencies are now considered resolved, as summarized here:

Efficacy: The efficacy data from CLAR-15012 supports the Sponsor's contention that Jatenzo provides testosterone replacement in adult men with hypogonadism.

Safety: The safety profile for Jatenzo is consistent with the known safety profile for TRT, as demonstrated by the data submitted in the original NDA, the 1st resubmission, and this 2nd resubmission, except for the following clinical safety issue, which is now considered resolved:

Blood Pressure Increases

Blood pressure (BP) data from CLAR-15012 showed that Jatenzo has the potential to raise BP. Based on ambulatory blood pressure monitoring (ABPM) conducted in CLAR-15012, Jatenzo was associated with an average increase in systolic BP of approximately 5 mm Hg, a clinically meaningful amount.

The Sponsor resolved this safety issue through clear and cautionary product labeling, including the following key elements:

- A Boxed Warning for BP Increases
- A new Contraindication that limits use of Jatenzo to men with hypogonadism due to structural or genetic conditions
- A comprehensive Medication Guide

In addition, the Sponsor agreed to conduct a required postmarketing study (PMR) to assess patients' comprehension of the Medication Guide

The Clinical review team considers this deficiency resolved.

Additionally, there was one Nonclinical issue that required further Clinical assessment during this third review cycle, as follows:

Adrenal Findings in Animals

In some dog studies, testosterone undecanoate was associated with findings of adrenocortical atrophy and hypocortisolemia. While no human subject in clinical studies demonstrated evidence of clinical hypoadrenalism, the Sponsor was asked to conduct a Cosyntropin stimulation testing substudy in CLAR-15012. Deficiencies in the design and procedures of the Cosyntropin substudy precluded conclusions from that data. However, there have been no reports of clinical hypoadrenalism in any of the Sponsor's studies with Jatenzo, and FDA's Bone, Reproductive and Urologic Drug Advisory Committee (BRUDAC) recommended that this issue be studied in the postmarketing period. Therefore, the Division requested that the Sponsor reassess this issue in a required postmarketing Cosyntropin stimulation testing clinical study (a PMR). The Sponsor agreed to conduct the requested PMR study. In addition, key information from the dog studies is provided in product labeling.

Therefore, this issue is considered resolved.

Risk Benefit Assessment

The Clinical review team concludes that Jatenzo is safe and effective as the Sponsor has made labeling revisions which addresses the prior Clinical safety deficiency. The risk/ benefit ratio for Jatenzo for TRT in men with hypogonadism is now considered acceptable for approval of this NDA.

The Sponsor made substantive labeling revisions, including changes to the Boxed Warning, a new Contraindication, and a comprehensive Medication Guide, as well as agreed to a PMR study that will assess patients' comprehension of the Medication Guide, and that these changes address the Clinical safety deficiency identified in the original submission and 1st resubmission response. Because of these changes and the Sponsor's agreement to conduct the PMR study to assess patient's comprehension of the Medication Guide, 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.

Recommendations for Postmarket Requirements and Commitments

The Clinical review team recommended and the Sponsor agreed to conduct the following two studies as PMRs:

- *Medication Guide comprehension study*: The Sponsor agreed to conduct this required postmarketing study with acceptable milestone dates for protocol submission, study completion and study report submission.
- *Cosyntropin stimulation testing study to re-assess the potential for hypoadrenalism*: The Sponsor agreed to conduct this required postmarketing study with acceptable milestone dates for protocol submission, study completion and study report submission.

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/s/

T D CHANG
03/26/2019 11:29:07 AM

MARK S HIRSCH
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I concur.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206089
Priority or Standard	Standard
Submit Date(s)	September 27, 2018
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PDUFA Goal Date	March 27, 2019
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Reviewer Name(s)	Debuene Chang MD
Review Completion Date	March 15, 2019
Established Name	Testosterone undecanoate-TU
(Proposed) Trade Name	Jatenzo®
Therapeutic Class	Testosterone replacement therapy (TRT)
Applicant	Clarus Therapeutics
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Table of Contents

1 EXECUTIVE SUMMARY	4
Recent Regulatory Overview	4
Recommendation on Regulatory Action	5
Risk Benefit Assessment	7
Recommendations for Postmarket Risk Evaluation and Mitigation Strategies (REMS)7	
Recommendations for Postmarket Requirements and Commitments	8
2 BACKGROUND.....	8
2.1 Product Information	8
2.2 Availability of Proposed Active Ingredient in the United States	9
2.3 Important Safety Issues with Consideration to Related Drugs.....	9
3 CLINICAL SAFETY ISSUES.....	10
3.1.1 Blood Pressure (BP) Increases	10
3.1.2 Heart Rate Increases.....	13
3.1.3 Changes in Anti-Hypertensive Medications During the Jatenzo Phase 3 Study CLAR-15012.....	14
3.2 Sponsor’s Proposal to Mitigate Increased Blood Pressure Risks	15
REMS Oversight Committee (ROC) Meeting	17
3.3 Cases of Depression and Suicide.....	18
3.4 Erythropoietic AEs, including Increased Hematocrit (HCT) and Polycythemia	20
3.5 Adrenocortical atrophy and Adrenal Insufficiency in Dogs.....	21
4 REVIEW OF EFFICACY	23
5 LABELING	27
6 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	30
6.1 Chemistry Manufacturing and Controls (CMC).....	30
6.2 Preclinical Pharmacology/Toxicology	30
6.3 Clinical Pharmacology	31
6.4 Biometrics.....	32
6.5 Division of Medication Error Prevention and Analysis (DMEPA)	32

Table of Tables

Table 1: Dosage Strengths and Components in Each Oral Capsule.....	9
Table 2: Systolic Blood Pressure Measured by ABPM: Change from Baseline at Visit 6 (ABPM Population) in Study CLAR-15012.....	10
Table 3: Diastolic Blood Pressure Measured by ABPM: Change from Baseline at Visit 6 (ABPM Population) in Study CLAR-15012.....	11
Table 4: Heart Rate (HR) Measured by ABPM: Change from Baseline at Visit 6 (ABPM Population) in Study CLAR-15012.....	13
Table 5: Patients Who Started on or Increased or Changed Their Anti-HTN Medications and Patients in Whom AEs of HTN, HTN Worsened, or Increased BP were Reported in CLAR-15012.....	15
Table 6: Summary of AE Reports of Depression, Suicidal Ideation, Suicidal Behavior, Aggression and Anger in All Jatenzo Studies.....	18
Table 7: Proportion of Subjects with Notable Post-Baseline Hematology Values by Treatment Group (Safety Population) in CLAR-15012.....	20
Table 8: Mean Hematocrit Changes of Subjects on Jatenzo (CLAR-15012).....	20
Table 9: Percentage of Patients Achieving Eugonadal Testosterone Cavg Values at Visit 7 for the Primary Analysis (MITT Population) in CLAR-0512 Using Success Criteria Range Adjusted for Plasma Testosterone Concentration. ...	24
Table 10: Percentage of Subjects with Testosterone C _{max} Values in the Pre-Specified C _{max} Outlier Ranges at Visit 7 in CLAR-15012* – Traditional Unadjusted Range Criteria.....	25
Table 11: Observed Testosterone, Dihydrotestosterone, and Dihydrotestosterone/ Testosterone Ratios in High Testosterone C _{max} Samples, and Estimated Testosterone Concentrations Assuming High Testosterone Includes Contamination from Exogenous Testosterone.....	26
Table 12: Number (Percentage) of Subjects at Day 105 in CLAR-15012 who Met C _{max} Outlier Criteria Adjusted for Plasma T Concentrations.....	26

1 Executive Summary

Recent Regulatory Overview

On January 3, 2014, Clarus Therapeutics (Sponsor) submitted an original NDA 206089 (testosterone undecanoate [TU]).

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) met with most members concluding that efficacy and safety had not been adequately established for this product. The questions posed to the members with voting results were the following items:

- ✚ 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, the Division issued a Complete Response Letter informing the Sponsor that “additional investigations of efficacy and safety and the effect of food, will be necessary, including possible changes to the dose and titration algorithm”. For more details, refer to the CRL November 3, 2014.

On April 3, 2015, the Sponsor submitted a formal Dispute Resolution Request, disputing the need to conduct additional clinical investigations of efficacy and safety and the effect of food, raised in the CRL.

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

On June 22, 2017, the Sponsor submitted a Complete Response Re-Submission to NDA 206089 after completing additional study CLAR 15012. Major amendments during the review added 3-month review extension time.

On March 22, 2018, the Division issued a second Complete Response Letter (2nd CRL). The Division listed three deficiencies precluding approvability which included clinical, clinical pharmacology, and pharmacology/ toxicology deficiencies as follows:

- 1) Clinical Deficiency: A clinically meaningful mean increase in blood pressure (BP) was observed with use of Jatenzo, with potential for an associated increased risk of major adverse cardiovascular events,

- 2) Clinical Pharmacology Deficiency: Accuracy or reproducibility of patient plasma total testosterone (T) concentrations on Jatenzo using sodium fluoride (Na/F) ethylenediaminetetraacetic acid (EDTA) tubes was not determined.
- 3) Pharmacology/Toxicology Deficiency: Unacceptable nonclinical studies for male fertility and carcinogenicity were submitted to support NDA approval through the 505(b)(1) pathway.

On June 12, 2018, the Division met with Clarus at a Type A meeting to discuss pathways to resolve the deficiencies listed in the 2nd CRL and identify any remaining issues. The reader is referred to the final Type A meeting minutes dated July 12, 2018.

On September 27, 2018, the Sponsor submitted a 2nd Complete Response NDA re-submission to NDA 206089 (testosterone undecanoate [TU] oral capsule).

No new efficacy and safety clinical data were submitted. To address the clinical deficiency of increased blood pressure for patients on Jatenzo, the Sponsor proposed revised product labeling.

To address the clinical pharmacology deficiency regarding accurate T concentration assessments, the Sponsor submitted data from one clinical study, study CLAR-18019, as well as data from 2 bioanalytical studies (Study CLAR-18016 and Study CLAR-18021) and 2 assay validation studies (Study CLAR-18018 and Study CLAR-18020). No hypogonadal patients were dosed with Jatenzo for the studies submitted in this 2nd NDA re-submission.

The 2nd CR submission contains revised labeling and proposals to address the 2nd CRL deficiencies. The reader is referred to the Clinical Reviews for NDA 209863, dated March 17, 2018 and October 24, 2014 for a review of clinical studies and data in the original two submissions.

Recommendation on Regulatory Action

The Clinical review team recommends an Approval action on the condition that the Sponsor fully resolves the outstanding Clinical safety deficiencies for this new drug application (NDA) for the following reasons:

Efficacy: The efficacy data from CLAR-15012 supports the Sponsor's contention that Jatenzo provides testosterone replacement in adult men with hypogonadism.

Safety: The safety profile for Jatenzo is consistent with the known safety profile for TRT, as demonstrated by the data submitted in the original NDA, the 1st resubmission response to the 1st CR Letter, and this 2nd resubmission response to the 2nd CR Letter,

except for the following two clinical safety issues which need to be fully resolved before Approval:

1. Blood Pressure Increases

Identification of the potential for Jatenzo to raise average systolic blood pressure (SBP) by approximately 5 mm Hg, a clinically meaningful amount.

Specifically, ABPM measurements in Study CLAR-15012 showed that treatment with Jatenzo was associated with mean systolic BP increases of 5 mm Hg.

The Sponsor can resolve this deficiency by addressing the Clinical safety deficiency through the following:

- a) Substantive labeling revisions, including the following elements:
 - A Boxed Warning
 - A new Contraindications that limits use of Jatenzo to the indicated patient population
 - A comprehensive Medication Guide (Med Guide)
- b) A Post marketing requirement (PMR) to assess patients' comprehension of the Med Guide

2. Adrenal Findings in Animals

In preclinical studies, adrenocortical atrophy and hypocortisolemia were observed in animals dosed with testosterone undecanoate. The Sponsor submitted inconclusive adrenal-related data from clinical Study CLAR-15012. Because there have been no reports of hypoadrenalism in studies with Jatenzo, and with the specific recommendation/agreement from the BRUDAC, the Sponsor can resolve this safety issue by conducting a required postmarketing clinical study (a PMR) involving Cosyntropin stimulation testing to rigorously assess for any potential adverse effects of Jatenzo on adrenal function in humans.

This issue is considered resolved if the Sponsor agrees to the PMR study.

Clinical Pharmacology Deficiency:

Accuracy or reproducibility of patient plasma total testosterone (T) concentrations on Jatenzo using sodium fluoride (Na/F) ethylenediaminetetraacetic acid (EDTA) tubes was not determined.

The Sponsor has resolved this deficiency by changing to plain tubes for serum collection of T concentrations and providing acceptable data and studies to support the change from the Clinical Pharmacology perspective, who considered this issue resolved and recommended approval.

Pharmacology/ Toxicology Deficiency:

Unacceptable nonclinical studies for male fertility and carcinogenicity were submitted to support NDA approval through the 505(b)(1) pathway.

The Sponsor has resolved this deficiency by submitting this 2nd resubmission as a 505(b)(2) and referenced published literature from the original submission and in this resubmission. The Pharmacology/ Toxicology determined that the change to a 505(b)(2) submission resolved this deficiency and recommended approval.

Risk Benefit Assessment

The Clinical review team concludes that Jatenzo is safe and effective on the condition that the Sponsor makes labeling revisions which addresses the prior Clinical safety deficiencies. The risk/ benefit ratio for Jatenzo for TRT in men with hypogonadism will then be considered acceptable for approval of this NDA.

In the prior review cycle, the Clinical review team had recommended a Complete Response (CR) action based on the blood pressure-related Clinical safety deficiency, provided in Section 1 above.

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 to 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 1st resubmission response to 1st CR Letter. For more detail, the reader is referred to the Section 5 of this review - Labeling. 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.

Recommendations for Postmarket Risk Evaluation and Mitigation Strategies (REMS)

The Clinical review team recommends substantive new labeling and that the label include the following elements:

- Boxed warning
- Contraindication that limits use of Jatenzo to the indicated patient population and excludes its use for the treatment of low testosterone concentrations due to conditions not associated with a structural or genetic etiology. Examples of excluded conditions include "age-related hypogonadism" and obesity-related hypogonadism.
- Medication Guide (Med Guide) - outside of a REMS

In addition, the Clinical review team recommends that the Sponsor conduct a postmarketing requirement study that will assess patients' comprehension of key safety aspects of the Medication Guide.

Recommendations for Postmarket Requirements and Commitments

The Clinical review team recommended and the Sponsor was requested to conduct the following two PMR studies:

- a) 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.
- b) 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.

2 Background

2.1 Product Information

Background:

The natural hormone testosterone and its derivatives have androgenic and anabolic properties. The indication for testosterone is replacement therapy in men with deficiency or absence of endogenous testosterone and clinical hypogonadism due to certain medical conditions that are associated with structural and genetic disorders. For more details, refer to the March 17, 2018 and October 24, 2014 prior Clinical Reviews of this NDA.

Product:

The Sponsor submitted a 505(b)(2) NDA for testosterone undecanoate (TU) capsules for oral administration. The proposed soft gelatin TU oral capsules, 158 mg TU, 198 mg TU, and 237 mg TU (b) (4)

Reviewer's Comment: The Sponsor has revised the application from a 505(b)(1) to a 505(b)(2) in this submission to use appropriate published literature references to address nonclinical deficiencies for dose selections in preclinical fertility and carcinogenicity studies as noted in Deficiency #3 in the 2nd CR Letter.

The following table identifies each component of the three proposed oral TU dosages.

Table 1: Dosage Strengths and Components in Each Oral Capsule

Ingredient	TU Amount 158 mg capsule	TU Amount 198 mg capsule	TU Amount 237 mg capsule	Function
Formulation				
Testosterone Undecanoate	158.30	197.88	237.46	Active Ingredient
Oleic Acid NF, EP	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Borage Seed Oil	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Butylated Hydroxytoluene NF, EP (BHT)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Peppermint Oil NF, FCC	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Polyoxyl 40 Hydrogenated Castor Oil, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total Fill Weight	(b) (4)	(b) (4)	(b) (4)	
<i>Reviewer Generated Table from Module 2.3, table 2.3.P.1-1 original NDA submission and Module 2.3, table 2.3 P.1-3, page 2 of CR submission #1 (June 22, 2017).</i>				

Reviewer’s Comment: *Patients with allergies to TU or other components of the capsule (oleic acid, borage seed oil, BHT, peppermint oil, or hydrogenated castor oil should be cautioned in the labeling.*

2.2 Availability of Proposed Active Ingredient in the United States

One TU product, Aveed injection (Endo Pharmaceuticals) is currently the only approved TU product approved for the US market. That product was approved March 5, 2014 under NDA 22219 for the same TRT indication. However, Aveed is approved with a REMS related to acute post-injection reactions; specifically, pulmonary oil microembolism (POME) and anaphylaxis.

2.3 Important Safety Issues with Consideration to Related Drugs

The most important, well-known safety issues for the TRT class include, but are not limited to, the following:

- Erythropoietic effects: increased hematocrit (Hct) and hemoglobin (Hb), polycythemia, with potential for cerebrovascular accident and/or deep venous thrombosis as a result

- Prostate effects: increased prostate volume, increased PSA, potential for worsening of BPH symptoms
- Lipid effects: potential for decreased HDL-cholesterol
- Other effects: exacerbation of sleep apnea, breast tenderness and/or breast enlargement, liver toxicity (associated with high doses of orally active 17-alpha-alkyl androgens, such as methyltestosterone), decreased spermatogenesis/azoospermia (especially at high doses), peripheral edema, acne, and mood disorders.

The currently available evidence is not sufficient to establish whether the use of testosterone by older men is associated with an increased risk of serious cardiovascular events and/or prostate cancer.

3 Clinical Safety Issues

3.1.1 Blood Pressure (BP) Increases

Jatenzo caused clinically meaningful increases in blood pressure in clinical studies. In CLAR-15012, the only phase 3 Jatenzo study that incorporated ambulatory blood pressure monitoring (ABPM), a 24-hour average systolic BP (SBP) increase of 4.9 mmHg was identified, with a larger increase among subjects with hypertension. 24-hour average diastolic BP (DBP) by ABPM was increased by 2.5 mmHg. The following two tables summarize changes from baseline in SBP and DBP by ABPM for Jatenzo and the comparator TRT used in CLAR-15012, topical Axiron. For Jatenzo, the table includes subgroup analysis results by patients with no history of HTN and those with treated HTN.

Table 2: Systolic Blood Pressure Measured by ABPM: Change from Baseline at Visit 6 (ABPM Population) in Study CLAR-15012

Systolic BP (mm Hg) Change from Baseline (CFB)	JATENZO						Axiron	
	<u>All ABPM Population</u> N=135		<u>Subgroup No HTN</u> N=63		<u>Subgroup Treated HTN</u> N=67		<u>All ABPM population</u> N=45	
	<u>Mean</u>	<u>95% CI</u>	<u>Mean</u>	<u>95% CI</u>	<u>Mean</u>	<u>95% CI</u>	<u>Mean</u>	<u>95% CI</u>
Daytime Average Systolic Blood Pressure	5.0	(3.6, 6.5)	4.4	(2.3, 6.4)	5.7	(3.4, 8.0)	-0.1	(-2.7, 2.5)
Nighttime Average Systolic Blood Pressure	4.9	(2.9, 6.8)	4.6	(2.0, 7.2)	5.1	(2.3, 8.0)	0.3	(-3.0, 3.6)

24 Hour Average Systolic Blood Pressure	4.9	(3.5, 6.4)	4.4	(2.3, 6.4)	5.4	(3.3, 7.6)	0.1	(-2.4, 2.6)
<i>CLAR-15012 All Jatenzo ABPM patients with acceptable readings N=135; Jatenzo Subgroup without hypertension (HTN) N=63; Jatenzo Subgroup Treated HTN N=67; All Axiron comparator ABPM with acceptable readings =45; 95% CI = 95% Confidence Interval</i> <i>Source: Reviewer created table from CLAR-15012 CSR tables 14.3.4.3.5 and 14.3.4.3.6</i>								

Table 3: Diastolic Blood Pressure Measured by ABPM: Change from Baseline at Visit 6 (ABPM Population) in Study CLAR-15012

Diastolic BP (mm Hg) Changes from Baseline (CFB)	JATENZO						AXIRON	
	<u>All ABPM Population</u> N=135		<u>Subgroup No HTN</u> N=63		<u>Subgroup Treated HTN</u> N=67		<u>All ABPM Population</u> N=45	
	<u>Mean</u>	<u>95% CI</u>	<u>Mean</u>	<u>95% CI</u>	<u>Mean</u>	<u>95% CI</u>	<u>Mean</u>	<u>95% CI</u>
Daytime Average Diastolic BP	2.4	(1.3, 3.5)	1.5	(-0.1, 3.1)	3.3	(1.7, 4.9)	0.5	(-1.4, 2.5)
Nighttime Average Diastolic BP	2.8	(1.5, 4.2)	2.5	(0.4, 4.5)	3.1	(1.1, 5.0)	0.6	(-1.8, 3.0)
24 Hour Average Diastolic BP	2.5	(1.5, 3.6)	1.8	(0.2, 3.3)	3.2	(1.7, 4.7)	0.6	(-1.3, 2.4)
<i>CLAR-15012 All Jatenzo ABPM patients with acceptable readings N=135; Jatenzo Subgroup without hypertension (HTN) N=63; Jatenzo Subgroup Treated HTN N=67; All topical Axiron ABPM patients with acceptable readings N=45; 95% CI = 95% Confidence Interval</i> <i>Source: Reviewer created table from CLAR-15012 CSR tables 14.3.4.3.5 and 14.3.4.3.6</i>								

In the same study, the Sponsor also reported increased SBP by in-office cuff BP pressure measurements from baseline to Visit 7/Early Termination in both Jatenzo and comparator (Topical Axiron) treatment groups (mean ± SD: Oral TU 2.8 ± 11.8 mm Hg, Topical Axiron 1.8 ± 10.8 mm Hg). Diastolic blood pressures (DBP) were unchanged by cuff measurements.

In September 2017, as part of the second cycle (1st resubmission) review, the Division of Cardiovascular and Renal products (DCARP) was asked to consult on the blood pressure increases with Jatenzo. DCARP was of the opinion that the ABPM data more accurately reflected the actual blood pressure changes compared to the cuff BP data. In this regard, DCARP made the following statement:

“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).”

The DCARP consultant also commented that the final Visit-7/ ET blood pressure data from Study CLAR-15012 suggested that blood pressures had not yet stabilized and appeared to be still increasing at the end of the study. In this regard, the consultant made the following comment:

“It is somewhat disconcerting that for both of these TU products (both Jatenzo and the comparator TRT product, Topical Axiron), the Visit-7/ET blood pressure data suggests that SBP increases had not plateaued at the end of the study (from the sponsor CRS).”

Reviewer’s Comment: Study CLAR-15012 demonstrated that Jatenzo causes increased SBP by both ABPM and cuff pressures and increased DBP by ABPM.

Specifically, by ABMP, mean 24-hr BP increases for SBP and DBP were 5 mm Hg and 2.5 mm Hg respectively. The BP increases were greater in patients with history of hypertension who were treated with anti-hypertensive medications with mean 24-hour SBP by ABPM increases of 5.5 mm Hg and DBP increases of 3.2 mm Hg. For comparison, the ABPM SBP and DBP 24-hour average mean changes for Topical Axiron were 0.1 and 0.6 mmHg respectively.

By cuff pressures, the Sponsor reported Jatenzo increased SBP 3 mm Hg and had unchanged DBP changes.

We agree with our DCARP consultant that the ABPM measurements summarize vastly more BP information compared to cuff BP measurements and probably are more accurate reflections of the true Jatenzo-related blood pressure increases. Therefore, data from both the ABPM and cuff measurements should be reflected in the labeling, with ABPM data given more prominence. In our view, these SBP and DBP increases are clinically meaningful and may be associated with an increased risk of serious CV events and need to be in the labeling.

Also, we share DCARP’s concern that the data from the 4-month study CLAR-15012 suggest that mean blood pressures increases had not fully plateaued and may still be rising at the last visit (Visit 7) for subjects on Jatenzo. This concern should be reflected in labeling with a recommendation for long-term blood pressure monitoring for patients on Jatenzo.

3.1.2 Heart Rate Increases

Jatenzo increased mean heart rate by an average of 2 beats per minute from baseline compared to comparator Topical Axiron which showed an average increase of 0.04 beats per minute in study CLAR-15012. The following table summarizes the average increase in heart rate with Jatenzo and includes subgroup analysis of patients without a history of HTN and those with treated HTN. The table also shows HR data for topical Axiron.

Table 4: Heart Rate (HR) Measured by ABPM: Change from Baseline at Visit 6 (ABPM Population) in Study CLAR-15012

Heart Rate (HR) bpm	JATENZO						AXIRON	
	All ABPM Population N=135		Subgroup No HTN N=63		Subgroup Treated HTN N=67		All ABPM Population N=45	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Daytime Average HR	2.4	(1.1, 3.6)	2.6	(0.6, 4.7)	2.4	(0.7, 4.1)	0.3	(-1.9, 2.5)
Nighttime Average HR	1.8	(0.5, 3.2)	2.8	(0.8, 4.9)	1.1	(-0.9, 3.1)	-0.3	(-2.7, 2.1)
24 Hour Average HR	2.2	(1.0, 3.3)	2.7	(0.8, 4.6)	1.9	(0.3, 3.5)	0.0	(-2.0, 2.1)

CLAR-15012 All Jatenzo ABPM patients with acceptable readings N=135; Jatenzo Subgroup without hypertension (HTN) N=63; Jatenzo Subgroup Treated HTN N=67; All topical Axiron patients with acceptable ABPM readings N=45
HR = Heart Rate; bpm = beats per minute; 95% CI = 95% Confidence Interval
Source: Reviewer created table from CLAR-15012 CSR tables 14.3.4.3.5 and 14.3.4.3.6

Overall, the table shows that 24-hour mean HR increases were 2 beats per minute (bpm) in the Jatenzo study population. The 24-hour mean HR increases were greater in patients without a history of HTN, with an increase of 2.7 bpm in that subgroup.

In their September 19, 2017 consult, our DCARP consultant noted that these small heart rate increases could amplify the risk of serious CV events possibly related to the mean blood pressure increases associated with Jatenzo, stating:

“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.”

Reviewer's Comment: Jatenzo causes small increases in mean HR with 24-hr average increases of 2 bpm. In patients without a history of HTN, the HR increases were slightly larger at 2.7 bpm and this difference could pose a greater risk of CV events for patients with Jatenzo-related BP increases.

While we agree with our DCARP consultant that the mean increases in HR could amplify the potential CV risks of increased BP due to Jatenzo, the observed HR increases in the study were small and may be difficult to establish in a clinical setting on patient follow-up. For this reason, we recommend listing the HR findings in the Adverse Reactions section (Section 6) of labeling to inform prescribers of this information.

3.1.3 Changes in Anti-Hypertensive Medications During the Jatenzo Phase 3 Study CLAR-15012

In the reviews of the original NDA and 1st resubmission, an important Clinical review issue was the percentage of subjects in whom anti-hypertensive medications were either initiated or adjusted while on treatment with Jatenzo in Study CLAR-15012. As previously mentioned, CLAR-15012 was the only phase 3 study that studied all the proposed to-be-marketed dosages/ titration and included both cuff BP measurements and ABPM. The percentage of patients who either start anti-hypertensive medications or change their anti-hypertensive medication regimens would reflect the clinical meaningfulness of the observed mean increases in SBP and DBP on ABPM and cuff BP measurements.

In the Division's 2nd Complete Response action letter for this NDA, the Division stated that "*approximately 7.2% of patients in the Safety Population started antihypertensive medications after baseline or required an antihypertensive dose increase initiation or adjustments of antihypertensive medications after initiation of treatment with Jatenzo...*"

To assist in the review of this issue, the Division of Biometrics was asked to help identify and analyze data on patients who had started or increased their anti-HTN medications as well as patients in whom AEs of "HTN", "worsening HTN", or "increased BP" were reported. For listing of details of the anti-HTN medications and individual subjects, the reader is referred to page 156 of 1216 of the CLAR-15012 CSR and Listings 16.2.4.4.2 and 16.2.4.4.4 for that study. The following table summarizes patients who started on or increased their anti-HTN medications and patients in whom AE reports of "HTN", "HTN Worsened", and "increased BP" were reported in CLAR-15012.

Table 5: Patients Who Started on or Increased or Changed Their Anti-HTN Medications and Patients in Whom AEs of HTN, HTN Worsened, or Increased BP were Reported in CLAR-15012

Patient	HTN History (Yes or No)	HTN History (Treated or Untreated)	AE Reported	Anti-HTN Medication Start/ Increase/ Change
(b) (6)	Yes	Treated	---	Increase
	Yes	Treated	Increased BP	Increase
	No	---	HTN	Start
	No	---	HTN	Start
	Yes	Treated	HTN worsened	Increase/ Add
	Yes	Untreated	---	Start
	Yes	Treated	Increased BP	Add
	Yes	Treated	HTN worsened	Add
	Yes	Untreated	---	Start
	Yes	Treated	HTN Worsened	Increase
	Yes	Treated	---	Increase
	Yes	Treated	---	Change Anti-HTN med
	Yes	Treated	HTN Worsened	No change

HTN= Hypertension; AE = Adverse Even; BP = Blood Pressure
 *Patient (b) (6) reported AE of HTN Worsened after last dose of Jatenzo but before end of participation in study and was NOT counted in the listing of anti-HTN med changes.
 Source: Table developed by Clinical and Biometric Reviewers from CLAR-15012 data files ADSL, ADAE, and ADCM.

Reviewer’s Comment: In evaluating the clinical meaningfulness of the BP data for Jatenzo, we considered the information shown in the table above. In our view, the 7% (12/ 166 patients) new or changed anti-HTN medication rate observed in Study CLAR-15012 is supportive of the need for labeling that emphasizes long-term BP monitoring and appropriate treatment in patients on Jatenzo therapy.

Table 5 shows that 6 of 166 patients (4%) in the Safety population had an AE report of “HTN” (2 patients) or “HTN worsened” (4 patients) and 2 of 166 patients reported “Increased BP”. This data should be reflected in labeling.

It should be noted that Jatenzo treatment in CLAR-15012 was approximately 4-months long and the rates of patients who need to start or change anti-HTN medications could increase with longer Jatenzo treatment. TRT can be used chronically. Patients should be monitored throughout treatment with Jatenzo and practitioners should actively manage BP and should consider discontinuing Jatenzo when appropriate. The labeling should reflect this caution.

3.2 Sponsor’s Proposal to Mitigate Increased Blood Pressure Risks

The Sponsor proposed to address the increased blood pressure CR deficiency through revised prescriber labeling including a “Boxed Warning, (b) (4) and Warnings

and Precautions about the risk of increases in blood pressure in some patients treated with JATENZO”, specifically targeting the patient population at highest risk with (b) (4)

For the Medication Guide, the Sponsor proposed to inform patients of potential risks of elevated blood pressures and to have regular monitoring during Jatenzo treatment, including a statement that management of blood pressure increases should successfully mitigate the risk of serious CV events. In this regard, the Sponsor provided the following statement in the resubmission:

(b) (4)

- The Sponsor’s original proposed Boxed Warning was as follows:

(b) (4)

- Key text proposed for the Medication Guide was:

(b) (4)

Reviewer’s Comment: In CLAR-15012, results of ABPM monitoring showed that Jatenzo was associated with an average 24-hr SBP increase of 5 mmHg and average DBP increase of 2.5 mm Hg, with larger increases among subjects with a history of hypertension which may be associated with an increased risk of serious CV events. In addition, in Jatenzo subjects, heart rate increased on average by 2 bpm with larger mean increases (2.7 bpm) observed in patients without a history of HTN. Furthermore, 7 % of Jatenzo patients either started or changed their anti-hypertensive medications.

Compared to the label proposed by the Sponsor in their original NDA, substantial revisions to labeling are needed, including a Boxed Warning and a Medication

Guide that would convey the risk of increased blood pressure. However, the language in the Sponsor's proposed Boxed Warning and Medication Guide was considered insufficient to fully convey the seriousness of the risk, and we do not agree with some of the Sponsor's specific labeling text. For example, we do not agree [REDACTED] (b) (4) [REDACTED] as stated in the Sponsor's proposed prescriber and patient labeling.

For these reasons, we recommend that the Sponsor add more robust labeling in the Boxed Warning; to add a Contraindication to limit use to the indicated population, and to provide a more substantive Medication Guide that will serve to convey the serious risk of increased blood pressure. The reader is referred to Section 5.1, Labeling for additional details related to the specific labeling for the risks of increased BP

In addition, we recommended that the Sponsor conduct a PMR study to assess patients' comprehension of the key risk information in the Medication Guide. We requested that the Sponsor conduct the following study:

"Conduct an appropriately designed label comprehension study to assess patients' understanding of key risk messages in the Medication Guide for Jatenzo. The primary objective of this study is to assess patient comprehension of materials related to increases in blood pressure and potential associated increased risk of major adverse cardiovascular events with Jatenzo. The study population should include men representative of those who use prescription testosterone therapy with a range of cardiac risk factors, a range of education levels, and various literacy levels. The results of this study may result in revisions to the Medication Guide to optimize patient's understanding of important risks of Jatenzo."

REMS Oversight Committee (ROC) Meeting

On July 12, 2018, the Division met with the REMS Oversight Committee (the ROC) to consider possible regulatory actions for two testosterone products, Xyosted and Jatenzo, that both caused increases in blood pressure in their Phase 3 clinical studies. For this meeting, the Committee included the Center Director, Deputy Center Director, Acting Directors of the Office of New Drugs, and Director of the Office of Surveillance and Epidemiology. The Committee concluded that these two products, including Jatenzo, should be required to have robust labeling with the following specific elements:

-  A Boxed Warning
-  A Contraindication to limit treatment to the indicated patient population
-  A Medication Guide (Med Guide) - outside of a REMS

The Committee recommended against a REMS, whether with or without Elements to Assure Safe Use (ETASU). The Committee members voiced several concerns about a REMS, including lack of assurance that a REMS would ensure safe use of Jatenzo beyond that associated with substantive labeling. The reader is referred to the final ROC meeting minutes for additional details of the meeting discussion.

Reviewer’s Comment: *We agree with the ROC’s recommendations, including the need for robust labeling, including a Boxed Warning, a Contraindication to limit use to the indicated population and to exclude hypogonadal conditions that are not associated with a structural or genetic disorder, such as “age-related hypogonadism” (b) (4) and a Med Guide outside of a REMS. The reader is referred to Section 5 (Labeling) for additional details on labeling revisions.*

3.3 Cases of Depression and Suicide

In total, six (6) cases of depression and one (1) case of suicidal ideation were reported in subjects who had received Jatenzo in clinical studies. To further evaluate this safety issue during our review of this NDA re-submission, we conveyed an information request to the Sponsor on November 30, 2018 to provide narratives of all AE reports of depression, suicidal ideation, suicidal behavior, aggression and anger from all clinical studies that support this application. The Sponsor responded on December 7, 2018 there were 10 such AE’s in 9 subjects and included narratives. The following table summarizes the 10 reported AE’s in 569 patients from all clinical studies which supported this application.

Table 6: Summary of AE Reports of Depression, Suicidal Ideation, Suicidal Behavior, Aggression and Anger in All Jatenzo Studies

Preferred Term	Number of Subjects with AEs (% of Total; N =569)
Depression*	6* (1.1%)
Suicidal ideation	1 (0.2%)
Suicidal behavior	0
Aggression	1 (0.2%)
Anger	2 (0.4%)
*Of the 6 subjects with an AE of depression, 4 had a history of depression prior to entry into a Clarus clinical study. Source: Sponsor’s Table A from IR response dated Dec 7, 2018 with reviewer edits.	

Four of the 6 patients with a reported AE of “depression” had prior history of depression. In addition, all 9 of the patients who reported an AE in these categories successfully completed the Jatenzo studies despite reporting these AEs.

Two patients who reported these AEs were in CLAR-15012. The following are brief narrative summaries of these 2 patients. The Sponsor did not report that any patients reported depression or suicidality AEs in the Topical Axiron comparator arm in CLAR-15012.

- ✚ Patient (b) (6), in the TU arm, reported an AE of “depression”, of moderate severity, on study day 91. The patient was treated with bupropion and the AE was reported as resolved by study day 121.

His oral TU dose at the time of the AE was 237 mg TU BID which he had been receiving for the entire study. At the visit prior to the AE (Visit 4b, Study Day 83) his T Cavg was 490 ng/dL and his T C_{max} was 1192 ng/dL. At the visit following the AE (Visit 7, Study Day 131, end of Study visit) his T Cavg was 430 ng/dL, and his T C_{max} was 598 ng/dL. No clinically significant lab abnormalities were reported during the study for this subject for any of the protocol-specified safety tests. The subject successfully completed the study.

- ✚ Patient (b) (6), in the TU arm, reported 2 AEs of “worsening depression” of moderate severity on study day 105 and “suicidal ideation” of mild severity on the same date. The patient had a history of depression, was on no medications for the condition and did not take any medications for depression during the study for treatment of the AEs. He reported that the worsening depression did not resolve by final study day 134. However, the AE of suicidal ideation did resolve on day 160, after study completion.

His oral TU dose at the time of the AEs was 396 mg TU BID which he had been receiving for the prior 20 days before his reported AEs. At the visit prior to the AE (Visit 4b, Study Day 85) his T Cavg was 261 ng/dL and his T C_{max} was 781 ng/dL. At the visit following the AEs (Visit 7 Study Day 134), his T Cavg was 260 ng/dL, and his T C_{max} 686 ng/dL. No clinically significant lab abnormalities were reported during the study for this subject for any of the protocol-specified safety tests. This subject successfully completed the study.

Reviewer’s Comment: While the available data do not establish an increased risk of depression and suicidality related to Jatenzo, it is still prudent to inform prescribers and patients of these potential serious risks in prominent parts of labeling.

3.4 Erythropoietic AEs, including Increased Hematocrit (HCT) and Polycythemia

Erythropoiesis is a known consequence of testosterone therapy. Increased HCT and polycythemia have been reported for all forms of TRT. In CLAR-15012, 8 of 166 (4.8%) patients on Jatenzo had HCT > 54% compared to 0% in the topical Axiron group. The following table summarizes the proportion of patients with HCT >54% and clinically significant abnormal hemoglobin with Jatenzo and the comparator in CLAR-15012:

Table 7: Proportion of Subjects with Notable Post-Baseline Hematology Values by Treatment Group (Safety Population) in CLAR-15012

Parameter: Assessment, n (%) Hematocrit:	Jatenzo (N=166)	Topical Axiron (N=54)
At least 1 post-baseline value Hct >54%	8 (4.8)	0
More than 1 post-baseline value Hct >54%	3 (1.8)	0
Hemoglobin: clinically significant abnormal	1 (0.6)	1 (1.9)

Source: CLAR-15012: Table 42 page 145 with reviewer edits.

The following table summarizes mean HCT changes from baseline during the study in subjects on Jatenzo.

Table 8: Mean Hematocrit Changes of Subjects on Jatenzo (CLAR-15012)

Hematocrit (%)	Jatenzo
Baseline Hematocrit	44.5%
Study Day 105	47.4%
Change from Baseline	2.9%

Source: Reviewer generated table from ISS, Table P3 2.2.9 page 1325

Reviewer's Comment: *The 4.8% incidence rate of at least one HCT > 54% in CLAR-15012 is roughly comparable to reported incidence rates for most other TRT products. However, because CLAR-15012 was a 4-month study, it is expected that higher incidence rates of elevated HCT could occur with longer-term Jatenzo treatment.*

For this reason, we recommend that the label encourage practitioners to check hematocrit every 3 months while patients are on Jatenzo and that this information be conveyed prominently in the Warning & Precautions section. Labeling should also convey the precaution that Jatenzo should be discontinued in patients with elevated hematocrit until the hematocrit return to a safe range and should be

discontinued permanently if clinical circumstances mandate permanent discontinuation.

3.5 Adrenocortical atrophy and Adrenal Insufficiency in Dogs

In dogs, testosterone undecanoate was associated with findings of adrenocortical atrophy and hypocortisolemia. While no previous clinical study had demonstrated evidence of adrenal insufficiency in humans, based on the findings in dogs, CLAR-15012 included Cosyntropin stimulation testing in a subset of subjects to study the potential clinical adrenal effects of Jatenzo. However, the results from the Cosyntropin stimulation testing in CLAR-15012 were inconclusive and were inadequate to either demonstrate or to rule out an adrenal effect of Jatenzo in humans.

To summarize, in CLAR-15012, after Cosyntropin injection, 5 of 24 Jatenzo patients had what appeared to be a low cortisol response at Visit 8. Four of these 5 patients appeared to have cortisol values that were only slightly below the usual normal response cutoff level of 18 µg/dL (values ranged from 16.5 to 17.6 µg/dL at 30 or 60 minutes after administration of cosyntropin).

The Sponsor asserted that to rule out primary adrenal insufficiency, the peak post-stimulation cortisol needs to be >15 µg/dL and all four of these patients met that criterion, thus, the testing ruled out adrenal insufficiency with Jatenzo.

Based on these test results, the Division made a request for Endocrinology to consult. For details, refer to the Clinical review of the 1st resubmission dated March 17, 2018) and the Endocrinology Consult (December 6, 2017).

The Endocrinology Consult concluded that the Sponsor's data was insufficient to demonstrate or to refute hypoadrenalism associated with Jatenzo, with the following statement:

“...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. 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. The decline in BP between study visit 1 and 8 is curious, particularly since TU appears to be associated with an increase in BP. However, no patients experienced hypotension.”

On the other hand, many subjects in both groups had low AM cortisol levels at baseline. This raises concerns about the performance of the (cortisol) 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 explain the findings.”

Based on this conclusion, the Endocrinology consultant made the following recommendations:

- A more robust study should be performed to evaluate the possibility of adrenal insufficiency with TU and the active comparator topical Axiron.
- The results of the current study can be used to inform power calculations.
- The consultant believes that the Cosyntropin 0.25 mg intravenous test with cortisol testing pre-injection and 30 and 60 minutes post-injection is an appropriate test for future studies.
- 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 simultaneous pre-Cosyntropin cortisol and ACTH levels should be obtained each timepoint.
- Samples should be batched for the cortisol and ACTH assays. The assays chosen should have optimal performance.
- Serial tests should be performed at baseline and at 6 month intervals, or sooner if clinically indicated, to determine if progressive adrenal insufficiency occurs with ongoing TU use.
- The Cosyntropin study protocol should be submitted for review prior to initiation of the study.

Reviewer’s Comment: We agree with our Endocrinology consultant and recommend that the Sponsor be asked to conduct another clinical Cosyntropin stimulation testing study due to inconclusive data from the Cosyntropin stimulation test substudy in study CLAR-15012. However, based on the lack of any signs or symptoms of hypoadrenalism noted in any patient in prior studies of Jatenzo, we agree with our advisors and consultants on the BRUDAC that the adrenal-related observations in dogs are likely not clinically relevant and that the next Cosyntropin stimulation testing study can be conducted in the postmarketing period as a postmarketing requirement (PMR) study. We recommend the following PMR request be made:

“Submit a protocol to evaluate for the development of adrenal insufficiency with long-term Jatenzo treatment, in which you assess adrenal function pre-treatment and at 6-months and then regular 6-month intervals or sooner, if necessary.

It is acceptable to perform a Cosyntropin stimulation test using Cosyntropin 0.25 mg with measurements of cortisol, adrenocorticotrophic hormone (ACTH) and corticosteroid binding globulin (CBG) pre-injection and cortisol 30 and 60 minutes post-injection. We recommend that you standardize testing time to 8AM, standardize the mode of Cosyntropin administration (i.e., intramuscular or intravenous) and perform hormone assays in a central laboratory on batched serum samples. Use a cortisol level ≥ 18 mcg/dL to interpret results as normal, and provide an algorithm for managing abnormal test results. Refer to your Cosyntropin substudy from CLAR-15012 to inform power calculations and include a statistical analysis plan”.

4 Review of Efficacy

Efficacy Summary

As no new clinical efficacy data were submitted in this 2nd NDA resubmission, the efficacy results are unchanged from the last submission. In brief, testosterone replacement with Jatenzo met the prospectively planned primary efficacy endpoint. While the efficacy results are very briefly described here, the reader is referred to the March 17, 2018, Clinical Review of the 1st resubmission for details.

Primary Efficacy Endpoint:

The table below summarizes the primary efficacy endpoint results for the phase 3 study, CLAR-15012. Key results from this table are reflected in labeling.

Table 9: Percentage of Patients Achieving Eugonadal Testosterone Cavg Values at Visit 7 for the Primary Analysis (MITT Population) in CLAR-0512 Using Success Criteria Range Adjusted for Plasma Testosterone Concentration.

Testosterone Cavg Range	FDA Target	Jatenzo n (%) (N=166)
Eugonadal range *	≥75%	145 (87.3%)
Lower bound 95% CI	≥65%	81.3%
Upper bound 95% CI		92.0%
Cavg mean 95% CI		401.2 ng/ dL (379.7, 422.7)
<i>CI=confidence interval; *Eugonadal range for Jatenzo is defined as 252 ng/dL ≤ Cavg ≤ 907 ng/dL</i>		
<i>Source: CLAR-Study 15012 report, Table 15, page 94 with reviewer edits</i>		

Reviewer’s Comment: Jatenzo met the standard primary efficacy range for testosterone.

Of note, in CLAR-0512, the Sponsor chose to assay plasma testosterone concentrations in NaF/ EDTA tubes, held on ice for 30 minutes after blood draw. The Sponsor’s intention was to minimize TU → T conversion in the specimen test tube itself. Due to the use of this methodology for the key bioanalyses, it was necessary to adjust the standard serum T concentration eugonadal range of 300-1000 ng/dL by a factor of 0.907 (1/1.102) to reflect the efficacy results when expressed as plasma T concentrations. See the Clinical Pharmacology review for details on the multiple factors that were considered in arriving at the adjustment factor as it relates to expression of the PK and efficacy data as nontraditional plasma T concentrations collected in NaF/EDTA tubes versus traditional serum T concentrations collected in standard, plain, red-top tubes, (b) (4)

Secondary Efficacy Endpoints:

Secondary efficacy endpoints are the following traditional testosterone Cmax outlier ranges:

- 1) ≥ 85% of patients with total T C_{max} < 1500 ng/dL
- 2) <5% of patients with total T C_{max} of 1800 to 2500 ng/dL (inclusive)
- 3) No patient with a total T C_{max} > 2500 ng/dL

The following table summarizes percentages of patients in CLAR-15012 who had C_{max} concentration levels in those three pre-specified ranges:

Table 10: Percentage of Subjects with Testosterone C_{max} Values in the Pre-Specified C_{max} Outlier Ranges at Visit 7 in CLAR-15012* – Traditional Unadjusted Range Criteria

Testosterone C _{max} Range N (%)	FDA Target	Jatenzo (N = 151) ^a	Topical Axiron (N = 48)
C _{max} ≤ 1500 ng/dL	≥ 85%	137 (90.7%)	47 (97.9%)
C _{max} > 1800 - 2500 ng/dL	≤ 5%	3 (2.0%)	1 (2.1%)
C _{max} > 2500 ng/dL	0	3 (2.0%) ^b	0

Abbreviations: C_{max} = maximum observed concentration over 24 hours; FDA = Food and Drug Administration; TU = testosterone undecanoate

** Of subjects who had testosterone C_{max} data at Visit 7*

^a Eight subjects had C_{max} values > 1500 - ≤ 1800 ng/dL.

^b All 3 subjects with C_{max} > 2500 ng/dL had C_{max} values suggestive of contamination. Source: Reviewer edits to [Post-text Table 14.2.2.1](#)

The Sponsor postulated that the three patients who had C_{max} >2500 ng/dL had C_{max} concentration levels consistent with topical Axiron contamination at the same clinic, study site #110, on the same visit (Visit 7), where Jatenzo patients were concurrently treated with other topical Axiron patients receiving their testosterone applications. The Sponsor based this conclusion of contamination on the following evidence:

- 1) same clinical site, #110
- 2) same time of draw 2 hours after dosing of both Jatenzo and topical Axiron in the same clinic
- 3) abnormally low DHT/T molar ratios in all 3 patients at the 2-hour time point, all between 0.0439 and 0.0602 as compared to all other Jatenzo dosed patients with expected DHT/T ratio 0.1484.

The following table summarizes these T, DHT, and DHT/T molar ratios in these 3 selected patients of interest from clinic #110:

Table 11: Observed Testosterone, Dihydrotestosterone, and Dihydrotestosterone/ Testosterone Ratios in High Testosterone C_{max} Samples, and Estimated Testosterone Concentrations Assuming High Testosterone Includes Contamination from Exogenous Testosterone

	Observed Values at Visit 7 for Subjects with High Testosterone C _{max} Samples					Estimated 2 Hour Testosterone Concentrations	
	2 h	2 h	2 h	4 h	14 h	Estimate from 4 h DHT/T	Estimate from 14 h DHT/T
Subject	T ng/dL	DHT ng/dL	DHT/T mole ratio	DHT/T mole ratio	DHT/T mole ratio	T ng/dL	T ng/dL
(b) (6)	4905	297.2	0.0602	0.1665	0.1625	1773	1817
	4485	198.3	0.0439	0.1378	0.0993	1429	1984
	2824	152.9	0.0538	0.1301	0.2305	1167	659

Abbreviations: C_{max} = maximum observed concentration over 24 hours; DHT = dihydrotestosterone; T = testosterone
 Source: CLAR-15012 CSR Listing 16.2.6.2.2.1; Appendix 16.5.2, Table 5 and Table 19 with Reviewer edits

If these three patients are eliminated from the analysis, Jatenzo met the secondary endpoint criteria in CLAR-15012, when using unadjusted C_{max} range criteria.

Reviewer’s Comment: The Sponsor’s scientific explanation regarding sample contamination in these 3 cases is plausible.

Because CLAR-15012 used NaF/EDTA-containing specimen test tubes and nontraditional plasma T concentration bioanalysis methods, the secondary endpoint analysis needed to be re-conducted using adjusted range criteria. The following table summarizes the results of the secondary efficacy endpoints, using the adjusted testosterone concentrations:

Table 12: Number (Percentage) of Subjects at Day 105 in CLAR-15012 who Met C_{max} Outlier Criteria Adjusted for Plasma T Concentrations

Testosterone C _{max} Adjusted Range ^a N (%)	FDA Target	Jatenzo (N = 151)	Topical Axiron (N = 48)
C _{max} ≤ 1361 ng/dL	≥ 85%	125 (82.8%)	47 (97.9%)
C _{max} > 1633 - 2268 ng/dL	≤ 5%	5 (3.3%)	1 (2.1%)
C _{max} > 2268 ng/dL	0	4 (2.6%)	0

Abbreviations: C_{avg} = average concentration over 24 hours; C_{max} = maximum observed concentration over 24 hours; FDA = Food and Drug Administration; TU = testosterone undecanoate
^a The adjustment factor was the ratio of 907 ng/dL applied to the traditional range criteria (i.e., 907/1000 = 0.907).
 Source: Reviewer edits on [Post-text Table 14.2.2.1b](#)

Using the criteria range adjusted for plasma T concentrations, Jatenzo did not fully meet the secondary efficacy endpoints, as four patients (not three patients) had total T C_{max} >2268 ng/dL (traditional range of > 2500 ng/dL) and the percentage of patients with $C_{max} \leq 1361$ was 82.8% (not 90.7%) which is less than the target of $\geq 85\%$. Of these four patients with $C_{max} > 2268$ ng/dL, 3 patients had potential inadvertent exposure to topical Axiron as noted in the prior paragraphs. The NDA review team identified a fourth patient, # (b) (6), who had a C_{max} concentration of 2467 ng/ dL but was also evaluated at the same clinic, #110, as the other 3 likely contaminated specimen patients.

Reviewer Comment: When using adjusted C_{max} range criteria for the C_{max} outlier secondary endpoints because of the use of NaF/ EDTA tubes in study CLAR-15012, by strict standard, Jatenzo did not meet all three secondary efficacy criteria limits. However, it is likely that all the 4 patients who exceeded the high range of C_{max} under the adjusted concentration ranges had specimens contaminated by Axiron at study site #110. If those 4 patients are eliminated from the analysis, then Jatenzo barely missed the secondary efficacy endpoint criterion of percentage of subjects with $C_{max} \leq 1361$ ng/dL by 2%: 83% met the criteria versus FDA target 85%. This difference is small not does not affect the overall efficacy evaluation of Jatenzo.

Taken in total, from a Clinical perspective, Jatenzo essentially met the primary efficacy endpoint as well as the secondary endpoints as it missed one secondary efficacy criterion by a small percentage (2%), when using the adjusted range criteria.

5 Labeling

This section provides an overview of the key labeling issues, including an explanation of the Clinical Review team's recommendations for final labeling for the key labeling issues. The section is subdivided as follows: Labeling for Risk of Increased BP , Labeling for Depression, and Labeling for Erythropoietic AEs. It is important to note here that the FDA and the Sponsor were continuing labeling discussions on key labeling issues at the time this clinical review was completed. The Clinical review team recommends approval of this NDA only on the condition that the Sponsor revise the label to fully address the Clinical safety deficiency in the 2nd CR Letter.

5.1 Labeling for Risk of Increased BP

Key elements of 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 are described briefly

here. These are not verbatim labeling texts. For details and for verbatim text, the reader is referred to the final agreed-upon Jatenzo product labeling.

➤ Boxed Warning

- a) JATENZO can increase blood pressure BP
- b) Increased BP can increase the risk of having a major adverse cardiovascular event (MACE), including myocardial infarction, stroke and cardiac death, especially in men with a history of, or risk factors for, cardiovascular disease.
- c) Practitioners need to monitor for and treat new-onset hypertension as well as exacerbations of pre-existing hypertension while patients are on JATENZO.
- d) Due to the risk of increased BP that can increase the risk of MACE, JATENZO should not be used to treat men 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 MACE, 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. The Indications section of labeling provides examples of conditions that cause low testosterone and are associated with structural and genetic disorders.

➤ Warnings & Precautions:

The Increased BP Warning & Precaution was added (as the first Warning) to convey the following information to prescribers:

- a) 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 MACE, especially in patients with established cardiovascular disease or risk factors for cardiovascular disease.
- b) 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.
- c) Prescribers should be counseled to check BP as early as 3 weeks after initiating JATENZO and periodically thereafter and treat new-onset hypertension and exacerbations of pre-existing hypertension.
- d) Very small increases in blood pressure may not be detected but still can increase the risk of MACE.

➤ 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:
 - a) Jatenzo can increase your BP which could increase your risk of heart attack, stroke, or cardiac death
 - b) Inform your Healthcare Providers if you have hypertension
 - c) 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
 - d) Take your antihypertensive medications as instructed
 - e) If your BP cannot be adequately managed, Jatenzo may need to be discontinued

5.2 Labeling for Depression and Suicidality

- Warnings & Precautions:
Despite insufficient evidence to conclude a causal relationship of the reported cases to Jatenzo, it is prudent to add a Warning & Precaution (as the final W&P) for Depression and Suicidality. It is important that patients on Jatenzo should report changes in mood to their health care providers.
- Adverse Reactions:
The Adverse Reactions section includes a special subsection that provides additional summary details regarding the reported cases of worsening or new-onset depression in patients who were on Jatenzo in clinical studies.

Additional labeling, including information to patients in Patient Counseling and the Medication Guide informs patients about possible changes in mood, including depressed mood and suicidal ideation, while on testosterone replacement therapy, including Jatenzo.

5.3 Labeling for Erythropoietic AEs

➤ Warnings & Precautions:

A Warning & Precaution was added (as the second W&P) to describe the observed increases in hematocrit that were reported as adverse events in the clinical studies of Jatenzo. Prescribers are reminded to monitor hematocrit approximately every 3 months in patients on Jatenzo.

➤ Adverse Reactions:

In addition to the showing the frequencies of adverse reactions related to erythropoiesis reported in clinical studies for Jatenzo, the Adverse Reactions section includes a subsection that provides additional summary details concerning the adverse events of Increased hematocrit in the clinical studies.

Additional labeling, including information to patients in Patient Counseling and the Medication Guide informs patients about possible increases in hematocrit, the risks associated with these increases, and the need to monitor hematocrit and either temporarily or permanently discontinue Jatenzo due to increases in hematocrit.

6 Significant Efficacy/Safety Issues Related to Other Review Disciplines

6.1 Chemistry Manufacturing and Controls (CMC)

There were no new CMC issues in this CR submission. The Chemistry review team recommended approval.

6.2 Preclinical Pharmacology/Toxicology

The 3rd deficiency listed on the 2nd CR letter (March 22, 2018) was a Pharmacology/ Toxicology deficiency stating the following: “*Unacceptable nonclinical studies for male fertility and carcinogenicity were submitted to support NDA approval through the 505(b)(1) pathway*”.

In this 2nd resubmission, the Sponsor changed the NDA submission type to a 505(b)(2) application and addressed the nonclinical deficiencies by referencing information in the original NDA submission with literature references. The Pharmacology/ Toxicology review team concluded that the referenced information as well as additional information submitted in this 2nd resubmission was sufficient to address the nonclinical deficiency

and recommended approval from the Pharmacology/ Toxicology standpoint. The reader is referred to the final Pharmacology/ Toxicology review for details.

6.3 Clinical Pharmacology

The 2nd deficiency listed on the 2nd CR letter (March 22, 2018) was a Clinical Pharmacology deficiency which stated the following: *“Accuracy or reproducibility of patient plasma total testosterone (T) concentrations on Jatenzo using sodium fluoride (NaF) ethylenediaminetetraacetic acid (EDTA) tubes was not determined.”*

The Sponsor chose NaF/ EDTA tubes to assay T concentration levels in plasma from blood drawn in CLAR-15012, the phase 3 study which primarily supported safety and efficacy for Jatenzo. However, the Sponsor now proposes that T concentrations should be measured in serum from blood drawn into plain tubes (red-top tubes), not NaF/ EDTA tubes, 6 hours after the morning dose and at least 7 days after starting treatment or following dose adjustment.

To support this change from NaF/ EDTA tubes in the studies to plain tubes, the Sponsor submitted 5 new Clinical Pharmacology/ Biopharmaceutics studies in this 2nd resubmission, which included three TU to T *ex vivo* conversion studies – following JATENZO administration (CLAR-18019), Andriol® administration (CLAR- 18016), and *in vitro* TU spiking (CLAR-18021), bioanalytical method correlation study (CLAR- 18020), and a TU cross-reactivity study with commercially available T immunoassays (CLAR-18018). Only Study CLAR-18019 included oral administration of Jatenzo to study participants and was conducted in healthy volunteers.

The Office of Clinical Pharmacology (OCP)/ Division of Clinical Pharmacology 3 reviewed the new data from these 5 studies and concluded that the information submitted is now acceptable and recommends approval from the Clinical Pharmacology standpoint. The reader is referred to the final Clinical Pharmacology review for details.

In addition, in the 2nd CR Letter (March 22, 2018), the Division stated that the Sponsor would need to address the drug-drug interaction (DDI) potential of testosterone undecanoate (TU) as the perpetrator. The Sponsor proposed to address this potential as a post-marketing study. The Division of Clinical Pharmacology determined that the proposal is acceptable from the Clinical Pharmacology standpoint and recommended the following post-marketing requirement (PMR) for the approval letter:

“Conduct in vitro studies to assess the potential of testosterone undecanoate 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.”

Reviewer's Comment: We agree with the Division of Clinical Pharmacology concerning acceptable resolution of the previous CR deficiency as well as the need to conduct a post-marketing study to assess the DDI potential of TU.

6.4 Biometrics

There are no new review issues for the Division of Biometrics in this 2nd resubmission as no new clinical data on the indicated population were submitted and the only new study results are from CLAR-18019, a clinical pharmacology study conducted in 9 healthy male volunteers. This study did not assess efficacy and therefore, did not need an efficacy review. Biometrics did assist in the review of a Clinical safety issue (see previous sections of this review).

6.5 Division of Medication Error Prevention and Analysis (DMEPA)

Proprietary Name

DMEPA had no new review issues in regards to the proprietary name - the name Jatenzo was confirmed to be acceptable.

Carton and Container Labeling

The Sponsor submitted revised carton and container labeling in this 2nd resubmission, based on previous DMEPA recommendations for revisions to those parts of labeling. DMEPA had no review issues regarding the revised carton and container labeling and stated in their review: *"The revised container label and shipping label for 'Jatenzo' is acceptable from a medication errors perspective."* From DMEPA's perspective, there are no outstanding container or carton labeling issues.

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/

T D CHANG
03/15/2019 05:28:28 PM

MARK S HIRSCH
03/15/2019 05:37:54 PM
I concur.

Cross-Discipline Team Leader Memo

Date	March 22, 2017
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Memo
NDA/BLA# /Supplement#	206089
Applicant	Clarus Therapeutics, Inc
Date of Submission	June 22, 2017
PDUFA Goal Date	March 22, 2018
Proprietary Name / Established (USAN) names	Jatenzo testosterone undecanoate
Dosage forms / Strength	158 mg, 198 mg, or 237 mg oral soft capsules (158mg, 198mg, 237mg, 316mg or 396mg twice daily)
Proposed Indication(s)	Replacement of testosterone in adult men with deficiency or absence of endogenous testosterone due to primary hypogonadism or hypogonadotropic hypogonadism
Recommended:	<i>Complete Response</i>

1. Introduction/Executive Summary

Jatenzo, formerly known as Rextoro, is proposed for use as a new testosterone replacement therapy (TRT). Jatenzo, a soft capsule containing either 158 mg, 198 mg, 237 mg of testosterone undecanoate (TU), is intended for twice daily chronic oral dosing. The starting dose is 237 mg twice daily, and the dose is to be adjusted up or down based on testosterone concentrations derived from blood samples drawn in sodium fluoride-containing (NaF-EDTA) test tubes at 3-5 hours after the morning dose and at least 7 days after starting Jatenzo therapy. The principal potential benefit of this new oral formulation is patient convenience.

TRT is the current standard of care for hypogonadal adult male patients with primary or secondary hypogonadism related to distinct, well-established conditions. Nonetheless, despite a Limitation of Use (LOU) in the Indications section of all approved TRT product labeling, TRT products are widely prescribed to older men with “low T” (or “age-related hypogonadism”). There are a host of FDA-approved TRT products available, including a variety of formulation types. Jatenzo would represent another therapeutic option for TRT; and as an oral capsule, it may prove to be an attractive option because the only other oral TRT product is methyltestosterone, which is rarely used because of hepatotoxicity.

The NDA for Jatenzo (referred to as “Jatenzo” and “Oral TU” in this memo), is supported by three (3) phase 3 studies, but principally the Sponsor’s most recently completed phase 3 study, Study CLAR-15012. CLAR-15012 is the only phase 3 study that utilized the to-be-marketed dose titration regimen. Principally for this reason, the efficacy and safety results from CLAR-15012 are the focus of this memo. For information concerning the Sponsor’s previously completed phase 3 studies CLAR-09007 and CLAR-12011, the reader is referred to my previous CDTL memo for Clarus’ original Oral TU NDA, as well as to the medical officers’ current and previous primary Clinical reviews of Clarus’ NDA 206089 for Oral TU. 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 all TRT products, along with study protocol modifications related to drug-specific issues and discussions held between Clarus and FDA subsequent to the FDA's November 3, 2014, Complete Response regulatory action on Clarus' original NDA, CLAR-15012 was designed to test: 1) the efficacy of Oral TU using standard TRT class testosterone exposure (PK) parameters, 2) the effect of food on exposure to testosterone from Oral TU, 3) the safety of Oral TU both unto itself, and 4) the safety of Oral TU in comparison to Topical Axiron for selected safety issues, including effects on blood pressure and on the adrenal response to adrenocorticotropin (Cosyntropin) stimulation testing.

In brief, the Efficacy data from the Phase 3 pivotal study CLAR-15012, along with the supporting data from the other phase 3 clinical studies of Oral TU, supports the Sponsor's contention that Jatenzo provides testosterone replacement in adult men with hypogonadism. However, we will be requiring the Sponsor to further assess the rate and extent of TU to T *ex vivo* conversion during the time course of plasma sample preparation to determine whether T concentration measurements from plasma in NaF/EDTA tubes in CLAR-15012 are accurate and reproducible. If these additional data do not confirm the reliability of the T measurements from this trial, a new Phase 3 trial may be needed.

For Safety, 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.
- 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
- 161 hypogonadal adult males who received 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 "pivotal" phase 3 studies. In addition, a total of 86 subjects received treatment for approximately 52 weeks in the Long-Term Extension Study to Study CLAR-09007, referred to as CLAR-12010; but again, the doses and dose regimen in that study were different than 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.

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.

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 overall mean body weight and body mass index (BMI) in the Oral TU group were 101.4 kg and 31.8 kg/m², 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 approved TRT products, including Topical Axiron, except for gastrointestinal adverse effects (presumably related to the oral route of administration) and one serious safety issue:

- The potential for Jatenzo to raise average blood pressure by a clinically meaningful amount was confirmed in CLAR-15012. Ambulatory blood pressure monitoring showed that treatment with Jatenzo was associated with a mean 24-hour average systolic/diastolic BP increase of 4.9/2.5 mmHg as compared to a minimal increase (0.1/0.5 mmHg) with Topical Axiron. When analyzed in key subgroups, the Jatenzo-related mean increases in 24-hour average BP were even larger. For example, in subjects with treated hypertension: 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 known 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, but the sub study evaluation was marred by procedural flaws, making the human data uninterpretable. Therefore, a repeat evaluation of the effect of Jatenzo on adrenal function in humans (e.g., a repeat Cosyntropin stimulation study) is deemed necessary to resolve the issue.

Based on the single remaining serious safety issue (BP increases), the Clinical review team has recommended a Complete Response action for the application. The Clinical team's proposal for a Clinical CR Deficiency and Information Needed to Resolve the Clinical CR Deficiency for an FDA regulatory action letter is provided here:

Clinical CR Deficiency

Ambulatory blood pressure monitoring in Study CLAR-15012 confirmed that Jatenzo increases the blood pressure in a clinically meaningful way, showing that treatment with Jatenzo was associated with a mean daytime average systolic BP increase of 5.0 mmHg as

compared to a minimal average decrease (-0.1 mmHg) with Topical Axiron. When analyzed in key subgroups, such as men with a history of hypertension, the Jatenzo-related mean increases in daytime average BP were even larger. Changes in 24-hour average and nighttime BP were consistent with the changes in the daytime 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. The magnitude of these observed increases in BP, if chronically sustained, are known to confer an increased risk of heart attack, stroke and cardiovascular death, especially in patients with increased baseline cardiovascular risk.

Information Needed to Resolve the Clinical CR Deficiency

To respond to the CR deficiency, the Sponsor should propose detailed strategies in labeling (including proposals for a Boxed Warning, Indication, Contraindication, and Warnings and Precautions) and strategies beyond labeling, such as a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use, together with an assessment of how this proposal will mitigate the risks and ensure a favorable benefit/risk profile. We will determine whether the proposed strategies can ensure that the benefits outweigh the risks after a complete review of your resubmission.

While the specific elements of labeling and the REMS will require further discussion with the Division of Risk Management, our cardiology consultants, and the REMS Oversight Committee (ROC), the clinical team's current thinking is that a REMS should include the following elements:

- Health care professionals who prescribe Jatenzo should formally acknowledge the risk of increased BP due to Jatenzo and should agree to monitor for increases in BP during Jatenzo therapy.
- Patients who are considering treatment with Jatenzo should be informed of the risk of increased BP and should formally acknowledge the risk and their willingness to be monitored for increased BP while on Jatenzo treatment.
- The REMS with ETASU should include:
 - Educational materials for the prescriber that expounds on the risk of increased BP; and in light of that specific risk, the prescriber should carefully consider the potential risks and benefits leading to a decision to treat each patient and should monitor for increased BP.
 - Prescriber training to enhance the success of the educational materials.
 - A patient communication plan to convey the risk and minimize its adverse consequences

The clinical team's current thinking is that Jatenzo labeling should elaborate on the increased BP risk and should instruct prescribers to avoid Jatenzo treatment in men with uncontrolled BP. Labeling should also inform prescribers to consider their patient's overall cardiovascular health, as well as potential clinical benefit and clinical risk in each patient, before deciding to administer Jatenzo to an individual patient, and periodically as treatment is ongoing.

In regard to the increased blood pressure risk, further discussion is needed as to whether a postmarketing clinical trial to assess the effect of Jatenzo on major adverse cardiovascular events (MACE) would be feasible in the setting of an ETASU REMS and ethical in light of the increased risk of major adverse cardiovascular events that are known to occur with the observed increases in BP.

In regard to the nonclinical signal of adrenocortical atrophy and hypoadrenalism in animals and the suboptimal evaluation by Cosyntropin stimulation testing in CLAR-15012, we recommend requiring a longer-term evaluation of the effect of Jatenzo on adrenal function in humans (e.g., a repeat Cosyntropin stimulation study) in the postmarketing period.

In regard to other approvability issues from the perspectives of other disciplines:

Clinical Pharmacology stated that the Sponsor took an approach of measuring total T concentrations from plasma in NaF/EDTA tubes instead of measuring T from serum in plain tubes in order to prevent the ex vivo conversion of TU to T in the tube. However, based on the limited data submitted, the extent that NaF/EDTA tubes actually prevents TU to T ex vivo conversion is unknown. As noted previously, 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 not conducted and remains warranted to determine whether T concentration measurements from plasma in NaF/EDTA tubes in the Phase 3 study CLAR-15012 are reliable.

In order to address this Clinical Pharmacology deficiency, Clinical Pharmacology requested that the Sponsor:

- Conduct an 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 various 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.
- Conduct a study comparing total T concentrations measured from serum (in plain tubes) and plasma (in NaF/EDTA tubes and non NaF-containing plasma tubes) collected in the same subjects without administering TU and then split, prepare, and analyze these samples in the same bioanalytical laboratory.

Pharmacology/Toxicology stated that the submitted nonclinical studies were not acceptable to support approval of the NDA through the 505(b)(1) pathway because the Oral TU doses were inadequate to characterize and provide a meaningful and valid evaluation of the chronic effects of Oral TU on male fertility and on carcinogenicity. In the fertility study, the tested doses did not produce the anticipated effects on spermatogenesis and/or fertility, which may reflect insufficient exposure to testosterone and/or TU but the Sponsor did not submit toxicokinetic data to demonstrate adequate drug exposure. With regards to the 6-month carcinogenicity study in male Tg-rasH2 mice, 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 carcinogenicity study.

In order to resolve this Nonclinical Deficiency, Pharmacology/Toxicology requested that the

Sponsor provide justification for dose selection for the fertility study, and conduct a new, adequately designed carcinogenicity study. Alternatively, Pharmacology/Toxicology stated that the Sponsor could classify their NDA as a 505(b)(2) application without submitting additional nonclinical studies provided that appropriate nonclinical published literature references were submitted to address the Nonclinical deficiencies.

Based on these Clinical, Clinical Pharmacology, and Nonclinical deficiencies, and with the current unfinished state of final product labeling, I concur with the Clinical, Clinical Pharmacology, and Pharmacology/Toxicology review teams that at this time, this application should not be approved and instead should receive a **Complete Response (CR)** regulatory action.

2. Background

2.1 DESCRIPTION OF PRODUCT

Testosterone undecanoate capsules, containing 158 mg, 198 mg and 237 mg testosterone undecanoate, are immediate release soft gelatin capsules. They are manufactured at the commercial manufacturing facilities of (b) (4)

In the initial NDA filing (submitted on January 3, 2014), the application including just two dosage strengths (158 mg and 237 mg). Since that time, Clarus added a 198 mg testosterone undecanoate capsule strength (which is equivalent to 125 mg testosterone). Information for the 158 mg and 237 mg capsules has been reviewed previously, therefore, only the 198 mg capsule is discussed here.

The 198 mg capsules are manufactured (b) (4) for the 158 mg and 237 mg capsules described previously. 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. One hundred twenty capsules are packaged in 300 cc HDPE bottles with a child resistant closure and induction seal. This container-closure system is identical to that used for the 158 mg and 237 mg testosterone undecanoate capsules.

Table 1: Testosterone Undecanoate 198 mg Capsules Unit Composition

Ingredient	Amount (mg) per 198 mg capsule	Function
Formulation		
Testosterone Undecanoate	197.88	Active Ingredient
Oleic Acid NF, EP	(b) (4)	(b) (4)
Borage Seed Oil	(b) (4)	(b) (4)
Butylated Hydroxytoluene NF, EP (BHT)	(b) (4)	(b) (4)
Peppermint Oil NF, FCC	(b) (4)	(b) (4)

Polyoxyl 40 Hydrogenated Castor Oil NF (Cremophor RH40)	(b) (4)	(b) (4)
Total Fill Weight		
Soft Gelatin Capsule Shell:		
	(b) (4)	
Gelatin (b) (4) NF		(b) (4)
Sorbitol (b) (4)		
Purified Water USP, EP		
Titanium Dioxide USP, EP		
Filled Gelatin Capsule		
Imprinting:		
Red (b) (4) Ink		
<i>Source: Module 2.3 Quality Overall Summary, Table 2.3.P.1-3, page 2</i>		

2.2 REGULATORY HISTORY

On June 29, 2007, new IND#78,104 for oral TU capsules was initially 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 elevated serum DHT:T concentration ratios observed 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 high DHT concentrations and high DHT/T ratios
- *May 28, 2010*: Division provides comments on the proposed 1-year, Androgen-controlled, Phase 3 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 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 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 NDA. The majority of panel members concluded that efficacy and safety had not been adequately established for this product. The questions posed to the AC 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 Dispute Resolution Request. This request appealed the need to conduct additional clinical investigations to demonstrate the efficacy and safety of

oral testosterone undecanoate and the effect of food on T exposure related to oral TU, including possible changes to the dose and dose titration algorithm.

On April 28, 2015, a meeting was held with the 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 the Sponsor. In brief, the following clinical issues were discussed relating to the additional requested 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., lower starting dose, C_{avg} thresholds of 350 and 800 ng/dL for titration, and 24-hour C_{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 measurement on all subjects seemed reasonable to the Division. Isolated assessment of SBP would be insufficient.
- T C_{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 assess the observed nonclinical effect on the adrenal gland. The Division recommended use of 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 postmarketing safety study for testosterone products, the Sponsor can ultimately expect to receive a request to conduct a required post marketing cardiovascular safety trial using oral TU.

Subsequent to the submission of the final protocol for the third phase 3 study CLAR-15012, the Sponsor submitted several protocol amendments, and the details of these protocol amendments are described fully in the medical officer’s Clinical review and not repeated here. With their stipulated protocol changes, Clarus chose to continue the protocol. 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.

In a July 19, 2016, correspondence to Clarus, the Division provided the following comments and recommendation on the protocol amendment 2.0: We strongly recommend that you halt your ongoing trial and provide a redlined protocol amendment that addresses our concerns, including an explanation of how you identified the problem and how you determined that the bioanalytical method is no longer appropriate for your Phase 3 trial. Provide:

1. Summary report of your findings regarding the bioanalytical method and laboratory issue for our review, an explanation of how you identified the problem and how you determined that the bioanalytical methods are no longer appropriate for your Phase 3 trial.
2. A summary report of the protocol revisions with rationale to explain each change.
3. A discussion of whether all subjects who have been participating in the trial meet the testosterone eligibility based upon your new bioanalytical method.
4. Discussion of whether the bioanalytical method problems affect any the other hormonal bioanalytical methods used in the trial.

Clarus chose not to halt the trial.

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

- Changing the testosterone assay while the Phase 3 trial is underway will require in-depth analysis once the NDA is received by FDA. 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.
- Comments pertaining to the ABPM analyses were offered.

On April 27, 2017, a Pre-NDA meeting was held. The following submission format issues were discussed:

- In providing a complete overview of the new efficacy data, the Clinical Summary of Efficacy in Module 2 should include a section that provides a summary of efficacy data from all 3 Phase 3 studies. Module 5 should include a complete Integrated Summary of Efficacy (ISE). The ISE should include a thorough description of new efficacy data followed by a comprehensive analysis of all Phase 3 studies focusing on similarities and differences in the individual study efficacy data and explanation of observed differences.
- Module 2 should include a Summary of Clinical Safety that includes both a section on the new safety data and a section on the safety data from all Phase 3 studies. Module 5 should include a complete Integrated Summary of Safety (ISS) that describes the new safety data in one section and the entirety of the safety data from safety data from all 3 Phase 3 studies in another section.
- Both the Clinical Summary of Safety and the ISS should contain an analysis and discussion of the impact of food, if any, on safety results, as should the ISE and Clinical Summary of Efficacy.
- The NDA will contain information to support the new 198 mg dosage strength.

On June 22, 2017, the NDA was resubmitted as a Complete Response.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary Clinical reviewer, Roger Wiederhorn, stated in his final review, dated March 17, 2017:

“Recommendation on Regulatory Action: We recommend that this NDA re-submission receive a Complete Response (CR) action:

Jatenzo has been shown to replace testosterone acceptably. However, Jatenzo was also shown to increase BP. Due to the risk of increased BP with Jatenzo, and lacking a formal risk evaluation and mitigation strategy (REMS) program to address the issue, the benefits of Jatenzo do not outweigh the potential risks associated with increased BP in the U.S. adult male population.

To respond to the CR deficiency, the Sponsor should provide a Risk Evaluation and Mitigation Strategy (REMS) that includes the following elements to assure safe use (ETASU):

- *Health care professionals who prescribe Jatenzo should formally acknowledge the risk of increased BP due to Jatenzo and should agree to monitor for increases in BP during Jatenzo therapy.*
- *Patients who are considering treatment with Jatenzo should be informed of the risk of increased BP and should formally acknowledge the risk and their willingness to be monitored for increased BP while on Jatenzo treatment.*
- *The REMS with ETASU should include:*
 - *Educational materials for the prescriber that expounds on the risk of increased BP; and in light of that specific risk, the prescriber should carefully consider the decision to treat each patient and should monitor for increased BP.*
 - *Prescriber training to enhance the success of the educational materials.*
 - *A patient communication plan to convey the risk and minimize its adverse consequences*

Jatenzo labeling should elaborate on the increased BP risk and should instruct prescribers to avoid Jatenzo treatment in men with uncontrolled BP. Labeling should also inform prescribers to consider their patient's overall cardiovascular health, as well as potential clinical benefit in each patient, before deciding to administer Jatenzo to an individual patient, and as treatment is ongoing.

We also recommend the following activities be required in the post-marketing period:

- *A clinical study to assess the effect of Jatenzo on major adverse cardiovascular events (MACE).*
- *A clinical study to assess the response to Cosyntropin in patients treated with Jatenzo.”*

The reader is also referred to the medical officer's, 131-page Clinical review in DARRTS.

3. CMC

The Chemistry review team, led by Mark Seggel, had the following recommendation in their final review dated February 26, 2018:

“In its present form, Clarus Therapeutics’ 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, container/carton) 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.”

4. Nonclinical Pharmacology/Toxicology

In their final review dated February 27, 2018, the Pharmacology/Toxicology (PharmTox) review team of Yangmee Shin and Mukesh Summan had the following Recommendation:

“Approvability: Pharmacology and Toxicology recommends a Complete Response action for this NDA. The submitted nonclinical studies are unacceptable to support the 505(b)(1) application of the NDA based on the doses tested that would not permit adequate characterization of the potential effect of the oral TU product following chronic treatment.”

PharmTox then outlined the following Nonclinical Deficiency and Information Needed to Resolve the Nonclinical Deficiency:

Nonclinical Deficiency:

Inadequate doses were used to allow adequate characterization of male fertility and carcinogenicity, which would preclude a meaningful and valid evaluation of the potential chronic effect of the oral TU product.

Information Needed to Resolve the Nonclinical Deficiency:

- The doses tested for the fertility study in male rats did not produce anticipated effects on the spermatogenesis and/or fertility that may reflect insufficient exposure to T and/or TU. No toxicokinetic data have been submitted to evaluate drug exposure. The Sponsor should provide a justification for dose selection for the fertility study combined with the in vivo micronucleus test.
- The Sponsor's rationale for adequacy of the 6-month carcinogenicity study in male Tg-rasH2 mice provided in their letter dated November 30, 2017 was not satisfactory to address the nonclinical deficiency communicated in the FDA's letter dated October 4, 2017. The Sponsor should conduct a new, adequately designed carcinogenicity study.

The Sponsor should submit the carcinogenicity study protocol for review by the Division and the Executive Carcinogenicity Assessment committee (CAC).

- Alternatively, the Sponsor could classify their NDA as a 505(b)(2) application without submitting additional nonclinical studies if they have provided appropriate nonclinical published literature references to address the nonclinical deficiencies above.

Also of note is information from a 13-week subchronic toxicity study in dogs, showing 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. TU exposure in dogs was only 2 times the worst-case exposure in human males.

In this 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 of oral TU, in which the testosterone exposure was approximately 12-fold higher than 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 subsequent 9-month chronic toxicity study was conducted in dogs using 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, there was no histopathological evidence of toxicity in the adrenal glands 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.

In order to address the potential clinical relevance of the nonclinical finding of adrenocortical atrophy and hypoadrenalism, at the request of the FDA, the Sponsor conducted Cosyntropin stimulation testing in a sub study of the phase 3 study CLAR-15102; however, results from these studies are not useful due to procedural flaws and deficiencies. Details of the human testing may be found in the medical officer’s Clinical review, in the Endocrine consult, and in later sections of this memo. In conclusion, the Clinical review team believes that a repeat human Cosyntropin stimulation testing is warranted, to be conducted in the postmarketing period.

5. Clinical Pharmacology/Biopharmaceutics

In their final review dated February 26, 2018, the Clinical Pharmacology review team of Chongwoo Yu and Donny Tran had the following Recommendation:

“The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) and Division of Pharmacometrics have reviewed NDA 206089 submitted on June 22, 2017, August 8, 2017, August 15, 2017, August 17, 2017, September 8, 2017, September 25, 2017, September 26, 2017, October 3, 2017, October 30, 2017,

November 13, 2017, November 22, 2017, November 24, 2017, December 5, 2017, December 18, 2017, and December 19, 2017. The overall Clinical Pharmacology information submitted to support this NDA is not acceptable and JATENZO is not recommended for approval from the Clinical Pharmacology standpoint”.

Clinical Pharmacology then outlined a Clinical Pharmacology Deficiency and Information Needed to Resolve the Clinical Pharmacology Deficiency, as follows:

Clinical Pharmacology Deficiency:

The Sponsor took an approach of measuring total T concentrations from plasma in NaF/EDTA tubes instead of serum in plain tubes. The Clinical Pharmacology review team notes that in the Sponsor’s Phase 3 study, CLAR-15012, samples collected in tubes containing NaF/EDTA were chilled on ice for 30 minutes and then centrifuged for 20 minutes before storage or analysis and in general, higher T concentrations were observed from serum in plain tubes compared to those from plasma in NaF/EDTA tubes following Oral TU administration. However, based on the limited data submitted, the extent that NaF/EDTA tubes prevents TU to T ex vivo conversion is unknown. Further investigation on the rate and extent of the TU to T ex vivo conversion during the time course of plasma sample preparation is warranted to determine whether T concentration measurements from plasma in NaF/EDTA tubes in the Phase 3 study CLAR-15012 are reliable.

Information Needed to Resolve the Clinical Pharmacology Deficiency:

In order to address the identified deficiency, the Sponsor should 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.

Clinical Pharmacology had the following *Additional Comments to Sponsor*:

- We note that there were no drug-drug interaction (DDI) study conducted with JATENZO. Considering that JATENZO is administered as TU orally, and high systemic concentrations of TU are observed, the DDI potential of TU should be addressed.
- Due to the similarities in the chemical structure of T and TU and because of the high concentration of TU relative to T in patient specimens, it is possible that commonly used T immunoassays would significantly cross-react with TU causing an overestimation of T concentration values regardless of sample type. Provide data demonstrating the rate of TU cross-reactivity with commonly-used immunoassays. If the Sponsor intends to propose the clinical use of a liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay, the Sponsor should submit a proposal for a companion diagnostic.

In regard to two additional important Clinical Pharmacology-related issues, Clinical Pharmacology had the following conclusions:

- While dose titration in the Phase 3 study, CLAR- 15012 was based on the 24-hour total T C_{avg} (using 0 - 24 hour sampling), the development of a dose titration algorithm based on a single blood draw sample was warranted as a practical approach in clinical practice. Accordingly, the Sponsor proposed titration based on a single sample in the 3-5

hour post-morning dose window with same thresholds of T concentration (350 and 800 ng/dL) for up-/down-titration as that applied to Cavg in the Phase 3 study. After reviewing all relevant data, the Clinical Pharmacology review team concludes that a 4-6 hour post-morning dose window for single blood draw sampling for titration decisions would be more appropriate than the 3- 5 hour window proposed by the Sponsor, using the Sponsor's same proposed titration thresholds (350 and 800 ng/dL) for up- and down-titrations.

- The effect of food on the bioavailability (BA) of Oral TU was evaluated in Study CLAR-16015. Based primarily on results from this study, the Sponsor proposed only that Jatenzo should be taken with food and not in a fasted state. Upon review of data from Studies CLAR-15012 and CLAR-16015, the Clinical Pharmacology review team agreed with the Sponsor's proposal.

It is also notable that the Office of In Vitro Diagnostics and Radiological Health (OIR) in the **Center for Device and Radiological Health (CDRH)** also contributed to the review of the bioanalytical methods used in CLAR-15012. The CDRH conclusion, as stated in a final January 18, 2018, consult authored by Eveline Arnold and Mariana Perez-Torres, is consistent with the Clinical Pharmacology review team's conclusion about the bioanalytical method. CDRH stated:

“Regarding the sponsor’s proposal that NaF/EDTA tubes are needed to ensure the safe and effective dosing of oral testosterone undecanoate (TU), CDRH identified several deficiencies in the studies provided to support the Sponsor’s conclusion. These include some of the following: differences in sample handling and storage conditions (including temperature and time), matrix differences, and inter-assay differences and lack of standardization of testosterone assays. Based on these variables, CDRH cannot conclude that the differences in testosterone (T) concentration as measured in samples collected in serum (red top) vs. those collected in NaF-EDTA plasma are due to the anticoagulant (NaF-EDTA) used. Data are not available to resolve this difference”.

CDRH's remaining concerns about the bioanalytical method were as follows:

- Uncertainty remains regarding whether TU converts to T ex vivo, and whether the use of NaF-EDTA plasma as a specimen matrix can resolve this proposed analytical issue.
- Data demonstrating the stability of TU and T in NaF/EDTA plasma compared to TU and T stability in serum is not available. Information regarding suitable specimen collection and handling procedures is not available for serum or NaF-EDTA plasma specimens.
- Adequate and robust data are not yet available to demonstrate that the analytical test methods used to measure T in NaF/EDTA plasma are accurate and reliable. Many analytical tests are subject to matrix effects and may produce different results when different specimen types are used (e.g., serum vs. plasma). The Sponsor has not provided data on their analytical test methods adequate to verify that the test is not under-recovering T in NaF-EDTA plasma specimens. In addition (as discussed in detail in the CDRH consult), in the Sponsor's normal range data, assay matrix effects appear to be present between NaF-EDTA plasma and serum.

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, the final 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 “pivotal” Phase 3 studies (CLAR-09007, CLAR-12011 and CLAR-15012), one long-term extension Phase 3 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 “pivotal” 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 study 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 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 did not meet the pre-defined efficacy criteria or achieved supraphysiological T exposures, the results from CLAR-15012 will be 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 on two repeated morning blood draws and symptoms suggestive of hypogonadism. The mean testosterone concentrations at Screen 1 and Screen 2 were 190.2 and 194.9 ng/dL, respectively in the Oral TU group and 183.9 and 174.4 ng/dL in the Topical Axiron group. 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%) and 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. Primary hypogonadism was the most common hypogonadism type in both treatment groups.

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/m² and 30.9kg/m² 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 the disposition of all subjects in CLAR-15012 with reasons provided for study discontinuation.

Table 2: Overall Subject Disposition by Treatment Group in CLAR-15012.

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

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

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

^a "Other" reasons included: subject had high PSA pre-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 TRT studies.

In Study CLAR-15012, the need for dose titration was based on a subject's total testosterone Cavg determined from serial pharmacokinetic samples obtained over a 24-hour period. According to the Sponsor, using the Cavg 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 1 of 2 dose levels (316 mg or 396 mg bid) or down titrated to 1 of 2 dose levels (158 mg or 198 mg BID). Topical Axiron was dosed as per approved label recommendations.

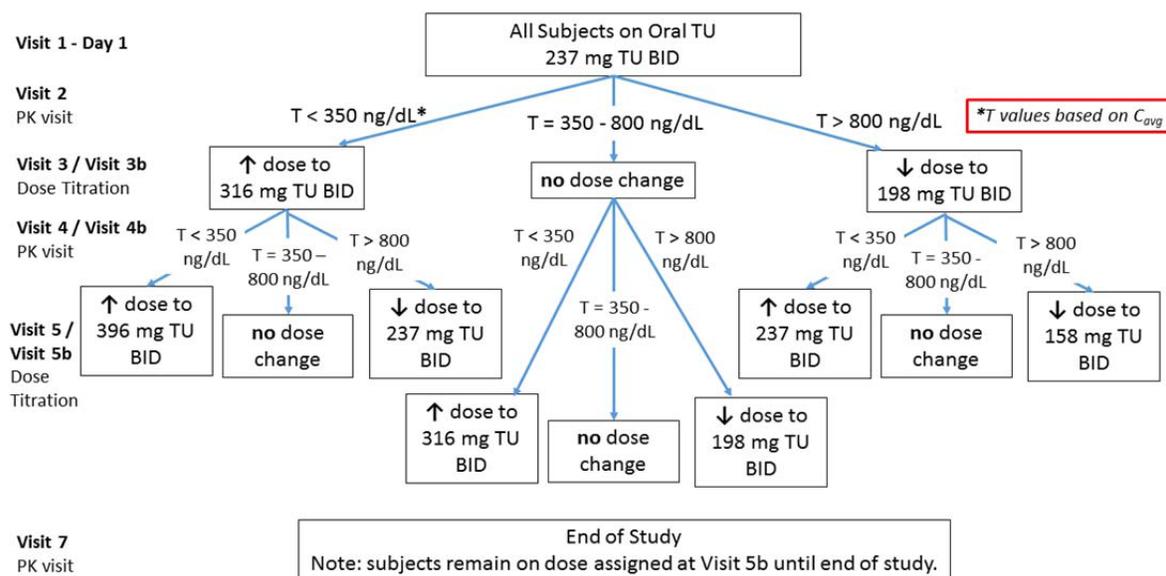
Therefore, in CLAR-15012, the dose and dosing regimen were:

- 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 only (consistent with the Axiron labeling).
- 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 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 Cavg within the normal range after dose titration is complete, and in CLAR-15012, that 24-hour 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 because of a cause not related to the study drug (e.g., the subject moved from study center area). For missing values not attributed to a study drug-related cause, the Visit 7 Cavg was imputed by last observation carried forward (LOCF), and then it was determined whether the Cavg was within the eugonadal range. Success required that at least 75% of subjects' Cavg fell within the eugonadal range, and the lower limit of a 95% CI must not be below 65%.

Due to the novel bioanalytical method conducted in this study, a new testosterone Cavg eugonadal range was required for adult men when their blood was collected in NaF-EDTA tubes. The Sponsor determined this new euogonadal range based on results for Study CLAR-16014. The reader is referred to the Clinical Pharmacology review for the details and conclusions from this study, but to summarize, morning blood samples were collected from 97 healthy young men, and the testosterone concentration was measured from the subjects' plasma from NaF-EDTA 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 NaF-EDTA-related bioanalytical method and the new 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 Cavg 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 Cavg at Visit 7 using the primary efficacy analysis in the modified ITT population. Table 3 also shows the mean Cavg for the treatment groups.

Table 3: Percentage of Subjects Achieving Eugonadal Testosterone Cavg Values at Visit 7 for Primary Analysis (Modified ITT Population)

Testosterone Cav Range, n (%)	FDA Target	Oral T (N=166)	Topical Axiron (N=55)
252 ng/dL \leq Cavg \leq 907 ng/dL	\geq 75%	145 (87.3%)	48 (87.3%)
Lower bound 95% CI	\geq 65%	81.3%	75.5%
Upper bound 95% CI		92.0%	75.5%
Cavg mean(SD) ng/dL		401.2 (140.2)	390.6 (139.9)
95% CI		379.7, 422.7	352.8, 428.5

CI=confidence interval, SD=standard deviation

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_{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_{avg} value for all subjects 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_{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 the new NaF-EDTA bioanalytical method - and included:

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

In the supplemental analysis, the usual C_{max} thresholds (as above) were adjusted for the upper limit of the 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_{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 ≤ 2268 ng/dL, and > 2268 ng/dL. This post hoc analysis was performed to understand how the revised upper limits of normal, based on the novel bioanalytical method might affect the frequency distribution of C_{max} outliers.

For the traditional C_{max} outlier criteria:

- 137 of 151 (90.7%) of Oral TU subjects and 47 of 48 (97.9%) of Topical Axiron subjects had T $C_{max} \leq 1500$ 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 $C_{max} > 1800$ -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 $C_{max} > 2500$ ng/dL at Visit 7;

For the adjusted C_{max} outlier criteria:

- 125 of 151 (82.8%) of Oral TU subjects and 47 of 48 (97.9%) of Topical Axiron subjects had T $C_{max} \leq 1361$ 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 Cmax >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 Cmax >2268 ng/dL at Visit 7;

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

Table 4: Percentage of Subjects with Testosterone Cmax Values in Protocol Specific Ranges

Testosterone Cmax at Visit 7 n (%)	FDA Target	Oral TU (N=151)	Topical Axiron (N=48)
≤1500 ng/dL	≥85%	137 (90.7%)	47 (97.9%)
>1800-2500 ng/dL	≤5%	3 (2.0%)	1 (2.1%)
>2500 ng/dL	0	3 (2.0%)	0

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

Figure 5: Percentage of Subjects with Testosterone Cmax Values in Selected Ranges at Visit 7 Based on Adjusted Cavg Upper Limit

Testosterone Cmax Adjusted at Visit 7 n (%)	FDA Target	Oral TU (N=151)	Topical Axiron (N=48)
≤1361 ng/dL	≥ 85%	125 (82.8%)	47 (97.9%)
>1633-2268 ng/dL	≤5%	5(3.3%)	1 (2.1%)
>2268 ng/dL	0	4 (2.6%)	0

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

The Clinical review team conducted a detailed analysis of the 3 outliers (or 4 outliers, if using the adjusted range value), with Cmax > 2500 ng/dL. For the original 3 patients with Cmax >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 Cmax values were >2500 ng/dL after the AM dose, but their Cmax values were substantially below 2500 ng/dL after the PM dose.
- The increase in the Cmax was not associated with the fat content of the preceding meal.

Based on this evidence, the Clinical team agreed with the Sponsor's conclusion that these 3 outliers were likely spurious and perhaps related to T contamination that may have occurred at the clinical investigative site. Based on the results from the supplemental analysis, one additional Cmax > 2268 ng/dL outlier was identified and a narrative for that subject (Subject (b) (6)) is provided in the medical officer's 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.

In summary, the observed distribution of C_{max} values at Visit 7 for subjects treated with Oral TU was within or close to the targeted distribution that is accepted by FDA for testosterone replacement 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_{max-am}, C_{max-pm}, C_{max24}, T_{max-am}, T_{max-pm}, AUC_{am}, AUC_{pm}, AUC₂₄, C_{avg-am}, C_{avg-pm}, and C_{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

Visit	PK Parameter	Units	Oral TU Subjects				Topical Axiron Subjects			
			N	Mean	SD	CV%	N	Mean	SD	CV%
Visit 7	C _{max-am}	ng/dL	155	773.3	584.03	75.5%				
	C _{max-pm}	ng/dL	151	838.4	368.55	44.0%				
	C _{max24}	ng/dL	151	1008.3	581.04	57.6%	48	664.0	319.23	48.1%
	T _{max-am} ^{a,b}	h	155	3.87 ^a	(0.00, 12.08)		48	4.01 ^{a,b}	(0.00, 24.00)	
	T _{max-pm} ^a	h	151	16.00 ^a	(12.00, 24.02)					
	C _{min-am}	ng/dL	155	141.8	60.78	42.9%				
	C _{min-pm}	ng/dL	151	145.9	56.28	38.6%				
	C _{min24}	ng/dL	151	131.3	53.90	41.1%	48	214.7	88.15	41.1%
	AUC _{am}	ng•h/dL	155	4566.6	2066.16	45.2%				
	AUC _{pm}	ng•h/dL	151	5083.3	1661.32	32.7%				
	AUC ₂₄	ng•h/dL	151	9659.1	3065.20	31.7%	48	9191.6	3152.69	34.3%
	C _{avg-am}	ng/dL	155	379.9	171.92	45.3%				
	C _{avg-pm}	ng/dL	151	424.6	139.23	32.8%				
	C _{avg24} ^c	ng/dL	151	402.5	127.72	31.7%	48	383.0	131.36	34.3%

^a T_{max} values shown are median (range);

^b Axiron T_{max} is relative to the AM dose since Axiron was applied just once daily, in the morning, T_{max-am} and T_{max24} are interchangeable for Axiron

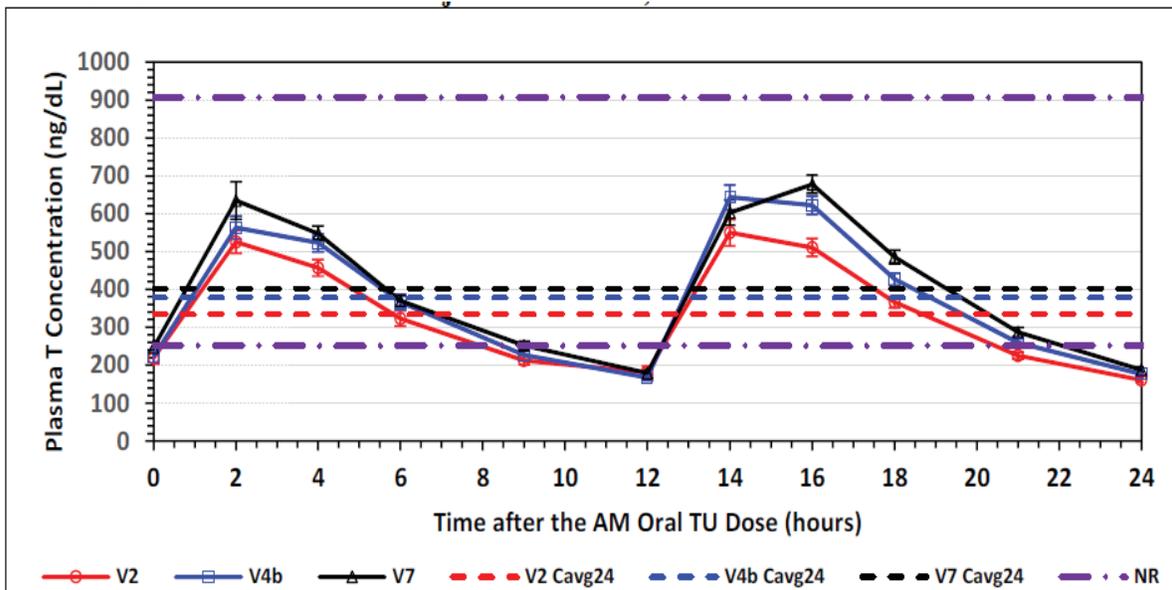
^c C_{avg24} calculated after study completion using actual sample collection times

^d C_{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.

Figure 2: Mean (\pm SEM) Concentration-Time Profile for Total T in Oral-Treated Subjects at Visits 2, 4b, and 7 in CLAR-15012



Source: Appendix 16.5.2, Table 10

Abbreviations: AM = morning; C_{avg24} = time-weighted average plasma concentration morning and evening doses combined; NR = normal range; V2 = Visit 2; V4b = Visit 4b; V7 = Visit 7; SEM = standard error of the mean; T = testosterone; TU = testosterone undecanoate

Error bars indicate SEM

In regard to the T metabolites dihydrotestosterone (DHT) and estradiol (E2):

For DHT, mean peak exposures (C_{max24}) and total exposures (AUC_{24}) for plasma DHT in the Oral TU- and Topical Axiron-treated subjects were very similar between groups at all 3 pharmacokinetic visits. At Visit 7, the DHT C_{max} , AUC , and C_{avg} values were very similar between the Oral TU and Topical Axiron groups. For example, the mean 24-hour DHT C_{avg} values were 73.3 ng/dL and 73.8 ng/dL, for Oral TU and Topical Axiron, respectively, which are both approximately 13% above the upper limit of the normal range for DHT in eugonadal men (65.0 ng/dL). Therefore, the mean DHT/T ratios for the 2 treatments were both above the upper limit of the normal range in eugonadal men, at 0.18 to 0.19, with normal range at 0.04-0.11.

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_{max} , AUC , and C_{avg} values were very similar between the Oral TU and Topical Axiron groups. For example, the mean 24-hour E2 C_{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 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 Cavg 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 78104, 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 78104.

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 Phase 3 pivotal study CLAR-15012 appear to support the Sponsor's contention that Jatenzo (oral TU) provides adequate testosterone replacement in adult men with hypogonadism. However, as noted previously, we will be requiring the Sponsor to further assess the rate and extent of TU to T *ex vivo* conversion during the time course of plasma sample preparation to determine whether T concentration measurements from plasma in NaF/EDTA tubes in CLAR-15012 are accurate and reproducible. If these additional data do not confirm the reliability of the T measurements from this trial, a new Phase 3 trial may be needed.

6. Safety

8.1 SAFETY RESULTS

For this re-submission, the Clinical Safety review focused on the safety results from CLAR-15012, the most recently completed 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-12011, and CLAR-09007 with its extension CLAR-12010, the reader is referred to my previous CDTL memo 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-12011, CLAR-09007 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.
- 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
- 161 hypogonadal adult males who received 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 "pivotal" phase 3 studies. And a total of 86 subjects received treatment for approximately 52 weeks in the Long-Term Extension Study to Study CLAR-09007, referred to as CLAR-12010. Again, the doses and dose regimen in that study were different than 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.

CDTL Comment: In my opinion, if further investigations support the bioanalytical methods used in CLAR-15012 and Oral TU is confirmed to replace T acceptably, then despite the accumulated safety data being just short of ICH E1 guidelines for a new molecular entity, I view this amount of safety data as sufficient to support the indication for testosterone replacement. Additionally, I am not aware of unique risks directly attributable to the presence of TU in the bloodstream.

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 the study.

- Subject (b) (6) 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 dose 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 (b) (6) 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 dose 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. Subject (b) (6) 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 at 2 weeks after dosing had completed: Subject (b) (6) 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 AE reporting definition.

- Subject (b) (6) 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 (b) (6)) but without stent placement. He also has a history of undescended testicle for which he underwent orchiectomy in (b) (6). He had a urologic history of azoospermia diagnosed in (b) (6), infertility diagnosed in (b) (6), and erectile dysfunction diagnosed in (b) (6). His hypogonadism was diagnosed in (b) (6). The Sponsor narrative did not contain information concerning prior TRT. Concomitant medications at the time of the event included metoprolol, simvastatin and omeprazole and simvastatin. On (b) (6) 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 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, October 1, 2016).

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 7):

Table 7: CLAR 15012 Subject (b) (6) Testosterone Concentrations

Visit	Study Day	T Cavg-24hr (ng/dL)	T Cmax (ng/dL)
Visit 2	21	262	587.3
Visit 4b	130	598	1426.9
Visit 7	179	384	778.2

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 their premature discontinuation from the study:

- Subject (b) (6) 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 the 316 mg BID dose 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 (b) (6) 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 the 396 mg BID dose 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 the 316 mg BID dose of Oral TU. Events of moderate dyspepsia on Day 134 and moderate nausea on Day 137 were also reported while he was taking the 396 mg BID

dose of Oral TU dose. Each of these TEAEs was considered related to study drug administration.

- Subject (b) (6) 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 mm Hg. 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 the 237 mg BID dose 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) (6) 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) (6), the Clinical review team conducted an analysis of reported headache AEs in CLAR-15012 and changes in BP in these subjects. 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 appear to have the TEAE of headache in conjunction with small increases from baseline in BP (e.g., Subject (b) (6) [described above] and Subjects (b) (6)). The single Topical Axiron subject who reported a headache AE did not appear to have an 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 plausible.

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 largely driven by the difference in 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 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

While not an SOC, the PT Headache had a notable result: 4.8% Oral TU versus 1.8% Topical Axiron.

CDTL Comment: The relationship between headache and increased BP in CLAR-15012 is not entirely clear, and was discussed in the previous section of this memo.

TEAEs by Preferred Term (PT) reported 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), and all TEAEs reported by at least 1% of subjects and assessed by the investigator as related to treatment.

Table 8: TEAEs Occurring in $\geq 2\%$ in Either Treatment Group in CLAR-15012

System Organ Class Preferred Term,^a n (%)	Oral TU (N = 166)	Topical Axiron (N = 55)
Subjects with any TEAE	78 (47.0)	20 (36.4)
Investigations	23 (13.9)	2 (3.6)
Haematocrit increased	8 (4.8)	0
High-density lipoprotein decreased	5 (3.0)	0
Gastrointestinal Disorders	20 (12.0)	0
Nausea	4 (2.4)	0
Infections and Infestations	16 (9.6)	5 (9.1)
Upper respiratory tract infection	6 (3.6)	0
Nervous system Disorders	12 (7.2)	4 (7.3)
Headache	8 (4.8)	1 (1.8)
Injury, Poisoning and Procedural Complications	6 (3.6)	4 (7.3)
Overdose	1 (0.6)	2 (3.6)
Skin and Subcutaneous Tissue Disorders	5 (3.0)	6 (10.9)
Rash	2 (1.2)	2 (3.6)
Vascular Disorders	6 (3.6)	0
Hypertension	5 (3.0)	0

a=Adverse Events by MedDRA Version 15.1

Source: CLAR-15012 CSR, Table 35 (Snapshot), page 130.

Table 9: TEAEs Considered Drug-Related and Occurring in $\geq 1\%$ of Subjects in Either Group in CLAR-15012

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

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

In regard to the reported 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, and a possible signal for headache that might be associated with increased BP, Oral TU is associated with similar adverse reactions as approved TRT.

8.1.3 Clinical Laboratories, Vital Signs and Electrocardiograms (ECGs)

Clinical Laboratories

In CLAR-15012, comprehensive safety laboratory testing was conducted at baseline, then periodically while on treatment, and again at end-of-treatment. These tests included: biochemistry with liver tests, complete blood count (CBC), serum lipid profiles, and serum 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 biochemistry 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 subsections 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 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 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. The eight (8) cases with clinically significant post-baseline hematocrit values occurred at greater than 120 days 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 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 consistent or slightly greater 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 that 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 is associated with increases in total cholesterol, LDL-cholesterol and triglycerides and decreases in HDL-cholesterol that appear consistent with or slightly worse than 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 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 increases in serum PSA. Oral TU also is associated with increases in serum PSA.

Vital Signs

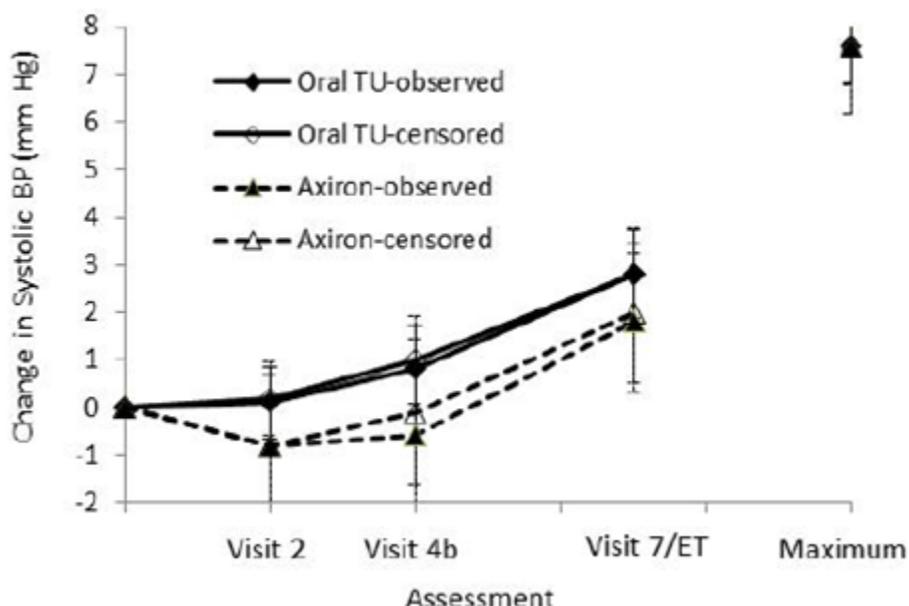
Vital signs, including sitting systolic and diastolic blood pressures (SBP/DBP) by sphygmomanometric cuff and heart rate (HR), were collected in CLAR-15012, and those data were analyzed at Baseline and at all scheduled post-dose visits.

In addition, based on increases from baseline observed in mean cuff BPs in the prior phase 3 study CLAR-12011, ambulatory blood pressure monitoring (ABPM) was requested as an essential component of CLAR-15012 and was conducted by the Sponsor at Baseline and at End-of-Treatment in that study. The CLAR-15012, ABPM data, as collected and analyzed by both the Sponsor and also by our FDA consultants from the Division of Cardiovascular and Renal Products (DCRP) confirm that Jatenzo significantly and clinically meaningfully increases SBP and DBP, but ABPM data for Topical Axiron showed no significant increase.

In CLAR-15012, SBP by cuff increased from baseline to Visit 7/Early Termination in both treatment groups (mean \pm 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 nominally statistically significant for SBP (by cuff) and HR within the Oral TU group only.

Figure 3 provides a graphic representation of mean increase from baseline in SBP in both groups, Oral TU greater than Topical Axiron, with the rise in BP not appearing to plateau at Visit 7.

Figure 3: Mean Change from Baseline (+/- Standard Error) in Systolic Blood Pressure by Treatment Group (Safety Population) in CLAR-15012



Source: CLAR-15012 CSR, Figure 16, page 154

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 6) and were included in the ABPM Population. 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 greater 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 increase 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 (\pm 8.75) mm Hg in the Oral TU group and by 0.18 (\pm 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 difference 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

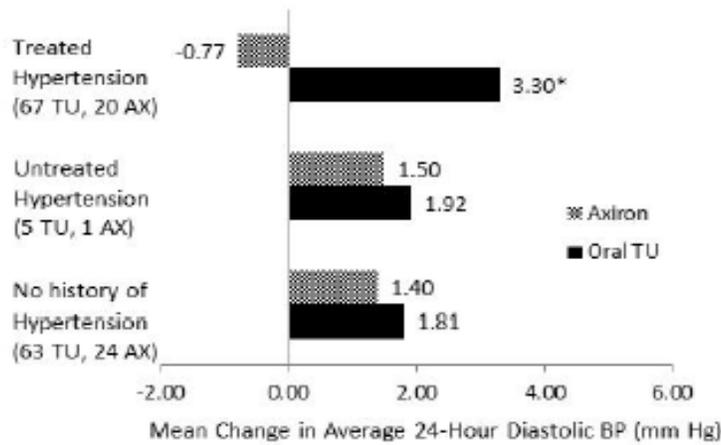
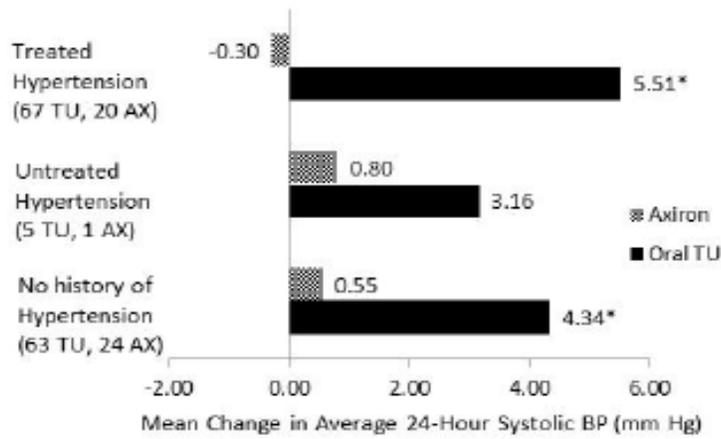
Vital Sign Measurement	Statistic	Oral TU (N = 135)		Topical Axiron (N = 45)	
		Baseline	Change	Baseline	Change
Systolic blood pressure (mm Hg) Daytime average	Mean (SD)	131.13 (10.149)	5.05 (8.855)	131.21 (14.101)	-0.14 (10.534)
	Median	131.50	5.30	131.50	0.60
	p-value ^a		0.008		
Nighttime average	Mean (SD)	120.05 (11.164)	4.72 (11.852)	118.33 (13.102)	0.74 (11.328)
	Median	120.10	3.10	117.50	-0.70
	p-value ^a		0.0209		
24-hour average	Mean (SD)	127.52 (9.747)	4.88 (8.749)	127.03 (13.243)	0.18 (9.384)
	Median	127.80	4.50	128.00	1.00
	p-value ^a		0.0013		
Diastolic blood pressure (mm Hg) Daytime average	Mean (SD)	78.93 (7.819)	2.51 (7.246)	79.94 (8.547)	0.29 (6.6266)
	Median	78.50	2.00	79.30	0.50
	p-value ^a		0.0951		
Nighttime average	Mean (SD)	70.07 (7.779)	2.78 (8.940)	69.40 (8.092)	0.77 (8.108)
	Median	69.60	1.80	69.00	0.50
	p-value ^a		0.1059		
24-hour average	Mean (SD)	76.04 (7.206)	2.56 (6.772)	76.53 (7.910)	0.44 (5.830)
	Median	75.90	1.90	75.80	-0.20
	p-value ^a		0.0653		

^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 graphically represents the mean changes in 24-hour average SBP and DBP in the ABPM population, shown as subpopulations with and without a 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.

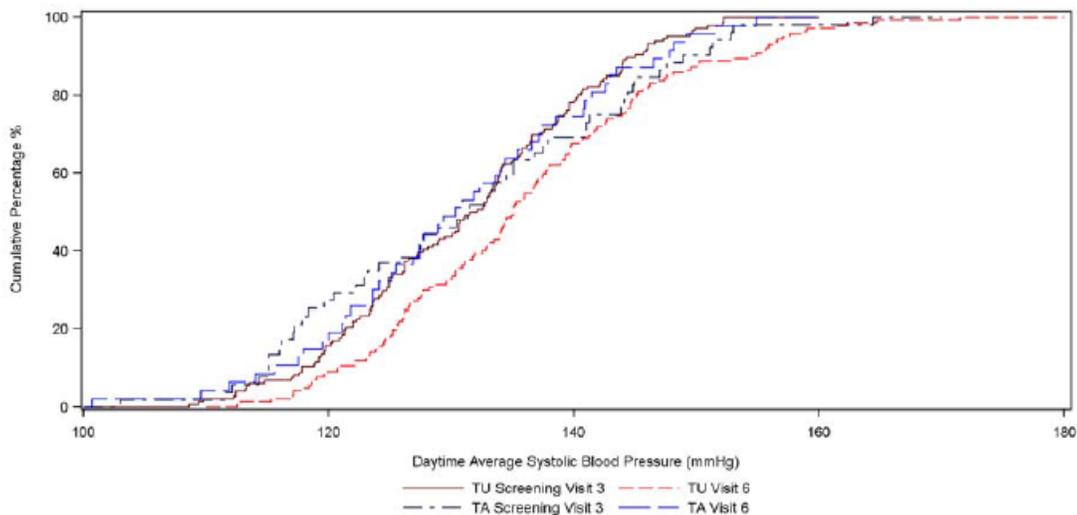
Figure 4: Mean Change from Baseline to Visit 6 in 24-Hour Average Systolic and Diastolic Blood Pressure by Treatment Group and History of Hypertension (ABPM Population)



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 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

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 the vital signs information, including the evidence for increased BP from both cuff and ABPM. The reader is referred to Section 11.6 of this memo for details from 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. They noted that this effect occurred in the setting of a disproportionate escalation of antihypertensive therapy in the Oral TU arm, and that the increase was of a larger magnitude than was seen for the topical comparator. DCRP also mentioned that Oral TU induced increases in HR, and those increases will amplify the clinical impact of the Oral TU-related elevations in BP with respect to the occurrence rate of future CV outcome events.

CDTL Comment: Cuff BP data showed a blood pressure increasing effect for Oral TU that was larger than that seen for Topical Axiron. On ABPM, there was a clear and confirmed, clinically meaningful increase in daytime, nighttime and 24-hour average SBP with Oral TU that was not observed with the concurrent active comparator, Topical Axiron. These findings were consultatively reviewed by DCRP and their analyses and conclusions are described in more detail later in this memo.

ECGs

Electrocardiograms were not performed in CLAR-15012.

8.2 Postmarketing Safety Findings

No marketing applications for Clarus' Oral TU formulation have been submitted to 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 undecanoate 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 60-80 mg titrated to 20-60 mg bid, which is 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 the analysis. Of these studies, 19 were controlled studies and 13 were open-label and uncontrolled studies.

Taking all the information together, the overall AE profile, including laboratory results, for the approved Oral TU product outside of the US, appeared 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 40-80 mg in TU, not T equivalents, which are far lower than doses used in the Jatenzo clinical trials.

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 gastrointestinal adverse events (likely related to the route of administration) and one serious and clinically important finding: a clearly defined, clinically meaningful increase in daytime, nighttime and 24-hour average SBP, 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 change (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, will increase the risk of heart attack, stroke and cardiovascular death in the expected target population, particularly in those already at increased risk of cardiovascular disease.

6. Advisory Committee Meeting

On January 9, 2018, a meeting of the BRUDAC was held to discuss the Jatenzo NDA. This was the second Advisory Committee meeting to discuss Clarus' Oral TU, and this meeting focused primarily on the evidence provided in the Sponsor's re-submission. There was one voting question posed to the committee, as follows:

Question to AC	Voting Result		
	Yes	No	Abstain
Is the overall benefit/risk profile of Jatenzo acceptable to support approval as a testosterone replacement therapy/	9	10	0

The following sections provide a general overview of the meeting discussion as well as the committee’s advice and recommendations to FDA:

Overview of the Committee’s Discussions: The committee expressed substantial concern of safety related to increased blood pressure in men with background cardiovascular disease. Committee members who voted for approval generally believed that the risks associated with increased BP could be mitigated through measures such as REMS, labeling, and required practitioner education. Members who voted “No” were concerned about harm from serious cardiac risks and widespread use of testosterone. Some committee members felt that Jatenzo could be safe and efficacious for younger men with little or no baseline cardiovascular risk and clearly defined causes of hypogonadism.

Prior to the voting question, three Discussion questions were posed by FDA for which the Committee’s discussions are very briefly summarized here:

1. **DISCUSSION QUESTION #1:** Discuss whether the safety of Jatenzo has been adequately characterized. If additional safety data are needed, discuss the type(s) of data that are needed and whether these data should be obtained pre-approval or whether these data can be obtained post-approval. Specifically cover:
 - a. The effects of Jatenzo on cardiovascular risk factors, including blood pressure and lipids, together with effects on hematocrit, and the potential for Jatenzo to increase the risk of adverse cardiovascular outcomes in the population that will likely use the drug, if it is approved.
 - b. Supraphysiologic dihydrotestosterone (DHT) concentrations in some subjects.
 - c. Subjects with maximal testosterone concentrations (C_{max}) exceeding the prespecified targets.
 - d. The adrenal-related findings, including adrenocorticotropin (ACTH) stimulation results.

Committee Discussion: The increased blood pressure in men with baseline cardiovascular risk was a major committee concern, especially as it pertains to the large number of older men who are likely to receive Jatenzo. There was less panelist concern about use in younger patients with primary hypogonadism. The significance of DHT elevations is

unknown. Maximal T concentrations outliers were not a concern. Adrenal effects on animals could be re-assessed in humans in the postmarketing period.

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

Committee Discussion: The panel considered the proposed titration regimen to be reasonable.

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

Committee Discussion: The committee members wanted to see more data to be convinced of the need to measure testosterone levels from blood in NaF/EDTA tubes instead of the more commonly used serum tubes. One committee member also expressed the need to determine serial testosterone levels at multiple time points in serum samples drawn from a sample of individual patients to determine how much and when TU is converted to T in a manner consistent with how samples would be processed in clinical laboratories.

6. 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 testosterone therapy in pediatric patients with permanent forms of hypogonadism. Others in FDA believe that the relevant pediatric population is too small and that given the small target population and complexity of studies that would need to be conducted, that PREA requirements could be waived due to lack of feasibility/practicality. These discussions are ongoing.

CDTL Comment: In regard to PREA requirements, my recommendation at this time is to promptly inform the Sponsor when FDA has reached a final determination.

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 the three sites.

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

“...based on the results of these inspections, the study 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 February 27, 2018, 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: DMEPA should be re-consulted after the NDA is resubmitted to re-review the tradename and to confirm acceptability of the container/carton labeling.

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

In their final memo dated February 16, 2016, Twanda Scales and LaShawn Griffiths of DMPP had the following conclusion

“Due to outstanding clinical deficiencies, DBRUP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant’s patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.”

CDTL Comment: DMPP should be consulted to participate in future labeling discussions that will take place after the NDA is resubmitted.

11.3 Consultation: Office of Prescription Drug Promotion (OPDP)

In her final memo dated February 16, 2018, Jina Kwak of OPDP had the following conclusion

“Due to outstanding deficiencies, DBRUP plans to issue a Complete Response letter. Therefore, OPDP defers comments on the proposed labeling at this time and requests that DBRUP submit a new consult during the subsequent review cycle.”

CDTL Comment: OPDP should be consulted to participate in future labeling discussions that will take place after the NDA is resubmitted.

11.4 Financial Disclosure

In compliance with 21 CFR Part 54, the Sponsor submitted a Final Certification/Disclosure Table listing all investigators who participated in the phase 3 trial CLAR-15012. All investigators had no disclosable information except for (b) (6)

(b) (6) in CLAR-15012. (b) (6) has been paid \$53,900.00 from Clarus for advisory services. Site (b) (6) was active between (b) (6) (first patient visit) and (b) (6) (last patient visit). A total of (b) (6) patients were enrolled at this site. This number represents approximately (b) (6) of the total enrollment in CLAR-15012. (b) (6) (b) (6) enrolled patients at Site (b) (6) were randomized to oral TU (b) (6) oral TU subjects).

CDTL Comment: Any bias at this site, if it were present, would be expected to have quite small 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.

11.5 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 conducted in CLAR-15012 that were intended to assess the clinical meaningfulness of the adrenocortical atrophy and hypoadrenalism observed in dogs in a nonclinical study.

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”.*

CDTL Comment: The Clinical team acknowledges the procedural flaws that occurred as part of the Cosyntropin stimulation testing sub study in CLAR-15012 and agrees that definitive conclusions cannot be drawn from the results. Nevertheless, some of the results in the Cosyntropin stimulation sub study continue to be of concern to us, and the clinical relevance of the nonclinical results still needs to be addressed by human testing. Therefore, I recommend that a robust Cosyntropin stimulation test be required as a postmarketing study.

11.6 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 (± 9.384) 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 \pm SD: Oral TU 2.8 \pm 11.84 mm Hg, Topical Axiron 1.8 \pm 10.76 mm Hg , whereas diastolic blood pressure was essentially*

unchanged at Visit 7/Early Termination”

- *“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. 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 for both of these TU products, 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: The DCRP consult is patently clear in its description of a confirmed and clinically impactful effect of Oral TU on increasing time-averaged daytime, nighttime and 24-hour blood pressure. The same BP effects are not obvious for Topical Axiron. Rather than reiterate the blood pressure-related data here, I will simply express my continued concerns in regard to the effect of sustained increases in BP such as these on increasing the risk of serious cardiovascular events such as myocardial infarction, stroke and cardiovascular death, especially in men with increased baseline cardiovascular risk, per our understanding of discussions with the Division of Epidemiology in the Office of Surveillance and Epidemiology and with DCRP.

11.7 Consultation: Controlled Substances Staff (CSS)

In their final consult review dated March 6, 2018, Joshua Hunt and Dominic Chiapperino offered the following Conclusion and Recommendations:

“Conclusion: Jatenzo contains testosterone undecanoate, a prodrug of testosterone, which is a Schedule III controlled substance as defined under the Anabolic Steroids Control Act (effective 1991)

Recommendations: We have no additional recommendations for Clarus, at this time. It is our (CSS) understanding that all labeling and PMR discussions have been cancelled and this NDA holder will be receiving a second CR letter, on or about March 22, 2018. We do request that the Division (DBRUP) consult CSS again if the NDA is ever re-submitted. We are currently reviewing other testosterone applications and are considering additional class-wide labeling recommendations.”

CDTL Comment: CSS should be consulted to participate in future labeling discussions that will take place after the NDA is resubmitted.

12. Labeling

Based on the Clinical, Clinical Pharmacology and Nonclinical Deficiencies and impending CR action, labeling discussions have been discontinued. Therefore, labeling discussions, including discussions of container/carton labels, should re-commence after the Sponsor resubmits the NDA.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend a Complete Response action for this application based on unresolved Clinical, Clinical Pharmacology and Nonclinical deficiencies.

The specific Clinical, Clinical Pharmacology and Nonclinical deficiencies and the specific Information Needed to Resolve those Deficiencies are shown in Sections 1 (“Introduction/Executive Summary”), 2.3 (“Primary Reviewer’s Recommendation for Approvability”), 4 (Nonclinical Pharmacology/Toxicology) and 5 (“Clinical Pharmacology”) of this memo.

13.2 Risk Benefit Assessment

At this time, based on the Clinical safety issue outlined in the medical officer's final Clinical review and in this CDTL's memo, I conclude that the risk / benefit ratio for Jatenzo (Oral TU) is unfavorable for the indication of testosterone replacement therapy in adult hypogonadal men.

While the efficacy data from CLAR-15012 currently supports the Sponsor's contention that Jatenzo acts to replace testosterone in hypogonadal men, ABPM data from CLR-15012 has unequivocally demonstrated a large (approximately 5 mmHg) and clinically meaningful average increase in daytime, nighttime and 24-hour average SBP. Increases in DBP and MAP are also observed and trend with the increases in SBP. The Oral-TU related increases are larger in men with a history of hypertension, including men with treated hypertension. ABPM identified negligible increases from baseline in BP for the concurrent active comparator, Topical Axiron. The observed Oral TU-related increases resulted in disproportionate increase in initiation of antihypertensive therapy or increase in dose of antihypertensive therapy.

In consultation with our colleagues in DEPI in OSE, and in DCRP, we understand that sustained BP increases of this sort will increase the risk of occurrence of serious cardiovascular events, including heart attacks, strokes and cardiovascular events, in the treated population, especially in men with increased baseline cardiovascular risk.

Taken together, this compelling safety risk information leads me to conclude that the benefits of Jatenzo do not outweigh its risks at this time, as the application currently stands.

In addition, there are NDA deficiencies for two other review disciplines, Nonclinical Pharmacology/Toxicology and Clinical Pharmacology, as elucidated in Sections 1, 4 and 5 of this memo. To reiterate,

- Pharmacology/Toxicology stated that the submitted nonclinical studies were not acceptable to support approval of the NDA through the 505(b)(1) pathway because the Oral TU doses were inadequate to characterize and provide a meaningful and valid evaluation of the chronic effects of Oral TU on male fertility and on carcinogenicity.
- Clinical Pharmacology stated that while the Sponsor took an approach of measuring total T concentrations from plasma in NaF/EDTA tubes instead of measuring T from serum in plain tubes with the intention of preventing the ex vivo conversion of TU to T in the tube, inadequate data was provided to demonstrate the extent that NaF/EDTA tubes actually prevents TU to T ex vivo conversion. 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 not conducted and remains warranted to determine whether T concentration measurements from plasma in NaF/EDTA tubes in CLAR-15012 are accurate and reproducible.

I concur with and I fully support the NDA Deficiencies stated by the Pharmacology/Toxicology and Clinical Pharmacology review teams.

13.2 Recommendation for Postmarketing Risk Management Activities

While the current CR action precludes a determination of formal risk management activities at

this time, as described in Section 1 of this memo, the Clinical review team believes that one pathway that might resolve the current Clinical NDA Deficiency is for the Sponsor to propose robust risk management and labeling strategies, including a Risk Elevation and Mitigation Strategy (REMS) perhaps including elements to assure safe use that would address the increased risk of serious cardiovascular events related to chronically increased BP. The reader is referred to Section 1 of this memo for the team's specific recommendations in this regard. I concur with and I fully support the Clinical recommendations.

13.4 Recommendation for other Postmarketing Study Requirements and Commitments

While the current CR action precludes a determination of formal postmarketing study requirements at this time, Sections 1 and 6 of this memo make mention of future Clinical postmarketing requirements, including:

- A clinical trial evaluating the effect of Jatenzo on adrenal function in humans (e.g., a repeat Cosyntropin stimulation study).
- Possible clinical trial to assess the effect of Jatenzo on major adverse cardiovascular events (MACE).
- Possible clinical trials of efficacy and safety in pediatric patients with permanent forms of hypogonadism, such as Klinefelter's syndrome.

These proposals for PMRs should be kept in mind when the NDA is re-submitted.

13.5 Recommended Additional Comments to Applicant

While there are no additional Clinical comments to the Applicant at this time, there are two comments from Clinical Pharmacology, in consultation with CDRH, as described in Section 5 of this memo, and they are:

- The Sponsor should address the drug-drug interaction potential of TU
- The Sponsor should address the concern that commonly used T immunoassays could cross-react with TU in the blood of patients treated with Jatenzo, causing an overestimation of T concentration values regardless of sample type. The Sponsor should be informed that if they intend to propose the clinical use of the LC-MS/MS assay for use in the assessment of T concentration in men being treated with Jatenzo, then they should submit a proposal for a companion diagnostic.

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/s/

MARK S HIRSCH
03/22/2018

HYLTON V JOFFE
03/22/2018
See my memorandum.



DIVISION DIRECTOR MEMORANDUM

Date: March 22, 2018

From: Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive, and Urologic Products (DBRUP)

Subject: New Drug Application (NDA) 206089 Resubmission for Testosterone Undecanoate Capsules

This memorandum documents my concurrence with the recommendation from the clinical team leader, Dr. Mark Hirsch, that this application receive a Complete Response letter for the reasons detailed in his Cross-Discipline Team Leader (CDTL) memorandum. One of the deficiencies relates to a clinically meaningful increase in blood pressure with this chronically used drug that will increase the risk of major adverse cardiovascular events, including myocardial infarction, stroke, and cardiovascular death. As noted in the memorandum by the Division of Risk Management we have had internal discussions, including discussions with the Risk Evaluation and Mitigation Strategies (REMS) Oversight Committee (ROC) about the possibility of a REMS with elements to assure safe use (ETASU) A, B, and D to mitigate this serious risk and ensure the benefits outweigh the risks. At the ROC, final agreement was not reached on a REMS program that could ensure the benefits of the drug outweigh its risks. The ROC determined that the review team should return there after the application is resubmitted and labeling is available to better frame a proposed REMS. While the clinical team has detailed in their reviews what they would like to include in a REMS program, it is premature to convey to the Applicant specific plans for risk mitigation beyond labeling. Therefore, the Complete Response letter will state:

In your resubmission, propose detailed strategies in labeling (including proposals for a Boxed Warning, Indication, Contraindication, and Warnings and Precautions) and strategies beyond labeling, such as a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use, together with an assessment of how your proposal will mitigate the risks and ensure a favorable benefit/risk profile. We will determine whether your proposed strategies can ensure that the benefits outweigh the risks after a complete review of your resubmission.

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/s/

HYLTON V JOFFE
03/22/2018

CLINICAL REVIEW

Application Type NDA
Application Number 206-089

Priority or Standard Complete Response

Submit Date(s) June 22, 2017
Received Date(s) June 22, 2017
PDUFA Goal Date March 22, 2018

Reviewer Name(s) Roger Wiederhorn MD
Medical Officer, Division of
Bone, Reproductive, and Urologic
Products (DBRUP)

Mark Hirsch MD, Medical Team
Leader, DBRUP

Review Completion Date

Established Name Oral Testosterone Undecanoate
(Proposed) Trade Name Jatenzo Capsules
Therapeutic Class Testosterone
Applicant Clarus Therapeutics Inc.

Formulation(s) Oral soft capsule
Dosing Regimen 200 mg bid and titration

Indication(s)	Primary and secondary male hypogonadism
Intended Population(s)	Adult males

Template Version: March 6, 2009

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	9
1.1	Recommendation on Regulatory Action	9
1.2	Risk Benefit Assessment	10
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies	12
1.4	Recommendations for Postmarket Requirements and Commitments	12
2	INTRODUCTION AND REGULATORY BACKGROUND	12
2.1	Product Information	12
2.2	Tables of Currently Available Treatments for Proposed Indications	15
2.3	Availability of Proposed Active Ingredient in the United States	15
2.4	Important Safety Issues With Consideration to Related Drugs	16
2.5	Summary of Presubmission Regulatory Activity Related to Submission	16
2.6	Other Relevant Background Information	21
2.6.1	Previous CR Deficiencies	21
2.6.2	Major Amendment	22
3	ETHICS AND GOOD CLINICAL PRACTICES	23
3.1	Submission Quality and Integrity	23
3.2	Compliance with Good Clinical Practices	23
3.3	Financial Disclosures	23
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....	24
4.1	Chemistry Manufacturing and Controls (CMC)	24
4.2	Clinical Microbiology	24
4.3	Preclinical Pharmacology/Toxicology	24
4.4	Clinical Pharmacology	25
4.4.1	Mechanism of Action	25
4.4.2	Pharmacodynamics	26
4.4.3	Pharmacokinetics	26
5	SOURCES OF CLINICAL DATA	26
5.1	Tables of Studies/Clinical Trials	26
5.2	Review Strategy	28
1.4	Discussion of Individual Studies/Clinical Trials	28
6	REVIEW OF EFFICACY	28
	Efficacy Summary	28
6.1	Indication	29
6.1.1	Methods	30
6.1.2	Demographics	30
6.1.3	Subject Disposition	31

6.1.4	Analysis of Primary Endpoint(s)	31
6.1.5	Analysis of Secondary Endpoints(s).....	32
6.1.6	Other Endpoints	33
6.1.7	Subpopulations	35
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations.....	36
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects	37
6.1.10	Additional Efficacy Issues/Analyses	37
7	REVIEW OF SAFETY	38
	Safety Summary.....	38
7.1	Methods.....	40
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	40
7.1.2	Categorization of Adverse Events	40
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	40
7.2	Adequacy of Safety Assessments.....	40
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	40
7.2.2	Explorations for Dose Response.....	42
7.2.3	Special Animal and/or In Vitro Testing.....	43
7.2.4	Routine Clinical Testing.....	43
7.2.5	Metabolic, Clearance, and Interaction Workup.....	44
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.....	44
7.3	Major Safety Results	44
7.3.1	Deaths	44
7.3.2	Nonfatal Serious Adverse Events	44
7.3.4	Significant Adverse Events.....	49
7.3.5	Submission Specific Safety Concerns	49
7.4	Supportive Safety Results	69
7.4.1	Common Adverse Events	69
7.4.2	Laboratory Findings.....	71
7.4.3	Vital Signs	73
7.4.4	Electrocardiograms (ECGs).....	73
7.4.5	Special Safety Studies/Clinical Trials	74
7.4.6	Immunogenicity	74
7.5	Other Safety Explorations	74
7.5.1	Dose Dependency for Adverse Events	74
7.5.2	Time Dependency for Adverse Events	74
7.5.3	Drug-Demographic Interactions	75
7.5.4	Drug-Disease Interactions	76
7.5.5	Drug-Drug Interactions.....	76
7.6	Additional Safety Evaluations.....	77
7.6.1	Human Carcinogenicity	77
7.6.2	Human Reproduction and Pregnancy Data.....	77

7.6.3	Pediatrics and Assessment of Effects on Growth	77
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound	77
7.7	Additional Submissions / Safety Issues.....	77
8	POSTMARKET EXPERIENCE	79
9	APPENDICES.....	81
9.1	Literature Review/References	81
9.2	Labeling Recommendations	81
9.3	Advisory Committee Meeting	81
9.4	Individual Trial Review	83
9.4.1	CLAR-15012 (3-month pivotal Phase 3 trial).....	83
	Subject Disposition	94
	Demographics	96
	Protocol Deviations	100
	Efficacy Evaluations	100
	Safety Findings	111

Table of Tables

Table 1 Risk Benefit Dimensions	10
Table 2 Testosterone Undeconoate 198 mg Capsules Unit Composition	22
Table 3: Currently Available Treatment Options for Male Primary Hypogonadism and Hypogonadotropic Hypogonadism.....	23
Table 4 CLAR-15012 Sites for Routine Clinical Inspection.....	31
Table 5 Listing of Completed Studies After the Complete Response Letter	35
Table 6 Percentage of Subjects Achieving Eugonadal Testosterone Cavg Values at Visit 7 for Primary Analysis (MITT Population)	40
Table 7 Summary of Oral TU and Topical Axiron Plasma Dihydrotestosterone Pharmacokinetic Parameters as Visit 7 for all Doses Combined	43
Table 8 Dihydrotestosterone (DHT) Cmax and Cavg Greater Than Upper Limit of Normal (ULN), 2-Fold ULN, 3-Fold ULN and 5-Fold ULN at Visit 7	43
Table 9 Summary of Serum Estradiol Pharmacokinetic Parameters in Oral TU and Topical Axiron-Treated Subjects in Pharmacokinetic Visit 1 and Visit 7	44
Table 10 Estradiol (E2) Cmax and Cavg Greater Than Upper Limit of Normal (ULN), 2-Fold ULN, 3-Fold ULN and 5-Fold ULN at Visit 7.....	45
Table 11 Phase 3 Study CLAR-15012: Duration of Exposure (Safety Analysis Set).....	50
Table 12 Phase 3 Study CLAR-15012: Duration of Exposure by Oral TU Dose (Safety Analysis Set).....	51
Table 13 Phase 3 Study CLAR-15012: Duration Exposure by Topical Axiron Dose (Safety Analysis Set).....	51
Table 14 All Oral TU Studies: Duration of Exposure to Oral TU by Study (Safety Analysis Set)	52
Table 15 CLAR 15012 Subject (b) (6) Lipid Concentrations	56
Table 16 CLAR 15012 Subject (b) (6) Testosterone Concentrations.....	56
Table 17: Headache TEAE and Associated Blood Pressure Determinations.....	58
Table 18 Oral TU subjects Hematocrit Changes by Phase 3 Study (Safety Analysis Set)	59
Table 19 Proportions of Subjects with Clinically Significant (Per Investigator) Post -Baseline Hematology Values by Treatment Group (Safety Population)	60
Table 20 ABPM Patients with Baseline Hypertension, Diabetes or Both.....	71
Table 21 Systolic and Diastolic Blood Pressure Measured by ABPM at Baseline and Visit 6 by Treatment Group (ABPM Population)	74
Table 22 T and DHT Exposure and BP Changes on Day 30 at the Same Fixed Oral TU dose between Study 09007 and Study 12011	76
Table 23 CLAR-15012 Lipid Profile Changes	77
Table 24 Treatment-Emergent Adverse Events Occurring in >=2% in Either Treatment Group (Safety Population).....	81
Table 25 Treatment Emergent Adverse Events Considered Related (by Sponsor) to Study Drug Occurring in >=1% of Subjects in Either Treatment Group (Safety Population)	82
Table 26 Drivers of Gastrointestinal Disorder Adverse Events CLAR-15012 versus CLAR-12011	83

Table 27	Proportions of Subjects with Clinically Significant (Per Investigator Judgment) Post-Baseline Chemistry Values by Treatment Group (Safety Population).....	84
Table 28	Oral TU Subjects with Clinically Significant (Per Investigator Judgment) Post-Baseline Lipid or Liver Test Values (Safety Population)	85
Table 29	BRUDAC Voting Question Result.....	93
Table 30	Number (Percentage of) Subjects in Efficacy Population (n=116) by the Pre-Determined Range of Serum Total Cmax on Day 114 in Study CLAR-12012	100
Table 31	Mean Blood Pressure Changes During CLAR-12011.....	109
Table 32	Schedule of Assessments CLAR-15012 Prior to Amendment 2.0.....	112
Table 33	CLAR-15012 Subject Disposition by Dose at Study Discontinuation.....	122
Table 34	Overall Subject Disposition by Treatment Group (ITT Population).....	123
Table 35	Distribution by Age Category in CLAR-15012 Study Subjects.....	123
Table 36:	Demographics at Baseline CLAR-15012 (ITT Population).....	124
Table 37:	Baseline Characteristics CLAR-15012 (ITT Population)	125
Table 38	CLAR-15012 Treatment Compliance Summary	126
Table 39	CLAR-15012 Data Sets Analyzed (All Randomized Subjects	127
Table 40	Percentage of Subjects Achieving Eugonadal Testosterone Cavg Values at Visit 7 for Primary Analysis (Modified ITT Population)	128
Table 41	Percentage of Subjects with Testosterone Cmax Values in Protocol Specific Safety Endpoints	129
Table 42	T, DHT, DHT/T Ratios in TU Subjects with Cmax >2500 ng/dL at Visit 7	129
Table 43	CLAR 15012 Subject (b)(6) Study PK Parameters	131
Table 44	Subject (b)(6) ABPM Results.....	131
Table 45	Subject (b)(6) Blood Lipids.....	132
Table 46	Summary of Serum Estradiol Parameters at Visit 1 and Visit 7	135
Table 47	Summary of Treatment Compliance (Safety Population) CLAR-15012	137
Table 48	Duration of Exposure by Treatment Group (Safety Population).....	140
Table 49	Duration of Exposure by Oral TU Dose (Oral TU Safety Population)	140
Table 50	Duration of Exposure by Topical Axiron Dose (Safety Population).....	141
Table 51	Treatment Emergent Events in CLAR-15012 (Safety Population)	142
Table 52	TEAEs Occurring in >= 2% of Subjects in Either Treatment Group (Safety Population)	142
Table 53	TEAEs Considered Drug-Related and Occurring in >=1% of Subjects in Either Group	143
Table 54	Oral TU Subjects with Treatment-Emergent Hematocrit Increased (Safety Population)	144
Table 55	Subjects with Treatment-Emergent AE of Hypertension or Blood Pressure Increased (Safety Population).....	146
Table 56	Oral TU Patients with TEAEs of High Density Lipoprotein Decreased (Safety Population)	148
Table 57	CLAR 15012 Subject (b)(6) Lipid Profile.....	151
Table 58	CLAR 15012 Subject (b)(6) Testosterone Concentrations.....	151
Table 59	Mean Change from Baseline to Final Visit/Early Termination in Hematology Values by Treatment Group (Safety Population)	153

Table 60	Shifts in Blood Pressure Classification from Baseline to Final Post-Baseline by Treatment Group (Safety Population)	157
Table 61	Systolic and Diastolic Blood Pressure Measured by ABPM at Baseline and Visit 6 by Treatment Group (ABPM Population)	158
Table 62	Mean Change from Baseline to Visit 7/Early Termination in International Prostate Symptom Score by Treatment Group (Safety Population).....	159
Table 63	Mean Changes of Prostate Specific Antigen (PSA) from Baseline to End of Study/Early Termination by Treatment Group.....	160
Table 64	Maximal Cortisol Concentration (ug/dL) following Cosyntropin Stimulation at Visit 1 and Visit 8 by Treatment Group (Excluding Subject (b) (6))	162

Table of Figures

Figure 1	Mean Change from Baseline (+/_ Standard Error) in Systolic Blood Pressure by Treatment Group (Safety Population)	63
Figure 2	Cumulative Distribution Curves for Systolic Blood Pressure and Visit 7 by Treatment Group (ABPM population).....	64
Figure 3	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)	65
Figure 4	Cumulative Distribution Curves for Systolic Blood Pressure for Visit 7/Early Termination and No Hypertension History	66
Figure 5	Cumulative Distribution Function of Daytime Systolic Blood Pressure at Screening and Visit 6 in Subjects with Exposure Time Less Than or Equal to 138 Days (TU Median) N=65	67
Figure 6	Cumulative Distribution Function of Daytime Systolic Blood Pressure at Screening and Visit 6 in Subjects with TU Exposure Time Greater Than 138 Days, N=70	68
Figure 7	Cumulative Distribution Function of Nighttime Systolic Blood Pressure at Screening and Visit in Subjects with TU Exposure Time Less Than or Equal to 138 Days (TU Median) N=65	69
Figure 8	Cumulative Distribution of Nighttime Systolic Blood Pressure at Screening and Visit 6 in Subjects with TU Exposure Time Greater Than 138 Days (TU Median) N=70.....	70
Figure 9	Mean Change (with Standard Error) From Baseline to Visit 7/Early Termination in Systolic Blood Pressure by Treatment Group.	72
Figure 10	Kaplan-Meier Plot of the Number of Days from Baseline to the First Occurrence of Stage 1 Hypertension (Safety Population)	73
Figure 11	Serum T Concentration-Time Profiles for 4 Subjects C _{max} >2500 ng/dL on Day 112 in Study CLAR-12011	100

Figure 12 Mean Serum DHT Concentrations-Time Profile on Day 114 on CLAR-12011.....	103
Figure 13 Oral Testosterone Undeconoate Titration Scheme.....	115
Figure 14 Testosterone Values for Oral TU Subjects with a T Cmax Value >2500 ng/dL at Visit 7	130
Figure 15 Percentage of Subjects with Testosterone Cmax Values in Selected Ranges at Visit 7 Based on Cavg Upper Limit (Subjects Who Had Testosterone Cmax at Visit 7).....	132
Figure 16 Mean (+/-SEM) Concentrations-Time Profile for Plasma Total Testosterone in the 5 Oral TU dose Groups at Visit 7, After 2 Dose Titration Opportunities	134

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

We recommend that this NDA re-submission receive a **Complete Response (CR)** action.

Jatenzo has been shown to replace testosterone acceptably. However, Jatenzo was also shown to increase BP. Due to the risk of increased BP with Jatenzo, and lacking a formal risk evaluation and mitigation strategy (REMS) program to address the issue, the benefits of Jatenzo do not outweigh the potential risks associated with increased BP in the U.S. adult male population.

To respond to the CR deficiency, the Sponsor should provide a Risk Evaluation and Mitigation Strategy (REMS) that includes the following elements to assure safe use (ETASU):

- Health care professionals who prescribe Jatenzo should formally acknowledge the risk of increased BP due to Jatenzo and should agree to monitor for increases in BP during Jatenzo therapy.
- Patients who are considering treatment with Jatenzo should be informed of the risk of increased BP and should formally acknowledge the risk and their willingness to be monitored for increased BP while on Jatenzo treatment.
- The REMS with ETASU should include:
 - Educational materials for the prescriber that expounds on the risk of increased BP; and in light of that specific risk, the prescriber should carefully consider the decision to treat each patient and should monitor for increased BP.
 - Prescriber training to enhance the success of the educational materials.
 - A patient communication plan to convey the risk and minimize its adverse consequences

Jatenzo labeling should elaborate on the increased BP risk and should instruct prescribers to avoid Jatenzo treatment in men with uncontrolled BP. Labeling should also inform prescribers to consider their patient's overall cardiovascular health, as well as potential clinical benefit in each patient, before deciding to administer Jatenzo to an individual patient, and as treatment is ongoing.

We also recommend the following activities be required in the post-marketing period:

- A clinical study to assess the effect of Jatenzo on major adverse cardiovascular events (MACE).
- A clinical study to assess the response to Cosyntropin in patients treated with Jatenzo.”

1.2 Risk Benefit Assessment

Jatenzo (oral testosterone undecanoate) is proposed for use as replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired)
- Hypogonadotropic hypogonadism (congenital or acquired)

Hypogonadism is a chronic condition requiring lifelong therapy. An oral testosterone replacement formulation would be a convenience benefit to men with the condition.

Based on results from the phase 3 study CLAR-15012, that tested a dose titration regimen of Jatenzo (158 mg, 198 mg, 237 mg, 326 mg or 396 mg bid), Jatenzo provided acceptable replacement levels of testosterone in hypogonadal men.

However, Jatenzo has been shown to increase blood pressure. Ambulatory blood pressure monitoring conducted in CLAR-15012, in 135 Jatenzo subjects and 45 Axiron subjects, demonstrated an average systolic BP increase for oral TU subjects of 5.0 mm Hg versus a -0.1 mm Hg decrease for Axiron subjects. The increase in BP observed in CLAR-15012 is consistent with increases observed in prior Jatenzo studies, and is directly related to treatment with Jatenzo.

An average 5 mmHg increase in systolic BP is a serious safety concern in the adult male U.S. population because such an increase is widely recognized to confer an increased risk of major cardiovascular adverse events (MACE), including myocardial infarction, stroke and cardiovascular death.

Other than the increased blood pressure finding and some mild gastrointestinal complaints, the evidence from human clinical studies generally supports the safety profile of Jatenzo as being consistent with testosterone replacement therapy. For example, there are expected increases in hemoglobin and hematocrit, and some modest effects on serum lipids.

The major Clinical safety concern, therefore, is the increased BP associated with Jatenzo, especially in aging men, and in men with certain comorbid conditions, such as hypertension and diabetes, that appear to further increase Jatenzo-related increase in BP.

Although the Sponsor has recently suggested the possibility of a risk evaluation and mitigation strategy (REMS), currently there is no formal REMS submission.

Based on the increased BP associated with Jatenzo, and currently lacking a REMS for this important safety issue, we find that the benefits of Jatenzo do not outweigh the potential risks associated with increased BP in the U.S. adult male population.

To address this safety concern, the Sponsor should provide a REMS that includes the following elements to assure safe use:

- Health care professionals who prescribe Jatenzo should formally acknowledge the risk of increased BP due to Jatenzo and should agree to monitor for increases in BP during Jatenzo therapy.
- Patients who are considering treatment with Jatenzo should be informed of the risk of increased BP and should formally acknowledge the risk and their willingness to be monitored for increased BP while on Jatenzo treatment.
- The REMS with ETASU should include:
 - Educational materials for the prescriber that expounds on the risk of increased BP; and in light of that specific risk, the prescriber should carefully consider the decision to treat each patient and should monitor for increased BP.
 - Prescriber training to enhance the success of the educational materials.
 - A patient communication plan to convey the risk and minimize its adverse consequences

Jatenzo labeling should:

- Elaborate on the increased BP risk
- Instruct prescribers to avoid Jatenzo treatment in men with uncontrolled BP
- Inform prescribers to consider their patient's overall cardiovascular health, as well as the potential clinical benefit in each patient, before deciding to administer Jatenzo.
- Recommend monitoring of the patient's blood pressure, overall cardiovascular health, and individual clinical benefits while on Jatenzo therapy
- Conduct periodic re-assessment of risks and benefits and overall acceptability of continuing Jatenzo therapy.

Based on the Jatenzo-related increases in BP, we also recommend that a postmarketing clinical study be required to assess the impact of Jatenzo on major adverse cardiovascular events (see the next two sections of this review).

Finally, we note that Jatenzo-related adrenal cortical atrophy involving the zona fasciculata was observed in animals. To assess this potential safety signal, a Cosyntropin stimulation test was conducted in a subset of subjects in CLAR-1512. While the results of this human testing demonstrated abnormal responses in Jatenzo subjects but not in Axiron subjects, the study was small and had multiple procedural and data anomalies that limit conclusions. Therefore, a clinical study to assess the response to Cosyntropin stimulation in patients treated with Jatenzo is recommended and should be conducted in the postmarketing period.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

To address the increased BP safety concern, the Sponsor should provide a Risk Evaluation and Mitigation Strategy (REMS) that includes the following elements to assure safe use:

- Health care professionals who prescribe Jatenzo should formally acknowledge the risk of increased BP due to Jatenzo and should agree to monitor for increases in BP during Jatenzo therapy.
- Patients who are considering treatment with Jatenzo should be informed of the risk of increased BP and should formally acknowledge the risk and their willingness to be monitored for increased BP while on Jatenzo treatment.
- The REMS with ETASU should include:
 - Educational materials for the prescriber that expounds on the risk of increased BP; and in light of that specific risk, the prescriber should carefully consider the decision to treat each patient and should monitor for increased BP.
 - Prescriber training to enhance the success of the educational materials.
 - A patient communication plan to convey the risk and minimize its adverse consequences

Jatenzo labeling should:

- Elaborate on the increased BP risk
- Instruct prescribers to avoid Jatenzo treatment in men with uncontrolled BP
- Inform prescribers to consider their patient's overall cardiovascular health, as well as the potential clinical benefit in each patient, before deciding to administer Jatenzo.
- Recommend monitoring of the patient's blood pressure, overall cardiovascular health, and individual clinical benefits while on Jatenzo therapy
- Conduct periodic re-assessment of risks and benefits and overall acceptability of continuing Jatenzo therapy.

1.4 Recommendations for Postmarket Requirements and Commitments

Based on the Jatenzo-related increases in BP, we recommend that a postmarketing clinical trial required to assess the impact of Jatenzo on major adverse cardiovascular events.

To assess the clinical relevance of the Jatenzo-related adrenal cortical atrophy in animals, we recommend that a postmarketing clinical trial be required to assess the impact of Jatenzo on response to Cosyntropin stimulation.

2 Introduction and Regulatory Background

2.1 Product Information

Testosterone undecanoate capsules, containing 158 mg, 198 mg and 237 mg testosterone

undecanoate, are immediate release soft gelatin capsules. They are manufactured at the commercial manufacturing facilities of (b) (4).

In the initial NDA filing (NDA # 206089, Sequence 0000, submitted on January 3, 2014), the application including just two dosage strengths (158 mg and 237 mg). Since that time, Clarus has added a 198 mg testosterone undecanoate capsule (which is equivalent to 125 mg testosterone). Information for the 158 mg and 237 mg capsules has been reviewed previously, therefore, only the 198 mg capsule is discussed here.

The 198 mg capsules are manufactured (b) (4) for the 158 mg and 237 mg capsules described previously. The 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. One hundred twenty capsules are packaged in 300 cc HDPE bottles with a child resistant closure and induction seal. This container-closure system is identical to that used for the 158 mg and 237 mg testosterone undecanoate capsules.

Table 1 Testosterone Undecanoate 198 mg Capsules Unit Composition

Ingredient	Amount (mg) per 198 mg capsule	Function		
Formulation				
Testosterone Undecanoate	197.88	Active Ingredient		
Oleic Acid NF, EP	(b) (4)	(b) (4)		
Borage Seed Oil				
Butylated Hydroxytoluene NF, EP (BHT)				
Peppermint Oil NF, FCC				
Polyoxyl 40 Hydrogenated Castor Oil NF (Cremophor RH40)				
Total Fill Weight				
Soft Gelatin Capsule Shell:				
(b) (4)			(b) (4)	(b) (4)
Gelatin			(b) (4)	NF
Sorbitol			(b) (4)	(b) (4)
Purified Water USP, EP	(b) (4)	(b) (4)		
Titanium Dioxide USP, EP	(b) (4)	(b) (4)		
Filled Gelatin Capsule Imprinting:				
Red	(b) (4)	Ink		

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

Clinical Review
{Roger Wiederhorn }
{NDA 2016089 }
{Jatenzo: Oral Testosterone Undeconoate}

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2.2 Tables of Currently Available Treatments for Proposed Indications

Currently there 50 approved testosterone products (Orange Book accessed June 8, 2017). Of these 50 testosterone products, 13 are reference listed drugs and 15 are reference standards. The table below illustrates the broad formulation categories.

Table 2: Currently Available Treatment Options for Male Primary Hypogonadism and Hypogonadotropic Hypogonadism

Formulation	Regimen/administration	Advantages	Disadvantages
Injectables, including T undecanoate, T enanthate, and cypionate	Every 2 weeks to every 10 weeks via IM injection depending on formulation (50 mg to 750 mg)	Does not require daily administration.	Requires injections; Peaks and valleys in serum T levels; Pain at injection site; Possible mood swings
T transdermal system	1 or 2 patches daily Dose 5-10 mg over 24h	Does not require injections; pK profile resembles diurnal rhythm	Skin site irritation
T gels/solutions	5-10g T gel containing 50-100 mg T daily	Does not require injection or patch; flexible dosing; ease of application; good skin tolerability	Potential skin transfer to partner or child
17- α -methyl T capsule or tablets	Oral administration daily 10-25 mg	Does not require injection or topical application	Effects on liver and cholesterol
Buccal bioadhesive T tablets	30 mg controlled release buccal tablet bid	Does not require injection or topical application	Gum-related adverse events
Nasal gel	Nasal administration 11 mg tid	Does not require injection or topical application	Three times a day administration
T pellets	4 to 6 200 mg pellets implanted sc	Infrequent dosing schedule	Requires incision to insert; Spontaneous extrusion/infection

Sources: Journal of Clinical Endocrinology and Metabolism 2006: 9(16), pages 1995-2010; Translational Andrology and Urology 2016: 5(6), pages 834-843; Urologic Clinics of North America, 2016, 43 pages 185-193.

2.3 Availability of Proposed Active Ingredient in the United States

There is currently one TU product approved for the US market, TU injection 750 mg/3 ml (*Aveed*). Aveed was approved on March 5, 2014 under NDA 22-219 (by Endo Pharmaceuticals Inc.) for the same indication as Jatenzo. Aveed is approved with a REMS related to acute post-injection reaction; specifically, pulmonary oil microembolism (POME) and anaphylaxis.

2.4 Important Safety Issues With Consideration to Related Drugs

The important, well-known safety issues for the TRT class due to androgenic effects of T and DHT include but are not limited to, the following:

- Hematologic effects: increased hematocrit (Hct) and hemoglobin (Hob), polycythemia, potential for cerebrovascular accident and/or deep venous thrombosis as a result
- Prostate effects: increase prostate volume and PSA, possibly worsening of BPH symptoms
- Possible modest serum lipid effects: decreased HDL-cholesterol

It remains unclear whether testosterone replacement therapy is associated with increased risk of serious cardiovascular events.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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

On March 23, 2009, a Type C Guidance Meeting was held with the Sponsor to discuss data from Phase 2 studies and a 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 concerns related to elevated serum DHT:T concentration ratios observed in Phase 2.

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

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 high DHT concentrations and high DHT/T ratios
- *May 28, 2010*: Division provides comments on the proposed 1-year, Androgel-controlled, Phase 3 study protocol (Study CLAR-09007)
- *August 2, 2010*: Division provides comments on the time for a single serum T concentration sample for use in titrating 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 Phase 3 study protocol (Study CLAR-12011)

NDA was submitted January 3, 2014.

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 on September 18, 2015 to discuss the Oral TU (Rextoro) NDA. The majority of members concluded that efficacy and safety had not been adequately established for this product. The questions posed to the AC were:

- Is there sufficient evidence to conclude that oral testosterone undeconoate 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.

A Complete Response action for NDA 206089 was issued on November 3, 2014.

On April 3, 2015, Clarus submitted a formal Dispute Resolution Request. This request appealed the need to conduct additional clinical investigations to demonstrate the efficacy and safety of oral testosterone undecanoate and the effect of food on T exposure related to oral TU, including possible changes to the dose and dose titration algorithm.

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 additional requested Phase 3 study:

- Sponsor was advised to conduct the proposed food effect study prior to the Phase 3 study.
- The changes to the proposed Phase 3 study design (e. g., lower starting dose, C_{avg} thresholds of 350 and 800 ng/dL for titration, and 24-hour C_{avg} based titrations) suggests, upon internal assessment, the likelihood of achieving the primary efficacy endpoint may be increased.
- The protocol as proposed would exclude patients with “poorly controlled” hypertension. The Sponsor concurred with the Agency’s rationale and recommendation for defining “poorly controlled” baseline blood pressure as $>150/90$ mmHg.
- A well conducted Ambulatory Blood Pressure Monitoring (ABPM) sub study comparing oral testosterone undecanoate to an active comparator, supplemented by rigorous cuff

pressure measurement on all subjects seemed reasonable to the Division. Isolated assessment of systolic blood pressure would be insufficient.

- $T C_{avg}$ 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 to assess the observed nonclinical effect on the adrenal. The Division recommended use of 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 postmarketing safety study for testosterone products, the Sponsor can expect to receive a request to conduct a required post marketing cardiovascular safety trial using oral TU.

Subsequent to the submission of the final protocol for the additional phase 3 study CLAR 15012, the Sponsor submitted several protocol amendments, and the details of these protocol amendments are summarized herein:

Amendment 1.0 (Protocol Version 2.0, April 16, 2016):

- Included subjects were to have signs/symptoms consistent with hypogonadism for testosterone-naïve subjects and a history of signs/symptoms for subjects who had received prior treatment), as well as testosterone levels consistent with hypogonadism
- Subjects on a stable dose of lipid- lowering medication at study entry were to remain on a stable dose throughout the study.
- Modified exclusion criterion regarding concomitant use of medications that could affect testosterone levels, testosterone metabolism or levels of testosterone metabolites.
- Removed exclusion criteria for subjects unwilling or unable to follow dietary guidelines for the study.
- Removed the stipulation that breakfast and dinner meals consumed on outpatient days to needed to contain approximately 20-40 g of fat. Counseling subjects regarding fat content of their diet was no longer needed..
- Modified exclusion criteria regarding screening blood pressure, detailing limits for subjects not on antihypertensive medications, subjects on antihypertensive medications and < 60 years of age, and subjects on antihypertensive medications and > 60 years of age.
- Modified criteria regarding discontinuation of subjects from the study due to elevated blood pressure, and alternatives to discontinuation such as increased antihypertensive medication therapy or additional antihypertension medication therapy.
- Specified that meals provided during 24-PK testing days would contain approximately 15, 30, or 45 g of fat and that subjects were advised to choose the meal that most reflected their usual diet

Amendment 2.0 (submitted to IND 78,104 on July 12, 2016):

In this amendment, Clarus informed the Division that the plasma testosterone (T) assay run by (b) (4) on samples collected in NaF-EDTA has yielded questionable results. The assay was used to measure plasma T in subjects in both the Oral TU and Topical Axiron treatment arms of the study. The Sponsor also informed the Division that at the time the assay problem was identified at the laboratory, 98 of the study subjects had been dose titrated at least once and 10 subjects had been titrated twice. The analysis laboratory was changed. The study protocol was amended to have subjects who completed Visit 3 (e.g., the first titration) return for a repeat Visit 3. These subjects would then progress through the study and repeat any visits that were completed previously. The Addendum 1 to Amendment 2.0 is summarized herein:

- 1.1.1 Initial Visit 3 that was delayed: For subjects who have completed Visit 2 but not Visit 3, Visit 3 was delayed pending the receipt of the assay results from (b) (4). Visit 3 should occur within 21 days of receipt of notification that the titration results are available.
- 1.1.2 Repeat Visit 3: The timing of this visit will be based upon the IRB approval of Amendment 2, IRB approval of the Informed Consent, and notification that dose titration can occur because assay results from (b) (4) are available. The acceptable window for the Repeat Visit 3 is within 21 days of receiving the IRB/ICF approval and dose titration results being available, whichever occurs last.
- 1.1.3 Initial Visit 4 occurring after Amendment 2: For subjects who have not had a Visit 4 prior to Protocol Amendment 2, the new acceptable window for Visit 4 will be from 10 to 21 days from the prior Visit 3 visit date.
- 1.1.4 Repeat Visit 4: For subjects whose dose is not changed at repeat Visit 3, the new acceptable window for Repeat Visit 4 will be from 1 to 21 days from the Repeat Visit 3 visit date. For subject whose dose is changed at repeat Visit 3, the new acceptable window for Repeat Visit 4 will be from 10 to 21 days from the repeat Visit 3 visit date.
- 1.1.5 Initial Visit 5 occurring after Amendment 2: For subjects who have not had a Visit 5 prior to Protocol Amendment 2, the new acceptable window for Visit 4 will be from 10-21 days from the prior Visit 4 visit date.
- 1.1.6 Repeat Visit 5: The window for Repeat Visit 5 will be from 10 days to 21 days from the prior Visit 4 visit date.

With these changes instituted, Clarus chose to continue the protocol. 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.

In a July 19, 2016, correspondence to Clarus, the Division provided the following comments and recommendation on protocol Amendment 2.0: We strongly recommend that you halt your ongoing trial and provide a redlined protocol amendment that addresses our concerns, including an explanation of how you identified the problem and how you determined that the bioanalytical method is no longer appropriate for your Phase 3 trial. Provide:

1. Summary report of your findings regarding the bioanalytical method and laboratory issue for our review, an explanation of how you identified the problem and how you

determined that the bioanalytical methods are no longer appropriate for your Phase 3 trial.

2. A summary report of the protocol revisions with rationale to explain each change.
3. A discussion of whether all subjects who have been participating in the trial meet the testosterone eligibility based upon your new bioanalytical method.
4. Discussion of whether the bioanalytical method problems affect any the other hormonal bioanalytical methods used in the trial.

Clarus chose not to halt the trial.

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

- Changing the testosterone assay while the Phase 3 trial is underway will require in depth analysis once the NDA is received by FDA. Sponsor was asked to consider washing subjects out, confirming that they are hypogonadal on the new assay, then the 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.
- Comments pertaining to the ABPM analyses were offered.

On April 27, 2017, a Pre-NDA meeting was held. The following format issues and requirements were discussed:

- In providing a complete overview of the new efficacy data, the Clinical Summary of Efficacy in Module 2 should include a section that provides a summary of efficacy data from all 3 Phase 3 studies. Module 5 should include a complete Integrated Summary of Efficacy (ISE). The ISE should include a thorough description of new efficacy data followed by a comprehensive analysis of all Phase 3 studies focusing on similarities and differences in the individual study efficacy data and explanation of observed differences.
- Module 2 should include a Summary of Clinical Safety that includes both a section on the new safety data and a section on the safety data from all Phase 3 studies. Module 5 should include a complete Integrated Summary of Safety (ISS) that describes the new safety data in one sections and the entirety of the safety data from safety data from all 3 Phase 3 studies in another section.
- Both the Clinical Summary of Safety and the ISS should contain an analysis and discussion of the impact of food intake, if any, on safety results as should the ISE and Clinical Summary of Efficacy.
- The NDA will contain information to support the new 198 mg dosage strength.

2.6 Other Relevant Background Information

2.6.1 Previous CR Deficiencies

In brief, the previous CR deficiencies consisted of:

- Increases in testosterone undecanoate, testosterone, and dihydrotestosterone (DHT) concentrations were noted as the fat content in meals increased. Endpoint and titration data were all obtained on days when food was chosen from pre-set menus. For this reason, the Sponsor has not shown that the product, as proposed, would lead to reliable and appropriate testosterone and DHT concentrations from one day to the next, as patients will be consuming food without fat restrictions.
- Specific concerns were identified in the open label, non-randomized, four-month, pivotal phase 3 study, CLAR-12011:
 - In the 116 subjects who completed the trial with sufficient data to calculate a 24-hour average total serum testosterone (T-C_{avg}) on Day 114, exactly 75% of subjects had a T-C_{avg} within the normal range. This barely achieves the pre-defined target threshold. However, when other analytical approaches are used that account for the approximately 19% of subjects who did not have sufficient data to calculate T-C_{avg} on Day 114, the primary efficacy results do not reach the target threshold for success.
 - None of the key secondary efficacy endpoints for testosterone C_{max} outliers met the pre-specified success targets for the three C_{max} outlier categories.
 - The starting dose of 200 mg twice daily was too high, resulting in the need to down titrate dose in a majority of subjects. Also, the titration regimen required that serum testosterone concentrations be lower than 250 ng/dL before the dose is increased, preventing some subjects from achieving adequate testosterone replacement. For example, nearly one-fourth of subjects had a T-C_{avg} <300 ng/dL at the primary efficacy endpoint subsequent to all titration.
 - The mean average serum DHT concentration was above the upper limit of normal, and the mean DHT-to-testosterone concentration was twice the upper limit of normal. These data are inconsistent with the goal of testosterone replacement therapy, which is to replace testosterone and its critical metabolites DHT and estradiol, to within the normal range.

The following safety concerns were also identified:

- Supraphysiologic concentrations of the potent androgen, DHT, as well as increased DHT-to-testosterone concentration ratios observed with the product pose an increased risk of serious androgen-related adverse events.
- Very high serum TU (testosterone undecanoate) and DHTU (dihydrotestosterone undecanoate) concentrations were observed with the product and the clinical

ramifications of this finding are unknown. While TU and DHTU appear to have weak affinities for the androgen receptor, at massive exposures they may have effects. TU and DHTU are further metabolized to DHT and to other steroid molecules that may have pharmacologic effects. The role that TU or its metabolites may have played, if any, in the hypocortisolemia and adrenocortical atrophy observed in dogs in the 23-week toxicity study is unknown.

- Significantly decreased sex hormone binding globulin (SHBG) was observed with the product and the clinical ramifications are unknown.
- Clinically meaningful increases in systolic and diastolic blood pressure were observed with the product in Study CLAR-09007, with larger blood pressure increases compared to Androgel 1%. The extent to which these blood pressure differences are explained by differences in exposure to testosterone, TU or other TU metabolites is unclear. Blood pressure was also meaningfully increased in Study CLAR-12011, albeit to a lesser degree than in Study CLAR-09007.
- Clinically meaningful increases in hematocrit were observed with the product in Study CLAR-09007, with larger increases compared to Androgel 1%. Almost 10% of subjects treated with product in Study CLAR-09007 had at least one hematocrit value >54%, a clinically meaningful level. The extent to which the hematocrit differences between the product and Androgel 1% are explained by differences in exposure to testosterone, TU or other TU metabolites is unclear. An increase in hematocrit was also observed with the product in Study CLAR-12011.
- A small number of cardiovascular adverse events were reported with the product in the Phase 3 studies, including events of acute myocardial infarction and stroke. The role played by the product in these events is currently unknown. However, several possible biomarkers of cardiovascular risk, including blood pressure (described above), HDL-cholesterol and high sensitivity C-reactive protein were adversely affected by the product. The extent of worsening of HDL-cholesterol and hs-CRP was greater for the product compared to Androgel 1% in Study CLAR-09007. The extent to which these differences are explained by differences in exposure to testosterone, TU or other TU metabolites is unclear.

2.6.2 Major Amendment

On September 20 and September 25, 2017, the Sponsor submitted NDA amendments related to:

- Additional analysis of ABPM and cuff BP monitoring,
- The effects of longer than planned period of protocol drug exposure upon safety and efficacy
- Measuring T concentration in serum versus in plasma blood samples
- Outliers and shift analysis for blood lipids, hemoglobin and hematocrit
- Analysis of changes in DHT and estradiol

These responses were determined to constitute a major amendment requiring full review. Therefore, the User Fee Goal date was extended to March 22, 2018.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the Clinical related data submitted in this NDA, including the summaries, individual study reports, post-text tables/figures and datasets, were well organized and easy to navigate.

3.2 Compliance with Good Clinical Practices

Three clinical sites from the pivotal phase 3 Study CLAR-15012 (based on the largest clinical enrollments) were selected for a routine inspection by consultation to the Office of Scientific Investigation (OSI), CDER. On January 8, 2018, OSI concluded the study appears to have been conducted adequately, and the data generated by these sites appears acceptable in support of the respective indication.

Table 3: CLAR-15012 Investigative Sites for Routine Clinical Inspection

Site # (Name, Address, Phone number, email, fax #)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Site#109: Urologic Consultants of SE PA, Bala Cynwd, PA	CLAR-15015	30	Testosterone replacement therapy Routine Clinical
Site #104: Alabama Clinical Therapeutics, Birmingham, Ala	CLAR-15015	32	Testosterone replacement therapy Routine Clinical
Site #122: Coastal Clinical Research Inc., Mobile, Ala	CLAR-15015	31	Testosterone replacement therapy Routine Clinical

3.3 Financial Disclosures

The Applicant submitted a Final Certification/Disclosure Table listing all investigators who participated in the CLAR-15012 phase 3 clinical trial. All investigators had no disclosable information except for the following (b) (6)

- (b) (6) for Study CLAR-15012. Since the FDA Complete Response letter (3 November 2014), (b) (6) has been paid \$53,900.00 from Clarus for advisory services. Site (b) (6) has been active between (b) (6) (first patient visit) and (b) (6) (last patient visit). A total of (b) (6) patients were enrolled at this site. 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 (b) (6) oral TU subjects).

Reviewer's Comment: Any bias at this site, if it were present, would be expected to have quite small 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.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

There were no significant CMC issues noted in the first review cycle review. In this review cycle, there were also no significant CMC issues, including the new dosage strength.

4.2 Clinical Microbiology

There are no Clinical Microbiology issues.

4.3 Preclinical Pharmacology/Toxicology

In the first review cycle, in a 13-week subchronic toxicity study in dogs, positive findings 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. Adrenal cortical atrophy was believed to be 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. TU exposure in dogs was only 2 times the worst case exposure in human males.

In this 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 of oral TU, in which the testosterone exposure was approximately 12-fold higher than observed in the Phase 3 clinical trials, reductions in cortisol levels and adrenal changes were again noted. This is believed by the Sponsor to reflect the expected pharmacological effect of supraphysiological levels of testosterone on the adrenal gland

A subsequent 9-month chronic toxicity study was conducted in dogs using 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, there was no histopathological evidence of toxicity in the adrenal

glands nor was TU exposure (average circulating TU concentration on Day 270 was 500 ng/dL) associated with a decrease in circulating levels of cortisol.

***Reviewer's Comment:** For details, the reader is referred to the Pharmacology-Toxicology reviews. The reader is also referred to later sections of this review, as well as to the Endocrinology consult in DARRTS, pertaining to the results of Cosyntropin stimulation testing in human males.*

4.4 Clinical Pharmacology

The Clinical Pharmacology review team focused their review on data from the newly conducted clinical studies, including the new Phase 3 study CLAR-15012.

Clinical Pharmacology considered the new information in order to resolve the prior clinical pharmacology concerns, that included: 1) the potential food effect with Jatenzo, 2) a modified dosing regimen to achieve normal range concentrations with fewer titrations and less overall initial exposure, 3) whether results from a single blood draw could reliably predict the Cavg-based dose titration used in CLAR-15012, 4) a more robust achievement of the prior efficacy endpoint (T Cavg within normal range in at least 75% of subjects), 5) a few T Cmax outliers with the old dosing regimen, and 6) PK results for the metabolites DHT and E2.

In addition, Clinical Pharmacology considered the issue of T bioanalysis in subjects taking Oral TU, especially whether T should be measured as plasma T in NaF-EDTA test tubes or as serum T in plain red top tubes. In this regard, Clinical Pharmacology reviewed information on the stability of TU in test tubes, and the potential of TU to convert to T conversion in test tubes due to plasma esterases.

Except for the test tube-related issue, which appears to require further information and review, all prior concerns were satisfactorily addressed by the Sponsor in this re-submission.

For a detailed and comprehensive discussion, the reader is referred to the final Clinical Pharmacology review of the re-submission.

4.4.1 Mechanism of Action

The active moiety that comes from oral TU for the proposed indication is testosterone (T). T is converted by nonspecific endogenous esterase from TU. In addition, T can be further reduced to another active molecule, dihydrotestosterone (DHT), by 5 α -reductase. Through the same reduction pathway, TU can also be metabolized to dihydrotestosterone undecanoate (DHTU) which can be further converted to DHT. Both T and DHT are potent androgen receptor agonists and can mediate androgenic effects via interaction with intracellular receptors, including normal skeletal and muscle growth and development, maintenance of the male sex organs, function of

the testes, prostate, and seminal vesicle, and secondary sex characteristics (deepening voice, muscular development, facial hair, etc.).

4.4.2 Pharmacodynamics

Pharmacodynamics (PD) were assessed in completed phase 2 and previous phase 3 trials, including exploratory efficacy assessments using the Psychosexual Daily Questionnaire to assess libido and sexual function, and DEXA scanning to assess bone mineral density and body composition. Pharmacodynamic safety evaluations, including CV biomarkers, hematocrit/hemoglobin, prostate assessment and lipid profiles, were also carried out in the Androgel-controlled, phase 3 trial, Study CLAR-09007. Hematocrit and hemoglobin, prostate, and lipid profile assessments were also conducted in some phase 2 trials as well as their all phase 3 trials. See the individual trial review for Study CLAR-12011 and CLAR 15012 in this NDA review and also see the Clinical Pharmacologist's review for details.

4.4.3 Pharmacokinetics

Pharmacokinetics (PK) of oral TU was characterized in hypogonadal males in four Phase 2 and three Phase 3 trials, which has been thoroughly assessed by the Clinical Pharmacology and Clinical review teams. See the Clinical Pharmacologist's review for details. The previous phase 3 efficacy and safety studies (Study CLAR-12011 and Study CLAR-09007) are primarily based upon pharmacokinetic assessments and these studies have already been reviewed by the Clinical Pharmacology and Clinical Review team. The new phase 3 study, CLAR-15012 is reviewed in this document, as well as in the Clinical Pharmacologist's review. See the individual study report reviews for Study CLAR-12011 and CLAR -5012 in the Appendices of this document.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4 Listing of Studies Completed Subsequent to the Complete Response Letter

Study ID	Study Design	Subjects	Dosage	Enrolled	Duration	Remarks
CLAR-15012	PK Phase 3 Open Label Included an Active Comparator	Hypogonadal Males	Oral TU: 158 mg bid 198 mg bid 237 mg bid 316 mg bid	166	Approx. 4 months	

			396 mg bid Axiron: 30 mg T qd 60 mg T qd 90 mg T qd 120 mg T qd	56		
CLAR-15013	PK, Safety Effect of blood collection tubes on T concentrations	Hypogonadal Males	Oral TU: 316 mg single dose	8	Single dose 1 day	
CLAR-16015	PK Food Effect 5 period crossover	Hypogonadal Males	Oral TU: 237 mg bid repeated dose	18	19 days	
CLAR-16014	Bioanalytical to establish eugonadal range for different blood collection tubes	Healthy young men	Not Applicable	97	Not applicable	

Source: CR NDA Submission, 5.2 Tabular Listing of All Clinical Studies
 Table 2 lists all completed studies after the CR letter, in the NDA submission.

For a listing of the studies and clinical trials that were submitted in the original January 3, 2014, NDA, the reader is referred to the October 23, 2014, Clinical NDA review Section 5.1, page 24.

5.2 Review Strategy

The reviewer focused on the efficacy and safety results from CLAR-15102 because those results included robust clinical data intended to address the areas of concern that identified in the first cycle review. The areas of clinical interest included:

- The new Phase 3 trial should show that Jatenzo consistently leads to reliable and appropriate exposures to testosterone and DHT in face of day-to-day variability in meal content.
- The new Phase 3 trial should avoid missing data, especially for the primary efficacy endpoint.
- The new Phase 3 trial should provide additional data concerning the effect of Jatenzo on blood pressure, hematocrit, and serum cholesterol, all possible markers of CV risk.
- The new Phase 3 trial should provide data from a subgroup of subjects who undergo Cosyntropin stimulation testing to assess for adrenal functional abnormalities.

The reviewer also considered the previous phase 2 and phase 3 efficacy and safety data to determine how it compared and contrasted to the data from the new Phase 3 study.

Finally, a repeat-dose toxicity study in dogs was submitted and the will be reviewed by Pharmacology Toxicology. The data from this study will be considered in conjunction with the data collected on adrenal function in the new Phase 3 trial.

1.4 Discussion of Individual Studies/Clinical Trials

This CR submission contained results from one additional Phase 3 study, CLAR-15012. This study and results are discussed in detail in Appendix 9.4.2 of this review.

6 Review of Efficacy

Efficacy Summary

The re-submission contains efficacy and safety results from an additional Phase 3 study (CLAR-15012) to support the proposed indication and in response to the CR action. The trial was designed as open-label, dose titration, PK (efficacy), safety and tolerability study in men with who had a repeated morning serum total T<300 ng/dL and symptoms suggestive of hypogonadism. Restoration of average serum total T to the eugonadal range was the primary outcome, as in all other clinical trials of T products. The key elements of the study were consistent with typical Phase 3 trials for T products.

Demographics in the overall study population reflected men who are overweight/obese: 95.2% for Oral TU versus 92.8% for Topical Axiron subjects. Men over 65 years of age were not eligible for study participation. 52.4% of Oral TU subjects and 46.4% of Topical Axiron subjects had a history of hypertension. Of the Oral TU patients, 77.8% at Baseline were either prehypertensive or class 1 hypertensive, as were 89.3% of the Topical Axiron patients. 37.3% of prehypertensive or class one hypertensive patients in the Oral TU group were not receiving anti-hypertensive treatment versus 25.0% of similar Topical Axiron patients (page 87 of CLAR-15012 CSR). 24.1% of the Oral TU patients and 26.8% of the Topical Axiron patients were type I or Type II diabetic. 36.1% of the Oral TU patients and 33.9% of the Topical Axiron patient were pre-diabetic.

154 of 166 (92.8%) of the randomized Oral TU patients completed the study versus 49 of 56 (87.5%) of the Topical Axiron subjects.

In CLAR-15012, the pre-specified threshold for the primary efficacy (Cavg) was achieved. Two of the three secondary efficacy (also referred to as the Cmax endpoints) were achieved, but the third secondary endpoint (zero subjects with Cmax>2500 ng/dL) was not achieved, but for that specific endpoint, all three of the subject's testosterone values appeared spurious due to T contamination. With re-evaluation of the efficacy results based on a new eugonadal range based upon the Sponsor's plasma collection methodology, primary efficacy was still achieved. With this re-evaluation efficacy, an additional subject was identified with a Cmax>2268 ng/dL for which there was no evidence of contamination to explain the result. In the opinion of the Clinical review team, this finding does not preclude approval and overall, efficacy of Jatenzo was demonstrated in CLAR-15012.

6.1 Indication

The proposed indication for Oral TU (Jatenzo) is for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- **Primary hypogonadism (congenital or acquired):** testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotrophins (follicle-stimulating hormone [FSH, luteinizing hormone [LH] above the normal range.
- **Hypogonadotropic hypogonadism (congenital or acquired):** idiopathic gonadotrophin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.

6.1.1 Methods

The efficacy assessment for Oral TU was based on the analysis of efficacy data from clinical trial CLAR-15012 without any pooling of efficacy data from other efficacy studies because those studies used different doses and different dose titration regimens. In addition, secondary to multiple protocol amendments during the performance of study CLAR-15012, the duration of exposure to Jatenzo in this trials may have been longer than in previous trials.

CLAR-15012 was conducted is in response to a CR action. The reader is referred to Section 2.6 Product Background Information.

6.1.2 Demographics

The demographics and baseline characteristics of the CLAR-15012 study population appear consistent with the proposed target population for the TRT class. See the individual clinical trial review in Appendix 9.4.2 CLAR-15012 Phase 3 Trial.

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 1 and Screen 2 were 190.2 and 194.9 ng/dL, respectively in the Oral TU group and 183.9 and 174.4 ng/dL in the Topical Axiron group. 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%) and 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 4.15 years in the Topical Axiron group. Primary hypogonadism was the most common hypogonadism type in both treatment groups.

Similar proportions of subjects in both treatment groups were categorized at baseline as prediabetic or diabetic (Type I or Type II) [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%). Baseline hypertension classifications based on blood pressures obtained at screening showed greater proportions of subjects in the Oral TU group compared with the Topical Axiron group who were pre-hypertensive (63.9% versus 50.5%) or had Stage 1 hypertension (13.9% versus 8.9%). In addition, among subjects not receiving treatment for hypertension, 72.1% of subjects in the Oral TU group had a baseline hypertension classification of pre-hypertensive or Stage 1 hypertension compared with 43.8% of subjects in the Topical Axiron group.

The mean ages of the study subjects in the Oral TU group was 51.6 years of age and for Topical Axiron was 53.4 years of age. The BMIs for the Oral TU group and the Topical Axiron groups were 31.8 kg/m² and 30.9kg/m² respectively. 80.1% of Oral TU and 75.0 % of Topical Axiron

subjects were white and 17.5 % of Oral TU subjects were black or African American versus 19.6 in the Topical Axiron group.

6.1.3 Subject Disposition

In CLAR-15012, 12 of 166 (7.2%) subjects who received at least one dose of Oral TU discontinued and 7 of 56 (12.5%) of Topical Axiron patients discontinued. 92.8 % of Oral TU subjects and 87.5% of Topical Axiron subjects completed the study. In CLAR-12011, 18.8% of Oral TU subjects discontinued and 19.4% of subjects did not have sufficient PK data to determine average serum total T at the primary endpoint time. In CLAR-15012, discontinuations related to AEs accounted for 2.4% of Oral TU subjects and 1.8% of Topical Axiron subjects. The reader is referred to Appendix 9.4.2 for additional disposition details.

Violations of enrollment criteria were reported for 4 (2.4%) Oral TU subjects including hematocrit value > 48% (2 subjects), inadequate washout of prior testosterone medication (1 subject), and Hb_{A1c} test not performed for a diabetic subject (1 subject). Violations of enrollment criteria were reported for 2 (3.6%) Topical Axiron subjects including participation in the Cosyntropin sub study despite having a pituitary adenoma (1 subject) and enrollment after Amendment 1.0 without documented signs and symptoms suggestive of hypogonadism (1 subject).

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint pre-specified in CLAR-15012 was the standard efficacy endpoint for all T products: $\geq 75\%$ of subjects have serum total T $C_{\text{avg-24hr}}$ within the normal range 300-1000 ng/dL, with a lower bound of the associated 95% CI $\geq 65\%$ on Visit 7.

The pre-specified primary analysis was the primary endpoint in the Efficacy population, which was defined as all subjects who had sufficient PK data of serum total T at the primary endpoint time. For the primary efficacy endpoint, the eugonadal range for testosterone C_{avg} was modified to 252-907 ng/dL for blood collected in NaF-EDTA tubes. Reference to data from other Clarus-sponsored studies supporting this change was included as part of an Amendment to the SAP (submitted 23 November 2016). The reader is referred to Appendix 9.4.2 for further details of this new eugonadal range based on the T bioanalysis methodology.

Table 5 Percentage of Subjects Achieving Eugonadal Testosterone Cavg Values at Visit 7 for Primary Analysis (MITT Population)

Testosterone Cav Range, n (%)	FDA Target	Oral T (N=166)	Topical Axiron (N=55)
252 ng/dL \leq Cavg \leq 907 ng/dL	$\geq 75\%$	145 (87.3%)	48 (87.3%)
Lower bound 95% CI	$\geq 65\%$	81.3%	75.5%
Upper bound 95% CI		92.0%	75.5%

Cavg mean(SD) ng/dL 95% CI		401.2 (140.2) 379.7, 422.7	390.6 (139.9) 352.8, 428.5
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CI=confidence interval, SD=standard deviation
 Source: CLAR-Study 15012 report, Table 15, page 94.

Reviewer’s Comment: The primary efficacy endpoint was achieved.

Secondary efficacy endpoints were Cmax “outliers”; defined as subjects with Cmax >1500 ng/dL, 1500 to 1800 ng/dL, and >2500 ng/dL.

The mean Cavg at Visit 7 for plasma T was 402.5 ng/dL for 151 Oral TU subjects on all doses. The mean Cavg at Visit for plasma T was 383.0 ng/dL for the 48 subjects on all doses of Topical Axiron (Table 22, page 105 of CLAR-15012 CSR).

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints pre-specified in CLAR-15012 were the same as for all efficacy trials of T products; and included C_{max} outliers for serum total T, PK for the metabolites DHT and E2, and measures of FSH and LH. See Appendix 9.4.2.

In CLAR-15012, using the traditional outlier ranges of C_{max} ≤ 1500 ng/dL ≥ 85%, C_{max} > 1800-2500 ng/dL ≤ 5% and C_{max} > 2500 ng/dL, the proportion of subjects with C_{max} above the pre-determined thresholds for C_{max} outlier categories was exceeded only in the C_{max} > 2500 ng/dL category by three patients transiently. In each of these patients, review of the evidence (e.g., DHT/T ratios) suggested inadvertent exposure to Topical Axiron during in-clinic PK. None of these subjects experienced an adverse event secondary to this exposure. See Appendix 9.4.2 for further detail.

The Sponsor also performed a supplemental analysis in which the Cmax boundaries were adjusted for the upper limit of the eugonadal range based on the assay methodology used in the clinical trial; e.g., 907 ng/dL. The adjustment factor was the ratio of 907 ng/dL to the typical eugonadal upper limit (907/1000 = 0.907). Testosterone Cmax over 24 hours was evaluated by estimating the proportions of Oral TU-treated subjects at Visit 7 according to the following categories: <1361 ng/dL (155 x 0.907), >1633 to ≤2268 ng/dL and >2268 ng/dL. In this analysis, one additional outlier was identified, Subject (b) (6). The narrative for this patient is provided in Appendix 9.4.2 under Secondary Endpoints. This subject had two single time point Cmax elevations at Visit 4b and Visit 7 >2268 ng/dL. This patient also had a possible increase in BP on ABPM that was not apparent by cuff BP assessment during the study.

Reviewer’s Comment: Three of the four Cmax > 2500 ng/dL outliers appear to have elevations of T secondary to contamination. We are left with one Cmax > 2500 ng/dL

outlier without any plausible explanation. In light of the fact that the analysis of the other safety secondary endpoints were within the acceptable incidence range based upon typical PK-based efficacy outlier analysis, unless there are other significant safety findings not remediable by labeling, this one outlier subject should not be grounds for not approving Jatenzo, in the opinion of the Clinical review team.

Overall, the efficacy results are improved as compared to the results in CLAR-12011.

6.1.6 Other Endpoints

Mean peak exposures (C_{max24}) and total exposure (AUC₂₄) for plasma DHT in the Oral TU- and Topical Axiron-treated subjects were similar at all 3 pharmacokinetic visits. By the end of the titration period (Visit 7), the DHT C_{max24} values were 117.1 ng/dL and 98.0 ng/dL for Oral TU and Topical Axiron subjects, respectively, and the AUC₂₄ values were 1758 and 1770 ng•h/dL, for Oral TU and Topical Axiron, respectively. The mean 24-hour C_{avg} values were also very similar at 73.25 ng/dL and 73.76 ng/dL, for Oral TU and Topical Axiron, respectively, which is approximately 13% above the upper limit of the normal range for DHT in eugonadal men (65.0 ng/dL). The mean DHT/T ratios for the 2 treatments were both above the upper limit of the normal range at 0.18 to 0.19 (normal range; 0.036-0.114).

Table 6 Summary of Oral TU and Topical Axiron Plasma Dihydrotestosterone Pharmacokinetic Parameters as Visit 7 for all Doses Combined

Visit	PK Parameter	Units	Oral TU, All Doses				Topical Axiron, All Doses			
			N	Mean	SD	CV%	N	Mean	SD	CV%
Visit 1	DHT	ng/dL	164	15.53	8.871	57.1%	54	13.86	5.957	43.0%
	DHT/T	mol ratio	164	0.08240	0.053935	65.5%	54	0.08231	0.067902	82.5%
Visit 7	C _{avg24}	ng/dL	152	73.25	30.088	41.1%	48	73.76	30.858	41.8%
	AUC ₂₄	ng•h/dL	152	1757.9	722.11	41.1%	48	1770.2	740.58	41.8%
	C _{max24}	ng/dL	152	117.1	46.03	39.3%	48	97.97	39.154	40.0%
	T _{max-am} ^{a,b}	h	155	4.00	(0.00, 12.08)		48	4.01	(0.00, 24.00)	
	T _{max-pm} ^a	h	152	16.13	(12.00, 24.13)					
	DHT/T	mol ratio	151	0.1822	0.05138	28.2%	48	0.1941	0.06392	32.9%

Source: Appendix 16.5.2, Table 6

Abbreviations: AM = morning; AUC₂₄ = area under the concentration-time curve morning and evening doses combined; C_{avg24} = time-weighted average plasma concentration morning and evening doses combined; C_{max24} = maximum observed concentration morning and evening doses combined; C_{max-am} = time-weighted average concentration over the daytime dosing interval following the AM dose; C_{max-pm} = time-weighted average concentration over the daytime dosing interval following the PM dose; CV = coefficient of variation; DHT/T = dihydrotestosterone/testosterone ratio; PK = pharmacokinetic; SD = standard deviation; T_{max-am}/T_{max-pm} = time to C_{max-am}/C_{max-pm}; TU = testosterone undecanoate
^a T_{max} values shown are median (range).
^b Topical Axiron T_{max} is relative to the morning dose since it was applied just once daily, in the morning.

Source: CLAR-15012 CSR, snapshot Table 23 page 111

On November 9, 2017, the Sponsor was asked to provide a comparative analysis of DHT concentrations for the two treatment groups (Oral TU and Axiron) in Study CLAR-15012, including the proportion of subjects with DHT C_{max} and C_{avg} levels greater the upper limit of

normal (ULN); greater than 2-fold the ULN; greater than 3-fold the ULN; and greater than 5-fold the ULN. The table below was provided in the Sponsor's November 10, 2017, response:

Table 7 Dihydrotestosterone (DHT) Cmax and Cavg Greater Than Upper Limit of Normal (ULN), 2-Fold ULN, 3-Fold ULN and 5-Fold ULN at Visit 7

		DHT Cmax24		DHT Cavg24	
		Oral TU N=152 n (%)	Axiron N=48 n (%)	Oral TU N=152 n (%)	Axiron N=48 n (%)
>ULN	>65 ng/dl	134 (88.2%)	38 (79.2%)	84 (55.3%)	25 (52.1%)
>2xULN	>130 ng/dl	52 (34.2%)	8 (16.7%)	8 (5.3%)	3 (6.3%)
>3xULN	>195 ng/dl	10 (6.6%)	2 (4.2%)	1(0.7%)	0
>5xULN	>325	0	0	0	0

Source: Snapshot Sponsor's Table 1 in November 10, 2017, IR response Cover Letter

Reviewer's Comment: Oral TU had a higher percentage of Cmax outliers in each outlier category compared to Topical Axiron.

Table 8 Summary of Serum Estradiol Pharmacokinetic Parameters in Oral TU and Topical Axiron-Treated Subjects in Pharmacokinetic Visit 1 and Visit 7

Visit	PK Parameter	Units	Oral TU, All Doses				Topical Axiron, All Doses			
			N	Mean	SD	CV	N	Mean	SD	CV
Visit 1	E ₂	pg/mL	156	17.55	8.635	49.2%	47	17.54	10.308	58.8%
	E ₂ /T	1000-mol ratio	156	9.470	7.350	77.6%	47	9.970	6.5577	65.8%
Visit 7	C _{avg24}	pg/mL	146	32.29	13.873	43.0%	47	33.03	18.302	55.4%
	AUC ₂₄	pg·h/mL	146	774.9	332.95	43.0%	47	792.8	439.24	55.4%
	C _{max24}	pg/mL	146	49.03	20.630	42.1%	47	49.11	25.581	52.1%
	T _{max-am} ^{a,b}	h	153	4.167	(0.00, 12.42)		47.00	12.00	(0, 24.15)	
	T _{max-pm} ^a	h	146	18.02	(12.00, 24.05)					
	E ₂ /T ₂₄ ^c	1000-mol ratio	145	9.042	3.8207	42.3%	47	9.429	4.7717	50.6%
Estradiol Change from Baseline ^d			Oral TU, All Doses				Axiron, All Doses			
Visit 7	Absolute	pg/mL	154	11.01	16.487	149.7%	46	14.84	25.098	169.1%
	Relative	% Baseline	154	149.8	385.00	257.0%	46	165.6	242.85	146.7%
	Ratio	Visit 7/Visit 1	154	2.50	3.85	154.1%	46	2.66	2.43	91.5%

Source: Appendix 16.5.2, Table 8

Abbreviations: AM = morning; AUC₂₄ = area under the concentration-time curve morning and evening doses combined; C_{avg24} = time-weighted average plasma concentration morning and evening doses combined; C_{max24} = maximum observed concentration morning and evening doses combined; C_{max-am} = time-weighted average concentration over the daytime dosing interval following the AM dose; C_{max-pm} = time-weighted average concentration over the daytime dosing interval following the PM dose; CV = coefficient of variation; E₂ = estradiol; E₂/T = estradiol/testosterone ratio; E₂/T₂₄ = estradiol/24-hour testosterone ratio; PK = pharmacokinetic; SD = standard deviation; T_{max-am}/T_{max-pm} = time to C_{max-am}/C_{max-pm}; TU = testosterone undecanoate

^a T_{max} values shown are median (range).

^b Topical Axiron T_{max} is relative to the morning dose since it was applied just once daily, in the morning

^c E₂/T ratio is calculated as the ratio of the respective AUC₂₄ values, adjusted for the difference in molecular weights of testosterone and estradiol. The ratio was multiplied by 1000 for reporting to reduce the number of leading zeros.

^d E₂ change from baseline presented as: absolute change (Visit 7-Visit 1, pg/mL); relative change (100% x [Visit 7-Visit 1]/Visit 1); and as a ratio (Visit 7/Visit 1, no units).

Source: Snapshot Table 23 in CLAR-15012 CSR page 112

Also on November 9, 2017, an Information Request to provide a comparative analysis of estradiol (E2) concentrations for the two treatment groups (Oral TU and Topical Axiron) in Study CLAR-15012, including the proportion of subjects with E2 Cmax and Cavg levels greater the upper limit of normal (ULN); greater than 2-fold the ULN; greater than 3-fold the ULN; and greater than 5-fold the ULN. The table below was provided in the Sponsor’s November 10, 2017, response:

Table 9 Estradiol (E2) Cmax and Cavg Greater Than Upper Limit of Normal (ULN), 2-Fold ULN, 3-Fold ULN and 5-Fold ULN at Visit 7.

ULN Criterion	Concentration	E2 Cmax24		E2 Cavg24	
		Oral TU N=146 n (%)	Axiron N=47 n (%)	Oral TU N=146 n (%)	Axiron N=47 n (%)
>ULN	>30.6 pg/ml	124 {84.9%}	37 {78.7%}	68 {46.6%}	23 {48.9%}
>2xULN	>61.2 pg/ml	33 (22.6%)	11(23.4%)	6 (4.1%)	2 (4.3%)
>3xULN	>91.8 pg/ml	5 (3.4%)	3 (6.4%)	0	1(2.1%)
>5xULN	>153 pg/ml	0	1 (2.1%)	0	0

Source: Sponsor’s Table 2 in November 10, 2017, IR response Cover Letter

Reviewer’s Comment: The percentages of outliers for each estradiol category appear comparable.

Results for FSH and LH appeared consistent with T replacement therapy.

6.1.7 Subpopulations

Other than the evaluation of the primary endpoint by subject weight, no subgroup analyses were performed.

A post hoc analysis of the primary endpoint by weight subgroups (≤ 100 kg and > 100 kg) was performed for both treatment groups. In both the Oral TU and Topical Axiron groups, a slightly higher percentage of subjects who weighed ≤ 100 kg had values in the eugonadal range (89.2%

and 90.3%, respectively) compared with subjects who weighed > 100 kg (85.5% and 83.3%, respectively).

The mean (\pm SD) last dose of study drug was also presented for each treatment group by weight subgroups. In the Oral TU group, the mean (\pm SD) of the last dose of study drug was higher for subjects who weighed > 100 kg [348.9 mg \pm 58.4] compared with those who weighed \leq 100 kg [298.1 \pm 64.5]; however, in the Topical Axiron group, the mean (\pm SD) of the last dose of study drug was comparable between the weight subgroups.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Food Effect:

In the previous review cycle, the Division expressed concern in regard to the effect of food on TU and T exposure. The Sponsor was advised to undertake a new assessment of the effect of food on T exposure using a “timed food effect” method. In subsequent discussions the Division did not object to the Sponsor’s assessment of the food effect issue in the phase 3 Study CLAR-15012. In addition, a new food effect study (CLAR-16015) was conducted. This study and its results are described here in brief.

Study CLAR-16015 was a Phase 2, multicenter, repeat-dose, food-effect study in which subjects were randomized to a sequence of meals that varied primarily in fat content. The study enrolled 18 hypogonadal subjects. The study included up to a 28-day Screening Phase (Screen 1 and Screen 2 visits), a 14-day Run-In Phase, a 6-day PK Phase, and a Safety Follow-Up Phase (phone contact or clinic visit 5 to 7 days after the last the dose of Oral TU). The final commercial softgel capsule was evaluated in this study.

On each of the PK Phase Periods 1 through 5, the subject was dosed immediately prior to the breakfast meal (or for the fasting period, in the morning [AM] with 240 mL of water). There were a total of 4 fed breakfast types, in addition to fasting. Three of the 4 fed breakfast types contained approximately 850 calories (including 15 g fat, 30 g fat, or 45 g fat), and the fourth fed breakfast type was a high-calorie, high-fat meal (approximately 1000 calories, with 50% of the calories from fat) consistent with the Guidance for Industry on Food-Effect Bioavailability and Fed Bioequivalence Studies. The evening (PM) doses of 237 mg TU were taken immediately prior to dinner. All dinners contained 30 g of fat. Notably, the 15 g, 30 g, and 45 g fat meals were meal options that were incorporated into the Phase 3 Study CLAR-15012.

The post-breakfast concentration-time profiles following the 30 g fat, 45 g fat, and high-calorie, high-fat breakfast were similar, and the profile of the 15 g fat breakfast was slightly lower. Since Oral TU should be taken with meals, as indicated on the proposed label, these are the relevant comparisons. Dosing of Oral TU in the fasted state was associated with

lower exposure. The concentration-time profiles for all the post-dinner meals were similar, and there was no food effect on total PM exposure as measured by C_{avg} and AUC.

Pharmacokinetic conclusions for the study included:

- Oral TU should be taken with food, as the proposed labeling will indicate.
- There was no effect on testosterone exposure when comparing the 45 g fat breakfast and FDA high-calorie, high-fat breakfast to the 30 g fat reference breakfast.
- There was a modest effect on testosterone AUC and C_{avg} during the AM dosing interval (AUC_{am} and C_{avg-am} , respectively) for the 15 g fat breakfast compared to the 39 g fat reference breakfast. The reduction in C_{avg} is at most 30%.
- The quantitative impact of the AM dose on exposure did not carry-over into the PM dosing interval, as evidenced by the observed bioequivalence among the fed regimens for AUC.
- For DHT concentrations, there was no food effect present for AM dosing, when Oral TU was administered with food. No food effect was present for 24-hour exposure or for the PM dosing interval.

Reviewer's Comment: The Office of Clinical Pharmacology expressed no further concerns related to food effect, as long as Jatenzo was taken with food. The reader is referred to the Clinical Pharmacologist's review for details.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

CLAR-15012 was planned as a 105-day study, and while some subjects' duration of exposure exceeded 105 days, the short overall duration precludes definitive conclusion about persistence of efficacy or tolerance effects. In Study CLAR-09007, the full PK of serum T and DHT was evaluated during the 12 months of treatment, and in some subjects, serum T and DHT assessments were carried out for 24 months in the extension study CLAR-12011. At least for 12 months, serum T and DHT concentrations appeared stable in the Oral TU group. There were no trends in accumulating or in declining serum total T, free T and DHT concentrations over the course of 12 months.

6.1.10 Additional Efficacy Issues/Analyses

Mean DHT levels were modestly above the upper limit of normal in CLA-15012, lower than those observed in previous Oral TU trials that utilized different doses and dose titration regimens.

7 Review of Safety

Safety Summary

The overall safety database that supports the proposed indication includes 8 clinical trials of Oral TU. The 8th study, CLAR-15012, was intended to address the deficiencies noted in the CR letter. All clinical trials had open-label designs and were conducted in adult men who had repeated total T < 300 ng/dL and signs and symptoms suggestive of hypogonadism.

The mean age of the Oral TU subjects in CLAR-15012 was 51.6 years and the mean BMI was 31.8 kg/m². Of the Oral TU patients, 77.8% at Baseline were either prehypertensive or class 1 hypertensive, as were 89.3% of the Topical Axiron patients. 37.3% of Oral TU prehypertensive or class one hypertensive patients were not receiving anti-hypertensive medications versus 25.0% of similar Topical Axiron patients (page 87 of CLAR-15012 CSR). 24.1% of the Oral TU patients and 26.8% of the Topical Axiron patients were type I or Type II diabetic. 36.1% of the Oral TU patients and 33.9% of the Topical Axiron patient were pre-diabetic.

The safety assessments in the clinical trials included collection of clinical adverse events (AE), routine clinical laboratory tests, vital signs and physical examinations with scheduled and additional unscheduled (as needed) on-treatment visits. The safety monitoring also focused on TRT-related risks, including prostate effects, hematology (Hct/Hgb), lipid profile and cardiovascular events and in Study CLAR-15012, included ambulatory blood pressure monitoring.

154 of 166 (92.8%) randomized Oral TU subjects completed the study versus 49 of 56 (87.5%) Topical Axiron subjects. 2.4% (4) Oral TU subjects and 1.8% (1) Topical Axiron subject discontinued secondary to adverse events (see Section 7.3.3). The mean duration of Oral TU exposure was 139.4 days for Oral TU subjects and 133.8 for Topical Axiron subjects. 166 Oral TU patients received at least one dose of medication while 55 or 56 Topical Axiron subjects received at least one dose of medication.

The dosing regimen for Oral TU in CLAR-15012 started with 237 mg bid with titrations up and down based upon 24 hour T C_{avg} at the two titration opportunities in the protocol. The daily doses ranged from 198 mg bid to 396 mg bid in 5 increments. Topical Axiron was an active comparator and was administered to 55 subjects in a concurrent parallel group with dosing based upon approved FDA labeling. Though not designed as a classical active control study, safety data for Topical Axiron was compared to safety data for Oral TU.

Except for an increase in blood pressure, the AE profile of Oral TU, including clinical laboratory parameters, appears consistent with other T products. Based on comparisons of data between Topical Axiron and Oral TU, some AEs as well as some laboratory and vital sign abnormalities

were more frequent in those who received Oral TU compared to those who received Topical Axiron.

In the oral TU group compared to Axiron, there were larger blood pressure and pulse increases, and modestly larger HDL decreases, and LDL and triglycerides increases. For Oral TU, the blood pressure changes did not appear to be dose-related but there is a suggestion of further increases with duration of treatment. The mean 24hr T Cavg for Oral TU was 402.5 ng/dL versus 383.3 ng/dL for Topical Axiron. The mean 24h DHT Cavg was 73.3 ng/dL for Oral TU and 73.8 ng/dL for Axiron.

Currently, the effect of Jatenzo to increase BP is a serious safety concern that precludes approval without a Risk Mitigation and Evaluation Strategy (REMS). Overall, relative to no effect on BP with Topical Axiron, Jatenzo increased the average systolic blood pressure by about 5 mm Hg and the heart rate by about 2 beats per minute. The average diastolic blood pressure was increased by about 2 mm Hg. In subjected treated for hypertension at baseline, the BP increasing effect was more pronounced. For more details, the reader is referred to Section 7.3.5 of this review, entitled, Submission Specific Safety Concerns.

7.1 Methods

The focus of the primary safety evaluation of Oral TU for this CR are the safety results from CLAR-15012. This trial was performed to address the CR deficiencies cited in **Section 2.6** of this NDA Review.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study CLAR-15012 is the new phase 3 study that is used to re-evaluate the safety of oral TU. The review will refer to safety results from study CLAR-12011 where appropriate. CLAR-12011 was the primary focus of the last review cycle, and for details of that study, the reader is referred to the previous Clinical review. In CLAR-15012, an additional to be marketed drug dose and a new titration scheme was used. For details of CLAR-15012 the reader is referred to the Appendix of this review.

All Phase 2 studies in the NDA used the hard-gelatin capsule formulation that was not demonstrated to be equivalent to the soft gelatin capsule formulation used in the Phase 3 studies. Thus, the Phase 2 studies is not a focus of the safety review. CLAR-12010 and CLAR-09007, long-term 12 months studies, are also not formally reviewed in this NDA review but may be referred to when relevant. These long-term studies used different doses and different titration methods than CLAR-15012. It should also be noted that CLAR-15012 used different analytic T testosterone methodology (collection tubes) and different eugonadal range than previous studies.

7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15.1. This was the same MedDRA version used in the previous review cycle.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

When appropriate, safety data were pooled for analysis as “Phase 3 Studies” and “All Studies” as shown:

- Phase 3 Studies (CLAR-09007, CLAR-12011 and CLAR-15012).
- All Studies

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 10 Phase 3 Study CLAR-15012: Duration of Exposure (Safety Analysis Set)

Duration of Exposure to Treatment	Oral TU (N=166)	Topical Axiron (N=55)
Overall (days)		
Mean(SD)	139.4 (24.8)	133.8 (33.7)
Median	138	141.0

SD=standard deviation source: Clinical Summary of Safety, Table 4, page 26

The overall mean duration of exposure was comparable between treatment groups

Table 11 Phase 3 Study CLAR-15012: Duration of Exposure by Oral TU Dose (Safety Analysis Set)

Duration of exposure to treatment (days)	Oral TU BID Dose (N=166)					
	158 mg	198 mg	237 mg	316	396 mg	overall
Overall	1	4	166	131	69	166
Mean(SD)	39.0 (N/A)	66.3 (33.66)	65.0 (38.09)	71.5 (29.85)	38.7 (11.11)	139.4 (24.87)
Median	39.0	60.0	49.0	70.0	36.0	138.0
Min, Max	39, 39	37, 108	32, 185	6, 149	6, 80	41, 21

Source: CSS, Table 5, page 27

Table 12 Phase 3 Study CLAR-15012: Duration Exposure by Topical Axiron Dose (Safety Analysis Set)

Duration of Exposure to Treatment (Days)	Topical Axiron QD Dose (N=55)				
	30 mg	60 mg	90 mg	120 mg	Overall
Overall					
n	0	55	35	11	55
Mean (SD)	N/A	80.1 (47.07)	72.2 (43.43)	39.1 (15.64)	133.9 (33.56)
Median	N/A	55.0	76.0	36.0	141.0
Min, Max	N/A	19, 177	9, 127	21, 80	19, 184

Source: Clinical Summary of Safety, Table 6, page 27

Reviewer's Comment: The Axiron label calls for a single blood draw for T concentration at 2-8 hours after applying Axiron for at least 14 days at the recommended starting dose of 60 mg. The titration schema is shown in the CLAR-15012 Appendix. CLAR-15012 actually included two single blood draws for T concentration, one at 14 days and one at 56 days after starting T. In our opinion, the Axiron patients were optimally titrated.

Table 13 All Oral TU Studies: Duration of Exposure to Oral TU by Study (Safety Analysis Set)

Duration of Exposure (days) to Treatment by Study	Total Duration of Exposure (Days)				
	N	Mean (SD)	Median	Minimum	Maximum
Phase 2 Studies					
CLAR-07004	12	3.0 (0.00)	3.0	3	3
CLAR-08005	29	26.2 (6.81)	29.0	7	31
CLAR-09008	16	5.0 (0.00)	5.0	5	5
CLAR-09009	15	32.0 (0.00)	32.0	32	32
CLAR-15013	8	1.0 (0.00)	1.0	1	1
CLAR-16015	18	18.8 (0.65)	19.0	17	19
Phase 3 Studies					
CLAR-09007	161	321.7 (99.48)	364.0	4	409
CLAR-12011	144	104.8 (25.30)	113.0	4	126
CLAR-15012	166	139.4 (24.87)	138.0	41	211
Long-Term Extension Study					
CLAR-12010	86	331 (87.75)	364.0	6	405

Source: Clinical Summary of Safety, Table 12, page 32

The study population demographics are discussed in detail in the individual study review for CLAR-15012 (Appendix and

Table 34).

Reviewer's Comment: Among subjects with no prior history of hypertension, larger proportions of Oral TU subjects had baseline BP classifications of pre-hypertensive or Stage 1 hypertension (69.6%) compared with Topical Axiron subjects (46.7%, prehypertensive only). Cuff blood pressures also appear to show at least a 3 mm Hg average difference in baseline means (\pm systolic SD) between Oral TU group (126.9 ± 11.47 mm Hg) and the Topical Axiron group (123.5 ± 13.18 mm Hg).

7.2.2 Explorations for Dose Response

The purpose of this CR NDA submission is to address the following safety concerns noted in the last review cycle for this NDA. These are:

- Supraphysiologic concentrations of the potent androgen, DHT, as well as increased DHT-to-testosterone concentration ratios observed with the product, that may pose an increased risk of serious androgen-related adverse events.
- Very high serum TU (testosterone undecanoate) and DHTU (dihydrotestosterone undeconoate) concentrations with the product and the unknown clinical ramifications of this finding. While TU and DHTU appear to have weak affinities for the androgen receptor, at massive exposures it is possible that they may have clinical effects. TU and DHTU are further metabolized to DHT and to other steroid molecules that may have pharmacologic effects. The role that TU or its metabolites may have played, if any, in the hypocortisolemia and adrenocortical atrophy observed in dogs in the 23-week toxicity study is unknown. TU and DHTU laboratory were not performed in CLAR-15012.
- Significantly decreased sex hormone binding globulin (SHBG) was observed with the product and the clinical ramifications of this finding are unknown.
- Clinically meaningful increases in systolic and diastolic blood pressure were observed with the product in Study CLAR-09007, with larger blood pressure increase compared to Androgel 1%. The extent to which these blood pressure differences are explained by differences in exposure to testosterone, TU or other TU metabolites is unclear. Blood pressure was also meaningfully increased in Study CLAR-12011, albeit to a lesser degree than in Study CLAR-09007.
- Clinically meaningful increases in hematocrit were observed with the product in Study CLAR-09007, with larger increases for Oral TU compared to Androgel 1%. Almost 10% of subjects treated with product in Study CLAR-09007 had at least one hematocrit value >54%, a clinically meaningful level. The extent to which the hematocrit differences between the product and Androgel 1% are explained by differences in exposure to testosterone, TU or other TU metabolites is unclear. An increase in hematocrit was also observed with the product in Study CLAR-12011.
- A small number of cardiovascular adverse events were reported with the product in the Phase 3 studies, including events of acute myocardial infarction and stroke. The role played by the product in these events is currently unknown. However, several possible biomarkers of cardiovascular risk, including blood pressure (described above), HDL-cholesterol and high sensitivity C-reactive protein were adversely affected by the product. The extent of worsening of HDL-cholesterol and hs-CRP was greater for the product compared to Androgel 1% in Study CLAR-09007. The extent to which these differences are explained by differences in exposure to testosterone, TU or other TU metabolites is unclear.

For complete dose response information from previous studies, the reader is referred to the Clinical Review of NDA 206-089 (SND-1) completed October 23, 2014.

7.2.3 Special Animal and/or In Vitro Testing

The reader is referred to Section 4.3 of the Clinical Review of NDA 206-089 completed October 23, 2014, for all studies reviewed during the last review cycle. Since the time of that review, the Sponsor has completed the following additional animal or in vitro testing:

- 9-month toxicology study in male dogs
- Battery of genotoxicity tests
- 6-month carcinogenicity study in Tg.rasH2 male mice (with a 28-day dose range finding study in male CByB6F1 mice)
- Male fertility study in rats
- In vitro binding on steroid receptors (10uM) study

7.2.4 Routine Clinical Testing

Safety assessments during the CLAR-15012 included clinical AE monitoring, clinical laboratory tests, vital signs including ABPM, physical examinations and prostate evaluation. The assessments occurred during periodic study site visits and also were based upon subject self-reporting for AEs.

7.2.5 Metabolic, Clearance, and Interaction Workup

There are no issues regarding metabolism, clearance and drug interactions of Oral TU.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The following are clinical AEs typically reported for the T class and these were evaluated as part of routine safety monitoring during CLAR-15012, including clinical AE monitoring and related clinical laboratory testing. See 7.4.2 Laboratory Findings of this review for detailed assessment of these AEs:

- Polycythemia and increase hematocrit/hemoglobin
- Prostate effects (including increased PSA, increased prostate volume and worsening BPH symptoms [IPSS]).
- Lipid profile changes (particularly decreased HDL)

Based on a signal of increased BP in previous Oral TU studies, ABPM was conducted in CLAR-15012. In addition, evidence for cardiovascular risk was evaluated by all relevant safety parameters in all studies.

Finally, a nonclinical study showing oral-TU related adrenocortical atrophy and adrenal insufficiency in dogs prompted human Cosyntropin testing in CLAR-15012.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in CLAR-15012.

7.3.2 Nonfatal Serious Adverse Events

Two subjects in the Oral TU group experienced serious treatment-emergent adverse events (TEAEs) during the study.

- Subject (b) (6) 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 dose 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 (Days 92 to 105; the event was noted as resolved on Day 92, study drug was restarted, and the subject completed the study.
- Subject (b) (6) 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 dose 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.

One subject in the Topical Axiron group experienced a serious AE prior to dosing. Subject (b) (6) experienced a serious AE of perforated appendicitis 13 days prior to randomization in the study (Listing 16.2.7.2). The event was considered severe in intensity and required hospitalization.

Reviewer's Comment: These SAEs appear unrelated to the study drug.

There is one additional serious AE experienced 2 weeks after dosing had completed, as follows:

Subject (b) (6) experienced a myocardial infarction 2 weeks after receiving his last dose of Oral TU. This is a time period longer than the 7-day follow-up after study completion per the protocol definition of an AE; however, the patient was on oral TU from (b) (6), until (b) (6) (179 days), which is somewhat longer than the original planned TU exposure period. A narrative for this patient is provided herein:

- Subject (b) (6) 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 (b) (6) but without stent placement. He also has a history of undescended testicle for which he underwent orchiectomy in 1962. He has a urologic history of azoospermia diagnosed in 1994, infertility diagnosed in 1995, and erectile dysfunction diagnosed in 2005. His hypogonadism was diagnosed in 2014. The narrative does not contain any information of previous testosterone replacement therapy. Concomitant medications at the time of the event included metoprolol, simvastatin and omeprazole and simvastatin. On (b) (6), 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's hematocrit 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 the Hct was 44.8%. At Visit 7, on study day 180 the Hct was 46.2%. The subject's blood pressures were 138/84 at Visit 1, 142/82 at Visit 4 (study day 21), 136/83 at Visit 4 (study day 57), 137/83 at Visit 4b (study day 130) and 138/80 at Visit 7 (study day 179, October 1, 2016).

The subject's serum lipid concentrations are shown in Table 15 below.

Table 14 CLAR 15012 Subject (b) (6) Lipid Concentrations

Visit	Study Day	HDL (mmol/L) [1-1.5 nl range]	LDL (mmol/L) [0-2.6 nl range]	Triglyceride (mmol/L) [0.168 nl range]
Screening Visit 2	-8	0.9	2.6	1.90
Visit 4	57	0.7	2.6	1.48
Visit 4b	130	0.7	3.1	2.24
Visit 7	179	0.8	3.8	2.29

Source: Unlabeled Table in SDN 34

The subject's two serum testosterone levels collected during screening were 142 ng/dL (Day-16) and 83 ng/dL (Day 83). The Visit 1 predose plasma testosterone level was 112 ng/dL. During the study, the subject's testosterone levels were (shown in Table 16):

Table 15 CLAR 15012 Subject (b) (4) Testosterone Concentrations

Visit	Study Day	T Cavg-24hr (ng/dL)	T Cmax (ng/dL)
Visit 2	21	262	587.3
Visit 4b	130	598	1426.9
Visit 7	179	384	778.2

Source: Unlabeled Table in SDN 34

Reviewer's Comment: The subject had hyperlipidemia on simvastatin at baseline, making it difficult to interpret his serum lipids while on study. The subject also had baseline hypertension, but there were no unfavorable blood pressure changes during the study. Due to protocol amendments, this subject's exposure to Oral TU was 179 days compared to the original expected exposure of 105 days. Definitive conclusions about drug causality and the serious AE are precluded by the subject's background medical condition and timing of the event. The case is confounded by past medical history.

7.3.3 Dropouts and/or Discontinuations

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

- Subject (b) (6) 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 the 316 mg BID dose 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 (b) (6) 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 the 396 mg BID dose 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, but the subject was withdrawn from the study (last dose received 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 the 316 mg BID dose of Oral TU. Events of moderate dyspepsia on Day 134 and moderate nausea on Day 137 were also reported while he was taking the 396 mg BID dose of Oral TU dose. Each of these TEAEs was considered related to study drug administration.
- Subject (b) (6) was a 44-year-old White male who was prematurely discontinued from the study due to headache. At screening, Day -16, the average blood pressure was 133/86 mm Hg. The subject's blood pressures 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

Clinical Review

{Roger Wiederhorn }

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headache AE began on Day 3 while the subject was receiving the 237 mg BID dose of Oral TU. The event was considered mild in intensity, definitely related to study drug, and required no treatment. The subject was withdrawn from the study (last dose received on Day 81); the event was noted as ongoing.

- One additional Oral TU subject ((b) (6)) 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 pharmacokinetic sampling 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.

Reviewer's Comment: In each of the two cases of premature study withdrawal for an AE of headache, modest increases in blood pressure were noted. In Subject (b) (6), while he was hypertensive at baseline, there was no appreciable increase in the blood pressure during the course of the study (see Table 17 below).

At total of 8 Oral TU subjects and 1 Topical Axiron subject reported the AE of headache (Listing 16.2.7.1). None were classified as serious adverse events. Four Oral TU subjects appear to have the TEAE of headache in conjunction with increases from baseline in blood pressure (Subject (b) (6) [described above] and Subjects (b) (6)). The single Topical Axiron subject who reported a headache AE did not appear to have an increase in blood pressure while on treatment. Table 17 below summarizes the subjects' blood pressures around the time that the headache AE was reported:

Table 16: Subjects Reporting a Headache TEAE and their BP Determinations Around the Time of Reporting the Headache AE

Subject ID	Event Start/End Date	Oral TU Dose	Action Taken	Baseline BP/Date	BP Prior to Event/Date	BP Post Event/Date
(b) (6)		316 mg	Drug Interrupted	106/61	103/62	111/61 (b) (6)
		396 mg	Drug Withdrawn	128/95	152/96	160/84 (b) (6)
		316 mg	No Action	126/78	Baseline	149/94 (b) (6)
		237 mg	No Action	127/74	136/71	141/74 (b) (6)
		316 mg	No Action	129/87	125/81	120/79 (b) (6)
		237 mg	Drug Withdrawn	119/86	119/86	125/80 (b) (6)
		237 mg	No Action	137/88	131/88	139/88 (b) (6)
		316 mg	No Action	117/70	136/93	127/83 (b) (6)
		60 mg Axiron	No Action	137/75	137/75	114/68 (b) (6)

BP=Blood Pressure Systolic/Diastolic in mm Hg; the blood pressures listed are the third determinations at each date listed for visits immediately before and after the occurrence of headache.

Source: Adam ADVS dataset.

7.3.4 Significant Adverse Events

Subject ((b) (6)), who has been described previously, experienced a myocardial infarction 2 weeks after receiving his last dose of Oral TU. This is a time period longer than the 7-day follow-up after study completion per protocol; however, the patient the patient was on oral TU from (b) (6) (179 days), which is somewhat longer than the original planned TU exposure period. A narrative for this patient has been provided and is reiterated ... in the CLAR-15012 study summary in the Appendix of this review. The patient started the protocol with a low HDL which did not appreciably rise during the course of the study. There were modest increases in LDL, triglycerides (which were elevated upon enrollment) and hematocrit. He had a past medical history of coronary artery disease and hyperlipidemia.

7.3.5 Submission Specific Safety Concerns

Polycythemia and increase hematocrit/hemoglobin:

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 exposure to study drug, six of the hematocrit values at or near the time of onset ranged from 54.3% to 57.8%. Three of the subjects had hematocrit values at Visit 1 that were > 48% (49.6% for Subjects (b) (6) and 48.1% for Subject (b) (6); 2 of these subjects also had elevated hematocrit values noted at screening, but were ≤ 48% based on repeat testing). The Oral TU dose at the time of the event was 198 mg BID for 1 subject, 237 mg BID for 3 subjects, 316 mg BID for 3 subjects, and 396 mg BID for 1 subject. For 1 of the subjects ((b) (6)), the site recorded that a concomitant procedure was performed (at Visit 6), which was obtaining a repeat hematocrit value, and the repeat value was < 54% (52.6%). The Visit 7 hematocrit for this subject was 54.5%. The remaining subjects required no treatment. The events resolved in 2 of the 8 subjects, with the outcome for the remaining events noted as ongoing. Each of the TEAEs events of hematocrit increased was considered mild in intensity and half were considered related to study drug. None of these events led to premature discontinuation of study drug.

Table 17 Oral TU Subjects' Mean Hematocrit Changes by Phase 3 Study (Safety Analysis Set)

Visit	CLAR-09007	CLAR-12011	CLAR-15012
Baseline Hematocrit	44.1%	45.0%	44.5%
Post Baseline Day	Day 114	Day 114	Day 105
	46.2%	48.4%	47.4%

Source: ISS, Table P3 2.2.9 page 1325

Table 18 Proportions of Subjects with Clinically Significant (Per Investigator) Post -Baseline Hematology Values by Treatment Group (Safety Population)

Parameter: Assessment, n (%)	Oral TU (N=166)	Topical Axiron (N=54)
Hematocrit:		
At least 1 post-baseline value >54%	8 (4.8)	0
More than 1 post-baseline value >54%	3 (1.8)	0
Hemoglobin: Abnormal, Clinically Significant	1 (0.6)	1 (1.9)

Source: CLAR-15012 CSR: Table 42 page 145.

Reviewer's Comment: The planned exposure to trial subjects was 105 days. This exposure was lengthened by approximately 1-2 months to account for protocol amendments. The extended treatment duration may have allowed time for accrual of more AEs of hematocrit increased. There was not a significant difference in frequency of increased hematocrit AEs between the phase 3 studies CLAR-12011 and CLAR-15012.

Prostate effects (including increased PSA, increased prostate volume and worsening BPH symptoms [IPSS]):

- Changes in the IPPS from baseline to Visit 7/Early termination were +1.1 points (SD 5.40) for Oral TU subjects and +1.7 points (SD 4.53) for Topical Axiron subjects. Changes in the IPSS for pooled Phase 3 data was also an increase of +1.1 points. Changes in serum PSA (in ng/mL) from baseline to Visit 7/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 nodularity, enlargement, or irregularity. No patient experienced urinary retention. 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.
- Subject (b) (6) had a PSA value of 0.73 ng/mL at baseline that rose to 2.86 ng/mL at Day 160; the event was considered moderate and probably not related to study drug. A follow-up value obtained approximately 2 weeks later was 1.23 ng/mL.

Reviewers Comment: Modest changes in IPSS, PSA are expected with TRT. These results do not raise a new safety concern.

Increased blood pressure, including hypertension, and peripheral edema:

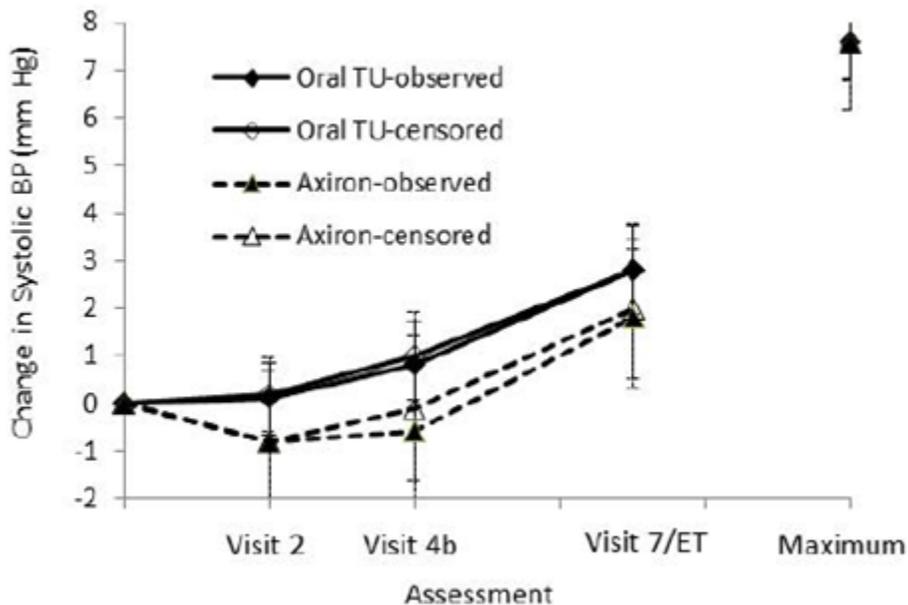
The Sponsor states that at baseline, using cuff BP measurements, there was a > 3 mm Hg mean difference systolic blood pressure (SBP) between the Oral TU group (126.9 ± 11.5 mm Hg) and the Topical Axiron group (123.5 ± 13.2 mm Hg). By cuff BP measurement, SBP increased from

baseline to Visit 7/Early Termination in both treatment groups (mean \pm SD: Oral TU 2.8 ± 11.8 mm Hg, Topical Axiron 1.8 ± 10.8 mm Hg), whereas diastolic blood pressure (DBP) was essentially unchanged at Visit 7/Early Termination. Censoring measurements collected after addition of, or an increase in dosage of, antihypertensive medications had little effect on estimates of mean change.

Reviewer's Comment: The above blood pressure findings relate to cuff pressure determinations. Data from ABPM measurements are shown later in this same section.

Figure 1 provides a graphic representation of mean increase from baseline in SBP in both groups, Oral TU greater than Topical Axiron.

Figure 1 Mean Change from Baseline (+/_ Standard Error) in Systolic Blood Pressure by Treatment Group (Safety Population)

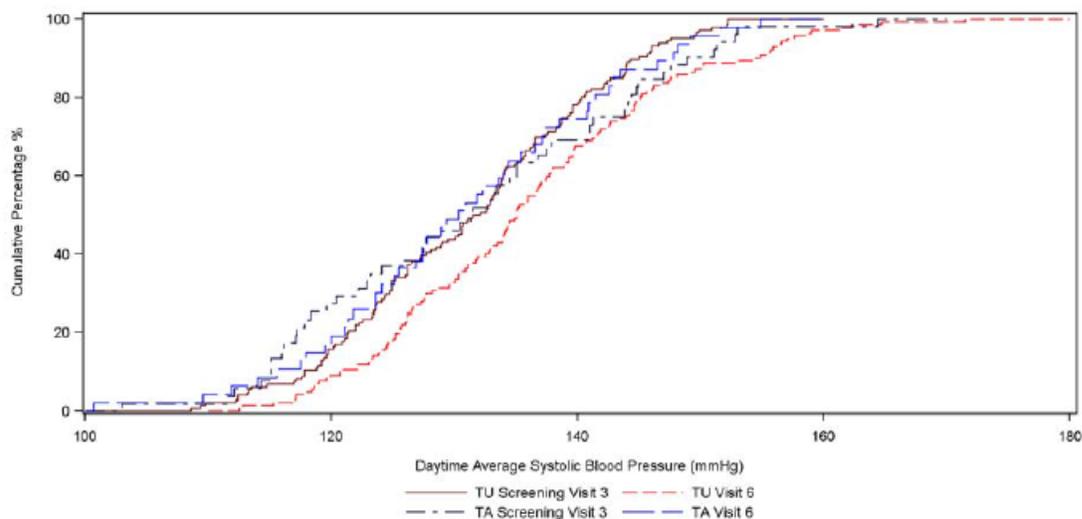


Source: CLAR-15012 CSR, Figure 16, page 154

Cumulative distribution curves for cuff SBP for baseline and Visit 7 by treatment also reflected a tendency for increased BP with Oral TU when comparing baseline to Visit 7 in the Oral TU group and when comparing Oral TU to Topical Axiron subjects (See Figure 2 below, taken from Sponsor's Figure 23 in the CLAR-15012 CSR).

Figure 2 Cumulative Distribution Curves for Systolic Blood Pressure and Visit 7 by Treatment

Group (ABPM population)



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

Reviewer's Comment: Compared to these cuff BP cumulative distribution curves, the ABPM cumulative distribution curves reveal a more pronounced blood pressure increasing effect for Oral TU compared to the Topical Axiron comparator.

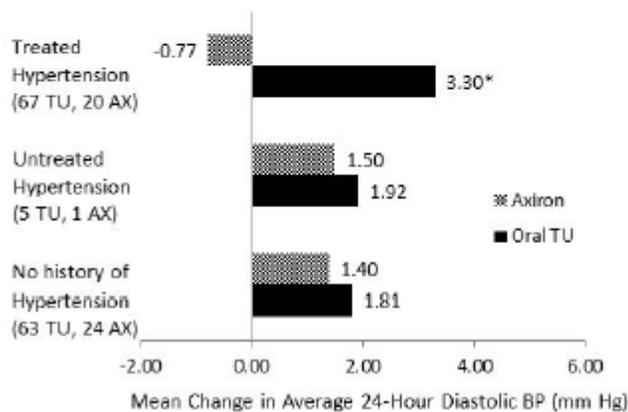
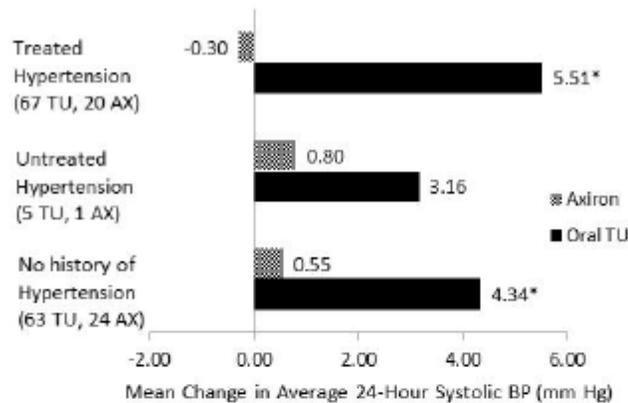
A history of hypertension was reported for 52.4% (87/166) of subjects in the Oral TU group and for 46.4% (26/56) of subjects in the Topical Axiron group. The history of hypertension had no clinically meaningful effect on treatment group differences for mean change from baseline to Visits 2, 4b, or 7/Early Termination in maximum SBP and DBP by cuff measurement. The Sponsor does observe, however, that the change from baseline in SBP were larger in subjects who had a history of hypertension compared to those with no history of hypertension.

The Sponsor also note that in the Oral TU group of the ABPM dataset, 5.9% of subjects started antihypertensive medication after baseline or required a dose increase compared to 2.2% of subjects in the Topical Axiron group.

In terms of ABPM determinations, the mean increases in daytime average, nighttime average, and 24-hour average SBP from baseline to Visit 6 for the Oral TU group was statistically significantly greater than the negligible changes observed for the Topical Axiron group, with 24-hour average SBP increasing 4.88 (\pm 8.749) mm Hg in the Oral TU group and 0.18 (\pm 9.384) mm Hg in the Axiron group. Similar results were observed for mean arterial pressure and pulse pressure. Mean increases in daytime average, nighttime average, and 24-hour average DBP from baseline to Visit 6 for the Oral TU group were also greater than for the Topical Axiron group, but the DBP differences between groups did not appear to be statistically significant. There were also no statistically significant treatment group differences for heart rate.

Figure 3 provides a graphic representation of the mean changes from baseline in 24-hour average SBP and DBP by ABPM in the treatment groups in CLAR-15012.

Figure 3 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)

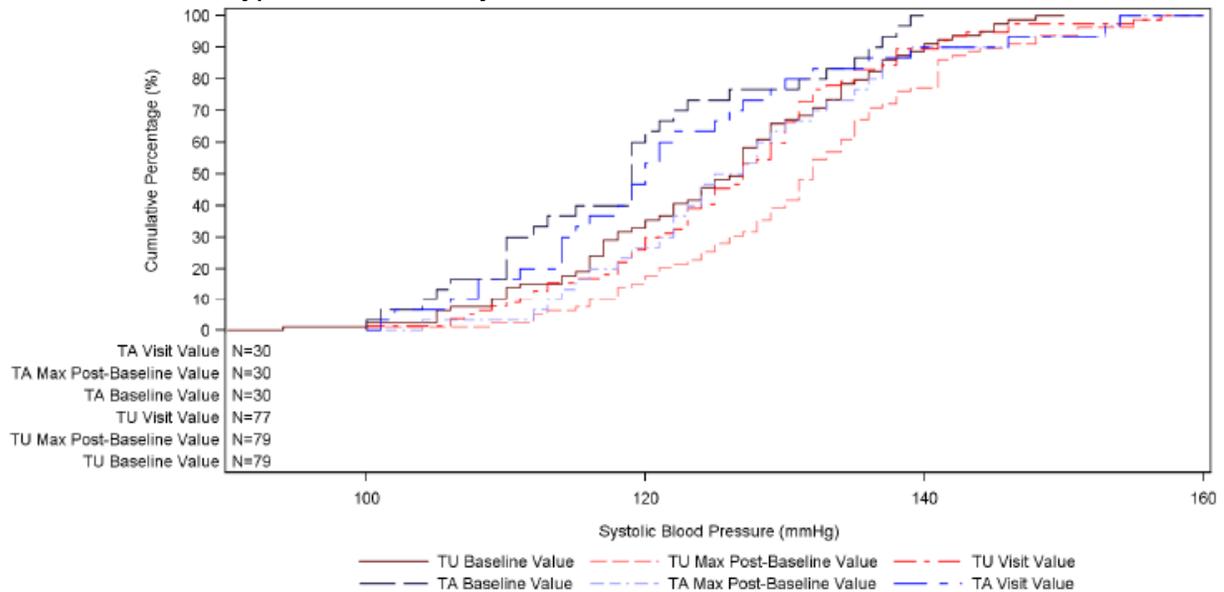


Source: Snapshot Figure 24, Clar-15012 CSR, page 166

Figure 4 provides cumulative distribution curves of SBP using ABPM at Visit 7/Early Termination for subjects without hypertension in CLA-15012.

Figure 4 Cumulative Distribution Curves for Systolic Blood Pressure for Visit 7/Early

Termination and No Hypertension History

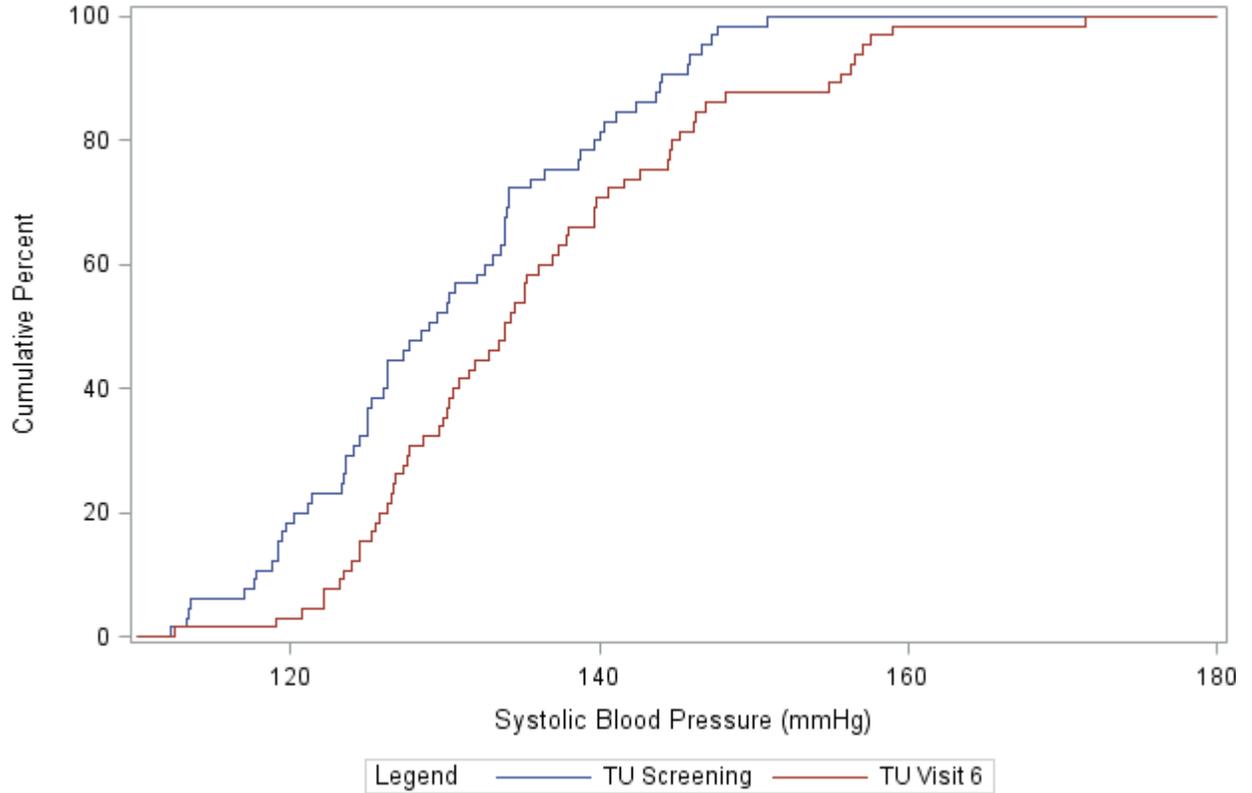


Source: Post Text Figure 14.3.4.2.11.5

Reviewer's Comment: In patients with no hypertensive history the curves reveal a more pronounced blood pressure increasing effect in the Oral TU group compared to the Topical Axiron comparator group.

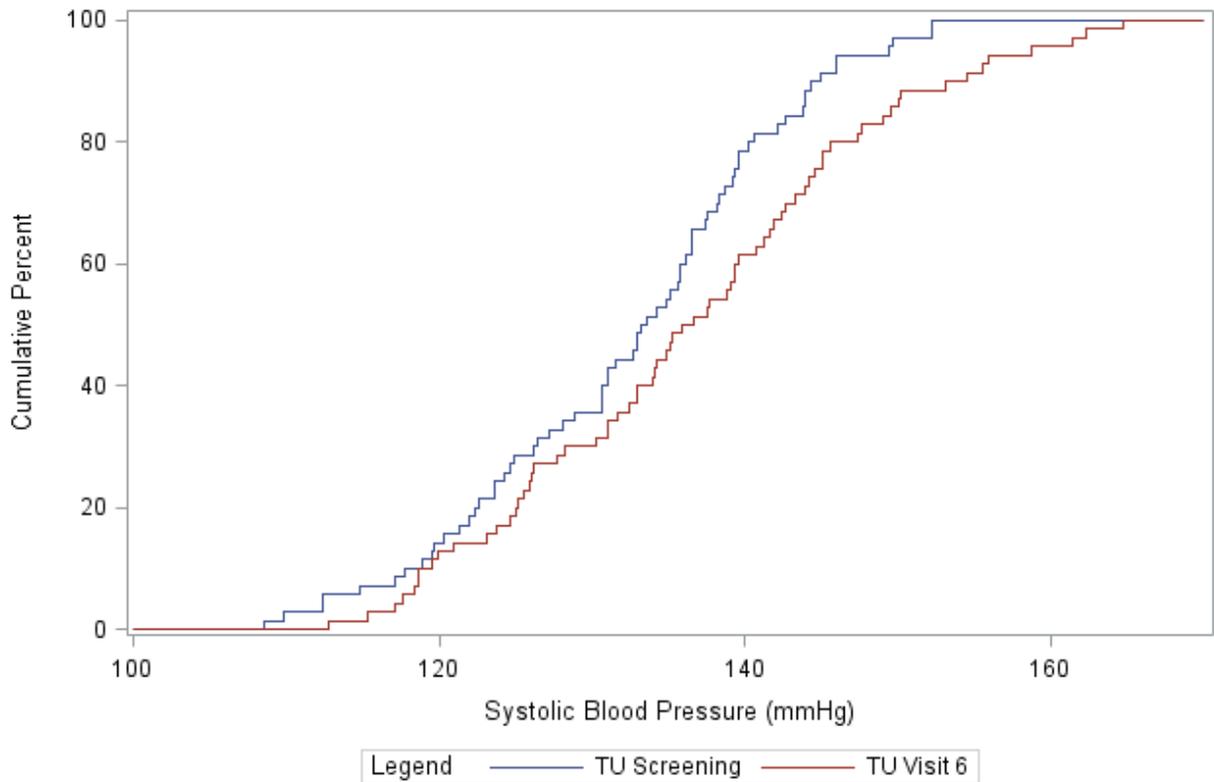
In addition, there is evidence to suggest an effect of duration of Oral TU exposure on BP as shown in the four figures below (illustrating SBP) for patients who received less than or equal to the median exposure to Oral TU (≤ 138 days) versus greater than the median exposure (>138 days) in CLAR-15102.

Figure 5 Cumulative Distribution Function of Daytime Systolic Blood Pressure at Screening and Visit 6 in Subjects with Exposure Time Less Than or Equal to 138 Days (TU Median) N=65



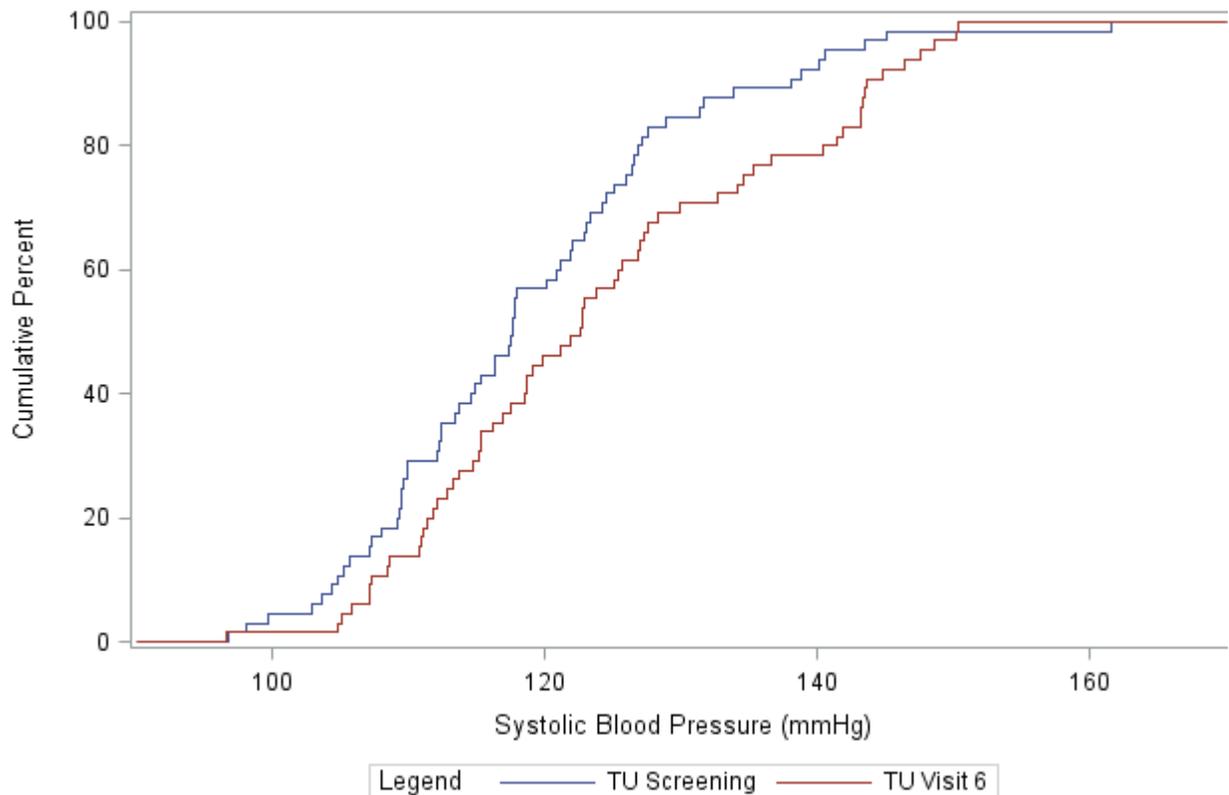
Source: Figure provided by FDA's Division of Biometrics, November 2, 2017

Figure 6 Cumulative Distribution Function of Daytime Systolic Blood Pressure at Screening and Visit 6 in Subjects with TU Exposure Time Greater Than 138 Days, N=70



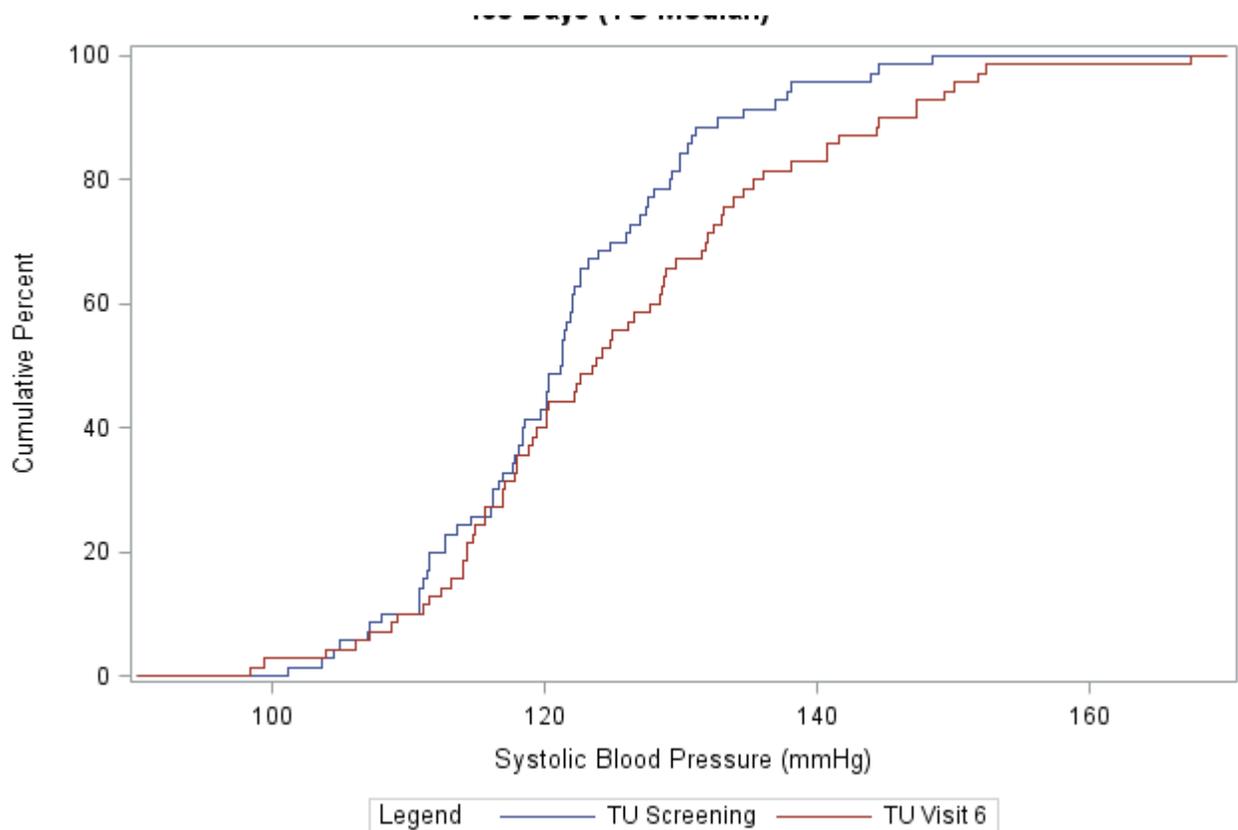
Source: Figure provided by FDA's Division of Biometrics, November 2, 2017

Figure 7 Cumulative Distribution Function of Nighttime Systolic Blood Pressure at Screening and Visit in Subjects with TU Exposure Time Less Than or Equal to 138 Days (TU Median) N=65



Source: Figure provided by FDA's Division of Biometrics, November 2, 2017

Figure 8 Cumulative Distribution of Nighttime Systolic Blood Pressure at Screening and Visit 6 in Subjects with TU Exposure Time Greater Than 138 Days (TU Median) N=70



Source: Figure provided by FDA’s Division of Biometrics, November 2, 2017

In their final consultation report, dated September 19, 2017, the Division of Cardiovascular and Renal Products (DCRP) pointed out that the effect of Oral TU to increase BP appears to be more pronounced in patients who have hypertension, diabetes mellitus, or both conditions. To further assess this issue, the Sponsor was asked to provide an analysis of the ABPM data by patient subgroup. The Sponsor’s response was received by the FDA on October 30, 2017. Table 20 below is derived from the Sponsor’s October 30, 107, response.

Table 19 ABPM Patients with Baseline Hypertension, Diabetes or Both

Increases Decreases (LS means)	ALL ABPM Patients		Baseline History Hypertension[§]		Baseline History Diabetes		Baseline History Hypertension and Diabetes	
	TU (N=135)	Axiron (N=45)	TU (N=72)	Axiron (N=21)	TU (N=33)	Axiron (N=13)	TU (N=27)	Axiron (N=9)
24 hr* (bpm)	+2.165	+0.044	+1.676	-0.360	+1.579	-3.577	+1.362	-2.819
Daytime systolic BP (mmHg)	+5.048	-0.123	+5.587	-1.404	+5.225	+0.198	+5.765	+0.783
Nighttime systolic BP (mmHg)	+4.851	+0.348	+5.044	+2.253	+5.974	-3.111	+4.997	+0.297
24 h average systolic BP (mmHg)	+4.907	+0.088	+5.338	-0.206	+5.332	-0.652	+5.351	+0.847

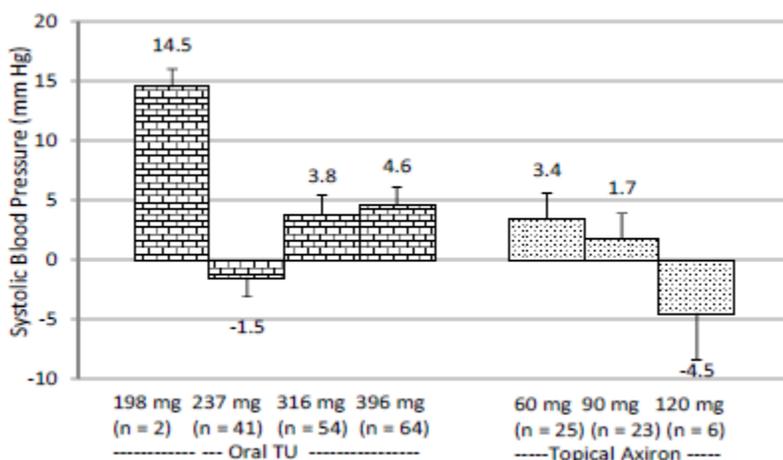
*24 hour average heart rate in beats per minute, LS=least squared means, §=treated and untreated

Sources: Revised Table 49 and Table 14.3.4.3.17.2 from Sponsor's October 30, 2017 Information Request Response.

In the Oral TU group, 7.2% of subjects started antihypertensive medication after baseline or required a dose increase compared with 1.8% of subjects in the Topical Axiron group. The mean increase from baseline to Visit 7/Early Termination was larger with Oral TU doses of 316 and 396 mg BID (reference page 157 of CLAR-15012). The opposite was observed with doses of Topical Axiron from 60 to 120 mg QD. There were only 2 subjects in the 198 mg BID Oral TU group at Visit 7 and both had large changes in SBP for reasons not are not readily apparent:

- Subject (b) (6) had a 16 mm Hg increase from baseline in SBP at Visit 7 (baseline 105 mm Hg; Visit 7: 121 mm Hg). Post-baseline values ranged from 113 to 121 mm Hg. The subject had no history of hypertension and experienced no adverse events during the study.
- Subject (b) (6), who was receiving antihypertensive medication at baseline, had a 13 mm Hg increase from baseline in systolic blood pressure at Visit 7 (baseline: 134 mm Hg; Visit 7: 147 mm Hg). Post-baseline values across visits ranged from 145 to 153 mm Hg; the subject required no change in antihypertensive medication during the study. No adverse events associated with an increase in blood pressure were noted; however, an adverse event of hematocrit increased was reported at Day 80 (Visit 4b), when the subject’s maximum value during the study was recorded (153 mm Hg).

Figure 9 Mean Change (with Standard Error) From Baseline to Visit 7/Early Termination in Systolic Blood Pressure by Treatment Group.

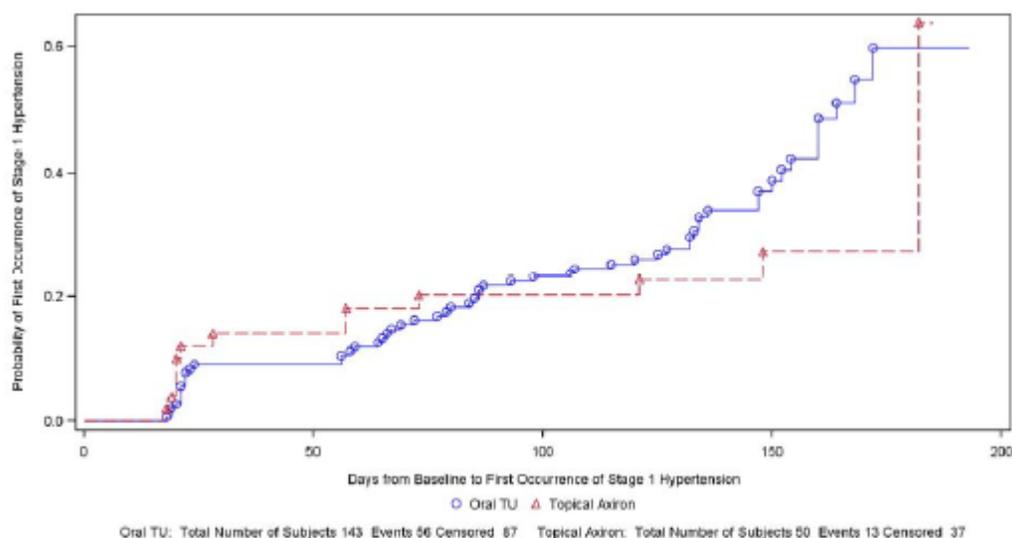


Source: CLAR-15012 CSR, Figure 19, page 159

Consistent with the higher baseline BP in the Oral TU group, there was a shift to the right in the distributions of BP classifications at baseline in that group. There was a greater percentage of subjects with pre-hypertension and Stage 1 hypertension in the Oral TU group compared to the Topical Axiron group. This shift in distribution persisted with treatment.

A Kaplan-Meier plot of the number of day from baseline to the first occurrence of Stage 1 hypertension by treatment group is shown in the Figure below. After approximately 125 days, there appears to be an increase for Oral TU patients.

Figure 10 Kaplan-Meier Plot of the Number of Days from Baseline to the First Occurrence of Stage 1 Hypertension (Safety Population)



Source: CLAR-15012 CSR, Figure 22, page 162.

In their final consultation report, the Division of Cardiovascular and Renal Products offered the following comments and recommendations:

- A total of 135 subjects in the Oral TU group and 45 subjects in the Axiron group had ABPM measurements with interpretable results at both the pre-dose visit (Screen 3 Day - 2) and Visit 6 and were included in the ABPM Population. Demographic characteristics of the ABPM Population were similar to those of 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 Axiron group (46.7%). Baseline hypertension classifications based on BPs obtained at screening showed a greater proportion of subjects in the Oral TU group compared with the 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%). Among subjects not receiving treatment for hypertension, 72.1% of subjects in the Oral TU group had a baseline hypertension classification of pre-hypertensive or Stage 1 hypertension compared with 52.0% of subjects in the Axiron group.

- The mean increase in daytime average, nighttime average, and 24-hour average SBP from baseline to Visit 6 for the Oral TU group was statistically significantly greater than for the Axiron group with 24-hour average SBP increasing by 4.88 (\pm 8.749) mm Hg in the Oral TU group and by 0.18 (\pm 9.384) mm Hg in the Axiron group. Similar results were observed for mean arterial pressure and pulse pressure. Mean increases in daytime average, nighttime average, and 24-hour average DBP from baseline to Visit 6 for the Oral TU group were greater than for the Axiron group, but the differences were not statistically significant. There were no statistically significant treatment group differences for heart rate.

Table 20 Systolic and Diastolic Blood Pressure Measured by ABPM at Baseline and Visit 6 by Treatment Group (ABPM Population)

Vital Sign Measurement	Statistic	Oral TU (N = 135)		Topical Axiron (N = 45)	
		Baseline	Change	Baseline	Change
Systolic blood pressure (mm Hg)					
Daytime average	Mean (SD)	131.13 (10.149)	5.05 (8.855)	131.21 (14.101)	-0.14 (10.534)
	Median	131.50	5.30	131.50	0.60
	p-value ^a		0.008		
Nighttime average	Mean (SD)	120.05 (11.164)	4.72 (11.852)	118.33 (13.102)	0.74 (11.328)
	Median	120.10	3.10	117.50	-0.70
	p-value ^a		0.0209		
24-hour average	Mean (SD)	127.52 (9.747)	4.88 (8.749)	127.03 (13.243)	0.18 (9.384)
	Median	127.80	4.50	128.00	1.00
	p-value ^a		0.0013		
Diastolic blood pressure (mm Hg)					
Daytime average	Mean (SD)	78.93 (7.819)	2.51 (7.246)	79.94 (8.547)	0.29 (6.6266)
	Median	78.50	2.00	79.30	0.50
	p-value ^a		0.0951		
Nighttime average	Mean (SD)	70.07 (7.779)	2.78 (8.940)	69.40 (8.092)	0.77 (8.108)
	Median	69.60	1.80	69.00	0.50
	p-value ^a		0.1059		
24-hour average	Mean (SD)	76.04 (7.206)	2.56 (6.772)	76.53 (7.910)	0.44 (5.830)
	Median	75.90	1.90	75.80	-0.20
	p-value ^a		0.0653		

^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

- When comparing SBP measured by cuff in those who were in the ABPM Population to SBP measured by ABPM, the results were similar (e.g., Oral TU ABPM Population change from baseline to Visit 7/Early Termination was 3.4 \pm 11.33 mm Hg by office cuff versus 4.88 \pm 8.749 mm Hg by 24-hour ABPM). To the Sponsor, this indicates that

systolic blood pressure changes measured by office cuff are similar to changes measured by ABPM. This conclusion appears to apply also to the Topical Axiron subjects. In Table 14.3.4.2.14.1 (page 793) for the Axiron population, change from baseline to Visit 7/Early Termination was 0.09 ± 0.435 mm Hg by office cuff versus 0.18 ± 9.9384 mm Hg by 24-hour ABPM.

- Daytime and nighttime cumulative distribution curves for SBP appear to indicate a shift to the right (increase) in blood pressure from screening to Visit 6.
- It is noted that all patients were supposed to have ABPM monitoring in the study. In the Oral TU group 135/166 subjects completed all ABPM assessments and 45/55 Axiron subjects completed all ABPM assessments.

In Study CLAR-09007 and its 12-month extension, CLAR-12010, studies that utilized different Oral TU doses and a different Oral TU dose regimen, both Oral TU and T-gel increased mean SBP and DBP, but there was a greater mean increase in the Oral TU group compared with the T-gel group over the course of the original 12 months (CLAR-09007) and the additional 12-month extension (CLAR-12010). The greatest increases occurred 12 hours after the morning dose across all visits in Studies CLAR-09007 and CLAR-12011; but, after the PM dose, while the blood pressure increases were smaller, the 12-hour timeframe for post-dose maximal blood pressure increases was still apparent. The largest blood pressure increases were not actually at Tmax of T and DHT but at the trough times. In theory, in CLAR-09007, the overall blood pressure increases observed in the Oral TU group may have been related to higher systemic testosterone and/ or DHT exposures compared to the T-gel group.

The table below shows the average blood pressure increases at the same fixed Oral TU dose in Studies CLAR-09007 and CLAR-12011.

Table 21 T and DHT Exposure and BP Increases on Day 30 at the Same Fixed Oral TU dose in Studies CLAR-09007 and CLAR-12011

PK and BP (± SD in safety population)	Study 09007		Study 12011
	Oral TU N=155	T-gel N=156	Oral TU N=133
T-Cavg (ng/dL)	606.8±299.3	378.7±155.7	509.2±222.1
DHT-Cavg (ng/dL)	123.6±67.0	61.5±42.5	106.7±68.1
Systolic BP Change			
Check-in	3.9±11.9	1.9±13.9	0.5±13.7
4 hr	4.5±13.2	2.4±15.1	1.3±13.0
12 hr	8.1±13.9	5.6±16.5	6.0±13.9
Diastolic BP Change			
Check-in	2.3±8.2	0.9±9.1	0.2±9.3
4 hr	1.2±9.5	0.4±8.9	-0.6±10.1
12 hr	2.7±9.1	2.1±9.5	1.7±9.6

Source: NDA 206-089 October 23, 2014 Clinical Review, Table 34, page 75.

Reviewer's Comment: While the differences in T and DHT exposures between Oral TU and Topical Axiron in CLAR-15012 were smaller than the differences in exposures between Oral TU and T-gel in CLAR-09007 and CLAR-12011, a significant difference in blood pressure increases was nonetheless still observed between Oral TU and Topical Axiron. Note also the increased SBP for Oral TU versus T-Gel in Study CLAR-09007.

The Division of Biometrics was asked to survey the ABPM results for subjects less than 40 years of age and ABPM results. There were 18 Oral TU subjects and 6 Topical Axiron subjects in this age subgroup. CDF plots for these 2 groups did not reveal an age difference for effects of Oral TU in increasing the blood pressure. (Email from Biometrics January 26, 2018),

The Division of Cardiovascular and Renal Products consultative review of the ambulatory blood pressure study had the following conclusions:

- APBM systolic and diastolic mean pressures after Oral TU were elevated in comparison to the Topical Axiron control in all three timeframes assessed (daytime, nighttime and 24 hour) [Table 16]. 95% CI limits are requested.
- Clinically significant (and what appear to be nominally statistically significant) daytime blood pressure and HR elevations in the Oral TU treatment arm are of greater magnitude than those seen to the TA comparator. Increased heart rate in association with increases in the blood pressure may amplify the adverse effects of blood pressure elevations over time.
- Scatter plots created from baseline to Visit 6 Tmax show the highest outliers for all three vital sign measures (HR, SBP, DBP) occur in the Oral TU treatment arm.
- Blood pressure effects are exaggerated in the subgroup of subjects with hypertension at baseline.
- SBP effects had not plateaued at the end of the study so that maximal SBP effects are not known.
- In the Safety population, 7.2% of subjects in the Oral TU treatment arm started antihypertensive therapy after baseline or required a dose increase compared with 1.8% of subjects in the Topical Axiron group.
- Shift analyses demonstrate the ongoing nature of BP elevations.
- Overall Conclusion: Oral TU raises the blood pressure in a clinically and statistically significant manner, particularly in subjects with pre-existing hypertension. The effect occurred in the setting of disproportionate escalation of antihypertensive therapy in the Oral TU arm. Oral TU-induced increases in heart rate are expected to amplify the clinical impact of Oral TU-induced elevations in blood pressure with respect to the occurrence of future CV outcome events

Reviewer's Comment: Oral TU increased the blood pressure to a greater extent than did an approved testosterone replacement therapy that was used in this study (CLAR-15012) as an active comparator for safety. The effects upon the blood pressure do not appear to

be dose dependent. This finding is the major safety issue of this application and represents a CR issue.

Lipid profile changes (particularly decreased HDL):

Table 22 CLAR-15012 Lipid Profile Changes

Parameter Statistic	Oral TU N=166		Topical Axiron N=55	
	n	mean (SD)	n	mean (SD)
Total Cholesterol (mmol/L)				
Baseline	166	4.755 (0.89)	55	4.795 (0.82)
Visit 7/Early Termination	162	4.496 (0.97)	53	4.525 (0.76)
HDL (mmol/L)				
Baseline	166	1.141 (0.30)	55	1.084 (0.27)
Visit 7/Early Termination	162	0.965 (0.24)	53	1.091 (0.24)
LDL (mmol/L)				
Baseline	166	2.936 (0.81)	55	2.885 (0.78)
Visit 7/Early Termination	162	3.017 (0.88)	53	2.811 (0.75)
Triglycerides (mmol/L)				
Baseline	166	1.784 (1.16)	55	2.102 (1.62)
Visit 7/Early Termination	162	1.893 (1.42)	53	7.127 (1.26)

Source: CLAR-15012 CSR: End of text table 14.3.4.1.2.1

Mean changes from baseline to the final visit (Visit 7/Early Termination) in total cholesterol values were similar between the treatment groups (Oral TU: -0.252 mmol/L [-9.74 mg/dL]; Topical Axiron: -0.292 mmol/L [-11.29 mg/dL]); 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/Early Termination); however, the mean decrease observed in the Oral TU group was modestly greater than that observed in the Topical Axiron group (-0.179 mmol/L [-6.92 mg/dL] versus -0.051 mmol/L [-1.97 mg/dL]); the mean percent decrease from baseline was -13.9% in the Oral TU group compared with -3.39% in the Topical Axiron group. In CLAR-09007, the change from baseline to Day 90 in HDL-cholesterol was -10.7 mg/dL. In CLAR-12011 the change from baseline to Day 105 in HDL-cholesterol was -5.1 ng/dL (Table 64 of ISE page 125).

A mean increase from baseline to the final visit (Visit 7/Early Termination) in LDL-cholesterol was noted in the Oral TU group (0.091 mmol/L [3.52 mg/dL]), while a mean decrease from baseline was observed in the Topical Axiron group (-0.104 mmol/L [-4.02 mg/dL]); the mean percent increase from baseline was 5.95% in the Oral TU group compared with a decrease of -2.14% in the Topical Axiron group. In the pooled Phase 3 studies (CLAR-09007, 12011 and 15012), the change in LDL for Oral TU subject from Baseline to EOT was 0.1 mg/dL (Table 63 ISE, page 124).

Reviewer's Comment: *The changes in HDL and LDL-cholesterol appear to be modest in degree and their clinical significance are unknown.*

Similar results were also observed for triglycerides, with a mean increase from baseline to the final visit (Visit 7/Early Termination) observed in the Oral TU group (0.105 mmol/L [9.30 mg/dL]), while a mean decrease from baseline was observed in the Topical Axiron group (-0.016 mmol/L [-1.42 mg/dL]). Although the Oral TU group showed a mean increase in triglycerides and the Topical Axiron group showed a mean decrease, both treatment groups had mean percent increases from baseline in triglycerides (12.99% and 8.07%, respectively); the median percent changes from baseline in triglycerides was 5.45% in the Oral TU group and -1.25% in the Topical Axiron group. In pooled Phase 3 studies (CLAR-09007, 12011 and 15012), the mean change in triglycerides from Baseline to EOT in Oral TU subjects was -4.4 ng/dL.

In the evaluation of lipid values, shifts from normal baseline to above the normal range occurred in greater proportions of Oral TU subjects compared with Topical Axiron subjects. Greater proportions of all Oral TU subjects shifted from normal HDL values at baseline to below the normal range (35.5% among minimum values and 28.9% for final visit values) compared with all Topical Axiron subjects (18.5% among minimum values and 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: 12.0% and 18.7%, respectively, among maximum values and 7.8% and 13.3%, respectively, for final visit values; Topical Axiron: 7.4% and 11.1%, respectively, among maximum values and 3.7% and 9.3% for final visit values).

Reviewer's Comment: Changes in lipid profile show modestly unfavorable trends for Oral TU compared to Topical Axiron. However, the clinical significance of these findings are unknown. Patients were on Oral TU for varying time periods. Comparison of results from CLAR-15012 to previous study results may be confounded because of the exposure time differences as well as increased T exposure in some to the pooled studies. It is also noted that in CLAR-15012, the Cavg for Oral TU subjects at Visit 7 was 401.2 ng/dL versus 390.6 ng/dL for Topical Axiron. It would be prudent to include a summary of lipid profile changes in product labeling but this is not a CR issue, in our opinion.

Adrenal cortical atrophic changes noted in dog and rat:

Based on nonclinical findings of adrenocortical atrophy and hypocortisolemia in dogs, Cosyntropin testing was conducted in a subset of subjects in CLAR-15012.

The Cosyntropin substudy in CLAR-15012 is also discussed in the CLAR-15012 study summary in the Appendix, but the study results and consultative Endocrine evaluation are summarized herein.

The Sponsor undertook a Cosyntropin stimulation test sub study in CLAR-15012. All of the subjects in both treatment groups in the Cosyntropin Stimulation Substudy Population (24 Oral

TU, 8 Topical Axiron) had a normal cortisol response to Cosyntropin stimulation at baseline. For the 8 subjects in the Topical Axiron group who completed the Cosyntropin substudy, all had normal responses at Visit 8. For the 24 subjects in the Oral TU group who completed the Cosyntropin substudy, 19 had a normal response at Visit 8. As indicated by the 95% CI, a statistically significantly smaller proportion of subjects in the Oral TU group had a normal cortisol response at Visit 8 as compared to Topical Axiron.

Among the 5 Oral TU subjects who had a low cortisol response after the test at Visit 8, 4 had cortisol values that were only slightly below the normal response cutoff level of 18 µg/dL (values ranged from 16.5 to 17.6 µg/dL at 30 or 60 minutes after administration of cosyntropin).

According to the Sponsor, these small excursions in cortisol levels below the normal response cutoff level are unlikely to be of clinical significance. The Sponsor asserts that in order to rule out primary adrenal insufficiency, the peak post-stimulation cortisol needs to be > 15 µg/dL. All 4 of these subjects' peak cortisol exceeded this value, thereby ruling out primary adrenal insufficiency, in the Sponsor's opinion.

Reviewer's comment: We are unable to concur with the Sponsor's above analysis, but for the reasons stated below, we find it impossible to interpret the study's findings.

A consultative Endocrinology evaluation of the study was obtained and completed on October 31, 2017. The Endocrinology reviewer's opinion was: "...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. 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. The decline in BP between study visit 1 and 8 is curious, particularly since TU appears to be associated with an increase in BP. However, no patients experienced hypotension.

On the other hand, many subjects in both groups had low AM cortisol levels at baseline. 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 explain the findings."

The Endocrinology consultative recommendations were:

- 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.

- The reviewer feels that the Cosyntropin 0.25 mg intravenous test with cortisol testing pre-injection and 30 and 60 minutes post-injection is 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 and ACTH level should be obtained each time.
- Samples should be batched for the cortisol and ACTH assays. The assays chosen should have optimal performance.
- Serial tests should be performed at baseline and 6 month intervals, or sooner if clinically indicated, to determine if progressive adrenal insufficiency occurs with ongoing TU use.
- The Cosyntropin study protocol should be submitted for review prior to initiation of the study.

***Reviewer's Comment:** The Endocrinologist's recommendations and conclusions seem reasonable. Another Cosyntropin stimulation test should be conducted in humans, but based upon the lack of any signs or symptoms of hypoadrenalism in three phase 3 studies, this additional human investigation may be conducted as a postmarketing requirement.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 23 Treatment-Emergent Adverse Events Occurring in $\geq 2\%$ in Either Treatment Group (Safety Population)

System Organ Class Preferred Term, ^a n (%)	Oral TU (N = 166)	Topical Axiron (N = 55)
Subjects with any TEAE	78 (47.0)	20 (36.4)
Investigations	23 (13.9)	2 (3.6)
Haematocrit increased	8 (4.8)	0
High-density lipoprotein decreased	5 (3.0)	0
Gastrointestinal Disorders	20 (12.0)	0
Nausea	4 (2.4)	0
Infections and Infestations	16 (9.6)	5 (9.1)
Upper respiratory tract infection	6 (3.6)	0
Nervous system Disorders	12 (7.2)	4 (7.3)
Headache	8 (4.8)	1 (1.8)
Injury, Poisoning and Procedural Complications	6 (3.6)	4 (7.3)
Overdose	1 (0.6)	2 (3.6)
Skin and Subcutaneous Tissue Disorders	5 (3.0)	6 (10.9)
Rash	2 (1.2)	2 (3.6)
Vascular Disorders	6 (3.6)	0
Hypertension	5 (3.0)	0

a=Adverse Events by MedDRA Version 15.1

Source: CLAR-15012 CSR, Table 35 (Snapshot), page 130.

The overall incidence of treatment-emergent adverse (TEAE) events was higher in the Oral TU group (47.0%) compared with the Topical Axiron group (36.4%), and was largely driven by the difference in Gastrointestinal Disorders. The incidences of TEAE events associated with system organ classes (SOCs) include:

- Investigations (largely “hematocrit increased” or “HDL-decreased”): 13.9% Oral TU versus 3.6% Topical Axiron
- Gastrointestinal Disorders: 12.0% Oral TU versus 0.0% Topical Axiron
- Vascular Disorders (such as “hypertension”): 3.6% Oral TU versus 0.0% Topical Axiron
- Headache: While not an SOC term, 4.8% Oral TU versus 1.8% Topical Axiron. The relationship between headache and increased BP is not entirely clear, and has been previously discussed in prior sections of this review.

Table 24 Treatment Emergent Adverse Events Considered Related (by Sponsor) to Study Drug Occurring in $\geq 1\%$ of Subjects in Either Treatment Group (Safety Population)

Clinical Review
 {Roger Wiederhorn }
 {NDA 2016089 }
 {Jatenzo: Oral Testosterone Undeconoate}

System Organ Class Preferred Term, ^a n (%)	Oral TU (N = 166)	Topical Axiron (N = 55)
Subjects with any related TEAE	31 (18.7)	8 (14.5)
Investigations	12 (7.2)	2 (3.6)
High-density lipoprotein decreased	5 (3.0)	0
Haematocrit increased	4 (2.4)	0
Blood pressure increased	2 (1.2)	1 (1.8)
Weight increased	1 (0.6)	1 (1.8)
Gastrointestinal Disorders	10 (6.0)	0
Gastroesophageal reflux disease	3 (1.8)	0
Abdominal distension	2 (1.2)	0
Dry mouth	2 (1.2)	0
Dyspepsia	2 (1.2)	0
Eructation	2 (1.2)	0
Nausea	2 (1.2)	0
Nervous system Disorders	4 (2.4)	1 (1.8)
Headache	4 (2.4)	1 (1.8)
Disturbance in attention	0	1 (1.8)
General Disorders and Administration Site Conditions	2 (1.2)	3 (5.5)
Oedema peripheral	1 (0.6)	1 (1.8)
Application site pain	0	1 (1.8)
Feeling jittery	0	1 (1.8)
Psychiatric Disorders	2 (1.2)	2 (3.6)
Insomnia	2 (1.2)	0
Anxiety	0	1 (1.8)
Libido increased	0	1 (1.8)
Skin and Subcutaneous Tissue Disorders	3 (1.8)	1 (1.8)
Hyperhidrosis	1 (0.6)	1 (1.8)
Blood and Lymphatic System Disorders	1 (0.6)	1 (1.8)
Anaemia	1 (0.6)	1 (1.8)
Injury, Poisoning and Procedural Complications	1 (0.6)	2 (3.6)
Overdose	1 (0.6)	2 (3.6)
Renal and Urinary Disorders	1 (0.6)	2 (3.6)
Pollakiuria	1 (0.6)	1 (1.8)
Urinary incontinence	0	1 (1.8)
Reproductive System and Breast Disorders	1 (0.6)	1 (1.8)
Ejaculation disorder	0	1 (1.8)

* = MedDRA Version 15.1 preferred term

Source: CLAR-15012 CSR: Table 36 (Snapshot), page 132

The differences between Oral TU and Topical Axiron in Investigations and Vascular Disorders have already been discussed in Section 7.3.5.

Table 25 Drivers of Gastrointestinal Disorder Adverse Events in Studies CLAR-15012 and CLAR-12011

	TU subjects CLAR-15012	TU subjects CLAR-12011
	N=166	N=144
Subjects with GI TEAEs	10 (6.0%)	21 (14.6%)
AE Preferred Term	n (%)	n (%)
Gastroesophageal reflux disease	3 (1.8)	1 (0.7)
Abdominal distention	2 (1.2)	0 (0.0)
Eructation	2 (1.2)	3 (2.1)
Nausea	2 (1.2)	1 (0.7)
Abdominal Pain	0 (0.0)	1 (0.7)
Vomiting	0 (0.0)	1 (0.7)
Diarrhea	0 (0.0)	5 (3.5)

Source: CLAR 15012 CSR Table 36 page 132 and NDA Clinical Review 206089 October 23, 2014, pages 55-56

***Reviewer's Comment:** The reported gastrointestinal AEs are comparable between studies. The AEs in the GI Disorder SOC do not raise major safety concerns and are attributable to the route of administration.*

7.4.2 Laboratory Findings

Testosterone replacement therapy (TRT) may be associated with changes in serum lipid profiles, therefore effects on serum lipids were assessed in the Oral TU clinical studies. The changes in serum lipid profiles are discussed in Section 7.3.5, Submission Specific Safety Concerns. TRT is widely recognized to increase hemoglobin and hematocrit, and therefore, those were also assessed in Oral TU trial. Changes in hemoglobin/hematocrit are also discussed in Section 7.3.5.

No clinically significant in liver function were observed in either treatment group in CLAR-15102.

The table below shows subjects with investigator-judged, clinically significant, post-baseline Chemistry values:

Table 26 Proportions of Subjects with Clinically Significant (Per Investigator Judgment) Post-Baseline Chemistry Values by Treatment Group (Safety Population)

Parameter: Assessment, n (%)	Oral TU (N = 166)	Topical Axiron (N = 54)
Alkaline Phosphatase: Abnormal, Clinically Significant	1 (0.6)	0
Aspartate Aminotransferase: Abnormal, Clinically Significant	3 (1.8)	0
Creatinine: Abnormal, Clinically Significant	1 (0.6)	0
Glucose: Abnormal, Clinically Significant	2 (1.2)	0
Calcium: Abnormal, Clinically Significant	1 (0.6)	0
Potassium: Abnormal, Clinically Significant	1 (0.6)	0
Sodium: Abnormal, Clinically Significant	1 (0.6)	0
Total Cholesterol: Abnormal, Clinically Significant	3 (1.8)	0
HDL Cholesterol: Abnormal, Clinically Significant	5 (3.0)	0
LDL Cholesterol: Abnormal, Clinically Significant	2 (1.2)	0
Triglycerides: Abnormal, Clinically Significant	5 (3.0)	1 (1.9)

Source: CLAR-15012 CSR Table 45 (Snapshot) page 150

The table that follows shows clinically significant (per investigator judgment) changes for lipids and liver tests only. It is notable that all of these occurred after Day 132 which is longer than the originally planned study treatment duration.

***Reviewer's Comment:** There was only one clinically significant laboratory change for lipids or liver function (per investigator's judgment) in the Topical Axiron group. There is some evidence that suggests, though the evidence is sparse for this conclusion, that duration of exposure in excess of 105-120 days results in more laboratory abnormalities in the Oral TU group.*

Table 27 Oral TU Subjects with Clinically Significant (Per Investigator Judgment) Post-Baseline Lipid or Liver Test Values (Safety Population)

Parameter Normal Range	Subject # (b) (6)	Clinical Chemistry Values			
		Screen	Baseline (Visit 1)	CS Values (Day) Dose BID at Time of Event	Final (Day)
Total cholesterol (mmol/L) 0 - 5.2		3.7	3.7	5.4 (D91) 316 mg	5.3 (D135)
		7.2	7.4	7.0 (D132) 237 mg	7.0 (D132)
		6.6	6.9	8.1 (D78) 316 mg	5.3 (D141)
HDL (mmol/L) 1 - 1.5		1.6	1.5	0.9 (D56) 1.0 (D65) 0.9 (D154) 316 mg	0.9 (D154)
		1.2	1.1	0.9 (D105) 0.8 (D148) 316 mg	0.8 (D148)
		1.6	1.4	0.8 (D149) 396 mg	0.8 (D149)
		1.0	0.9	0.8 (D135) 396 mg	0.8 (D135)
		0.9	1.1	0.8 (D79) 316 mg	0.8 (D135)
LDL (mmol/L) 0 - 2.6		2.4	2.3	4.6 (D79) 4.4 (D91) 316 mg 4.4 (D135) 396 mg	4.4 (D135)
		5.0	5.4	5.2 (D132) 237 mg	5.2 (D132)
Triglycerides (mmol/L) 0 - 1.68		2.27	2.93	3.41 (D79) 316 mg	2.19 (D135)
		1.53	1.54	2.25 (D132) 237 mg	2.25 (D132)
		1.29	3.03	12.81 (D78) 316 mg	2.28 (D141)
		3.66	3.60	6.22 (D59) 11.64 (D136) 11.66 (D185) 316 mg	11.66 (D185)
		5.99	4.80	10.85 (D64) 316 mg	3.96 (D119)
AST (U/L) 14 - 39		16	NA	67 (D120) 316 mg	17 (D167)
		19	NA	72 (D141) 237 mg	72 (D141)
		36	NA	42 (D119) 237 mg	42 (D119)

Source: CLAR-15012 CSR, Table 46 (snap shot), page 151

7.4.3 Vital Signs

Blood pressure changes are discussed extensively in Section 7.3.5 Submission Specific Safety Concerns.

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed in Study CLAR-15012.

7.4.5 Special Safety Studies/Clinical Trials

The Cosyntropin stimulation substudy test results were difficult to interpret due to deficiencies in design and conduct of that substudy. Three subjects had abnormally low test results suggesting abnormally low adrenal responsiveness. In addition, a number of patients had abnormal results that were intermediate between normal and below normal adrenal responsiveness. The results have been discussed previously in this review and are discussed again in the CLAR-15012 Summary in the Appendix.

7.4.6 Immunogenicity

No tests for immunogenicity were conducted during the clinical development program of Oral TU. It appears that no immunogenicity-related AEs and no laboratory abnormalities reflective of immunogenicity were reported in the clinical trials and in CLAR-15012.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

All subjects in CLAR-15012 started with a fixed dose of 237 mg of TU BID and were titrated up or down based upon total T concentration at Visit 3 or Visit 3b and at Visit 5 or Visit 5b. The days on which the titration occurred are based upon the conditions outlined in Amendment 2. Based on the study design and protocol amendments, the subject's cumulative exposure to a given dose of oral varied. The number of subjects in dose subgroups was also variable and not of sufficient size to provide meaningful conclusions about dose comparisons. The titration feature of CLAR-15012 also minimized the range of testosterone concentrations.

Reviewer's Comment: Despite the inherent difficulties in comparing doses, the Sponsor observed (page 157 of the CLAR-151012 CSR) "...the mean increase in systolic blood pressure from baseline to Visit 7/EOT became larger with Oral TU doses of 316 and 396 mg BID". There is no post-text table(s) relating to drug dose groups and TEAEs.

7.5.2 Time Dependency for Adverse Events

CLAR-15012 was planned with a 105 to 121-day treatment duration. The average exposure time was longer due to protocol amendments. For example, the longest subject treatment duration was 211 days. Table 2 in this review shows the mean total days of exposure for Oral TU subjects to be 139.4 days and for Topical Axiron subjects, 133.8 days. Within this limited time frame, with exposures over 120 days, there appeared to be larger increases in blood pressure, changes in serum lipids, and increases in hematocrit.

In the Clinical review conducted for the first review cycle, the review team noted that the total number of adverse events appeared to increase over time.

7.5.3 Drug-Demographic Interactions

CLAR-15012 added 166 Oral TU subjects to overall Oral TU safety data base. Among Oral TU subjects, notable differences between age subgroups were observed for upper respiratory tract infection (9.8% Oral TU vs. 4.0% Topical Axiron), hypertension (5.9% vs. 2.9%), and prostate-specific antigen increased (3.9% vs. 1.2%), which were more commonly observed among subjects > 65 years of age. The incidence of other commonly reported TEAEs was similar between the Oral TU subgroups.

Among subjects \leq 65 years of age, notable differences between the treatment groups were observed for polycythemia/hematocrit increased (5.0% Oral TU vs. 2.1% Topical Axiron), diarrhea (3.3% vs. 1.6%), and edema peripheral (3.1% vs. 1.1%), whereas prostate-specific antigen increased was more commonly observed among Transdermal T subjects (3.2% Topical Axiron vs. 1.2% Oral TU). In CLAR-15012, there were no subjects older than 65 years of age.

Among subjects > 65 years of age in the safety data base, notable differences between the treatment groups were observed for upper respiratory tract infection (9.8% Oral TU vs. 0.0% Topical Axiron), nasopharyngitis (3.9% vs. 0.0%), and diarrhea (3.9% vs. 0.0%), whereas sinusitis (12.0% Topical Axiron vs. 2.0% Oral TU) and prostate-specific antigen increased (12.0% vs. 3.9%) were more commonly observed among Transdermal T subjects.

Among Oral TU subjects, notable differences between race subgroups were observed for polycythemia/hematocrit increased (5.9% Oral TU vs. 2.4% Topical Axiron), edema peripheral (3.9% vs. 1.2%), and prostatomegaly (2.8% vs. 1.2%), which were more commonly observed among White subjects compared with non-White subjects. In CLAR-15012, 80% of oral TU subjects were white versus 75% of Topical Axiron subjects.

Among Oral TU subjects, notable differences between weight subgroups were observed for headache (5.4% Oral TU vs. 1.8% Topical Axiron) and prostatomegaly (3.8% vs. 1.8%), which were more commonly observed among subjects weighing > 100 kg, whereas nasopharyngitis (3.5% vs. 1.6%) and arthralgia (2.1% vs. 0.5%) were more commonly observed among subjects weighing \leq 100 kg. The incidence of other commonly reported treatment-emergent adverse events was similar between the Oral TU weight subgroups.

Among subjects weighing \leq 100 kg, notable differences between the treatment groups were observed for polycythemia/hematocrit increased (4.6% Oral TU vs. 2.1% Topical Axiron), upper respiratory tract infection (4.2% vs. 2.1%), diarrhea (4.2% vs. 0.7%), and edema peripheral (2.8% vs. 0.0%), whereas hypertension (6.4% Topical Axiron vs. 2.5% Oral TU), headache (3.6% vs. 1.8%) and prostatic-specific antigen increased (5.7% vs. 1.4%) were more commonly observed among Transdermal T subjects.

Among subjects weighing > 100 kg, notable differences between the treatment groups were observed for upper respiratory tract infection (5.4% Oral TU vs. 1.3% Topical Axiron), and headache (5.4% vs. 1.3%), whereas sinusitis (4.0% Topical Axiron vs. 1.1% Oral TU) and arthralgia (2.7% vs. 0.5%) were more commonly observed among Transdermal T subjects.

The low incidence of serious treatment-emergent adverse events across the Phase 3 studies precludes meaningful comparisons of individual serious events with respect to demographic subgroups.

***Reviewer's Comment:** The overall total safety database of 545 subjects treated with Oral TU is relatively small for meaningful subgroup analysis. The increased incidence in adverse events in subjects > 65 years of age and >100 kg is not unexpected. In CLAR-15012, there were no subjects older than 65 years of age.*

7.5.4 Drug-Disease Interactions

The study population in CLAR-15012 had some commonly-observed comorbidities: diabetes mellitus (24.1%), “pre-diabetes” (36.1%), hypertension (52.4%), and hypercholesterolemia or hypertriglyceridemia (24.1%). In the prior studies in the clinical development program, the comparable commonly observed comorbidities were: diabetes mellitus (18.8%), “pre-diabetes” (31.5%), hypertension (42.5%), and hyperlipidemia or similar condition (34.3%). Potential interactions of Oral TU with these commodities and associated medications should be covered by the overall safety profile.

7.5.5 Drug-Drug Interactions

No specific analyses were performed in the Oral TU Phase 2 and Phase 3 studies to evaluate drug-drug interactions.

In the previous phase 3 trials (not including CLAR-15012), approximately 55% (n=169) of Oral TU subjects were listed as “current drinkers” and 11% as “former drinkers.” In the current submission, the Clinical review team could not find such information. It is not known whether alcohol may potentially impact solubility of the oral TU formulation in the GI tract and thus absorption. The alcohol PK interactions with the oral TU formulation were not assessed; however, there were no limitations on alcohol use in the Phase 3 studies, including 1 year studies, and no signs or symptoms of alcohol interaction were observed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

In CLAR-15012, one squamous cell carcinoma was reported by one Oral TU subject on Day 44. In CLAR-09007, one basal cell carcinoma was reported by one Oral TU subject on Day 343 and one prostate cancer was reported in one T-gel subject on Day 130. In CLAR-12011, one nasal cavity cancer was reported in one Oral TU subject.

7.6.2 Human Reproduction and Pregnancy Data

One Oral TU subject in CLAR-15012 reported the AE of ejaculation disorder as did one subject using Topical Axiron.

The reporting frequency of AEs under the Reproductive System and Breast Disorders (SOC) appears comparable between Oral TU and Topical Axiron. Prostate events (discussed under other sections of this review) appears comparable between oral TU and Topical Axiron.

No human reproductive assessments for Oral TU capsules were conducted in males, and none were conducted in their spouses or female partners in the clinical development program. Pregnancy information of the subject's spouses or partners was not reported.

7.6.3 Pediatrics and Assessment of Effects on Growth

All clinical trials submitted in this NDA were conducted in adult men who had repeated serum testosterone concentrations that were low. No pediatric patients (<18 years old) were enrolled in any of the clinical trials.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no overdose cases reported during the Phase 2 and Phase 3 trials. Potential abuse and withdrawal associated with this product were not specifically assessed.

7.7 Additional Submissions / Safety Issues

Mean peak exposures (C_{max}24) and total exposure (AUC₂₄) for plasma DHT in the Oral TU- and Topical Axiron-treated subjects were similar at all 3 pharmacokinetic visits. By the end of the titration period (Visit 7), the DHT C_{max}24 values were 117.1 ng/dL and 98.0 ng/dL for Oral TU and Topical Axiron subjects, respectively, and the AUC₂₄ values were 1758 and 1770

ng•h/dL, for Oral TU and Topical Axiron, respectively. The mean 24-hour Cavg values were also very similar at 73.25 ng/dL and 73.76 ng/dL, for Oral TU and Topical Axiron, respectively, which is 13% or less above the normal range for DHT in eugonadal men (65.0 ng/dL). The mean DHT/T ratios for the 2 treatments were 0.18 to 0.19.

Mean concentrations of calculated free testosterone at baseline were 4.457 ng/dL in the Oral TU group and 4.442 ng/dL in the Topical Axiron group. Mean concentrations of calculated free testosterone following dosing with Oral TU followed a similar pattern as the testosterone concentrations. The mean Cavg24 of calculated free testosterone at Visit 7 was 11.685 ng/dL in the Oral TU group and 9.184 ng/dL in the Topical Axiron group; both of which are within the normal range (6.1 to 19.4 ng/dL) published for that parameter.

Overall, estradiol (E2) concentrations increased with the administration of exogenous testosterone. Mean change from baseline in the serum concentrations of E2 at Visit 7 (AM predose concentration) in the Oral TU-treated subjects showed an approximately 150% increase from the baseline value. The mean baseline E2 concentration at Visit 1 was 17.55 pg/mL and the mean predose concentration for the AM dose of Oral TU was 28.6 pg/mL with both values within the normal range (7.5 to 30.6 pg/mL) for E2 in eugonadal men at the laboratory that conducted the assays. The 24-hour Cavg value (Cavg24) at Visit 7 (32.3 pg/mL), was slightly above the upper bound of the normal range and was approximately equal to the mean E2 concentration in the Topical Axiron-treated subjects (33.03 pg/mL).

Mean SHBG concentrations decreased by approximately 31% to 36% with Oral TU Treatment (from approximately 29 nmol/L to approximately 17 nmol/L). The decrease in SHBG concentration was complete by Visit 2, and the mean SHBG concentrations did not show any additional decline between Visit 2 and Visit 7. The normal range for SHBG in eugonadal men is 10.78 to 46.62 nmol/L; so the mean values were within the normal range from the beginning to the end of treatment. At Visit 2, approximately 25% of the Oral TU-treated subjects had SHBG concentrations less than the lower bound of the SHBG normal range, but that percentage decreased to 17% by Visit 4b and Visit 7. Topical Axiron treatment also resulted in a small decline in the SHBG concentrations but the maximal extent of the mean decline, observed at Visit 2, and that decline was only approximately 4%. Between Visit 2 and Visit 7, the mean SHBG concentrations in the Topical Axiron-treated subjects may have returned towards baseline, the mean difference being less than -0.5% by Visit 7 (from approximately 27nmol/L to 26.4nmol/L).

Reviewer's Comment: The differences in effect on SHBG between Oral TU versus Topical Axiron are small and of unknown clinical significance.

The mean baseline serum FSH concentration was approximately 5.5 mIU/mL in the Oral TU group, which is within the normal range for eugonadal men (normal range: 1.4 to 9.5 mIU/mL). By Visit 7, the mean concentration in the AM predose sample had declined by approximately 71% to 1.8 mIU/mL. The percentage of Oral TU subjects with FSH concentrations assayed as BLQ increased from 0% (0/151) at Visit 1 baseline to approximately

32% (48/151) at Visit 7. A similar pattern was observed for FSH concentrations in the Topical Axiron-treated subjects. Their mean FSH concentrations declined 69% from the Visit 1 baseline value (6.4 mIU/mL) to the morning predose Visit 7 mean value of 1.9 mIU/mL).

The mean baseline serum LH concentration was approximately 4.2 mIU/mL in the Oral TU group, which is within the normal range for eugonadal men (normal range: 1.3 to 8.1 mIU/mL). By Visit 7, the mean concentration in the AM predose sample had declined by approximately 76% to 1.1 mIU/mL (Table 25). The percentage of Oral TU subjects with LH concentrations assayed as BLQ (below the limit of quantitation) increased from approximately 0.7% (1/151) at Visit 1 baseline to approximately 41% (62/151) on Visit 7. A similar pattern was observed for LH concentrations in the Topical Axiron-treated subjects. Their mean LH concentrations declined 75% from the Visit 1 baseline value (4.1 mIU/mL) to the morning predose Visit 7 mean value of 0.96 mIU/mL (Table 25).

The effect of food on drug PK and dosing recommendations relative to food intake are discussed in Section 6.1.8.

8 Postmarket Experience

No marketing applications for Clarus' Oral TU formulation have been submitted to 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 marketed in 80 countries, including Europe and Canada, for up to 30 years by a different pharmaceutical company. The applicant provided a brief review of publicly available post marketing experience with Andriol. A Clinical review of this material was undertaken during the first cycle and will not be reiterated here. The dosing regimen for Andriol based on the Product Monograph for Andriol (approved by Health Canada, Nov 15, 2011) is different than for Jatenzo. The starting dose for Andriol is 60-80 mg titrated to 20-60 mg bid, which is 4-5 times lower than for Jatenzo (starting dose is 200 mg bid in T equivalents). The specific starting dose in CLAR-15012 was 237 mg TU BID.

To summarize the Andriol postmarketing experience, the post marketing surveillance reports included search /analysis of the WHO global individual case safety report database, (VigiBase) and two published studies base on post marketing surveillance database. Based on the Vigibase search, it did not appear that there were specific clusters of PTs under any SOC.

To summarize the published studies:

A GPRD-based epidemiology study (Jick and Hageberg, 2013: BR J Clin Pharmacol 75 (1): 260-270) appeared to demonstrate similar risks of polycythemia, prostate cancer, BPH and BPH-related symptoms, and hypertension for oral TU versus injectable TU. However, the study was not properly designed to provide risk assessments for oral or injectable TU as compared to

background occurrences of polycythemia, prostate cancer, BPH and BPH-related symptoms and hypertension, the tested risks.

In the Austrian Surveillance study (Jungwirth et al, 2007, Aging Male 10(4):183-187), which involved a survey of 189 patients in 43 Austrian centers and 185 doctors, no safety assessments other than serum PSA were performed.

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 the analysis. Of these studies, 19 were controlled studies and 13 were open-label and uncontrolled studies.

The safety monitoring in these studies included AE reports and clinical laboratory tests, but reporting was highly variable across studies. The overall AE profile, including laboratory results, appeared consistent with the TRT class except for some non-specific Gastrointestinal Disorders. The doses used in the studies for Andriol were mostly 40-80 mg in TU, not T equivalents, which are lower than doses used in the Jatenzo clinical trials.

No marketing applications for Clarus' Oral TU formulation have been submitted to any country outside of the United States. In the re-submission, no new data was submitted related to testosterone undecanoate in any formulation.

9 Appendices

9.1 Literature Review/References

See the section of this review entitled POSTMARKETING EXPERIENCE.

9.2 Labeling Recommendations

Based on the Clinical recommendation for a CR action, specific labeling recommendations are premature at this time.

9.3 Advisory Committee Meeting

On January 9, 2018, a meeting of the BRUDAC was held to discuss the Jatenzo NDA, focused primarily on evidence provided in the re-submission. There was one voting question posed to the committee:

Table 28 BRUDAC Voting Question Result

Question to AC	Voting Result		
	Yes	No	Abstain
Is the overall benefit/risk profile of Jatenzo acceptable to support approval as a testosterone replacement therapy/	9	10	0

Committee Discussion: There was a substantial concern of safety related to increased blood pressure in men with age-related hypogonadism. Committee members who voted for approval generally believed that the off-label risks could be mitigated through measures such as REMS, labeling, and required practitioner education. Members who voted “No” were concerned about harm from cardiac risks and off-label use. Some committee members felt that Jatenzo could be safe and efficacious for those with primary hypogonadism and were of a younger age with less cardiac risk factors.

Prior to the voting question, there were three discussion questions for which the discussion will be very briefly summarized here:

1. **DISCUSSION:** Discuss whether the safety of Jatenzo has been adequately characterized. If additional safety data are needed, discuss the type(s) of data that are needed and whether these data should be obtained pre-approval or whether these data can be obtained post-approval. Specifically cover:

- a. The effects of Jatenzo on cardiovascular risk factors, including blood pressure and lipids, together with effects on hematocrit, and the potential for Jatenzo to increase the risk of adverse cardiovascular outcomes in the population that will likely use the drug, if it is approved.
- b. Supraphysiologic dihydrotestosterone (DHT) concentrations in some subjects.
- c. Subjects with maximal testosterone concentrations (C_{max}) exceeding the prespecified targets.
- d. The adrenal-related findings, including adrenocorticotropin (ACTH) stimulation results.

Committee Discussion: The increased blood pressure in men with baseline cardiovascular risk was a major committee concern, especially as it pertains to the large number of older men who are likely to receive Jatenzo. There was less panelist concern about use in younger patients with primary hypogonadism. The significance of DHT elevations is unknown. Maximal T concentrations outliers was not a concern. Adrenal effects on animals could be re-assessed in humans in the postmarketing period.

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

Committee Discussion: The proposed titration regimen was noted to be reasonable by the panel.

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

Committee Discussion: The committee members wanted to see more data to be convinced of the need to obtain testosterone levels from blood in NaF/EDTA tubes instead of the more commonly used serum tubes. One committee member also expressed the need to determine serial testosterone levels at multiple time points in serum samples drawn from a sample of individual patients to determine how much and when TU was converted to T in samples exposed to room temperature.

9.4 Individual Trial Review

9.4.1 CLAR-15012 (3-month pivotal Phase 3 trial)

Title: “A Phase 3, Randomized, Active-Controlled, Open-Label Study of the Safety and Efficacy of Oral Testosterone Undeconoate (TU) in Hypogonadal Men”

Study location: 27 sites in US (24 sites enrolled ≥ 1 subject)

Study duration: 14 March 2016 to 02 November 2016

Study indication: Male hypogonadism

GCP compliance: Yes

Central Lab: (b) (4)

Objectives:

Primary: To determine the efficacy of oral TU in hypogonadal males based on the percentage of treated subjects with 24-hour average serum T concentration (C_{avg}) within the eugonadal range of 252 to 907 ng/dL for blood collected in NaF-EDTA tubes at Visit 7.

Secondary: The secondary objective of the study is to determine the percentage of treated subjects with maximum T concentrations (C_{max}): ≤ 1500 ng/dL, >1800 to ≤ 2500 ng/dL, and >2500 ng/dL.

Other Objectives:

- To compare the Oral TU treated subjects and the Topical Axiron treated subjects with respect to the following:
 - C_{avg} DHT concentration at Visit 7
 - The proportion of subjects in the cosyntropin stimulation test sub study with a normal maximum post-stimulation (cosyntropin stimulation) cortisol level at baseline and Visit 8.
- To summarize calculated free testosterone, estradiol, and DHT in the Oral TU- and Topical Axiron-treated subjects during treatment.
- To summarize baseline and end-of-treatment concentrations and change from baseline to end-of-treatment for LH, follicle-stimulating hormone (FSH), and SHBG in the Oral TU- and Topical Axiron treated subjects.
- To summarize the responses of the Oral TU- and Topical Axiron-treated subjects with respect to change from baseline in the Psychosexual Daily Questionnaire (PDQ)

Safety Objectives

- To estimate the proportion of Oral TU-treated patients who had a total testosterone C_{max} : ≤ 1500 ng/dL, >1800 to ≤ 2500 ng/dL, and >2500 ng/dL.
- To summarize the Oral TU- and Topical Axiron-treated subjects with respect to the following safety parameters:

- Testosterone C_{max} : ≤ 1500 ng/dL, >1800 to ≤ 2500 ng/dL, and >2500 ng/dL.
- Treatment-emergent adverse events
- Changes in high density lipoprotein (HDL) cholesterol levels.
- Changes in hematocrit
- Changes in prostate-specific antigen (PSA).
- Change in the International Prostate Symptom Score (IPSS)
- Change in AM predose blood pressure by routine cuff assessment during the course of the study.
- Change in daytime, nighttime, and 24-hour blood pressure assessed by ambulatory blood pressure monitor (ABPM) from baseline (defined as the last non-missing value before or on the first dose of study drug to Visit 6).

Study Design and Conduct:

This was an open-label, active-controlled, open-label, dose titration study. The duration of treatment was 3 months. Eligible hypogonadal males were randomized in a 3:1 ratio to two arms ($n \approx 165$ /TU arm and $n = 55$ / Axiron arm).

Each subject will participate in the study for approximately 3.5 months including up to a 21-day Screening Period, a 70-day Titration Phase and a 35-day Maintenance Phase.

There were 8 on drug treatment study visits: Visit 1 (Day 1 for randomization, baseline assessment and first dose), Visit 2 (Day 21), Visit 3 (Day 35), Visit 4 (Day 56), Visit 5 (Day 70), Visit 6 (Day 102), Visit 7 (Day 105) and Visit 8 (Day 106: Cosyntropin stimulation test). These visits were preceded by 3 Screening Visits: at Day -21 to Day -3, approximately 7 days after Screen 1 and Screen 3 on Day -2 \pm 1 day.

At all 3 pharmacokinetic visits (Visits 2, 4b and 7) after Amendment 1.0, subjects had a choice of 15 g fat, 30 g fat, or 45 g fat breakfasts and dinners at their pharmacokinetic visits. The fat content of the meals was not explicitly presented to the patient as part of their choice making. Once a choice was made, the same meal was used for all 3 pharmacokinetic visits. All lunch options were 30g fat content and lunch fat composition was not incorporated into the analysis. On non-clinic days, there were no fat or caloric dietary restrictions. The AM- and PM-specific pharmacokinetic parameters were examined for a dependence on AM or PM meal type, respectively. The comparisons were examined using dose-normalized AUC_x values.

Table 29 Schedule of Assessments CLAR-15012 Prior to Amendment 2.0

Activity	Screening			Treatment/Maintenance								Early Withdrawal
	Screen 1	Screen 2	Screen 3	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	
Study Days	Day -21 to Day-3	~7 Days After Screen 1	Day -2 (=1 Day)	Day 1 ^a	Day 21 (=3 days)	Day 35 (=2 days)	Day 56 (=3 days)	Day 70 (=2 days)	Day 102 (=2 days)	Day 105 (=3 days)	Day 106	
Informed consent signed	X											
Inclusion/exclusion	X	X	X									
Medical history review	X											
Review of prior and concomitant medications	X	X	X	X	X	X	X	X	X	X		X
Physical with DRE ^b		X								X		X
Brief physical ^b					X		X					
Weight and height	X											
Adverse event assessment		X		X	X	X	X	X	X	X		X
Vital signs (sitting BP and HR in triplicate)	X			X	X		X			X		X
Randomization number				X								
Sample collection												
Abbreviated safety laboratory tests (fasting) ^c				X								
Complete safety laboratory tests (fasting) ^d		X					X			X		X
Urine dipstick		X										
Total T between 6:00 and 10:00 AM	X	X										
SHBG, albumin, LH, and FSH (predose)				X	SHBG only					X		
PSA		X								X		X
Predose total T, DHT, estradiol between 6:00 and 10:00 AM				X ^e								
Serial sampling (24 hour over-night stay) total T, DHT, estradiol ^f					X		X			X		
Saliva for T ^g					X		X			X		

Activity	Screening			Treatment/Maintenance								Early Withdrawal
	Screen 1	Screen 2	Screen 3	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	
Study Days	Day -21 to Day-3	~7 Days After Screen 1	Day -2 (=1 Day)	Day 1 ^a	Day 21 (=3 days)	Day 35 (=2 days)	Day 56 (=3 days)	Day 70 (=2 days)	Day 102 (=2 days)	Day 105 (=3 days)	Day 106	
Sample collection (cont.)												
Predose exploratory serum sample for ApoA1 assessment, cholesterol efflux analysis, and hepcidin ^b				X						X		
Dose titration (based on 24-hour T C _{avg})						X		X				
I-PSS	X									X		X
Dispense PDQ ^c		X						X				
Collect PDQ				X						X		
24-hour ABPM assessment ^d			X						X			X ^e
Study drug administration				X	X	X	X	X		X		
Study drug accountability					X	X	X	X		X		X
Study drug dispensed				X	X	X	X	X				
Cosyntropin stimulation test sub-study – only												
Cosyntropin stimulation test ^f				X							X	

ABPM = ambulatory blood pressure monitor; ApoA1 = apolipoprotein A-1; BP = blood pressure; C_{avg} = average concentration; DHT = dihydrotestosterone; DRE = digital rectal examination; EDTA = ethylenediaminetetraacetic acid; FSH = follicle-stimulating hormone; HR = heart rate; I-PSS = International Prostate Symptom Score; LH = luteinizing hormone; NaF = sodium fluoride; PDQ = Psychosexual Daily Questionnaire; PSA = prostate-specific antigen; SHBG = sex hormone binding globulin; T = testosterone; TU = testosterone undecanoate

^a Visit 1 was to have occurred between 6:00 and 10:00 AM.

^b A complete physical examination included, at minimum, an examination of head/eyes/ears/nose/throat, a DRE of the prostate, breast and testicular exams. An abbreviated physical examination included, at minimum, examination of head/eyes/ears/nose/throat. On those visits where PSA was collected, the PSA was to have been collected before the DRE.

^c Subjects were to be reminded to fast from food but to take all concomitant medications before the study visit. Chemistry panel (sodium, potassium, chloride, bicarbonate, glucose, calcium), lipids (total cholesterol, high-density lipoprotein, low-density, triglycerides), complete blood count.

^d Chemistry panel (sodium, potassium, chloride, bicarbonate, glucose, calcium), albumin aminotransferase, aspartate transaminase, alkaline phosphatase, bilirubin, creatinine, lipids (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides), albumin, complete blood count.

^e Blood samples for total T, DHT, and estradiol: Subjects had 1 Plain tube (for serum) and 1 NaF-EDTA-containing tube (for plasma) collected.

^f Blood samples for total T, DHT, and estradiol: Subjects had 1 Plain tube (for serum) and 1 NaF-EDTA-containing tube (for plasma) collected. Subjects in the Oral TU treatment group: blood samples were collected -30 minutes and 0, 2, 4, 6, 9, and 12 hours after AM dose and 2, 4, 6, 9, and 12 hours after PM dose. Subjects in the

Topical Axiron treatment group: blood samples were collected -30 minutes and 0, 2, 4, 6, 9, 12, 14, 16, 18, 21, and 24 hours after AM dose. Estradiol was not assayed in the Visit 2 or Visit 4 samples.

- ^g Saliva was collected into clean sterile cups 4 hours after the AM dose, frozen immediately and samples stored at -20 °C. The subject was to have avoided food for 1 hour before saliva collection and was not to have brushed or flossed his teeth 30 minutes before collecting saliva. Saliva samples were stored for possible future analysis.
- ^h Samples were collected, frozen, and stored for potential future analysis to address questions related to lipid-related analyses and/or hematocrit changes, and/or other changes observed with testosterone replacement therapy.
- ⁱ The PDQ was dispensed as paper booklets at Screen 2 and Visit 5b. Subjects were instructed to complete the questionnaire for 7 consecutive days before Visit 1 and Visit 7.
- ^j Ambulatory BP monitor was placed on subject at Screen 3 and again at Visit 6. The subject returned the monitor to the study center the following day and study center determined whether a minimum number of readings for a valid ABPM interpretation was seen, if not, the subject was asked to repeat the 24-hour ABPM (unscheduled visit).
- ^k 24-hour ABPM at early withdrawal, if feasible.
- ^l A subset of subjects participated in the cosyntropin stimulation test at selected study centers. A separate informed consent was signed. Subjects were injected with 0.25 mg cosyntropin and blood samples for cortisol assay were collected immediately before the injection, as well as 30 and 60 minutes after the injection at each visit. At Visit 1, the cosyntropin stimulation test was conducted before administration of study drug. At Visit 8, subjects remained at the study center after the last 24-hour serial blood sample had been obtained before beginning the cosyntropin stimulation test.

Source: Table 2: CLAR-15012 Study Report page 43

Study Treatment and Dose Titration:

The following summary provides a rationale for the selection of the dose regimen in CLAR-15012: At the final pharmacokinetic visit in Study CLAR-12011, 75.0% of the subjects had serum testosterone C_{avg} values within the pre-specified eugonadal range. Approximately 3% of subjects had a C_{max} > 2500 ng/dL and 6% of the subjects had a C_{max} of 1800 to 2500 ng/dL. Approximately 75% of the subjects' final TU dose was lower than the starting dose (316 mg TU BID); suggesting that a lower starting dose might reduce the likelihood that a subject was exposed to too high a dose prior to his first dose titration. Pharmacokinetic modeling of the Study CLAR-12011 data, combined with the data from CLAR-09007, was used to further refine the dose-titration algorithm for CLAR-15012. Subjects randomly assigned to Oral TU in this study started with a dose of 237 mg TU BID, with the goal of having few subjects requiring a reduction in dose.

The time point for the testosterone sample upon which titration decisions were made was modestly revised from a 4- to 6-hour window after dosing in Study CLAR-09007, to a 3- to 5-hour window after dosing in Study CLAR-12011. In contrast, in Study CLAR-15012, the need for dose titration was based on a subject's total testosterone C_{avg} determined from serial pharmacokinetic 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.

Therefore, in CLAR-15012, the dose and dosing regimen 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 only (consistent with the Axiron labeling).
- 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.

During the course of the trial (approximately 23 June 2016) it was discovered that the assay for testosterone concentrations in the NaF-EDTA collected during the study were not yielding reproducible results. Amendment 2.0 (Protocol Version 3.0, 30 June 2016) addressed this concern. A new bioanalytic laboratory with a fully validated NaF-plasma testosterone assay was identified, so the trial could be continued with a modification of the study design and plan. Continuation of the trial was justified for various reasons by Sponsor. First, subjects were enrolled based on a fully validated serum testosterone assay, ensuring that the population included in the study was appropriate. Second, CLAR-15012 is a pharmacokinetic study with the primary objective based on the pharmacokinetic variable of 24-hour plasma testosterone C_{avg} at the end of the 35-day Maintenance Phase (Visit 7). No subjects had reached this visit at the time of the protocol amendment, and the Amendment assured that subjects would be at steady state prior to Visit 7. Since testosterone concentration at steady state is unaffected by the testosterone dose which was administered during dosing periods prior to the 35-day Maintenance Phase (preceding Visit 7), the validity of the Visit 7 pharmacokinetic results was unaffected by the protocol modification. Third, the results of the re-assay of the Visit 2 samples at [REDACTED] (b) (4) yielded reliable results as the assay was reliable and the samples were within proven stability conditions. Fourth, blood sampling for all titrations occurred at steady state. The Visit 4b samples were taken after subjects had been titrated at Visit 3b based on valid pharmacokinetic results (re-assay of Visit 2 samples). Amendment 2 was introduced to detail the re-assay of Visit 2 serial pharmacokinetic samples for testosterone to guide dose titration based on a validated assay. Visit windows were changed to accommodate the new testing methodology for testosterone with Visit designations of 3b, 4b, and 5b.

Reviewer's Comment: *The impact of these amendments has been analyzed by the Division. We have determined that the amendments do not preclude conclusions from the safety or efficacy results.*

Study CLAR-16014 was conducted to determine whether the assayed total T concentration is dependent on the type of sample collection tube. According to the Sponsor, sample collection tubes containing NaF (an inhibitor of nonspecific esterases) plus EDTA (an anticoagulant) had assayed total T concentrations that averaged approximately 86% of the total T concentration in plain sample collection tubes with no additives. It is notable that the eugonadal range for healthy young men in plasma from blood collected in NaF-EDTA tubes is 252-907 ng/dL.

Reviewer's Comment: *The reader is referred to the Clinical Pharmacology review for specific details of this study and for conclusions related to specific tube type.*

Subjects randomly assigned to Oral TU underwent 24-hour pharmacokinetic samples over 24 hours at Visit 2, Visit 4 (depending on subject's progress prior to Amendment 2.0) and Visit 4b. The need for dose titration was based upon C_{avg} at Visits 2 and 4. Depending on subject's progress prior to Amendment 2.0, dose titrations might have occurred at Visits 3 or 5. Dose titration boundaries were based on pharmacokinetic modeling and simulation using testosterone concentration data collected during studies CLAR-09007 and CLAR-12011.

Specific Drug Doses and Titration Steps:

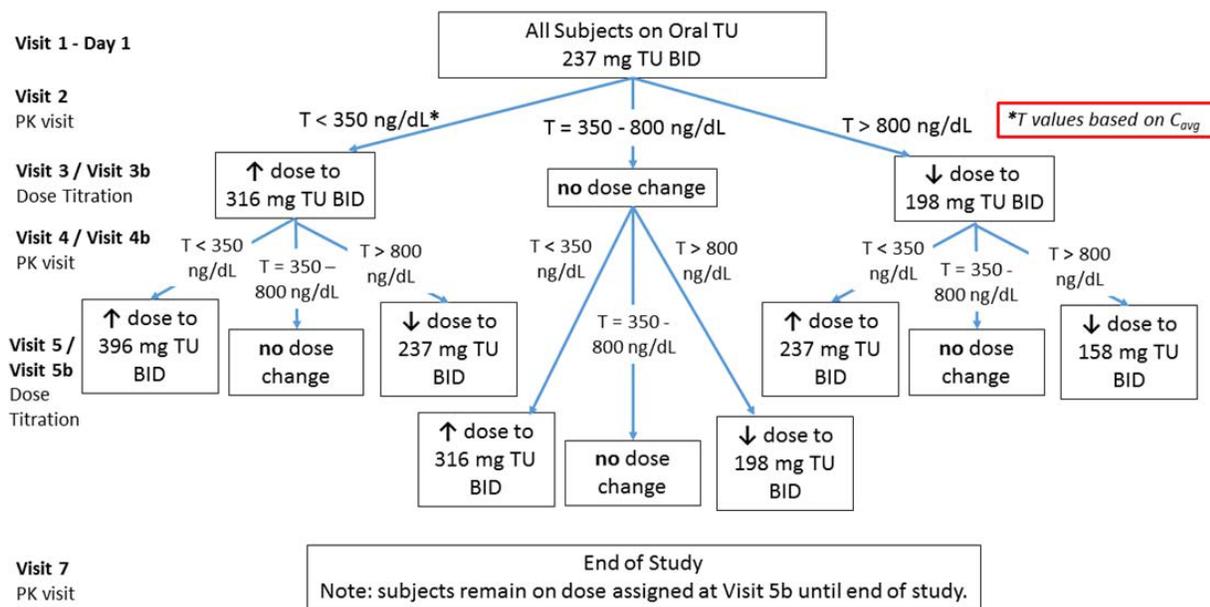
Following Amendment 2.0, but prior to the final pharmacokinetic visit (Visit 7), there were 2 titration opportunities for Oral TU, Visit 3b and Visit 5b. The final Oral TU dose could remain at the 237mg starting dose or be up titrated to 1 of 2 dose levels (316 or 396 bid or down titrated from the starting dose of 237mg.

Following Amendment 2.0, but prior to the final pharmacokinetic visit (Visit 7), there were 2 titration opportunities for Topical Axiron, Visit 3b and Visit 5b. The final dose could remain at the 60 mg starting dose or be up titrated to 1 of 2 dose levels (90 or 120 once daily or down titrated from the starting dose of 60mg to 30 mg once daily.

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

Figure 11 Oral Testosterone Undeconoate Titration Scheme

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



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

The titration of Topical Axiron was as follows:

Based on Visit 2 total testosterone C_{avg} results, a subject on Topical Axiron may have had his dose adjusted at Visit 3/Visit 3b, based on a total testosterone C_{avg} result obtained at Visit 2 (starting dose was 60 mg):

- $C_{avg} < 300$ ng/dL: dose increased to 90 mg testosterone every morning
- $C_{avg} > 1000$ ng/dL: dose decreased to 30 mg testosterone every morning
- $C_{avg} = 300$ ng/dL to 1000 ng/dL: dose maintained at 60 mg testosterone every morning

Based upon Visit 4/Visit 4b total testosterone C_{avg} results, a subject on Topical Axiron may have had his dose adjusted at Visit 5/Visit 5b, based on a total testosterone C_{avg} result obtained at Visit 4/Visit 4b:

- For subjects whose dose was previously increased to 90 mg testosterone, and the resulting testosterone C_{avg} at Visit 4/Visit 4b was:
 - $C_{avg} < 300$ ng/dL: dose increased to 120 mg testosterone every morning
 - $C_{avg} > 1000$ ng/dL: dose decreased to 60 mg testosterone every morning
 - $C_{avg} = 300$ ng/dL to 1000 ng/dL: dose maintained at 90 mg testosterone every morning

• For subjects whose dose was previously decreased to 30 mg testosterone, and the

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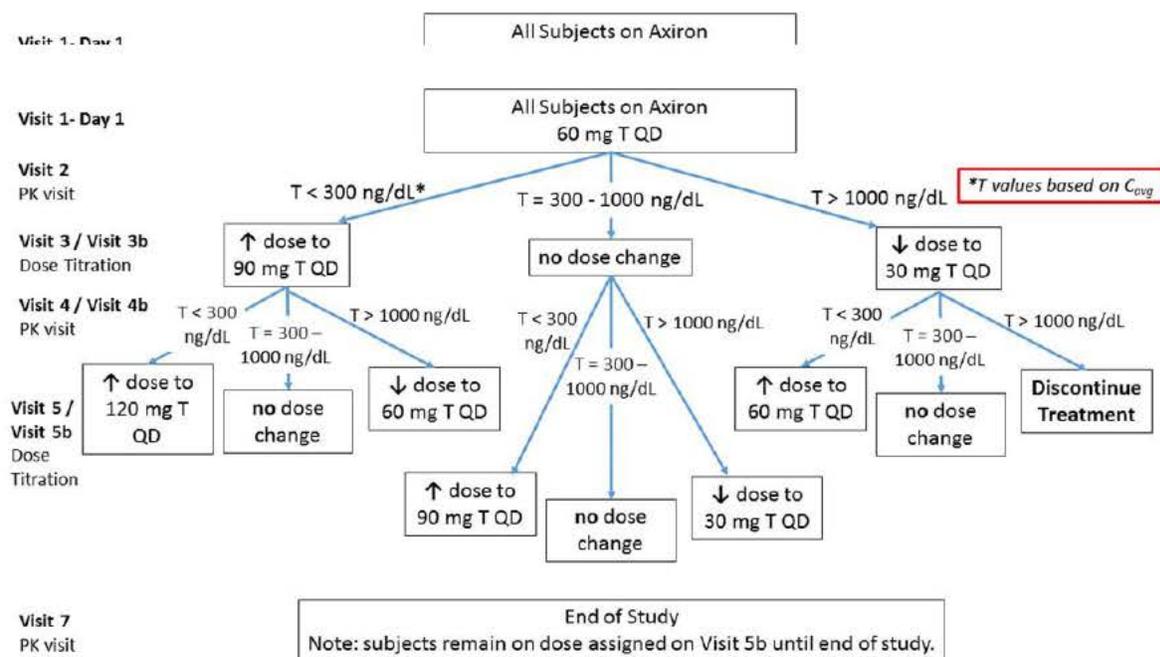


Table 2: Schedule of Assessments After PK Amendment 2

Activity	Visit 3b (Repeat Titration Visit 3)	Visit 4b (Repeat Serial PK Visit 4)	Visit 5b (Repeat Titration Visit 5)	Visit 6	Visit 7	Visit 8	Early Withdrawal
Amended informed consent signed	X						
Review of prior and concomitant medications	X	X	X	X	X		X
Physical examination with DRE					X		X
Brief physical examination		X					
Adverse event assessment	X	X	X	X	X		X
Vital signs (sitting blood pressure and heart rate in triplicate)		X			X		X
Sample collection							
Complete safety laboratory tests (fasting)		X			X		X
SHBG, albumin, LH, and FSH (predose)		X			X		
PSA					X		X
Serial sampling (24 hour over-night stay) total T, DHT, estradiol		X ^a			X		
Saliva for T		X			X		
Predose exploratory serum sample for ApoA1 assessment, cholesterol efflux analysis, and hepcidin					X		
Dose titration (based on 24-hour T C _{avg})	X		X				
I-PSS					X		X
Dispense PDQ			X				
Collect PDQ					X		
24-hour ABPM assessment				X			X
Study drug administration	X	X	X		X		
Study drug accountability	X	X	X		X		X
Study drug dispensed	X	X	X				
Cosyntropin stimulation test substudy – only							
Cosyntropin stimulation test						X	

ApoA1 = apolipoprotein A-1; C_{avg} = average concentration; DHT = dihydrotestosterone; DRE = digital rectal examination; FSH = follicle-stimulating hormone; I-PSS = International Prostate Symptom Score; LH = luteinizing hormone; PDQ = Psychosexual Daily Questionnaire; PK = pharmacokinetic; PSA = prostate-specific antigen; SHBG = sex hormone binding globulin; T = testosterone

^a Estradiol was not assayed in the Visit 4b samples.

Source: Table 3 CLAR-15012 Study Report page 43

Inclusion/Exclusion Study Criteria

To be eligible for the study, subjects were required to meet the following criteria:

1. Male aged 18 to 65 years, inclusive, with a clinical diagnosis of hypogonadism (signs/symptoms consistent with hypogonadism for testosterone-naïve subjects and history of signs/symptoms for subjects who had received prior treatment) as well as serum testosterone levels consistent with hypogonadism as defined by 2 morning total testosterone values of < 300 ng/dL (between 6:00 and 10:00 AM drawn in a Plain tube on 2 separate days [approximately 7 days apart]).
2. Adequate venous access in the left or right arm to allow collection of a number of blood samples via a venous cannula.
3. Must have been naïve to androgen-replacement therapy or washed out of prior androgen-replacement therapies; that is, was willing to cease current testosterone treatment or was not currently taking testosterone treatment, (washout durations specified in exclusion criterion #1). Subjects must have remained off all forms of testosterone, except for dispensed study drug, throughout the entire study.
4. Subjects on replacement therapy for hypopituitarism or multiple endocrine deficiencies must have been on stable doses of thyroid hormone and adrenal replacement hormones for at least 14 days before Screen 1.

Subjects meeting any of the following criteria are not eligible for participation in this study:

1. Received oral, topical (e.g., gel or patch), intranasal, or buccal testosterone therapy within the previous 2 weeks, intramuscular testosterone injection of short-acting duration (e.g., testosterone enanthate, testosterone cypionate) within the previous 4 weeks, intramuscular testosterone injection of long-acting duration (e.g., AVEED®) within the previous 20 weeks, or testosterone implantable pellets (Testopel®) within the previous 6 months.
2. Received Oral TU in a previous Clarus-sponsored investigational study. Had significant intercurrent disease of any type; in particular, liver, kidney, uncontrolled or poorly controlled heart disease, including hypertension, congestive heart failure or coronary heart disease, or psychiatric illness, including severe depression.
3. Had a recent (within 2 years) history of stroke, transient ischemic attack, or acute coronary event.
4. At screening,
 - a. If the subject was not on antihypertensive medications, regardless of age, and had a mean of the triplicate assessment of systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 90 mm Hg;
 - b. If the subject was on antihypertensive medications and < 60 years of age, and had a mean of the triplicate assessment of systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg; or
 - c. If the subject was on antihypertensive medications and > 60 years of age, and had a mean of the triplicate assessment of systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 90 mm Hg.
5. Had recent (within 2 years) history of angina or stent (coronary or carotid) placement.
6. Had untreated, severe obstructive sleep apnea.
7. Had clinically significant abnormal laboratory values, including serum transaminases > 2 × upper limit of normal (ULN), serum bilirubin > 1.5 × ULN, or serum creatinine > 1.5 × ULN.
8. Had a hematocrit value of < 35% or > 48%.
9. Had a history of polycythemia, either idiopathic or associated with TRT treatment.
10. Was a diabetic subject with a glycosylated hemoglobin > 8.5%.
11. Had a body mass index ≥ 38 kg/m².
12. If receiving the following medications:
 - a. Had been on stable doses of lipid-lowering medication for < 3 months (Note: subject was expected to remain on a stable dose of lipid-lowering medication(s) throughout the study);
 - b. Had been on stable doses of oral medication for diabetes for < 2 months;
 - c. Had been on stable doses of antihypertensive medication for < 3 months; or
 - d. Had been on stable doses of anticonvulsant therapy for < 3 months.
13. Had an abnormal prostate digital rectal examination (palpable nodules), elevated PSA (serum PSA > 4.0 ng/mL), I-PSS > 19 points at screening, and/or history of, or current or suspected, prostate cancer.

14. Had a history of, or current or suspected, breast cancer.
15. Had a history of abnormal bleeding tendencies or thrombophlebitis unrelated to venipuncture or intravenous cannulation within the previous 2 years.
16. Used dietary supplements such as saw palmetto or phytoestrogens and any dietary supplements that may have increased total testosterone, such as androstenedione or dehydroepiandrosterone within the previous 4 weeks.
17. Had known malabsorption syndrome and/or current treatment with oral lipase inhibitors (e.g., orlistat [Xenical®]) and/or bile acid-binding resins (e.g., cholestyramine [Questran®], colestipol [Colestid®]).
18. Inability to refrain from smoking during the confinement periods as required by the individual study center.
19. Had history of abuse of alcohol or any drug substance within the previous 2 years.
20. Poor compliance or unlikely to keep clinic appointments.
21. Had received any drug as part of another research study within 30 days of initial dose administration in this study.
22. Donated blood (≥ 500 mL) within the 12-week period before the initial study drug dose.
23. Current use of the following groups of drugs that affect testosterone levels, testosterone metabolism, or levels of testosterone metabolites, namely antiandrogens, 5-alpha-reductase inhibitors (e.g., dutasteride, finasteride), estrogens, long-acting opioid analgesics (e.g., methadone hydrochloride, buprenorphine hydrochloride) or human growth hormone.

Changes In Study Conduct

The original protocol, dated 04 January 2016, was amended 3 times. A total of 27 subjects were enrolled under original protocol, Version 1.0, and 195 subjects were enrolled under Version 2.0, Amendment 1.0 of the protocol. No subjects were recruited under Version 3, Amendment 2, which revised the conduct of the study to adapt to the new bioanalytic lab analysis of NaF-plasma testosterone. No subjects were recruited under Version 4, Amendment 3, which occurred after the last subject had completed the study and revised the protocol in large part to adapt to changes in the analysis suggested by the FDA, after the in-life phase of the study was complete.

Amendment 1.0 (Protocol Version 2.0, 19 April 2016) per 15 April 16 Advice Letter in brief:

- Included subjects were to have signs/symptoms consistent with hypogonadism for testosterone-naïve subjects and a history of signs/symptoms for subjects who had received prior treatment), as well as testosterone levels consistent with hypogonadism
- Subjects on a stable dose of lipid- lowering medication at study entry were to remain on a stable dose throughout the study.
- Modified exclusion criterion regarding concomitant use of medications that could affect testosterone levels, testosterone metabolism or levels of testosterone metabolites.
- Removed exclusion criteria for subjects unwilling or unable to follow dietary guidelines for the study.

- Removed the need for breakfast and dinner meals consumed on outpatient days to contain approximately 20-40 g of fat and the need to counsel subjects regarding fat content of their diet for days when meals were not provided.
- Modified exclusion criteria regarding screening blood pressure, detailing limits for subjects not on antihypertensive medications, subjects on antihypertensive medications and < 60 years of age, and subjects on antihypertensive medications and > 60 years of age.
- Modified criteria regarding discontinuation of subjects from the study due to elevated blood pressure, and alternatives to discontinuation such as increased antihypertensive medication therapy or additional therapy.
- Specified that meals provided during confinement would contain approximately 15, 30, or 45 g of fat and that subjects were advised to choose the meal that most reflected their usual diet.

Amendment 2.0 Protocol Version 3.0 30 June 2016:

This amendment has been described in the section entitled *Treatment and Dose Titration*

Amendment 3.0 (Protocol Version 4, 6 March 2017) per 10 February 2017 Advice Letter which was received after the last subject had completed the study. In brief:

- Amended primary analysis to include all randomized patients who took at least one dose of study drug (Modified ITT Population)
- Amended primary efficacy analysis with respect to how missing data were handled. The primary efficacy analysis was amended to treat 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 the study, namely the subject moved from area prior to Visit 7, withdrew consent without indicating that it was related to the therapy, was lost to follow-up, or did not have adequate plasma pharmacokinetic samples at Visit 7 to allow the calculation of testosterone C_{avg} . In these cases, the Visit 7 testosterone C_{avg} value was imputed by LOCF.
- Adjusted the way multiple imputation was performed for sensitivity analyses of the primary endpoint.
- For the primary efficacy endpoint, the eugonadal range for testosterone C_{avg} was modified to 252-907 for blood collected in NaF-EDTA tubes. Reference to data from other Clarus-sponsored studies supporting this change was included as part of an amendment to the statistical analysis plan (submitted 23 November 2016) which occurred prior to database lock.
- Specified that free testosterone would be calculated using the measured total free testosterone, SHBG, and albumin concentration using the Vermeulen formula.

Changes in Planned Analyses

Changes from the analysis planned in the protocol in brief:

- Repeated measures analysis planned for the Psychosexual Daily Questionnaire (PDQ) were changed to ANCOVA analysis as the PDQ was only collected at Visit 1 and Visit 7

Changes to the SAP implemented after database lock based on FDA Advice Letter dated 10 February 2017:

- Replaced the Traditional Testosterone Population with the Modified ITT Population
- Addressed issues raised in the Advice Letter, including the primary analysis requested by FDA and adjusted the way multiple imputation was performed.

New analyses that were not detailed in the final SAP or changes to the analyses described in the final SAP included:

- An additional analysis of the cosyntropin stimulation test sub study was performed excluding 1 Oral TU subject who had received 14 days of treatment with a corticosteroid. In addition, an analysis of mean change from baseline in cortisol levels was performed.
- Summaries of total I-PSS Score and Quality of Life Assessment Index were to be completed separately for those who completed Visit 7 and those whose assessment was completed at the time of early withdrawal; however, these analyses were not performed.
- An analysis of vital sign measurements for subjects not included in the ABPM Population was performed and displayed alongside the ABPM Population (by Division request).
- In the food-effect analysis, distributions of the final titrated dose were to be examined for specific breakfast-dinner meal combinations; however, these analyses were not performed.
- The primary endpoint was analyzed by median weight.
- The SAP indicated that, for subjects receiving lipid-modifying agents, baseline concomitant medication would be examined and those subjects taking HMG CoA reductase inhibitors, fibrates, niacin, omega-3 fatty acids, or fish oils would be identified; however, this was not performed.

Reviewer's Comment: *In CLAR-16015, a food effect study, completed January 2017, concluded "Although there is a food effect when comparing the 15 g fat meal to the 30 g fat reference meal, based on the lower confidence bound being less than 0.70, the reduction in exposure is at most 30%, which is relatively small in comparison to the width of the target eugonadal range. Oral TU should be taken with meals and there is no need to provide further instruction on the fat content of meals." FDA's Clinical Pharmacologists have determined that results from CLAR-16015 support the Sponsor's contention that it is not necessary to specify the fat content of meals for eventual product labeling.*

Subject Disposition

A total of 537 subjects were screened for entry into the study. Of these, 315 (58.7%) subjects failed screening. The most common reasons for screen failure were not meeting criteria for diagnosis of hypogonadism, primarily due to screening serum testosterone levels ≥ 300 ng/dL (183 subjects), unable to commit to appointment schedule or compliance with study procedures

(29 subjects), and elevated hematocrit values (23 subjects). The remaining 222 subjects were randomized in a 3:1 ratio to Oral TU (166 subjects) or Topical Axiron (56 subjects); all but 1 subject randomized to Topical Axiron received at least 1 dose of study drug. The proportions of subjects who completed the study were similar between the treatment groups (Oral TU: 92.8%; Topical Axiron: 87.5%). 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.

165/166 (100%) of TU subjects and 55/56 (98.2%) of Axiron subjects had a least 1 PK profile and 165/166 (99.4%) and 54/56 (96.4%) had a PK profile at End-of-Study Visit 7.

Table 30 CLAR-15012 Subject Disposition by Dose at Study Discontinuation

Oral TU N=166					
Subjects n(%)	158 mg bid	198 mg bid	237 mg bid (starting dose)	326 mg bid	396 mg bid
randomized	1(0.6)	2(1.2)	44(26.8)	55(33.1)	64(38.6)
treated	1(0.6)	2(1.2)	44(26.5)	55(33.1)	64(38.6)
completed	1(0.6)	2(1.2)	40(24.1)	50(30.1)	61(36.7)
discontinued	0	0	4(2.4)	5(3.0)	3(1.8)
Topical Axiron N=56					
	30 mg qd	60 mg qd	90 mg qd	120 mg qd	
randomized	0	27(48.2)	23(41.1)	6 (10.7)	
treated	0	26(46.4)	23(41.1)	6 (10.7)	
completed	0	22(39.3)	21(37.5)	6 (10.7)	
discontinued	0	5(8.9)	2(3.6)	0	

Source: Study CLAR-15012, end-of-study Tables 14.1.1.3.1 and 14.1.1.3.2, pages 190-191

Table 31 Overall Subject Disposition by Treatment Group (ITT Population)

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

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

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

^a Other reasons included: subject had high PSA prestudy, 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.

Reviewer's Comment: Three TU 396 mg patients discontinued secondary to adverse events. These will be analyzed in safety review of this Study

Demographics

The Oral TU population's demographics were notable for body weight, with most categorized as overweight or obese (95.2%) versus 92.8% for Topical Axiron subjects. Men over 65 years of age were not eligible for study participation, serving to limit the number of geriatric subjects in the study. The table below shows the distribution by age in study subjects.

Table 32 Distribution by Age Category in CLAR-15012 Study Subjects

	Age Group n (%)					Total
	20 years or less	21 to 30 years	31 to 40 years	41 to 50 years	51 to 65 years	
Oral TU	0	4 (2.4)	22 (13.2)	28 (16.9)	112 (67.5)	166
Axiron	0	0	3 (5.4)	14 (25.0)	39 (69.6)	56

Source: Biometrics email February 13, 2018

Table 33: Demographics at Baseline CLAR-15012 (ITT Population)

Characteristic	Oral TU (N = 166)	Topical Axiron (N = 56)
Age (years)		
Mean (SD)	51.6 (9.08)	53.4 (7.86)
Median	53.0	53.0
Minimum, Maximum	24, 65	31, 65
Race, n (%)		
American Indian or Alaska Native	0	1 (1.8)
Asian	3 (1.8)	2 (3.6)
Black or African American	29 (17.5)	11 (19.6)
White	133 (80.1)	42 (75.0)
Other	1 (0.6)	0
Ethnicity, n (%)		
Hispanic or Latino	25 (15.1)	15 (26.8)
Not Hispanic or Latino	141 (84.9)	41 (73.2)
Height (cm)		
Mean (SD)	178.4 (6.81)	178.4 (7.61)
Median	179.0	177.8
Minimum, Maximum	159, 194	163, 193
Weight (kg)		
Mean (SD)	101.4 (15.75)	98.2 (14.24)
Median	100.1	97.5
Minimum, Maximum	50, 136	64, 131
BMI (kg/m²)^a		
Mean (SD)	31.8 (4.16)	30.9 (4.13)
Median	32.2	30.6
Minimum, Maximum	17, 38	21, 38
BMI Categories, n (%)		
Under Weight: < 18.50 (kg/m ²)	1 (0.6)	0
Normal Weight: 18.50-24.99 (kg/m ²)	7 (4.2)	4 (7.1)
Overweight: 25.00-29.99 (kg/m ²)	50 (30.1)	20 (35.7)
Obese: ≥ 30.00 (kg/m ²)	108 (65.1)	32 (57.1)

Source: Table 10, CLAR-15012 Study Report page 86

Table 34: Baseline Subject Characteristics CLAR-15012 (ITT Population)

Characteristic	Oral TU (N = 166)	Topical Axiron (N = 56)
Serum Testosterone at Screen 1 (ng/dL)		
Mean (SD)	190.2 (69.37)	183.9 (66.38)
Median	202.0	199.5
Minimum, Maximum	2, 299	8, 298
Serum Testosterone at Screen 2 (ng/dL)		
Mean (SD)	194.9 (70.21)	174.4 (65.58)
Median	205.5	167.5
Minimum, Maximum	11, 297	2, 294
Type of Hypogonadism, n (%)		
Primary	75 (45.2)	25 (44.6)
Secondary	28 (16.9)	6 (10.7)
Combined	3 (1.8)	3 (5.4)
Unknown/Undefined	60 (36.1)	22 (39.3)
Duration of Hypogonadism, years		
Mean (SD)	5.87 (5.355)	4.88 (3.553)
Median	4.20	4.15
Minimum, Maximum	0.0, 27.3	0.0, 16.4
At Least 1 Reported Hypogonadal Symptom, n (%)	165 (99.4)	55 (98.2)
Randomized prior to Amendment 1.0, n/N (%)	42/43 (97.7)	15/15 (100)
Randomized after Amendment 1.0, n/N (%)	123/123 (100)	40/41 (97.6)
Baseline Diabetic Status, n (%)		
Prediabetic	60 (36.1)	19 (33.9)
Type I or Type II Diabetic	40 (24.1)	15 (26.8)
Duration of Type I or Type II Diabetes, years		
Mean (SD)	9.99 (7.558)	6.81 (6.851)
Median	8.40	4.30
Minimum, Maximum	0.3, 28.3	0.0, 21.4
History of Hypertension, n (%)		
Yes	87 (52.4)	26 (46.4)
No	79 (47.6)	30 (53.6)
Baseline Hypertension Classification, n (%)		
Normal	37 (22.3)	22 (39.3)
Pre-hypertensive	106 (63.9)	28 (50.0)
Stage 1 Hypertension	23 (13.9)	5 (8.9)
Stage 2 Hypertension	0	0
Not Currently Treated for Hypertension	86 (51.8)	32 (57.1)
Baseline Hypertension Classification		
Normal	24 (14.5)	17 (30.4)
Pre-hypertensive	50 (30.1)	14 (25.0)
Stage 1 Hypertension	12 (7.2)	0
Stage 2 Hypertension	0	0

Source: Table 11, CLAR-15012 Study Report page 89

52.4% of Oral TU subjects and 46.4% of Axiron subjects had a history of hypertension. Of the TU patients, 77.8% at Baseline were either prehypertensive or class 1 hypertensive as were 89.3% of the Axiron patients. 37.3% of TU prehypertensive or class one hypertensive patients were not receiving anti-hypertensive treatment versus 25.0% of similar Axiron patients (page 87 of CLAR-15012 CSR).

Patient Compliance

Mean and median percent compliance during the study was high and comparable between the

treatment groups. The proportion of subjects who were 80% to 120% compliant with their dosing regimen throughout the study was 91.0% in the Oral TU group and 85.5% in the Topical Axiron group.

Table 35 CLAR-15012 Treatment Compliance Summary

Characteristic	Oral TU (N=166)	Topical Axiron (N=55)
Percent Compliance with Study Drug	n=162	n=55
Mean (SD)	96.6 (11.06)	94.3 (15.33)
Median	98.1	93.3
Minimum, Maximum	42, 154	43, 136
Proportions of Subjects by Compliance Category, n(%)		
<80% Compliance	8 (4.8)	4(7.3)
≥80% to ≤120% Compliance	151 (91.0)	47 (85.5)
≥120% Compliance	3 (1.8)	4 (7.3)
Unknown	4	0

Source: CLAR-15012 Study Report, Table 13, page 91.

The mean and median percent compliance from Visit 5b to Visit 7 was 102.6% and 100.7%, respectively, in the Oral TU group; and 99.5% and 93.4%, respectively, in the Topical Axiron group. The proportion of subjects who were 80% to 120% compliant with their dosing regimen from Visit 5b to Visit 7 was 88.6% in the Oral TU group and 65.5% in the Topical Axiron group.

Compliance was unable to be determined for 4 Oral TU subjects as they failed to return at least 1 of the study drug bottles dispensed and the site was unable to provide any additional information regarding these missing bottles. Several other subjects in both treatment groups also failed to return their study drug bottles; however, the sites were able to confirm that those bottles had been discarded in error. Compliance for those subjects was calculated assuming that all study drug from the non-returned bottles was taken/applied. This assumption resulted in very high calculated compliances for some subjects.

Two additional subjects with substantial over-compliance include:

- Subject (b) (6) (Oral TU) had an overall compliance of 153.5%. This subject was over-compliant at every visit, resulting in high overall compliance.
- Subject (b) (6) (Topical Axiron) had an overall compliance of 135.9%. This subject was lost to follow up and never returned his partially used Axiron container. For this

subject, an assumption was made that all of the Topical Axiron had been applied, which resulted in a high calculated compliance.

Protocol Deviations

All Protocol deviations were reviewed (study report Listing 16.2.2.1). Seven (7) subjects were found to have hematocrit elevations that resulted in a protocol violation:

- Subjects (b) (6) were found to have baseline Hct >48.0 %. These subjects were allowed to enroll in study violating screening standards. Neither subject had a hematocrit >54% during the study.
- Subject (b) (6) had an Hct of 54.3% at Visit 4b which was not repeated or reported. An Hct at Visit 7 was 51.0%.
- Subjects (b) (6) had Hcts at Visit 7 of 56.3%, 54.4% and 54.9% respectively. These were not noted or repeated.
- Subject (b) (6) at Visit 4b had an Hct of 56.0%. This value was not repeated, but at his early termination Visit, three weeks later, the Hct was 55.6% and patient was terminated from study participation.
- All patients with treatment emergent Hct >54.0% were included in Table 37 (Oral TU Subjects with Treatment-Emergent Adverse Events of Hematocrit Increased) on page 134 of CLAR-15012 CSR.

There were no protocol deviations of significance relating to serum PSA, serum lipids, or vital signs.

Reviewer's Comment: *The above protocol deviations did not, in my opinion, appreciably affect study outcome safety measures.*

In addition, some of the serum cortisol determinations in the Cosyntropin Stimulation Sub study were obtained out of window. This issue has been discussed in previous sections of this review.

Efficacy Evaluations

All subjects randomized in the study were included in the ITT Efficacy Population. The 1 subject randomized to Topical Axiron who was never dosed was excluded from the Modified Efficacy ITT, Safety, and PK Populations.

In regard to Safety subpopulations (also see previous sections of this review, as well as sections that follow in this Appendix),

- Approximately 80% of the subjects in both treatment groups had ambulatory blood pressure monitoring (ABPM) measurements with interpretable results at Screening and at Visit 6 and were included in the ABPM Population.
- Approximately 30 subjects (15 subjects randomly assigned to Oral TU and 15 subjects to Topical Axiron) were planned to participate in the Cosyntropin stimulation sub study;

however, the numbers of subject enrolled was instead consistent with the 3:1 overall randomization ratio used in the study (thus, 24 Oral TU and 8 Topical Axiron).

Table 36 CLAR-15012 Data Sets Analyzed (All Randomized Subjects)

Population, n(%)	Oral TU (N=166)	Topical Axiron (N=56)
ITT(all randomized subjects)	166 (100.0)	56 (100.0)
Modified ITT(≥ 1 study drug dose)	166 (100.0)	55 (98.2)
PK(at least one evaluable PK profile)	166 (100.0)	55 (98.2)
Safety(all randomized and (≥ 1 study drug dose)	166 (100.0)	55 (98.2)
ABPM	135 (81,3)	45 (80.4)
Cosyntropin Sub study	24 (14.5)	8 (14.3)

Source: Study CLAR-15012 Report, Table 14, page 93

Primary Efficacy Endpoint

The primary efficacy variable was the 24-hour testosterone Cavg at Visit 7. The primary efficacy endpoint was an estimate of the proportion of Oral TU-treated subjects with a T Cavg within the normal range. 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 because of a cause not related to the study drug (e.g., the subject moved from study center area). For missing values not attributed to a study drug-related cause, the Visit 7 Cavg was imputed by LOCF, and then it was determined whether the Cavg was within the eugonadal range. Success required that at least 75% (the lower limit of a 95% CI must not be below 65%) of subjects' Cavg fell within the eugonadal range. Due to the bioanalytical method conducted in this study, a new testosterone Cavg eugonadal range for men when their blood is collected in NaF-EDTA tubes was determined by the Sponsor in Study CLAR-16014. The reader is referred to the Clinical Pharmacology review for details of and conclusions base on this study. To summarize, in that study, blood was collected from 97 healthy young men, and the testosterone concentration was measured from the subjects' plasma from the NaF-EDTA tubes. The mean, calculated using natural-log transformed testosterone concentrations, was 478 ng/dL; and the eugonadal range was determined as the exponential of the mean \pm 2 SDs of the population, namely 252 to 907 ng/dL.

Primary efficacy endpoint results are shown in the table below.

Table 37 Percentage of Subjects Achieving Eugonadal Testosterone Cavg Values at Visit 7 for Primary Analysis (Modified ITT Population)

Testosterone Cav Range, n (%)	FDA Target	Oral T (N=166)	Topical Axiron (N=55)
252 ng/dL ≤ Cavg ≤ 907 ng/dL	≥ 75%	145 (87.3%)	48 (87.3%)
Lower bound 95% CI	≥ 65%	81.3%	75.5%
Upper bound 95% CI		92.0%	75.5%
Cavg mean(SD) ng/dL		401.2 (140.2)	390.6 (139.9)
95% CI		379.7, 422.7	352.8, 428.5

CI=confidence interval, SD=standard deviation

Source: CLAR-Study 15012 report, Table 15, page 94.

For details in regard to the specific analysis that generated this summary data, the reader is referred to the review by Office of Biometrics. A summary is provided here. A total of 22 subjects (15 Oral TU, 7 Topical Axiron) had missing values for testosterone C_{avg} at Visit 7. In addition the primary analysis, three (3) sensitivity analyses, including LOCF, multiple imputation, and imputation from baseline, were performed. All 3 sensitivity analyses provided an imputed testosterone Cavg value for all subjects 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 ≥ 75% of subjects with a testosterone Cavg in the eugonadal range and the lower bound of the 95% CI ≥ 65%.

The Sponsor performed a post-hoc analysis of the primary endpoint by weight subgroups (≤100 kg and >100 kg). In both the Oral TU and Topical Axiron groups, a slightly higher percentage of subjects who weighed ≤ 100 kg had values in the eugonadal range (89.2% and 90.3%, respectively) compared with subjects who weighed > 100 kg (85.5% and 83.3%, respectively).

In the Oral TU group, the mean (± SD) of the last dose of study drug was higher for subjects who weighed > 100 kg compared with those who weighed ≤ 100 kg; however, in the Topical Axiron group, the mean (± SD) of the last dose of study drug was comparable between the weight subgroups. The mean last dose of Oral TU was greater in the subjects weighing >100 kg (an upward shift). The distribution of the last dose taken in the Topical Axiron group was nearly the same in the 2 weight groups. For subjects weighing > 100 kg in the Oral TU group, both the estimated percentage of subjects (85.5%) and the lower bound of the 95% CI (76.1%) met the FDA target of ≥ 75% and ≥ 65%, respectively.

Reviewer's Comment: *The weight subgroup analysis is post hoc, and still demonstrates acceptable results in lighter as well as in heavier subjects.*

Secondary Endpoints

The table below summarizes the results of the secondary (C_{max}-related) endpoints in this protocol.

Table 38 Percentage of Subjects with Testosterone C_{max} Values in Protocol Specific Safety Endpoints

Testosterone Cav Range, n (%) at Visit 7	FDA Target	Oral TU (N=151)	Topical Axiron (N=48)
C _{max} ≤1500 ng/dL	≥85%	137 (90.7%)	47 (97.9%)
C _{max} >1800-2500 ng/dL	≤5%	3 (2.0%)	1 (2.1%)
C _{max} >2500 ng/dL	0	3 (2.0%)	0

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

Two of the three required categories were successfully achieved. For the third category, C_{max} >2500 ng/dL, the Sponsor states that there are several common features in these three patients with a T C_{max} > 2500 ng/dL indicating contamination of samples with T:

- All three subjects were at the same clinical site and underwent pharmacokinetic sampling on the same day and at the same time.
- A subject receiving Topical Axiron ((b) (6)) was having pharmacokinetic sampling at the same time as Oral TU subjects (b) (6) and (b) (6).
- The sampling occurred 2 hours after Topical Axiron was applied in the clinical site which is the earliest time after application for PK sampling.
- Transference from application site or Axiron bottle is warned about in drug labeling.

All other concentrations for the 3 subjects, during both the AM and PM dosing intervals, were < 1500 ng/dL, except in Subject (b) (6) who had a concentration of 1855 ng/dL 4 hours following the AM Oral TU dose.

The table below summarizes the observed testosterone (T) and metabolite levels in the three TU subjects with a T C_{max} of > 2500 ng/dL.

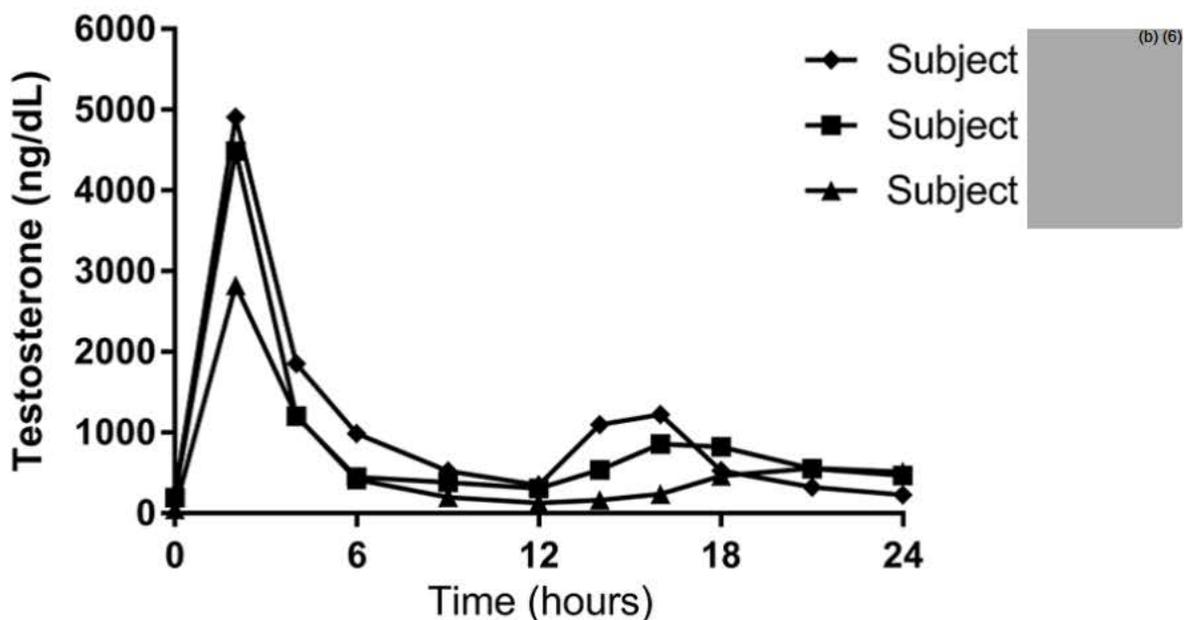
Table 39 T, DHT, DHT/T Ratios in TU Subjects with Cmax >2500 ng/dL at Visit 7

	Observed Testosterone(T), Dihydrotestosterone (DHT), and DHT/T Ratios For Subjects with High T Cmax Samples					Estimated 2h T concentrations	
	2h	2h	2h	4h	14h	Estimate from 4h DHT/T	Estimate from 14h DHT/T
Subject	T ng/dL	DHT ng/dL	DHT/T mole ratio	DHT/T mole ratio	DHT/T mole ratio	T ng/dL	T ng/dL
(b) (6)	4905	297.2	0.0602	0.1665	0.1625	1773	1817
	4485	198.3	0.0439	0.1378	0.0993	1429	1984
	2824	152.9	0.0538	0.1301	0.2305	1167	659

Source: CLAR-15012, Table 19, page 101

The figure below is a graphic representation of the T values in these three subjects at Visit 7.

Figure 12 Testosterone Values for Oral TU Subjects with a T Cmax Value >2500 ng/dL at Visit 7



Source: CLAR-15012, Figure 8, page 100

The Sponsor performed an additional safety analysis using new Cmax cutoff values, equivalent to T>2500 ng/dL (2268 ng/dL), to account for the new assay technique consisting of a plasma substrate in a NaF-EDTA collection tube. In that analysis, the Sponsor identified one additional subject with a Cmax value >2268 ng/dL. This patient, Subject (b) (6), did not have a readily

apparent source for sample contamination on Visit 7 as did the other three subjects. This subject's two serum testosterone levels during Screening were 18 ng/dL (Day -22) and 29 ng/dL (Day -15). His Visit 1 plasma pre-dose testosterone level was 21.8 ng/dL. In brief, this subject was a 57-year-old Hispanic male with a prior history of hypogonadism, fatigue, low libido (all diagnosed in 2001). He had been using a testosterone patch until Day -39 but was using no other concomitant medications. His 24-hour testosterone plasma PK parameters are shown in the table below:

Table 40 CLAR 15012 Subject (b) (6) Study PK Parameters

Visit	Study Day	Oral TU dose	TCav-24hr (ng/dL)	TCmax-24hr (ng/d/L)
Visit 2	18	237 mg BID	487	1732
Visit 4b	94	237 mg BID	455	2562
Visit 7	137	237 mg BID	511	2467

Source: Unlabeled Table, NDA 206089 SDN 35

In this subject, at both Visits 4b and 7, the Cmax outlier points were present at a single time point with a T concentration >2268 ng/dL. The patient's Cavg exposures were otherwise in the eugonadal range for each PK determination. Visit 4 was to have occurred at Day 56 ±3 and Visit 7 was to have occurred at Day 105 ±3, but the visits were modestly delayed secondary to protocol amendments, as previously discussed.

The subject's hematocrit value was slightly high at Screening Visit 2 (study Day -15) at 48.9%. He returned for a second draw, as allowed by the protocol, on study day -7, and qualified for study participation with a HCT of 46.9%. Visit 1 HCT obtained prior to first dose of study drug was 49.1%, HCT on study day 94 was 47.1%, and HCT on study day 137 was 51.5% at Visit 7.

The subject's mean cuff blood pressures were 105/70 at Visit 1 (study day1), 106/66 at Visit 2 (study day 18), 112/70 at Visit 4b (study day 94) and 106/68 (study day 137).

Results for the subject's 24-hour mean blood pressure, as measured by ABPM, are shown below:

Table 41 Subject (b) (6) ABPM Results

Visit	Systolic BP (mmHg)	Diastolic BP (mmHg)	Mean Arterial Pressure (mmHg)	HR (bpm)
Screening Visit 3	110.4	65	79.6	77.5
Visit 6 (Study Day 136)	119.9	72.6	87.5	82.8
Change from Baseline	9.5	7.6	7.9	5.3

Source: Unlabeled Table, NDA 206089 SDN 35

Reviewer's Comment: In this subject, the ABPM results, but not the cuff BP, showed an increase from baseline in mean arterial blood pressure.

The changes in this subject's serum lipids are shown in the table below:

Table 42 Subject (b) (6) Serum Lipids

Visit	Study Day	HDL(mmol/L) [nl range: 1-1.5]	LDL(mmol/L) [nl range: 0-2.6]	Triglyceride (mmol/L) [nl range: 0-1.68]
Screening Visit 2	-15	1.8	2.6	0.69
Visit 4b	94	1.4	2.3	0.61
Visit 7	137	1.7	1.7	0.63

nl=normal Source: Unlabeled Table, NDA 206089 SDN 35

For the original 3 patients with Cmax >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 Cmax values were >2500 ng/dL after the AM dose, but their Cmax values were substantially below 2500 ng/dL after the PM dose.
- The increase in the Cmax was not associated with the fat content of the preceding meal.

Reviewer's Comment: The Sponsors analysis appears reasonable. Each subject had only one time point with T concentration >2500 ng/dL.

A supplemental analysis was performed in which the Cmax criteria boundaries were adjusted for the upper limit of the 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). Testosterone Cmax 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 might affect the frequency distribution of outliers.

One additional outlier was identified and a narrative for this subject (Subject (b) (6)) has been provided above. Using the new criteria, the C_{max} outlier results are shown here:

Figure 13 Percentage of Subjects with Testosterone C_{max} Values in Selected Ranges at Visit 7 Based on Cavg Upper Limit (Subjects Who Had Testosterone C_{max} at Visit 7)

Testosterone C_{max} Adjusted Range, n (%)	FDA Target	Oral TU (N=151)	Topical Axiron (N=48)
\leq 1361 ng/dL	\geq 85%	125 (82.8%)	47 (97.9%)
$>$ 1633-2268 ng/dL	\leq 5%	5(3.3%)	1 (2.1%)
$>$ 2268 ng/dL	0	4 (2.6%)	0

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

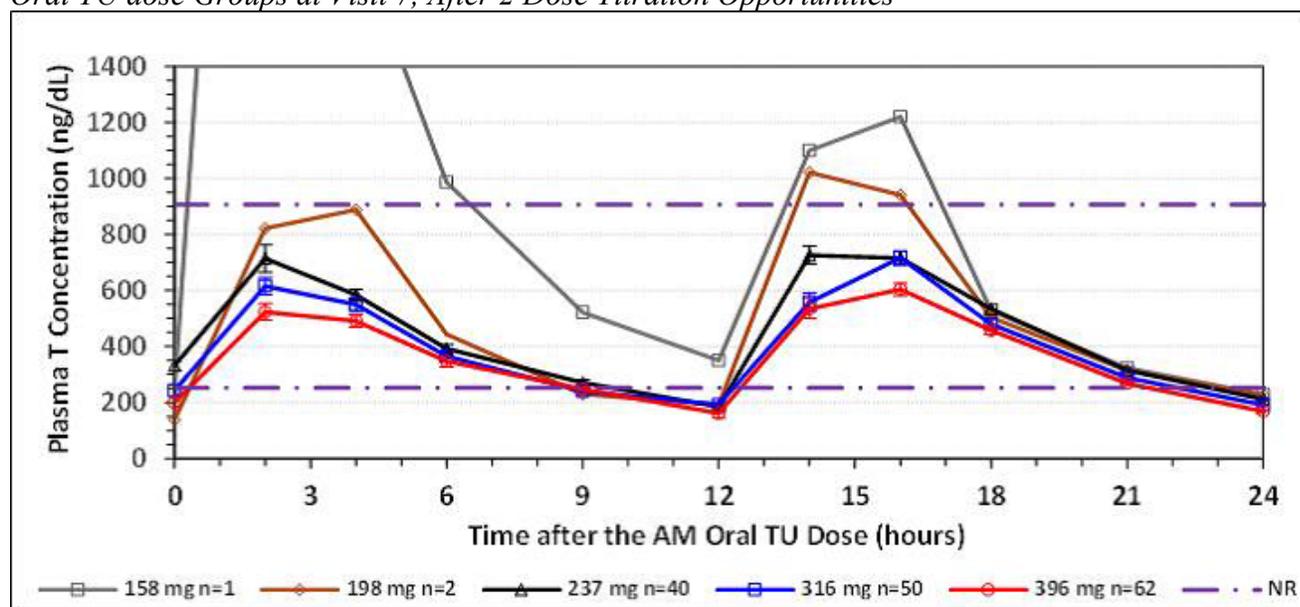
The testosterone C_{max} was \leq 1361 ng/dL at Visit 7 for 82.8% of subjects in the Oral TU group and 97.9% of subjects in the Topical Axiron group. In the Oral TU group at Visit 7, testosterone C_{max} was $>$ 1633 to \leq 2268 ng/dL for 5 (3.3%) subjects and was $>$ 2268 ng/dL for 4 (2.6%) subjects. One (2.1%) subject in the Topical Axiron group had testosterone C_{max} $>$ 1633 ng/dL at Visit 7. The observed distribution of C_{max} values at Visit 7 for subjects treated with Oral TU was within or close to the targeted distribution suggested by the FDA for testosterone replacement products.

The figure below shows the mean concentration-time profiles at Visit 7 for the groups of subjects at each of the Oral TU doses relative to the plasma total testosterone normal range of 252 ng/dL to 907 ng/dL. One subject, who had been titrated to the lowest possible Oral TU dose (158 mg BID), still had plasma testosterone concentrations at Visit 7 that were too high for continued treatment with this formulation. The other dose groups had C_{avg24} values (time-weighted average concentrations over the 24-hour period) between 364 ng/dL and 513 ng/dL (of note, the mean C_{avg24} value for the 198 mg dose group needs to be interpreted with caution since that group contained only 2 subjects). The profiles in figure below do not show dose dependence in their pattern because they are the final doses to which the subjects have been titrated; the subjects within a dose group have been titration-selected. Subjects in the higher dose groups are believed to have higher testosterone clearance and/or lower testosterone bioavailability than subjects in the lower dose groups. The expected trend is that, as the number of subjects included in the study increases, all 5 dose groups approach having similar mean values, such as is already apparent for the 3 higher dose groups of 237, 316 and 396 mg with their 40 to 62 subjects each. This similarity in the mean concentration-time profiles after the titration process is complete indicates that the titration process successfully identified the Oral TU dose that addresses the between-subject variability in testosterone clearance and in testosterone oral bioavailability when administered as TU, in the Sponsor's opinion.

The tendency for the exposure parameters to follow the simple pharmacokinetic expectations of dose proportionality was assessed by comparing the geometric means of the dose-normalized

pharmacokinetic parameters C_{max} , and AUC over the 3 pharmacokinetic visits (Visit 2, Visit 4b and Visit 7). The point estimates of the ratios of the geometric means in all comparisons were between 0.904 and 1.013; the 90% CIs about the point estimates all fell within 0.80 to 1.25. In this case, the result is interpreted by Sponsor as demonstrating dose proportionality between 2 administrations of the same formulation (although possibly at different doses) separated by periods of 5 to 15 weeks.

Figure 14 Mean (+/-SEM) Concentrations-Time Profile for Plasma Total Testosterone in the 5 Oral TU dose Groups at Visit 7, After 2 Dose Titration Opportunities



Source: CLAR 15012, Figure 10, page 106

Mean peak exposures (C_{max24}) and total exposure (AUC_{24}) for plasma DHT in the Oral TU- and Topical Axiron-treated subjects were similar at all 3 pharmacokinetic visits. By the end of the titration period (Visit 7), the DHT C_{max24} values were 117.1 ng/dL and 98.0 ng/dL for Oral TU and Topical Axiron subjects, respectively, and the AUC_{24} values were 1758 and 1770 ng•h/dL, for Oral TU and Topical Axiron, respectively. The mean 24-hour C_{avg} values were also very similar at 73.25 ng/dL and 73.76 ng/dL, for Oral TU and Topical Axiron, respectively, which is approximately 13% above the normal range for DHT in eugonadal men (65.0 ng/dL). The mean DHT/T ratios for the 2 treatments were 0.18 to 0.19.

Mean concentrations of calculated free testosterone at baseline were 4.457 ng/dL in the Oral TU group and 4.442 ng/dL in the Topical Axiron group. Mean concentrations of calculated free testosterone following dosing with Oral TU followed a similar pattern as the testosterone concentrations. The mean C_{avg24} of calculated free testosterone at Visit 7 was 11.685 ng/dL in the Oral TU group and 9.184 ng/dL in the Topical Axiron group; both of which are within the normal range (6.1 to 19.4 ng/dL) published for that parameter.

Overall, estradiol concentrations increased with the administration of exogenous testosterone. Mean change from baseline in the serum concentrations of E₂ at Visit 7 (AM predose concentration) in the Oral TU-treated subjects showed an approximately 150% increase from the baseline value. The mean baseline E₂ concentration at Visit 1 was 17.55 pg/mL and the mean predose concentration for the AM dose of Oral TU was 28.6 pg/mL. Both values were within the normal range (7.5 to 30.6 pg/mL) for E₂ in eugonadal men at the laboratory that conducted the assays. The 24-hour C_{avg} value (C_{avg24}) at Visit 7 (32.3 pg/mL), was slightly above the upper bound of the normal range and was approximately equal to the mean E₂ concentration in the Topical Axiron-treated subjects (33.03 pg/mL).

Table 43 Summary of Serum Estradiol Parameters at Visit 1 and Visit 7

Visit	PK Parameter	Units	Oral TU, All Doses				Topical Axiron, All Doses			
			N	Mean	SD	CV	N	Mean	SD	CV
1	E ₂	pg/mL	156	17.55	8.635	49.2%	47	17.54	10.308	58.8%
Estradiol Change from Baseline										
7	Absolute	pg/mL	154	11.01	16.487	147.9%	46	14.84	25.098	169.1%
	Relative	%Baseline	154	149.8	385.00	257.0%	46	165.6	242.85	146.7%
	Visit7/Visit1	Ratio	154	2.50	3.85	154.1%	46	2.66	2.43	91.5%

Source: CLAR 15012, Table 24, page 112

Mean SHBG concentrations decreased by approximately 31% to 36% with Oral TU treatment (from approximately 29 nmol/L to approximately 17 nmol/L). The decrease in SHBG concentration was complete by Visit 2, and the mean SHBG concentrations did not show any additional decline between Visit 2 and Visit 7. The normal range for SHBG in eugonadal men is 10.78 to 46.62 nmol/L, so the mean values were within the normal range from the beginning to the end of treatment. At Visit 2, approximately 25% of the Oral TU-treated subjects had SHBG concentrations less than the lower bound of the SHBG normal range, but that percentage decreased to 17% by Visit 4b and Visit 7. Topical Axiron treatment also resulted in a small decline in the SHBG concentrations but the maximal extent of the mean decline, observed at Visit 2, was only approximately 4%. Between Visit 2 and Visit 7, the mean SHBG concentrations in the Topical Axiron-treated subjects may have returned towards baseline, the mean difference being less than -0.5% by Visit 7 (from approximately 27nmol/L to 26.4nmol/L).

Reviewer's Comment: *The clinical significance of the decline in SHBG is unknown, but the concentration of free testosterone at Visit 7 was slightly higher for Oral TU subjects than for Topical Axiron subjects.*

The mean baseline serum FSH concentration was approximately 5.5 mIU/mL in the Oral TU group, which is within the normal range for eugonadal men (normal range: 1.4 to 9.5 mIU/mL). By Visit 7, the mean concentration in the AM predose sample had declined by approximately 71% to 1.8 mIU/mL. The percentage of Oral TU subjects with FSH

concentrations assayed as BLQ increased from 0% (0/151) at Visit 1 baseline to approximately 32% (48/151) at Visit 7. A similar pattern was observed for FSH concentrations in the Topical Axiron-treated subjects. Their mean FSH concentrations declined 69% from the Visit 1 baseline value (6.4 mIU/mL) to the morning predose Visit 7 mean value of 1.9 mIU/mL). The percentage of Topical Axiron-treated subjects with FSH concentrations assayed as BLQ increased from 0% (0/48) at Visit 1 baseline to approximately 24% (12/49) at Visit 7. These decreases in FSH concentrations are consistent with expectations in subjects receiving TRT in the Sponsor's opinion.

The mean baseline serum LH concentration was approximately 4.2 mIU/mL in the Oral TU group, which is within the normal range for eugonadal men (normal range: 1.3 to 8.1 mIU/mL). By Visit 7, the mean concentration in the AM predose sample had declined by approximately 76% to 1.1 mIU/mL (Table 25). The percentage of Oral TU subjects with LH concentrations assayed as BLQ increased from approximately 0.7% (1/151) at Visit 1 baseline to approximately 41% (62/151) on Visit 7. A similar pattern was observed for LH concentrations in the Topical Axiron-treated subjects. Their mean LH concentrations declined 75% from the Visit 1 baseline value (4.1 mIU/mL) to the morning pre-dose Visit 7 mean value of 0.96 mIU/mL (Table 25). The percentage of Topical Axiron-treated subjects with LH concentrations assayed as BLQ increased from 0% (0/48) at Visit 1 baseline to approximately 49% (24/49) at Visit 7. These decreases in LH concentrations are consistent with expectations in subjects receiving TRT, since testosterone has negative feedback on the release of LH from the pituitary gland in the Sponsor's opinion.

Overall Efficacy Conclusions

- The primary and secondary efficacy analysis endpoints were achieved in Study CLAR-15012
- In the Oral TU group, subjects who weighed >100 kg on average were on higher study drug doses at Visit 7 than those weighing ≤ 100 kg; For Topical Axiron, at Visit 7 the mean of the last dose of study drug was comparable in the weight subgroups.
- The proportions of Oral TU subjects with testosterone C_{max} values ≤ 1500 ng/dL (90.7%) and > 1800 ng/dL to 2500 ng/dL (2.0%) at Visit 7 met the FDA-specified targets (≥ 85% and ≤ 5%, respectively) for testosterone replacement products. Although 3 Oral TU subjects had single, transient testosterone C_{max} values > 2500 ng/dL, inspection of the data shows that the high values are spurious and likely due to specimen contamination with exogenous testosterone.
- Plasma DHT concentrations and DHT/T ratios for the Oral TU- and Topical Axiron-treated subjects were comparable, and both approximately 13% above the upper limit of the normal eugonadal range.
- Calculated free testosterone C_{avg24} at Visit 7 was within the normal range in both the Oral TU and Topical Axiron treatment groups.
- Estradiol concentrations increased in both treatment groups, with similar mean concentrations observed at Visit 7.

- Mean serum SHBG concentrations in Oral TU- and Topical Axiron-treated subjects were within the normal range both before start of treatment and after approximately 3 to 4 months of TRT, although SHBG declined significantly in the Oral TU group. The clinical significance of that decline is unknown.
- Consistent with expected hormonal feedback at the hypophyseal/pituitary level in subjects receiving TRT, similar reductions in mean serum FSH and LH concentrations were observed in both Oral TU- and Topical Axiron-treated subjects.
- There was no meaningful difference in dose-normalized C_{avg} and C_{max} among the meal types according to Sponsor, suggesting that dose titration based on post-AM blood samples will not be significantly affected by the AM meal fat composition. The reader is referred to the Clinical Pharmacology review for details.
- A single status sample drawn 4 hours after the morning dose can effectively guide dose titration in the Sponsor's opinion. A C_{3-5} window yielded comparable results. The reader is referred to the Clinical Pharmacology review for details.

Safety Findings

Extent of Exposure

The overall mean duration of study drug exposure was comparable between the treatment groups (Oral TU: 139.4 days; Topical Axiron: 133.8 days). The mean duration of study drug exposure from Visit 5b to Visit 7 was comparable between the treatment groups (Oral TU: 35.6 days; Topical Axiron: 36.5 days). Steady-state for Oral TU is reached within 7 days of dosing, and among the 159 subjects with exposure to Oral TU during Visit 5b to Visit 7 only 1 subject received ≤ 7 days of therapy. In that case, Subject (b) (6) received 6 days of Oral TU between Visit 5b to Visit 7 and prematurely discontinued from the study due to an adverse event of headache.

Table 44 Duration of Exposure by Treatment Group (Safety Population)

Duration of Exposure to Treatment (Days)	Oral TU N=166	Topical Axiron N=55
Overall		
n	166	55
Mean (SD)	139.4(24.81)	133.8(33.67)
Median	138.0	141.0
Minimum, Maximum	41, 211	18, 184
From Visit 5b to Visit 7/Early Termination		
n	159	50
Mean (SD)	35.6(6.08)	36.5(5.43)
Median	36.0	35.0
Maximum, Minimum	6, 51	28, 52

Source: CLAR-15012 Study Report, Table 31, page 127

Table 45 Duration of Exposure by Oral TU Dose (Oral TU Safety Population)

Duration of Exposure to Treatment (Days)	Oral TU BID Dose (N = 166)					
	158 mg	198 mg	237 mg	316 mg	396 mg	Overall
Overall						
n	1	4	166	131	69	166
Mean	39.09	66.3	65.0	71.5	38.7	139.4
Median	39.0	60.0	49.0	70.0	36.0	138.0
Min, Max	39, 39	37, 108	32, 185	6, 149	6, 80	41, 211
From Visit 5b to Visit 7/Early Termination						
n	1	2	41	51	64	159
Mean	39.0	37.5	35.8	35.1	35.7	35.6
Median	39.0	37.5	36.0	36.0	36.0	36.0
Min, Max	39, 39	30, 45	9, 51	10, 49	6, 47	6, 51

Source: CLAR-15012 Study Report, Table 32, page 128

Table 46 Duration of Exposure by Topical Axiron Dose (Safety Population)

Duration of Exposure to Treatment (Days)	Topical Axiron QD Dose (N=55)				
	30 mg	60 mg	90 mg	120 mg	Overall
Overall					
n	0	55	35	11	55
Mean	N/A	80.1 (47.07)	72.2 (34.43)	39.1 (15.64)	133.9 (33.56)
Median	N/A	55.0	76.0	36.0	141.0
Min, Max	N/A	19, 177	9, 127	21, 80	19, 184
Early Termination					
n	0	23	21	6	50
Mean	N/A	35.8	36.8	38.3	36.5
Median	N/A	35.0	35.0	37.5	35.0
Min, Max	N/A	31, 46	30, 51	28, 52	28, 52

Source: CLAR-15012 Study Report, Table 33, page 129

Reviewer’s Comment: *The durations of exposures by dose appear comparable between Oral TU and Topical Axiron.*

Adverse Events

The overall incidence of TEAEs was higher in the Oral TU group (47.0%) compared with the Topical Axiron group (36.4%). TEAEs considered related to study drug occurred in 18.7% of subjects in the Oral TU group and in 14.5% of the Topical Axiron group.

Two subjects in the Oral TU group had serious TEAE (small intestinal obstruction and periumbilical abscess), neither of which was considered related to study drug administration. The incidence of TEAEs leading to discontinuation of study drug was 1.8% in both treatment groups. No subject died during the study.

Table 47 Treatment Emergent Events in CLAR-15012 (Safety Population)

Event, n (%)	Oral TU (N=166)	Topical Axiron (N=55)
Subjects with any TEAE	78 (47.0)	20 (36.4)
Subjects with any serious TEAE	2 (1.2)	0
Subjects with any treatment-related TEAE	31 (18.7)	18 (14.5)
Subjects with any serious treatment-related TEAE	0	0
Subjects with any TEAE leading to discontinuation	3 (1.8)	1 (1.8)
Subjects with any TEAE leading to interruption of study medication	4 (2.4)	1 (1.8)
Subjects with any TEAE leading to death	0	0

Source: CLAR-15012 Study Report, Table 34, page 130

The TEAE preferred terms “hematocrit increased”, “high-density lipoprotein decreased”, “nausea”, “headache”, “upper respiratory infection”, and “hypertension” occurred in a greater percentage of Oral TU subjects as compared to Topical Axiron subjects.

Table 48 TEAEs Occurring in >= 2% of Subjects in Either Treatment Group (Safety

Population)

System Organ Class Preferred Term, n (%)	Oral TU (N)	Topical Axiron
Subjects with any TEAE	78 (47.0)	20 (36.4)
Investigations	23 (13.9)	2 (3.6)
Hematocrit increased	8 (4.8)	0
High-density lipoprotein decreased	5 (3.0)	0
Gastrointestinal Disorders	20 (12.0)	0
Nausea	4 (2.4)	0
Infections and Infestations	16 (9.6)	5 (9.1)
Upper respiratory tract infection	6 (3.6)	0
Nervous system Disorders	12 (7.2)	4 (7.3)
Headache	8 (4.8)	1 (1.8)
Injury, Poisoning and Procedural	6 (3.6)	4 (7.3)
Overdose	1 (0.6)	2 (3.6)
Skin and Subcutaneous Tissue Disorders	5 (3.0)	6 (10.9)
Rash	2 (1.2)	2 (3.6)
Vascular Disorders	6 (3.6)	0
Hypertension	5 (3.0)	0

Source: CLAR-15012 Study Report, Table 35, page 130

The following table shows TEAEs considered related to study drug by the investigator and occurring in $\geq 1\%$ in either treatment group and occurring in 0% of the second treatment group.

Table 49 TEAEs Considered Drug-Related and Occurring in $\geq 1\%$ of Subjects in Either Group

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

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

The overall incidence of TEAEs considered related (possibly, probably, or definitely) to study drug was comparable between the Oral TU (18.7%) and Topical Axiron (14.5%) groups. The incidence of TEAEs associated with Gastrointestinal Disorders was 6.0% in the Oral TU group, whereas none of the subjects in the Topical Axiron group. The related GI events included: gastroesophageal reflux disease, abdominal distension, dry mouth, dyspepsia, eructation, and nausea, each of which was reported in $< 2\%$ of Oral TU subjects.

In the system organ class of Investigations, TEAEs of high-density lipoprotein decreased and hematocrit increased were reported by 3.0% and 2.4%, respectively, of Oral TU subjects; and none of the Topical Axiron subjects reported these events.

In oral TU subjects, the incidences of TEAEs in the SOCs of Investigations (13.9% versus 3.6%), Gastrointestinal Disorders (12.0% versus 0), and Vascular Disorders (3.6% versus 0) were larger than those observed for Topical Axiron subjects. TEAEs by preferred term that occurred in $\geq 2\%$ of Oral TU subjects but were not observed in Topical Axiron subjects included hematocrit increased (4.8%), upper respiratory tract infection (3.6%), hypertension (3.0%), high-density lipoprotein decreased (3.0%), and nausea (2.4%). In addition, headache was experienced by a greater proportion of Oral TU subjects compared with Topical Axiron subjects (4.8% versus 1.8%).

Among the 8 Oral TU subjects who reported TEAEs of hematocrit increased, the events occurred between Days 80 and 159. Hematocrit values at or near the time of onset ranged from 54.3% to 57.8%. Three of the subjects had hematocrit values at Visit 1 that were $> 48\%$ (specifically, 49.6% for Subjects (b) (6) and (b) (6) and 48.1% for Subject (b) (6); 2 of these subjects also had elevated hematocrit values noted at screening, but were $\leq 48\%$ based on repeat testing). The Oral TU dose at the time of the event was 198 mg BID for 1 subject, 237 mg BID for 3 subjects, 316 mg BID for 3 subjects, and 396 mg BID for 1 subject. For 1 of the subjects ((b) (6)), the site recorded that a concomitant procedure was performed, which was obtaining a repeat hematocrit value, and the repeat value was $< 54\%$ (52.6%). The remaining subjects required no treatment. The events resolved in 2 of the 8 subjects, with the outcome for the remaining events noted as ongoing. Each of the TEAEs of hematocrit increased was considered mild in intensity and half were considered related to study drug by the investigator. None of these events led to premature discontinuation of study drug.

Table 50 Oral TU Subjects with TEAE of Hematocrit Increased

Subject #	TEAE Start Day/ Dose BID	TEAE End Day	Sev	Rel	Hematocrit (%) Values (Day)				
					Screen	Visit 1	Visit 4	Visit 4b	Visit 7/ET
(b) (6)	105/ 316 mg	148	Mild	Not	44.1 (D -8)	43.4 (D 1)	NA	54.3 (D 105)	51.0 (D 148)
	118/ 316 mg	Ong	Mild	Def	47.9 (D -7)	49.6 (D 1)	51.5 (D 56)	56.9 CS (D 118)	55.6 (ET; D 139)
	159/ 237 mg	Ong	Mild	Not	49.2 (D -14)	47.9 (D 1)	NA	53.2 (D 98)	56.3 (D 159)
	123/ 237 mg	129	Mild	Prob	44.1 (D -11)	46.8 (D 1)	50.7 (D 56)	56.0 CS (D 120)	54.5 CS (D 169)
								52.6 (D 125)	
	144/ 237 mg	Ong	Mild	Not	50.1 (D -12)	49.6 (D 1)	53.9 (D 53)	52.4 (D 95)	54.4 (D 144)
					48.0 (D -5)				
	140/ 316 mg	Ong	Mild	Not	47.9 (D -15)	47.5 (D 1)	NA	52.0 (D 91)	54.9 (D 140)
	135/ 396 mg	Ong	Mild	Poss	48.7 (D -13)	48.1 (D 1)	NA	NA	57.8 (D 135)
					46.0 (D -8)				54.0 (D 171)
80/ 198 mg	Ong	Mild	Poss	47.6 (D -16)	45.3 (D 1)	NA	55.0 (D 80)	57.1 (D 140)	

Source: CLAR-15012 Study Report, Table 37, page 134 ong= ongoing

Among the 6 Oral TU subjects who reported TEAEs of upper respiratory tract infection, 1 had a medical history of intermittent upper respiratory tract infections. Onset of the URI events ranged from Day 7 to Day 108. The Oral TU dose at the time of the event was 237 mg BID for 3 subjects and 316 mg BID for 3 subjects. Each of the events was noted as resolved, with only 2 requiring treatment with antibiotics. One of the events was considered severe, but required no treatment; the remaining 5 events were considered mild or moderate in intensity. None of the events were considered related to study drug and none led to premature discontinuation of study drug.

A total of 7 Oral TU subjects reported TEAEs of hypertension (5 subjects) or blood pressure increased (2 subjects). Onset of the events ranged from Day 1 to Day 211. Five of the 7 subjects had a history of hypertension and were receiving antihypertensive medication at study entry; 4 of these subjects required an increase in dose or the addition of another antihypertensive medication during the study. Among the 5 subjects with a history of hypertension, blood pressures increased from normal to pre-hypertensive in 1 subject, from pre-hypertensive to Stage 2 hypertension in 1 subject, and from Stage 1 hypertension to Stage 2 hypertension in 2 subjects; 1 subject remained at Stage 1 hypertension throughout the study. Two of the 7 subjects had no past medical history of hypertension, although 1 of these subjects had a baseline blood pressure classified as Stage 1 hypertension and the other had a baseline blood pressure classified as pre-hypertensive. Both of

these subjects started antihypertensive medication during the study; one on Day 8 and one on Day 88. Among all 7 subjects with TEAEs of hypertension or blood pressure increased, the Oral TU dose at the time of the event was 237 mg BID for 2 subjects, 316 mg BID for 3 subjects, and 396 mg BID for 2 subjects. All of the hypertension TEAEs were considered mild or moderate in intensity and 3 were considered related to study drug by the investigator. All but 1 of the events was noted as ongoing. None of the events led to premature discontinuation of study drug.

One Topical Axiron subject reported a TEAE of blood pressure increased on Day 166 while receiving the 90 mg dose; the event was considered moderate in intensity and related to study drug by the investigator.

Table 51 Subjects with TEAE of Hypertension or Blood Pressure Increased (Safety Population)

Subject #/ Treatment Group	TEAE Start Day/ Dose BID	TEAE End Day	Sev	Rel	Systolic/Diastolic Blood Pressure (mm Hg) Values (Day) Blood Pressure Classification					
					Screen	Visit 1	Visit 2	Visit 4	Visit 4b	Visit 7/ET
Hypertension (b) (6)										
	211/ 316 mg	Ong	Mild	Poss	146/90 (D -16)	152/91 (D 1) S1	158/89 (D 23) S1	142/82 (D 57) S1	159/100 (D 149) S2	167/105 (D 211) S2
	8/ 237 mg	Ong	Mod	Not	144/83 (D -15)	145/81 (D 1) S1	135/81 (D 24) Pre	141/78 (D 59) S1	138/76 (D 101) Pre	119/76 (D 164) Normal
	88/ 316 mg	Ong	Mod	Not	144/88 (D -17)	127/83 (D 1) Pre	149/88 (D 23) S1	NA	151/100 (D 86) S2	146/92 (D 142) S1
	1/ 237 mg	Ong	Mod	Not	147/90 (D -22)	159/97 (D 1) S1	157/98 (D 21) S1	NA	158/100 (D 78) S2	154/102 (ET D 114) S2
	163/ 396 mg	Ong	Mild	Not	136/84 (D -21)	116/74 (D 1) Normal	123/78 (D 24) Pre	NA	128/75 (D 101) Pre	122/71 (D 164) Pre
Blood Pressure Increased (b) (6)										
	130/ 396 mg	144	Mod	Poss	140/88 (D -17)	135/76 (D 1) Pre	137/86 (D 20) Pre	NA	138/84 (D 83) Pre	163/104 (D 132) S2
	118/ 316 mg	Ong	Mod	Prob	148/82 (D -14)	128/95 (D 1) S1	138/95 (D 21) S1	153/94 (D56) S1	152/96 (D 118) S1	143/84 (ET D 139) S1
	166/ 90 mg	174	Mod	Def	148/81 (D -16)	140/77 (D -1) S1	129/72 (D 20) Pre	133/77 (D55) Pre	131/72 (D 109) Pre	152/87 (D 166) S1 126/79 (D 174) Pre

^asubject with medical history hypertension and receiving an antihypertensive agent at screening

^bsubject began treatment with antihypertensive agent during study

^csubject had a dose change or new antihypertensive agent added during study

Abbreviations: BID = twice daily; Def = definitely related; ET = early termination; Mod = moderate; NA = not applicable; Ong = ongoing; Poss = possibly related; Pre = pre-hypertensive; Prob = probably related; Rel = relationship; S1 = Stage 1 hypertension; S2 = Stage 2 hypertension; Sev = severity; TEAE = treatment-emergent adverse event; TU = testosterone undecanoate

Source: CLAR-15012 Study Report, Table 38, page 136

There were 5 Oral TU patients who reported TEAEs of high-density lipoprotein decreased. All of these TEAEs were reported at a single investigative site. 3 had a medical history of dyslipidemia and were receiving lipid-modifying agents at baseline. Screening HDL values ranged from 0.9 to 1.6 mmol/L (34.8 to 61.9 mg/dL). The onset of the HDL decreased TEAEs ranged from Day 56 to Day 149, with values ranging from 0.8 to 0.9 mmol/L (30.9 to 34.8 mg/dL). The Oral TU dose at the time of the event was 316 mg BID for 3 subjects and 396 mg BID for 2 subjects. Three of the events were noted as resolved. Each of the HDL decreased events was considered mild in intensity and related to study drug by the investigator. None of the events led to premature discontinuation of study drug. Among the 3 subjects receiving lipid-modifying agents at baseline, none required a change in drug or dose due to the event. Neither of the remaining 2 subjects was treated for the event.

Table 52 Oral TU Patients with TEAEs of High Density Lipoprotein Decreased (Safety Population)

Subject #	TEAE Start Day/ Dose BID	TEAE End Day	Sev	Rel	units	HDL Values (Day)				
						Screen	Visit 1	Visit 4	Visit 4b	Visit 7
(b)(6)	56/ 316 mg	177	Mild	Poss	mmol/L	1.6 (D-7)	1.5 (D1)	0.9 CS (D56)	1.0 (D98)	0.9 CS (D154)
					mg/dL	61.9	58.0	34.8	38.7	34.8
					mmol/L			1.0 CS (D65)		
					mg/dL			38.7		
	105/ 316 mg	168	Mild	Poss	mmol/L	1.2 (D-8)	1.1 (D1)	NA	0.9 CS (D105)	0.8 CS (D148)
					mg/dL	46.4	42.5	NA	34.8	30.9
	149/ 396 mg	167	Mild	Poss	mmol/L	1.6 (D-8)	1.4 (D1)	NA	0.9 (D105)	0.8 CS (D149)
					mg/dL	61.9	54.1	NA	34.8	30.9
	141/ 396 mg	Ong	Mild	Poss	mmol/L	1.0 (D-14)	0.9 (D1)	NA	0.8 (D79)	0.8 CS (D135)
					mg/dL	38.7	34.8	NA	30.9	30.9
					mmol/L				0.8 (D91)	
	79/ 316 mg	Ong	Mild	Poss	mmol/L	0.9 (D-7)	1.1 (D1)	NA	0.8 CS (D79)	0.8 (D135)
mg/dL					34.8	42.5	NA	30.9	30.9	

Source: CLAR-15012 CSR, Table 39, page 137

HDL normal range 1 to 1.5 mmol/L, 38.7 to 58.0 mg/dL

Abbreviations: BID = twice daily; CS = clinically significant as determined by investigator; HDL = high-density lipoprotein; NA = not applicable; Ong = ongoing; Poss = possibly related; Rel = relationship; Sev = severity;

TEAE = treatment-emergent adverse event; TU = testosterone undecanoate

a Subject had a medical history of dyslipidemia and was receiving lipid modifying agents at baseline.

Four Oral TU subjects reported TEAEs of nausea. The onset of the events ranged from Day 2 to Day 137. The Oral TU dose at the time of the event was 237 mg BID for 2 subjects, 316 mg BID

Clinical Review

{Roger Wiederhorn }

{NDA 2016089 }

{Jatenzo: Oral Testosterone Undeconoate}

for 1 subject and 396 mg BID for 1 subject. Three of the events were noted as resolved after 1 or 2 days, with 1 event noted as ongoing. Each of the nausea events was considered mild or moderate in intensity and 2 were considered related to study drug by the investigator. None of the events required treatment or led to premature discontinuation of study drug.

Eight Oral TU subjects reported TEAEs of headache. The onset of the events ranged from Day 1 to Day 135. The Oral TU dose at the time of the event was 237 mg BID for 3 subjects, 316 mg BID for 4 subjects and 396 mg BID for 1 subject. Each of the events was considered mild or moderate in intensity and 4 were considered related to study drug by the investigator. Three of the events required treatment with analgesics or non-steroidal anti-inflammatory drugs, 1 required dose interruption, and 2 led to premature discontinuation from the study. In the majority of the subjects (5 of 8), the events were noted to resolve within 1 to 2 days. One subject's (b) (6) headache event lasted for 5 days and led to premature discontinuation from study; the subject had an event of blood pressure increased approximately 2 weeks earlier (Day 118), although the subject's hypertension classification (Stage 1 hypertension) remained unchanged throughout the study (Day 1: 128/95 mm Hg; Day 21: 138/95 mm Hg; Day 56: 153/94 mm Hg; Day 118: 152/96 mm Hg; early termination [Day 139]: 143/84 mm Hg). Another subject's (b) (6) headache event lasted for the first 17 days of the study, with no clinically significant change in blood pressure (Day 1: 134/87 mm Hg, Day 23: 139/87 mm Hg). The remaining subject's (b) (6) headache event started on Day 3, led to premature discontinuation from study (last dose on Day 81), and was noted as ongoing; the subject had no other events of increased blood pressure and the subject's hypertension classification at his final visit was unchanged from Visit 1 (pre-hypertensive; Day 1: 119/86 mm Hg; Day 24: 125/80 mm Hg; Day 59: 115/78 mm Hg; early termination [Day 86]: 130/87 mm Hg).

One Topical Axiron subject reported a TEAE of headache on Day 2 while receiving the 60 mg dose; the event was considered mild in intensity, related to study drug by the investigator, and resolved the same day.

Reviewer's Comment: It is notable that 3 of the 8 patients with the AE of headache also had increases in the blood pressure. However, none of the increases in BP in these 3 cases resulted in changes in the subjects' hypertension categories, only one BP increase was described as moderate and none as severe in intensity. In these subjects, it is not possible to determine whether the subject's increase in BP was related to their event of headache.

In regard to overall TEAEs, the majority of TEAEs reported during the study were considered mild or moderate in intensity. Among the 78 Oral TU subjects who reported a TEAE, 3 had events that were considered severe; none of the Topical Axiron subjects reported a severe event. TEAEs considered severe in the Oral TU subjects included upper respiratory tract infection (1 subject), dry mouth and panic reaction (1 subject), and periumbilical abscess (1 subject). The severe events of panic reaction and dry mouth were considered possibly and probably related to study drug by the investigator, respectively; whereas the events of URI and periumbilical abscess were considered unrelated to study drug by the investigator. The dry mouth event was

reported on Day 3 at the 237 mg BID Oral TU dose and the panic reaction event was reported on Day 125 during pharmacokinetic sampling at Visit 7 at the 396 mg BID Oral TU dose.

There were no deaths reported during the study. Two subjects in the Oral TU group experienced serious TEAEs during the study:

- Subject (b) (6) 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 dose of Oral TU. The event required hospitalization, and was considered moderate in intensity and not related to study drug by the investigator. Study drug was interrupted and the subject was treated with 14 days of oral prednisone; the event was noted as resolved on Day 92, study drug was restarted, and the subject completed the study.
- Subject (b) (6) 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 dose of Oral TU. The event required hospitalization, and was considered severe in intensity and not related to study drug by the investigator. 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.

One subject in the Topical Axiron group experienced a serious AE prior to dosing. Subject (b) (6) experienced an SAE of appendicitis perforated 13 days prior to randomization in the study (Listing 16.2.7.2). The event was considered severe in intensity and required hospitalization.

Reviewer's Comment: These SAEs appear unrelated to the study drug.

There was one subject ((b) (6)) who experienced a myocardial infarction 2 weeks after receiving his last dose of Oral TU. This is a time period longer than the 7-day follow-up after study completion to classify the event as a TEAE per protocol; however, the case is notable. The subject was on Oral TU from (b) (6) (179 days), which is longer than the original planned TU treatment duration. A brief narrative for this patient is provided herein:

Subject (b) (6) 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 (b) (6)) but without stent placement. He also has a history of undescended testicle for which he underwent orchiectomy in (b) (6). He has a urologic history of azoospermia diagnosed in (b) (6), infertility diagnosed in (b) (6) and erectile dysfunction diagnosed in (b) (6). His hypogonadism was diagnosed in (b) (6). Previous use of testosterone replacement therapy is not specifically stated. Concomitant medications at the time of the event included metoprolol, simvastatin and omeprazole and simvastatin. On (b) (6), 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 period of 7 days for classification as a TEAE.

The subject's hematocrit values during study were within normal limits. At Screening, his Hct was 45.7%. Prior to the first dose of study drug the Hct was 44.8%. At Visit 7, on study day 180 the Hct was 46.2%. The subject's blood pressures were 138/84 at Visit 1, 142/82 at Visit 4 (study day 21), 136/83 at Visit 4 (study day 57), 137/83 at Visit 4b (study day 130) and 138/80 at Visit 7 (study day 179, (b) (6)). The subject's serum lipid profile is shown in the table below.

Table 53 CLAR 15012 Subject (b) (6) Serum Lipid Profile

Visit	Study Day	HDL (mmol/L) [1-1.5 nl range]	LDL (mmol/L) [0-2.6 nl range]	Triglyceride (mmol/L) [0-168 nl range]
Screening Visit 2	-8	0.9	2.6	190
Visit 4	57	0.7	2.6	148
Visit 4b	130	0.7	3.1	224
Visit 7	179	0.8	3.8	229

Source: Unlabeled Table in SDN 34

The patient's two serum testosterone levels collected during Screening were 142 ng/dL (Day-16) and 83 ng/dL (Day 83). The Visit 1 pre-dose plasma testosterone level was 112 ng/dL.

While on treatment, the subject's testosterone levels are shown in the table below:

Table 54 CLAR 15012 Subject (b) (6) Testosterone Concentrations

Visit	Study Day	T Cavg-24hr (ng/dL)	T Cmax (ng/dL)
Visit 2	21	262	587.3
Visit 4b	130	598	1426.9
Visit 7	179	384	778.2

Source: Unlabeled Table in SDN 34

Reviewer's Comment: The patient had modest increases in LDL cholesterol and triglycerides while on treatment. Of note, he was taking simvastatin. There were no unfavorable blood pressure changes observed. This patient's exposure to Oral TU exceeded the planned treatment duration due to protocol amendments. The case is confounded by past medical history. To date, the number of serious cardiovascular AEs reported in Oral TU studies is too small, and the studies too varied in dose, exposure and dose regimen, to draw conclusions about relatedness of CV SAEs to Oral TU.

Three (1.8%) subjects in the Oral TU group and 1 (1.8%) subject in the Topical Axiron group experienced TEAEs that led to premature discontinuation of study drug.

- Subject (b) (6) 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 the 316 mg BID dose 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 by the study investigator. The subject was withdrawn from the study (last dose received on Day 62; and the events were noted as ongoing).
- Subject (b) (6) was a 56-year-old White male who was prematurely discontinued from the study due to headache. This subject was receiving treatment for Type 1 hypertension. His blood pressure averages at screening were systolic 132 mm hg (133, 148, and 126) and 83 diastolic (87, 82, and 80). The event began on Day 135 while receiving the 396 mg BID dose of Oral TU. The patient's blood pressures on Day 139 (the nearest time to the acute event) 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 headache event was noted as resolved on Day 138, but the subject was withdrawn from the study (last dose received) on Day 139; the subject also experienced treatment-emergent adverse events of moderate flushing, hyperhidrosis, and hypoaesthesia beginning on Day 104, and moderate blood pressure increased and mild hematocrit increased beginning on Day 118, all during receipt of the 316 mg BID Oral TU dose. Events of moderate dyspepsia on Day 134 and moderate nausea on Day 137 were also reported while receiving the 396 mg BID Oral TU dose. Each of these TEAEs was considered related to study drug by the investigator.
- Subject (b) (6) was a 44-year-old White male who was prematurely discontinued from the study due to headache. At screening, Day -16, the average blood pressure was 133/86 mm hg. The highest blood pressures were 126/90 (Day 1), 129/81 (Day 24), 118/83 (Day 59) and 134/88 (Day 86). The event began on Day 3 while receiving a 237 mg BID dose of Oral TU. The event was considered mild in intensity, definitely related to study drug by the investigator, and required no treatment. The subject was withdrawn from the study (last dose received on Day 81; the event was noted as ongoing).
- One additional Oral TU subject (b) (6) was indicated as having discontinued from the study due to an AE; however, no specific TEAE was indicated as having led to his premature discontinuation. The subject had a severe panic reaction event reported on Day 125 during PK sampling at Visit 7 and couldn't complete all procedures for the visit. At the time of discontinuation his oral TU dose was 396 mg bid.

Four (2.4%) subjects in the Oral TU group and 1 (1.8%) subject in the Topical Axiron group experienced TEAEs that led to interruption of study treatment. No trends were observed between the treatment groups for the types of TEAEs that led to treatment interruption, with no single

event reported by more than 1 subject. One of the events that led to treatment interruption was moderate overdose for Oral TU Subject (b) (6), who incorrectly took twice the assigned study drug dose (237 mg BID) over a 25-day period. Apart from the overdose event, other TEAEs that led to treatment interruption and were considered related to study drug by the investigator included mild abdominal distension and mild gastroesophageal reflux disease in an Oral TU subject (b) (6) and mild urinary incontinence, moderate libido increased, and moderate ejaculation disorder in a Topical Axiron subject (b) (6).

Laboratory Parameters

A summary of the mean changes from baseline in hematology values is presented by treatment group in the table below:

Table 55 Mean Change from Baseline to Final Visit/Early Termination in Hematology Values by Treatment Group (Safety Population)

Parameter Statistic	Oral TU (N = 166)		Topical Axiron (N = 55)	
	n	Mean (SD)	n	Mean (SD)
Hemoglobin (g/L)				
Baseline	166	144.584 (10.1910)	55	143.564 (10.0862)
Δ to Final Visit/ET	160	6.819 (11.4369)	53	5.113 (10.9907)
Hematocrit (L/L)				
Baseline	166	0.445 (0.0275)	55	0.441 (0.0275)
Δ to Final Visit/ET	160	0.026 (0.0329)	53	0.020 (0.0292)
Platelets (10⁹/L)				
Baseline	166	239.741 (51.2600)	55	251.055 (100.4636)
Δ to Final Visit/ET	160	11.400 (34.6218)	53	-11.792 (76.6870)
Erythrocytes (10¹²/L)				
Baseline	166	4.911 (0.3711)	55	4.855 (0.4016)
Δ to Final Visit/ET	160	0.312 (0.4016)	53	0.240 (0.3044)
Leukocytes (10⁹/L)				
Baseline	166	6.765 (1.7965)	55	6.756 (1.9521)
Δ to Final Visit/ET	160	0.474 (1.6362)	53	-0.009 (1.5338)

ET=early termination Source: Clarus 15012 CSR, Table 40, page 143

The mean baseline hematocrit values were within the normal range for both treatment groups (Oral TU: 0.445 L/L; Topical Axiron: 0.441 L/L). At Visit 4b, mean increases 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 6.41% in the Oral TU group and 4.36% in the Topical Axiron group. Mean increases from baseline in hematocrit were also noted for both treatment groups at the final visit (Visit 7/Early Termination; Oral TU: 0.026 L/L; Topical Axiron: 0.020 L/L), representing a mean percent increase from baseline of 5.97% in the Oral TU group and 4.73% in the Topical Axiron group. Although mean increases from baseline in hematocrit values were observed in both treatment groups at each study visit, the mean values at those time points remained within the normal range. Similar results were also observed for

hemoglobin and erythrocytes. The reader is referred to Table 19 and preceding text for discussion of hematocrit outliers.

Consistent with the increases in mean hematocrit and hemoglobin, in the evaluation of maximum post-baseline erythrocyte counts, 11.4% of all Oral TU subjects shifted from normal values at baseline to above the normal range compared with 1.9% of Topical Axiron subjects; the incidence of shifts from normal to above the normal range at the final visit was 10.2% in the Oral TU group compared with 1.9% in the Topical Axiron group. There were 8 (4.8%) Oral TU subjects with clinically significant post-baseline hematocrit values (>54%) as compared to 0 (0%) for Axiron per investigator judgement.

Reviewer's Comment: The data suggest, but are not conclusive, that Oral TU may have an increased tendency to increase erythrocytosis compared to Topical Axiron. The hematocrit effects should be reflected in eventual labeling.

Mean changes from baseline to the final visit (Visit 7/Early Termination) in total cholesterol values were similar between the treatment groups (Oral TU: -0.252 mmol/L [-9.74 mg/dL]; Topical Axiron: -0.292 mmol/L [-11.29 mg/dL]); 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/Early Termination); however, the mean decrease observed in the Oral TU group was greater than that observed in the Topical Axiron group (-0.179 mmol/L [-6.92 mg/dL] versus -0.051 mmol/L [-1.97 mg/dL]); the mean percent decrease from baseline was -13.9% in the Oral TU group compared with -3.39% in the Topical Axiron group.

A small mean increase from baseline to the final visit (Visit 7/Early Termination) in LDL cholesterol was noted in the Oral TU group (0.091 mmol/L [3.52 mg/dL]), while a small mean decrease from baseline was observed in the Topical Axiron group (-0.104 mmol/L [-4.02 mg/dL]); the mean percent increase from baseline was 5.95% in the Oral TU group compared with a decrease of -2.14% 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/Early Termination) observed in the Oral TU group (0.105 mmol/L [9.30 mg/dL]), while a small mean decrease from baseline was observed in the Topical Axiron group (-0.016 mmol/L [-1.42 mg/dL]). The median percent changes from baseline in triglycerides were 5.45% in the Oral TU group and -1.25% in the Topical Axiron group.

A greater proportions of Oral TU subjects shifted from normal HDL cholesterol values at baseline to below the normal range (35.5% among minimum values and 28.9% for final visit values) compared with Topical Axiron subjects (18.5% among minimum values and 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: 12.0% and 18.7%, respectively, among maximum values and

7.8% and 13.3%, respectively, for final visit values; Topical Axiron: 7.4% and 11.1%, respectively, among maximum values and 3.7% and 9.3% for final visit values).

Reviewer's Comment: The clinical significance of the small changes in LDL cholesterol, triglycerides and HDL-cholesterol are unknown. The changes in serum lipid profile should be reflected in eventual labeling.

No clinically significant changes in the liver function tests were observed in either treatment group. In the Oral TU group, mean decreases from baseline to the final visit (Visit 7/Early Termination) were observed for alanine aminotransferase (-3.541 U/L), aspartate aminotransferase (-0.365 U/L) and total bilirubin (-0.800 μ mol/L), with generally similar results observed in the Topical Axiron group (-4.078 U/L, -1.745 U/L, and 0.311 μ mol/L, respectively).

No other clinically relevant trends were apparent between the treatment groups in the analyses of mean changes from baseline for chemistry parameters, except that the mean decreases from baseline to the final visit (Visit 7/Early Termination) in alkaline phosphatase values was greater in the Oral TU group (-11.407 U/L) compared with the Topical Axiron group (-3.717 U/L).

Vital Signs

At the site, there was a > 3 mm Hg difference in baseline mean (\pm SD) SBP between the Oral TU group (126.9 ± 11.47 mm Hg) and the Topical Axiron group (123.5 ± 13.18 mm Hg). SBP by cuff increased from baseline to Visit 7/Early Termination in both treatment groups (mean \pm 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. Censoring measurements collected after addition of, or an increase in, dosage of antihypertensive medications had little effect on estimates of mean change.

Mean changes in SBP and DBP by cuff from baseline to Visit 4 were also examined to assess the potential impact on subjects who might have been erroneously titrated to higher doses based on unreliable plasma testosterone concentrations obtained prior to Amendment 2.0. A total of 54 Oral TU subjects and 16 Topical Axiron subjects had SBP and DBP values at baseline and Visit 4. In this limited analysis, in the Oral TU group, a mean (\pm SD) decrease in SBP was observed at Visit 4 (-1.1 ± 11.24 mm Hg), compared with a mean (\pm SD) increase in the Topical Axiron group (5.6 ± 15.13 mm Hg). In this limited analysis, for DBP, the Topical Axiron group had a larger mean increase at Visit 4 (1.9 ± 7.83 mm Hg) compared with the Oral TU group (0.1 ± 7.18 mm Hg).

While there were no statistically significant treatment group differences in change from baseline to maximum post-baseline value for BP by cuff and HR, based on analyses without censoring and with censoring, the change from baseline to the last post-baseline value was statistically significant for the SBP and HR within the Oral TU group.

Cumulative distribution curves for SBP by cuff for baseline and Visit 7 by treatment did not reflect a tendency for increased BP for Oral TU patients comparing baseline to Visit 7 and comparing Oral TU to Topical Axiron (Figure 17 of CLAR-15012 CSR), in the Sponsor’s opinion.

In the Oral TU group, 7.2% of subjects started antihypertensive medication after baseline or required a dose increase compared with 1.8% of subjects in the Topical Axiron group.

The mean increase in SBP by cuff from baseline to Visit 7/Early Termination became larger with Oral TU doses of 316 and 396 mg BID. The opposite trend was observed with doses of Topical Axiron from 60 to 120 mg QD.

Among subjects with no prior history of hypertension, larger proportions of Oral TU subjects had baseline BP classifications of pre-hypertensive or Stage 1 hypertension (69.6%) compared with Topical Axiron subjects (46.7%, pre hypertensive only). Although none of the Topical Axiron subjects had BP classifications of Stage 1 hypertension at baseline, 13.3% were classified as such at Visit 7/Early Termination; the proportions of Oral TU subjects with BP classifications of Stage 1 hypertension were similar between baseline and Visit 7/Early Termination (15.2% and 14.3%, respectively). Among subjects with a history of hypertension, both treatment groups showed increases in the proportions of subjects with BP classifications of Stage 1 hypertension at Visit 7/Early Termination compared with baseline (13.8% to 32.1% in Oral TU and 20.8% to 30.4% in Topical Axiron), although the Oral TU group also had a 7.7% incidence of Stage 2 hypertension at Visit 7/Early Termination, whereas none of the subjects had this classification at baseline. There were no notable treatment group differences for shifts in blood pressure classification by cuff from baseline to Visit 7/ Early Termination.

Table 56 Shifts in Blood Pressure Classification by Cuff from Baseline to Final Post-Baseline by Treatment Group (Safety Population)

Treatment Group	Baseline Classification	Post-Baseline Classification			
		Normal	Pre-Hypertensive	Stage 1 Hypertension	Stage 2 Hypertension
Oral TU, n (%)					
	Normal (n = 37)	20 (54.1)	15 (40.5)	2 (5.4)	0
	Pre-hypertensive (n = 106)	15 (14.2)	54 (50.9)	33 (31.1)	4 (3.8)
	Stage 1 hypertension (n = 23)	2 (8.7)	14 (60.9)	3 (13.0)	4 (17.4)
	Stage 2 hypertension	0	0	0	0
Topical Axiron, n (%)					
	Normal (n = 22)	10 (45.5)	11 (50.0)	1 (4.5)	0
	Pre-hypertensive (n = 28)	4 (14.3)	17 (60.7)	7 (25.0)	0
	Stage 1 hypertension (n = 5)	1 (20.0)	2 (40.0)	2 (40.0)	0
	Stage 2 hypertension	0	0	0	0

Source: CLAR-15012 CSR, Table 47, page 162

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 (Screen 3 Day -2) and Visit 6 and were included in the ABPM Population. Demographic characteristics of the ABPM Population were similar to those of 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 greater 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%). Among subjects not receiving treatment for hypertension, 72.1% of subjects in the Oral TU group had a baseline hypertension classification of pre-hypertensive or Stage 1 hypertension compared with 52.0% of subjects in the Topical Axiron group.

The mean increase in daytime average, nighttime average, and 24-hour average SBP from baseline to Visit 6 for the Oral TU group was statistically significantly greater than for the Topical Axiron group with 24-hour average SBP increasing 4.88 (\pm 8.749) mm Hg in the Oral TU group and 0.18 (\pm 9.384) mm Hg in the Topical Axiron group. Similar results were observed for MAP and pulse pressure. Mean increases in daytime average, nighttime average, and 24-hour average DBP from baseline to Visit 6 for the Oral TU group were greater than for the Topical Axiron group, but the differences were not statistically significant. There were no statistically significant treatment group differences for HR.

Table 57 Systolic and Diastolic Blood Pressure Measured by ABPM at Baseline and Visit 6 by Treatment Group (ABPM Population)

Vital Sign Measurement	Statistic	Oral TU (N = 135)		Topical Axiron (N = 45)	
		Baseline	Change	Baseline	Change
Systolic blood pressure (mm Hg) Daytime average	Mean (SD)	131.13 (10.149)	5.05 (8.855)	131.21 (14.101)	-0.14 (10.534)
	Median	131.50	5.30	131.50	0.60
	p-value ^a		0.008		
Nighttime average	Mean (SD)	120.05 (11.164)	4.72 (11.852)	118.33 (13.102)	0.74 (11.328)
	Median	120.10	3.10	117.50	-0.70
	p-value ^a		0.0209		
24-hour average	Mean (SD)	127.52 (9.747)	4.88 (8.749)	127.03 (13.243)	0.18 (9.384)
	Median	127.80	4.50	128.00	1.00
	p-value ^a		0.0013		
Diastolic blood pressure (mm Hg) Daytime average	Mean (SD)	78.93 (7.819)	2.51 (7.246)	79.94 (8.547)	0.29 (6.6266)
	Median	78.50	2.00	79.30	0.50
	p-value ^a		0.0951		
Nighttime average	Mean (SD)	70.07 (7.779)	2.78 (8.940)	69.40 (8.092)	0.77 (8.108)
	Median	69.60	1.80	69.00	0.50
	p-value ^a		0.1059		
24-hour average	Mean (SD)	76.04 (7.206)	2.56 (6.772)	76.53 (7.910)	0.44 (5.830)
	Median	75.90	1.90	75.80	-0.20
	p-value ^a		0.0653		

^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

According to the Sponsor (page 170 of CLAR-15012 CSR), although there were no clear trends, the Visit 7 change from baseline in cuff SBP was smaller in subjects who were not part of the ABPM Population than those who were. In the Oral TU group, the subjects in the ABPM Population (N = 135) had a 3.4 (± 11.33) mm Hg increase in cuff SBP while those who were not in the ABPM Population (N = 27) had a -0.1 (± 13.96) decrease in cuff SBP. Similarly, in the Topical Axiron group, subjects in the ABPM Population (N = 45) had a 2.0 (± 10.14) mm Hg increase in cuff SBP while those who were not in the ABPM Population (N = 9) had a 0.9 (± 14.17) increase in cuff SBP. When comparing SBP measured by cuff in those who were in the ABPM Population with that measured by ABPM, the results were similar (e.g., Oral TU ABPM Population change from baseline to Visit 7/Early Termination was 3.4 ± 11.33 mm Hg by office cuff versus 4.88 ± 8.749 mm Hg by 24-hour ABPM). This indicates that SBP changes measured by office cuff are similar to changes measured by ABPM. In Table 14.3.4.2.14.1 (page 793) for the Topical Axiron population, change from baseline to Visit 7/Early Termination was 0.09 ± 0.435 mm Hg by office cuff versus 0.18 ± 9.9384 mm Hg by 24-hour ABPM.

Daytime and nighttime cumulative distribution curves for systolic blood pressure indicate a shift to the right (increase) in BP from screening to Visit 6.

It is noted that all patients were to have ABPM monitoring in the study. In the Oral TU group 135/166 subjects completed ABPM assessment and 45/55 Axiron subjects completed ABPM assessments.

Reviewer's Comment: Both cuff and ABPM show a blood pressure effect for Oral TU that is larger than that seen for Topical Axiron. These findings were consultatively reviewed by DCRP. The effects upon the BP of JATENZO are discussed in SECTION 7.3.5 of this review.

Prostate-Related Endpoints: International Prostate Symptom Score (I-PSS), Serum PSA and Digital Rectal Examination

Symptom scores obtained from the I-PSS fall into one of 3 categories: 1 to 7 = mild; 8 to 19 = moderate; and 20 to 35 = severe. At baseline, the mean I-PSS score for both treatment groups fell within the mild category (Oral TU: mean 5.9, median 4.0; Topical Axiron: mean 5.4, median 4.0; Table 51). Small mean increases in I-PSS were observed in both treatment groups at the final visit (Visit 7/Early Termination; Oral TU: 1.1; Topical Axiron: 1.7).

Table 58 Mean Change from Baseline to Visit 7/Early Termination in International Prostate Symptom Score by Treatment Group (Safety Population)

I-PPS Score	Oral TU (N=166)	Topical Axiron (N=55)
Baseline		
n	166	55
mean (SD)	5.0 (5.02)	5.4 (5.08)
Change from Baseline (V7)		
n	161	54
mean (SD)	1.1 (5.40)	1.7 (4.53)

Source: CLAR-15012 CSR, Table 51, page 171

No statistically significant difference was observed between the treatment groups for the proportion of subjects with serum PSA values > 4 ng/mL or with a change-from-baseline > 1.4 ng/mL at the end of study (Oral TU: 1.9%; Topical Axiron: 3.8%; difference of -1.92%; 95% CI: -7.456, 3.613).

Table 59 Mean Changes of Prostate Specific Antigen (PSA) from Baseline to End of Study/Early Termination by Treatment Group

Prostate-Specific Antigen(PSA) (ng/mL)	Oral TU (N=166)	Topical Axiron (N=55)
Baseline		
n	165	53
mean (SD)	0.908 (0.6777)	0.945 (0.7595)
Change from Baseline to V7		
n	162	53
mean (SD)	0.169 (0.4835)	0.255 (0.3778)
Subjects with PSA Values >4 ng/mL or with a Change from Baseline >1.4 ng/mL at the End of Study		
n	162	53
Yes (%)	3 (1.9)	2 (3.8)
No (%)	159 (98.1)	51 (96.2)
Difference of Proportions (95% CI)	-1.92 (-7.456, 3.613)	

Source: CLAR-15012 CSR, Table 52, page 172

Two Oral TU subjects had TEAEs of prostatic-specific antigen increased:

- Subject (b) (6) had a serum 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 by the investigator. A follow-up value obtained approximately 2 months later was 3.0 ng/mL.
- Subject (b) (6) had a serum PSA value of 0.73 ng/mL at baseline that rose to 2.86 ng/mL at Day 160; the event was considered moderate and probably not related to study drug by the investigator. A follow-up value obtained approximately 2 weeks later was 1.23 ng/mL.

In addition, one Oral TU subject ((b) (6)) was randomized in the study despite having an elevated serum PSA. A screening PSA was not available for the subject, but values obtained during the study were elevated (5.56 ng/mL on Day 54; 4.90 ng/mL on Day 69; and 4.09 ng/mL on Day 78). Subsequent information provided by the site indicated that the subject had an elevated PSA value performed at a local laboratory approximately 1 month prior to entry in the study (5.77 ng/mL); thus, the subject was not eligible for the study and was withdrawn on Day 78.

Physical examinations with a digital rectal examination were performed at Screening and at Visit 7/Early Termination. No prostate exam abnormalities were reported as AEs and no terms indicative of prostate nodule, prostatic irregularity or prostatomegaly were reported. No episode of urinary retention was reported in the trial.

Cosyntropin Stimulation Test Substudy Results

In the first review cycle, in a 13-week toxicity study in dogs, positive findings included marked atrophy of the adrenal cortex with reduced adrenal weights. The reduced adrenal weight did not reverse upon drug discontinuation. 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.

The Sponsor therefore undertook a Cosyntropin stimulation test sub study in CLAR-15012. All of the subjects in both treatment groups in the Cosyntropin stimulation Substudy Population (24 Oral TU, 8 Topical Axiron) were supposed to have a normal cortisol response to Cosyntropin stimulation at baseline. For the 8 subjects in the Topical Axiron group who completed the cosyntropin sub study, all had normal responses at Visit 8. For the 24 subjects in the Oral TU group who completed the cosyntropin substudy, 19 had a normal response at Visit 8. As indicated by the 95% CI, a statistically significantly smaller proportion of subjects in the Oral TU group had a normal cortisol response at Visit 8 as compared to Topical Axiron.

Among the 5 Oral TU subjects who had a low cortisol response after the test at Visit 8, 4 had cortisol values that were only slightly below the normal response cutoff level of 18 µg/dL (values ranged from 16.5 to 17.6 µg/dL at 30 or 60 minutes after administration of cosyntropin). The remaining subject (Subject (b) (6)) had received high-dose systemic corticosteroid therapy (prednisone 20 mg, 3 times daily for 14 days) due to a small bowel obstruction from Days 92 to 105, approximately 2 months before the Visit 8 test. This exposure would be expected to profoundly suppress endogenous hypothalamic-pituitary-adrenal function. One of the exclusion criteria for the sub study was use of corticosteroids. Initiating corticosteroids during the study was not considered, and therefore, no provision was made for its occurrence.

In summary, both treatment groups had clinically normal mean responses at the end of treatment after accounting for the subject who inappropriately received high-dose corticosteroid therapy and the 4 subjects in the Oral TU group whose maximum post-stimulation cortisol level was slightly below the normal response cutoff, in the Sponsor’s opinion.

A post hoc analysis conducted by the Sponsor, of maximal cortisol concentrations following Cosyntropin stimulation at Visit 1 and Visit 8, excluding Oral TU Subject (b) (6), is presented by treatment group in the Table below. Mean changes from pre-injection to maximum cortisol concentrations were statistically significant within both the Oral TU and Topical Axiron treatment groups at Visit 1 (14.17 and 17.81 µg/dL, respectively) and Visit 8

(11.50 and 12.65 µg/dL, respectively); however, no statistically significant differences were observed between the treatment groups for maximum cortisol concentrations or mean changes from pre-injection to maximum at either of these time points. Differences between Visit 8 and Visit 1 for maximum cortisol concentrations post-injection and changes in cortisol concentrations from pre-injection showed no statistically significant differences between treatment groups.

Table 60 Maximal Cortisol Concentration (ug/dL) following Cosyntropin Stimulation at Visit 1 and Visit 8 by Treatment Group (Excluding Subject (b) (6))

Maximal Cortisol Concentration (µg/dL)	Oral TU (N = 23)		Topical Axiron (N = 8)		p-value	
	Visit 1/Day 1 (Baseline)	Visit 8	Visit 1/Day 1 (Baseline)	Visit 8	Visit 1	Visit 8
Pre-injection						
Mean (SD)	9.14 (3.304)	10.11 (3.676)	7.39 (3.631)	10.85 (4.441)	0.2064 ^a	0.1661 ^a
Median	9.80	9.30	6.95	9.55		
Min, Max	1.5, 15.4	3.1, 17.5	2.1, 13.5	6.5, 18.2		
Max Concentration					0.1056 ^b	0.1916 ^b
Mean (SD)	23.30 (2.688)	21.62 (3.271)	25.20 (5.495)	23.50 (3.095)		
Median	24.00	21.40	22.70	22.65		
Min, Max	18.9, 29.0	16.5, 28.8	20.6, 35.4	20.3, 29.4		
Change from Pre-injection						
Mean (SD)	14.17 (3.747)	11.50 (3.633)	17.81 (5.136)	12.65 (3.700)		
Median	14.00	11.30	16.85	13.60		
Min, Max	5.1, 20.2	3.7, 18.6	13.1, 29.0	7.8, 16.9		
Within Treatment p-value ^c	<0.0001	<0.0001	<0.0001	<0.0001		
Difference in Maximum Concentration Post-injection (Visit 8 - Visit 1)					0.5255 ^d	
Mean (SD)	-1.69 (3.456)		-1.70 (3.411)			
Median	-1.50		-1.10			
Min, Max	-7.5, 7.7		-6.0, 3.9			
Within Treatment p-value ^c	0.0287		0.2015			
Difference in Change from Pre-injection (Visit 8 - Visit 1)					0.9914 ^d	
Mean (SD)	-2.66 (4.384)		-5.16 (4.509)			
Median	-2.60		-4.90			
Min, Max	-13.2, 4.5		-12.2, 0.9			
Within Treatment p-value ^c	0.0081		0.0143			

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation; TU = testosterone undecanoate

Source: CLAR-15012 CSR, Table 53, page 174.

The results of the Cosyntropin stimulation test were consultatively evaluated by Endocrinology expertise within DBRUP, who determined that flaws in the study design and conduct precluded conclusions from the Substudy. The results were reviewed at the BRUDAC, who drew the same conclusion. The results of the Substudy and Endocrine consultation are discussed in SECTION 7.3.5 of this review.

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/s/

A R WIEDERHORN
03/17/2018

MARK S HIRSCH
03/17/2018
I concur.

Memorandum of Endocrine Consultation

NDA 206089

SDN (eCTD) 0031 (0030)

Drug Testosterone undecanoate, oral

Sponsor Clarus Therapeutics, Inc.

Indication Testosterone replacement in hypogonadal men

Requested by Roger Wiederhorn, MD

Date of Request August 22, 2017

Date Completed December 5, 2017

Reviewer Linda S. Jaffe, MD/DBRUP

Team Leader Theresa Kehoe, MD/DBRUP

Materials Reviewed Protocol CLAR-15012

Preclinical data for IND 78104

Referenced literature

Background:

Clarus is developing oral testosterone undecanoate (TU) for testosterone replacement therapy in hypogonadal men. TU is a fatty acid ester of testosterone. TU is an inactive pro-drug which is hydrolyzed by esterases in vivo to yield testosterone and undecanoic acid. The relative binding affinity of TU for the androgen receptor is only 1% that of testosterone. TU taken orally is absorbed in the intestinal lymphatics such that a first pass hepatic effect is avoided.

The current submission under review is in response to a Complete Response action dated November 3, 2014. In the previous cycle, adrenal atrophy was noted in both rats and dogs exposed to testosterone undecanoate. These findings included cortical atrophy and/or vacuolation associated with small adrenals and decreased adrenal weights in rats and dogs following repeated dosing of TU for up to 9 months for both oral (NDA 206089, NDA (b) (4)) and intramuscular (NDA 22219) TU at clinically relevant AUC for TU and its metabolites. The reduced adrenal weight did not reverse upon drug discontinuation. In a 13-week repeated dose toxicity study in dogs, after 90 days of treatment with TU, cortisol levels were below the lower limit of detection in the TU treated group whereas they were well within the normal

range in the control group. TU exposure in dogs according to AUC was only 2 times the worst case exposure in human males.

In prior Phase 3 studies, the sponsor reported no treatment-emergent adverse events of cortisol insufficiency.

As part of the complete response, the Sponsor undertook a cosyntropin stimulation test in patients exposed to testosterone undecanoate or active comparator testosterone replacement Topical Axiron. The clinical portion of the response is a single protocol CLAR-15012.

The cosyntropin stimulation testing resulted in abnormal findings in 5/24 subjects exposed to testosterone undecanoate (105 to approximately 170 days) and none in subjects exposed to Topical Axiron (8). Four of the five subjects with abnormal end of study cortisol responses had post-stimulation cortisol levels that were in the range of 16.5-17.6 mcg/dL which may be intermediate or “gray zone” findings.

The Sponsor states on page 173 of the CLAR-15012 CSR, “Among the 5 Oral TU subjects who had a low cortisol response after the test at Visit 8, 4 had cortisol values that were only slightly below the normal response cutoff level of 18 µg/dL (values ranged from 16.5 to 17.6 µg/dL at 30 or 60 minutes after administration of cosyntropin). These small excursions in cortisol levels below the normal response cutoff level are unlikely to be of clinical significance. To rule out primary adrenal insufficiency, as is the concern with TRT, the peak post-stimulation cortisol only needs to be > 15 µg/dL [Dorin 2003]. All 4 of these subjects’ peak cortisol exceeded this value, thereby ruling out primary adrenal insufficiency.”

We have been asked to address the following questions with respect to protocol CLAR-15012:

- 1. Was the study performed properly and were appropriate doses of cosyntropin utilized?**
- 2. Were adequate numbers of subjects studied?**
- 3. Interpretation of study results.**

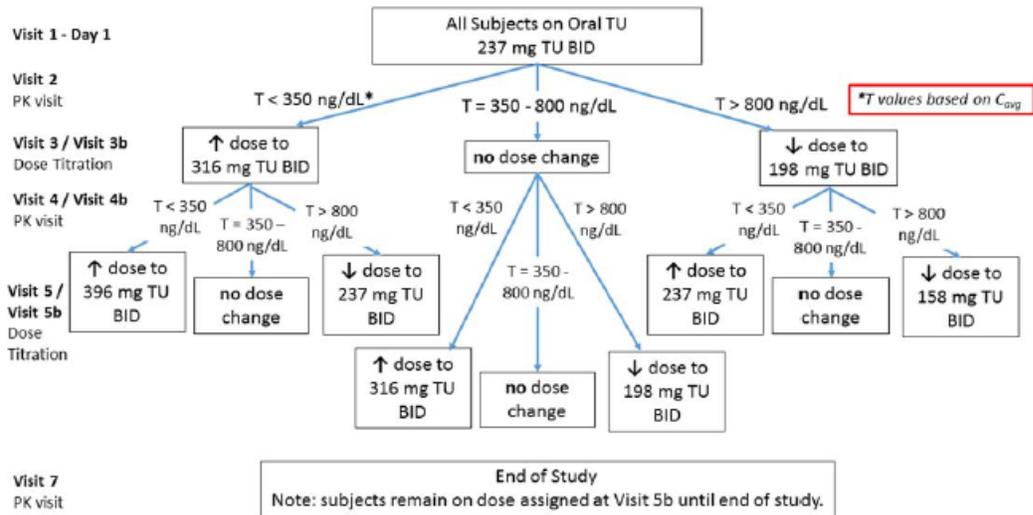
Study CLAR-1502

Study Design

This was a multicenter, Phase 3, randomized, open-label, active-comparator group, dose-titration, efficacy (based on Cavg of total testosterone), and safety study in adult hypogonadal male subjects. Enrollment into the study was based on consistently low morning serum testosterone levels (< 300 ng/dL on 2 separate occasions) and a history of signs and symptoms consistent with hypogonadism. Approximately 600 subjects were to be screened. Subjects who met all eligibility criteria were randomly assigned in a 3:1 ratio such that 166 subjects (mean

age 51.6) received Oral TU and 56 subjects (mean age 53.4) received Topical Axiron. Subjects randomly assigned to Oral TU began treatment at a dose of 237 mg TU BID with dose titration according to the scheme below to achieve testosterone levels of 350 to 800 ng/dL.

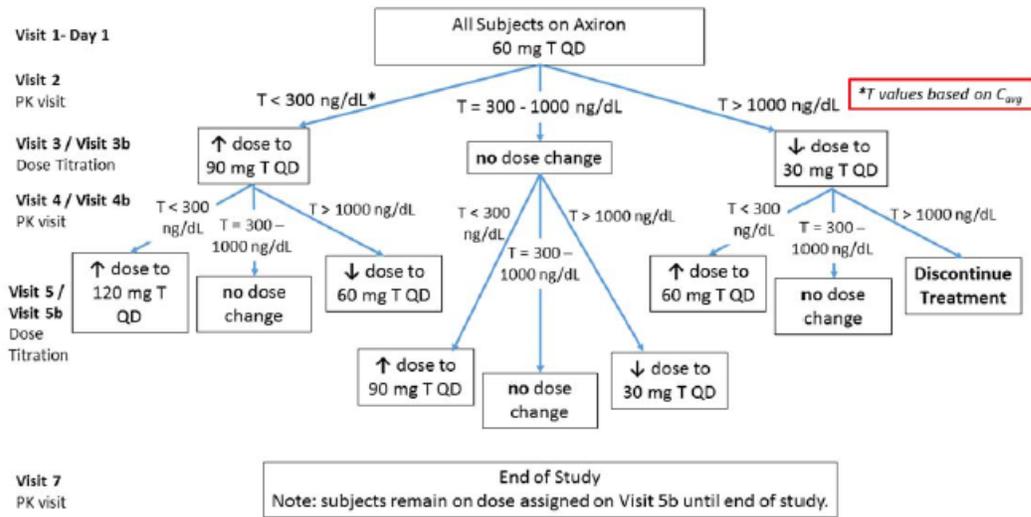
Figure 3: Oral Testosterone Undecanoate Dose-Titration Scheme



Abbreviations: BID = twice daily; C_{avg} = average concentration; PK = pharmacokinetic; T = testosterone; TU = testosterone undecanoate; ↑ = increase; ↓ = decrease

Subjects randomly assigned to the Topical Axiron group began treatment at a dose of 60 mg once daily (QD) in the morning. The titration boundaries of 300 to 1,000 ng/dL were based on the clinical development of Axiron.

Figure 4: Topical Axiron Dose-Titration Scheme



Abbreviations: C_{avg} = average concentration; PK = pharmacokinetic; QD = daily; T = testosterone; ↑ = increase; ↓ = decrease

The study included a 21-day Screening Phase, a Titration Phase, a 35-day Maintenance Phase, and an end-of-study visit (Visit 7). Visit 8 was added for the post-treatment cosyntropin stimulation test for those subjects who participated in the sub-study.

The cosyntropin stimulation sub-study was included in this study as a safety endpoint of interest to evaluate the effect of testosterone on the adrenal gland and determine if chronic Oral TU or Topical Axiron treatment suppresses the adrenal glands' capacity to produce cortisol.

In addition to the exclusion criteria in Section 9.3.2.1, a subject was not eligible to participate in the cosyntropin stimulation test sub-study if he was receiving corticosteroids (oral or inhaled) or had a pituitary abnormality (eg, hypopituitarism, post-surgery, post-radiotherapy, or history of abnormalities on imaging such as an adenoma).

Cosyntropin Stimulation Sub-study

Protocol

The test was conducted at Visit 1 before administration of study drug and at Visit 8 after the last 24-hour serial blood sample had been obtained. At each of the 2 study time points, subjects were injected with 0.25 mg of cosyntropin intravenously and blood samples were obtained for cortisol assay immediately before the injection, as well as 30 and 60 minutes after the injection. Separate informed consent was obtained for this sub-study.

Statistical analysis

Subjects with a normal cortisol response (defined as a serum cortisol concentration ≥ 18 $\mu\text{g}/\text{dL}$ either prior to the injection or at either 30 minutes or 60 minutes post cosyntropin administration) and subjects with an abnormal cortisol response (defined as a serum cortisol concentration < 18 $\mu\text{g}/\text{dL}$ prior to cosyntropin administration and at 30 minutes and 60 minutes post cosyntropin administration) were identified at each visit. Among those subjects who had a normal cortisol response at Visit 1, the proportion of subjects with an abnormal cortisol response at Visit 8 (approximately Treatment day 106) was compared between treatment groups. A 95% CI for the difference in proportions was computed.

Protocol Deviations

One subject in the Axiron group who had a pituitary adenoma was included in this sub-study.

In the TU group, one subject was discovered to have taken high dose prednisone 60 mg daily for 2 weeks, approximately 2 months prior to the cosyntropin test. A second subject used topical hydrocortisone cream for approximately 1 week.

All eight study sites (100, 101, 102, 105, 107, 115, 117, and 123) included subjects in the oral TU arm in the cosyntropin stimulation test. However, only sites 100, 101, 102, and 115 included Axiron subjects.

Results

24 subjects in the TU arm and 8 subjects in the Axiron arm underwent cosyntropin stimulation tests.

At Visit 1, 100 % of subjects in both groups had normal cosyntropin stimulation tests (CSR Table 14.2.2.3 and 14.2.2.3b).

At Visit 8, 5 subjects in the TU group and none in the Axiron group had abnormal cosyntropin stimulation test results. 20.8% of subjects had an abnormal test (95% CI 4.586, 37.081). Maximum post-stimulation cortisol levels in these 5 subjects ranged from 11.6-17.6 mcg/dL.

Subject (b) (6) had an abnormal Visit 8 cosyntropin stimulation test with cortisol levels of 1.8, 8.3 and 11.6 mcg/dL at times 0, 30 and 60 minutes post injection. This subject was noted to have taken high dose prednisone 20 mg tid x 14 days for Days 92-105, approximately 2 months before the Visit 8 test. While exclusion of this subject still demonstrated a significantly greater proportion of subjects in the TU group (17.4%) had abnormal cosyntropin test results on Visit day 8 as compared to the Axiron Group (0), maximum post-stimulation cortisol levels for the

remaining subjects were only just below the cut-off for normal response (≥ 18 mcg/dL) at 17.3, 17.6, 17.5 and 16.5 mcg/dL.

The sponsor also performed a post hoc analysis of maximal cortisol concentrations following cosyntropin stimulation at Visit 1 and Visit 8, excluding Oral TU Subject (b) (6), by treatment group. Results are presented in Table 53 below. Overall, there was no difference in the mean incremental increase in cortisol levels or the maximum levels achieved after cosyntropin stimulation between the 2 treatment arms at both study time points. However, both treatment groups had significantly lower mean incremental increases from pre-injection cortisol levels on visit 8 as compared to visit 1. On the other hand, mean pre-injection cortisol levels were nonsignificantly higher at Visit 8 in both groups. Both groups also had slightly lower peak post-injection cortisol levels on visit 8 as compared to visit 1 of approximately 1.7 mcg/dL, but this change was only statistically significant for the TU group

Reviewer Comment: The time of day at which the cosyntropin tests was performed varied between Visit 1 and Visit 8 in some subjects and could have affected the mean pre-injection cortisol levels. Overall, the modest changes in mean pre-injection cortisol levels and incremental changes after cosyntropin stimulation between the Visit 1 and 8 described in this post hoc analysis are of uncertain significance.

Table 53: Maximal Cortisol Concentration (µg/dL) Following Cosyntropin Stimulation at Visit 1 and Visit 8 by Treatment Group (Cosyntropin Stimulation Test Substudy Population Excluding Subject (b) (6))

Maximal Cortisol Concentration (µg/dL)	Oral TU (N = 23)		Topical Axiron (N = 8)		p-value	
	Visit 1/Day 1 (Baseline)	Visit 8	Visit 1/Day 1 (Baseline)	Visit 8	Visit 1	Visit 8
Pre-injection						
Mean (SD)	9.14 (3.304)	10.11 (3.676)	7.39 (3.631)	10.85 (4.441)		
Median	9.80	9.30	6.95	9.55		
Min, Max	1.5, 15.4	3.1, 17.5	2.1, 13.5	6.5, 18.2		
Max Concentration						
Mean (SD)	23.30 (2.688)	21.62 (3.271)	25.20 (5.495)	23.50 (3.095)	0.2064 ^a	0.1661 ^a
Median	24.00	21.40	22.70	22.65		
Min, Max	18.9, 29.0	16.5, 28.8	20.6, 35.4	20.3, 29.4		
Change from Pre-injection						
Mean (SD)	14.17 (3.747)	11.50 (3.633)	17.81 (5.136)	12.65 (3.700)	0.1056 ^b	0.1916 ^b
Median	14.00	11.30	16.85	13.60		
Min, Max	5.1, 20.2	3.7, 18.6	13.1, 29.0	7.8, 16.9		
Within Treatment p-value ^c	<0.0001	<0.0001	<0.0001	<0.0001		
Difference in Maximum Concentration Post-injection (Visit 8 - Visit 1)					0.5255 ^d	
Mean (SD)	-1.69 (3.456)		-1.70 (3.411)			
Median	-1.50		-1.10			
Min, Max	-7.5, 7.7		-6.0, 3.9			
Within Treatment p-value ^c	0.0287		0.2015			
Difference in Change from Pre-injection (Visit 8 - Visit 1)					0.9914 ^d	
Mean (SD)	-2.66 (4.384)		-5.16 (4.509)			
Median	-2.60		-4.90			
Min, Max	-13.2, 4.5		-12.2, 0.9			
Within Treatment p-value ^c	0.0081		0.0143			

Source: Post-text Table 14.2.2.3.2b

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation; TU = testosterone undecanoate

a P-value from an analysis of variance comparing maximum concentration between treatment groups.

b P-value from an analysis of covariance conducted at each visit with treatment as a factor and pre-injection concentration as a covariate. For the maximum concentration, the pre-injection concentration at Visit 1 was used as the covariate. For the change from pre-injection, the change from pre-injection at Visit 1 was used.

c P-value from a paired t-test completed for each treatment group.

d P-value from an analysis of covariance with treatment as a factor and baseline value as a covariate. For the maximum concentration, the pre-injection concentration at Visit 1 was used as the covariate. For the change from pre-injection, the change from pre-injection at Visit 1 was used.

Reviewer Responses:

1. Was the study performed properly and were appropriate doses of cosyntropin utilized?

Response: The location of the abnormality along the hypothalamus-pituitary-adrenal (HPA) axis needs to be considered when deciding upon the appropriate screening test for adrenal insufficiency as well as test interpretation. The potential mechanism by which TU might cause adrenal insufficiency is unknown and therefore, it is uncertain as to whether subjects may be at risk for primary or secondary adrenal insufficiency. As an initial screen for possible adrenal insufficiency of uncertain type, this reviewer believes that simultaneous baseline

morning ACTH and cortisol levels as well as the 0.25 mg cosyntropin stimulation test are reasonable screening tests. The sponsor performed the cosyntropin stimulation test in the standard fashion using standard dosing of cosyntropin 0.25 mg intravenously and with cortisol levels tested at times 0 (pre-injection), and 30 and 60 minutes post-injection. Although some experts do not believe time of day affects the test results, this reviewer recommends that the test be standardized to early morning (i.e. 6-8 AM) to allow for standardization and for measurement of simultaneous ACTH and cortisol levels prior the cosyntropin injection. Additionally, in the case of testosterone supplementation which would be expected to be taken chronically, the test should be repeated at regular intervals for up to at least one year (ie, every 6 months) in subjects who remain on drug treatment to assess whether longer use of this drug results in progressive adrenal insufficiency.

Discussion: The potential mechanism by which TU might cause adrenal insufficiency is unknown. If metabolites of the drug cross-react with the glucocorticoid receptor at the level of the hypothalamus and or pituitary gland, secondary or tertiary adrenal insufficiency could result. In the case of secondary/tertiary adrenal insufficiency, the standard cosyntropin stimulation test may not be sensitive to detect early dysfunction. Primary adrenal insufficiency is also possible. Blunting of cortisol responsiveness to CRH was seen in a small study of testosterone replacement in subjects with acute leuprolide-induced hypogonadism (Rubinow DR et al 2005).

The standard cosyntropin stimulation test administered as 0.25 mg intravenously or intramuscularly is generally accepted for the initial screening for both primary and secondary insufficiency (Bornstein S et al. 2016, Grossman AB 2010). The important caveat to consider is that in early secondary adrenal insufficiency, as may be the case in this study where subjects were tested between 105-170 days after TU exposure, despite reduced ACTH stimulation, the adrenal gland could still be responsive to supraphysiologic doses of cosyntropin. The 1 mcg cosyntropin stimulation test has been advocated by some experts as the test of choice for the detection of early mild secondary or tertiary adrenal insufficiency since cosyntropin levels are more physiologic (Brodie J et al. 1995). However, it is controversial as to whether this test actually performs better than the standard test 0.25 mg test. In addition, the 1 mcg solution requires preparation by the investigator/clinician, and its preparation is another potential source of error and unreliability (Dorin RI, et al. 2003). When the 2 tests have been compared, they generally perform similarly, except in the case of early secondary insufficiency.

The gold standard for the evaluation of secondary adrenal insufficiency is the insulin tolerance test, whereby insulin-induced hypoglycemia activates the HPA axis. However, given the risks to patients, particularly those with ischemic heart disease, and burden to investigators, this test is rarely performed as an initial screen for hypoadrenalism. The metyrapone stimulation test may be more sensitive for detecting early secondary hypoadrenalism. Metyrapone interferes with the synthesis of cortisol, thereby reducing cortisol levels. Patients with hypothalamic/pituitary dysfunction are not able to appropriately increase CRH/ACTH levels to restore cortisol synthesis. Glucagon has also been used to activate the HPA axis, but is often associated with nausea and vomiting and may require up to 5 hours to perform.

As an initial screen for possible adrenal insufficiency of uncertain type, this reviewer believes that both simultaneous morning cortisol and ACTH levels, as well as the 0.25 mg cosyntropin stimulation test are appropriate screening tests. Since peak stimulated levels could vary according to time of day in healthy individuals (Park YJ et al, 1999), this reviewer recommends that the cosyntropin stimulation test in subjects without known HPA axis pathology should be performed at 8 AM. Early morning simultaneous ACTH and cortisol levels should also be checked prior to the cosyntropin injection to help elucidate the level of the potential defect within the HPA axis. Additionally, in the case of chronic use of a medication that might be associated with progressive adrenal insufficiency, the test should be repeated at regular intervals (ie, every 6 months) in subjects who remain on drug treatment.

2. Were adequate numbers of subjects studied?

Response: The number of subjects included in each arm of the sub-study was below the goal of 15 in each group. However, it is not clear how this sample size was derived, and, in turn, why the protocol was not followed. Power calculations were not provided. A post-hoc analysis with meaningful statistics cannot be performed. We recommend that the sponsor uses the results of this sub-study to plan a formal analysis (including sample size) for a subsequent study.

3. Interpretation of study results.

Response: The data submitted by the sponsor demonstrate a subnormal cosyntropin stimulation response in 5 subjects treated with TU and in none of the subjects treated with Axiron. Of note, one subject in the Axiron group had a pituitary adenoma and a normal test. One of the 5 TU treated subjects had been on high dose prednisone approximately 2 months before the test and this could account for secondary hypoadrenalism in this patient. A second subject was treated with topical hydrocortisone for 1 week, which was unlikely to affect the results. As the sponsor points out, in the remaining 4 subjects, post-stimulation values were only mildly abnormal. The sponsor suggests using a cut off of 15 mcg/dL, which would have resulted in no abnormal test results. The manuscript by Dorin does not support use of this cut off, particularly for secondary adrenal insufficiency. Although cortisol assays vary, a cortisol cut off of ≥ 18 mcg/dL has been widely accepted in clinical practice (Bornstein S 2016).

One possible explanation for the mildly abnormal values in the TU treated group is early secondary hypoadrenalism, particularly since the stimulation test used causes supraphysiologic stimulation of the adrenal gland. Alternative explanations are that the slightly low cortisol levels might be related to the performance characteristics of the cortisol assay itself or to a possible decrease in corticosteroid-binding globulin (CBG) levels, and adrenal function might actually be normal in these subjects.

It is noteworthy that 5 subjects had abnormal baseline cortisol levels prior to exposure to testosterone supplementation and none of these subjects had an abnormal cosyntropin

stimulation test at the end of study. This finding raises concerns about the performance of the assay.

Discussion:

As discussed above, excluding the subject with high dose prednisone exposure, 4 subjects in the TU group had abnormal cosyntropin stimulation test results which were mild in nature and could be due to early mild adrenal insufficiency, performance of the assay, or declines in CBG.

Low morning pre-injection cortisol levels were an unexpected finding that raises concerns about the performance of the assay. As shown in Table 1 below, subjects in both groups tended to have low baseline cortisol levels both at Visit 1 prior to testosterone treatment and at Visit 8. Cortisol secretion has a robust circadian rhythm, with an early morning peak and late afternoon trough. Early morning levels are typically ≥ 10 mcg/dL. Morning cortisol levels < 5 mcg/dL have been associated with adrenal insufficiency (Bornstein S, 2016, Kazlauskaite R et al, 2008).

In the current study, the cosyntropin tests were conducted between 6:25 am and 3:45 pm, although the majority of tests were performed in the morning. The cortisol levels in the 3 subjects in the TU group with baseline Visit 1 cortisol levels < 5 mcg/dL were 1.5, 3.7, and 4.6 mcg/dL but were drawn at 8:31 am, 9:19 am, and 9:22 am respectively. Two subjects in the Axiron group had Baseline Visit 1 cortisol levels of 4.9 and 2.1 mcg/dL and were tested at 10:35 am and 8:15 am, respectively. None of these 5 subjects had abnormal stimulation tests. The large proportion of subjects with low morning cortisol levels observed prior to testosterone treatment is an unexpected finding that raises concern about the performance of the cortisol assay itself.

The 2 subjects in the TU arm with low baseline cortisol levels on visit 8 had levels of 1.3 and 3.7 mcg/dL tested at 8:31 am and 9:12 am respectively. Both had abnormal stimulation tests with maximum post-stimulation levels of 11.6 and 16.5 mcg/dL respectively. The first subject had been on high dose oral prednisone 2 months prior. Adrenal dysfunction with suppression of the HPA axis by TU treatment is a possible explanation for the abnormal test results in these 2 subjects.

Table 1. Pre-stimulated cortisol levels

Study Arm	Baseline Cortisol < 10 mcg/dL		Baseline Cortisol < 5 mcg/dL	
	Visit 1	Visit 8	Visit 1	Visit 8
TU (N=24)	15	13	3	2
Axiron (N=8)	6	4	2	0

It is also theoretically possible that TU could lower CBG levels. Cortisol predominantly circulates bound to CBG. If CBG levels were to decline with TU exposure, then total cortisol levels would also be expected to decline, without lowering free cortisol levels or affecting adrenal function. As seen in Table 2, overall, mean pre-injection cortisol levels increased from Visit 1 to Visit 8 in both groups.

Table 2. Mean Pre-injection Cortisol Level (mcg/dL) by Visit

Treatment Group	Visit 1	Visit 8
Oral TU (n=24)		
Mean	9.1	9.7
(Min, Max)	(1.5, 15.4)	(1.3, 17.5)
Axiron (n=8)		
Mean	7.4	16.8
(Min, Max)	(2.1, 13.5)	(6.5, 18.2)

As Table 3 shows, an equal proportion of individuals in the TU group had increases and decreases in their baseline cortisol levels from Visit 1 to Visit 8, while most in the Axiron group had increases. Variability in the time the cosyntropin tests were performed may have contributed to changes in baseline cortisol levels in some subjects. Of the 5 subjects with abnormal Visit 8 cosyntropin stimulation tests, 2 had a marked decline in baseline cortisol levels, one who was treated with glucocorticoids and a second subject whose 7:34 AM cortisol was 13.1 mcg/dL at Visit 1 with normal stimulation and 9:15 AM cortisol was 3.1 mcg/dL at visit 8, with stimulation to 16.5 mcg/dL. It is difficult to attribute the decline in AM cortisol to the time differences alone.

Table 3. Direction of Change in Visit 8 Pre-injection Cortisol Levels Relative to Visit 1 Pre-injection Cortisol Levels

	Oral TU (n=24)	Axiron (n=8)
Visit 8 value increased compared to Visit 1 value	11 (45.8%)	7 (87.5%)

Visit 8 value the same compared to Visit 1 value	2 (8.3%)	0
Visit 8 value decreased compared to Visit 1 value	11 (45.8%)	1 (12.5%)

Clinical parameters of the 4 subjects with abnormal cosyntropin stimulation results:

The subject taking exogenous glucocorticoids was not included in this analysis.

None had hyponatremia, hyperkalemia or hypoglycemia.

1 of the 4 subjects (subject (b) (6)) had hypertension that was treated with Lisinopril.

No subjects experienced hypotension assessed by 24-hour ambulatory monitoring (ABPM) (see Table 4).

Subjects with abnormal cosyntropin stimulation tests had post-stimulation cortisol levels that were only slightly below the target of 18 mcg/dL, and thus clinical signs and symptoms of adrenal insufficiency would not be expected.

Table 4. Average BP according to ABPM in the 4 subjects with abnormal Cosyntropin Stimulation Results not on exogenous glucocorticoids

Subject	Visit 3		Visit 6	
	BP	MAP	BP	MAP
	(mm Hg)	(mm Hg)	(mm Hg)	(mm Hg)
(b) (6)	120/65	83	118/68	84
	126/79	95	137/82	101
	123/78	92	156/101	118
	131/76	95	125/73	92

Values presented are mean 24-hr blood pressure rounded to the nearest whole number.

Visit 3 is considered the baseline ABPM assessment.

MAP=mean arterial pressure

*History of hypertension treated with Lisinopril

Conclusions:

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.

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/s/

LINDA S JAFFE
12/06/2017

THERESA E KEHOE
12/06/2017



Center for Drug Evaluation and Research

Division of Cardiovascular and Renal Products

DCRP Consult NDA 206089

DATE: Date of Document: 6/22/2017
Date of Consult: 7/11/2017
Desired Completion Date: 9/11/2017
Date of Completion: 9/15/2017

FROM: Preston M. Dunnmon, M.D., M.B.A., Medical Officer
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THROUGH: Shari L. Targum, M.D., M.P.H., Medical Team Leader
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Division of Cardiovascular and Renal Products, HFD-110

TO: Jeannie Roule, RPM, DBRUP
Scientific Reviewer, OIR/DCTD

PRODUCT NAME: Testosterone undecanoate (TU, oral)

PRODUCT CLASS: Androgen

SPONSOR: Clarus Therapeutics

INVESTIGATIONAL INDICATION: Replacement therapy in adult men

BACKGROUN AND CONSULT QUESTIONS:

DCRP was consulted in October 2015 to provide input to this sponsor regarding the assessments of cuff blood pressures and the ABPM sub-study that was requested to be incorporated into the proposed Phase 3 trial CLAR-15012. The DCRP consultative input was conveyed to the Sponsor in writing, and DCRP attended the follow-up meeting with the Sponsor, whose representatives and consultants agreed to the DCRP recommendations for blood pressure assessments. The Sponsor subsequently submitted their formal CLAR-15012 protocol to the Agency in January 2016, at which time DCRP was re-consulted to assess the cuff and ABPM acquisition and analysis plans. The Sponsor subsequently submitted a revised statistical analysis plan (SAP) for CLAR-15012 (Version 2.0 – 19 Apr 2016), at which time DCRP was re-consulted to confirm the acceptability of the cuff blood pressure and ABPM sub-study safety analysis plans. The Sponsor submitted another revised SAP for CLAR-15012 (Version 3.0 – 30 June 2016),

NDA 206089

for which DCRP again performed consultative review of the acceptability of the cuff blood pressure and ABPM sub-study safety analysis plans on February 5, 2017. DCRP's additional comments were included in the Division's February 10, 2017 Advice letter. That most recent DCRP consult is embedded here for ease of reference and is linked to this consult in DARRTS:



170205 DCRP
Consult.pdf

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 (± 9.384) 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 \pm SD: Oral TU 2.8 \pm 11.84 mm Hg, Topical Axiron 1.8 \pm 10.76 mm Hg), whereas diastolic blood pressure was essentially unchanged at Visit 7/Early Termination.

DBRUP has the following questions for DCRP:

1. We request your DCRP opinion on whether the Ambulatory Blood Pressure Monitoring sub-study in Phase 3 Study CLAR-15102 was performed in accordance with your recommendations.
2. We request your DCRP analysis concerning the differences noted in the ABPM and cuff blood pressure determinations and the clinical significance of those differences.
3. We request your DCRP opinion concerning the results from ABPM and cuff blood pressure assessments.
4. We request your DCRP recommendations for additional studies, labeling, the post-approval period, etc.

DOCUMENTS REVIEWED:

- Most recent DCRP consult (February 5, 2017)
- Most recent DBRUP consult (July 11, 2017)

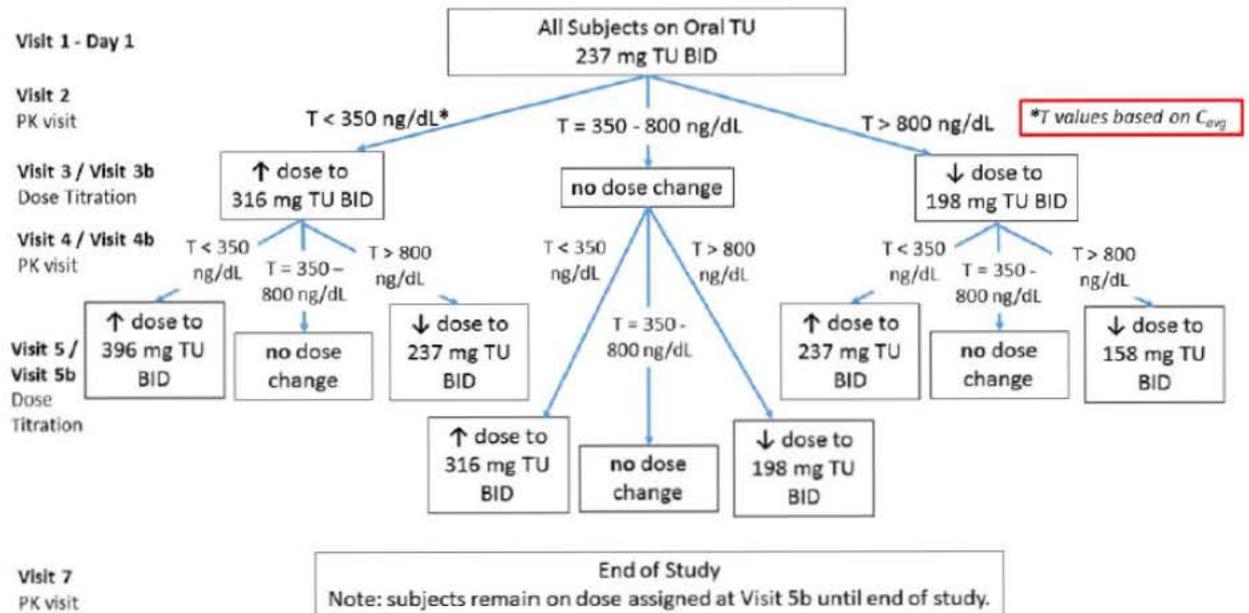
BLOOD PRESSURE ANALYSIS FROM CLAR-15012:

NDA 206089

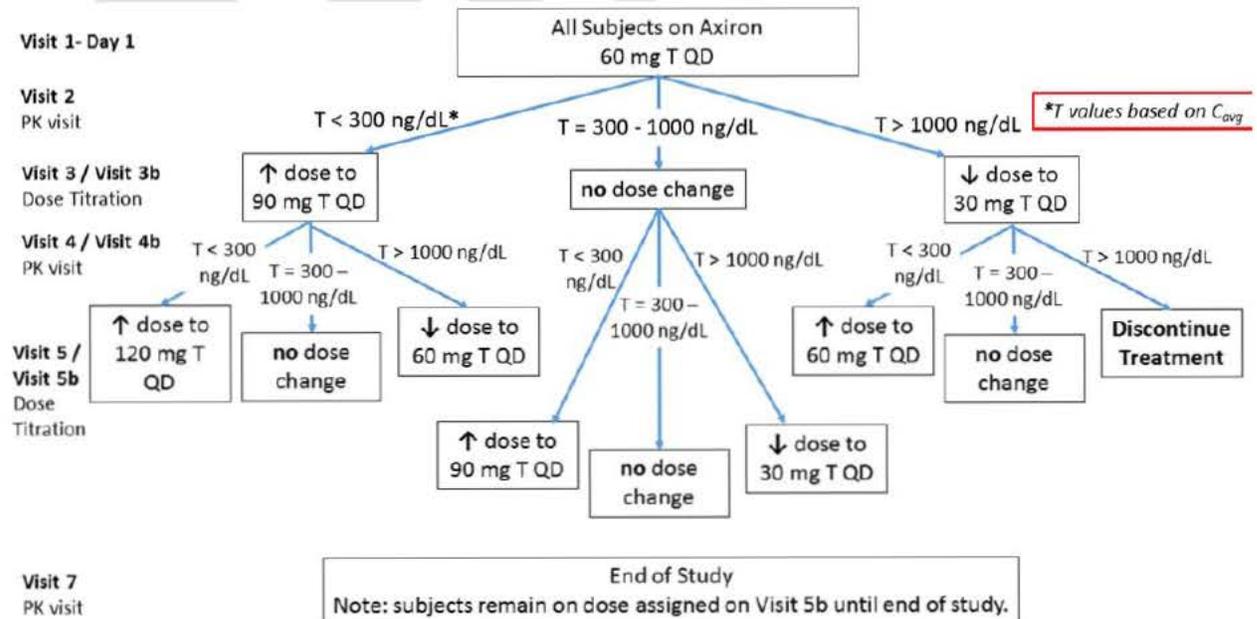
Study Design and Dosing Schedule

Multicenter, randomized, open-label, active-comparator group study of Oral TU administration in hypogonadal men, incorporating dose titration based on total testosterone C_{avg} over 24 hours. The active comparator is Topical Axiron (TA).

Oral Testosterone Undecanoate Dose Titration Scheme (per Fig 3, sponsor CSR)



Topical Axiron Dose-Titration Scheme (per Fig 4, sponsor CSR)



Schedule of procedures for Vital Sign acquisition (cuff and ABPM, sponsor CSR)

Table 2: Schedule of Assessments – Main Study and Cosyntropin Stimulation Test Substudy (Planned Prior to Amendment 2.0)

Activity	Screening			Treatment/Maintenance								Study Days	Early Withdrawal
	Screen 1	Screen 2	Screen 3	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8		
	Day -21 to Day -3	~7 Days After Screen 1	Day -2 (±1 Day)	Day 1 ^a	Day 21 (±3 days)	Day 35 (±2 days)	Day 56 (±3 days)	Day 70 (±2 days)	Day 102 (±2 days)	Day 105 (±3 days)	Day 106		
Informed consent signed	X												
Inclusion/exclusion	X	X	X										
Medical history review	X												
Review of prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X		X
Physical with DRE ^b		X								X			X
Brief physical ^b					X		X						
Weight and height	X												
Adverse event assessment		X		X	X	X	X	X	X	X	X		X
Vital signs (sitting BP and HR in triplicate)	X			X	X		X			X			X

Activity	Screening			Treatment/Maintenance								Study Days	Early Withdrawal
	Screen 1	Screen 2	Screen 3	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8		
	Day -21 to Day -3	~7 Days After Screen 1	Day -2 (±1 Day)	Day 1 ^a	Day 21 (±3 days)	Day 35 (±2 days)	Day 56 (±3 days)	Day 70 (±2 days)	Day 102 (±2 days)	Day 105 (±3 days)	Day 106		
Sample collection (cont.)													
Predose exploratory serum sample for ApoA1 assessment, cholesterol efflux analysis, and hepcidin ^b				X							X		
Dose titration (based on 24-hour T C _{avg})						X		X					
1-PSS	X										X		X
Dispense PDQ ^c		X						X					
Collect PDQ				X						X			
24-hour ABPM assessment ^d			X						X				X ^e

Key Inclusion Criteria

- Men 18 to 65 years of age, inclusive, with a clinical diagnosis of hypogonadism
- Naïve to androgen-replacement therapy or washed out of prior androgen-replacement therapies
- Stable doses of antihypertensive medication for ≥ 3 months

Key Exclusion Criteria

- Received oral topical (e.g., gel or patch), intranasal, or buccal T therapy within the previous 2 weeks, intramuscular T injection of short-acting duration (e.g., T enanthate, T cypionate) within the previous 4 weeks, intramuscular T injection of long-acting duration (e.g., AVEED) within the previous 20 weeks, or T implantable pellets (Testopel®) within the previous 6 months.
- Received oral TU in a previous Clarus-sponsored investigational study
- Significant intercurrent disease of any type; in particular, liver, kidney, uncontrolled or poorly controlled heart disease, including hypertension, congestive heart failure or coronary heart disease, or psychiatric-illness
- Recent (within 2 years) history of stroke, transient ischemic attack, or acute coronary event
- Recent (within 2 years) history of angina or stent (coronary or carotid) placement

NDA 206089

- Untreated, severe obstructive sleep apnea
- Clinically significant abnormal laboratory values
- History of polycythemia, either idiopathic or associated with TRT treatment
- Glycosylated hemoglobin > 8.5%
- Body mass index (BMI) ≥ 38 kg/m²
- Known malabsorption syndrome and/or current treatment with oral lipase inhibitors

RELEVANT PK

- TU Tmax (parent)
- T Tmax (metabolite)
- The sponsor states that,
 - *The change in systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate at the time point associated with the estimated Tmax (and AM Tmax) for testosterone was analyzed. Based on Studies CLAR-09008, CLAR-09007 and CLAR-16015, it is known that the TU Tmax precedes the testosterone Tmax, as would be expected given the parent metabolite relationship of TU (parent) and testosterone (metabolite). Because the TU Tmax occurs a short period prior to the testosterone Tmax, this analysis will also represent an analysis of blood pressure changes associated with the TU Tmax.*
 - *Because no pharmacokinetic assessment was completed on the day of the ABPM assessment at Visit 6, the time of AM dosing and the Tmax (and AM Tmax) associated with the pharmacokinetic assessment done at Visit 7, if available, were associated with the ABPM assessment at Visit 6. If the subject did not have a Visit 7 pharmacokinetic assessment, but did have a pharmacokinetic assessment completed at Visit 4b, then the time of AM dosing associated and the Tmax associated with Visit 4b was used.*
- PK results from this study are shown below (sponsor CSR):

Table 22: Summary of Oral TU and Topical Axiron Plasma Total Testosterone Pharmacokinetic Parameters at Visit 7 by Treatment for All Doses Combined

Visit	PK Parameter	Units	Oral TU, All Doses				Topical Axiron, All Doses			
			N	Mean	SD	CV%	N	Mean	SD	CV%
Visit 1	Plasma T	ng/dL	165	206.8	80.72	39.0%	54	202.7	91.82	45.3
Visit 7	C_{avg24}^a	ng/dL	151	402.5	127.72	31.7%	48	383.0	131.36	34.3%
	AUC_{24}	ng•h/dL	151	9659.1	3065.20	31.7%	48	9191.6	3152.69	34.3%
	C_{max24}	ng/dL	151	1008.3	581.04	57.6%	48	664.0	319.23	48.1%
	$T_{max-am}^{b,c}$ T_{max-pm}^b	h	155	3.87	(0.00, 12.08)		48	4.01	(0.00, 24.00)	
		h	151	16.00	(12.00, 24.02)					

Source: Appendix 16.5.2, Tables 2 and 10

Abbreviations: AM = morning; AUC_{24} = area under the concentration-time curve morning and evening doses combined;

C_{avg24} = time-weighted average plasma concentration morning and evening doses combined; C_{max24} = maximum observed concentration morning and evening doses combined; C_{max-am} = time-weighted average concentration over the daytime dosing interval following the AM dose; C_{max-pm} = time-weighted average concentration over the daytime dosing interval following the PM dose; CV = coefficient of variation; PK = pharmacokinetic; SD = standard deviation;

T_{max-am}/T_{max-pm} = time to C_{max-am}/C_{max-pm} ; TU = testosterone undecanoate

^a C_{avg24} calculated using actual sample collection times.

^b T_{max} values shown are median (range).

^c Topical Axiron T_{max} is relative to the AM dose since it was applied just once daily, in the morning.

Population Definitions

- **ABPM Population:** All subjects who had ABPM measurements and had interpretable results at both the predose visit (Screen 3) baseline and Visit 6. Approximately 80% of the subjects in both treatment groups had ABPM measurements with interpretable results at Screening and Visit 6 and were included in the ABPM Population.
- **Safety Population:** All subjects randomly assigned into the study who took at least 1 dose of study drug (identical to the Modified ITT Population). This population was used to analyze all safety endpoints, with the exception of the ABPM-measured blood pressures.
- The sizes of these datasets are seen in the following table (sponsor CSR):

Table 14: Data Sets Analyzed (All Randomized Subjects)

Population, n (%)	Oral TU (N = 166)	Topical Axiron (N = 56)
ITT ^a	166 (100.0)	56 (100.0)
Modified ITT ^b	166 (100.0)	55 (98.2)
PK ^c	166 (100.0)	55 (98.2)
Safety ^d	166 (100.0)	55 (98.2)
ABPM ^e	135 (81.3)	45 (80.4)
Cosyntropin Substudy ^f	24 (14.5)	8 (14.3)

Source: Post-text Table 14.1.2.4

The issue of how to handle missing ABPM data had been the topic of a prior DCRP consult. In follow-up to our recommendations in that consult, the sponsor stated the following:

All subjects were to have ABPM assessments. If ABPM failed on the first attempt at either Screen 3 or Visit 6, an attempt was made to repeat the ABPM assessment. In order for ABPM data to be considered interpretable, the assessment had to be at least 23 hours in duration, have no more than 2 hours of missing data with 80% successful readings. Subjects not included in the ABPM Population (Oral TU: 31 subjects; Topical Axiron: 10 subjects) were missing Screen 3 and/or Visit 6 ABPM results. At the request of the FDA, an analysis of cuff vital signs was presented by treatment group for those subjects included in the ABPM Population and those subjects not included in the ABPM Population (Post-text Table 14.3.4.2.14.1). Changes from baseline in cuff systolic blood pressure, diastolic blood pressure, heart rate and mean arterial pressure were generally similar between ABPM and non-ABPM subjects within each treatment group, and no trends were observed comparing between the treatment groups.

When comparing systolic blood pressure measured by office cuff in those who were in the ABPM Population with that measured by ABPM, the results were similar (e.g., Oral TU ABPM Population change from baseline to Visit 7/Early Termination was 3.4 ± 11.33 mm Hg by office cuff versus 4.88 ± 8.749 mm Hg by 24-hour ABPM). This indicates that systolic blood pressure changes measured by office cuff are similar to ABPM.

Results: ABPM

ABPM systolic and diastolic mean pressures for TU were elevated in comparison to the topical Axiron control in all three timeframes assessed (daytime, nighttime, and 24 hour) as below (sponsor CSR):

Table 49: Systolic and Diastolic Blood Pressure Measured by ABPM at Baseline and Visit 6 by Treatment Group (ABPM Population)

Vital Sign Measurement	Statistic	Oral TU (N = 135)		Topical Axiron (N = 45)	
		Baseline	Change	Baseline	Change
Systolic blood pressure (mm Hg)					
Daytime average	Mean (SD)	131.13 (10.149)	5.05 (8.855)	131.21 (14.101)	-0.14 (10.534)
	Median	131.50	5.30	131.50	0.60
	p-value ^a		0.008		
Nighttime average	Mean (SD)	120.05 (11.164)	4.72 (11.852)	118.33 (13.102)	0.74 (11.328)
	Median	120.10	3.10	117.50	-0.70
	p-value ^a		0.0209		
24-hour average	Mean (SD)	127.52 (9.747)	4.88 (8.749)	127.03 (13.243)	0.18 (9.384)
	Median	127.80	4.50	128.00	1.00
	p-value ^a		0.0013		
Diastolic blood pressure (mm Hg)					
Daytime average	Mean (SD)	78.93 (7.819)	2.51 (7.246)	79.94 (8.547)	0.29 (6.6266)
	Median	78.50	2.00	79.30	0.50
	p-value ^a		0.0951		
Nighttime average	Mean (SD)	70.07 (7.779)	2.78 (8.940)	69.40 (8.092)	0.77 (8.108)
	Median	69.60	1.80	69.00	0.50
	p-value ^a		0.1059		
24-hour average	Mean (SD)	76.04 (7.206)	2.56 (6.772)	76.53 (7.910)	0.44 (5.830)
	Median	75.90	1.90	75.80	-0.20
	p-value ^a		0.0653		

Source: Post-text Tables 14.3.4.3.1 and 14.3.4.3.5

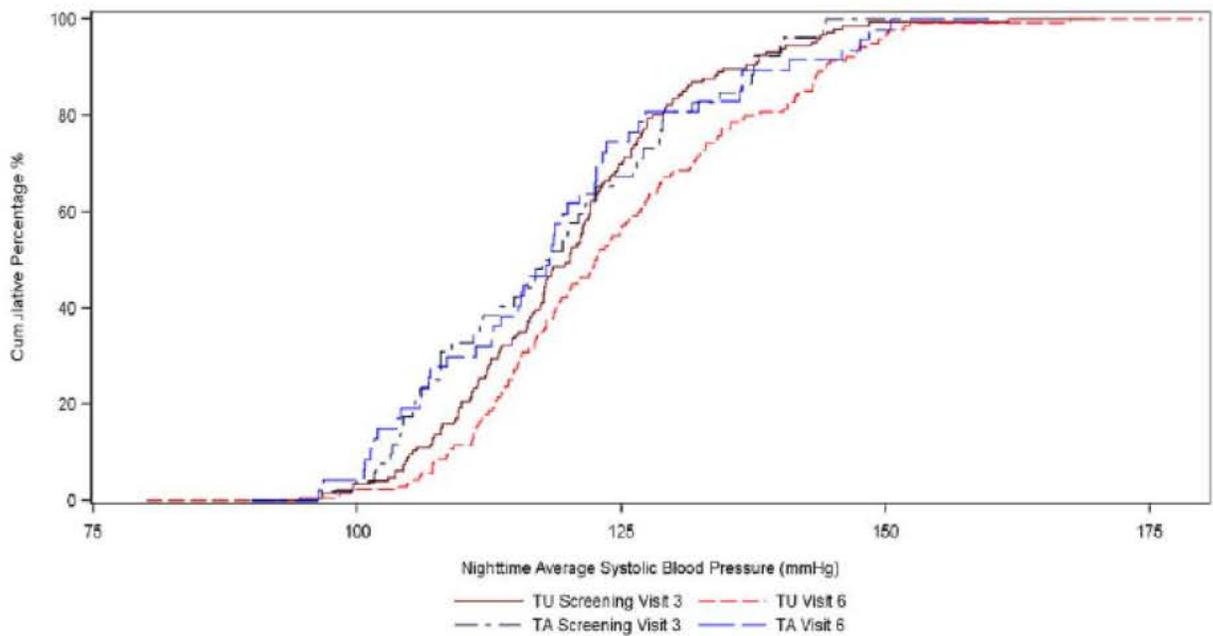
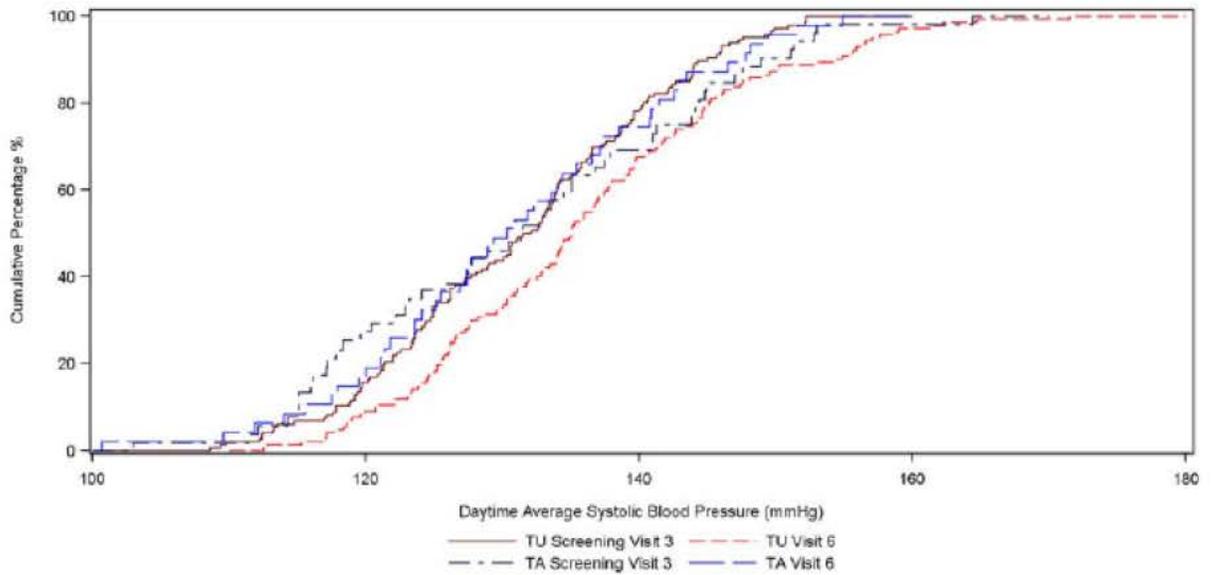
Abbreviations: ABPM = ambulatory blood pressure monitor; SD = standard deviation; TU = testosterone undecanoate

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

Reviewers Comment: Table should be regenerated with 95% confidence intervals. Heart Rate data should be added as three additional rows.

These TU induced elevations were present across the entire SBP/DBP ranges as shown by cumulative function distributions (CDFs). The CDFs of SBP, DBP, and HR for the daytime and nighttime periods are shown as follows, respectively, with baseline (Screening Visit 3) and Visit 6 shown for both TU and TA (sponsor CRS):

Figure 23: Cumulative Distribution Curves for Daytime and Nighttime Average Systolic Blood Pressure (ABPM Population)



Source: [Figures 14.3.4.3.12.1](#) and [14.3.4.3.12.2](#)

Abbreviations: ABPM = ambulatory blood pressure monitor; TA = Topical Axiron, TU = testosterone undecanoate

Figure 14.3.4.3.12.1
 Cumulative Distribution Curves of Daytime Averages of ABPM Vital Sign Data by Treatment Group
 (ABPM Population)

Daytime Average Diastolic Blood Pressure (mmHg)

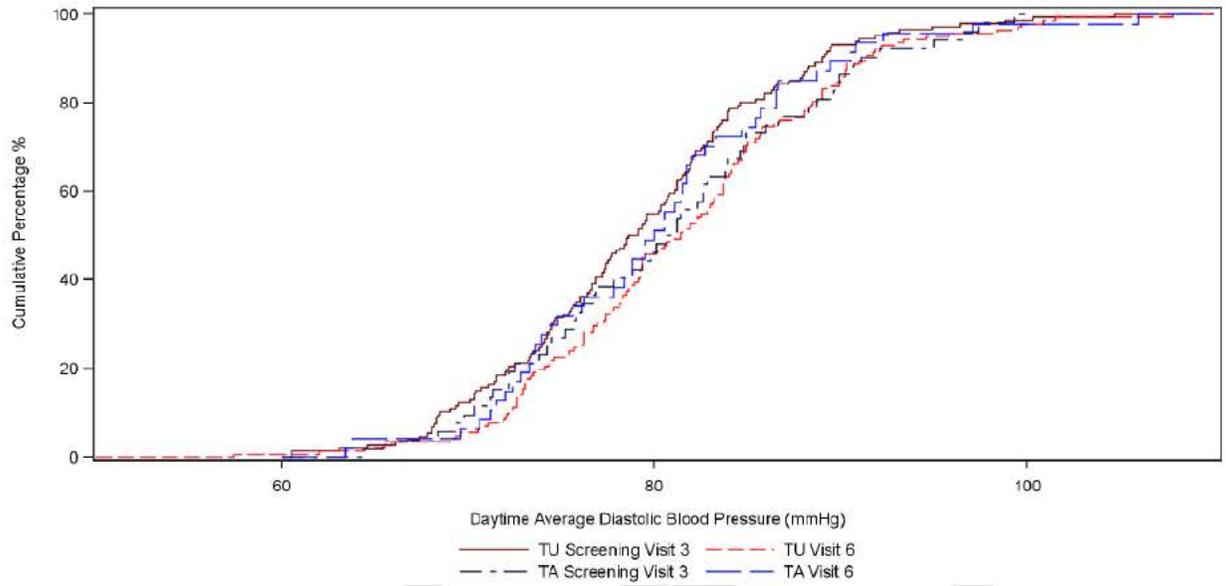


Figure 14.3.4.3.12.2
 Cumulative Distribution Curves of the Nighttime Averages of ABPM Vital Sign Data by Treatment Group
 (ABPM Population)

Nighttime Average Diastolic Blood Pressure (mmHg)

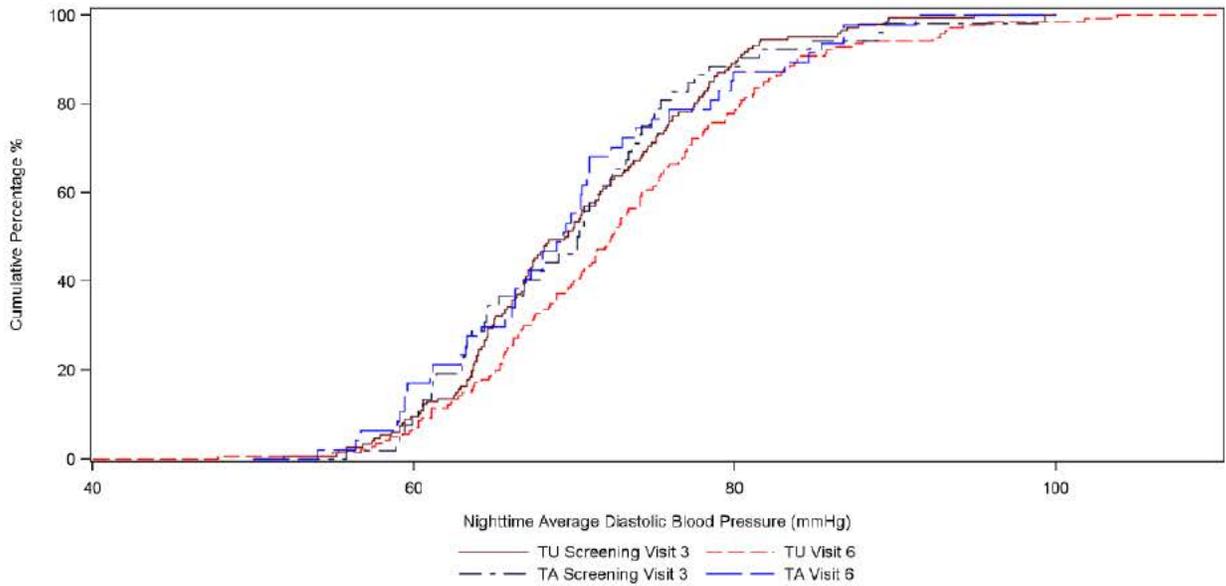


Figure 14.3.4.3.12.1
 Cumulative Distribution Curves of Daytime Averages of ABPM Vital Sign Data by Treatment Group
 (ABPM Population)

Daytime Average Heart Rate (bpm)

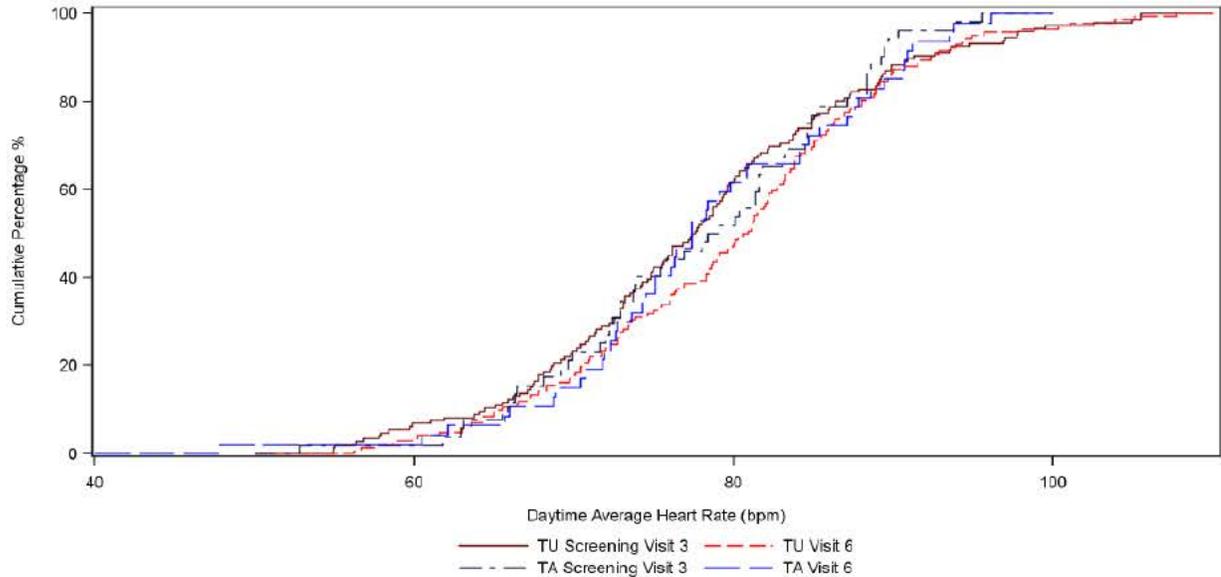
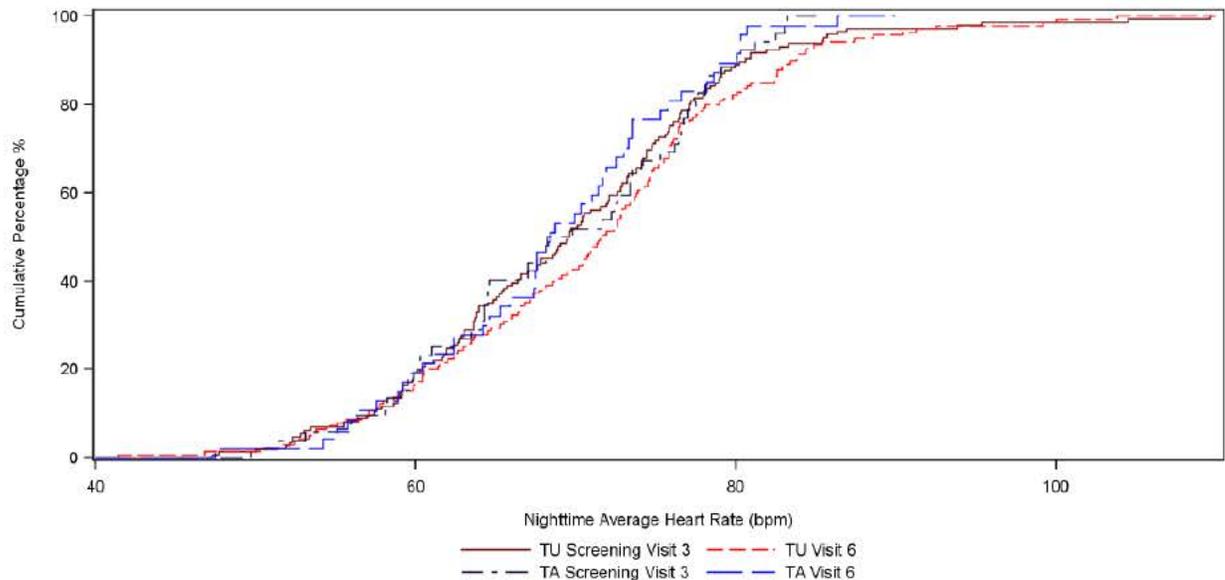


Figure 14.3.4.3.12.2
 Cumulative Distribution Curves of the Nighttime Averages of ABPM Vital Sign Data by Treatment Group
 (ARPM Population)

Nighttime Average Heart Rate (bpm)



Reviewer's Comment: Clinically significant (and what appear to be nominally statistically significant) daytime blood pressure and HR elevations in the TU treatment arm that are of greater magnitude than is seen for the TA comparator. Scatter plots created from baseline to Visit 6 T_{max} are difficult to interpret but show that the highest outliers for all three vital sign measures occur in the TU treatment arm, as shown by the following figures (sponsor CSR):

Figure 14.3.4.3.13.1

Scatter Plot of the Change in ABPM Vital Signs from Predose to Estimated Tmax at Visit 6 vs. Screening Visit 3 (ABPM Population)

Hourly Average Systolic Blood Pressure (mmHg)

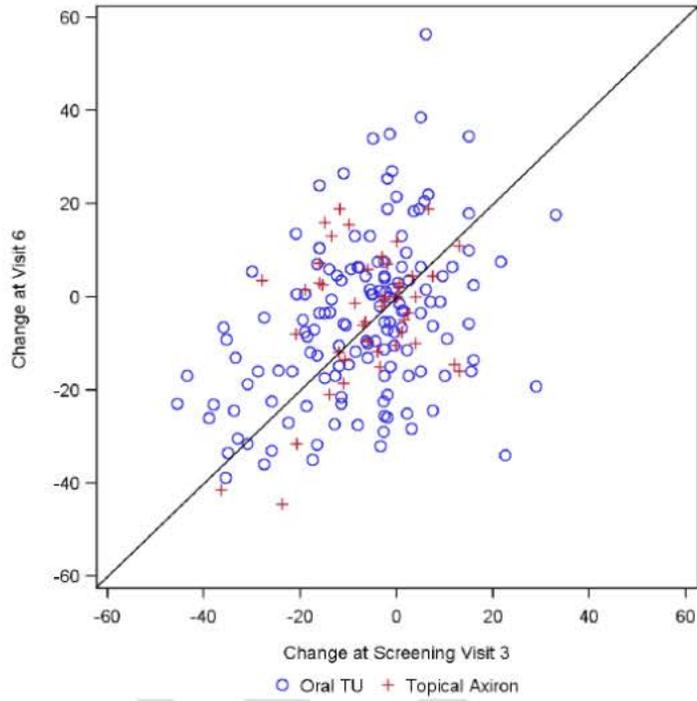


Figure 14.3.4.3.13.1

Scatter Plot of the Change in ABPM Vital Signs from Predose to Estimated Tmax at Visit 6 vs. Screening Visit 3 (ABPM Population)

Hourly Average Diastolic Blood Pressure (mmHg)

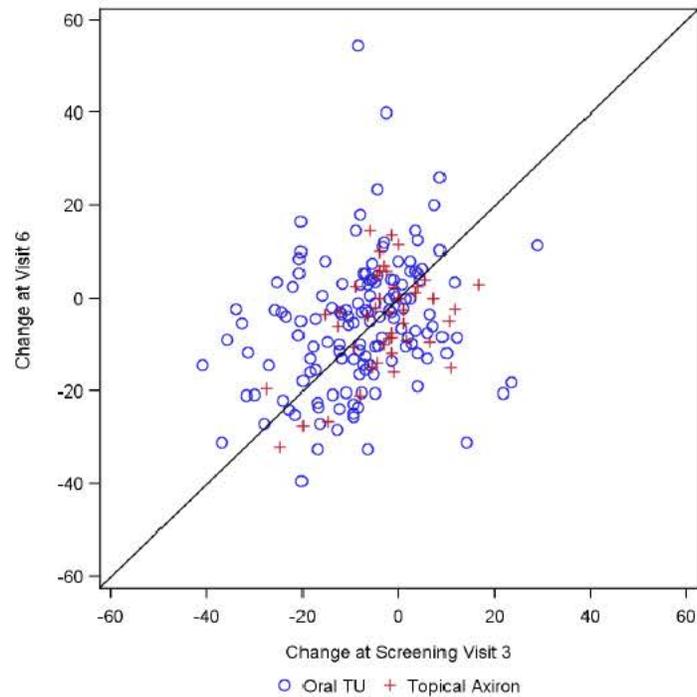
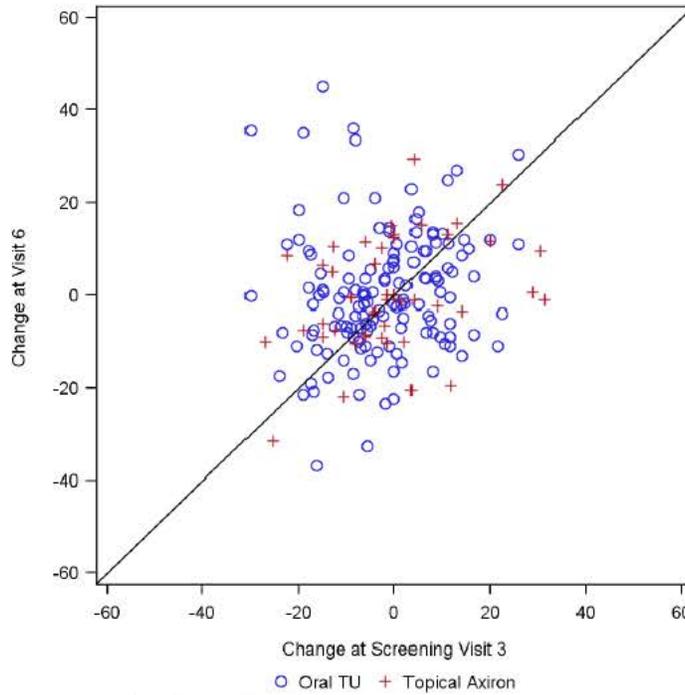


Figure 14.3.4.3.13.1

Scatter Plot of the Change in ABPM Vital Signs from Predose to Estimated Tmax at Visit 6 vs. Screening Visit 3 (ABPM Population)

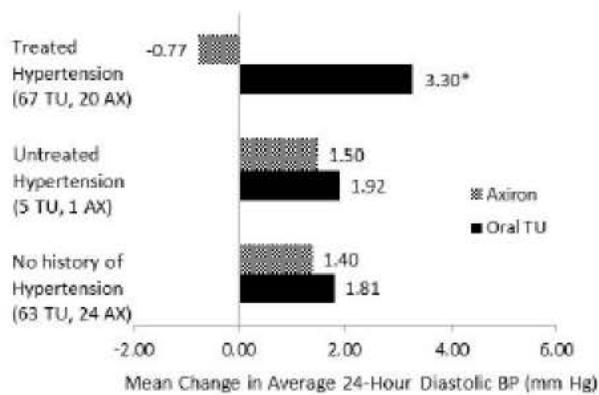
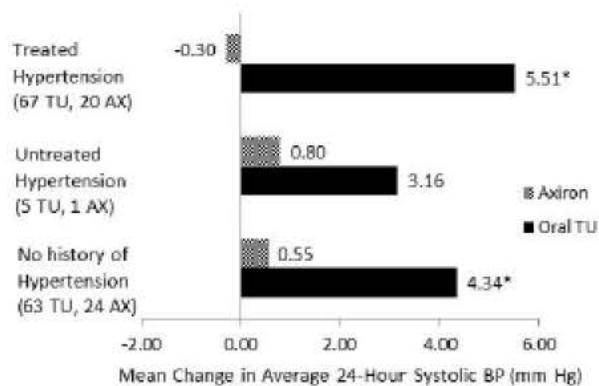
Hourly Average Heart Rate (bpm)



It is unclear what time period that these scatter plots represent. These scatter plots should be rendered as CDFs for daytime, nighttime, and 24 hour time periods. The scatterplots showing changes in ABPM vital signs by dose are uninterpretable, and should also be rendered as CDFs. All of these analyses should also be displayed in tabular form (i.e. like table 49 on page 8 of this consult), with confidence intervals included as a column for each analysis row.

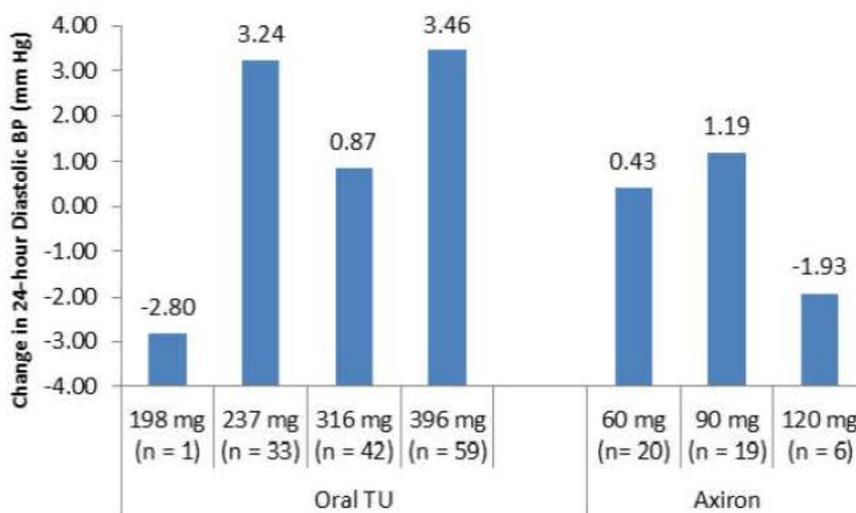
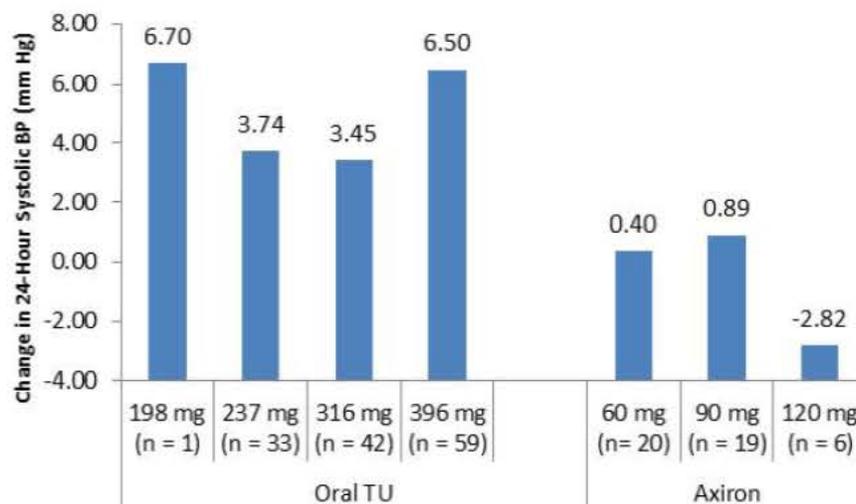
As would be expected, blood pressure effects were exaggerated in the subgroup of subjects with hypertension at baseline (sponsor CSR):

Figure 24: 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)



The sponsor notes that there was no clear relationship between doses of study drug and mean increase from baseline to 24-hour average blood pressure, as shown below (sponsor CSR):

Figure 25: Mean Change From Baseline to Visit 6 in 24-Hour Average Systolic and Diastolic Blood Pressure by Treatment Group and Dose (ABPM Population)



Source: Post-text Table 14.3.4.3.3

Abbreviations: ABPM = ambulatory blood pressure monitor; BP = blood pressure; TU = testosterone undecanoate

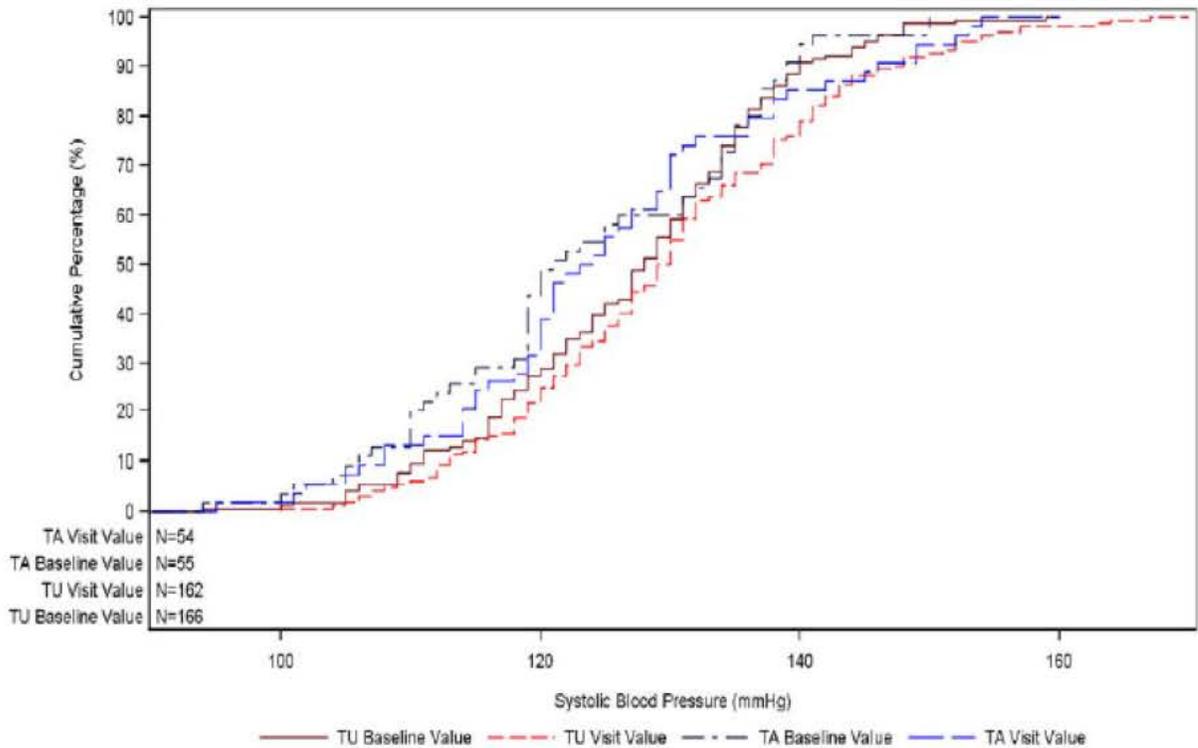
Reviewer's comment: Heart rate changes should be added to this figure.

In addition, the sponsor notes that in the Oral TU group of the ABPM dataset, 5.9% of subjects started antihypertensive medication after baseline or required a dose increase compared with 2.2% of subjects in the Topical Axiron group.

Results: Cuff/Clinic Blood Pressures

Cuff pressures in the safety population show a more subtle rightward shift of the SBP CDF curve for SBP, especially notable in the higher blood pressure ranges (sponsor CRS):

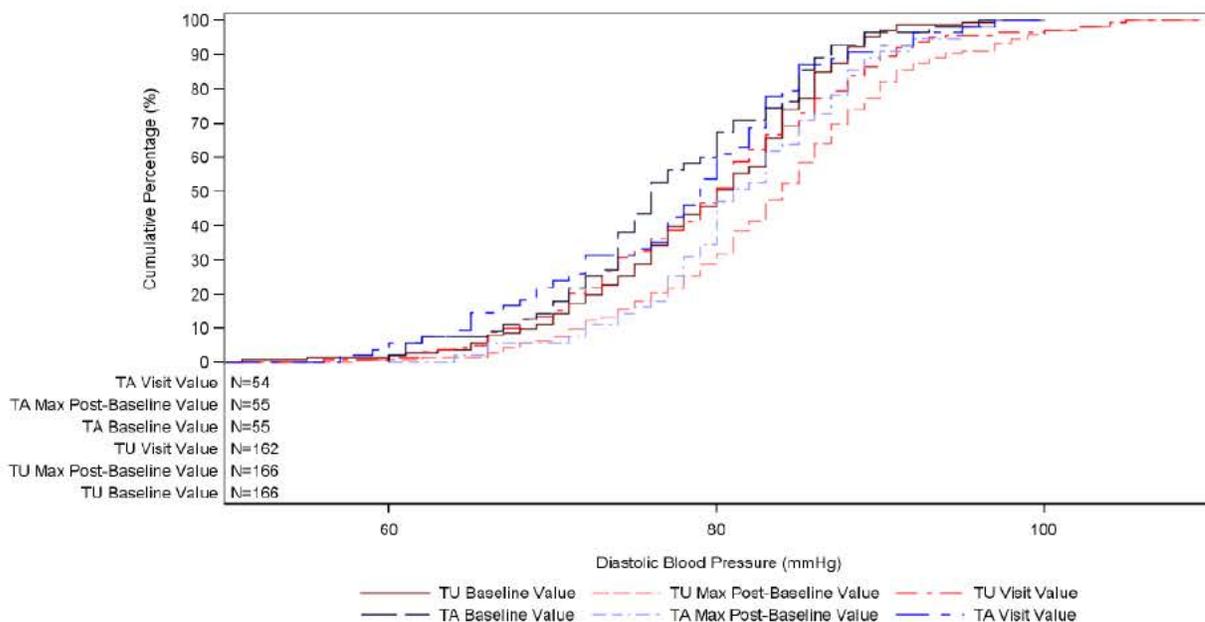
Figure 17: Cumulative Distribution Curves for Systolic Blood Pressure for Baseline and Visit 7 by Treatment Group (Safety Population)



The DBP cuff pressures for visit 7 demonstrate a similar trend for DBP, with TU also demonstrating the most extreme post-baseline shifts (sponsor CSR):

Figure 14.3.4.2.11.2
 Cumulative Distribution Curves for Diastolic Blood Pressure (mmHg) by Visit and Treatment Group
 (Safety Population)

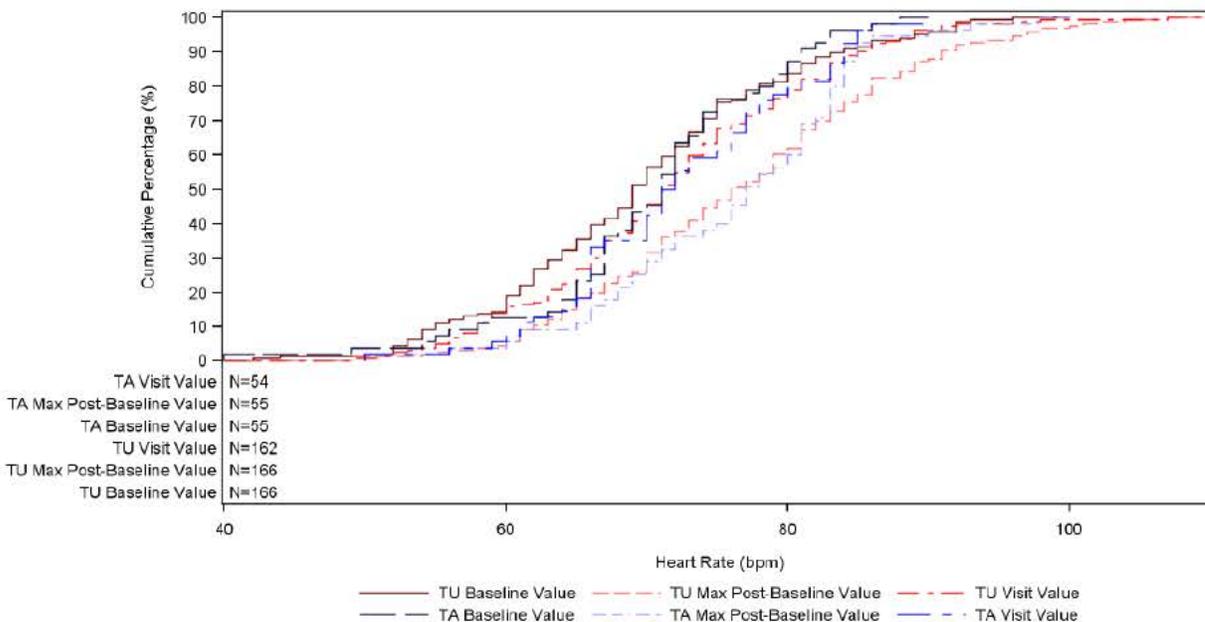
Visit: Visit 7 or ET



TU and TA effects on cuff/clinic heart rates were similar between the two treatment groups (sponsor CSR):

Figure 14.3.4.2.11.4
 Cumulative Distribution Curves for Heart Rate (bpm) by Visit and Treatment Group
 (Safety Population)

Visit: Visit 7 or ET

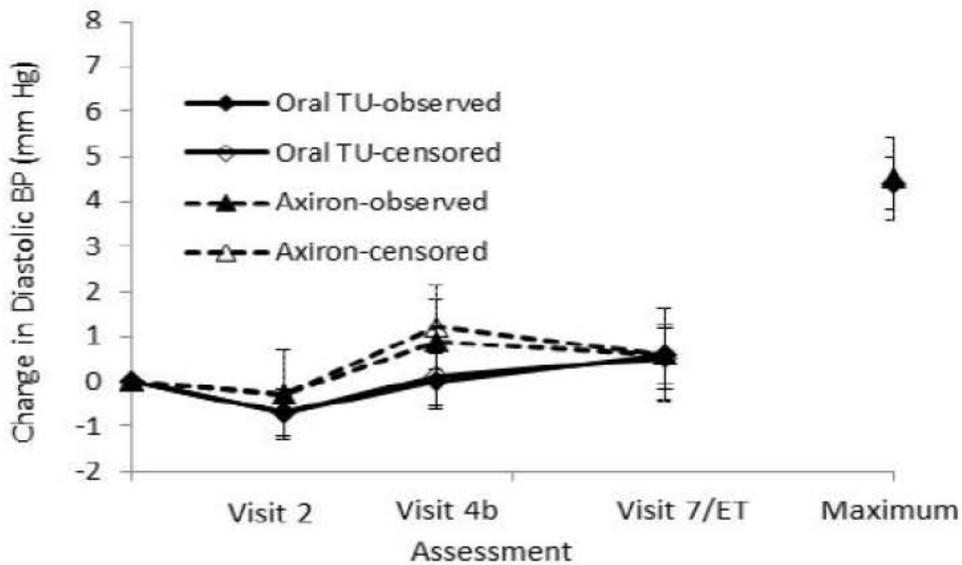
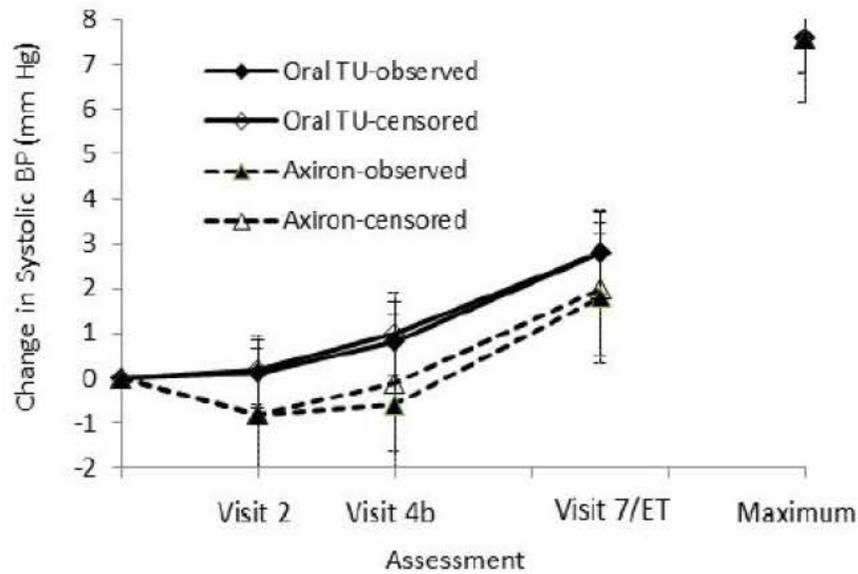


Because more cuff/clinic vital sign readings were acquired, the trend of changes becomes more apparent than for the ABPM data for which there were only two data points in time.

NDA 206089

It is somewhat disconcerting that for both of these TU products, the Visit-7/ET blood pressure data suggests that SBP increases had not plateaued at the end of the study (from the sponsor CRS):

Figure 16: Mean Change (\pm Standard Error) From Baseline in Systolic and Diastolic Blood Pressure by Treatment Group (Safety Population)



Source: [Post-text Tables 14.3.4.2.1](#) and [14.3.4.2.2](#)

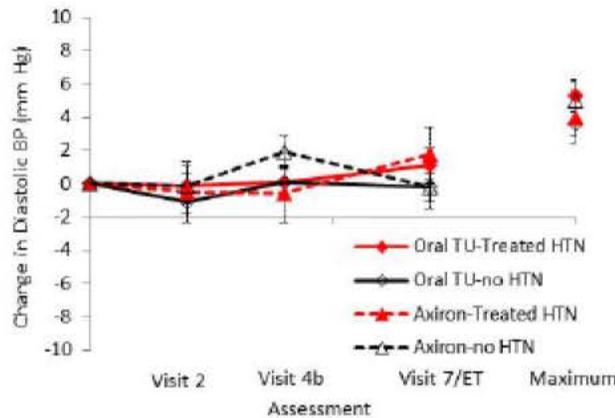
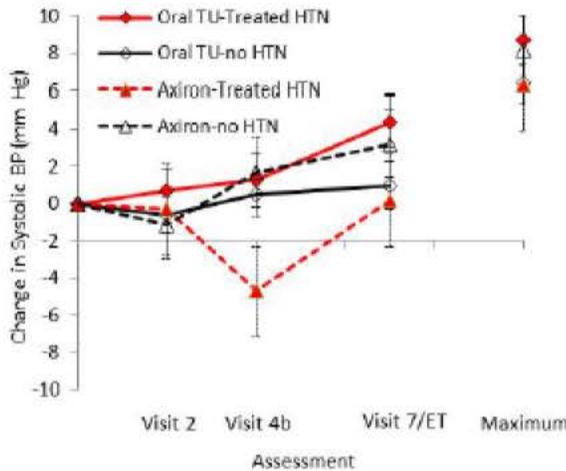
Abbreviations: BP = blood pressure; ET = early termination; TU = testosterone undecanoate

Note: For censored analysis, blood pressure was excluded if collected after an increase in dosage or addition of antihypertensive medications.

In the safety population, 7.2% of subjects in the TU treatment arm started antihypertensive medication after baseline or required a dose increase compared with 1.8% of subjects in the Topical Axiron group.

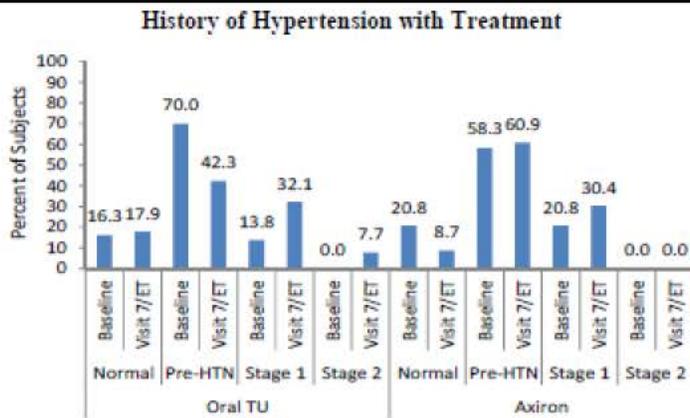
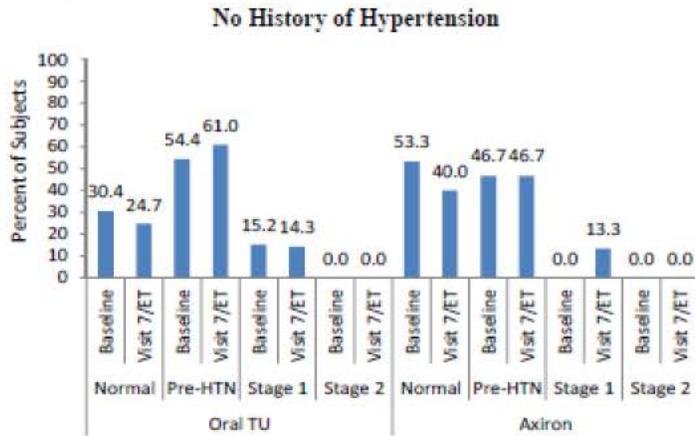
The clinically and statistically significant changes in SBP and DBP as a function of pre-existing hypertension that was demonstrated above for the ABPM data (page 14 figure 24 of this consult) was not as clearly detected by cuff pressures, as seen in the figure below (from the sponsor CRS):

Figure 18: Mean Change (\pm Standard Error) From Baseline in Systolic and Diastolic Blood Pressure by Treatment Group and History of Hypertension (Safety Population)



Categorical blood pressure grouping classifications based on JNC-7 definitions as expected did demonstrate the higher likelihood of drug-induced shifting into higher blood pressure categories with both TU and TA, though the percent increases into stage one and stage 2 hypertension were higher for TU, as seen in the following figure (from sponsor CSR):

Figure 21: Blood Pressure Classification of Subjects at Baseline and Visit 7/Early Termination by Treatment Group and History of Hypertension (Safety Population)



Source: Post-text Table 14.3.4.2.8
 Abbreviations: ET = early termination; HTN = hypertension; TU = testosterone undecanoate

The K-M analyses of time to shift to Stage I and Stage II pressures demonstrates the ongoing nature of these elevations, which again are more prominent in the TU treatment group, per the figures below, respectively (sponsor CSR):

Figure 22: Kaplan-Meier Plot of the Number of Days From Baseline to the First Occurrence of Stage 1 Hypertension (Safety Population)

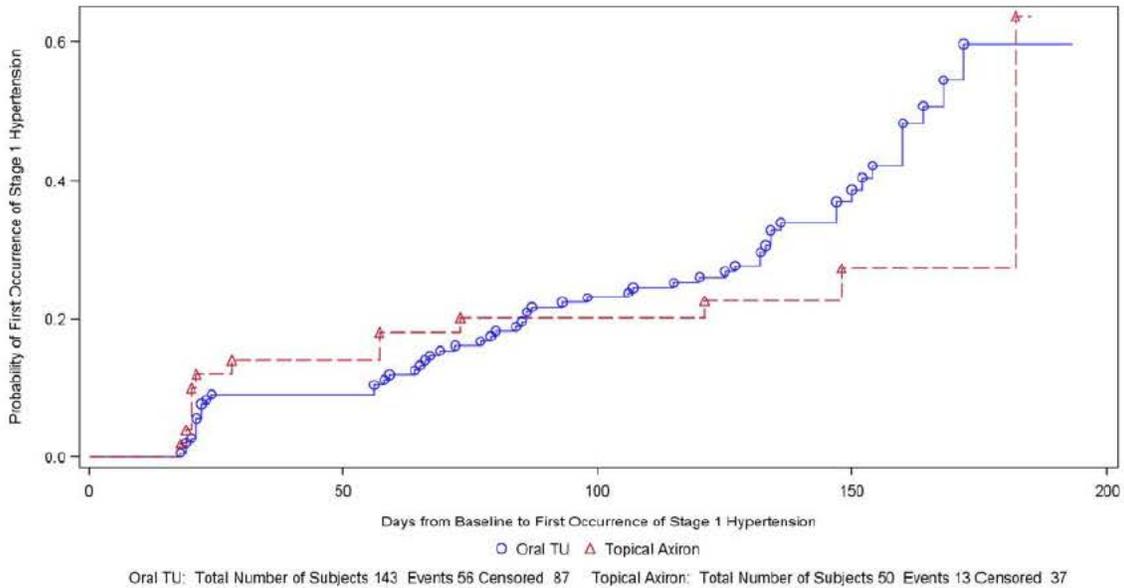
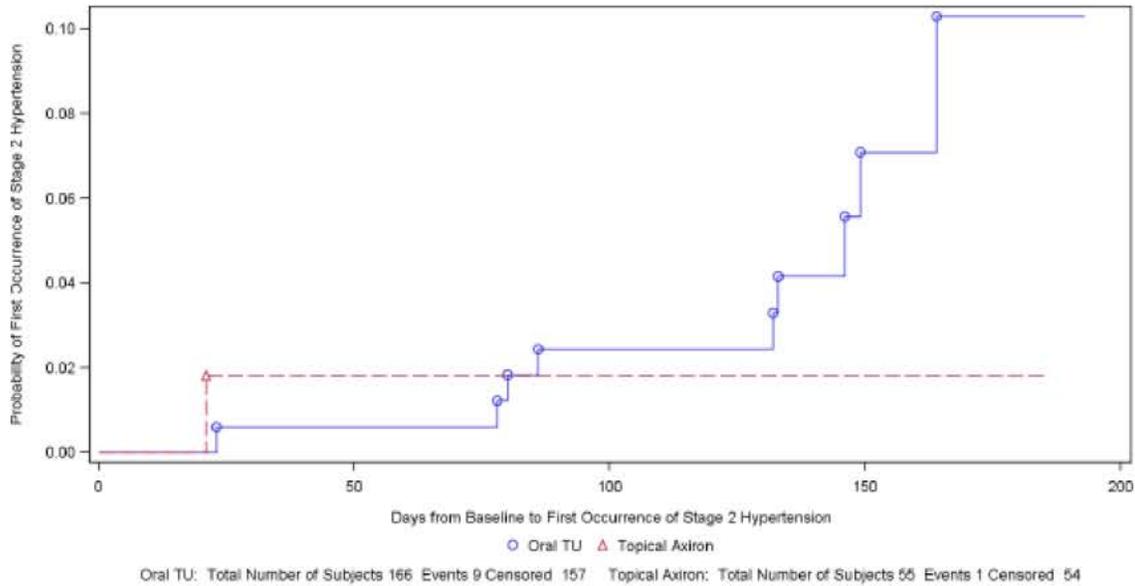


Figure 14.3.4.2.12.2
Kaplan-Meier Plot for the Days from Baseline to the Stage 2 Hypertension by Treatment Group (Safety Population)



The sponsor reports a very small number of outlier blood pressures occurring per the table below, which seems to be at odds with the K-M data points above (per the sponsor CSR):

Table 48: Incidence of Outlying Blood Pressure Values by Treatment Group (Safety Population)

Vital Sign	Criterion	Oral TU	Topical Axiron
Systolic Blood Pressure (mm Hg)	< 100 and decrease \geq 20	0	1 (1.8)
	\geq 160 and increase \geq 20	2 (1.2)	0
Diastolic Blood Pressure (mm Hg)	< 90 and decrease \geq 20	2 (1.2)	1 (1.8)
	\geq 100 and increase \geq 20	2 (1.2)	0

Source: Post-text Table 14.3.4.2.13.1

Abbreviations: TU = testosterone undecanoate

DCRP RESPONSES TO CONSULT QUESTIONS:

1. We request your DCRP opinion on whether the Ambulatory Blood Pressure Monitoring sub-study in Phase 3 Study CLAR-15102 was performed in accordance with your recommendations.

For the most part, the sponsor has done a good job responding to our analysis requests. However, there are several deficiencies in the data presentation as follows:

- Sponsor Table 49 (on page 8 of this consult) showing vital sign ABPM outcomes should be regenerated with an additional column for 95% confidence intervals. Heart Rate data for all three time periods should be added as three additional rows.
 - It is unclear what time period that the scatter plots of ABPM changes from baseline to Tmax parameters represents. These scatter plots should be re-rendered as CDFs for daytime, nighttime, and 24 hour time periods.
 - The scatterplots showing changes in ABPM vital signs by dose are uninterpretable, and should also be re-rendered as CDFs. All of these analyses should also be displayed in tabular form (i.e. like table 49 on page 8 of this consult, with confidence intervals included as a column entry for each analysis row).
 - It appears that the numbers of blood pressure outliers with respect to table 48 above does not reconcile with the event numbers in the time to stage II hypertension K-M curve in Fig 22 (prior page of this consult). The sponsor should explain this.
2. We request your DCRP analysis concerning the differences noted in the ABPM and cuff blood pressure determinations and the clinical significance of those differences.

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).

3. We request your DCRP opinion concerning the results from ABPM and cuff blood pressure assessments.

NDA 206089

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. 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. If approved, labeling should reflect these TU-induced effects on vital signs.

4. We request your DCRP recommendations for additional studies, labeling, the post-approval period, etc.

DCRP recommends only the additional analyses and clarifications as noted in our response above to question 1, as the current ABPM study has adequately defined the impact of TU on vital signs.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRESTON M DUNNMON
09/15/2017

SHARI L TARGUM
09/18/2017

NORMAN L STOCKBRIDGE
09/19/2017

Cross-Discipline Team Leader Memo

Date	November 3, 2014
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Memo
NDA/BLA #	206089
Applicant	Clarus Therapeutics
Date of Submission	January 3, 2014
PDUFA Goal Date	November 3, 2014
Proprietary Name / Established (USAN) names	Rextoro testosterone undecanoate
Dosage forms / Strength	100 mg and 150 mg soft-gelatin capsules Initial dose: 200 mg (two 100 mg capsules) twice daily Subsequent dose adjustment allowed: As low as 100 mg (one 100 mg capsule) twice daily As high as 300 mg (two 150 mg capsules) twice daily
Proposed Indication(s)	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
Recommended:	<i>Complete Response (CR)</i>

1. Background

1.1 DESCRIPTION OF PRODUCT

Rextoro is an oral formulation of testosterone undecanoate (TU). It is formulated as immediate-release soft gelatin capsules, containing either 158.3 mg TU (equivalent to 100 mg testosterone) or 237.5 mg TU (equivalent to 150 mg testosterone).

TU is a fatty-acid ester of testosterone, chemically described as 17 β -hydroxyandrost-4-en-3-one undecanoate. Rextoro contains TU and a “self-emulsifying drug delivery system” (SEDDS) (b) (4)

The TU-SEDDS formulation is designed to increase the absorption of TU via the intestinal lymphatics with the intent of reducing first-pass hepatic clearance of T. TU is converted to T by endogenous non-specific esterases.

Rextoro is intended for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

1.2 REGULATORY HISTORY

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

On March 23, 2009, a Type C Guidance Meeting was held with the Sponsor to discuss data from Phase 2 studies and a 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 concerns related to elevated serum DHT:T concentration ratios observed in Phase 2.

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

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 high DHT concentrations and high DHT/T ratios
- *May 28, 2010*: Division provides comments on the proposed 1-year, Androgel-controlled, Phase 3 study protocol (Study CLAR-09007)
- *August 2, 2010*: Division provides comments on the time for a single serum T concentration sample for use in titrating 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 Phase 3 study protocol (Study CLAR-12011)

1.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary Clinical reviewer, Jin Chen, stated in his final review dated October 24, 2014:

*“Recommendation on Regulatory Action: From the clinical perspective, I recommend a **Complete Response (CR) action** for this NDA because efficacy and safety for this product, oral TU (testosterone undecanoate soft gelatin capsules), has not been established for the proposed indication due to lack of substantial evidence.*

Risk Benefit Assessment: A favorable benefit/risk ratio for the proposed indication has not been demonstrated for this product based upon our review of the Clinical data submitted in this NDA. The deficiencies include: 1) lack of sufficient evidence for efficacy, 2) unknown potential risks associated with very high TU and DHTU (dihydrotestosterone undecanoate) exposures, 3) known potential risks, such as increased blood pressure and increased hematocrit, associated with DHT (dihydrotestosterone) concentrations and DHT/T ratios above the normal range, and 3) an unmanageable effect of food on testosterone exposure, with severe impact on variations in testosterone PK (pharmacokinetics) parameters, resulting in an inability to write labeling that will provide reliable guidance for dosing.”

The Clinical reviewer provided justifications for his recommendation and his risk/benefit assessment. Some, but not all, of the reasons are shown here:

1. Lack of substantial evidence for efficacy, due to a very small amount of efficacy data and questions about how missing data was handled.
2. Very high serum TU and DHTU concentrations with potential adverse effects on efficacy and safety.
3. Lack of substantial evidence for safety, due to a very small amount of safety data as it relates, at least in part, to very high serum TU, DHTU concentrations and high DHT concentrations
4. A cardiovascular safety signal observed in the first Phase 3 study CLAR-09007, including evidence of increased blood pressure, sporadic CV adverse events, and adverse changes in CV biomarkers (such as hs-CRP and HDL-cholesterol).
5. Lack of applicability of the postmarketing safety experience for Andriol, an oral TU product approved outside of the United States.
6. A dramatic effect of food on TU absorption and serum T concentrations, with no current measures that could effectively limit the wide exposure variability related to food.

[CDTL Comment: I concur with Dr. Chen’s overall recommendation, his risk/benefit assessment, and his justifications.]

2. CMC/Device

In their first final review, dated September 25, 2014, the ONDQA review team (Hamid Shafei and Moo Jhong Rhee) concluded that the NDA is not recommended for Approval until:

- 1) CMC labeling issues are satisfactorily resolved , and
- 2) the Office of Compliance issues an overall Acceptable recommendation for the facilities involved.

In their second final review, dated October 29, 2014, ONDQA (Hamid Shafei and Moo Jhong Rhee) stated that the Office of Compliance had issued an overall “*Acceptable*” recommendation for the manufacturing facilities involved. However, resolution of Chemistry-related labeling issues was deferred to the next review cycle. Therefore the final recommendation from ONDQA was:

*“...this NDA is **not** recommended for approval in its present form, per 21 CFR 314.125(b)(6)”.*

The September 25, 2014, CMC review contained the following statements of note:

- *“...this NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product, Rextoro (testosterone undecanoate) soft gelatin capsules 158 mg, 237 mg.”*

- There are two proposed drug substance manufacturers, (b) (4). The review states, “*In general, the drug substance, testosterone undecanoate, produced by both manufacturers is adequate for use in the manufacture of the drug product*”.
- The 158 mg Rextoro capsules are red and the 237 mg Rextoro capsules are orange.
- The capsule (b) (4) formulation contains: (b) (4) testosterone undecanoate, (b) (4) oleic acid, NF, (b) (4) borage seed oil, (b) (4) peppermint oil, NF, (b) (4) polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), NF, and (b) (4) butylated hydroxytoluene, NF.
- The soft gelatin capsule shells are manufactured from gelatin (b) (4). The capsule shells also contain sorbitol, coloring, and imprinting ink.
- All excipients are compendial, with the exception of borage seed oil. The reviewer notes that borage seed oil is found in dietary supplements, and in addition, it “*is tested and accepted according to a well-established specification*”. The reviewer concludes, “*Therefore the use of borage seed oil in this formulation of this drug product is acceptable.*”
- A 30-month expiration dating period was granted.
- The reviewer notes that the drug product is non-sterile and microbiological testing for bioburden according to USP <61> and USP <62> was adequate.
- The Environmental Assessment review was conducted by Dr. James Laurenson, who on July 10, 2014, concluded that the categorical exclusion from environmental assessment analysis should be granted.

There is one additional ONDQA review from Kelly Kitchens and Tapash Ghosh, the Biopharmaceutics review team for this NDA. In their review, dated September 18, 2014, they concluded the following:

“From the Biopharmaceutics perspective, NDA 206089 for Rextoro (testosterone undecanoate) capsules is recommended for approval.”

The following are notable comments from the ONDQA/Biopharmaceutics review:

- The proposed dissolution method and method validation are acceptable.
- The proposed acceptance criterion ($Q = (b) (4)\%$ at 30 minutes) is acceptable.
- Differences were observed in dissolution between the hard shell capsules used in Phase 2 studies versus the soft gelatin capsules used in Phase 3 studies. The Sponsor did provide a justification for these differences, yet the Biopharmaceutics team did not conclude that the comparative dissolution profiles were comparable. Instead, the Biopharmaceutics team noted that “*Since PK data was generated using both the hard shell capsules and the soft gelatin capsules, comparative dissolution profiles are unnecessary to bridge the hard shell capsule and the soft gelatin capsule formulations*”.

[CDTL Comment: Despite the “loss” of Phase 2 data to FDA review due to lack of an adequate bridge from Phase 2 to the to-be-marketed formulation, the Office of Clinical Pharmacology agreed with this statement by ONDQA/Biopharmaceutics.]

3. Nonclinical Pharmacology/Toxicology

In their final review, dated August 4, 2014, the Pharmacology/Toxicology review team (Eric Andreasen and Lynnnda Reid) concluded that

*“Overall, the nonclinical program supports **approval** of this product for the proposed population and indication and a maximum single dose of 475 mg of TU to be administered twice daily.”*

The reviewers’ overall conclusion states:

“The safety profile of testosterone is well known. The preponderance of clinical data with testosterone and TU supercedes nonclinical findings. Other than expected androgen related findings in dogs, no significant safety concerns associated with TU were identified in the nonclinical program. Referenced literature and nonclinical data suggest that there should be no non-androgen related findings at the maximal clinical dose proposed for marketing.”

The PharmTox reviewers noted the following:

- Because there is extensive clinical and nonclinical data regarding testosterone from the published literature, the nonclinical evaluation of Rextoro was limited to assessing binding affinities for the androgen receptor and the toxicity of TU in a 13-week toxicity study in male dogs.
- The product contains a novel excipient, borage seed oil. The safety of the borage seed oil was qualified with published literature and lack of adverse findings in the 13-week dog toxicity study.
- The relative binding affinity of TU for the androgen receptor (AR) is approximately 1% of the affinity that testosterone has for the AR.
- After absorption, a fraction of the TU is metabolized in the intestinal wall to dihydrotestosterone undecanoate (DHTU). TU and DHTU are distributed systemically and further metabolized to testosterone, dihydrotestosterone (DHT), estradiol, “numerous steroid metabolites”, and glucuronide and sulfate conjugates.
- Positive findings in the 13-week toxicity study were limited to androgen responsive tissue and were consistent with excessive exposure to an androgen. 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. TU exposure in dogs was only 2 times the worst case exposure in human males. The positive findings in dogs 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. Adrenal cortical atrophy was believed to be a result of “feedback suppression of androgen synthesis in the adrenals”.

[CDTL Comment: I was not previously aware that androgens, even at supraphysiologic exposures, induce adrenocortical atrophy. However, it is well known that exogenous glucocorticoids, such as cortisol, have the potential to induce atrophy of the adrenal cortex through feedback inhibition of the hypothalamic-pituitary-adrenal axis. With this in mind, coupled with the comment in the PharmTox review that testosterone undecanoate is metabolized not just to T, DHT, DHTU, and estradiol, but also to “numerous steroid metabolites”, I conducted additional analysis of the PharmTox review. I refer to the section of the review in which the 13-week toxicity study is reviewed; specifically, the Toxicokinetics subsection, the section entitled “Cortisol” (located on page 45 of the review). In this subsection, the PharmTox review team notes that differences were observed between the placebo and high dose TU groups for serum cortisol. In the placebo group, on Day 1, the mean cortisol level was marginally above the lower limit of detection (>10 ng/ml) but on Day 90, the mean cortisol level in the placebo group was approximately 20 ng/mL for a 12 hour period of measurement. In contrast, on Day 90, in the high-dose TU group, the mean cortisol level was below the lower limit of detection (10 ng/mL) for all 12 hours. Although the Sponsor surmises that the high androgen exposures suppressed the adrenal cortex, I have concerns about this conclusion. First, the TU exposure (by AUC) in this dog study was only approximately 2 times the TU exposure in humans at “worst case”. Second, I am not familiar with the conclusion that androgens suppress the entire adrenal cortex. On the other hand, if the “numerous steroid molecules” derived from TU were acting as exogenous glucocorticoids, it would not be surprising to observe hypocortisolemia and adrenocortical atrophy in these dogs. I have broached my concern with the supervisory pharmacologist, Dr. Reid. It would be prudent to investigate this issue in human males as part of some future clinical study.]

4. Clinical Pharmacology/Biopharmaceutics

In their final review, dated October 17, 2014, the Clinical Pharmacology review team (signers of the review included Sayed Al Habet, Dhananjay Marathe, Jeffry Florian, and Dennis Bashaw) provided a Recommendation as part of their Executive Summary. Their Recommendation is shown below.

In addition, Dr. Dennis Bashaw provided a separate Supervisory Clinical Pharmacology Memo on October 17, 2014. Dr. Bashaw’s memo included a separate Recommendation that constitutes the final, official Recommendation from the Division of Clinical Pharmacology-3 (DCP3). The final DCP-3 Recommendation is also shown below.

OCP Review Team Recommendation:

*“From the Clinical Pharmacology perspective, this NDA is **NOT ACCEPTABLE** due to the following deficiencies”:*

- There was high variability in T levels and other metabolites associated with food intake (fasting versus fed) and per cent of fat in meals. The high variability was observed both day-to-day and within the same day. Based on the observed product variability, there is insufficient information at this time to provide labeling in the Dosage and Administration section for administration of this product with

reference to food. Any approach identified by the review team was limited by the substantial variability in product PK and by patient compliance to the labeling language (e.g., administer in a fasting state or maintain a consistent diet) that could not be ensured.

- There was high exposure to the parent drug, testosterone undecanoate (TU), and its metabolite dihydrotestosterone undecanoate (DHTU). For example, the TU exposure was approximately 20 fold higher than the T exposure. Implications of these high TU levels on safety cannot be assessed with the available data.
- The pivotal study marginally met the established primary efficacy criteria of 75% of patients falling within the target T Cavg of 300 ng/dL to 1000 ng/dL. However, based on sensitivity analyses that accounted for the missing data, the primary efficacy parameters become lower than 75%. In addition, the pivotal study had a few subjects with on-treatment testosterone (T) Cmax levels exceeding safety thresholds that are commonly utilized by the Agency. The observed fraction of Cmax outliers further underscores the high variability associated with the product.
- The proposed starting dose should be revisited, particularly in subjects with lower body weight. Consideration should be given to initiating therapy at a lower dose. Baseline body weight showed some correlation to exposure, with higher exposures in subjects with low body weights. Such subjects could be initiated at a lower starting dose. Additional dose strengths, including doses that would permit an increment or decrease by 25 mg would permit more flexibility in dosing.
- The titration process should be revisited in a subsequent trial. Specifically, the criteria for up-titration should be increased from the currently selected level - 250 ng/dL. The T concentration level of 250 ng/dL appears too low to adequately identify patients who require up-titration to achieve T levels within the desired target range of 300-1000 ng/dL.
- There were adverse changes observed in various cardiovascular (CV) biomarkers, including increases in blood pressure, with administration of oral TU in the clinical trials and relative to the control arms. These observations may be associated with higher androgen exposure with oral TU as compared to other marketed T products.

Supervisory OCP Recommendation:

*“The Division of Clinical Pharmacology-3 recommends that a **C/R (complete response) action** be issued at this time. The Clinical Pharmacology section of this NDA is not sufficient to provide guidance on dosing instructions with regards to meals or dosing/titration, as outlined below:*

***Food Effect:** In regards to the effect of food the Sponsor is advised to undertake a new assessment of the effect of food using a ‘timed food effect trial’. Such a trial could utilize a fasted treatment leg and treatment legs where a single dose is administered 1 hr before, 1 hr after, and two hours after a standardized meal. The results of the trial could then be used to design dosing instructions with regards to meals that would be more practical (i.e, reproducible) with unsupervised use.*

In addition to the recommended “timed food effect trial”, the Sponsor is strongly advised, should a new in vivo clinical study be necessary, to use a standardized meal and not a varying diet as was used in the CLAR-12011 trial during the pharmacokinetic sampling phase. The use of a non-standardized diet without recording the amounts and types of food consumed (specifically the fat content of ingested foods) made any attempt to standardize the results of CLAR-12011 futile.

Dosing and Titration: *The starting dose and titration schema proposed by the Sponsor needs to be re-evaluated. Evaluation of the proposed dosing scheme by the FDA suggested that initiation of therapy at a lower dose (150mg BID) and using a boundary of 300 ng/dL for up-titration rather than 250 ng/dL would enhance the number of subjects within the therapeutic range of 300-1000 ng/dL. Another strategy that should be considered is the development of a 75mg dosage form. Such a dosage form would allow for a finer control of plasma T (and TU) level by allowing for more dosing flexibility, ie., 100, 150, 175, 200, 225, 250, 275, and 300mg doses would be available instead of 100, 150, 200, 250, and 300mg doses that the 100 and 150mg capsules allow for.”*

The Clinical Pharmacology team review contained the following additional comments of note:

- The Sponsor submitted results from 6 clinical pharmacology studies, including two Phase 3 studies (Studies CLAR-09007 and CLAR-12011). In addition, there is an ongoing, long-term extension safety study (Study CLAR-1210) to the 12-month Study CLAR-09007.
- T and TU concentrations were determined by validated liquid chromatography tandem mass spectrometry (LC-MS/MS). The Sponsor also conducted a series of experiments that demonstrated that TU is not hydrolyzed to T in the blood collection tubes (i.e., there was no *in vitro* hydrolysis of TU to T by esterase enzymes during the blood collection and assay process).
- Two studies demonstrated an increase in the absorption and exposure of T and TU with food consumption. Specifically, in one study the effect of different percentages of fat in consumed meals was evaluated. Compared to fasting, the T-Cavg was tripled after consumption of food containing 50% fat. In addition, there was a trend for higher T levels after evening (PM) doses as compared to after morning (AM) doses that may be related to higher fat content in dinners as compared to breakfasts, as well as to the greater total volume of food consumed at dinner as compared to at breakfast. In these studies, there was high inter-subject variability in T levels, which is primarily related to differences in food quality/content and food quantity/volume among patients.
- From the PK studies,
 - It appears that there is dose proportionality in T levels up to a dose of 400 mg.
 - Steady-state concentrations for T and its main metabolites, dihydrotestosterone (DHT) and estradiol (E₂), are reached within the first 7 days of dosing.
 - There was no accumulation of T after 4 weeks of 200 mg BID dosing.
 - There was wide variability in T levels throughout all studies, in particular after ingestion of foods.

- The levels of the parent drug (the pro-drug), TU, and its metabolite, 5 α -dihydrotestosterone undecanoate (DHTU) were considerably higher than T levels - by approximately 20-fold, on a ng/dL basis. The binding affinities to the androgen receptor (AR) for TU and DHTU are low: 1.23% and 0.7% for TU and DHTU, respectively. The long-term safety implications of the high TU and DHT exposures are currently unknown.
- The ratio of DHT to T was also high. The AR binding affinities are 100% and 83% for T and its metabolite DHT, respectively. The long-term, safety implications of the high DHT/T ratio are also currently unknown.
- Increases in blood pressure (BP) were observed after oral TU. The magnitude of the BP increase was greater for oral TU than for AndroGel® in Study CLAR-09007. A similar, but reduced, increase in blood pressure was also seen for oral TU in Study CLAR-12011.
- The proposed dose titration algorithm, which calls for a starting dose of 200 mg BID, with changes in dose by 50 mg BID increments based on PK measurements obtained 3-5 hours after the morning dose after at least 7 days of treatment, has two major limitations:
 - The proposed titration threshold (down titrate at 700 ng/dL; uptitrate at 250 ng/dL) results in down-titration of a subset of subjects with C_{avg} within the normal T level range of 300-1000 ng/dL, and also does not allow for up-titration of subjects with C_{avg} <300 ng/dL unless their T concentration are <250 ng/dL. Overall, the titration algorithm employed in Study CLAR-12011 and proposed in the label resulted in C_{avg} <300 ng/dL for 23.3% of patients and an overall population C_{avg} of 388 ng/dL. Revised titration thresholds, which take into account the high product variability and normal target T levels, should be evaluated for this product.
 - The 50 mg BID dose titration increments may be too large. The number of C_{max} outliers could be further reduced by developing 25 mg and/or 75 mg strengths to permit 25 mg BID dose titration increments.
- FDA analyses demonstrated that patients with baseline body weight < 82 kg had a higher median C_{avg} and a higher probability of exceeding the C_{max} safety thresholds (>1500, >2500 ng/dL, etc.) compared to the rest of the population while taking the starting dose of 200 mg BID. While awaiting down-titration, the safety risks associated with transiently increased T exposures are not known. An alternative, and perhaps safer, dosing algorithm could be proposed wherein this subgroup of patients (body weight < ~80 kg) could be started with an initial dose of 150 mg BID instead of 200 mg BID.

In their final review, the Clinical Pharmacology review team concluded: “Based on all the above, from the Clinical Pharmacology perspective, the NDA is **deficient** in several aspects as listed our Recommendation”.

[CDTL Comment: I agree with the overall Clinical Pharmacology team Recommendation and in large part, the listed Clinical Pharmacology concerns and recommendations.]

The Clinical Pharmacology Supervisor's memo contained the following additional comments of note (under the headings "Issue 2" and "Issue 4"):

- The proposed formulation of TU has demonstrated significant variability in the face of meals. Members of the joint BRUDAC and DSARM AC panels were very concerned about this variability and noted that controlling diet in patients would be an impossibility.
- One potential means for addressing the high variability with food is dosing on an empty stomach ("fasted"), although such a regimen might lead to an unacceptably high rate of Cmax outliers; and in addition, fasting around the time of the evening dose may not be feasible due to difficult timing of the evening meal.
- Dr. Bashaw recommends a "timed food effect" trial to investigate whether dosing instructions can be developed to minimize the impact or "modulate" the degree of food effect to an acceptable level. The trial would evaluate the impact of meals on exposure when meals are given at pre-defined times from dosing.
- Dr. Bashaw comments on the need for additional Clinical Pharmacology review of analytical methods validation when this NDA is resubmitted. Dr. Bashaw's recommendation is based not on the possible conversion of TU to T in samples awaiting analysis (which has been determined *not* to occur), but rather to a submission by Sponsor within the last 4 months of the PDUFA date in response to a July 25, 2014, FDA request, which contained a large amount of information concerning "*Incurred Sample Reanalysis (ISR)*". Dr. Bashaw states that this submission contained information that would help to address "*the recent Cetero analytical issues*", and further, "*This information, will need to be fully evaluated in the future in the light of any new trials that are conducted in support of this application*".

[CDTL Comments: It appears that the ISR information submitted in support of analytical methods validation represents another outstanding issue that needs to be addressed in the next review cycle. In addition, I agree with Dr. Bashaw's Overall Recommendation. I also agree with the exploratory investigation of timing of food to dosing and its impact on T concentration.]

There was one additional Clinical Pharmacology memo, authored by Chongwoo Yu and Dennis Bashaw and dated September 19, 2014, related to an external communication from (b) (4) concerning the possible conversion of TU to T during sample processing. For the review of this issue, Dr. Yu's review concluded:

"All bioanalytical laboratories should thoroughly assess the stability of TU and the potential of TU to T conversion during the development and validation of their bioanalytical methods."

Further, Dr. Yu's review states that the bioanalytical site for the Clarus NDA, the (b) (4), was well aware of the potential for conversion of TU to T during sample processing, having published on that specific topic. In addition, Dr. Al-Habet's Clinical Pharmacology review stated that Clarus

had conducted a series of experiments demonstrating that TU was not hydrolyzed to T in the blood collection tubes (i.e., that there was no in vitro hydrolysis of TU to T by esterase enzymes during the blood collection and assay process).

In addition, Dr. Yu's review informs the Division that the methods validation report for the Clarus NDA was deficient in several ways, including lacking detailed information on how incurred sample re-analysis (ISR) was conducted. On July 25, 2014, the Division conveyed an information request to Sponsor, including a request for detailed information on how the ISR was conducted. The Sponsor subsequently responded to this request with a large submission that was not fully reviewed by FDA due to the impending Complete Response action for this NDA. Therefore, the detailed information concerning the ISR will need to be reviewed by OCP in the next cycle.

5. Clinical Microbiology

There are no Clinical Microbiology issues for this NDA. From a product quality microbiology standpoint, the microbiological testing information was reviewed by Bryan Riley and Stephen Langille of OPS/NDMS on January 13, 2014. The reviewers conclude that "*the microbiological quality of the drug product is controlled via a suitable testing protocol*". The Chemistry review team concurred.

6. Clinical/Statistical - Efficacy

6.1 OVERVIEW OF CLINICAL PROGRAM

For efficacy, the NDA is supported by a single, 4-month, Phase 3, uncontrolled, single-arm, open-label study (Study CLAR-12011) that evaluated the efficacy and safety of Rextoro in the treatment of male hypogonadism.

An additional Phase 3 study, CLAR-09007, was conducted prior to CLAR-12011, but it failed to demonstrate efficacy as a consequence of excessive C_{max} outliers; that is, too many subjects with C_{max} beyond the pre-defined limits (e.g., >2500 ng/dL). CLAR-09007 employed the same doses as employed in CLAR-12011, but with a different titration regimen that led to higher overall testosterone and dihydrotestosterone concentrations as compared to CLAR-12011. For details of the efficacy results for CLAR-09007, the reader is referred to the medical officer's primary Clinical review.

The remainder of this section and the rest of Section 6 (Clinical/Statistical Efficacy) pertains only to CLAR-12011, the single trial that tested the efficacy of the to-be-marketed (TBM) dose regimen and TBM formulation.

Study CLAR-12011 was a 4-month (114-day), open-label, repeat dose, dose-titration, multicenter, Phase 3 study in hypogonadal men. Eligible subjects were adult men 18 to 75 years of age with a diagnosis of hypogonadism who had morning serum total testosterone level < 300 ng/dL at screening. Subjects were also to have been naïve to androgen replacement

therapy or adequately washed out of prior androgen replacement therapies. About 120 subjects were planned to be enrolled.

All subjects began at an oral dose of 200 mg T twice daily (BID) and could be titrated in 50 mg BID increments up to as high as 300 mg T BID or as low as 100 mg T BID. Subjects were instructed to take their study medication with food; however, the type of food was not specified. Dose titration, if necessary, occurred on Days 42 and 84, based on the serum T concentration derived from a single blood sample drawn at 3 to 5 hours after the morning dose on Days 30 and 72, respectively. Titration was according to the following schema:

- T < 250 ng/dL: Increase dose by 50 mg BID
- T 250 ng/dL to 700 ng/dL: Maintain dose
- T > 700 ng/dl: Decrease dose by 50 mg BID

If the T concentration consistently exceeded 700 ng/dL at the lowest dose, then treatment was to have been discontinued.

Serum total testosterone concentration was measured as: 1) the mean of two samples collected one hour apart between 6:00 and 10:00 AM at Screening and at Baseline, 2) the 12-hour post morning dose serial sampling average concentration (Cavg) on Days 30 and 72, and 3) the 24-hour (12 hours post morning dose and 12 hours post evening dose) serial sampling Cavg on Day 114. Of note, subject diets on PK days e.g., Days 30, 72 and Day 114) were limited to several major types (e.g., regular, diabetic, vegetarian, etc.), although subjects had access to a variety of foods within that major type. During the rest of the study, food type was not limited or restricted.

6.2 DEMOGRAPHICS

The main diagnostic criteria for inclusion in Study CLAR-12011 were men at least 18 years of age with morning screening serum testosterone concentration < 300 ng/dL and a diagnosis of hypogonadism.

Key exclusion criteria included: 1) Hematocrit >48% at Screening, 2) Serum prostate specific antigen level \geq 3.9 ng/mL, 3) International Prostate Symptom Score \geq 19 points, 4) Uncontrolled diabetes mellitus, 5) Body Mass Index \geq 38 kg/m².

In brief, the demographics of the CLAR-12011 study population were:

There were 144 male subjects in total. The overall mean age of subjects was 55 years. The mean weight was 94 kg. Mean height was 177 cm, and mean BMI was 30 kg/m². The majority of subjects were White (79%), followed by Black or African American (10%) and Asian (9%). Approximately, half of the participants had “pre-diabetes”, diabetes or hypertension at baseline. The type of hypogonadism is distributed as follows: 46 subjects (32%) had primary hypogonadism, 14 subjects (10%) had secondary hypogonadism, 72 subjects (50%) had combined hypogonadism, and 12 subjects (8%) had an unknown type. The mean screening serum T concentration was 209 ng/dL.

6.3 DISPOSITION OF SUBJECTS

A total of 148 subjects were enrolled in CLAR-12011. Of those, 144 subjects took at least 1 dose (the Safety population), 133 had sufficient PK data to calculate at least one PK parameter (the PK population), and 116 completed Visit 6 (Day 114) with sufficient PK data to calculate C_{avg} (the Efficacy population).

The dropout rate on Day 114 was 18.8%, mainly due to withdrawal of consent (5.6%), loss to follow-up (3.5%), “Other” reason (3.5%), adverse event (2.1%), hematocrit >54% (2.1%), non-compliance (1.4%), and protocol violation (0.7%).

Of note, of the 144 subjects in the Safety population who took study drug, 28 did not have a serum T C_{avg} on Day 114. Of these 28 subjects, 17 did not have sufficient pharmacokinetic data to calculate serum T C_{avg} on Day 114 and 11 subjects had no post-baseline T data at all.

6.4 EFFICACY FINDINGS

6.4.1 Assessment of Efficacy

The primary endpoint in CLAR-12011 was the percentage of subjects with average serum total testosterone concentrations within the normal range on Day 114. The threshold for success was set as 75% with a lower bound of the 95% CI of 65%.

A key secondary endpoint was serum total T C_{max} within 3 pre-determined ranges on Day 114:

- < 5% of subjects with a serum total T C_{max} in the range of 1800-2500 ng/dL
- No subjects with a serum total T C_{max} of > 2500 ng/dL
- At least 85% of subjects with a serum total T $C_{max} \leq 1500$ ng/dL

In addition, the following secondary endpoints were evaluated:

- Other pharmacokinetic assessments of testosterone, including time of maximum concentration (T_{max}), and area-under-the-curve at 12 and at 24 hours (AUC_{0-12} and AUC_{0-24})
- The PK profile of free testosterone on Days 30, 72, and 114.
- The PK profile of serum estradiol on Day 114.
- The PK profile of serum DHT on Days 30, 72, and 114.
- The ratio of DHT AUC to total testosterone AUC.
- Serum LH and FSH on Day 114.

6.4.1.1 Primary Efficacy Analysis

The primary efficacy endpoint in this study was the percentage of responders defined as C_{avg} within the normal range (300 – 1050 ng/dL) on Day 114. To meet the primary efficacy criterion, the point estimate for the pre-determined primary endpoint was set as at least 75% and the lower bound of the two-sided 95% confidence interval was set as not lower than 65%.

Based on this analysis, the percentage of subjects with a serum total T C_{avg} within the

normal range on Day 114 was 75.0% (87 of 116 subjects) with a corresponding 95% confidence interval of 66.1% to 82.6%.

The majority of subjects who did not have T C_{avg} within the normal range (n=42) on Day 114 had serum total T C_{avg} below the normal range (<300 ng/dL; n=40) rather than serum T C_{avg} above the normal range (>1000 ng/dL; n=2).

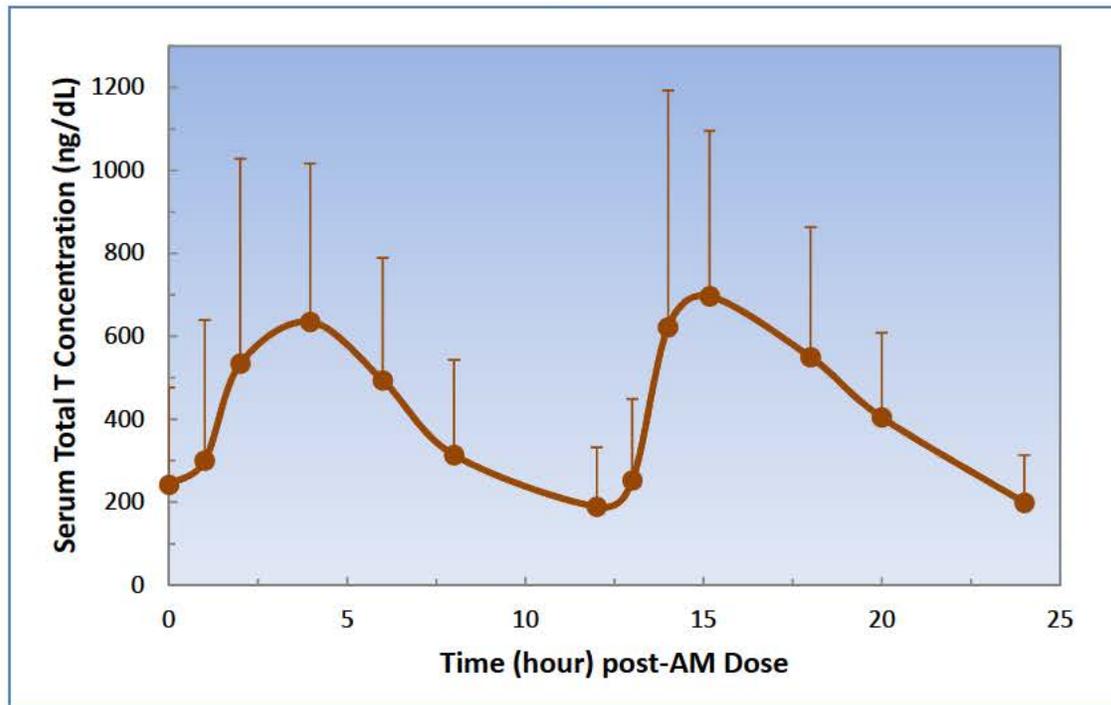
Table 1 and Figure 1 summarize the mean pharmacokinetic parameters of serum total T on Day 114 for the 116 subjects who had sufficient data on Day 114 to allow for these assessments.

Table 1: Mean (SD) PK Parameters of Serum Total T on Day 114 in Study CLAR-12011 (n=116)

	Mean/SD
C _{max} (ng/dL)	1062 (581)
C _{min} (ng/dL)	251 (199)
C _{avg} (ng/dL)	422 (171)
T _{max} (hr) ^a	4.2 (2.3)

^a Following AM dose

Figure 1: Plot of Mean (+SD) Serum Total T Concentration on Day 114 in Study CLAR-12011 (n=116)



Reference to FDA's Clinical review Figure 10.

Although the pre-specified primary efficacy analysis met the criteria for demonstration of efficacy, the analysis did not include 19.4% of subjects who did not have serum total T C_{avg} on Day 114 but who took at least 1 dose of study drug (the Safety population). Sensitivity analyses were conducted to assess the impact of this missing data on the consistency of the

results by using all subjects who took study treatment. The *post-hoc* analyses were performed using all 144 subjects who took at least one dose of oral TU and accounted for missing data in different ways. One approach used last observation carried forward (LOCF), including baseline, while another approach used the “Worst Case” scenario (WCS), that is, subjects with missing data were considered failures.

For the LOCF analysis, the percentage of subjects with a serum total T C_{avg} within the normal range on Day 114 was 70.8% (102 of 144 subjects) with a 95% confidence interval of 62.7% to 78.1%. For the WCS analysis, the percentage of subjects with a serum total T C_{avg} within the normal range on Day 114 was 60.4% (87 of 144 subjects) with a 95% confidence interval of 51.9% to 68.5%. Both sensitivity analyses did not meet the thresholds for efficacy

6.4.1.2 Secondary Efficacy Analysis

C_{max} was a critical (or “key”) secondary efficacy endpoint in Study CLAR-12011. To meet the C_{max} efficacy criterion, the following criteria must have been met:

- Having < 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- No subject with a serum total T C_{max} of > 2,500 ng/dL
- Having a serum total T C_{max} ≤ 1,500 ng/dL in at least 85% of subjects

In Study CLAR-12011, the three criteria of this critical secondary endpoint were not met:

- Instead of having at least 85% of subjects with a T C_{max} ≤ 1,500 ng/dL, there were 82% of subjects with T C_{max} ≤ 1,500 ng/dL.
- Instead of having < 5% of subjects with a serum total T C_{max} in the range of 1800-2500 ng/dL, there were 6% of subjects with a T C_{max} in the range of 1800-2500 ng/dL.
- Instead of no subjects having a T C_{max} >2500 ng/dL, there were four subjects in CLAR-12011 who had C_{max} >2500 ng/dL

Table 2 presents the number and percentage of subjects in these categories on Day 114.

Table 2: Number (Percentage) of Subjects in Efficacy Population (n=116) by the Pre-Determined Ranges of Serum Total T C_{max} on Day 114 in Study CLAR-12011

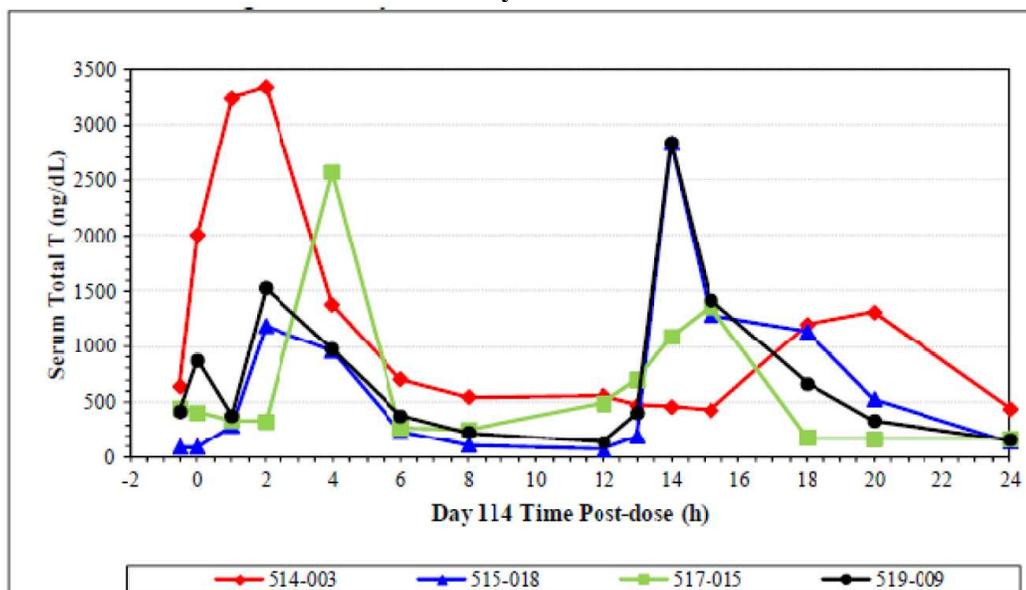
Number of subjects ^a	116
C _{max} ≤ 1,500 ng/dL	95 (81.9%)
1800 ng/dL ≤ C _{max} ≤ 2,500 ng/dL	7 (6.0%)
C _{max} > 2,500 ng/dL	4 (3.4%)

^a The number of subjects who had a C_{max} value on Day 114

Of note, in the 4 cases where T C_{max} exceeded 2500 ng/dL, the T concentration was transiently above 2500 ng/dL, resulting from a single timepoint on Day 114, except in the case of Subject # (b) (4) in whom two consecutive timepoints on Day 114 showed T

concentration >2500 ng/dL. The individual serum T concentration-time profiles for these 4 subjects are shown in *Figure 2*.

Figure 2. Serum T Concentration-Time Profiles for 4 Subjects with C_{max}>2500 ng/dL on Day 114 in Study CLAR-12011



Reference to FDA's Clinical review Figure 9.

In addition to the observed increase in serum total T concentration, serum concentrations of the known metabolites, dihydrotestosterone (DHT) and estradiol (E2), were also increased in Study CLAR-12011.

In regard to serum DHT, the mean baseline DHT concentration was approximately 18 ng/dL, which is near the lower limit of normal for serum DHT (13.7-76.9 ng/dL). The mean serum DHT concentration after the fixed dose of 200 mg bid for 30 days increased to 137 ng/dL, which is approximately 1.8-fold the upper limit of normal. The mean serum DHT concentration was lower on Day 114 as compared to on Day 30, but was still 1.1-fold above the upper limit of normal.

The data from each of the 3 PK assessments (conducted on Days 30 and 72 [for 12 hours], and on Day 114 [for 24 hours]), shows that the mean DHT C_{avg} and C_{max} was higher on Day 30 than on either Days 72 or 114, but the mean DHT C_{avg} on *all* PK days was above the normal range, with the mean DHT C_{max} even higher, as shown in following data:

- DHT C_{baseline}: 18 ng/dL
- DHT C_{avg}:
 - 137 ng/dL on Day 30
 - 96 ng/dL on Day 72
 - 87 ng/dL on Day 114
- DHT C_{max}:
 - 209 ng/dL on Day 30
 - 142 ng/dL on Day 72

- 147 ng/dL on Day 114

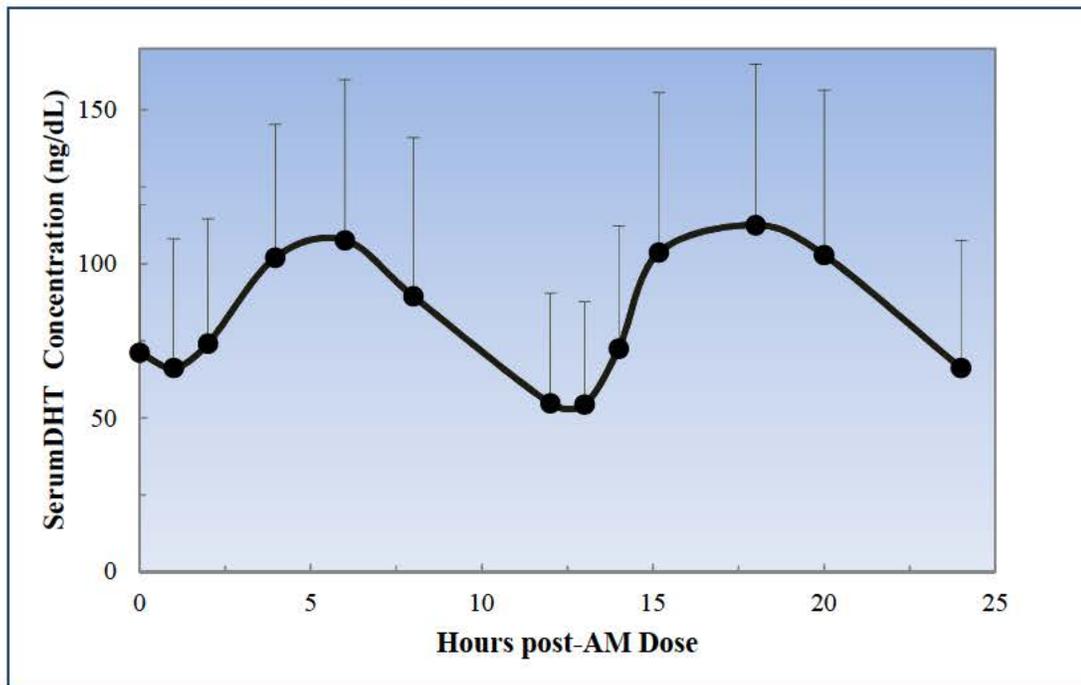
Figure 3 shows the mean serum concentration-time profile for serum DHT on Day 114 for the 116 subjects who had sufficient data on Day 114.

In regard to the DHT:T ratio, the baseline mean DHT:T ratio was 0.076 ± 0.03 , which is within the normal range (0.036 – 0.114) for eugonadal males. After thirty consecutive days on 200 mg BID, the mean DHT:T ratio increased to 0.29, which is 2.6 times the upper limit of normal. The mean serum DHT:T ratio was lower on Day 114 as compared to on Day 30, but was still 2-fold above the upper limit of normal.

The data from each of the 3 PK assessments (conducted on Days 30 and 72 [for 12 hours], and on Day 114 [for 24 hours]), shows that the mean DHT:T ratio was higher on Day 30 than on either Days 72 or 114, but the mean DHT Cavg on all PK days was well above the normal range, as shown in following data:

- DHT:T ratio Baseline: 0.076
- DHT:T ratio:
 - 0.29 on Day 30
 - 0.22 on Day 72
 - 0.22 on Day 114

Figure 3. Mean Serum DHT Concentration-Time Profile on Day 114 on CLAR-12011



Reference to FDA's Clinical review Figure 11.

[CDTL Comment: The mean serum DHT concentration is above the upper limit of normal on Day 114, subsequent to all titration. The mean DHT:T ratio is 2-fold the upper limit of normal on Day 114, subsequent to all titration. DHT is a potent androgen, with a binding

affinity for the AR receptor that is at least as strong as T. In my view, the DHT results are concerning, both from an efficacy and safety perspective.]

Mean serum estradiol (E2) concentrations increased from baseline to Day 114 in Study CLAR-12011 by approximately 50-60%. The Day 114 serum E2 concentration-time profile showed fluctuation during the 24-hour monitoring period, but the mean E2 concentration remained within the normal range (7.5-30.6 pg/ml).

In regard to changes in serum LH and FSH:

- Mean serum LH Cavg decreased from 4.7 mIU/mL at baseline to 1.2 mIU/mL on Day 114 in Study CLAR-12011.
- Mean serum FSH Cavg decreased from 7 mIU/mL at baseline to 2 mIU/mL on Day 114 in Study CLAR-12011.

The mean serum LH Cavg concentration on Day 114 (1.2 mIU/mL) was slightly below the lower limit of normal for eugonadal males (1.3 – 8.1 mIU/mL), while the mean serum FSH Cavg concentration on Day 114 (2 mIU/mL) was slightly above the lower limit of normal for eugonadal males on Day 114 (1.4 – 9.5 mIU/mL).

Finally, in regard to sex hormone binding globulin (SHBG), the mean baseline SHBG concentration was 34.5nM. On Day 114, the mean SHBG concentration was 22.4nM, representing a decrease of 35%. The Day 114 SHBG concentration remained within the normal range (10.8 – 46.6 nM).

The reader is referred to the FDA primary Clinical review, the Biometrics team review, and the Clinical Pharmacology review for additional efficacy-related details, tables and figures.

Statisticians' Conclusion

In their final review dated October 2, 2014, the Biometrics team (Sonia Castillo and Mahboob Sobhan) stated the following conclusion:

*“The one submitted study does **not** provide evidence demonstrating the efficacy of oral testosterone undecanoate capsules for the treatment of adult male hypogonadism based on inconsistent results between the pre-specified analysis and various post hoc sensitivity analyses conducted to account for missing data.”*

The Biometrics review team had the following notable statements:

- The pre-specified primary efficacy analysis was based on the completer population that did not include 19.4% of subjects who took study drug but did not have a serum total testosterone data at the time point of interest (Day 114). To address the issue of missing data, which appeared to be non-random, various post hoc sensitivity analyses were conducted by the Biometrics reviewers and also by the Applicant to assess the impact of missing data on the consistency of the efficacy results. Although the pre-

specified analysis in the completer population achieved success, *none* of the post hoc sensitivity analyses achieved success. Therefore, from a statistical perspective, the evidence of efficacy from this submitted study is considered *not robust*.

- The pre-specified primary efficacy analysis was based on the completer population that did not include 19.4% of subjects who took study drug but did not have endpoint data. *The primary efficacy analysis should be conducted in all subjects who took study drug, that is, the intent-to-treat (ITT) population.* In addition, the protocol did not address how missing data would be accounted for in the primary efficacy analysis.
- Sensitivity analyses are important for this product because of the extent of missing data (19.4%) and because *the pre-specified primary analysis result in the completer population is exactly the threshold value used to demonstrate efficacy*, which needs to be re-evaluated to determine how it is affected by the missing data.
- The Applicant has submitted *one* pivotal clinical study (CLAR-12011) designed to demonstrate the efficacy and safety of oral TU capsules for the treatment of adult male hypogonadism.
- The statistical analysis plan (SAP), for CLAR-12011, finalized on August 7, 2013, was *not* submitted to the FDA for review but was instead, included in the NDA submission. The SAP is the first place and first time that any mention is made by Sponsor of the primary efficacy population and other analysis populations. The handling of missing data for the primary analysis was *not* addressed in the SAP.
- The statistical analysis plan specified the following three populations for efficacy
 - The Efficacy population, defined as all subjects who completed the Day 114 visit with sufficient pharmacokinetic data to calculate serum T Cavg, is the primary efficacy population. This is also referred to by Biometrics as the Completer population.
 - The Safety population is defined as all subjects who receive at least one dose of the study drug.
 - The Pharmacokinetic (PK) population is defined as all subjects who have sufficient data points to calculate at least one PK parameter.

The Biometrics review team did not agree with the designation of the Efficacy population as the population for efficacy analyses. Instead, the Biometrics review team stated that the Safety population should be the primary population for efficacy analyses because it includes all subjects who received at least one dose of study drug. The Biometrics review team stated that the use of the Efficacy population for the primary efficacy analysis resulted in the exclusion from the analysis of 19.4% of subjects who took study drug and did not have Day 114 serum T Cavg values. They stated that they considered this amount of missing data to be large for a study that is short term (4 months), open-label, and single-arm, for a product that is indicated for chronic use. Also, Biometrics stated that reducing the number of subjects in the success rate

denominator by 20% when calculating a success rate percentage biases the value towards a more favorable result.

- The Biometrics review team conducted two post hoc sensitivity analyses (“*Last Observation Carried Forward*” [LOCF] and “*Worst Case*” analyses) using the Safety population to assess the impact of missing data on the consistency of the efficacy results. The Applicant also submitted five additional sensitivity analyses in different analysis populations and based on different methodologies.
- The LOCF analysis carried forward the last available serum total T Cavg value (baseline, or Day 30 or Day 72 during the treatment period) and used the Safety population. The “*Worst Case*” analysis assumed that the missing Day 114 serum total T Cavg value was outside the normal range and also used the Safety population.
- A total of 148 subjects were enrolled, of whom 144 took study product at 24 centers in the U.S. The overall discontinuation rate was 18.8% (27 subjects). Reasons for premature discontinuation included: Withdrawal of consent (5.6%; 8 subjects), Lost to follow-up (3.5%; 5 subjects), Other (3.5%; 5 subjects), Adverse event (2.1%; 3 subjects), Hematocrit greater than 54% (2.1%; 3 subjects), Noncompliance with study drug (1.4%; 2 subjects), and Protocol violation (0.7%; 1 subject).
- The Safety population included 144 subjects who took study drug. The Efficacy population included 116 subjects, 28 subjects (19.4%) less than the Safety population, and the Pharmacokinetic (PK) population included 133 subjects, 11 subjects (7.6%) less than the Safety population.
- Efficacy was demonstrated for the Sponsor’s pre-specified analysis with the percentage of subjects with a serum total T Cavg within the normal range at Day 114 of 75% (87 of 116 subjects) with 95% CI of 66.1% to 82.6%.
- For the Biometrics review team’s LOCF sensitivity analysis, efficacy fell below the success threshold, with the percentage of subjects with a serum total T Cavg level within the normal range at Day 114 being 70.8% (102 of 144 subjects) with 95% CI of 62.7% to 78.1%.
- For the Biometrics review team’s “*Worst Case*” sensitivity analysis, efficacy fell below the success threshold, with the percentage of subjects with a serum total T Cavg within the normal range at Day 114 being 60.4% (87 of 144 subjects) with 95% CI of 51.9% to 68.5%.
- Whether conducted by FDA (2 sensitivity analyses) or by the Applicant (5 sensitivity analyses), all sensitivity analyses generated results for the primary endpoint that fell below the success threshold.

[CDTL Comment: I concur with the Biometrics Overall Recommendation and in large part, the additional Biometrics comments and remarks.]

6.4.2 Overall Assessment of Efficacy

Based on a number of factors, it is my opinion that reliable replacement of serum testosterone has not been demonstrated for Rextoro. I conclude that substantial evidence of efficacy has not yet been provided for Rextoro.

Herein, I describe the factors that I consider important in coming to that overall conclusion:

1. The efficacy evidence for the to-be-marketed Rextoro dose regimen is limited and comes from a *single* study, CLAR-12011:
 - a. A previously conducted Phase 3 study, CLAR-09007, which employed the same doses as in CLAR-12011 administered via a modestly different dose titration regimen, convincingly failed to demonstrate reliable testosterone replacement into the normal range – maximum testosterone concentrations in a substantial percentage of subjects clearly fell outside the normal range in that study.
 - b. Several small Phase 2 studies were conducted using oral TU in a hard-shell capsule, a formulation different from the Phase 3 soft-gelatin oral TU capsule. Unfortunately, the Phase 2 and Phase 3 formulations were not successfully “bridged” by comparative dissolution data, thus, the evidence from Phase 2 is not available to support efficacy.
 - c. The single, remaining Phase 3 (CLAR-12011) was small (n=144 dosed subjects), uncontrolled, and unblinded.
 - d. CLAR-12011 included only the minimally acceptable endpoints for a testosterone replacement product: percent responders for Cavg (within the normal range), percent outliers for Cmax (using the three traditional outlier criteria), serum concentrations of the key metabolites DHT and E2, and serum LH and FSH).
 - e. The statistical analysis plan (SAP) for the study was not submitted in advance of submitting the NDA. The SAP submitted with the NDA included no plan for handling missing data.
2. The limited amount of available efficacy evidence is not convincing of reliable testosterone replacement, and additional clinical studies appear necessary:
 - a. Using the best possible results; that is, from the completer’s analysis (n=116 subjects), exactly 75% of subjects achieve a normal range T-Cavg, a per cent success that just barely achieves the pre-defined target threshold. Using any other approach that accounts for the approximately 19% of subjects who did not have sufficient data for generating a T-Cavg on Day 114, the efficacy results do not reach the target threshold for success.
 - b. In my view, it is entirely reasonable to conduct limited and appropriate sensitivity analyses in this situation, whether or not these “post-hoc” analyses were “pre-specified” in the late-arriving SAP. FDA must, in fact, conduct these analyses because we lack “confirmatory evidence” of efficacy from any other source, and these analyses inform us about the reliability, or “robustness”, of

testosterone replacement that is achieved by Rextoro. I concur with the Biometrics review team that the sensitivity analyses do not support the drug's benefit.

- c. Some of the reasons given for subject discontinuation are concerning. For example, a total of 18 subjects withdrew consent, were lost to follow-up, or are listed simply as "Other". In a short-term (4 month), open-label, uncontrolled, second Phase 3 study that followed a failed Phase 3 study, that was intended to support a new oral T product for widespread, lifelong use, it concerns me that efficacy data on Day 114 was simply unavailable on so many subjects.
- d. By strict definition, the key secondary efficacy endpoint, C_{max} outliers, was not achieved successfully for any of the three pre-determined categories.
- e. The PK profile of twice daily oral TU demonstrates two sharp increases in serum T with two sharp declines. Therefore, nearly half of the 24-hour sampling period is spent with serum T concentration below the normal range. Thus, the mean average concentrations of serum T, even when viewed in the best possible light, are in the low-normal range. The clinical efficacy endpoints that were tested in Study CLAR-09007, were not convincing of meaningful clinical benefit.
- f. Food, especially fatty food, has a profound effect on the absorption of oral TU and subsequent effect on serum T. Currently, the precautions proposed to reduce the large food-related variability are insufficient. Wide intra-person and inter-person variability should be expected when Rextoro is used by hypogonadal men in the real world. While the 24-hour T-C_{avg} assessments in CLAR-120011 were conducted under at least limited controlled diet conditions, the use of Rextoro in the real world (and, in fact, on the non-PK study days of CLAR-12011) is not under controlled diet conditions. This factor alone poses a very serious challenge to reliable testosterone replacement.
- g. The mean average serum DHT concentration, even following two dose titrations in Study CLAR-12011 is above the normal range, and the mean DHT:T ratio is well above the normal range. In my opinion, the supraphysiologic mean DHT concentration and mean DHT:T ratio challenges any conclusion that Rextoro is reliable testosterone replacement. Testosterone replacement should not increase concentrations of the potent androgen metabolite DHT to levels outside the normal range, nor raise the DHT:T ratio to well above the normal range.
- h. The starting dose of 200 mg BID was too high, leading to excessive T concentrations at Day 30, with the need to down titrate many subjects. Once down-titrated, a significant percentage of subjects were "locked into" excessively low serum concentrations as a consequence of fixed titration parameters that limited up-titration unless the C_{3-5hr} single draw was below 250 ng/dL. Taken together, these results imply that the starting dose and dose titration regimen are suboptimal and that clinical efficacy might be improved by revisions to the current dose regimen.

Therefore, for these reasons, I conclude that the application does not contain substantial evidence in support of Rextoro as an effective testosterone replacement therapy.

7. Safety

7.1 SAFETY FINDINGS

Safety Contents

This Original NDA contained safety data from **377 hypogonadal men** exposed to at least one dose of oral testosterone undecanoate (TU) capsules. Of this total, a total of **305 men** participated in Phase 3 studies, and **72 men** participated in Phase 2 studies of oral TU capsules.

A total of seven (7) clinical trials were included in the safety evaluation of oral TU. All clinical trials were open-label studies conducted in adult men with hypogonadism, defined as having a repeated A.M. serum total T concentration <300 ng/dL, and a diagnosis of hypogonadism.

The original NDA contained safety data from six (6) completed and one (1) ongoing clinical trials, as follows:

- 4 Phase 2 trials
 - CLAR-07004 (n=12, 1-day)
 - CLAR-08005 (n=29, 7-day)
 - CLAR-09008 (n=16, single dose, food effect)
 - CLAR-09009 (n=15, 28-day)

- 3 Phase 3 trials
 - CLAR-09007 (n=325 [161 oral TU, 160 T-gel], 12-months)
 - CLAR-12011 (n=144, 4-months)
 - CLAR-12010 (n=182 continuing treatment from CLAR-09007 [88 oral TU, 94 T-gel], 12-months, ongoing at time of original NDA submission)

Of the 305 subjects from the Phase 3 trials, 246 completed 4 months, 129 completed 12 months, and 69 completed 24 months of treatment with oral TU capsules.

For the extension study CLAR-12010, an interim analysis report was submitted in the 120-Day Safety Update to the NDA, which was followed by additional safety updates submitted later in the review cycle.

In evaluating the safety data for oral T, the following issues were considered:

- All Phase 2 studies were conducted using a hard-gelatin capsule formulation that was not demonstrated to be equivalent to the soft-gelatin capsule formulation used in the Phase 3 studies. Safety data from the small, short-term, Phase 2 studies were not the primary focus of the overall Safety review.

- While the oral TU dose levels were the same in the two Phase 3 studies CLAR-09007 and CLAR-12011, the dose titration regimens were different. The differences in regimens are shown below. The different regimens led to different mean serum androgen concentrations (T and DHT), with higher exposures observed in Study CLAR-09007 compared to CLAR-12011.

The dose titration regimen in CLAR-12011 was:

All subjects began at an oral dose of 200 mg T twice daily (BID) and could be titrated in 50 mg BID increments up to as high as 300 mg T BID or as low as 100 mg T BID. Dose titration, if necessary, occurred on Days 42 and 84, based on the serum T concentration derived from a single blood sample drawn at 3 to 5 hours after the morning dose on Days 30 and 72, respectively. Titration was according to the following schema:

- T < 250 ng/dL: Increase dose by 50 mg BID
- T 250 ng/dL to 700 ng/dL: Maintain dose
- T > 700 ng/dl: Decrease dose by 50 mg BID

The dose titration regimen in CLAR-09007 was:

All subjects began at an oral dose of 200 mg T twice daily (BID) and could be titrated in 100 mg BID increments up to as high as 300 mg T BID or as low as 100 mg T BID. Dose titration, if necessary, occurred on Days 42 and 74, based on the serum T concentration derived from a single blood sample drawn at 4 to 6 hours after the morning dose on Days 30 and 60, respectively. The initial titration on Day 42 was according to the following schema:

- T < 250 ng/dL: Increase dose by 100 mg BID
- T 250 ng/dL to 1100 ng/dL: Maintain dose
- T >1100 ng/dl: Decrease dose by 100 mg BID

Based on the Safety contents of the NDA, and the issues mentioned in this section, the focus of the remainder of Section 7(Safety) is on Study CLAR-12011, which was the single Phase 3 study that used the to-be-marketed dose titration regimen and TBM formulation. Safety data are also shown from Studies CLAR-09007 and CLAR-12010, the other Phase 3 study and its extension.

7.1.1 Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events

Deaths and Serious Adverse Events (SAEs)

No deaths were reported during the clinical trials.

In the overall safety database, consisting of the 6 completed clinical trials (not including the extension study CLAR-12010), a total of 20 subjects (3.7% of 537 total subjects) experienced at least one SAE. The overall incidence of SAEs was comparable between the oral TU and T-gel groups (approximately 3.7% in each group).

In Study CLAR-12011, a total of 2 SAEs (1.4%) were reported. These SAEs were: cerebrovascular accident (CVA) and COPD. The CVA is a case of interest and is summarized here:

This 74-year old white male experienced vertigo on Day 110 which was relieved without treatment. He was diagnosed with a moderate stroke on imaging work-up done on Day 114 (MRI) and Day 116 (cerebral angiogram and CT scan) to determine the etiology of the patient's vertigo. The patient was hospitalized for 2 days and discharged in stable condition. Oral TU dose was titrated down to 150 mg bid at the first titration opportunity and remained 150 mg BID until the end of study (Day 114). The patient's medical history included hypertension and previous TIA. He was taking anti-hypertensive therapy. The patient's BP at screening was 135/79 mmHg and his BMI was 26.6 kg/m². During the study, his systolic BP ranged from 129 to 162 mmHg and his diastolic BP from 72 to 83 mmHg. The patient's Hct and Hb increased during the study (hematocrit increased from 46.9% at baseline to 54.7% at endpoint). The serum total T was in the normal range after dose down-titration.

[CDTL Comment: It is difficult to attribute the patient's CVA directly to oral TU because the patient had a medical history of hypertension and TIA. However, a causal relationship cannot be excluded, especially in light of the increase in blood pressure and increase in hematocrit while on drug.]

In Study CLAR-09007, SAEs were reported in a total of 17 subjects over the 12-month treatment period, including 11 subjects (6.8%) in the oral TU group and 6 subjects (3.8%) in the T-gel group. In the oral TU group, SAEs reported by more than one subject each were acute myocardial infarction (n=2) and coronary artery disease (n=2). For the T-gel group, the only SAE reported by more than one subject was appendicitis (n=2). The complete list of reported SAEs is shown here:

- *For oral TU:* acute myocardial infarction (n=2), coronary artery disease (n=2), angina pectoris, gastroenteritis, pneumonia, sinusitis, urosepsis, hypoglycemia, arthralgia, intervertebral disc degeneration, spinal stenosis, musculoskeletal pain, osteoarthritis, spondylolisthesis, basal cell carcinoma, epilepsy, lumbar radiculopathy, and nervous system disorder (1 each).
- *For T-gel:* appendicitis (n=2), coronary artery disease, peritonitis, brachial plexus injury, joint injury, rhabdomyolysis, prostate cancer and aortic aneurysm (1 each).

In the extension Study CLAR-12010, at the time of the 120-day Safety Update, SAEs were reported in a total of 11 subjects, including 7 subjects (8.1%) in the oral TU group, and 4 subjects (4.3%) in the T-gel group. The list of SAEs is shown here:

- *For oral TU:* cerebrovascular accident, Prinzmetal's angina, syncope, abdominal pain, hip surgery, osteoarthritis, and neck injury (1 each).
- *For T-gel:* cerebrovascular accident, gastric ulcer hemorrhage, duodenal ulcer hemorrhage, adenocarcinoma of prostate, and sepsis (1 each).

[CDTL Comment: There is a slight difference observed between oral TU and T-gel for serious AEs and serious CV AEs, with several more reported for oral TU. The number of serious adverse events and CV AEs is too small to draw definitive conclusions. In addition, the potential adverse impact of increased serum androgen concentrations in the oral TU group in Study CLAR-09007 and CLAR-12010 is not known.]

Discontinuations due to Adverse Events

In the overall safety database, a total of 18 subjects (3% of 537 total subjects) discontinued study treatment due to adverse events. The overall incidence of discontinuations due to AEs was comparable between the oral TU (n=13/377; 3.4%) and T-gel groups (n=5/160; 3.1%). The list of notable AEs leading to discontinuation includes:

- *For oral TU:* polycythemia (n=2), hypoglycemia (n=2), acute MI, hypertension and increased PSA (1 each).
- *For T-gel:* increased PSA, rash (1 each).

In Study CLAR-12011, a total of 3 subjects (2.1%) discontinued due to adverse events. The events that led to these discontinuations were: worsened hypertension, palpitations and hypercalcemia.

In Study CLAR-09007, discontinuations due to AEs were reported in a total of 13 subjects over the 12-month treatment period, including 8 subjects (5.0%) in the oral TU group and 5 subjects (3.0%) in the T-gel group. All adverse events leading to discontinuation were reported by 1 subject each, except for: polycythemia (n=2, both oral TU), and hypoglycemia (n=2, both oral TU).

In the extension Study CLAR-12010, at the time of the 120-day Safety Update, discontinuations due to AEs were reported in a total of 7 subjects, including 1 subject (1.2%) in the oral TU group, and 6 subjects (6.5%) in the T-gel group. The list of AEs leading to discontinuation is shown here:

- *For oral TU:* increased PSA.
- *For T-gel:* polycythemia (n=2), cerebrovascular accident, atrial fibrillation, nocturia, and rash (1 each).

[CDTL Comment: The number of discontinuations due to AEs is too small to draw definitive conclusions.]

7.1.2 Other Adverse Events

Overall Adverse Events

Based on the pooled safety database, the overall incidence of subjects experiencing at least 1 AE was approximately 59% (222 of 377 subjects) in the oral TU group, and 63% (101 of 160 subjects) in the T-gel group.

In CLAR-12011, 49% of subjects (70 of 1144 subjects) reported at least 1 adverse event.

In CLAR-09007, 68% and 63% of subjects in the oral TU and T-gel groups, respectively, reported at least 1 adverse event.

In CLAR-12010, at the time of the 120-day Safety Update, 44% and 40% of subjects in the oral TU and T-gel groups, respectively, reported at least 1 adverse event.

In CLAR-12011, the most commonly reported adverse events ($\geq 2\%$) were: *diarrhea* (3.5%), *upper respiratory infection* (3.5%), *peripheral edema* (2.8%), *hypertension* (2.8%), *prostatomegaly* (2.1%), and *nasopharyngitis* (2.1%).

In CLAR-09007, adverse events reported more frequently for oral TU compared to T-gel were:

- Polycythemia (8.1% vs 3.8%)
- Upper respiratory infection (6.8% vs 2.5%)
- Nasopharyngitis (6.2% vs 4.4%)
- Diarrhea (5.6% vs 1.9%)
- Peripheral edema (5.6% vs 1.3%)
- Prostatomegaly (5.6% vs 3.1%)
- Abdominal discomfort (3.1% vs 0%)
- Eructation (2.5% vs 0%)
- Gastroenteritis viral (2.5% vs 1.3%)
- Prostatitis (2.5% vs 1.3%)
- Dizziness (2.5% vs 1.3%)

In CLAR-12010, adverse events reported by $\geq 2\%$ of subjects in the oral TU group were: *polycythemia* (4.7%), *bronchitis* (3.5%), *sinusitis* (3.5%), *PSA increased* (2.3%), *seasonal allergies* (2.3%), *depression* (2.3%), *hypertension* (2.3%), and *rash* (2.3%).

[CDTL Comment: The list of adverse events is consistent with an androgenic effect. Other adverse events are those related to the GI system. There may be a slight excess of reporting in the oral TU group compared to T-gel, but the incidences of AEs are too small to draw definitive conclusions.]

Adverse Events of Special Interest

For this NDA, the “*adverse events of special interest*” were those related to testosterone replacement therapy itself (e.g., PSA increased, serum lipid abnormalities, increased hematocrit, worsening of benign prostatic hypertrophy, and mood disorders, among others). Of particular interest were potential adverse effects of oral TU on the cardiovascular system, including clinical CV adverse events, and changes in CV biomarkers, such as high-sensitivity C-reactive protein (hs-CRP), HDL-cholesterol, and blood pressure.

This section focuses on observations related to cardiovascular AEs and biomarkers, serum lipids, blood pressure, and changes in hematocrit / hemoglobin. Also discussed in this section are effects on the prostate. These data come primarily from Study CLAR-09007 and its extension CLAR-12010.

Cardiovascular Adverse Events and Cardiovascular Biomarkers

For the overall database, the incidence of cardiovascular adverse events was approximately 3% with oral TU treatment versus 1.3% with T-gel treatment. Most of the CV events were reported from the 12-month study CLAR-09007.

In CLAR-09007, when oral TU was compared with T-gel for all CV AEs reported by $\geq 1\%$, the list is shown here:

- Coronary artery disease: (3 cases [1.9%] vs 1 case [0.6%])
- Acute myocardial infarction: (2 cases [1.2%] vs 0 cases [0%])
- Angina pectoris: (2 cases [1.2%] vs 0 cases [0%])
- Cardiac failure-congestive: (2 cases [1.2%] vs 1 case [0.6%])
- Palpitations: (2 cases [1.2%] vs 0 cases [0%])

In CLAR-12010, three (3) CV AEs in 3 subjects in the oral TU group were coded as SAEs (one each of cerebrovascular accident, syncope, and Prinzmetal's angina) and one CV AE in 1 subject in the T-gel group was coded as a SAE (cerebrovascular accident).

Taken together, for the 24-months of treatment in CLAR-09007 and CLAR-12010 combined, a total of 6 subjects (3.7%) reported a serious CV AE in the oral TU group vs 2 subjects (1.3%) in the T-gel group.

Two cardiovascular biomarkers, high-sensitivity C-reactive protein (hs-CRP) and lipoprotein-associated phospholipase A2 (Lp-PLA2), were assessed in CLAR-09007 and its 12-month extension CLAR-12010. The measurements and analysis of these biomarkers were pre-specified in both trial protocols.

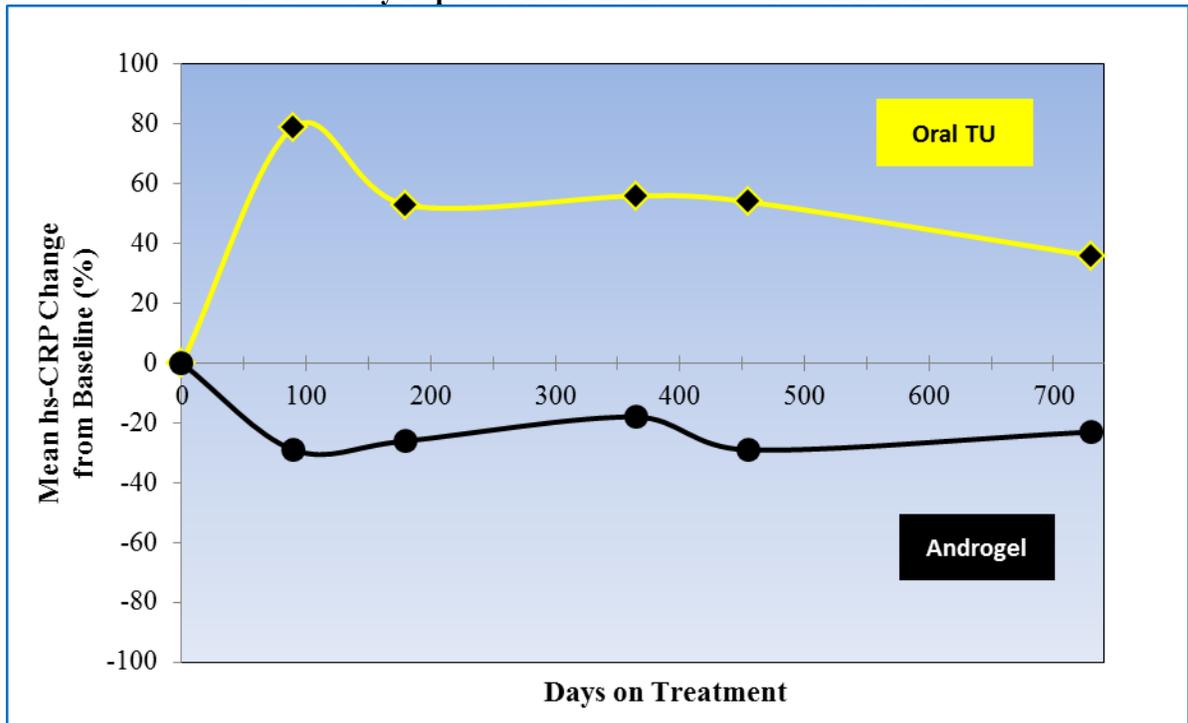
Treatment with oral TU *increased* - but T-gel treatment *decreased* – mean serum hs-CRP from baseline over the course of the 24 months, after excluding subjects with serum hs-CRP >10 mg/L (as per the American Heart Association's recommendation because such high values are generally considered to be related to acute inflammation). The difference between the oral TU and T-gel groups for hs-CRP was statistically significant in the first 12-month study (CLAR-09007). *Figure 4* is based on an analysis of interim data from Study CLAR-12010 that was submitted with the 120-day Safety Update to this NDA.

In regard to the other CV biomarker, serum Lp-PLA2, the mean value was slightly decreased from baseline in both treatment groups, with less decrease in the oral TU group.

Finally, a pre-specified responder analysis was conducted of subjects with worsened ("worse") CV biomarkers, defined as at least a 50% change from baseline. This analysis showed a higher incidence of subjects in the oral TU group compared to the T-gel group with "worse"

biomarkers. The upper bound of the 95% CI for the difference between groups in percent of subjects with “worse” CV biomarkers was 17% on Day 365 in Study CLAR-09007 which was beyond the original pre-specified non-inferiority (NI) margin of 10%. The reader is referred to the Clinical review (the *Individual Trial Reviews Appendix*) for details.

Figure 1. Serum hs-CRP Change from Baseline over 24 Months of Treatment in the Safety Population in CLAR-09007 and CLAR-12010*



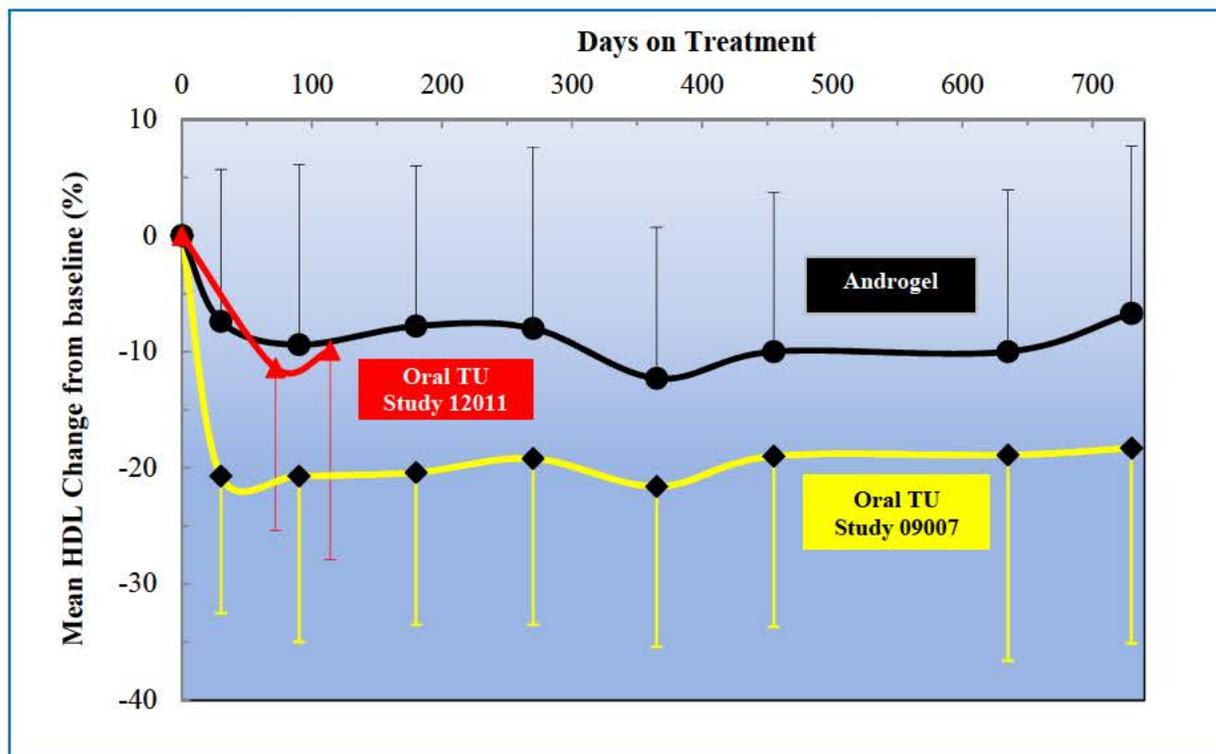
*These data come from the subjects who received at least one dose of study drug, entered the extension study and had hs-CRP measures at the corresponding time-points in the Study CLAR-09007 (the first 12-month) and in Study CLAR-12010 (the second 12 months): n=82-63 on oral TU and n=85-55 on T-gel across time-points. Reference to the FDA’s Clinical review Figure 4.

Serum Lipids

Serum lipids were assessed during Study CLAR-09007 and its extension CLAR-12010. Assessments included triglycerides (TG), total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL). All tested lipids decreased from baseline. Of potential clinical relevance is the observed decrease in serum high-density lipoprotein cholesterol (HDL-cholesterol).

Serum HDL decreased from baseline, with greater decreases in the oral TU group, at all time-points over 24 months of dosing compared to the T-gel group in Study CLAR-09007 and its extension CLAR-12010. Figure 5 reflects the differences between treatment groups in per cent changes in mean HDL concentrations in Study CLAR-09007 and CLAR-12010. Also shown is the mean per cent change in the 4-month, open-label Study CLAR-12011.

Figure 5. Mean Serum HDL Changes from Baseline over 24 months in the Safety Population in CLAR-09007, CLAR-12010 and CLAR-12011 *



* The data are from the subjects who received at least one dose of study drug and had HDL measure at the corresponding time-points. Reference to the FDA's Clinical review Figure 3.

Blood Pressure

Vital signs were monitored during the Phase 2 and 3 trials. There were notable changes in blood pressure (BP) in the Phase 3 studies. Although the BP values were highly variable across visits in all trials, there appeared to be a trend for increased mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) from baseline for both T products, greater with oral TU than with T-gel.

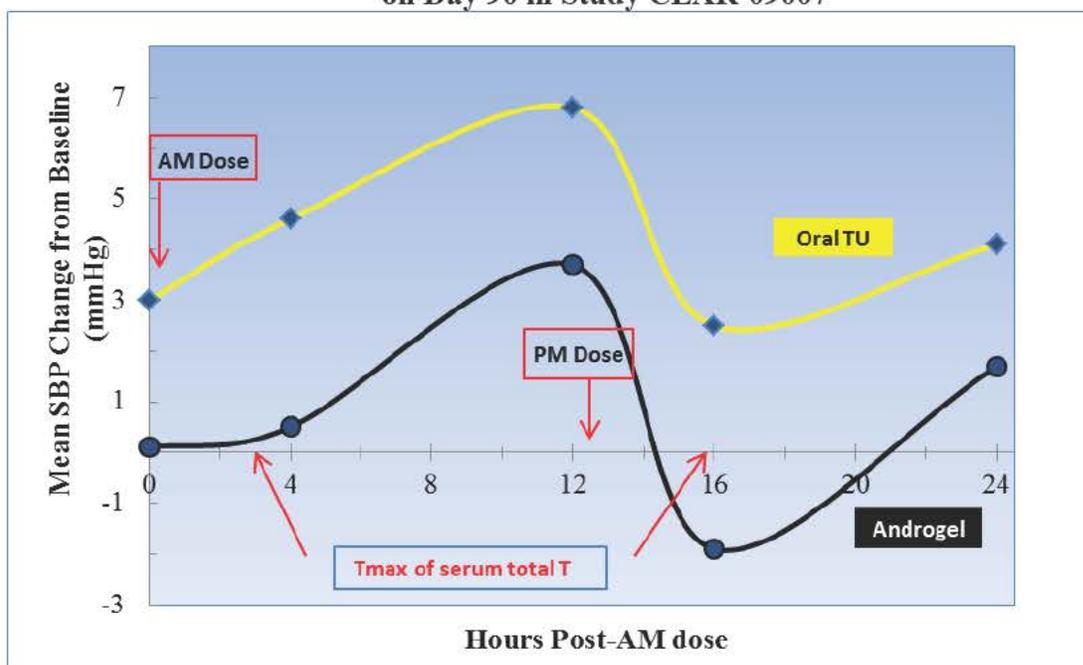
In CLAR-09007 and its extension CLAR-12010, both oral TU and T-gel appeared to increase mean SBP and DBP, but there was a greater increase in BP in the oral TU group compared to the T-gel group over the course of the original 12 months (CLAR-09007) and the additional 12-month extension (CLAR-12010). The greatest increases in BP appeared to occur at 12 hours after the morning dose across all visits in Studies CLAR-09007 and CLAR-12011, as opposed to at earlier times. *Table 3* and *Figure 6* reflect the changes in mean blood pressure over 24 hours after the A.M. dose on Day 90 (or Day 105) for both treatment groups in Study CLAR-09007.

Table 3. Mean BP Changes from Baseline Over 24 hours on Day 90/105 in Study CLAR-09007

BP Time (post-AM dose) [†]	SBP (mmHg)		DBP (mmHg)	
	Oral TU	T-gel	Oral TU	T-gel
Check-in	3.0±13.4	0.1±13.4	2.0±8.7	-0.8±9.7
4 hr	4.6±14.3	0.5±13.7	0.9±9.3	-0.6±9.4
12 hr	6.8±15.3	3.7±14.1	2.0±10.5	0.6±9.2
16 hr [†]	2.5±15.9	-1.9±15.2	-1.2±10.7	-2.1±10.2
24 hr [†]	4.1±14.0	1.7±14.5	2.1±9.6	0.9±10.5

[†] The time-points 16/24 hours post AM dose were 4/12 hours post-PM dose. Reference to the FDA's Clinical review Table 33.

Figure 6. Mean Systolic Blood Pressure Change from Baseline over 24 Hours Post Dose on Day 90 in Study CLAR-09007*



*Data shown are from Safety population n=149 on oral TU and n=151 on T-gel. Reference to the FDA's Clinical review Figure 7.

In CLAR-12011, again, both systolic and diastolic blood pressures appear to increase from baseline at each study visit (on Days 30, 72 and 114), particularly at 12 hours after the morning dose. Over all study visits in CLAR-12011, the increase from baseline at Hour 12 was between 3.8 and 6.1 mmHg for systolic blood pressure and between 0.8 and 2 mmHg for diastolic blood pressure.

Changes in Hematocrit and Hemoglobin

Hematocrit and hemoglobin were monitored in the Phase 3 studies of oral TU. Overall, oral TU was associated with a larger increase in hematocrit (Hct) from baseline compared to T-gel, with a larger number of subjects experiencing a Hct > 54%.

In Study CLAR-12011, the mean increase from baseline in hematocrit was 6.3%

In Study CLAR-09007, the mean baseline hematocrits were approximately 44% for both oral TU and T-gel groups. On Days 90/105 and Day 365, the per cent increases from baseline in hematocrit showed larger increases in the oral TU group compared to the T-gel group, as follows:

- On Day 90/105: 4.9% increase vs. 1.3% increase
- On Day 365: 6.8% increase vs. 3.2% increase

Also in Study CLAR-09007, a greater percentage of subjects in the oral TU group (9.9%; 16 of 161 subjects) as compared to the subjects in the T-gel group (3.1%; 5 of 160 subjects) showed at least one hematocrit value > 54%, a potentially clinically significant value as pre-specified by the Sponsor. In contrast, in Study CLAR-12011, the per cent of subjects with at least one hematocrit > 54% was 2.8%, considerably lower than was observed for oral TU in Study CLAR-09007.

[CDTL Comments: My assessment of data for cardiovascular AEs, cardiovascular biomarkers, serum lipids, blood pressure, and hematocrit and hemoglobin suggests a possible deleterious effect of oral TU, worse than the effects that were concurrently or previously observed for T-gel. While this deleterious effect of oral TU may simply be related to increased testosterone exposure for oral TU in Study CLAR-09007 compared to CLAR-12011, I am unable to make that conclusion with assurance at this time. Increases in blood pressure and hematocrit are particularly notable to me and these are not limited to Study CLAR-09007 only, they were also observed in CLAR-12011, at a dose regimen and formulation that the Sponsor proposes for marketing. Therefore, at this time, the available data for biomarkers of CV risk, such as data on blood pressure, HDL-cholesterol, hs-CRP, and hematocrit all appear to worsen with oral TU and are concerning to me.]

Effects on the Prostate

Serum PSA was monitored in the Phase 3 studies and increased from baseline, as expected.

“Increased PSA” (pre-defined by the Sponsor as an increase from baseline in serum PSA > 1.4 ng/mL) was reported in 0.7% of subjects in CLAR-09007. In Study CLAR-09007, increases in PSA were reported in 7.5% of oral TU subjects versus 10.6% of T-gel subjects. In the extension study CLAR-12010, increases in PSA were more frequent in the oral TU group (9.3%) as compared to the T-gel group (3.3%).

Prostate volume by transrectal ultrasound was measured only in CLAR-09007 and increased from baseline in both oral TU and T-gel groups, slightly worse for oral TU (3 mL) compared to T-gel (1.8 mL).

Prostate related AEs (reported under the AE term “prostatomegaly”) were reported by only 3 subjects in CLAR-12011, but by a larger number of subjects in CLAR-09007. In that 12-month study, 10 of 160 (6.3%) oral TU subjects reported “prostatomegaly” versus 5 of 160 (3.1%) of T-gel subjects.

7.1.3 Postmarketing Safety Findings

There is no postmarket experience with Rextoro, worldwide. However, a different oral TU product, Andriol capsules, has been marketed by a different pharmaceutical company in 80 countries, including in Europe and Canada. The Applicant provided a brief review of publicly available postmarketing experience with Andriol, including postmarketing surveillance reports and published studies based on postmarketing surveillance databases. These items are reviewed in detail in the FDA’s Clinical review under Section 8. Although oral TU appeared to be associated with typical androgen side effects, it is important to note that the dosing regimen of Andriol used to generate the data in these reports is different from the dosing regimen of Rextoro. Based on the Product Monograph for Andriol (approved by Health Canada, Nov 15, 2011), the starting dose is 60 to 80 mg twice daily, with possible dose adjustment to as low as 20 mg twice daily, which is 4-5 times lower than Rextoro (starting dose of 200 mg twice daily in T equivalents). Correspondingly, the systemic T exposure to TU, DHTU, T and DHT for Andriol is lower as compared to Rextoro, based on cross-study comparisons.

7.1.4 Overall Assessment of Safety

My overall assessment is that the safety is not adequately established for Rextoro. Safety signals have emerged from the relatively small safety database and in my opinion, these raise concerns of potentially serious risks of the product. The following issues reflect the safety signals I observed:

1. Reliable testosterone replacement has not been demonstrated, and the lack of reliable testosterone replacement, is itself, a safety signal. At the current dose regimen, Rextoro has not been shown to successfully replace testosterone into the normal range. The following comments provide evidence of this assertion and expand upon these issues:
 - a. On one hand, *lack of efficacy* is itself a safety concern for me. The threshold for efficacy was barely achieved in a pre-specified analysis in one study, but any method of accounting for the 19% missing data in the Phase 3 Study CLAR-12011 leads to a result for Cavg that is below the threshold for success. There are no other studies that demonstrate adequate T replacement by Rextoro, at the proposed TBM dose regimen and formulation. As a twice daily oral product, the PK profile of Rextoro is such that a considerable number of hours of the day are spent with T concentrations below the normal range. Even in the best light, the mean Cavg for Rextoro is in the low-normal range as a consequence of Rextoro’s inherent PK profile. Also, clinical measures of efficacy in Study CLAR-09007 did not reveal evidence of meaningful clinical benefit for Rextoro, even when Rextoro was administered using a titration regimen that led to supraphysiologic concentrations in an unacceptably high percentage of subjects.

Therefore, testosterone replacement and its expected clinical benefit actually may be unacceptably low with Rextoro.

- b. On the other hand, I have safety concerns in regard to *excessive testosterone concentrations* with Rextoro. In the single, pivotal study CLAR-12011, none of the three Cmax outlier categories were achieved successfully. Results for all three categories were above the maximum thresholds, suggesting that in a meaningful percentage of Rextoro-treated patients, maximum testosterone concentrations will be excessive. This result in CLAR-12011 is consistent with the excessive Cmax outliers that were observed in Study CLAR-09007 prompting a change in the dose titration regimen to achieve lower T exposures. Further, the *known effect of fatty food on increasing absorption of TU and resultant increased T concentration* can reasonably be expected to result in sporadic (though largely uninvestigated), excesses in serum T concentrations in some patients and perhaps in the same patient depending on the time of his taking the dose and his eating habits. The high variability in T concentration and expected excessive T concentrations due to fatty food is a major concern for me.
- c. The *mean DHT concentration achieved by Rextoro is above the upper of limit of normal* during the titration process and even at the end of a successful titration regimen. DHT is a potent androgen with affinity for the androgen receptor at least as great as testosterone itself. Both T and DHT are well known to be associated with androgenic side effects, including effects on increasing red blood cell mass, provoking acne and mood changes, and possibly adversely affecting serum lipids, blood pressure and the cardiovascular system. The *mean DHT:T concentration ratio associated with Rextoro is well above the upper limit of normal*, and this too is a major concern for me. The fact that mean DHT concentration and the DHT:T ratio are supraphysiologic present a clear signal of safety risk to me. I question whether a product should be considered or handled as “testosterone replacement therapy” when it provides hormone replacement that is inconsistent with the normal physiologic profile of testosterone and its metabolites. The requirement that DHT and the DHT:T ratio remain within normal physiologic has been a consistent stipulation for all recently approved testosterone replacement products, of which I am aware.
- d. The *very high TU and DHTU concentrations* that are associated with Rextoro may seem irrelevant, but they may not be clinically irrelevant. First, TU and DHTU themselves do have some, albeit weak, affinity for the androgen receptor, and at massive concentrations, as observed with Rextoro, TU and DHTU may have androgenic effects, or may compete with testosterone for receptor interaction. In addition, TU and DHTU are themselves further metabolized, to a variety of known and unknown steroid molecules, which themselves may have pharmacologic effects. In that light, TU and DHTU may play some role in the increased serum DHT concentrations and high DHT:T concentration ratios. Also, the role that TU metabolites may have played, if any role, in the hypocortisolemia and adrenocortical atrophy observed in dogs in the 13-week toxicity study is unknown, but possible.
- e. Reductions in *sex hormone binding globulin (SHBG)* were observed in both Phase 3 studies, with a particularly large effect observed for oral TU versus T-gel in CLAR-09007. The ultimate clinical risk associated with reductions in SHBG is unknown, but

potential increase in free testosterone and excessive androgen pharmacologic effect is not implausible.

2. Clinical evidence of safety risks has emerged from the limited clinical safety database and this clinical evidence represents the second category of safety signal. The following comments provide examples of this evidence and expand upon the issues:
 - a. *A small number of cardiovascular adverse events* were reported in the Phase 3 studies, including acute myocardial infarction and cerebrovascular accident, and although those events might be related to co-morbid conditions, they might also be related to treatment with oral TU. The slightly larger number of serious CV events for oral TU compared to T-gel may not comprise a statistical difference, and might be related, at least in part, to excessive T exposure due to a more aggressive oral TU dose titration regimen in Study CLAR-09007 and CLAR-12010 as compared to the dose regimen planned for marketing, but nonetheless, the small difference in serious CV events concerns me. It may also be a consequence of DHT, TU, or other downstream metabolites, with adverse effects on blood pressure, serum lipids, and hematocrit.
 - b. *Blood pressure (BP) increases* were observed in both Phase 3 studies, with a considerably larger increase associated with oral TU compared to T-gel in Study CLAR-09007. The extent of the oral TU-related BP increase in CLAR-09007 appears large. Whether this clinically significant finding is a direct consequence of the old dose titration regimen and higher T exposure is unclear, but it is notable that a BP increase, albeit of a lesser magnitude, was again observed in CLAR-12011 when T exposures were lower. I remain concerned that oral TU is associated with a BPH increase, which may be due to something unique to oral TU, such as high TU/DHT concentrations, or supraphysiological DHT and DHT:T concentrations. Either way, the BP increases are of real clinical import, in my opinion.
 - c. *Hematocrit increases* were observed in both Phase 3 studies, greater for oral TU compared to T-gel in Study CLAR-09007. Notably, almost 10% of oral TU subjects in Study CLAR-09007 had at least one hematocrit value >54%, despite a study exclusion criterion of serum hematocrit >48% at Screening, and as compared to approximately 3% in oral TU subjects. Hematocrit >54% was pre-determined to be a clinically meaningful threshold. Whether this clinically significant finding is a direct consequence of the old dose titration regimen and higher T exposure is unclear, but it is notable that an increase in hematocrit, of approximately the same magnitude as that observed in CLAR-09007 at Day 365, was again clearly observed in CLAR-12011 when T exposures were lower. I am quite concerned by the effect of oral TU on hematocrit, especially in light of the elevated DHT concentrations and DHT:T ratios. Red blood cell production may be spurred by supraphysiological DHT.
 - d. *Biomarkers of CV risk, including blood pressure (as described in item b. above), serum lipids (HDL-cholesterol), and high-sensitivity C-reactive protein (hs-CRP)* were adversely affected by oral TU capsules. The data from CLAR-09007 reveal worsening in HDL-cholesterol and hs-CRP for oral TU as compared to T-gel. Again, whether this clinically significant finding is a direct consequence of the old dose titration regimen and higher T exposure is unclear, especially considering the lesser degree of worsening

of serum HDL-cholesterol observed in CLAR-12011, but in my opinion, it would be imprudent to draw such a conclusion prematurely.

8. Advisory Committee Meeting

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 on September 18, 2014 to discuss the Rextoro NDA. The Questions to the Committees and the voting results are summarized in Table 4 below.

The majority of members concluded that efficacy and safety had not been adequately established for this product.

Table 4. Questions for the AC and voting results

Question to AC	Voting Result		
	Yes	No	Abstain
1. VOTE: Is there sufficient evidence to conclude that oral testosterone undecanoate is effective as testosterone replacement therapy? <i>Please provide a rationale for your vote.</i>	8	12	1
2. VOTE: Is the overall benefit/risk profile of oral testosterone undecanoate acceptable to support approval of this product for testosterone replacement therapy? <i>Please provide a rationale for your vote.</i>	4	17	0

The following summarizes the voting results, voting rationales, and other discussions that took place at the September 18, 2014, AC meeting:

- VOTE:** Is there sufficient evidence to conclude that oral testosterone undecanoate is effective as testosterone replacement therapy?
Please provide a rationale for your vote.

Yes: 8 No: 12 Abstain: 1

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

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

2. **DISCUSSION:** Discuss whether the safety of oral testosterone undecanoate has been adequately characterized. If additional safety data are needed, discuss the type(s) of data that are needed and whether these data should be obtained pre-approval or whether these data can be obtained post-approval.

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

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

Yes: 4 No: 17 Abstain: 0

(Note that Drs. Howards' and Erstad's votes were incorrectly documented into the record. Dr. Howards provided justification for voting "No" despite having pressed "Yes" on his control panel. He clarified that he had intended to vote "No". Dr. Erstad had pressed "No" on his control panel but stated afterwards that he had intended to vote "Yes". He clarified that he had mistakenly voted "No" but also stated that his vote "could go either way". These errors were accounted for in the committee's discussion.)

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

9. Pediatrics

All clinical trials submitted in this NDA were conducted in adult men who had repeated serum testosterone concentrations that were low. No pediatric patients (<18 years old) were enrolled in any of clinical trials.

This NDA nonetheless triggered PREA because it is for a drug with a new route of administration (testosterone undecanoate oral). The Sponsor requested a full waiver of the requirement to conduct assessments in pediatric patients because studies in pediatric patients are impossible or highly impractical because the disease/condition (primary and secondary permanent hypogonadism) is rare in children. The Division agreed with Sponsor that there are too few children with permanent (lifelong) hypogonadism to feasibly conduct clinical studies in the population. On September 30, 2014, the Pediatric Review Committee (PeRC) agreed that a full waiver was appropriate and that the Sponsor's request should be granted.

10. Other Relevant Regulatory Issues

Office of Prescription Drug Promotion (OPDP)

In his final review dated October 22, 2014, Trun-Hieu (Brian) Tran noted that OPDP will provide comments regarding labeling during a subsequent review cycle because DBRUP is planning to issue a Complete Response action for the current application.

Office of Scientific Investigations (OSI)

Three clinical and one bioanalytical site inspections were conducted by the Office of Scientific Investigations. The three clinical sites were Tower Urology in Los Angeles, California, University Urology Associates in New York, NY (b) (4) also served as the single bioanalytical site for the application. (b) (4)

In their final memo dated August 8, 2014 concerning the inspection of the (b) (4) (b) (4) bioanalytical site, the OSI team (Young Moon Choi, William Taylor and Sam Haidar) had the following conclusion:

“Following the inspections, this DBGLPC (Division of Bioequivalenc and Good Laboratory Practice Compliance) reviewer concludes that the clinical and bioanalytical data from (b) (4) are acceptable for further Agency review.”

The memo noted that no objectionable conditions were observed at the bioanalytical site and no Form FDA-483 was issued.

The memo further noted that site inspection audits for the remaining two clinical sites ((b) (4)) were scheduled to be conducted at another time.

In their final memo, dated October 31, 2014, Jyoti Patel, Sam Haidar and William Taylor had the following conclusion:

“Following the review of inspection reports, these DBGLPC reviewers conclude that data from clinical portions of study CLAR-12011 conducted at University Urology and Tower Urology are acceptable for further review.”

Although no objectionable conditions were encountered and no Form FDA-483 was issued, one item of clinical relevance was noted. Subject # (b) (6) at Tower Urology (Los Angeles, Ca) had a serum T concentration of 1320 ng/dL and a concurrent hematocrit of >54%. The subject’s dose was not decreased as stipulated in the protocol, and the patient was ultimately terminated from the study due to a hematocrit >54% observed at the subsequent next visit.

[CDTL Comment: The observation is indeed clinically relevant and demonstrates the potential difficulty with compliance, and associated potential risk, associated with drugs that require complicated titration regimens.]

Financial Disclosure

All of the clinical investigators in the United States pivotal Phase 3 Studies CLAR-09007 and CLAR-12011 responded to the request for financial disclosure, and only two ((b) (6) and (b) (6) both of the (b) (6) had relevant financial disclosure information to declare, as follows:

(b) (6) served as a (b) (6) for both Phase 3 trials and received payment from the Applicant in the amount of \$62,679 for consultative advisory services. (b) (6) clinical site enrolled the following numbers of subjects:

- In Study CLAR-12011: n= (b) (6) subjects
- In Study CLAR-09007: n= (b) (6) subjects

(b) (6) served as (b) (6) for Study CLAR-09007 and received payment from the Applicant in the amount of \$39,500 for the use of a validated translated questionnaire and for consultative advisory services.

(b) (6) and (b) (6) were (b) (6), respectively, for the same clinical sites in CLAR-09007 and CLAR-12011.

Overall, (b) (6) and (b) (6) sites accounted for approximately (b) (6) of subjects in Study CLAR-09007 and approximately (b) (6) of subjects in CLAR-12011. Thus, (b) (6) and (b) (6) site contributed only a small proportion of the analysis populations, and therefore, from a Clinical perspective, any potential bias from this site is not likely to have a major effect on the final safety or efficacy conclusions.

It should be also be noted that (b) (4) also served as the single bioanalytical site for all PK sample processing and sample analysis for both Phase 3 trials. This site underwent clinical and bioanalytical inspection by the Office of Scientific Investigations (OSI) who found no objectionable conditions at the site and no Form FDA-483

was issued. OSI concluded that the clinical and bioanalytical data from [REDACTED] (b) (4) [REDACTED] were acceptable for Agency review.

Office of Surveillance and Epidemiology: Division of Medication Error Prevention and Analysis (DMEPA)

For this review cycle, DMEPA provided consultation on the container/carton and Package Insert labeling from the medications errors perspective; as well as on the tradename.

DMEPA/Container/Carton Labeling/PI

In their final review dated September 5, 2014, Walter Fava and Tingting Gao provided several recommendations for improvements in the container and carton labels to minimize the risk of wrong strength selection errors, including:

- More clearly differentiate the appearance of the principal display panel for each strength (100 mg vs 150 mg), for example:
 - Change the [REDACTED] (b) (4) font of the dose strength (158 mg) to a different color in order to avoid similarity to the [REDACTED] (b) (4) font used for the tradename.
 - Avoid NDC product codes that are identical or very similar.
- Add an asterisk near the dose strength with a reference to “*Equivalent to 100 mg testosterone”. The referenced text should appear on the side panel.

DMEPA also provided another recommendation that applies to both the carton and prescriber (Full Prescribing Information [FPI]) labeling; specifically, that the dosage strength should be expressed as the amount of testosterone *provided* by each softgel capsule of testosterone undecanoate. [REDACTED] (b) (4)

[REDACTED] The dosage strength is actually the amount of *TU* contained in the product, which *provides* a certain amount of testosterone (e.g., 158 mg TU capsule provides 100 mg testosterone).

DMEPA’s comments on the carton, container and FPI were conveyed to the Applicant on September 16, 2014. Since a Complete Response action is being taken, these items will be addressed at such time as appropriate in a subsequent cycle.

DMEPA/Tradename

In their final review dated August 26, 2014, Danielle Neupauer, Tingting Gao, Irene Chan and Kellie Taylor stated that the proposed tradename, [REDACTED] (b) (4) is acceptable from a promotional perspective but not from a safety perspective. [REDACTED] (b) (4)

Subsequently, on September 15, 2015, the Sponsor submitted a request for FDA to review an alternative tradename, [REDACTED] (b) (4), in the event that [REDACTED] (b) (4) was not approved. On September 24, 2014, the Sponsor requested that a different alternative tradename, [REDACTED] (b) (4), be considered

as the first alternative in the event that the tradename (b) (4) was not approved, and (b) (4) should be considered the second alternative. Finally, on September 26, 2014, the Sponsor requested withdrawal of (b) (4) as a possible tradename.

Office of Medical Policy / Division of Medical Policy Programs (DMPP)

In their final review dated October 22, 2014, Shawna Hutchins and Robin Duer stated that DMPP was deferring comment on the Applicant's patient labeling because DBRUP was planning a Complete Response action due to outstanding clinical and clinical pharmacology deficiencies. DMPP noted that a final review of patient labeling would be completed after the Applicant submits a Complete Response.

Office of Compliance

On October 29, 2014, the Office of Compliance had issued an ACCEPTABLE recommendation in EES for NDA 206089.

Controlled Substances Staff

In their final review dated October 24, 2014, Alicja Lerner, Jovita Randall-Thompson and Michael Klein of Controlled Substances Staff had the following final recommendation:

Future consideration should be given to including in Section 9 (Drug Abuse and Dependence) of the label a description of the abuse potential of the drug product based on current epidemiological information, (as) reported in the Tracked Safety Information (TSI) file that was opened on March 19 2014. The TSI goal is to review current abuse and misuse information of all testosterone products.

In addition, the CSS consult noted the following:

"The proposed future language in the label under Section 9 (Drug Abuse and Dependence) will be finalized pending completion of the ongoing Tracked Safety Information for testosterone products."

11. Labeling

Discussions with the Sponsor in regard to the Package Insert and Patient Package Insert labeling did not occur during this review cycle as a result of the planned CR action.

12. Recommendations/Risk Benefit Assessment

12.1 Recommended Regulatory Action

I recommend that the NDA receive a "Complete Response" action at this time.

12.2 Risk Benefit Assessment

My overall assessment, based upon the evidence that I reviewed for this application, is that neither efficacy nor safety has been adequately established for Rextoro. The risk: benefit assessment is, in my opinion, unfavorable for Rextoro for the proposed indication at this time.

In my opinion, the data submitted for efficacy and for safety is rather limited for this product, for reasons that I will explain in this section. The evidence that has been submitted, though, has raised efficacy and safety concerns.

From an *efficacy* perspective, I conclude that reliable replacement of serum testosterone has not been demonstrated for Rextoro. The following list constitutes the specific reasons for my efficacy conclusion:

1. The efficacy evidence for the to-be-marketed Rextoro dose regimen is limited to data from a single, small, open-label, uncontrolled study, CLAR-12011. Although there is one other Phase 3 study, and a few, small, short-term Phase 2 studies, those do not provide support for efficacy because 1) the Phase 3 study, CLAR-09007, which employed the same doses as in CLAR-12011 just via a modestly different dose titration regimen, convincingly failed to demonstrate efficacy, and 2) the results from small, Phase 2 studies are not able to be used for this purpose because the Phase 2 formulation could not be “bridged” to the to-be-marketed formulation.
2. Study CLAR-12011 was designed with the minimal elements necessary to support efficacy for a traditional, uncomplicated testosterone replacement therapy (TRT) product. These elements include no control group, no blinding, the minimal endpoints for a TRT product, and approximately 100 subjects. While such a trial might be capable of supporting efficacy for a simple TRT product, the efficacy and safety results to date do not demonstrate Rextoro to be a simple TRT product, as I explain below.
3. The limited efficacy evidence from CLAR-12011 is not convincing of reliable testosterone replacement because:
 - a. Using a completer analysis (n=116 subjects), exactly 75% of subjects achieved a normal range T-Cavg, a per cent success that just barely achieved the pre-defined target threshold. Using any other approach that accounted for the approximately 19% of subjects who did not have sufficient data for generating a T-Cavg on Day 114, the efficacy results did not reach the target threshold for success.
 - b. By strict definition, the key secondary efficacy endpoint, Cmax outliers, was not achieved successfully for any of the three pre-determined and required Cmax outlier categories.
 - c. The mean average serum DHT concentration associated with Rextoro, even with appropriate dose titration, is above the upper limit of normal. The mean DHT:T concentration ratio is 2-fold greater than upper limit of normal. These results are inconsistent with current standards for successful testosterone replacement therapy, which intends to replace male hormones to within the normal range only.

- d. The starting dose of 200 mg BID was too high, with the resultant need to down-titrate many subjects. In addition, some subjects with serum T below the normal range were prevented from appropriate up-titration by a parameter that required serum T concentrations to be lower than 250 ng/dL, effectively preventing some subjects from successful TRT.
 - e. Clinical efficacy endpoints investigated in Study CLAR-09007, at higher serum testosterone concentrations, did not confirm clinical benefit.
4. Fat in foods, has a profound and acute effect on the absorption of oral TU and serum T concentrations. Precautions currently proposed to reduce the known, very large, food-related effect on testosterone exposure associated with Rextoro are minimal, and will not lead to well-controlled testosterone replacement.

From a *safety* perspective, I find that safety has not been adequately established for Rextoro. Safety signals of potentially serious risks have emerged from the small safety database. The following list constitutes the specific reasons for my safety conclusion:

1. Reliable testosterone replacement has not been demonstrated, and the lack of reliable testosterone replacement is itself a safety signal.
2. Despite insufficient efficacy, treatment with Rextoro has led to excessive testosterone concentrations in some patients and under certain conditions.
 - a. In the single, pivotal study CLAR-12011, none of the three required Cmax outlier categories were achieved successfully. All three were exceeded.
 - b. The known effect of fatty food on increasing absorption of TU and resultant increased T concentration can reasonably be expected to result in sporadic (though largely uninvestigated), excesses in serum T concentrations.
3. The mean DHT concentration achieved by Rextoro is above the upper of limit of normal, and the mean DHT:T concentration ratio is 2-fold the upper limit of normal. DHT is a potent androgen with affinity for the androgen receptor at least as great as testosterone itself.
4. Very high TU and DHTU concentrations are associated with Rextoro and may not be clinically irrelevant. TU and DHTU have weak affinity for the androgen receptor, and at massive concentrations, as observed in Rextoro, these substances may have androgenic effects, or may compete with testosterone for androgen receptors. In addition, TU and DHT are themselves further metabolized, to DHT and to a variety of known and unknown steroid molecules, which themselves may have pharmacologic effects. Finally, the role that TU metabolites may have played, if any role, in the hypocortisolemia and adrenocortical atrophy observed in dogs in the 13-week toxicity study is unknown, but a role is possible.
5. Reductions in sex hormone binding globulin (SHBG) were observed in both Phase 3 studies. The ultimate clinical risk associated with reductions in SHBG is unknown, but potential increase in free testosterone and excessive androgen pharmacologic effect is not implausible.
6. Clinical safety risks that emerged from the limited safety database include:

- a. A small number of cardiovascular (CV) adverse events were reported in the Phase 3 studies, including acute myocardial infarctions and cerebrovascular accidents, and although those CV adverse events might be related to co-morbid conditions, they might also be related to treatment with oral TU.
- b. Blood pressure (BP) increases were observed in both Phase 3 studies, with a larger increase associated with oral TU compared to T-gel in Study CLAR-09007. BP was also increased, albeit to a lesser degree, in Study CLAR-12011.
- c. Hematocrit increases were observed in both Phase 3 studies, greater for oral TU compared to T-gel in Study CLAR-09007. Almost 10% of oral TU subjects in Study CLAR-09007 had at least one hematocrit value >54%, a level that was pre-determined to be clinically meaningful. An increase in hematocrit was again observed in Study CLAR-12011.
- d. Other biomarkers of CV risk, including HDL-cholesterol and high-sensitivity C-reactive protein (hs-CRP) were adversely affected by oral TU. Data from Study CLAR-09007 reveal worsening in HDL-cholesterol and hs-CRP for oral TU as compared to T-gel.

12.3 Recommendation for Postmarketing Risk Management Activities

Based upon the Complete Response action, there are no specific recommendations for postmarketing risk management activities at this time.

12.4 Recommendation for other Postmarketing Study Commitments

Based upon the Complete Response action, there are no specific recommendations for postmarketing study commitments

12.5 Recommended Comments to Applicant

The recommended comments to Applicant for the Complete Response letter are summarized in Section 13.2 (Risk Benefit Assessment).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARK S HIRSCH
11/03/2014

HYLTON V JOFFE
11/03/2014

I agree that this Application should receive a Complete Response action. See the Division Director memorandum.

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Division Director Summary Review
NDA #	206089
Applicant Name	Clarus Therapeutics, Inc.
Date of Submission	January 3, 2014
PDUFA Goal Date	November 3, 2014
Proprietary Name / Established (USAN) Name	Testosterone undecanoate (oral)
Dosage Forms / Strength	Soft gelatin capsules containing 158 mg and 237 mg testosterone undecanoate
Proposed Indication	For replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
Action	<i>Complete Response</i>

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Jin Chen, M.D., Ph.D., M.P.H.
Statistical Review	Sonia Castillo, Ph.D. and Mahboob Sobhan, Ph.D.
Pharmacology Toxicology Review	Eric Andreasen, Ph.D. and Lynnda Reid, Ph.D.
ONDQA Review	Hitesh Shroff, Ph.D., Donna Christner, Ph.D. and Moo Jhong Rhee, Ph.D.
Clinical Microbiology	Bryan Riley, Ph.D. and Stephen Langille, Ph.D.
Clinical Pharmacology Review (Includes Pharmacometrics)	Sayed (Sam) Al Habet, R.Ph., Ph.D., Chongwoo Yu, Ph.D., Dhananjay Marathe, Ph.D., Jeff Florian, Ph.D., and E. Dennis Bashaw, Pharm.D.
Biopharmaceutics Review	Kelly Kitchens, Ph.D. and Tapash Ghosh, Ph.D.
CDTL Review	Mark Hirsch, M.D.
Environmental Assessment	James Laurenson
OSE/DMEPA	Danielle Neupauer, R.Ph., CPSO, Tingting Gao Pharm.D., Irene Chan, Pharm.D., BCPS and Kellie Taylor, Pharm.D., M.P.H. Walter Fava, R.Ph., MSED and Tingting Gao, Pharm.D.
Office of Scientific Investigations	Young Moon Choi, Ph.D., Sam Haidar, R.Ph., Ph.D. and William Taylor, Ph.D.

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

Clarus Therapeutics, Inc. submitted this New Drug Application (NDA) for oral testosterone undecanoate (TU), seeking an indication for replacement therapy in adult men for conditions associated with a deficiency or absence of endogenous testosterone. The Applicant is seeking approval through the 505(b)(2) approval pathway by relying, in part, upon published literature for testosterone. This document serves as FDA's decisional memorandum on the application.

2. Background

Currently marketed testosterone products include topical formulations that are applied to the skin, a buccal system that is applied to the gums, an intranasal gel, formulations administered by intramuscular injection and subcutaneously implanted pellets. Methyltestosterone, which is the only other orally administered testosterone therapy is rarely used because of concerns for hepatotoxicity. Therefore, if the Clarus product is approved, it will likely dramatically change the landscape with regard to testosterone therapies, because the oral route of administration will be considerably easier to use than the more cumbersome routes of administration available with the commonly used marketed products.

Testosterone itself has poor oral bioavailability (4-7%) because of the first-pass hepatic effect. The formulation developed by Clarus allows for oral dosing by targeting absorption via the intestinal lymphatics into the thoracic duct and then into the bloodstream. In the blood, TU is widely metabolized to testosterone by circulating esterases. Clarus has developed two strengths of the product: 158 mg TU (equivalent to 100 mg of testosterone) and 237 mg TU (equivalent to 150 mg of testosterone). Throughout this memorandum, I will refer to the doses based on testosterone equivalents.

The Applicant is proposing a starting dose of 200 mg twice daily with food. Dose adjustment is based on serum testosterone concentrations measured on a single blood draw 3-5 hours after a morning dose, at least 7 days after starting treatment or following a change in dose. The maximum recommended dose is 300 mg twice daily.

This memorandum will focus on the strength of the efficacy data as well as the key safety concerns, including a clinically relevant food effect, very high serum concentrations of TU and one of its metabolites, dihydrotestosterone undecanoate (DHTU), elevated dihydrotestosterone (DHT) concentrations in many patients, and potential adverse cardiovascular effects based on changes in some cardiovascular risk factors.

3. CMC/Device

The Chemistry/Manufacturing/Controls (CMC) reviewers have concluded that the Applicant has provided sufficient information to assure the identity, strength, purity and quality of the drug product.

The Applicant proposes two manufacturers for the TU drug substance. The CMC reviewers have found the corresponding Drug Master Files adequate. Both manufacturers have acceptable drug substance specification criteria.

The drug product is formulated as soft gelatin capsules for oral administration. The two strengths are differentiated by capsule color and imprinting. The drug product contains borage seed oil as one of its excipients [REDACTED] (b) (4). According to the CMC reviewers, this excipient is non-compendial but is used in currently marketed dietary supplements and has a well-established specification. The remaining excipients are all compendial. The CMC reviewers agree with an expiration dating period of 30 months for the drug product.

This application qualifies for a categorical exclusion from the requirement to submit an Environmental Assessment. See the review by James Laurenson for further details.

The Office of Compliance issued an overall acceptable recommendation for the manufacturing facilities.

All outstanding CMC issues have been resolved except for labeling, which is deferred because the NDA has non-CMC deficiencies that preclude approval. See the reviews by Hitesh Shroff, Ph.D., for further details.

4. Nonclinical Pharmacology/Toxicology

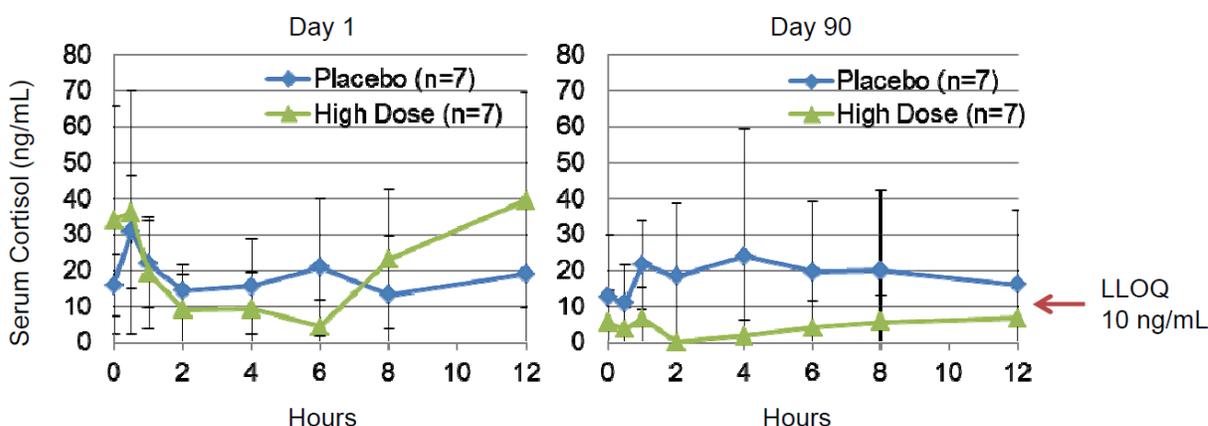
The Applicant is abbreviating its nonclinical pharmacology/toxicology program by relying upon published literature to support the absorption, distribution, metabolism, elimination, reproductive toxicity and carcinogenicity of testosterone.

The Applicant conducted an oral, repeat-dose toxicity bridging study in dogs given vehicle, 38 mg/kg TU twice daily (low-dose) or 126 mg/kg TU twice daily (high-dose) for 13 weeks. The Applicant assessed recovery four weeks after the last dose in the control and high-dose groups. Safety margins were calculated based on area under the concentration-time curve (AUC) compared to men given the maximum recommended TU dose with a high fat meal. This is the worst case scenario because men have the highest exposures to TU, DHTU, testosterone and dihydrotestosterone (DHT) following a high fat meal compared to lower fat meals or the fasted state (see Clinical Pharmacology section below). Compared to these men, dogs in the high-dose group had a 5-6-fold higher exposure to TU, an 8-fold higher exposure to testosterone and a 2-fold higher exposure to DHT. The nonclinical pharmacology/toxicology reviewer

identified expected androgen-dependent effects (e.g., marked prostate hypertrophy, marked testicular atrophy/degeneration, severe reduction in epididymal sperm) and noted no other significant safety findings. The nonclinical pharmacology/toxicology reviewer concluded that the lack of other significant safety findings in this study, as well as other referenced nonclinical data, provides sufficient support for the safety of the noncompensial borage seed oil excipient.

One noteworthy finding is the moderate to marked atrophy of the adrenal cortex with 30-35% reduction in adrenal weight observed in all dogs at Week 13. As shown in Figure 1 (adapted from page 45 of Dr. Andreasen’s review), there appears to be an accompanying reduction in serum cortisol. Dr. Andreasen recommends caution when interpreting these cortisol concentrations because the data are highly variable and the lower limit of detection of the assay was near or above the reported concentrations. Nonetheless, the findings raise the possibility that TU or its metabolite(s) may have glucocorticoid activity that can suppress the hypothalamic-pituitary-adrenal axis in dogs, leading to secondary adrenal insufficiency.

Figure 1. Mean serum cortisol concentration in the 13-week dog toxicity study.



The Applicant conducted an *in vitro* androgen receptor binding study to compare the affinity of TU, DHTU, testosterone and DHT for the androgen receptor. This study used a commercial kit to evaluate the ability of each test compound to displace a fluorescent androgen receptor ligand from a fragment of the rat androgen receptor. The Applicant did not conduct this testing with the human androgen receptor. The nonclinical pharmacology/toxicology reviewer stated that the results may still be predictive for humans because the positive and negative controls responded as expected and there were only seven amino acid differences between the human and rat ligand binding domains. Table 1 summarizes the relative binding potency for each of the tested compounds. The relative binding potency is calculated by dividing the EC₅₀ for testosterone by the EC₅₀ for the test compound then multiplying that result by 100. EC₅₀ refers to the concentration of the test compound that gives the half-maximal response with regard to displacement of the fluorescent androgen receptor ligand from the rat androgen receptor. These data suggest that TU and DHTU have low potential to act as ligands at the rat androgen receptor, similar to that of DHEA. It is unclear whether these findings with the rat androgen receptor are representative of what would happen at the human androgen receptor.

Testosterone	100%
Dihydrotestosterone (DHT)	83%
Testosterone undecanoate (TU)	1.2%
Dihydrotestosterone undecanoate (DHTU)	0.7%
DHEA	0.8%

The nonclinical pharmacology/toxicology reviewer had pending labeling recommendations but otherwise recommended approval of the NDA. See the review by Eric Andreasen, Ph.D., for details.

5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacology recommends a Complete Response for this NDA. See the primary review by Sayed Al Habet, R.Ph, Ph.D., the pharmacometrics review by Dhananjay Marathe, Ph.D. (embedded within Dr. Al Habet's review), and the supervisory memorandum by CAPT E. Dennis Bashaw, Pharm.D., for details.

This section focuses on the following specific issues:

- General clinical pharmacology aspects of the product
- The impact of food and meal fat content on the exposure to TU and its metabolites
- Missing analytical validation data that were submitted late in the review cycle

The following issues have some overlap with Clinical Pharmacology but are covered in the Efficacy or Safety sections of this memorandum:

- The Phase 3 studies conducted to establish efficacy and safety
- High concentrations of TU, DHTU, and DHT
- A starting dose of TU that may be too high for a majority of patients
- Whether additional dosage strengths would permit more flexibility in dosing
- Whether the titration criteria should be modified

Steady-State: The Applicant showed that serum testosterone and DHT concentrations reach steady-state by Day 7 with repeated dosing of oral TU. This supports the Applicant's proposal to adjust dosing based on serum testosterone concentrations measured at least seven days after starting treatment or following dose adjustments.

Formulations: The formulation used in the earlier studies (e.g., the food-effect study, and the 28-day repeat-dose clinical pharmacology study) was a hard gelatin capsule. The phase 3 studies used soft gelatin capsules, which are the final to-be-marketed formulation. The Biopharmaceutics team reviewed the Applicant's proposed dissolution method, method validation and acceptance criteria for the phase 3 (to-be-marketed) soft gelatin capsules and found these to be acceptable. However, the Applicant was not able to use dissolution testing to

bridge the soft gelatin capsule to the earlier hard gelatin capsule formulation because each formulation used a different dissolution method. Because these two formulations are not bridged, we cannot rely on the earlier studies to support efficacy. However, per the clinical pharmacology team, the data from those earlier studies are sufficient to support the food-effect findings and the Applicant's proposal to adjust dosing based on serum testosterone concentrations measured at least seven days after starting treatment or following dose adjustments. Biopharmaceutics concluded that dissolution testing is not needed to bridge these products because there is extensive pharmacokinetic data for both formulations, and recommends approval of the NDA. See the review by Kelly Kitchens, Ph.D. for details.

Drug Interactions: Clinical pharmacology did not require the Applicant to conduct drug-drug interaction studies. TU is not metabolized by CYP450 to any meaningful extent, if at all. TU is metabolized to testosterone by non-specific, ubiquitous esterases and there are no known drugs that impact these esterases. Dr. Al Habet states in his review that it is unknown whether the absorption of TU could be affected by drugs that modify stomach pH (e.g., proton pump inhibitors). I discussed this issue further with Dr. Bashaw who states that such an interaction is not expected because TU is insoluble in water, regardless of pH. The need to use surfactant agents in the dissolution testing media is cited as evidence of the relative insolubility of TU in aqueous media.

Based on the physicochemical properties of the product, it is possible that co-administration with alcohol could either increase or decrease the bioavailability of TU. For example, if alcohol solubilizes the product leading to increased absorption via the portal vein, there will be a high first-pass effect and TU bioavailability would fall. It is also possible, however, that alcohol could enhance absorption via the lymphatics, leading to increased TU bioavailability.

In vitro Hydrolysis and Bioanalytical Data: We considered whether TU could be hydrolyzed to testosterone during sample processing – for example, due to metabolism of TU by non-specific esterases in the blood collected in the test tube. If this were to occur, the measured testosterone concentration in the test tube could be artifactually higher than the true circulating serum testosterone concentrations. Chongwoo Yu, Ph.D., another clinical pharmacology reviewer was assigned to evaluate this possibility and determined that the bioanalytical method validation report in the NDA did not contain documentation of how this issue was handled. During his review, he also discovered late in the review cycle (Month 6) that there were several other deficiencies in this report and determined that there were missing sections in the bioanalytical study (method performance) reports. The Applicant subsequently adequately addressed the hydrolysis issue and the clinical pharmacology team concluded that the measured serum testosterone concentrations are reliable from this standpoint. The remainder of the late-cycle submission pertaining to the bioanalytical reports has not been fully reviewed by clinical pharmacology. Per Dr. Bashaw, clinical pharmacology will review the complete analytical validation section of the NDA in a future resubmission in light of any new trials that are conducted to support the NDA.

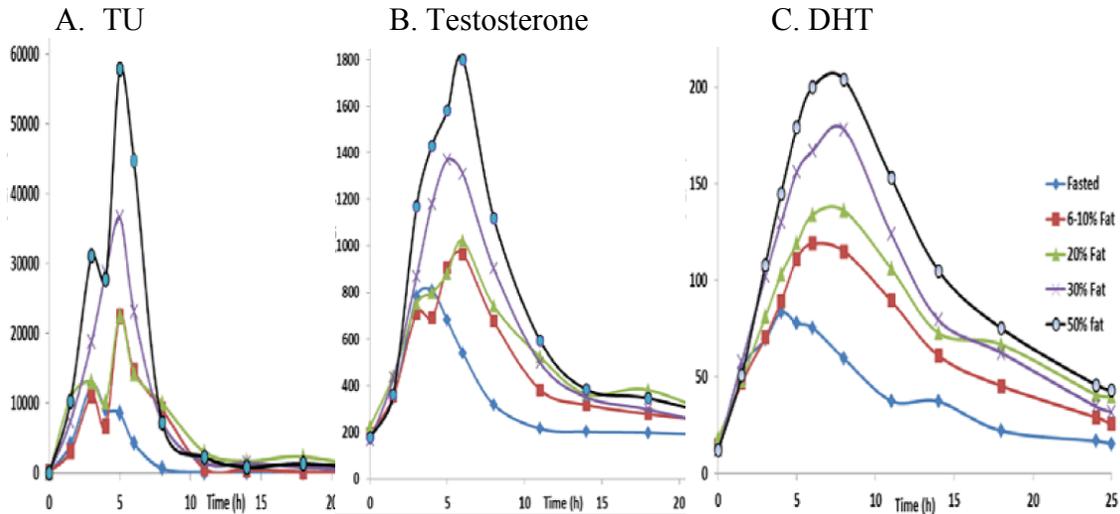
Food Effect: Study CLAR-09008 was a crossover study in 16 hypogonadal men who received the proposed maximum recommended dose of TU (300 mg testosterone equivalents) fasting and also 30 minutes after breakfast containing 6-10%, 20%, 30% or 50% fat. The study used

the hard gelatin capsule formulation. As shown in Figure 2, there are progressive increases in TU, testosterone, and DHT compared to the fasted state as the fat content in the meal increases. There is a 4.1-fold increase in the C_{max} for TU and a 2.3-fold increase in the C_{max} for serum testosterone and DHT when the product is taken after a meal with 50% fat compared to the fasted state. Based on AUC, the corresponding increases are 4.9-fold for TU, 2.1-fold for serum testosterone, and 2.8-fold for DHT.

In the pivotal phase 3 trial (CLAR-12011), the Applicant asked subjects to take the product daily within 15 minutes after completion of breakfast and dinner. The Applicant is proposing that the product be approved for dosing once in the morning and once in the evening with meals. I agree that it is not reasonable to label the product for the fasted state, particularly because this is not practical for the evening dose. However, taking the product with food will not lead to consistent serum TU, testosterone and DHT concentrations unless the fat content for every breakfast and every dinner is kept relatively constant from day to day. It is not reasonable to expect patients to be able to maintain such consistency every day while taking this chronic medication nor is it reasonable to expect that patients will always be able to know the fat content of their meals. With variations in the fat content from day-to-day, a given dose of TU may sometimes be too high (if the fat content of the accompanying meal is high) and sometimes too low (if the fat content of the accompanying meal is low). During the pivotal phase 3 trial, there was no restriction on the types of food that subjects could eat except on the three pharmacokinetic sampling days (Day 30, 72 and 114) when subjects had to choose foods from a preset menu. Therefore, the TU, testosterone and DHT concentrations on these pharmacokinetic sampling days (on Days 30 and 72 for determining titration and on Day 114 for the primary efficacy timepoint) likely do not reasonably reflect the day-to-day testosterone exposures that occurred when subjects had unrestricted access to whatever food they desired.

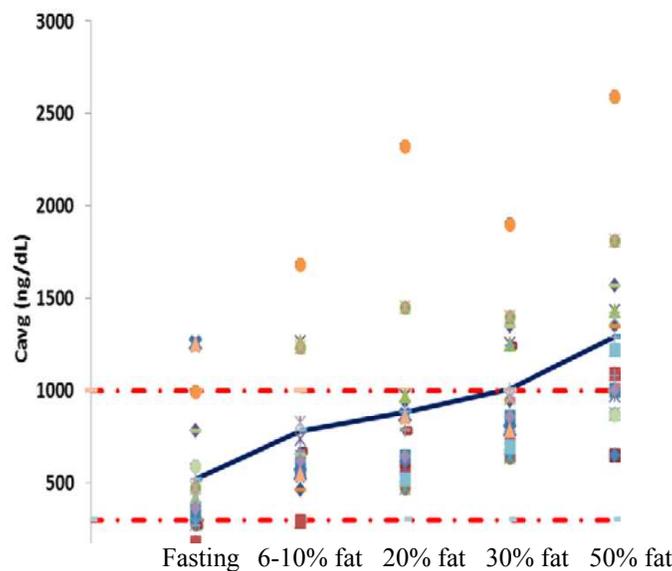
Dr. Bashaw states that this food effect issue is an approvability issue because there are insufficient data to provide guidance on how to appropriately dose the product. He is recommending a timed food effect study to assess whether taking the product before or after food (e.g., 1 hour before food, or 1 or 2 hours after food) could minimize the food effect and lead to more predictable TU, testosterone and DHT concentrations. Dr. Bashaw also recommends that a standardized diet (e.g., with known fat content) be used during the pharmacokinetic sampling phase of any new phase 3 trials that are conducted. Although this would allow for an assessment of the fat content consumed by each subject on the pharmacokinetic sampling day, this proposal would not reflect what happens with TU, testosterone, and DHT exposures on other days in the trial when subjects eat whatever they desire.

Figure 2. Food effect study: Mean concentrations of TU, testosterone and DHT with fasting and fed conditions after a 300 mg TU dose. Y-axis is concentration in ng/dL. (Adapted from Figure 2.5.1.2. in Dr. Al Habet’s review)



This food effect study also showed considerable inter-subject variability with regard to serum TU and testosterone concentrations. Figure 3 shows these data for serum testosterone Cavg. Each data point reflects a single subject and the solid line passes through the mean for each fed/fasted condition. As shown, regardless of whether subjects are fasting or fed, and regardless of the fat content of the meal, there is considerable spread between the subject with the lowest testosterone Cavg and the subject with the highest testosterone Cavg.

Figure 3. Individual and mean (solid line) testosterone Cavg in fed and fasted conditions after a 300 mg TU dose (Adapted from Figure 2.5.1.3. in Dr. Al Habet’s review)



6. Clinical Microbiology

The Product Quality Microbiology reviewer has concluded that the microbiological quality of the drug product is adequately controlled. See the review by Bryan Riley, Ph.D. for details.

7. Clinical/Statistical-Efficacy

This section focuses on the key design features and efficacy results of the phase 3 trials. See the clinical review by Jin Chen, M.D., Ph.D., M.P.H., the statistical review by Sonia Castillo, Ph.D., and the Cross-Discipline Team Leader memorandum by Mark Hirsch, M.D., for further details.

The Applicant conducted two open-label phase 3 trials, CLAR-09007 and CLAR-12011 as well as CLAR-12010, an extension to CLAR-12011. CLAR-09007 and CLAR-12011 enrolled subjects with an existing diagnosis of hypogonadism and confirmed low serum testosterone concentrations (<300 mg/dL) but did not require subjects to have signs or symptoms of hypogonadism. These trials were designed to assess whether the product can reliably increase serum testosterone concentrations into the normal range for healthy, eugonadal men, and whether the product is safe in the intended population.

For the primary efficacy endpoint, the trials had to show that the product achieves C_{avg} for testosterone within the range of 300-1000 ng/dL for at least 75% of subjects and that the lower bound of the corresponding 95% confidence interval for this point estimate is at least 65%. C_{avg} is a time-averaged calculation that divides total testosterone exposure (AUC, calculated from pharmacokinetic sampling over 24 hours) by 24.

The trials also included the following three standard key secondary endpoints for testosterone C_{max} (the maximal, post-dose concentration of serum testosterone) to assess for unacceptably high maximal exposures to testosterone that could raise safety concerns:

- Testosterone $C_{max} \leq 1500$ ng/dL in at least 85% of subjects
- Testosterone $C_{max} > 1800$ and ≤ 2500 ng/dL in not more than 5% of subjects
- Testosterone $C_{max} > 2500$ ng/dL in no subjects

Other efficacy endpoints included serum DHT and estradiol concentrations (both metabolites of testosterone) and the DHT-to-testosterone concentration ratio.

These primary and secondary efficacy endpoints are the contemporary standard efficacy endpoints used to support approval of testosterone replacement therapies.

The first phase 3 trial, CLAR-09007, was a 12-month, open-label, active-controlled trial that randomized 162 subjects to 200 mg of oral TU twice daily and 163 subjects to 5 grams of AndroGel 1% applied topically to the skin once daily. The Applicant measured serum testosterone 4-6 hours after the morning dose on Days 30 and 60. Subjects could then undergo dose titration on Day 42 (based on the Day 30 results) and/or Day 74 (based on the Day 60

results). The Applicant then assessed the primary efficacy endpoint on Day 90 (if no titration occurred on Day 74) or Day 105 (if titration occurred on Day 74).

The titration algorithm for oral TU in CLAR-09007 is shown below.

Day 30 testosterone

- <250 ng/dL, increase TU dose to 300 mg twice daily starting on Day 42
- 250-1100 ng/dL, continue TU 200 mg twice daily on Day 42
- >1100 ng/dL, decrease TU dose to 100 mg twice daily starting on Day 42

Day 60 testosterone while on 300 mg twice daily

- <1100 ng/dL, continue TU 300 mg twice daily on Day 74
- >1100 ng/dL, decrease TU dose to 250 mg twice daily starting on Day 74

Day 60 testosterone while on 100 mg twice daily

- <250 ng/dL, increase TU dose to 150 mg twice daily on Day 74
- 250-1500 ng/dL, continue TU 100 mg twice daily on Day 74
- >1500 ng/dL, discontinue the subject

Both oral TU and Androgel 1% met the primary efficacy endpoint on Day 90/105. For oral TU, the Day 90/105 Cavg for serum testosterone was within the prespecified normal range of 300-1000 ng/dL for 83% of subjects (95% confidence interval 76%, 89%). However, 14% of subjects had a testosterone Cmax >2500 ng/dL and 13% of subjects had a testosterone Cmax between 1800 and 2500 ng/dL. Because of these unacceptably high Cmax values that substantially exceeded the pre-specified targets, the Applicant modified the dose titration algorithm and then tested this revised algorithm in a new phase 3 trial, CLAR 12011.

CLAR-12011 is the pivotal phase 3 trial because it is the only trial that uses the proposed to-be-marketed formulation, dosing and titration regimen for oral TU. CLAR-12011 was a non-randomized, single-arm (TU only), multicenter trial with a four-month treatment period that enrolled a total of 148 subjects. The Applicant measured serum testosterone 3-5 hours after the morning dose on Days 30 and 72. Subjects could then undergo dose titration on Days 42 (based on the Day 30 results) and/or Day 84 (based on the Day 72 results). The primary efficacy endpoint and key secondary efficacy endpoints were assessed on Day 114.

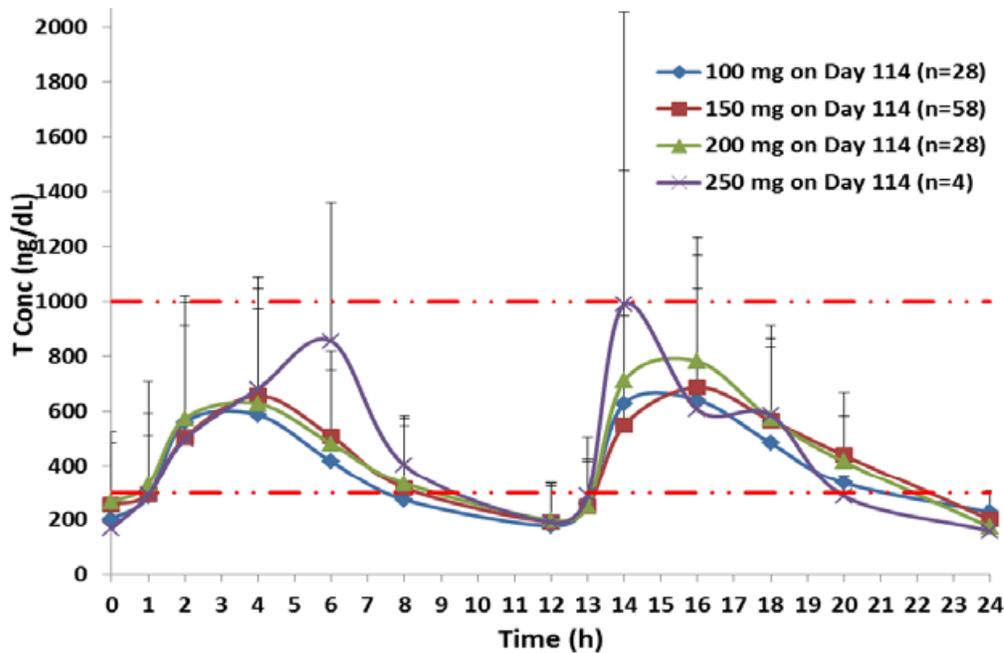
CLAR-12011 used a less aggressive titration algorithm than that used in CLAR-09007 in an attempt to limit unacceptably high maximum serum testosterone concentrations. The revised titration algorithm on Days 30 and 60 was as follows:

Day 30 or Day 60 testosterone

- <250 ng/dL, increase TU dose by 50 mg twice daily
- 250-700 ng/dL, continue current TU dose
- >700 ng/dL, decrease TU dose by 50 mg twice daily

Figure 4 shows the 24-hour pharmacokinetic profile of oral TU on Day 114 in the completer population.

Figure 4. CLAR-12011: 24-hour testosterone pharmacokinetic profile on Day 114 (adapted from Figure 12011-1B in Dr. Al Habet’s review)



A total of 144 subjects received at least one dose of study drug. The Applicant’s pre-specified analysis used the 116 subjects in the completer population (those who completed the Day 114 visit and had sufficient pharmacokinetic data to calculate the primary efficacy endpoint). The completer population is the typical population used for the primary efficacy analysis for virtually all contemporaneous testosterone products. This analysis just met the primary efficacy criteria, with 75% of subjects having Cavg within the normal range of 300-1000 ng/dL on Day 114 (95% confidence interval 66%, 83%). However, this analysis excluded 28 treated subjects (19%) who had missing Day 114 efficacy data. Seventeen of these 28 patients did not have sufficient pharmacokinetic data to calculate serum testosterone Cavg on Day 114 and the remaining 11 subjects did not have any post-baseline efficacy data. The biometrics review team raised concerns with this extent of missing data, particularly given the borderline primary efficacy results for this single, open-label, non-randomized, short-term pivotal phase 3 trial. Unfortunately, the protocol did not prospectively address how missing data would be handled for the primary efficacy analysis. The biometrics review team conducted two *post hoc* sensitivity analyses using all 144 subjects who had received at least one dose of study drug to assess the impact of missing data on the consistency of the efficacy results. Dr. Castillo’s review also shows four other *post hoc* sensitivity analyses conducted by the Applicant. Of these six sensitivity analyses, four used either last-observation-carried-forward (including the pre-treatment value if there were no post-baseline data) or the worst case scenario (subjects with missing data were considered treatment failures). These approaches are conservative. For example, eight of the 11 subjects without post-baseline data had screening and baseline testosterone concentrations <300 ng/dL, consistent with the entry criteria for the trial.

Similarly, worst case scenario assumes that all missing data were below the threshold for success even though there may be other reasons for the missing data that are unrelated to efficacy. Dr. Castillo notes that all sensitivity analyses yield point estimates less than 75% for the proportion of subjects with Cavg in the normal range (Table 2). Based on the above considerations, the biometrics review team concluded that the single pivotal trial does not provide evidence demonstrating the efficacy of oral TU.

Imputation	Statistical Population	n	Percentage (95% CI)
Primary efficacy analysis	Completer population ¹	116	75.0 (66.1, 82.6)
FDA post-hoc sensitivity analyses			
LOCF, including baseline	Safety ²	144	70.8 (62.7, 78.1)
Worst case	Safety ²	144	60.4 (51.9, 68.5)
Applicant’s post-hoc sensitivity analyses			
Worst case	Pharmacokinetic ³	133	65.4 (56.7, 73.4)
LOCF, including baseline	Pharmacokinetic ³	133	74.4 (66.2, 81.6)
MMRM with multiple imputation	Pharmacokinetic ³	133	74.8 (66.9, 82.7)
MMRM with multiple imputation with demographics	Safety ²	144	73.1 (65.2, 80.9)

CI=confidence interval; LOCF=last-observation-carried-forward; MMRM=mixed model repeated measures
¹Completer population: Subjects who completed Day 114 with sufficient data to calculate testosterone Cavg
²Safety: All subjects who received at least one dose of study drug
³Pharmacokinetic: All subjects with sufficient data points to calculate at least one pharmacokinetic parameter

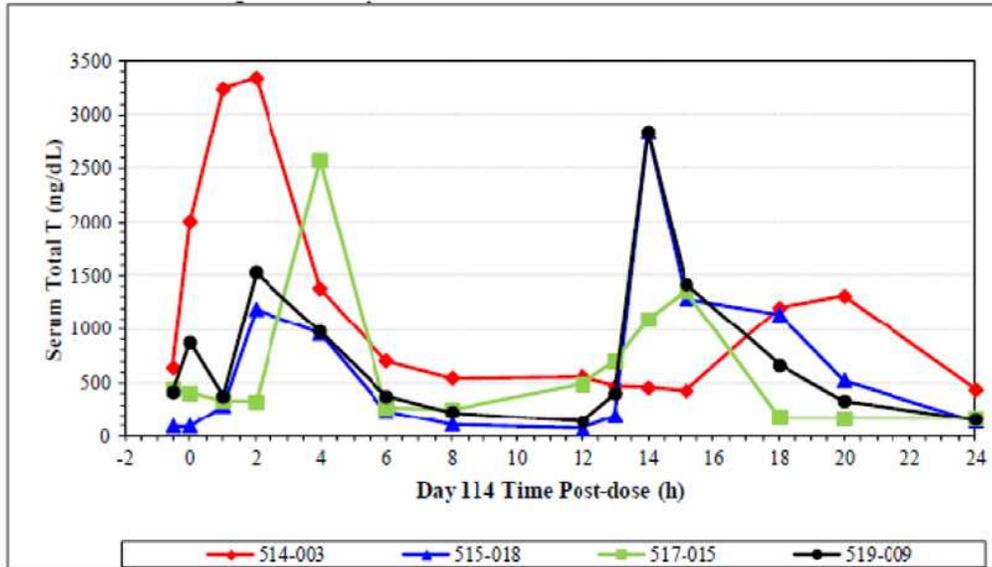
As shown in Table 3, the Applicant did not strictly meet the targets for all three key secondary Cmax efficacy endpoints. An additional four subjects would have needed to have Cmax ≤1500 ng/dL to meet the target of ≥85%. Two fewer subjects would have needed to have Cmax >1800 to ≤2500 ng/dL to meet the target of <5%.

Cmax (ng/dL)	Actual N=116 n (%)	Target
≤1500	95 (82%)	≥85%
>1800 to ≤2500	7 (6%)	<5%
>2500	4 (3%)	0%

Dr. Chen discusses the findings for the four subjects who had Cmax >2500 ng/dL on Day 114, which are shown graphically in Figure 5. Two of these subjects had Cmax >2500 ng/dL after the morning dose on Day 114, but not after the evening dose (Subject (b) (4) was suspected of having double-dosed in the morning). The other two subjects had Cmax >2500 ng/dL after the evening dose on Day 114 but not after the morning dose. Per Dr. Chen, these transient

Cmax elevations were not associated with notable adverse events.

Figure 5. Serum testosterone profiles on Day 114 in the four subjects who had Cmax >2500 ng/dL (from Figure 9 in Dr. Chen’s review)



Other issues raised by the review team include the following:

- The starting dose of 200 mg twice daily appears too high for most subjects. At the primary efficacy timepoint, only 24% of the 116 completers were still taking this dose. Most of the completers had been down-titrated to 150 mg twice daily (51%) or 100 mg twice daily (25%), and few subjects had been up-titrated (4% were on 250 mg twice daily and none were on 300 mg twice daily). The Pharmacometrics team noted that testosterone Cavg and Cmax outliers appeared higher among subjects with lower body weight and stated that an initial dose of 150 mg twice daily might be a better alternative for those with body weight less than about 80 kg. The inverse relationship between body weight and change in serum testosterone is most apparent in CLAR-09007 and is less pronounced in CLAR-12011, as shown in Figure 09007-5 in Dr. Al Habet/Dr. Marathe’s review.
- The titration algorithm calls for uptitration if the serum testosterone 3-5 hours after the morning dose is <250 ng/dL and calls for downtitration if the value is >700 ng/dL. The Pharmacometrics team noted that these criteria lead to downtitration in a subset of subjects who actually have testosterone Cavg within the normal range and would not lead to uptitration in a subset of subjects with testosterone Cavg <300 ng/dL. In CLAR-12011, Dr. Al Habet/Dr. Marathe report that 23% of subjects had testosterone Cavg <300 ng/dL at the primary efficacy time point.
- Clinical Pharmacology recommends that the Applicant consider developing additional dosage strength(s) to allow fine tuning of the oral TU dose. For example, Dr. Bashaw

mentions that a 75 mg dosage form would allow for doses of 175, 225, and 275 mg in addition to the current doses of 100, 150, 200, 250 and 300 mg.

Free Testosterone and Sex-Hormone Binding Globulin: Testosterone is transported in the plasma largely bound to albumin and sex hormone-binding globulin (SHBG). In healthy eugonadal men, about 1% of plasma testosterone is free, and the remainder is bound strongly to SHBG or weakly to albumin and other proteins. Oral TU does not appear to lead to alterations in the concentration of serum albumin. However, the proposed dosing regimen in CLAR-12011 led to a 35% decline in mean SHBG from 35 nmol/L at baseline to 22 nmol/L on Day 114 (reference range 11-47 nmol/L). Normal men remain eugonadal even in the face of changes in SHBG concentrations because the hypothalamus and pituitary detect any changes in bioavailable testosterone and adjust testosterone synthesis accordingly. In contrast, if exogenously administered testosterone renders a man eugonadal and then there is a subsequent reduction in SHBG concentrations, the total testosterone concentration (bound plus free) will remain the same but the amount of free testosterone will go up and the amount of bound testosterone will go down. In this setting, there will be more bioavailable testosterone for tissue uptake and, if suprathysiologic, the man could develop hyperandrogenism, even though the total testosterone concentration has not changed. Therefore, with SHBG changes, it is particularly important to assess the unbound testosterone concentration using a reliable assay. In CLAR-12011, Day 114 mean C_{avg} for free testosterone was 9.0 ng/dL, mean C_{max} for free testosterone was 23.5 ng/dL, and the range for free testosterone (min-max) was 3.8-27.7 ng/dL (normal range is 3.7-16.6 ng/dL). The Applicant reports that five subjects (4%) had a free testosterone concentration above the upper limit of the reference range on Day 114.

Dihydrotestosterone (DHT): The 5-alpha-reductase enzyme converts testosterone to DHT. DHT is also a potent androgen. In CLAR-12011, 58% of subjects had a Day 114 DHT C_{avg} that exceeded the upper limit of normal and 90% of subjects had a Day 114 DHT C_{max} that exceeded the upper limit of normal. The mean DHT C_{avg} for TU in CLAR-12011 was 1.1-fold above the reference range on Day 114, and the mean ratio of DHT-to-testosterone (based on a ratio of AUCs) was 0.22, which is about twice the upper limit of the reference range. These data are not consistent with the goal of testosterone replacement therapy, which is to replace testosterone and its key metabolites to within the normal range for healthy, eugonadal men.

8. Safety

Safety Database: A total of 377 subjects received at least one dose of oral TU across all clinical studies. Of the 305 subjects who received oral TU in the phase 3 program, 246 completed four months of treatment, 129 completed 12 months of treatment and 69 completed 24 months of treatment. In the phase 3 trials, few subjects were uptitrated to 250 mg twice daily (n=3) or 300 mg twice daily (n=4).

As discussed by Dr. Chen, oral TU has some adverse effects that are consistent with the class of testosterone replacement therapies. This section of the memorandum will focus on unique safety concerns with oral TU as well as safety concerns that appear worse with oral TU

compared to Androgel 1%. These head-to-head data with Androgel 1% come from CLAR-09007 and its 12-month extension, CLAR-12010. Subjects who entered CLAR-12010 continued on the same testosterone treatment they had received during CLAR-09007. When interpreting these comparative data, it is important to consider the following:

- In CLAR-09007, testosterone C_{avg} exposures were higher with oral TU (628 ± 342 ng/dL) than with Androgel (485 ± 20 ng/dL) and the oral TU dosing regimen led to unacceptably high testosterone C_{max} values that substantially exceeded the pre-specified targets. Therefore, this titration algorithm is not proposed for marketing and was subsequently revised for the pivotal phase 3 trial (CLAR-12011). It is possible that differences in safety findings between oral TU and Androgel 1% may, at least in part, be due to these differences in exposures, particularly for adverse effects that are known to be androgen-mediated (e.g., increases in hematocrit). Also, it is unknown how other approved testosterone products compare to Androgel 1% with regard to these safety parameters.
- The number of subjects who entered and completed the ongoing extension study (CLAR-12010) is considerably smaller than the number of subjects randomized into Study CLAR-09007. For example, of the 162 subjects who were randomized to oral TU in Study CLAR-09007, 129 (80%) completed the trial, 88 (54%) entered the extension study, and 26 (16%) completed the extension study at the time of the 120-Day Safety Update to the NDA. The extent of missing data in the extension study considerably limits conclusions that can be drawn from the comparative analyses.

TU and DHTU Concentrations: The Applicant measured TU and DHTU concentrations in the food effect study and in a subset of subjects in CLAR-09007. As discussed by the clinical pharmacology and clinical reviewers, the product leads to serum TU and DHTU concentrations that are substantially higher than serum testosterone and DHT concentrations. As shown in Table 72 in Dr. Chen's review, the ratio of TU to testosterone is about 20:1 based on AUC and about 35:1 based on C_{max}. The ratio of DHTU to DHT is about 75:1 based on AUC and about 120:1 based on C_{max}. Even if TU and DHTU have low relative binding potency to the androgen receptor compared to testosterone and DHT, the large concentrations seen here may have androgenic effects or may compete with testosterone for the androgen receptor. In addition, TU and DHTU are themselves further metabolized to a variety of steroid molecules that could potentially also have pharmacologic effects.

Cardiovascular Risk:

- **Cardiovascular Adverse Events:** As discussed by Drs. Chen and Hirsch, there were a few more cardiovascular adverse events with oral TU compared to Androgel 1% in CLAR-09007, such as coronary artery disease (3 cases vs. 1 case), acute myocardial infarction (2 cases vs. 0 cases) and angina pectoris (2 cases vs. 0 cases). For the 24-month treatment period, including CLAR-09007 and its extension, six subjects reported a serious cardiovascular adverse event (3.7%) with oral TU compared to two subjects (1.3%) with Androgel. These trials were not designed to assess cardiovascular outcomes and incidence rates are low, limiting conclusions. It is not possible to

determine whether the findings are due to co-morbid conditions, random variability, or treatment with oral TU.

- **Blood Pressure:** In the phase 3 trials, the Applicant measured blood pressure in the clinic prior to dosing and, on some days, 4 and 12 hours post-dosing. Subjects were seated for at least three minutes before the measurement. Only single blood pressure measures were obtained at each time point, and there was no specific instruction on the type of sphygmomanometer to use. Also, blood pressures at baseline were measured at only one time point during the day, which does not allow for time-matched analyses when calculating change from baseline (e.g., for the 4-hour and 12-hour post-dosing measurements at some clinic visits). This is an important consideration because blood pressure is not constant over the course of the day – it has a circadian rhythm. Despite these limitations and considerable variability in blood pressure measurements, subjects in CLAR-09007 treated with oral TU had an increase in mean systolic and diastolic blood pressure compared to Androgel 1%. This finding was consistently seen at almost all clinic visits. For Day 365, the Applicant calculated a maximum group difference in systolic blood pressure of 4.8 mmHg and a maximum group difference in diastolic blood pressure of 2.7 mmHg. The Applicant states that these changes may be related to the limitations of the methodologies used to measure blood pressure, and also to sodium retention resulting from the higher testosterone concentrations achieved with oral TU compared to Androgel 1%. The Applicant also notes that blood pressure changes with oral TU in CLAR-12011 were smaller, and appear similar to the changes seen with Androgel 1% in CLAR-09007, based on cross-study comparisons.
- **HDL-Cholesterol:** In CLAR-09007, both oral TU and Androgel 1% resulted in a reduction from baseline in HDL-cholesterol, but the decline was greater with oral TU at all measured time points. For example, the median percent reduction from baseline in HDL-cholesterol was about 25% for oral TU on Day 90 and Day 365 and about 13% for Androgel 1% on Day 90 and Day 365. The percentage of subjects who shifted HDL-cholesterol concentrations from normal at baseline to below the normal range on Day 365 was 57% for oral TU and 32% for Androgel. As shown in Figure 3 in Dr. Chen's review, the reduction in HDL-cholesterol with oral TU in CLAR-12011 appears similar to that seen with Androgel in CLAR-09007, based on cross-study comparisons.
- **Other cardiovascular biomarkers:** The Applicant measured C-reactive protein (CRP) and other less established biomarkers for cardiovascular risk in CLAR-09007 and its extension. CRP was not measured in CLAR-12011. When excluding subjects with CRP >10 mg/L (per the American Heart Association guidelines for assessing cardiovascular risk), there were mean increases from baseline for oral TU (+0.5 mg/L on Day 90/105 and +0.2 mg/L on Day 365), compared to mean decreases in CRP with Androgel 1% (-0.1 mg/L on Day 90/105 and -0.3 mg/L on Day 365).

Hematocrit: In CLAR-09007, both treatment groups had a mean baseline hematocrit of 44% and the highest baseline hematocrit was 48%. In this study, oral TU increased hematocrit to a greater extent than did Androgel 1%. For example, 39% of the oral TU group and 22% of the

Androgel group had a shift from a normal hematocrit at baseline to a high hematocrit on Day 365. At least one hematocrit >54% occurred in 16 subjects (9.1%) in the oral TU group and five subjects (3.1%) in the Androgel group. In CLAR-12011, fewer subjects (2.8%) had at least one hematocrit >54%, which is similar to what was seen with Androgel in CLAR-09007, based on cross-study comparisons.

Available Literature: As discussed in detail by Dr. Chen and summarized by Dr. Hirsch, the Applicant provided published literature for another oral TU product, Andriol, which is marketed in many countries but is not approved in the United States. These published data are not particularly relevant because the studies used doses of Andriol (40-120 mg of TU equivalents twice daily) that are lower than the proposed doses for the Clarus product (158-474 mg of TU equivalents twice daily). Exposures to TU and its metabolites are higher for the Clarus product than Andriol, based on cross-study comparisons.

9. Advisory Committee Meeting

This NDA was discussed on September 18, 2014 at a joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. There were two voting questions and one discussion question.

The committee was first asked whether there is sufficient evidence to conclude that oral TU is effective as testosterone replacement therapy. Eight panel members voted “yes”, 12 panel members voted “no”, and one abstained. The committee was next asked to discuss whether the safety of oral TU has been adequately characterized. Finally, the committee was asked to vote on whether the overall benefit/risk profile of oral TU is acceptable to support approval for testosterone replacement therapy. Four panel members voted “yes” and 17 panel members voted “no”.

The committee raised much of the same concerns that have been mentioned in this memorandum. Concerns with the efficacy findings included the extent of missing data, the failure to meet all key secondary endpoints, the substantial effect of dietary changes on exposures to TU and its metabolites, a starting dose that was too high for a majority of subjects and a dose titration algorithm that forced subsequent exposures to be too low in some subjects. Safety concerns included unfavorable elevations in some cardiovascular risk factors or biomarkers (e.g., blood pressure, HDL-cholesterol), the high variability in exposure related to dietary fat content, and the high concentrations of TU. There was general agreement that safety had not been well characterized.

10. Pediatrics

The Division in consultation with the Pediatric Review Committee (PeRC) agreed with the Applicant’s request for a full waiver from conducting pediatric studies under the Pediatric Research Equity Act (PREA). Hypogonadism is rare in children; therefore, studies of oral TU in the pediatric population are impossible or highly impractical.

11. Other Relevant Regulatory Issues

Financial Disclosures: The only relevant financial disclosure involved two investigators at one site who had received payments from the Applicant totaling approximately \$100,000 for consultative advisory services and/or use of a translated questionnaire. However, as noted by Drs. Chen and Hirsch, this site enrolled a small proportion ((b) (6)) of the total subjects in CLAR-09007 and CLAR-12011, limiting the impact that any potential bias could have on the efficacy or safety conclusions. This same site served as the single bioanalytical site for all pharmacokinetic sample processing and analysis for both phase 3 trials. The Office of Scientific Investigations (OSI) inspected this site, identified no concerns and concluded that the clinical and bioanalytical data were acceptable.

Tradename: The Applicant proposed the tradename (b) (4). The Division of Medication Error Prevention and Analysis (DMEPA) determined that this tradename is unacceptable (b) (4).

(b) (4)
The Applicant can continue to work with DMEPA on alternative tradename(s), which will undergo final review if/when TU can be approved.

Office of Scientific Investigations: OSI inspected three clinical sites (one for CLAR-09007 and two for CLAR-12011). One of these clinical sites also served as the single bioanalytical site for all pharmacokinetic sample processing and analysis for both phase 3 trials. OSI found an unreported protocol deviation at one clinical site involving a subject who should have been dextromethorphan because of an elevated hematocrit. This isolated observation does not impact the overall quality and integrity of the study data. OSI concluded that the data from all three clinical sites and the bioanalytical site are acceptable for review. See the OSI reviews by Young Moon Choi, Ph.D. and Jyoti Patel, Ph.D., for details.

There are no unresolved regulatory issues.

12. Labeling

All labeling is deferred because we will be issuing a Complete Response letter.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
 - Complete Response
- Risk Benefit Assessment

The clinical pharmacology discipline, the biometrics discipline, the clinical reviewer and the Cross-Discipline Team Leader all recommend a Complete Response action because of major deficiencies in the NDA. I concur with this decision.

The Applicant has not shown that their product can reliably replace testosterone in hypogonadal men. The Applicant is proposing that the product be approved for dosing once in the morning and once in the evening with meals. However, based on the food effect study, there are considerable increases in TU, testosterone, and DHT as the fat content in the meal increases. I agree that it is not reasonable to label the product for the fasted state, particularly because this is not practical for the evening dose. However, taking the product with food will not lead to consistent serum TU, testosterone and DHT concentrations unless the fat content for every breakfast and every dinner is kept virtually constant from day to day. It is not reasonable to expect patients to be able to maintain such consistency every day while taking this chronic medication nor is it reasonable to expect that patients will always be able to know the fat content of their meals. With variations in the fat content from day-to-day, a given dose of TU may sometimes be too high (if the fat content of the accompanying meal is high) and sometimes too low (if the fat content of the accompanying meal is low). This could lead to erratic and variable exposures to TU, DHTU, testosterone and DHT from one day to the next. Even if there were no concerns with the Day 114 primary and key secondary efficacy results, the data from the pivotal phase 3 trial would still not be able to address the food effect problem. In this trial, subjects chose foods from a preset menu on the three pharmacokinetic sampling days (Days 30, 72 and 114). For all the other days, subjects had no food restrictions. Investigators used serum testosterone measurements 3-5 hours after the morning dose on Days 30 and 72 to determine whether to titrate the oral TU dose at subsequent visits. On Day 114, subjects underwent 24 hour pharmacokinetic sampling for the primary efficacy endpoint. Therefore, data used for deciding on titration as well as data collected for the primary efficacy and key secondary endpoints were all obtained on days when the subjects chose food from a preset menu. The comparability of the fat content in the meals on these three days to the unrestricted meals that the subjects could eat on the other 111 days of the trial is highly questionable.

The Applicant will need to conduct at least one new phase 3 trial to show that their product consistently leads to reliable exposures to TU and its metabolites in the face of day-to-day variability in meal content that is expected to occur in men who will use the product, if approved. One possible approach, as proposed by Dr. Bashaw, may be for the Applicant to first conduct a timed food effect study to assess whether taking the product before or after food (e.g., 1 hour before food, or 1 or 2 hours after food) could minimize the food effect and lead to more predictable TU, testosterone and DHT concentrations. If this is successful, the next step would be for the Applicant to conduct a new phase 3 trial with subjects following the appropriate timing of product administration in relation to food, as determined from the timed food effect study. This new phase 3 trial will need to consider the optimal starting dose and titration thresholds to ensure that exposures to testosterone and DHT, and the DHT-to-testosterone ratios are within the normal range for eugonadal men. If this new titration algorithm is again expected to lead to considerable reductions in SHBG, the Applicant will need to address whether bioavailable testosterone concentrations

are within an acceptable range for replacement therapy. In addition, this new trial would need to be adequately designed to avoid other deficiencies involving the completed phase 3 trial that were identified by the clinical and statistical reviewers, such as the large extent of missing data for the primary efficacy endpoint. The Applicant will also need to provide convincing evidence that the effects of oral TU on important cardiovascular risk factors, such as blood pressure, hematocrit and HDL cholesterol, do not pose an unacceptable risk to the indicated population.

The Applicant will also be asked to address the following concerns related to the very high TU and DHTU concentrations:

- Whether the product has effects on the human hypothalamic-pituitary-adrenal axis. In the nonclinical repeat-dose toxicity study, dogs developed moderate to marked atrophy of the adrenal cortex with an accompanying reduction in serum cortisol. These findings raise the possibility that TU or its metabolite(s) may have glucocorticoid activity, leading to secondary adrenal insufficiency.
- Whether the findings from the *in vitro* androgen receptor binding study (which compared the affinity of TU, DHTU, testosterone and DHT for the rat androgen receptor) are generalizable to the human androgen receptor.
- Whether the very high concentrations of TU and DHTU compete with testosterone and DHT at the androgen receptor and whether any of the metabolites of TU and DHTU have pharmacologic effects.

In the letter, we will inform the Applicant that we did not review all the bioanalytical data contained in their large, late-cycle submission, which had been missing in the original NDA. The complete analytical validation section of the NDA will need to undergo review in a future resubmission in light of any new trials that are conducted to support the NDA.

Lastly, we will ask the Applicant to consider a study to determine whether co-administration of oral TU with alcohol could alter the bioavailability of TU and exposure to its metabolites. It is possible that alcohol will solubilize the product, leading to increased absorption via the portal vein, a high first pass effect, and reduced TU bioavailability. It is also possible that alcohol could instead enhance absorption via the lymphatics, leading to increased bioavailability of TU. This is not an approvability issue but could impact labeling.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None at this time.

- Recommendation for other Postmarketing Requirements and Commitments

None at this time.

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/s/

HYLTON V JOFFE
11/03/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206-089 (SND-1)
Priority or Standard	Standard
Submit Date(s)	January 3, 2014
Received Date(s)	January 3, 2014
PDUFA Goal Date	November 3, 2014
Division / Office	ODE-3/DBRUP
Reviewer Name(s)	Jin Chen, MD, PhD, MPH
Review Completion Date	October 23, 2014
Established Name	Oral Testosterone Undecanoate
(Proposed) Trade Name	 (b) (4)
Therapeutic Class	Testosterone
Applicant	Clarus Therapeutics Inc.
Formulation(s)	Oral soft capsule
Dosing Regimen	200 mg bid and titration
Indication(s)	Primary and secondary male hypogonadism
Intended Population(s)	Adult males

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT.....	9
1.1	Recommendation on Regulatory Action	9
1.2	Risk Benefit Assessment	9
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies.....	11
1.4	Recommendations for Postmarket Requirements and Commitments	11
2	INTRODUCTION AND REGULATORY BACKGROUND.....	11
2.1	Product Information.....	11
2.2	Tables of Currently Available Treatments for Proposed Indications	12
2.3	Availability of Proposed Active Ingredient in the United States	12
2.4	Important Safety Issues with Consideration to Related Drugs.....	12
2.5	Summary of Presubmission Regulatory Activity Related to Submission	13
2.6	Other Relevant Background Information	13
3	ETHICS AND GOOD CLINICAL PRACTICES	14
3.1	Submission Quality and Integrity	14
3.2	Compliance with Good Clinical Practices.....	14
3.3	Financial Disclosures.....	14
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....	15
4.1	Chemistry Manufacturing and Controls (CMC).....	15
4.2	Clinical Microbiology.....	16
4.3	Preclinical Pharmacology/Toxicology	16
4.3.1	A 13-week toxicity study in Dog	17
4.3.2	In vitro androgen receptor binding (Study 013325-02).....	18
4.3.3	In vitro androgenic/non-androgenic target screening	18
4.4	Clinical Pharmacology	21
4.4.1	Mechanism of Action	21
4.4.2	Pharmacodynamics.....	21
4.4.3	Pharmacokinetics.....	21
4.4.4	PK-related safety concerns:	22
5	SOURCES OF CLINICAL DATA.....	23
5.1	Tables of Studies/Clinical Trials	24
5.2	Review Strategy.....	25
5.3	Discussion of Individual Studies/Clinical Trials	25
5.3.1	Study CLAR-12011 (pivotal Phase 3 trial).....	25
5.3.2	Study CLAR-09007 (12-month, Androgel-controlled Phase 3 trial).....	31
5.3.3	Study CLAR-12010 (12-month extension study).....	35
6	REVIEW OF EFFICACY	36
	Efficacy Summary	36
6.1	Indication	37
6.1.1	Methods	37

6.1.2	Demographics.....	37
6.1.3	Subject Disposition.....	38
6.1.4	Analysis of Primary Endpoint(s).....	39
6.1.5	Analysis of Secondary Endpoints(s).....	39
6.1.6	Other Endpoints.....	41
6.1.7	Subpopulations.....	41
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations.....	41
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	41
6.1.10	Additional Efficacy Issues/Analyses.....	42
7	REVIEW OF SAFETY.....	42
	Safety Summary.....	42
7.1	Methods.....	45
7.1.1	Studies/Clinical Trials Used to Evaluate Safety.....	45
7.1.2	Categorization of Adverse Events.....	45
7.1.3	Pooling of Data Across Studies/Trials to Estimate and Compare Incidence.....	45
7.2	Adequacy of Safety Assessments.....	46
7.2.1	Overall Exposure and Demographics of Target Populations.....	46
7.2.2	Explorations for Dose Response.....	50
7.2.3	Special Animal and/or In Vitro Testing.....	50
7.2.4	Routine Clinical Testing.....	50
7.2.5	Metabolic, Clearance, and Interaction Workup.....	51
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.....	51
7.3	Major Safety Results.....	51
7.3.1	Deaths.....	51
7.3.2	Nonfatal Serious Adverse Events.....	51
7.3.3	Dropouts and/or Discontinuations.....	54
7.3.4	Significant Adverse Events.....	54
7.3.5	Submission Specific Primary Safety Concerns.....	54
7.4	Supportive Safety Results.....	55
7.4.1	Common Adverse Events.....	55
7.4.2	Laboratory Findings.....	60
7.4.3	Vital Signs.....	70
7.4.4	Electrocardiograms (ECGs).....	75
7.4.5	Special Safety Studies/Clinical Trials.....	75
7.4.6	Immunogenicity.....	75
7.5	Other Safety Explorations.....	75
7.5.1	Dose Dependency for Adverse Events.....	75
7.5.2	Time Dependency for Adverse Events.....	76
7.5.3	Drug-Demographic Interactions.....	76
7.5.4	Drug-Disease Interactions.....	76
7.5.5	Drug-Drug Interactions.....	76
7.6	Additional Safety Evaluations.....	77
7.6.1	Human Carcinogenicity.....	77
7.6.2	Human Reproduction and Pregnancy Data.....	77
7.6.3	Pediatrics and Assessment of Effects on Growth.....	77
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	78

7.7	Additional Submissions / Safety Issues.....	78
8	POSTMARKET EXPERIENCE.....	78
8.1	Comparison of PK profile with Andriol.....	78
8.2	Postmarketing surveillance reports:.....	79
8.1.1	VigiBase postmarketing surveillance reports:.....	79
8.1.2	GPRD-based epidemiology study (<i>Jick and Hagberg, 2013</i>):.....	80
8.1.3	Austrian surveillance study (<i>Jungwirth et al 2007</i>).....	81
9	APPENDICES.....	82
9.1	Literature Review of oral TU safety.....	82
9.1.1	Literature search method:.....	82
9.1.2	Literature search outcome:.....	82
9.1.3	Safety evaluation:.....	83
9.2	Literature review of DHT and DHT/T ratio.....	83
9.2.1	Literature search method:.....	84
9.2.2	Literature search outcome:.....	84
9.2.3	DHT concentration and DHT/T ratios.....	84
9.2.4	Potential risks of the elevated DHT and DHT/T ratios.....	85
9.3	Labeling Recommendations.....	88
9.4	Advisory Committee Meeting.....	88
9.5	Clinical Investigator Financial Disclosure (Template).....	88
9.6	Individual Trial Review.....	91
9.6.1	CLAR-12011 (<i>4-month pivotal Phase 3 trial</i>).....	91
9.6.2	CLAR-09007 (<i>12-month “supportive” Phase 3 trial</i>).....	115
9.6.3	CLAR-12010 (<i>12-month extension of CLAR-09007</i>).....	168

Table of Tables

Table 1. Approved products for the treatment of male hypogonadism in the US Market.....	12
Table 2. Selected Study Site for the OSI inspection.....	14
Table 3. Human serum TU and DHTU exposure relative to Dog	17
Table 4. Binding affinity of TU and DHTU to androgen receptor <i>in vitro</i> †	18
Table 5. Inhibition/stimulation ($\geq 10\%$) of androgenic and non-androgenic targets.....	20
Table 6. Clinical trials submitted in this NDA	24
Table 7. Comparison in study design and PK outcome between two Phase 3 trials	26
Table 8. Serum total T and DHT concentrations on Day 30	26
Table 9. PK parameters of serum total T, free T and DHT at the primary endpoint time.....	27
Table 10. Pre-specified analysis of the primary endpoint in Study CLAR-12011	29
Table 11. Subgroup analyses of serum T Cavg on Day 114 by demographics	31
Table 12. Primary and key secondary endpoints in Study CLAR-09007.....	33
Table 13. Proportion of serum TU and its metabolites based on AUC	33
Table 14. Hypogonadism history of study subjects in Phase 3 trials.....	38
Table 15. Serum DHT concentration on Day 114 compared with the normal range	40
Table 16. Serum DHT concentration on Day 90 compared with the normal range	40
Table 17. Integrated oral TU dose group for drug exposure summary.....	46
Table 18. Subject disposition in six completed trials	47
Table 19. Demographics and baseline characteristics in safety population.....	48
Table 20. Safety database of Oral TU submitted in this NDA	49
Table 21. Exposure duration to oral TU doses in the safety population.....	50
Table 22. Serious adverse events in the safety database.....	53
Table 23. Overall AEs in the safety database	55
Table 24. Subjects experiencing any AEs by SOC in the safety database	56
Table 25. AEs reported by $\geq 1\%$ Subjects in the two Phase 3 trials.....	57
Table 26. Mean changes in Hct and Hb in the safety database.....	61
Table 27. Hb/Hct shift from normal baseline to abnormal high in safety population	61
Table 28. Mean Changes in TG, total cholesterol and LDL from baseline	62
Table 29. Comparison of the HDL decreases between the two Phase 3 trials.....	64
Table 30. Abnormal lipid change based on pre-specified criteria	65
Table 31. Subjects with PSA increase by >1.4 ng/ml in Phase 3 trials	68
Table 32. Mean blood pressure increase from baseline at 12 hours post-dose.....	72
Table 33. Mean BP changes from baseline over 24 hours on Day 90.....	74
Table 34. T and DHT exposure and BP changes on Day 30 at the same fixed oral TU dose	75
Table 35. Cross-study PK comparisons between Rextoro and Andriol.....	79
Table 36. Risks of oral TU and injectable TU in the GPRD cohort study	81
Table 37. Published studies on oral TU safety	82
Table 38. Randomized placebo-controlled studies of transdermal DHT-gel from literature	86
Table 39. Questions for the AC discussion and voting.....	88
Table 40. Study schedule and assessment of CLAR-12011	92
Table 41. Normal range of tested hormones in eugonadal males	96
Table 42. Subject disposition in Study CLAR-12011	97
Table 43. Demographics and baseline characteristics in the safety population.....	99
Table 44. Primary endpoint analyses in Study CLAR-12011.....	100

Table 45. Serum total T Cmax on Day 114	101
Table 46. Narrative summary of subjects with serum T Cmax>2500 ng/dL on day 114.....	102
Table 47. PK profile of serum total T over 114 days in PK population	104
Table 48. Duration of serum T total concentrations on Day 114.....	105
Table 49. Subgroup analysis of serum T Cavg	106
Table 50. PK parameters of serum DHT and DHT/T ratios in PK population.....	108
Table 51. PK parameters of serum FSH and LH	110
Table 52. Dose titration on Days 42 and 84 in the safety population	111
Table 53. Percentage of subjects on a given dose on Days 0, 30, 72 and 114 of the study.....	111
Table 54. Laboratory and PK parameters of Subject (b) (6) with SAE (stroke)	113
Table 55. Mean blood pressure changes during the study	114
Table 56. Study Schedule and Assessment.....	117
Table 57. Subject disposition in CLAR-09007	125
Table 58. Demographics of subjects in ITT population	126
Table 59. Primary endpoint analyses in Study CLAR-09007.....	127
Table 60. Percentage of subjects with serum T Cmax in pre-specified range on Day 90/105 ...	128
Table 61. PK profile of serum total testosterone on Day 90.....	129
Table 62. Serum total T concentration at baseline and pre-dose	130
Table 63. Duration (% of 24-hour) of serum total T within the normal range on Day 90/105 ..	131
Table 64. Time-averaged serum total T concentration (Cavg) at the final dose.....	131
Table 65. Subgroup analysis of Serum T Cavg within normal range on Day 90/105	133
Table 66. Serum DHT, T and DHT/T ratio from 24-hour PK on Day 90	134
Table 67. Time-course of serum total T, DHT and DHT/T ratios	134
Table 68. Serum DHT/T ratios (Cavg) at highest maintenance doses of oral TU.....	135
Table 69. DHT/T ratios of Cavg at highest maintenance doses of T-gel	136
Table 70. Cmax of serum DHT.....	136
Table 71. C4-6 of serum DHT concentration (4-6 hours post-AM dose).....	137
Table 72. Serum TU/T, DHTU/TU and DHTU/DHT ratios at oral TU dose of 200 mg	138
Table 73. PK profile of serum TU on Day 90 (12-hour post-AM dose)	139
Table 74. Serum SHBG concentration over 12 months of treatment	142
Table 75. Treatment-Emergent AEs in ≥2% Subjects in the Safety Population	146
Table 76. Subjects with AEs related to T-Cmax>1500 mg/dL in safety population.....	147
Table 77. Serious Treatment-Emergent Adverse Events in Safety Population	148
Table 78. Serious Cardiovascular Adverse Events during the 12-month treatment.....	149
Table 79. Narrative summary of subjects with CV SAEs in Study CLAR-09007	150
Table 80. Discontinuations due to AEs in the safety population.....	152
Table 81. Mean BP changes during 12 months of treatment in safety population	153
Table 82. Prostate volume change on Day 365 in subjects with BPH.....	158
Table 83. Serum hs-CRP concentration in safety population (primary analysis).....	160
Table 84. Applicant’s amendment on the NI Margin	162
Table 85. Applicant’s non-inferiority analysis of CV biomarkers	163
Table 86. Agency’s non-inferiority analysis of “Worse” CV biomarkers.....	164
Table 87. Agency’s non-inferiority analysis of “Worse” CV biomarkers.....	165
Table 88. Cholesterol efflux capacity <i>in vitro</i>	166
Table 89. Schedule of assessment in Study CLAR-12010	171
Table 90. Subject disposition at the Database snapshot date.....	174

Table 91. Extent of exposure at the database snapshot date in the safety population 175
Table 92. Summary of TEAEs up to 24 months in the safety population 176
Table 93. TEAEs occurred in $\geq 2\%$ subjects over 24 months in safety population 177
Table 94. Serious ARs reported during the extension study..... 180
Table 95. Changes in blood pressure and pulse rate from baseline 181
Table 96. Serum PSA changes during the extension study in the safety population..... 182
Table 97. PSA increase >1.4 ng/ml during extension period in safety population..... 183
Table 98. Mean change in the IPSS scores during the 12-month extension study 184
Table 99. CV-associated AEs in the extension study 185
Table 100. Serum hs-CRP profile over 24 months in safety population 186
Table 101. Change in Hb during the 12-month extension study 187
Table 102. Change in Hct during the 12-month extensions study..... 187
Table 103. Subjects with confirmed Hct $\geq 54\%$ during the extension study..... 188
Table 104. Changes in serum lipid profile during the 12-month extension..... 191
Table 105. Change in serum HDL during the 12-month extension study 191
Table 106. Mean serum T and DHT concentrations and DHT/T ratios 192

Table of Figures

Figure 1. Serum DHT concentrations over 12 months of oral TU treatment	28
Figure 2. Serum TU and DHTU profile compared to serum T and DHT.....	34
Figure 3. Mean serum HDL changes from baseline over 24 months in safety population.....	63
Figure 4. Serum hs-CRP change from baseline over 24 months of treatment.....	66
Figure 5. Median Changes in serum PSA from baseline over 24 months of treatment.....	68
Figure 6. Mean blood pressure change from baseline over 24 months in safety population†	71
Figure 7. Mean blood pressure change from baseline over 24 hours post dose on Day 90.....	73
Figure 8. Dose titration of oral TU in Study CLAR-12011	94
Figure 9. Serum T profile of four subjects with Cmax>2500 ng/dL on Day 114.....	102
Figure 10. Serum total T profile following oral TU on Day 114.....	103
Figure 11. Serum DHT profile following oral TU on Day 114	107
Figure 12. Serum SHBG decreases over various dose level of oral TU.....	109
Figure 13. Dose Titration of Oral TU	118
Figure 14. Dose titration of T-Gel	118
Figure 15. Dose titration of oral TU and T-Gel for Days 180-365.....	119
Figure 16. Serum total T profile following oral TU and T-gel on Day 90/105	129
Figure 17. Mean serum T concentration-time profile at various oral TU dose levels	132
Figure 18. Relationship of DHT/T ratios with T Cavg-24hr on Day 90.....	137
Figure 19. PK profile of serum TU and total T following 200 mg oral TU on Day 90.....	140
Figure 20. PK profile of serum DHTU and DHT following 200 mg oral TU on Day 90	140
Figure 21. Serum SHBG profile over 12 months of treatment in safety population	142
Figure 22. Mean serum HDL change from baseline over the 12-month treatment	157
Figure 23. Dose Titration for subjects entering Study CLAR-12010.....	170
Figure 24. Mean PSA change (\pm SD) from baseline over 24 months in safety population.....	183
Figure 25. Mean Hct changes from baseline over 24 months in safety population.....	189
Figure 26. Serum DHT/T ratio profile over the 24 months of dose	194

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical perspective, I recommend a ***Complete Response (CR)*** action for this NDA because efficacy and safety for this product, ***oral TU*** (testosterone undecanoate soft gelatin capsules), has not been established for the proposed indication due to lack of substantial evidence.

1.2 Risk Benefit Assessment

A favorable benefit/risk ratio for the proposed indication has not been demonstrated for this product based upon our review of the Clinical data submitted in this NDA. The deficiencies include:

- 1) Lack of sufficient evidence for efficacy
- 2) Unknown potential risks associated with very high TU and DHTU (dihydrotestosterone undecanoate) exposures
- 3) Known potential risks, such as increased blood pressure and increased hematocrit, associated with DHT (dihydrotestosterone) concentrations and DHT/T ratios above the normal range
- 4) An unmanageable effect of food on testosterone exposure and high variations in testosterone PK (pharmacokinetics) parameters, resulting in an inability to write labeling that will provide reliable guidance for dosing

The proposed oral TU capsule is a pro-drug with high lipophilicity. Its pharmacologic effect is highly dependent on reliable adsorption from GI (gastrointestinal) track and conversion to the active metabolites T and DHT (dihydrotestosterone). The PK studies submitted in this NDA indicate that the GI absorption of this product was significantly affected by food and was highly variable. Based on all analyzed metabolites, approximately 6% of the absorbed TU was converted to the androgens, T (5%) and DHT (1%). The majority of the absorbed TU remained as TU (56%) and also as another TU metabolite, DHTU (38%). These moieties remain in the circulation for the entire dosing interval (12 hours). The high TU/DHTU exposure and high variations of PK parameters may potentially impact on safety and efficacy of this product, which, in the opinion of the clinical reviewer, has not been adequately assessed in the current submission. In addition, the product is associated with high DHT concentrations and DHT/T ratios, which also pose safety concerns.

Unsubstantial efficacy evidence:

Although the pre-specified primary analysis of the PK-based primary efficacy endpoint marginally met the criteria for demonstration of efficacy in the pivotal phase 3 trial (Study CLAR-12011), the primary endpoint failed in all sensitivity analyses. In the single pivotal study, CLAR-12011, the reported dropout rate was twice (19.4% vs. 9.3%) the dropout rate reported in the first failed phase 3 trial, Study CLAR-09007. The role of 19.4% dropout in the pre-specified completer's analysis and *post-hoc* sensitivity analyses for the single pivotal trial CLAR-12011 is unclear.

In addition, it is notable that the serum TU and DHTU concentrations were approximately 11 and 8 times higher, respectively, compared to serum total T concentration (by comparison of molar concentrations) and 56 and 38 times higher, respectively, compared to serum DHT concentrations. Although the binding affinities of TU and DHTU for androgen receptors are markedly less than the binding affinities of T and DHT, the concentrations of TU and DHTU may be high enough to compete with T and DHT for androgen receptors and this could potentially impact efficacy of this product. Further, the product's PK profile is such that a significant amount of time during the dosing interval is spent with serum testosterone concentration below the normal range, another factor that may adversely effect the efficacy.

Thus, the efficacy evidence for this product is considered insufficient to support the proposed indication.

Unsubstantial safety evidence:

Although the overall safety profile of this product appears consistent with the testosterone class, the safety database (n=377 hypogonadal adult males) is considered insufficient to conduct an adequate assessment of the potential risks, especially in light of the considerable systemic exposure to TU, DHTU and DHT following oral administration of this product.

In addition, a cardiovascular (CV) safety signal for this product has emerged from the submitted safety database, included increased BP (systolic and diastolic), sporadic serious CV event reports, increased CV biomarkers (such as hs-CRP), and decreased HDL-cholesterol. Additional thorough assessments of BP and other CV risks are warranted for this product prior to its marketing.

A different oral formulation of TU, Andriol capsules, has been marketed outside US for more 20 years. However, the postmarketing safety data and published literature for Andriol is considered not directly relevant to the proposed product because Andriol has lower labeled dosage (4 times lower) and has lower systemic exposure to TU and all its metabolites.

Thus, at this time, the current safety evidence for this product is considered not sufficient to support safe use for the proposed indication.

Substantial food-effect and variations of efficacy endpoints:

High-fat food dramatically increases the absorption of TU, and subsequently T and DHT, from this product. Serum T and DHT were dramatically variable when taken without regard to diet ("regular" meals). The food effect is believed to play at least some role in the high variability observed in serum T concentrations. Other factors, some yet to be fully explained (e.g., potential drug-drug/disease interactions, including effects of co-morbidity and concomitant medications) may contribute to the high variability. Effective measures to limit the high variability and allow for reliable testosterone replacement with clearly labeled dosing instructions have yet to be established. Thus, safe and effective dosing of this product for the proposed indication has not been ensured.

Although an oral formulation for TRT product may offer certain advantages over currently available routes of administration, such as less risk of secondary exposure (vs. topical routes), no injection site reactions (vs. IM and implant formulations), and more convenience, the observed high fluctuations in serum T and DHT associated this oral formulation outweigh these advantages at this time.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

It is premature to provide a recommendation for postmarket REMS at this review cycle.

1.4 Recommendations for Postmarket Requirements and Commitments

It is premature to provide final recommendations on postmarketing requirements and commitments. Nonetheless, the Clinical reviewer tentatively recommends that should this product eventually be approved, that a long-term safety study should be requested, either as a PMR or a PMC, because of the potential risks associated with the chronic and high TU and DHTU exposures associated with the product.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed product, oral formulation of testosterone undecanoate (TU) is immediate-release soft gelatin capsules, containing either 158.3 mg TU (equivalent to 100 mg testosterone) or 237.5 mg TU (equivalent to 150 mg testosterone). (b) (4)

TU is a fatty-acid ester prodrug of testosterone (T-ester), chemically described as 17 β -hydroxyandrost-4-en-3-one undecanoate (C₃₀H₄₈O₃) with molecular weight of 456.7. It is formulated with a self-emulsifying drug delivery system (SEDDES) (b) (4)

The soft gelatin capsule shell contains gelatin, sorbitol, glycerin, purified water, iron oxide red, FD&C Yellow #6, and titanium dioxide.

The TU-SEDDES formulation is designed to increase the absorption of TU via the intestinal lymphatics thereby reducing first-pass hepatic clearance. The prodrug TU is converted to T by endogenous non-specific esterases. The proposed indication for this product is the same as for other approved testosterone replacement therapy products (TRT).

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are 14 testosterone replacement therapy products (as Reference List Drugs) in the US market for the same indication proposed for Rextoro capsules, including 10 NDAs and 5 ANDAs, as summarized in **Table 1**.

Table 1. Approved products for the treatment of male hypogonadism in the US Market

Trade Name	Dosage Form/Strength	Route of Administration	Dosage	NDA ANDA	Holder	Date of Approval
Androgel	T-gel, 1.62%	Transdermal	40.5 mg T qd	22-309	Abbvie	Apr 29, 2011
Androgel	T-gel, 1%	Transdermal	50 mg T qd	21-015	Abbvie	Feb 28, 2000
Axiron	T-solution, 30mg/1.5ml	Transdermal	60 mg qd (30 mg/axilla)	22-504	Eli Lilly	Nov 23, 2010
Androderm	T-film, 2 and 4 mg	Transdermal	4 mg qd nightly	20-489	Watson Labs	Oct 20, 2011
Testim	T-gel, 1%	Transdermal	50 mg qd	21-454	Auxilium	Oct 31, 2002
Fortesta	T-gel (metered), 10 mg/actuation	Transdermal	40 mg qd	21-463	Endo Pharm	Dec 29, 2010
Android	Methyl-T Tablet, 10 and 25 mg	Oral	10-50 mg qd	86-450 87-147	Valeant Pharm	Feb 9, 1981
Testred	Methyl-T Capsule, 10 mg	Oral	10-50 mg qd	83-796	Valeant Pharm	Dec 3, 1973
Aveed	TU injection, 750mg TU/3 ml	Deep IM	750 mg q10-weeks	22-219	Endo Pharms	Mar 4, 2014
Delatestryl	TE injection, 200 mg/ml	Deep IM	50-400 mg q2-4 weeks	09-165	Endo Pharm	Dec 24, 1953
Depo-testosterone	TC injection, 100 and 200 mg/ml	Deep IM	50-400 mg q2-4 weeks	85-635	Pharmacia and Upjohn	July 15, 1979
Testopel	Pellet crystalline T 75 mg	SC implantation	150-450 mg q3-6 months	80-911	Actient Pharms	July 13, 1972
Striant	T-Tablet ER, 30 mg	Buccal	30 mg bid	21-543	Auxilium Pharm	Jun 19, 2003
Natesto	T-gel (metered), 5.5 mg/actuation	Nasal	2 actuations tid	205-488	Trimel BioPharma	May 28, 2014

Source: the FDA's OrangeBook, Drug@FDA and DARRTS

T-gel: testosterone gel; TE: Testosterone Enanthate; TU: testosterone undecanoate; TC: Testosterone cypionate
IM: intramuscular injection; SC; subcutaneous

2.3 Availability of Proposed Active Ingredient in the United States

There is one TU product approved for the US market, TU injection 750 mg/3 ml (*Aveed*). Aveed was approved on March 5, 2014 under NDA 22-219 (by Endo Pharmaceuticals Inc.) for the same indication as proposed for Rextoro (Oral TU).

2.4 Important Safety Issues with Consideration to Related Drugs

The important, well-known safety issues for the TRT class due to androgenic effects of T and DHT include, but are not limited to, the following:

- Hematologic effects: increased hematocrit (Hct) and hemoglobin (Hb), polycythemia, potential for cerebrovascular accident and/or deep venous thrombosis as a result
- Prostate effects: increase prostate volume and PSA, worsening of BPH symptoms
- Lipid effects: decreased HDL-cholesterol

It remains unclear whether testosterone replacement therapy is associated with increased risk of serious cardiovascular outcomes.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following is a very brief overview of the pre-submission regulatory history:

The oral TU capsule product was developed under IND 78,104, which was opened on June 29, 2007. The Division provided guidance at the different stages during clinical development of this product through following milestone communications, particularly on study designs for Phase 3 trials and especially in regard to safety concerns, such as elevated DHT concentrations and elevated DHT/T concentration ratios observed in Phase 2 studies.

- Initial IND:
 - T-con on July 30, 2007
 - AD/IR letter conveyed: non-hold comments
- Type C meetings:
 - March 23, 2009: Phase 2 data and Phase 3 trial plan discussed
 - February 1, 2010: Phase 3 trial design and safety related to elevated DHT/T ratio
- AD/IR letters:
 - March 7, 2008: Comments on Phase 2a protocol (Study CLAR-07004)
 - March 26, 2010: Comments on long-term safety related to high DHT concentrations and DHT/T ratios
 - May 28, 2010: Comments on the first Phase 3 protocol (Study CLAR-09007)
 - August 2, 2010: Comments on time for a single PK sampling for serum T
 - September 11, 2012: Comments on the open-label extension study (Study CLAR-12010) to Study CLAR-09007
 - May 8, 2013: Comments on the second Phase 3 trial (Study CLAR-12011)
- Pre-NDA meeting: October 8, 2013
 - NDA submission format discussed
 - Safety related to high DHT and DHT/T ratios again discussed

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the Clinical related data submitted in this NDA, including the summaries, individual study reports, post-text tables/figures and datasets, were well organized and easy to navigate. The two phase 3 study reports (Studies CLAR-12011 and CLAR-09007) submitted in the original NDA actually excluded the primary efficacy analyses. They instead cross-referenced the PK report located in the Appendix. This was considered an NDA deficiency and the Applicant was asked to correct the incompleteness of the major study reports at the filing review. The Applicant revised the study reports in response to the Division's requests and submitted the final revised study reports on Mach 28, 2014, approximately one month post NDA filing.

3.2 Compliance with Good Clinical Practices

Two clinical sites from the pivotal phase 3 trial Study CLAR-12011 (based on largest enrollments) and the bioanalytical site for PK sample analysis (for both Phase 3 trials, Studies CLAR-12011 and CLAR-09007) were selected for a routine inspection by consultation to the Office of Scientific Investigation (OSI), CDER. The OSI concluded that no outstanding deficiencies in clinical and bioanalytical data were identified from the selected sites (**Table 2**). The final OSI inspections and conclusions are pending for Sites 526 and 515 in CLAR-12011.

Table 2. Selected Study Site for the OSI inspection

Site	Protocol#	Location	Inspection Request	Conclusion
526	CLAR-12011	Tower Urology Tower Research Institute Los Angeles, CA	Routine clinical	pending
515	CLAR-12011	University Urology Associates New York, NY	Routine clinical	pending
524	CLAR-12011	(b) (4)	Routine analytic and clinical	NAI†
102	CLAR-09007			

† Final OST inspections and conclusions are pending as of October 23, 2014

‡ NAI (No Action Indicated) as per the OSI inspection consult memo dated Aug 8, 2014

3.3 Financial Disclosures

The applicant submitted a Final Certification/Disclosure Table listing all investigators who participated in the two phase 3 trials (Studies CLAR-09007 and CLAR-12011). All investigators had no disclosable information (b) (6)

- (b) (6) for both Phase 3 trials and received payment of \$62,679 from the Applicant for advisory services (as a consultant)
 - Study CLAR-12011: (b) (6) subjects were enrolled from this site (Site # (b) (6))
 - Study CLAR-09007: (b) (6) were enrolled from this site (Site # (b) (6))
- (b) (6) for Study CLAR-09007 (Site # (b) (6)) received payment of \$39,500.00 from the Applicant for the use of a validated translated questionnaire and consultant fees.

The subjects enrolled from this site contributed approximately (b) (6) for Study CLAR-09007 and (b) (6) for Study CLAR-12011. (b) (6) site contributed only a relatively small proportion to the analysis populations. Thus, from a Clinical perspective, any potential bias from this site is not likely to have a major effect on safety or efficacy conclusions.

It should be noted that this site was also the single bioanalytic site for all PK sample processing and analysis for both phase 3 trials, therefore, the payments to (b) (6) could be viewed as a source of potential bias for efficacy and/or safety results. However, this site was selected for clinical and analytical inspection and the OSI concluded that No Action was Indicated (NAI) for both clinical and analytic data collected from this site (see the above [3.2 Compliance with Good Clinical Practices](#) for details).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

As per the CMC review team, the Applicant provided sufficient information to assure identity, strength, purity, and quality of the drug product, oral TU soft gelatin capsules 158 mg and 237 mg (100 and 15 mg T equivalents). There are no outstanding CMC issues except for a final recommendation from Office of Compliance based upon inspections of the manufacturing facilities involved in this NDA. See CMC reviewer Dr. Hamid Shafiei for details.

During the clinical development of this product, the formulation was changed from the original hard shell gelatin capsules to the to-be-marketed soft gelatin capsules. Although the final formulation, soft capsules, was used for all phase 3 trials (including Studies CLAR-12011, CLAR-09007 and CLAR-12010), the old formulation, hard-shell capsules, was used in several phase 2 trials, including studies of food effects (Study CLAR-09008) and a 28-day multiple-dose studies (Study CLAR-09009). The PK data from these two phase 2 studies support the food-drug interaction potential (Study 09008) and justify the timing for the first dose titration at ≥ 7 days post initial dose. The Applicant submitted an in vitro comparative dissolution study to “bridge” the old hard capsule to the new soft capsule.

The Biopharmaceutics review team concluded “*the Applicant has provided adequate justification for the differences observed between the hard shell capsule and soft gelatin capsule dissolution profiles using the proposed dissolution method. Since PK data was generated using both the hard shell capsules and soft gelatin capsules, comparative dissolution profiles are*

unnecessary to bridge the hard shell capsule and soft gelatin capsule formulations.” In addition, the Clinical Pharmacology review team stated that the data from the food effects study could be used despite the soft gelatin capsule serving as the test article. Finally, PK data from Phase 3, not from Phase 2, serves as the primary source of efficacy and safety information. See the Biopharmaceutics and Clinical Pharmacology reviews for details.

4.2 Clinical Microbiology

No clinical microbiology data were submitted and none were required.

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology (Pharm/Tox) review team has no outstanding concerns for the proposed product submitted in this NDA.

The Pharm/Tox team described in their review that the Applicant had conducted one animal toxicity study and three in vitro studies. The NDA also contained published data for nonclinical studies of Andriol, a different formulation of oral TU that is marketed outside US. This section of the review summarizes the Pharm/Tox data. The following were nonclinical data submitted to this NDA:

- A 13-week repeated-dose toxicity study in dogs (**Study CLAR-PC-11001**): The study included toxicokinetics of serum T, DHT, TU and DHTU following the to-be-marketed oral TU capsule formulation. The final report was submitted with the original NDA.
- In vitro androgen receptor binding study (**Study 013325-02**): The final report was submitted with the original NDA.
- Literature data of nonclinical study on oral TU (Andriol) in support of the following:
 - Absorption, distribution, metabolism, and elimination of TU
 - Reproductive toxicity
 - Carcinogenicity
- In vitro androgenic and non-androgenic target screening study for TU (**Study AB23843**): The summary results were submitted on May 2, 2014
- In vitro androgenic and non-androgenic target screening study for DHTU (**Study AB25004**): The summary results were submitted on July 24, 2014

The dog toxicity study (**Study CLAR-PC-11001**), the in vitro androgen receptor binding study (**Study 013325-02**) and the Applicant’s literature were reviewed by the Pharm/Tox team (see the Pharm/Tox review in DARRTS for details). The Pharm/Tox team concluded:

“Other than expected androgen related findings in dogs, no significant safety concerns associated with TU were identified in the nonclinical program. Referenced literature and nonclinical data suggest that there should be no non-androgen related findings at the maximal clinical dose proposed for marketing. Overall the nonclinical program supports approval of this product for the proposed population and indication and a maximum single dose of 475 mg of TU to be administered twice daily.”

It should be noted that the “*maximum single dose of 475 mg of TU*” is equivalent to 300 mg T, which is the maximum daily dose of this product for proposed labeling.

The evidence for the Pharm/Tox conclusion came from the 13-week dog study of oral TU and the published literature on Andriol. The Clinical reviewer points out that significant androgenic toxicities were observed at all tested doses of oral TU (see the summary of the dog toxicity study below for details). The multiple of safe exposure to humans based on serum TU AUC was approximately 11-15 but for serum DHTU it was ≤ 1 (Table 3).

4.3.1. A 13-week toxicity study in Dog

The Clinical reviewer here provides a summary of the results from the 13-week dog study. The reader is referred to the Pharm/Tox review for details.

This was a repeat-dose placebo-controlled study in beagle dogs. The animals received the final formulation of oral TU capsules at a dose of 38 mg/kg, 126 mg/kg or placebo for 13 weeks followed by a 4-week recovery period.

Toxic findings: As per the Pharm/Tox review, the dogs who received oral TU at both low and high doses developed toxicities consistent with androgenic effects. Specific toxicity findings included: adrenal cortex atrophy, testes atrophy/degeneration, epididymis-hypospermia, and prostate hypertrophy. The no adverse effective dose (NOAEL) and maximum tolerated dose were not established.

PK profile of serum TU and DHTU in dog: Based on TK/PK comparisons presented in the Pharm/Tox review, dogs receiving the 126 mg/kg dose had systemic TU exposures (by AUC) that were approximately 11 times higher than exposures seen in humans given a single oral TU dose of 200 mg, whereas the DHTU exposures in dogs and humans were similar (Table 3).

Table 3. Human serum TU and DHTU exposure relative to Dog

PK Parameter	Serum TU			Serum DHTU		
	Human	Dog [†]	Ratio (D/H) [‡]	Human	Dog [†]	Ratio (D/H) [‡]
AUC (ng.h/ml)	1103.5	12,067	11x	736.9	645	~1x
Cmax (ng/ml)	329.2	5,031	15x	147.3	166	~1x

Source: From Table 72 in this review and the toxicokinetics (TK) review of the 13-week dog toxicity study (Study CLAR-PC-11001) in the pharm/tox review.

[†] The Dog TK was based on a single dose of oral TU at 126 mg/kg on Day 90.

[‡] D/H: the ratio of dog to human

4.3.2 In vitro androgen receptor binding (Study 013325-02)

The Clinical reviewer here provides a summary of the results from the in vitro androgen binding studies. The reader is referred to the Pharm/Tox review for details.

The Applicant conducted an *in vitro* androgen receptor (AR) binding study using a commercially-available *PolarScreen AR Fluorescence Polarization Assay*.

[Reviewer’s Comment: The AR in the assay system was a rat recombinant AR protein and its compatibility to human ARs in terms of binding and activities to AR ligands is unknown. See the Pharm/Tox review for interpretations, assessment of acceptability, and additional details.]

The AR binding affinity was about 81 times lower with TU and 143 times lower with DHTU compared with T (Table 4).

[Reviewer’s Comment: Although the AR binding affinity was low for TU and DHTU, the substantially high serum TU and DHTU exposures may still potentially compete for AR binding sites with T and DHT which theoretically could pose either agonistic (intrinsic) or antagonistic (to T) effects. Potential competitive androgenic interaction with T and DHT could potentially impact efficacy and safety of this product.]

Table 4. Binding affinity of TU and DHTU to androgen receptor *in vitro*†
(From the Applicant’s Table 1 in Study 013325-02)

	T	DHT	TU	DHTU
IC50 (nM)	7.04	8.51	573	1005
Relative Binding Affinity	100%	83%	1.23%	0.7%
Ki (nM)‡	7.4	9.0	603	1058

† Using “*PolarScreen™ Androgen Receptor Competitor Assay*” kit. The final 40- μ l assay volume contained 1 nM fluorescence-labeled androgen ligand (L), 25 nM recombinant (rat) androgen receptor (R) and test drugs at various concentrations

‡ Converted by this reviewer with the formula: $K_i = IC_{50} / [1 - (L/K_d)]$, where $K_d (L/R) = 20 \pm 10$ nM (according to the assay kit labeling)

4.3.3 In vitro androgenic/non-androgenic target screening

The Clinical reviewer here provides additional information and comments on the in vitro androgen binding studies. The reader is referred to the Pharm/Tox review for details.

During the review, the Division conveyed concerns related to high TU and DHTU concentrations associated with this product. In responses, the Applicant provided results from two additional in vitro studies that screened for potential androgenic and non-androgenic targets of TU and DHTU. Brief summary of the results were submitted on May 2, 2014 (for TU, Study AB23843) and on July 18, 2014 (for DHTU, Study AB25004).

The study was conducted by (b) (4) using a commercial safety screening kit (b) (4), which contains 13 enzymes and 74 receptors, including the androgen receptor.

The potential for competitive receptor binding or inhibitory/stimulator enzyme activity of TU and DHTU was tested using radiolabeled ligands (for receptors or ion channels) or substrates (for enzyme activity) specifically designed for each receptor and enzyme in the assay kit. The tested concentration of TU and DHTU was 10 uM, which was approximately 10 and 13 times, respectively higher than the upper-bound of 95% CI of Cmax of serum TU and DHTU in humans at the to-be-marketed dose.

The TU testing results: Competitive receptor binding or enzyme activity changes (inhibited shown as “-”, and stimulated shown as “+”) of $\geq 10\%$ are summarized in **Table 5**. The main targets of TU were the androgen receptor, progesterone receptor and the enzyme, acetylcholinesterase (inhibition).

The DHTU testing results: Competitive receptor binding or enzyme activity changes (inhibited shown as “-”, and stimulated shown as “+”) of $\geq 10\%$ are summarized below. The greatest interactions were with the androgen receptor and the calcium channel L-Type.

- Androgen receptor by 29%
- Calcium channel L-type (Phenylalkylamine) by 25%
- Glycine, Strychnine-sensitive by 19%
- Cyclooxygenase COX-1 by 18%
- Calcium channel N-type by 17%
- GABAA, Chloride Channel by 14%
- Adenosine A2A by 14%
- Leukotriene, Cysteinyl CysLT1 by 13%
- Glutamate, Kainate by 13%
- Dopamine D2L by 13%
- Serotonin transporter by 12%
- Phosphodiesterase PDE4 by 12%
- Dopamine D2S by 11%
- Adenosine A1 by 11%
- Calcium Channel L-Type (Benzothiazepine) by -11%

Table 5. Inhibition/stimulation ($\geq 10\%$) of androgenic and non-androgenic targets by TU *in vitro*

(From the applicant's Study AB23843 submitted on May 2, 2014)

Assay Name	Species	Inhibition (-), or Stimulation (+) (%) [†]	IC50 of Reference [‡]
Androgen receptor	Human	-76	2.1 nM Testosterone
Progesterone Receptor	Human	-46	0.53 nM Progesterone
Acetylcholinesterase	Human	-36	0.12 nM Physostigmine
Adrenergic $\alpha 2B$	Human	-17	14 nM Yohimbine
Calcium channel L-Type	Rat	-17	22 nM Methoxyverapamil
GABA _{B1A}	Human	-17	6.4 nM CGP-54626
Glutamate receptor	Rat	-15	5.4 nM Kainate
Norepinephrine transporter	Human	-11	0.93 nM Desipramine
Dopamine transporter	Human	-11	1.7 nM GBR-12909
Serotonin 5-HT3		-11	11 nM MDL-72222
Sodium channel	Rat	-10	610 nM Dibucaine
Serine/threonine kinase	Rat	+19	>10 nM Staurosporine
Vasopressin V1A	Human	+18	0.33 nM Vasopressin
Nicotinic receptor	Human	+17	0.076 nM Epatatidine
Cholecystokinin CCK1	Human	+16	0.95 nM devazepide
Cyclooxygenase COX-2	Human	+16	0.17 nM rofecoxib
Dopamine D2s	Human	+12	0.25 nM spiperone
Serotonin 5-HT2b	Human	+12	290 nM ketanserin
Bradykinin B2	Human	+12	1.8 nM bradykinin
Chemokine CCR1	Human	+11	6 nM MCP-3
GABA _A	Rat	+10	16 nM diazepam
Adenosine transporter	GP	+10	0.85 nM nitrobenzylthioinosine

[†] The inhibition (-%) or stimulation (+%) of 10 μ M TU to radioligand (receptor or ion channel binding) or enzyme substrate (enzyme activity) specifically designed for each enzyme and receptor in the assay kit (b) (4) for example, 0.5 nM [3H]-methyltrienolone used for the androgen receptor binding assay and 10 μ M acetylthiocholine used for acetylcholinesterase activity assay (b) (4) (b) (4)

[‡] The IC50 of "standard reference" (chemical) designed for each particular assay (b) (4) and the data are extracted from the above *Panlabs* webpage.

[Reviewer's Comment: *The Clinical reviewer recommends that these results should be interpreted with caution. The TU and DHTU concentrations (at μ M level) in the assays system were much higher than the expected concentrations in humans. Thus, the assay system may not be directly clinically relevant. In the opinion of the Clinical reviewer, these results do not exclude the possibility that TU and DHTU may non-specifically bind to receptors, and may stimulate or inhibit enzymes. The Clinical reviewer believes that clinically meaningful pharmacological activity of TU and DHTU is unknown despite the *in vitro* testing. It should also be noted that the receptor/enzyme targets in the screening kit were limited to a total of 87 types, which cannot represent all potential clinical targets.*]

4.4 Clinical Pharmacology

The Clinical Pharmacology team concluded that PK profile of serum T and DHT has been adequately characterized in this submission. However, the Clinical Pharmacology team stated that significant food effects and high variation in PK prevented reliable exposures from this product and in addition, adequate dosing had not yet been achieved in the target population. Therefore, Clinical Pharmacology recommended a CR for this NDA.

4.4.1 Mechanism of Action

The active moiety that comes from oral TU for the proposed indication is testosterone (T). T is converted by nonspecific endogenous esterase from TU. In addition, T can be further reduced to another active molecule, dihydrotestosterone (DHT), by 5 α -reductase. Through the same reduction pathway, TU can also be metabolized to dihydrotestosterone undecanoate (DHTU) which can be further converted to DHT. Both T and DHT are potent androgen receptor agonists and can mediate androgenic effects via interaction with intracellular androgen receptors, including normal growth and development, maintenance of the male sex organs, function of the testes, prostate, and seminal vesicle, and secondary sex characteristics (deepening voice, muscular development, facial hair, etc.).

Male hypogonadism results from insufficient endogenous testosterone as shown by low serum T concentrations (usually <300 ng/dL) and hypogonadal signs/symptoms that may include: erectile dysfunction and decreased sexual desire (libido), fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, loss of lean muscle mass, increase in adiposity, and osteoporosis. Oral TU may be viewed as a prodrug (T-ester) that provides T and DHT through oral administration and intestinal lymphatic absorption to correct androgenic deficiency in the hypogonadal males.

4.4.2 Pharmacodynamics

Pharmacodynamics (PD) were assessed in both phase 2 and phase 3 trials, including exploratory efficacy assessments using a Psychosexual Questionnaire, and DEXA scanning to assess bone mineral density and body composition. Pharmacodynamic safety evaluations, including CV biomarkers, hematocrit/hemoglobin, prostate assessment and lipid profiles, were also carried out in the Androgel-controlled, phase 3 trial, Study CLAR-09007. Hematocrit and hemoglobin, prostate, and lipid profile assessments were also conducted in some phase 2 trials. See the individual trial review for Study CLAR-09007 and also the Clinical Pharmacology review for details.

4.4.3 Pharmacokinetics

Pharmacokinetics (PK) of Oral TU was characterized in hypogonadal males in four Phase 2 and two Phase 3 trials, which has been thoroughly assessed by the Clinical Pharmacology review team. See the Clinical Pharmacology review for details. The phase 3 efficacy and safety studies (Study CLAR-12011 as a pivotal phase 3 trial and Study CLAR-09007 as a supportive phase 3

trial) are based upon pharmacokinetic assessments and these studies have also been reviewed by the Clinical Review team. See [Appendix 9.6 Individual Trial Review](#) for details.

The Clinical Pharmacology review team stated concerns related to high variations in T exposure and high TU concentrations. They concluded that reliable systemic exposure to TU, T, DHT and DHTU has not yet been achieved with this product due to:

- Significant food (fat) effects on TU absorption: There is lack of effective instructions for patients.
- High variations in PK (for serum TU, total T, free T, DHT etc.)
- High systemic TU and DHTU exposure.

4.4.4 PK-related safety concerns:

In this section, the Clinical reviewer summarizes the current outstanding PK-related safety concerns:

Food effect: High fat-containing meals increase systemic exposure to TU, T and all of their metabolites (See the Clinical Pharmacology review for details). The high variability observed in PK parameters in the Phase 3 trials, when Oral TU was to be taken with “regular meals” is related at least in part to the impact of food effects. Similarly high variations of systemic exposure to TU and T may be expected in the target population if the product was to be approved under the current circumstances, based upon the food effect, and could impact efficacy and/or safety of this product. Although no restriction was placed on diet during most of the Phase 3 studies, subjects were offered one of 3 meal plans for breakfast, lunch, dinner and snack on the PK sampling day: either “regular”, “vegetarian” or “diabetic”.

Potential alcohol interactions: Although there was no restriction on alcohol use in the Phase 3 studies, based on the physicochemical properties of a fatty acid, TU and the oil and (b) (4) excipients in the Rextoro formulation may dissolve better when taken with alcohol. The enhanced dissolution may increase and/or decrease the TU absorption through lymphatic and/or portal circulation, which has not been assessed in this NDA submission. These potential alcohol effects may impact efficacy and/or safety of this product.

High systemic TU and DHTU exposures: Oral TU results in high systemic exposures (AUC and C_{max}) to TU and DHTU in the target population. The potential risks of such exposure, if any, are unknown. Although the elimination of TU and DHTU from the circulation appears complete based on their PK profiles, the clearance pathway from intra- and extra-vascular compartments is unknown. TU and DHTU (which are highly lipophilic) can easily cross biological barriers to extravascular tissues and may be further metabolized (into T and DHT) in the extravascular tissues. In addition, it is unknown what limits the conversion of TU and DHTU to T and DHT in the circulation. However, potential interactions of TU and DHTU with androgen receptors are less likely because the binding affinity to androgen receptors was about 81 times lower with TU and 143 times lower with DHTU compared with T in an in vitro receptor binding study.

Supraphysiological DHT exposure: In the pivotal Phase 3 trial Study CLAR-12011, the mean serum DHT concentrations were approximately 2x ULN (C_{avg-12}) and 1.1x ULN (at C_{trough}) on Day 30 following a fixed 200 mg twice daily dose of oral TU, and was still slightly above the ULN following a full course of dose titration. While a high DHT exposure may lead to potentially beneficial androgenic effects, the safety risks associated with the supraphysiological DHT exposure are unknown.

Sex hormone binding globulin (SHBG) decrease: Rextoro decreased serum SHBG concentrations from baseline in Phase 2 and 3 trials, and these decreases appeared to be greater than the SHBG decreases observed for Androgel. For example, in the 12-month randomized, Androgel-controlled, Phase 3 trial (CLAR-09007), the SHBG decreased from baseline by approximately 50% in the oral TU group and by 5-12% in the Androgel group. In the 4-month single-arm pivotal Phase 3 trial (CLAR-12011), SHBG decreased by approximately 35%, which is similar to what was observed in the Phase 2 trials. Treatment with oral TU did not decrease serum albumin and total serum protein in Phase 2 trials. There were no clinically significant abnormalities of the liver tests reported in the safety database. A recently-approved TU injection product, Aveed (NDA 22-219), intramuscular TU injection did not demonstrate a decrease in SHBG in clinical trials. It is unknown whether the oral TU-induced SHBG decrease and its underlying causes (decreased production or increased clearance or both) pose any potential safety risk.

Questionable comparability of PK profile with Andriol: Data for Andriol, an oral TU capsule marketed outside US for a number of years for a similar indication, has been cited as support for the safety of Rextoro. However, Andriol has a lower dosage (according to Monograph of Product approved by Health Canada) and provides lower systemic exposure to TU and its metabolites, as shown in published literature (See **Table 35** in [Appendix 9.1 Literature Review of oral TU safety](#) for details). Thus, the safety experience with Andriol from post-marketing reports and published literature is not directly extrapolable to Rextoro.

5 Sources of Clinical Data

The primary source of clinical data to support this product included four Phase 2 studies, two Phase 3 studies, and one Phase 3 study extension, all of which were conducted in adult males with low serum testosterone concentrations at baseline, as summarized in **Table 6**.

The 4-month open-label single-arm study CLAR-12011 was a pivotal Phase 3 trial to establish substantial evidence of efficacy for this product using the proposed to-be-marketed dosing regimen and titration regimen.

The results from the six completed clinical studies were submitted with the original NDA and interim results from the ongoing Phase 3 study extension CLAR-12010 were submitted in the 120-Day Safety Update, followed by additional safety data submitted later during the review cycle.

In addition, the Applicant provided a literature review to support the safety of high systemic exposure to TU, as well as the safety of dihydrotestosterone (DHT) concentrations above the upper limit of normal that are associated with this product.

5.1 Tables of Studies/Clinical Trials

The Applicant submitted six completed clinical trials and one interim report (an ongoing Phase 3 trial extension) to support the proposed indication for Oral TU in this NDA. The completed trials included four Phase 2 trials and two Phase 3 trials. The seven clinical trials are summarized in **Table 6**.

Table 6. Clinical trials submitted in this NDA

Study ID/Phase	Study Design	Subject	Dosage‡	Remark
CLAR-07004 Phase 2a	OL†, single-day dosing, cross-over PK study	N=12 Hypogonadal males Age 53±12 yrs	100 mg TU bid 200 mg TU qd, bid 499 mg TE qd/bid	SEDDS hard capsules Completed in March 2008
CLAR-08005 Phase 2a	OL, 7-day repeated-dose, crossover (TU vs. TU+TE), PK study	N=29 Hypogonadal males Age 49±10yrs	300 mg TU bid 400 mg TU+TE bid 200 mg TU bid 300 mg TU+TE bid	SEDDS hard capsules Completed in Oct 2008
CLAR-09008 Phase 2	OL, single-dose, cross-over, food effects, PK study	N=16 Hypogonadal males Age 44±14 yrs	300 mg TU Fasted and 6-50% fat meals	SEDDS hard capsules Completed in Sept 2008
CLAR-09009 Phase 2	OL, 28-day repeated-dose, PK study (for T-Csteady-state)	N=15 Hypogonadal males Age 48±11yrs	200 mg bid	SEDDS hard capsules Completed in Aug 2009
CLAR-09007 Phase 3	R, OL, 12-month repeated-dose, 2-arm, active-controlled PK and safety study	N=325 (161 oral TU and 160 T-gel) Hypogonadal males Age 55±11 yrs	200 mg TU bid or 5g Androgel 1% x42 days, then titrated up/down	SEDDS soft capsules Completed in April 2013
CLAR-12011 Phase 3 (pivotal)	OL, single-arm, 4-month repeated-dose, PK/safety study	N=144 Hypogonadal males Age 55±11 yrs	200 mg TU bid x42 days then titrated up/down	SEDDS soft capsules Completed in July 2013
CLAR-12010 Phase 3 (ext)*	OL, 12-month extension of CLAR-09007	N=182 (88 Oral TU, 94 T-gel) Hypogonadal males Age 57±11 yrs	Mean daily dose: Oral TU 334±101 mg/day T-gel: 6±2 g/day	SEDD soft capsules Ongoing

Source: From Applicant's Table 1 in the ISS and the 120-day safety update

† OL: open-label; TU: testosterone undecanoate, TE: testosterone enanthate; SEDDS: self-emulsifying drug delivery system;

‡ All doses expressed as testosterone equivalents;

* The interim analysis report with cut-off date Feb 5, 2014 was submitted in the 120-day safety update to this NDA on May 1, 2014 (n=26, or 30% subjects, on oral TU had completed the Day 365 visit), as updated by the Applicant on July 18, 2014, the study completed and database was locked on June 10, 2014.

5.2 Review Strategy

The Clinical review was primarily focused on evaluation of data from the two individual Phase 3 trials (CLAR-09007 and CLAR-12011) as well as the Phase 3 study extension CLAR-12010, in collaboration with the Statistical review team and the Clinical Pharmacology review team. Detailed reviews of each individual phase 3 trial are provided below. See the Statistical and Clinical Pharmacology reviews for further details (such as for sensitivity analyses, food effects, and detailed PK parameters).

5.3 Discussion of Individual Studies/Clinical Trials

The Clinical review was focused primarily on evaluation of data from the two Phase 3 trials (Studies CLAR-09007 and CLAR-12011, final full reports) submitted with the original NDA and one Phase 3 study extension (Study CLAR-12010, interim report) submitted during the NDA review. The review was conducted in collaboration with the Statistical and Clinical Pharmacology review teams. Detailed individual trial reviews are provided for each of the three trials in [Appendix 9.6 \(Individual Trial Review\)](#). The reader is also encouraged to see the Clinical Pharmacology review and the Statistical review for additional details. Following is overall summary and discussion of the three Phase 3 trials.

5.3.1 Study CLAR-12011 (pivotal Phase 3 trial)

This trial was conducted with a revised dose titration algorithm after the first Phase 3 study (See the individual trial review in [Appendix 9.6.2 CLAR-09007](#)) showed unacceptably high serum T concentrations in some patients dosed with oral TU. The main differences between the two phase 3 studies were the timing of single blood draw for serum T post dose, the pre-determined serum T concentration that would prompt dose down-titration, and the pre-determined increment/decrement in dose (**Table 7**).

Study 12011 was a 4-month, open-label, single-arm, dose titration PK study in adult men who had repeated morning serum total T concentration <300 ng/dL. A total of 148 subjects were enrolled and 144 subjects received at least one dose of oral TU capsule.

The subjects were treated with a fixed dose of 200 mg bid for the first 30 days followed by up to two titrations based on serum total T concentrations at 3-5 hours post dose. No clinical efficacy endpoints were planned and none were conducted in this study. The primary efficacy assessment was based on the proportion of subjects achieving average serum total T concentrations within the normal range.

A total of 19.4% subjects discontinued treatment prior to the end of the study (on Day 114). Among the 116 subjects who completed the study with sufficient data for PK evaluation on Day 114, the majority had their oral TU dosage titrated downward to 150 mg bid (50% subjects) or to 100 mg bid (24% subjects). Approximately 23% subjects remained at the initial dosage of 200 mg bid.

Table 7. Comparison in study design and PK outcome between two Phase 3 trials

Study Design and PK outcome	Study CLAR-09007	Study CLAR-12011	Study 09007 vs. Study 12011
Starting dose	200 mg bid x42 days	200 mg bid x42 days	Same
First full PK visit	Day 30	Day 30	Same
Dose titration day	Days 42, 74, 180, 270	Days 42 and 84	Same
Single serum T sample to guide titration	4- 6 hours post-AM dose	3-5 hours post-AM dose	Different
Down-titration			
Serum T (ng/dL)	>1100	>700	Different
Dose decrement	Initial: 100 mg bid Subsequent: 50 mg bid	50 mg BID	Different
Up-titration			
Serum T (ng/dL)	<250	<250	Same
Dose increment	Initial: 100 mg bid Subsequent: 50 mg bid	50 mg bid	Different

PK profile of serum T and DHT:

The serum T and DHT concentrations following oral TU on Day 30 in CLAR-12011 are generally comparable to T and DHT concentrations on Day 30 in Study CLAR-09007 (**Table 8**) because the oral TU dose was fixed at 200 mg bid for the first 42 days in both studies (**Table 7**).

Table 8. Serum total T and DHT concentrations on Day 30

PK on Day 30	Study CLAR-12011	Study CLAR-09007	Difference [†]
T-Cavg (ng/dL)	509.2 ±222.1	606.8 ±299.3	1.2x
T-Cmax (ng/dL)	1106.5 ±707.9	1261.4 ±785.0	1.1x
DHT-Cavg (ng/dL)	137.1 ±65.8	123.6 ±67.0	0.9x
DHT-Cmax (ng/dL)	209.2 ±106.2	195.8 ±129.4	0.9x

Source: From **Table 46**, **Table 50**, **Table 67** and **Table 70** of the individual trial reviews [CLAR-12011](#) and [CLAR-09007](#))

[†] Study CLAR-09007 over CLAR-12011

At the end of dose titration (on Day 114) both serum T and DHT concentrations were reduced as compared to the oral TU group on Day 90 in Study CLAR-09007 (**Table 9**). As shown in **Table 9**, the less aggressive dose titration regimen used in CLAR-12011 resulted in lower serum T-Cavg and lower serum DHT-Cavg as compared to concentrations observed in Study CLAR-09007.

Serum DHT concentrations were similarly reduced by the less aggressive dose titration regimen employed in CLAR-12011. Cross-study comparisons suggest that DHT concentrations observed with oral TU in CLAR-12011 were similar to DHT concentrations observed in the T-gel group in CLAR-09007 (**Figure 1**). However, conclusions based upon these comparisons should be approached with caution as this interpretation is based upon a cross-study comparison.

Table 9. PK parameters of serum total T, free T and DHT at the primary endpoint time in the two Phase 3 trials

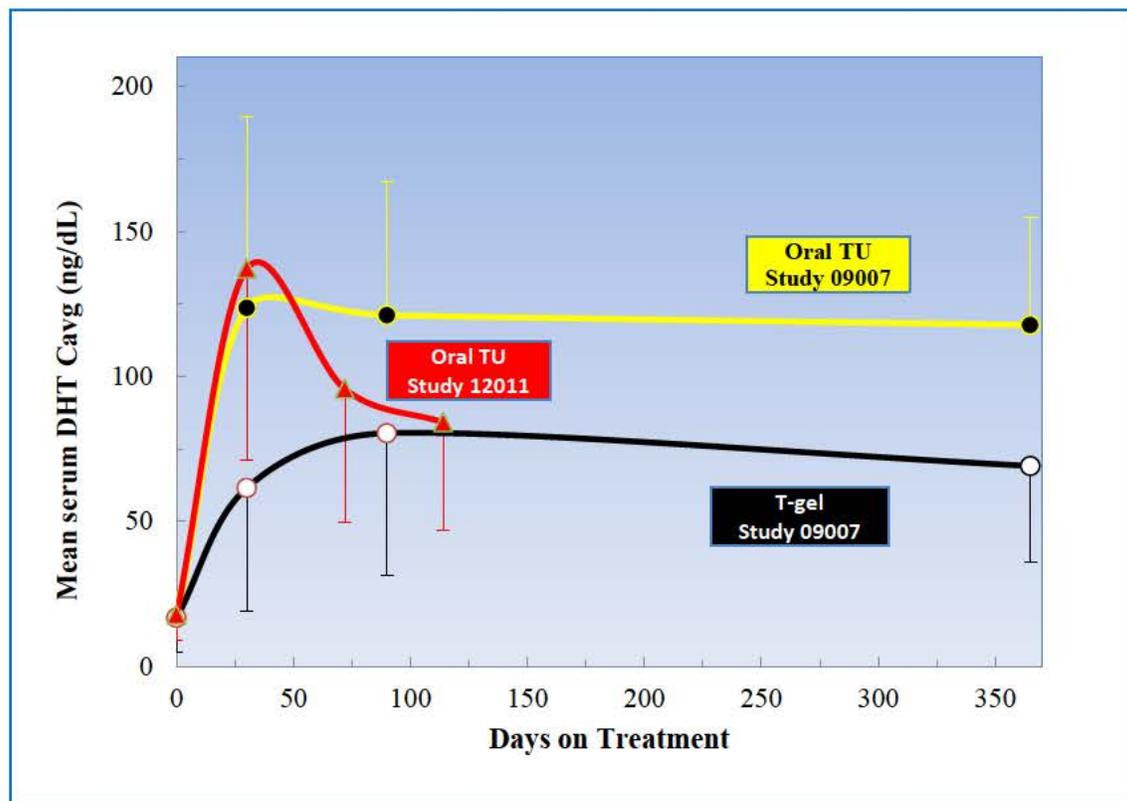
PK Parameter	Oral TU on Day 114 (CLAR-12011) N=116				Oral TU on Day 90/105 (CLAR-09007) N=147				T-gel on Day 90/105 (CLAR-09007) N=150			
	Total T	DHT	DHT/T	Free T	Total T	DHT	DHT/T	Free T	Total T	DHT	DHT/T	Free T
AUC (ng h/dL)	10134.7 ±4111.1	2084.7 ±864.8	0.21	216.9 ±90.2	15079.9 ±8226.4	2994.7 ±1766.4	0.20	320.8 ±189.3	11641.0 ±5282.4	1916.9 ±1108.6	0.16	189.9 ±112.4
Cmax (ng/dL)	1061.7 ±581.1	147.5 ±59.7	0.14	23.5 ±14.1	1676.0 ±1408.5	228.0 ±137.3	0.14	37.0 ±30.5	817.5 ±480.5	124.6 ±73.8	0.15	14.7 ±11.2
Cavg (ng/dL)	422.3 ±171.3	86.9 ±36.0	0.21	9.0 ±3.8	628.3 ±342.8	124.8 ±73.6	0.20	13.4 ±7.9	485.0 ±220.1	79.9 ±46.2	0.16	7.9 ±4.7
Tmax (hour)†	4.2±2.3	4.7 ±2.6		4.2 ±2.2	3.8±1.9	4.9 ±2.7		3.8 ±1.9	5.5 ±3.7	5.2 ±3.9		5.3 ±3.8
C-base (ng/dL)	246.5 ±84.8	17.8 ±8.6	0.076 ±0.034	3.5 ±1.5	209.0 ±108.4	16.8 ±10.8	0.11 ±0.18	3.0 ±1.8	218.9 ±103.7	16.7 ±11.7	0.10 ±0.09	3.2 ±1.7
Cmin (ng/dL)‡	189.3 ±143.3	54.7 ±35.8	0.23 ±0.09	3.8 ±2.8	274.1 ±420.5	80.6 ±73.3	0.21 ±0.10	5.2 ±6.9	430.1 ±223.0	74.2 ±48.4	0.17 ±0.07	6.7 ±4.5

Source: From the Applicant's Tables 23, 34 and 35 in Study CLAR-09007 and Tables 22, 29 and 32 in Study CLAR-12011

† Tmax post-AM dose

‡ Cmin or C12: the concentrations at 12 hours post-AM dose for both oral TU and T-gel groups. Since T-gel was a once daily dosing regimen, the trough concentrations (Cmin) of the PK parameters at the end of 24-hr dosing interval (post-PM on Day 90) were consistent with C12.

Figure 1. Serum DHT concentrations over 12 months of oral TU treatment in evaluable population



Source: Figure generated by an analysis of data from Applicant's Table 32 in the Study CLAR-09007 PK report and from Applicant's Table 29 in the Study CLAR-12011 PK report. Data were mean±SD of serum DHT Cavg-12h.

Primary endpoint analyses:

Pre-specified primary analysis: For the primary analysis, efficacy would be demonstrated if the proportion of subjects with serum total T-Cavg-24hr within the normal range (300-1000 ng/dL) on Day 114 was at least 75% and the lower bound of the 95% confidence interval for this proportion was at least 65%. T Cavg-24hr refers to the average serum T concentration over 24 hours and is calculated by taking the area-under-the-(concentration-time) curve (AUC) for total testosterone and dividing this measurement by 24 hours. The pre-specified primary analysis in the efficacy population (all 116 subjects with sufficient data for PK evaluation on Day 114) demonstrated that the oral TU capsule at the tested dosage and titration regimen just met the primary endpoint: 75.0% subjects achieved serum T Cavg-24hr within the normal range on Day 114. The lower bound of the associated 95% CI was 66.1% (Table 10). The mean serum T Cavg-12hr ranged from 398 ng/dL to 509 ng/dL across the three full PK visits (Days 30, 72 and 114).

Post-hoc sensitivity analyses: Although the pre-specified primary efficacy analysis just met the criteria for demonstration of efficacy, the analysis did not include 19.4% of subjects who did not have serum total T-Cavg-24hr data on Day 114 and who took at least one dose of oral TU. Post-

hoc sensitivity analyses were done to assess the impact of missing data on the consistency of the efficacy results by using all subjects who took study treatment.

These post-hoc sensitivity analyses were performed using all 144 subjects who took at least one dose of oral TU (the safety population) and accounted for missing data in various ways. One approach used last observation carried forward (LOCF), including baseline. Another approach used the worst case scenario (WCS), that is, subjects with missing data were considered failures. The worst case scenario is a conservative approach because it assumes that all missing data were below the threshold for success even though there may be other reasons for the missing data that are unrelated to efficacy. The LOCF approach is not as conservative as the worst case scenario because 17 of the 28 subjects did have post baseline data and 11 subjects did not have any post-baseline data even though they took study product.

For the LOCF analysis, the percentage of subjects with a serum total T-Cavg-24hr within the normal range on Day 114 was 70.8% (102 of 144 subjects) with a 95% confidence interval of 62.7% to 78.1%. For the WCS analysis, the percentage of subjects with a serum total T-Cavg-24hr within the normal range on Day 114 was 60.4% (87 of 144 subjects) with a 95% confidence interval of 51.9% to 68.5%. Both sensitivity analyses did not meet the thresholds for the primary endpoint (**Table 10**).

Table 10. Pre-specified analysis of the primary endpoint in Study CLAR-12011

Analysis	Analysis Population† (N)	Subjects with normal T-Cavg-24h* %	95% CI
Pre-Specified Primary Analysis			
Completer	E (116)	75.0%	66.1%, 82.6%
Post-hoc Sensitivity Analyses‡			
LOCF	S (144)	70.8%	62.7%, 78.1%
WCS	S (144)	60.4%	51.9%, 68.5%

Source: From the Applicant's Table 7 in Study CLAR-12011 and confirmed by the Statistical Review Team

* T-Cavg-24hr: Time-weighted average concentration of serum total T over 24 hours on Day 114. The normal range of serum total T is 300-1000 ng/dL.

† E - Efficacy Population: subjects with sufficient PK data on Day 114

S - Safety Population: subjects received ≥1 dose during the study

‡ LOCF: last observation carried forward

WCS: the worst case scenario, all subjects with missing data on Day 114 considered failures

Key secondary endpoints:

The proportion of subjects with serum T Cmax <1500 ng/dL, serum T Cmax >1800 – 2500 ng/dL, and serum T Cmax > 2500 ng/dL are key secondary endpoints and results for these met the target pre-specified limits expect for T Cmax >2500 ng/dL. Four subjects (3%) had a Cmax >2500 ng/dL, as compared to the targeted result of 0%. In these 4 subjects, the supratherapeutic

exposures were sporadic and transient (e.g., occurring at a single measurement in three of the 4 cases) without reports of clinically meaningful adverse events.

Serum DHT and serum estradiol concentrations are also assessed as secondary endpoints.

The average and maximum DHT concentrations on Day 114 were above the upper limit of normal (ULN), and the DHT/T concentration ratio (>0.20) also appeared to be supraphysiological (**Table 9**). The clinical impact of these DHT results is not definitively known, but they do raise some concern.

As a consequence of the bid dosing regimen and oral route, the time within the normal serum T range (abbreviated as TWNR) is approximately 50% of a 24-hour period. Further, the trough serum total T concentrations (C_{pre} - pre-dose and C_{12} - 12 hours after the dose) were approximately 200 ng/dL, which is below the lower limit of normal (LLN) across all three PK visits. Finally, there are no data from clinical efficacy endpoints to support clinical benefit of these fairly low serum T concentrations. In response to this concern, the Applicant stated that the PK profile for oral TU is consistent with the normal physiologic diurnal rhythm of serum T and that the average serum DHT, a potent androgen, was above the upper limit of normal.

Subgroup analyses were conducted to assess testosterone repletion in important subgroups. Serum total T-Cavg-24hr on Day 114 showed that subjects >65 years old, those with body weight >93 kg and those with $BMI \geq 30$ kg/m² were less likely to have T Cavg reaching the normal range. Also, a lower proportion of black and Hispanic patients achieved T Cavg in the normal range (**Table 11**). However, the sizes of the subsets for age >65 years old, black and Hispanic subjects were small, which limits conclusions from these analyses.

The PK profile of serum FSH, LH and estradiol (E2, including E2/T ratios) evaluated on day 114 appeared consistent with T replacement therapy.

- Mean serum E2 increased from baseline on Day 114 by approximately 50-60% with fluctuation during the 24-hour monitoring and remained within the normal range (7.5-30.6 pg/ml). The E2/T ratios decreased from 8.4×10^3 at baseline to 5.8×10^3 post-PM dose on Day 114.
- Both serum FSH and LH decreased from baseline on Day 114 by more than 70% (based on Cavg) but without fluctuation. This suggests that most patients had primary or “combined” hypogonadism, as opposed to hypogonadotropic hypogonadism alone.

Table 11. Subgroup analyses of serum T Cavg on Day 114 by demographics in the efficacy population (Study CLAR-12011)

Subgroup	Efficacy Population N	Subjects with Cavg 300-1000 ng/dL		
		n	%	95% CI
Age (year)				
≤65	97	73	75.3	65.5%, 83.5%
>65	19	14	73.7	48.8%, 90.9%
Body Weight (kg)				
≤93	58	45	77.6	64.7%, 87.5%
>93	58	42	72.4	59.1%, 83.3%
BMI (kg/m²)				
<30	60	47	78.3	65.8%, 87.9%
≥30	56	40	71.4	57.8%, 82.7%
Race				
Black	12	8	66.7	34.9%, 90.1%
White	95	70	73.7	63.7%, 82.2%
Ethnicity				
Hispanic	16	11	68.8	41.3%, 89.0%
Non-Hispanic	100	76	76.0	66.4%, 84.0%

Source: From the Applicant's Table 18 in Studies CLAR-12011

Discussion of safety results:

The overall clinical safety profile of oral TU with the tested dose regimen in Study CLAR-12011 appeared consistent with the T class, including clinical AE reports and clinical laboratory parameters. However, there appeared to be a small mean increase from baseline in systolic and diastolic BP as well as a 35% reduction in serum SHBG concentration. Finally, the average and maximum serum DHT concentrations, as well as the DHT/T concentration ratio, were above normal. See Section [7 Review of Safety](#) for details.

5.3.2 Study CLAR-09007 (12-month, Androgel-controlled Phase 3 trial)

This was a 12-month, open-label, randomized, Androgel-controlled, parallel-arm study in hypogonadal males with repeated morning serum total T < 300 ng/dL. This study was originally planned as a pivotal trial. However, due to an overly aggressive dose titration regimen, some patients had excessive serum T exposure, as demonstrated by a large number of outliers of serum T Cmax, exceeding the pre-specified criteria. Based on this failed result, an additional phase 3 trial (Study CLAR-12011) was conducted (results summarized in the preceding section). The

main revision to the new phase 3 trial (the above Study CLAR-12011) was to use a less aggressive titration regimen, as summarized in **Table 7**.

In Study CLAR-09007, approximately 320 subjects were randomized (in a 1:1 ratio) to the oral TU group (n=161) or Androgel group (n=160) and received at least one dose of study medication during the 12-month study. The initial dose was 200 mg (T equivalents) bid for oral TU and 5 g of Androgel 1% for T-gel with two dose titrations (Day 42 and 74) based on serum T concentration 4-5 hours after the morning dose on Day 30 and 60, respectively.

Efficacy results:

The target for success for the primary efficacy endpoint was that $\geq 75\%$ of the subjects (with the lower bound of the associated 95% CI $\geq 65\%$) would achieve a serum T $C_{avg-24hrs}$ within the normal range (300 and 1000 ng/dL) and serum T C_{max} within several pre-specified limits (e.g., no subjects with $C_{max} > 2500$ ng/dL) on Day 90. The primary analysis in the efficacy population (all subjects with sufficient data for PK evaluation on Day 90) showed that oral TU at the tested dosage and titration regimen met the primary endpoint, with 83.6% of subjects (lower bound of 95% CI: 76.5%) having a serum total T $C_{avg-24h}$ on Day 90 within the normal range. However, oral TU failed badly for the key secondary endpoint, C_{max} . Approximately 14% (n=20) of subjects in the oral TU group had serum T $C_{max} > 2500$ ng/dL, which far exceeded the pre-specified threshold of 0% for this critical secondary endpoint (**Table 12**). The higher T exposure with oral TU compared to T-gel in Study 09007 should be considered when comparing T-related safety parameters between oral TU and T-gel.

This study had several additional secondary endpoints that assessed clinical pharmacodynamics (PD) measures, including the Psychosexual Questionnaire, the Short Form Health Survey-36 and bone mineral density and total body composition by DEXA. Overall, all PD measures were very modestly improved from baseline and the findings were comparable between oral TU and T-gel. However, we view these findings as exploratory because the study was not double-blinded and many of these endpoints are not sufficiently validated for labeling claims.

Compared to Study CLAR-12011, the mean trough serum T concentration with oral TU in Study CLAR-09007 was slightly higher (274 ng/dL, but still $< LLN$ (**Table 9**)), and the duration of the serum total T concentrations below the LLN was slightly shorter (approximately 40% of the 24-hour dosing or about 10 hours). However, in Study CLAR-09007, T-gel maintained trough serum T concentrations in the normal range with a shorter duration of serum T below the normal range (< 300 ng/dL) as compared to oral TU. The clinical relevance of the daily fluctuation of serum T as seen with oral TU is unknown.

Table 12. Primary and key secondary endpoints in Study CLAR-09007

Serum Total T (ng/dL)	Oral TU (N = 146) % (n)	T-gel (N=149) % (n)	Pre-specified Target
Percent of subjects with normal Cavg* 95% CI Lower bound	83.6% (122) 76.5%	79.2% (118) 71.8%	≥75% ≥65%
C _{max} ≤1500	58.9% (86)	92.6% (138)	≥85%
C _{max} >1500 – 1800	14.4% (21)	2.0% (3)	<10%
C _{max} >1800 – 2500	13.0% (19)	4.0% (6)	<5%
C _{max} >2500	13.7% (20)	0.7% (1)	0%

Source: From the Applicant's Table 17 in the Study CLAR-09007 PK Report

* Based on 24-hour full PK (12 hours post-AM dose and 12 hours post-PM dose) in the efficacy population (subjects with sufficient data for PK evaluation on Day 90); normal T-Cavg is in the 300 to 1000 ng/dL range.

PK profile of serum TU and DHTU

A 12-hour full PK of serum TU and its metabolite DHTU were evaluated in a subset of subjects (n=26) at the final titration dose on Day 90. The detailed PK profile is summarized and discussed in the individual trial review in [Appendix 9.6.2 CLAR-09007](#).

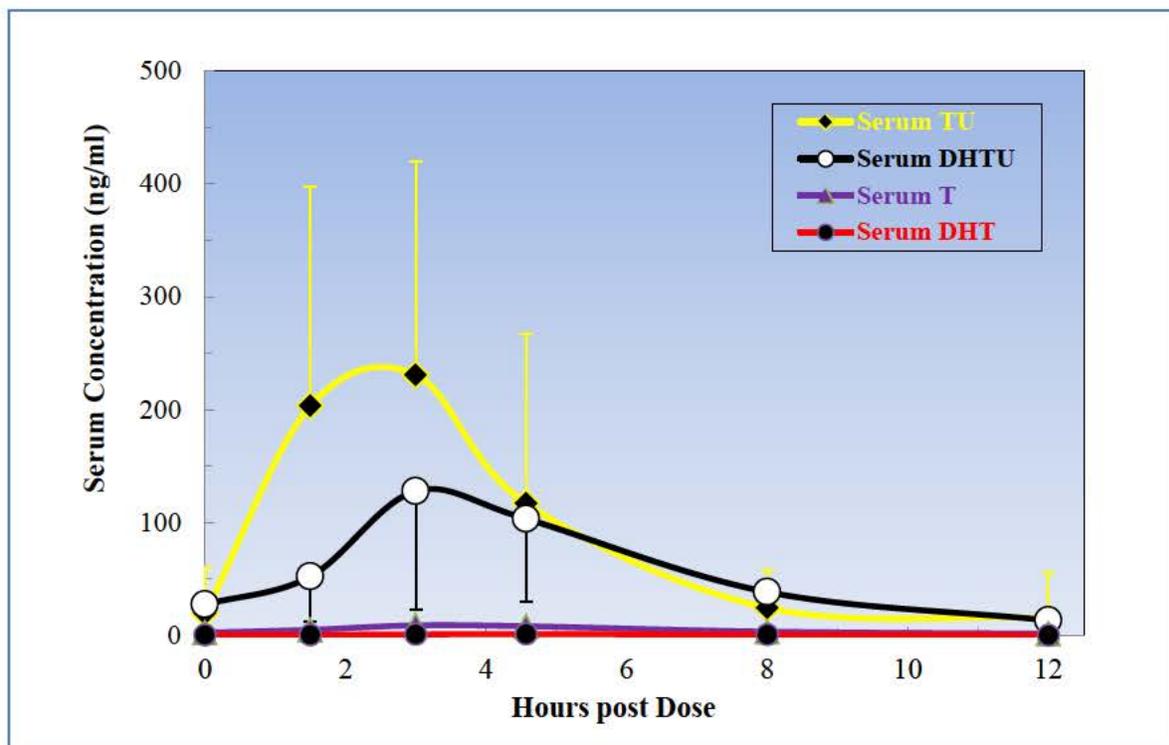
Based on AUC in a molar concentration, the majority (94%) serum exposure following oral TU dose of 200 mg was parent molecule TU and another molecule DHTU; and the active metabolites, T and DHT, were approximately 6% (**Table 13**). Both TU and DHTU appear to be completely eliminated from the circulation (**Figure 2**). However, clearance pathways are not fully known; therefore, the potential for sequestration of TU and DHTU in extra-vascular tissues has not been ruled out.

Table 13. Proportion of serum TU and its metabolites based on AUC

Molecule	% AUC	
	by ng/dL	by nM
TU	58%	56%
DHTU	39%	38%
T	3.1%	5.1%
DHT	0.6%	0.9%
Total	1914 (100%)	4.3 (100%)

Source: from **Table 72** of this review

Figure 2. Serum TU and DHTU profile compared to serum T and DHT following a single oral TU dose of 200 mg (n=21) on Day 90



Discussion of safety results from CLAR-09007:

A total of 161 subjects in the oral TU group and 160 subjects in the T-gel group received at least one dose during the 12-month study. The mean duration of exposure to the study drug was 323 (± 99) days for oral TU and 334 (± 86) days for T-gel with mean daily doses of 350.5 (± 96.1) mg and 5.6 ± 1.6 g, respectively. The overall discontinuation rate during the 12 months was 19% and was balanced between the two groups (20% in the oral TU group and 19% in the Androgel group).

Overall, the safety profile of oral TU in this study appeared consistent with the T class and was similar to T-gel except for a higher reported frequency of GI disorders, including diarrhea and abdominal discomfort in the oral TU group. The GI disorders may be related to the physicochemical nature of this oral TU formulation (TU and/or excipients). See [Appendix 9.6.2 CLAR-09007](#) and [Section 7 Review of Safety](#) for more details.

The following are safety-related concerns based on the results of Study CLAR-09007:

1. Persistently high serum TU and DHTU concentrations
2. Higher serum DHT concentrations and larger DHT/T ratios for oral TU vs. T-gel
3. Greater decreases in SHBG for oral TU vs. T-gel

4. Differences between groups in CV biomarkers:
 - a. Greater increase in mean values of hs-CRP for oral TU vs. T-gel
 - b. More subjects with “worse” CV biomarkers for oral TU vs. T-gel (failed non-inferiority analysis when using the original NI margin)
 - c. Cholesterol efflux capacity decreased for oral TU
5. Though few in number, there was a numerically higher incidence of CV SAEs with oral TU vs. T-gel.
6. Both systolic and diastolic BP increased in both oral TU and T-gel groups at all visits, particularly at 12 hours post-AM dose on Days 90 and 365, with greater increases observed in the oral TU group compared to the T-gel group.

5.3.3 Study CLAR-12010 (12-month extension study)

This study was a 12-month safety extension of Study CLAR-09007, in which the same study design was continued except for no full PK evaluation (only single PK sample at 4-6 hours post-AM dose). The interim analysis report of the study was submitted in the 120-day safety update to this NDA. The study was ongoing when the interim report was submitted and the cut-off date for overall safety was Feb 5, 2014 (up to March 26, 2014 for SAEs). Additional information on more subjects who completed Days 180 and 365 was submitted on June 10, 2014 subsequent to a Division information request. The related safety sections of this review are accordingly updated based on the Applicant’s response. See [Appendix 9.6.3 CLAR-12010 \(12-month extension of CLAR-09007\)](#) and [Section 7 Review of Safety](#) for details.

A total of 182 subjects who completed the first 12-month study (Study 0CLAR-09007) entered the 12-month extension study. All subjects were from the study sites in US, with n=88 on oral TU and n=94 on T-gel. At the time of the interim report contained in the 120-Day safety update, the number of subjects who completed the Day 270 visit was 76 (approximately 86%) on oral TU and 68 (approximately 72%) on T-gel, while the number completing the Day 365 visit was 26 (approximately 30%) and 24 (approximately 26%) on T-gel (n=24). The overall discontinuation rate was 17% on oral TU and 28% on T-gel. The mean exposure to the study drug in both groups was approximately 9 months, 276 days on 334.1 mg/day oral TU and 270.5 days on 6.1 g T-gel. However, detailed information on dosage, exposure and dosing compliance was not provided.

Of note, on June 14, 2014, the Applicant informed the Division that in the oral TU group, n=79 subjects had completed the Day 180 visit and n=69 had completed the Day 365 visit. The Applicant stated that no new safety signals had emerged in that additional long-term experience.

Discussion of safety in CLAR-12010:

Interpretation of the safety data in CLAR-12010 is made difficult by the extensive discontinuation rate and substantial amount of missing data. A large number of the originally randomized patients in Study 09007 did not continue into the extension and a small percentage had data out to extension day 365 (overall Day 730). Approximately 54% (n=86) subjects on the oral TU group and 57% (n=92) subjects in the T-gel group entered the extension study.

Nonetheless, the AE profile from the 12-month extension study CLAR-12010 appears consistent with the T class and similar to the first 12 months in both treatment groups. The incidences of all AEs and TRT-related AEs (including clinical laboratory parameters) decreased in the second 12 months in both treatment groups but were still slightly higher in incidence in the oral TU group vs T-gel. There were no new AEs clustered under certain SOCs during the second 12 months of treatment. The Applicant provided only a brief summary of the additional experience in 69 subjects out to Day 365 in the extension study, stating that no new safety signals had emerged.

Drug-specific safety:

No particular safety concerns emerged from the second 12-months of therapy in this extension study, including no new information concerning CV events and CV biomarkers. The known potential risks, including prostate effects, hematology, and lipid profiles did not worsen. Overall, those safety parameters appeared to be stable over the 12-month extended treatment with perhaps some improvement and without further progression, although conclusions based on this data are limited by the extensive subject discontinuation and missing data.

6 Review of Efficacy

Efficacy Summary

The Applicant submitted two pharmacokinetic (PK)-based Phase 3 efficacy trials to support the proposed indication, one as a pivotal efficacy trial (Study CLAR-12011) and another as a supportive efficacy trial (Study CLAR-09007). Both Phase 3 trials were designed as open-label, dose-titration PK studies in men who had a repeated morning serum total T <300 ng/dL, with restoration of average serum total T to the eugonadal range as the primary efficacy outcome. The key elements of the study designs were consistent with typical efficacy trials for the T replacement products.

Demographic and baseline characteristics of the study population were similar in both Phase 3 studies with a mean age of 55 years (20-75) and mean body mass index (BMI) of 30 kg/m². Most trial participants were white males. The proportion of baseline medical conditions differed slightly between studies CLAR-12011 and CLAR-09007, including the presence of “pre-diabetes” (31% vs. 39%), diabetes mellitus (17% vs. 19%) and hypertension (45% vs. 41%).

The proportion of subjects with missing data (mostly dropouts) at the time-point of primary endpoint was approximately 19% in the Study CLAR-12011 (on Day 114) and 9% in the Study CLAR-09007 (on Day 90/105). The main reasons for the discontinuations were withdrawal of consent and loss to follow-up.

In the pivotal Phase 3 study (CLAR-12011), the pre-specified threshold for the primary efficacy was just achieved in the sponsor’s pre-specified primary efficacy analysis. The key secondary endpoint, zero subjects with C_{max} > 2500 ng/dL, was not achieved. In addition, the thresholds for primary efficacy were not achieved in *post-hoc* sensitivity analyses that accounted for missing data.

Although the pre-specified primary efficacy analysis met the criteria for demonstration of efficacy, the analysis did not include 19.4% of subjects who did not have serum total T-Cavg-24 data on Day 114 and who took at least one dose of oral TU. *Post-hoc* sensitivity analyses were done to assess the impact of missing data on the consistency of the results by using all subjects who took study treatment. None of the post-hoc analyses demonstrated the required level of efficacy. See the more detailed Review of Efficacy and the Individual Review of Study CLAR-12011 for details.

In the supportive efficacy trial (CLAR-09007), oral TU was administered with a different titration regimen than that used in Study CLAR-12011 and demonstrated efficacy with the pre-specified primary analysis, which was similar to the analysis in CLAR-12011. This analysis did not include 9.3% of subjects who did not have serum total T-Cavg-24 data on Day 90 and who took at least one dose of oral TU. A *post-hoc* sensitivity analysis using all subjects who took at least one dose of oral TU gave similar results. However, the proportion of subjects with excessive maximum serum concentrations (e.g., serum T-Cmax>2500 ng/dL) far exceeded the pre-specified limits. See the more detailed Review of Efficacy and the Individual Review of Study CLAR-09007 for details.

6.1 Indication

The proposed indication for Oral TU (Rextoro) is for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- **Primary hypogonadism (congenital or acquired):** testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- **Hypogonadotropic hypogonadism (congenital or acquired):** idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.

6.1.1 Methods

The efficacy assessment of oral TU are based on analysis of each individual clinical trial without any pooled analysis due to different dose titration regimens and different duration of treatment across all Phase 2 and 3 trials.

6.1.2 Demographics

The demographics and baseline characteristics of the study population in both phase 3 trials appear consistent with the proposed target patient population for TRT class. See the individual trial reviews at [Appendix 9.6.1 CLAR-12011](#) and [9.6.2 CLAR-09007](#) for details.

The study subjects in the two phase 3 trials were adult hypogonadal males with serum total T concentration at the screening visit <300 ng/dL by two repeated morning blood draws. However, the type and diagnosis of hypogonadism were not presented in the study reports and there were also no assessments or criteria for hypogonadal sign and symptom at screening and baseline visits. Based on the Applicant’s medical history dataset, hypogonadism history as assessed by the investigator in the pivotal phase 3 trials Study CLAR-12011 was approximately 32% primary, 10% secondary and 50% combined or undefined (**Table 14**).

Table 14. Hypogonadism history of study subjects in Phase 3 trials

Hypogonadism History	Study CLAR-12011 n (%)			Study CLAR-09007 n (%)	
	All N=144	Age <65 years N=114	Age ≥65 years N=30	Oral TU N=161	Androgel N=160
Primary	46 (31.9)	32 (22.2)	14 (9.7)	57 (35.4)	74 (46.2)
Secondary	14 (9.7)	12 (8.3)	2 (1.4)	28 (17.4)	20 (12.5)
Combined/Undefined	72 (50.0)	58 (40.3)	14 (9.7)	62 (38.5)	57 (35.6)
Missing	12 (8.3)	12 (8.3)	0	14 (8.7)	9 (5.6)

Source: the applicant’s medical history dataset “*ADMH*”, analyzed by the statistical reviewer.

The overall demographics and baseline characteristics were comparable between the two phase 3 trials and between the oral TU group and Androgel-controlled group. The mean ages of the study subjects was 55 years (20-75 years) with a mean BMI of 30 kg/m² (17-38). The majority of subjects were White (79-84%), followed by Black or African American and Asian.

The majority of subjects had at least one co-morbidity based on medical history, including 30-37% with “pre-diabetes”, 17-20% with diabetes mellitus, 45% with hypertension, and 38-44% taking lipid-lowering agents.

6.1.3 Subject Disposition

In the pivotal phase 3 trial Study CLAR-12011, 27 (18.8%) of 144) subjects who received at least one dose of oral TU discontinued from the study and 19.4% of the subjects did not have sufficient PK data to determine average serum total T at the primary endpoint time (on Day 114). The major reason for subject discontinuation was withdrawal of consent (30%) followed by loss to follow-up (19%), and other (19%). Discontinuations related to AEs accounted for 2.1% (n=3) and the dropouts due to Hct >54% (one of pre-specified stopping criteria) was 2.1% (n=3). See the individual trial review at [Appendix 9.6.1 CLAR-12011](#) for details.

In the supportive phase 3 trial Study 09007, the dropout rate at the time of assessment of the primary endpoint (Day 90/105) was 9.3%, half that of the pivotal Phase 3 study. The reasons for subject discontinuation in CLAR-09007 were similar to the reasons reported in the pivotal study. See the individual trial review at [Appendix 9.6.2 CLAR-09007](#) for details.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint pre-specified in both phase 3 trials was consistent with the efficacy endpoint for TRT products: $\geq 75\%$ of subjects have serum total T Cavg-24h within the normal range 300-1000 ng/dL with a lower bound of the associated 95% IC $\geq 65\%$ on Day 114 (Study CLAR-12011) or Day 90/105 (Study CLAR-09007).

The pre-specified primary analysis was the primary endpoint in an efficacy population, which was defined as all subjects who have sufficient PK data of serum total T at the primary endpoint time.

Additional key secondary endpoints were Cmax “outliers”; subjects with Cmax >1500 ng/dL, 1500 to 1800 ng/dL, and >2500 ng/dL.

The result of the primary endpoint in the efficacy population just achieved the threshold for success, 75% subjects with normal T-Cavg24h. In addition, there was a 19.4% discontinuation rate in the study. Therefore, sensitivity analyses were conducted to assess of missing data on the primary efficacy results and overall efficacy conclusions. The success threshold was not achieved in any sensitivity analysis as performed by the Applicant and confirmed by the Agency’s Statistical Review team (see the Statistical review for details). The primary and sensitivity analysis results were summarized in [Section 5 of this review](#) and [Section 9 the individual trial reviews](#).

6.1.5 Analysis of Secondary Endpoints(s)

The key secondary endpoints pre-specified in both phase 3 trials were consistent with a typical PK-based efficacy trial for TRT class, including outliers of Cmax of serum total T and PK profile of T-related hormones (DHT, E2, FSH, and LH). See Section 5 ([5.3.1 Study CLAR-12011](#) and [5.3.2 Study CLAR-09007](#)) and Section 9 ([9.6.1 CLAR-12011](#) and [9.6.2 CLAR-09007](#)) of this review for details.

In Study CLAR-09007, the proportion of subjects with Cmax above the pre-determined thresholds for all Cmax outlier categories, particularly percentage of subjects with Cmax >2500 ng/dL, was far beyond the pre-determined safety thresholds. In Study CLAR-12011, which incorporated a different, less aggressive dose titration regimen, the percentage of subjects with Cmax beyond the pre-determined limits was achieved for T-Cmax <1500 ng/dL and T-Cmax 1800 ng/dL to 2499 ng/dL, but not for T-Cmax ≥ 2500 ng/dL. Four (4) subjects had a transient T-Cmax >2500 ng/dL without developing serious adverse event.

The PK profile of T-related hormones such as DHT, E2, FSH and LH were also assessed.

The serum DHT increased more dramatically as compared with serum T after oral TU treatment in both phase 3 trials. In Study CLAR-12011, subjects having serum DHT concentration beyond the upper limit of normal (ULN) was approximately 58% for Cavg and 90% for Cmax (**Table 15**). In the Androgel-controlled trial Study CLAR-09007, which utilized a more aggressive

titration regimen for oral TU, approximately 76% subjects in the oral TU group had DHT-Cavg >1 ULN while 43% in the Androgel group (Table 16).

Table 15. Serum DHT concentration on Day 114 compared with the normal range in Study CLAR-12011

Serum DHT Range	Baseline DHT N=144	DHT-Cavg N=116	DHT-Cmax N=116
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Normal	94 (65%)	49 (42%)	12 (10%)
< LLN	50 (35%)	0	0
>1x ULN		67 (58%)	104 (90%)
>2x ULN		3 (3%)	43 (37%)
>3x ULN		2 (2%)	9 (8%)
>4x ULN			2 (2%)
>5x ULN			1 (1%)

Source: from the Applicant's dataset "PK_DHT" in Study CLAR-12011
LLN and ULN: lower limit of normal and upper limit of normal of serum DHT 13.7-76.9 ng/dL
Baseline serum DHT concentration: 1-44 ng/dL

Table 16. Serum DHT concentration on Day 90 compared with the normal range in Study CLAR-09007

Serum DHT	Baseline DHT		Cavg (ng/dL)		Cmax (ng/dL)	
	Oral TU N=159	T-gel N=162	Oral TU N=147	T-gel N=148	Oral TU N=147	T-gel N=148
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Normal	87 (55%)	81 (50%)	36 (25%)	84 (57%)	8 (5%)	37 (25%)
< LLN	72 (65%)	81 (50%)	0	0	0	0
>1x ULN			111 (76%)	64 (43%)	137 (93%)	111 (75%)
>2x ULN			37 (25%)	9 (6%)	98 (66%)	39 (26%)
>3x ULN			9 (6%)	2 (1%)	55 (37%)	11 (7%)
>4x ULN					26 (18%)	5 (3%)
>5x ULN					16 (11%)	1 (0.7%)
>6x ULN					7 (5%)	1 (0.7%)

Source: From Applicant's dataset PK_DNT in Study CLAR-09007
Baseline serum DHT concentration: 1-39 ng/dL in the oral TU group and 1-50 ng/dL in the T-gel group

Mean serum DHT was slightly above the upper limit of normal on the day of primary efficacy endpoint analysis.

Results for the other relevant hormones, including serum estradiol (E2), FSH and LH, appeared consistent with TRT replacement.

6.1.6 Other Endpoints

Clinical efficacy endpoints were assessed as exploratory endpoints in Study CLAR-09007 only. CLAR-09007 was a randomized, open-label, Androgel-controlled study. These endpoints included the Psychosexual Questionnaire, body composition and bone mineral density (BMD) by DEXA scan, and the Short Form Health Survey-36. See [Appendix 9.6.2 CLAR-09007](#) for details.

In this study, in general, both oral TU and Androgel treatments showed very slight mean improvements from baseline in these measures. The improvements were comparable between oral TU and Androgel. However, the study was not open-label and not powered for comparisons of these endpoints. In addition, the instruments for these measures have not been adequately validated for assessment of male hypogonadism.

6.1.7 Subpopulations

The subgroup analyses of serum total T-Cavg-24hr at the primary endpoint time were performed by demographics, including age (≤ 65 vs. > 65 years), BMI (< 30 vs. ≥ 30 kg/m²) and Race/Ethnicity in both phase 3 trials. The percentage of Cavg responders were lower in older men (> 65 years), heavier men (BMI ≥ 30 kg/m²), and black and Hispanic men in the pivotal study CLAR-12011. Conclusions based on these analyses are limited due to the small sizes of the subgroups. See the individual trial review in [Section 9](#) for details.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The efficacy evidence and PK parameters to support the proposed dose for this product are based on single and multiple-dose PK studies, including a Phase 2 food-effect study. The food effect study demonstrated a clear effect of fat-containing food on increasing exposure, resulting in high variations in serum testosterone. This factor significantly affects the reliability of the proposed dosage (including the starting dose and titration regimen to ensure that serum T and DHT concentrations remain in an effective and safe range for the proposed hypogonadism indication. The reader is referred to the Clinical Pharmacology review for additional details.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In the Study CLAR-09007, the full PK of serum T and DHT was evaluated during the 12 months of treatment, and in some subjects, serum T and DHT assessments were carried out for 24 months in Study CLAR-12011. At least for 12 months, serum T and DHT concentrations

appeared stable in both oral TU and T-gel groups. There were no trends in accumulating or declining of serum total T, free T and DHT concentration over the course of 12 months of treatment. The minimal changes in exploratory clinical efficacy parameters (sexual function, lean body mass and bone density, and SF-36) also appeared stable over the 12 months in both treatment groups. However, those clinical efficacy measures are not validated for purpose of supporting efficacy for the hypogonadism indication and the study design did not include blinding.

6.1.10 Additional Efficacy Issues/Analyses

Despite treatment with oral TU, the serum total T was below the lower limit of normal (LLN), at or around the baseline hypogonadal level (around 200 ng/dL), for a period of up to 6 hours following each oral TU dose. The clinical significance of this pattern of T exposure is unknown. The Sponsor argues that this pattern may be justified by the diurnal nature of physiological T level in eugonadal males. The Sponsor also remarks that serum DHT concentrations were near ULN during the trough T period. Nonetheless, it is not possible for this reviewer to conclude a clinical benefit of oral TU based on the available evidence.

In addition, the very high levels of serum TU and DHT pose a concern to this reviewer. Potential interactions of TU/DHTU with T/DHT at the level of the androgen receptor are unknown. Although the receptor binding affinities of TU and DHTU are markedly lower than T and DHT, the very high concentrations of TU and DHTU could potentially pharmacologically compete for the androgen receptor with T and DHT. The clinical impact of the potential competitive interactions is unknown.

7 Review of Safety

Safety Summary

The safety data submitted in this NDA to support the proposed indication included seven clinical trials of oral TU and a literature review of published clinical studies on oral TU and DHT (DHT-gel product).

Clinical Trials

The safety database included seven clinical trials: four Phase 2 trials, two Phase 3 trials, and one Phase 3 extension trial. See [Appendix 9.6 Individual Trial Review](#) for details.

All clinical trials had open-label designs and were conducted in adult men who had repeated serum total T <300 ng/dL. While these trials did require an existing diagnosis of hypogonadism, they did not require clinical signs and symptoms of hypogonadism. The mean age of the study population was 54 (\pm 11) years with a mean BMI of 30 kg/m². More than one-half of the subjects had a medical history of “pre-diabetes”, diabetes mellitus or hypertension or were using lipid-modifying medications at baseline.

The safety assessments in the clinical trials included collection of clinical adverse events (AE), routine clinical laboratory tests, vital signs and physical examinations with scheduled and unscheduled on-treatment visits. The safety monitoring also focused on TRT-related risks, including prostate effects, hematology (Hct/Hb), lipid profile, and cardiovascular events.

In the seven clinical trials, a total of 377 subjects received at least one dose of oral TU capsules and 313 subjects completed their studies (approximately 16% dropout rate). The majority of subjects came from the two Phase 3 trials (n=305 on oral TU) with a planned duration of treatment ranging from 4 to 24 months, and the remaining subjects were from four Phase 2 trials (n=72 on oral TU) with short-term exposure (1-28 days). Of the 305 subjects from the Phase 3 trials, 246 completed 4 months, 129 completed 12 months, and 69 completed the additional 12-month extension, with a total exposure duration of 24 months.

The dosing regimen of oral TU in the Phase 3 trials started with 200 mg bid (T equivalents) for 42 days followed by titrations up and down based on serum total T levels at 3-5 hours after the morning dose for Study CLAR-12011, or 4-6 hours after the morning dose for studies CLAR-09007 and CLAR-12010. The mean total daily dose ranged from 334 to 350 mg/day (in bid regimen) with a compliance rate of more than 90%. Most subjects were either titrated down to 150 mg bid or remained at 200 mg bid and few subjects were titrated up to 250 mg bid (n=3) or 300 mg (n=4).

As a comparator, Androgel 1% (T-gel) was given to 160 subjects as a parallel-group in the 12-month randomized, open-label Phase 3 trial Study CLAR-09007 and 92 of them entered into the extension study CLAR-12010. The T-gel dosing regimen followed the FDA-approved labeling. A total of 160 subjects received at least one dose of T-gel, 83% (n=133) completed the 12-month study, and 39% (n=62 of 160) completed the second 12-month extension study. The safety data for oral TU was compared to the safety data from T-gel using the head-to-head data from Study CLAR-09007 and CLAR-12010.

Overall, the AE profile of oral TU, including clinical laboratory parameters, appears consistent with other TRT products. However, based on the head-to-head data with Androgel, some AEs, including some SAEs and some common AEs, as well as some laboratory and vital sign abnormalities were more frequent in those who received oral TU compared to those who received Androgel.

In the oral TU group compared to Androgel, there were a few more CV SAEs, larger blood pressure increases, larger HDL decreases, and larger changes in some other CV biomarkers. The differences between oral TU and T-gel may be related to the higher T exposure in the oral TU group than in the Androgel group (mean T C_{avg-24hrs} for oral TU was 628 ng/dL vs. 485 ng/dL for T-gel) in Study CLAR-09007. It is notable that the exposure to T from Oral TU was reduced in the second Phase 3 study, CLAR-12011 when the dose titration regimen was adjusted. It is also possible that systemic exposure to higher concentrations of DHT, or to the parent molecule, TU, and its metabolite DHTU, may have played some role.

Literature review:

In addition to data from the Phase 3 studies, the Applicant provided results from two literature reviews to support the safety of Rextoro, one pertaining to TU safety in published studies and another pertaining to the supraphysiological DHT concentrations and DHT/T ratios.

The oral TU safety literature review (see [Appendix 9.1 Literature Review](#)): The review included 34 published clinical studies. A total of 1431 hypogonadal males or elderly males 15 to 83 years of age were treated with oral TU (mostly identified as Andriol, which is not approved in the United States but is approved in some foreign countries), The dose ranged from 20 to 200 mg/day of TU, given in divided doses twice daily for durations of 6 to 24 months (except for 33 patients who were treated for 10 years). The primary objective of all studies was to assess the effectiveness of oral TU. Routine safety monitoring (AEs and clinical laboratory tests) was also performed.

The overall AE profile, including laboratory abnormalities, reported in these clinical studies appear consistent with the TRT class except for some non-specific gastrointestinal disorders. However, it is notable that the TU exposure from the oral TU products in those studies is much lower than the TU exposure that occurs with the proposed dose of Rextoro. Therefore, the safety data for oral TU from these published studies may not be directly related to risk assessment for Rextoro.

The DHT DHT/T ratio safety literature review (see [Appendix 9.2 Literature review](#)): The review included 58 published studies that the Applicant identified from PubMed for the following two comparisons with Rextoro: 1) DHT concentrations and DHT/T ratios with other TRT products as published in the literature, and 2) the safety of supraphysiological DHT concentrations and DHT/T ratios associated with transdermal DHT-gel as reported in the literature. DHT-gel is a topical gel/cream formulation of DHT that has been marketed in some countries outside the U.S. for treating gynecomastia or hypogonadism in men.

According to the Applicant, the DHT concentrations and DHT/T ratios observed in hypogonadal men taking Rextoro appeared comparable to the DHT concentrations and DHT/T ratios observed in hypogonadal men using approved T products (mostly T-gel) as reported in the literature. However, this conclusion is limited by cross-study comparisons. In contrast, in the head-to-head comparison in Study CLAR-09007, the DHT concentrations and DHT/T ratios associated with Rextoro were significantly higher than those associated with T-gel.

The safety of supraphysiological DHT concentrations and DHT/T ratios from treatment with DHT-gel was assessed based on five randomized placebo-controlled trials. A total of 207 subjects (70% healthy males and 30% hypogonadal males) in the five studies completed DHT-gel treatment (25-70 mg/day) for 1-24 months. Serum DHT concentrations increased 3 to 10-fold above the upper limit of normal (ULN) following DHT-gel dosing. According to the Applicant, and as reported in brief in the literature articles, the safety monitoring (AE and routine clinical laboratory) showed no serious adverse prostatic and no serious non-prostatic reactions associated with DHT-gel treatment. According to the Applicant, and as reported in brief in the literature articles, the overall safety profile appeared consistent with known androgenic effects. However, these studies were small, particularly the long-term studies (only 58 patients were treated with

DHT-gel for 24 months), and the literature reports provided limited information on safety results. In addition, significantly increased hematocrit and hemoglobin were reported in trials of DHT-gel; although increased hematocrit and hemoglobin are also reported for TRT.

7.1 Methods

The primary safety evaluation of oral TU is focused on the individual phase 3 trials because of different dose titration regimens and durations of treatment, particularly when compared to T-gel. Analyses using pooling methods were nonetheless performed for all phase 2 and 3 trials as the Applicant submitted such analyses in their ISS.

Safety analyses were based on the Safety population, including all enrolled subjects who received at least one dose of the study drug, which was a total of 377 subjects on oral TU and 160 on T-gel. For all evaluations, the last non-missing measurement obtained prior to the first dose of study drug was considered to be the baseline value.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A total of seven clinical trials were included in the safety evaluation of oral TU. All clinical trials were designed as open-label studies conducted in adult hypogonadal males (defined as serum total T <300 ng/dL and a diagnosis of hypogonadism).

- Six completed clinical trials (4 phase 2 and 2 phase 3) as summarized in **Table 6**.
- The interim analysis report of an ongoing phase 3 extension study (Study CLAR-12010) submitted as a 120-Day Safety Update, followed by further updates/submissions during this review cycle.

7.1.2 Categorization of Adverse Events

The applicant's categorization of adverse events (AE) was based on MedDRA 15.1 dictionary.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety data were pooled in the following categories:

- Phase 2 trials: CLAR-07004, CLAR-08005, CLAR-09008, and CLAR-09009
- Phase 3 trials: CLAR-09007 and CLAR-12011
- Original Phase 3 trial and its extension: CLAR-09007 and CLAR-12010
- All Phase 2 and 3 trials, excluding the extension study CLAR-12010
- All oral TU dose groups: 200-600 mg/day (for drug exposure purposes only) (**Table 17**)

Table 17. Integrated oral TU dose group for drug exposure summary
(From the applicant’s Table 3 in the ISS)

Daily Dose	Dosing Regimen	Study Number
200 mg/day	200 mg T (as TU) QD, 100 mg T (as TU) BID	CLAR-07004, CLAR-09007, CLAR-12011
300 mg/day	300 mg T (as TU) QD, 150 mg T (as TU) BID	CLAR-09008, CLAR-09007, CLAR-12011
400 mg/day	200 mg T (as TU) BID	CLAR-07004, CLAR-08005, CLAR-09009, CLAR-09007, CLAR-12011
500 mg/day	250 mg T (as TU) BID	CLAR-09007, CLAR-12011
600 mg/day	300 mg T (as TU) BID	CLAR-08005, CLAR-09007, CLAR-12011
TU+TE†	300 mg T (as TU+TE) BID, 400 mg T (as TU+TE) BID	CLAR-08005

† A few subjects (n=12) were exposure to oral TE alone at an early phase 2 trial and were not summarized.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The total number of subjects who received at least one dose of the study drug in the clinical development program submitted to this NDA was 377 subjects on oral TU and 160 subjects on T-gel (Table 18). All study subjects were adult men who had repeated morning serum total T <300 ng/dL at the screening visits.

[Reviewer’s Comment: Although all subjects had T < 300 ng/dL at screening, it is notable that 20% of subjects had a T >300 ng/dL at baseline in Study CLAR-12011.]

Most of the 377 patients exposed to oral TU in the pooled phase 2 and 3 trials come from the two Phase 3 trials (the 4-month study CLAR-12011 and the 12-month study CLAR-09007; see Table 20 for details). The T-gel exposure (n=160) data come only from the 12-month study CLAR-09007 and its extension study CLAR-12010, which were studies that compared oral TU to T-gel.

[Reviewer’s Comment: About one-half of the completers from Study CLAR-09007 chose to enter the 12-month extension study (CLAR-12010). This should be taken into consideration when interpreting safety comparisons between oral TU and T-gel from the extension study and when combining data from CLAR-09007 and CLAR-12010.]

Approximately 83% of subjects in the oral TU group (n=313) and the T-gel group (n=133) completed the study in which they were enrolled. The main reason for dropout in the oral TU group was withdrawal of consent (6.6%, n=26) followed by loss to follow-up (3.2%, n=12) and AEs (2.4%, n=9), which were comparable between the Oral TU and the T-gel groups (Table 18).

Table 18. Subject disposition in six completed trials

Disposition	Oral TU N=377 [†]	T-gel N=160 [‡]	Total N=537
Safety population (≥1 dose)	377	160	537
Completed, <i>n</i> (%)	313 (83.0)	133 (83.1)	446 (83.1)
Discontinued, <i>n</i> (%)	64 (17.0)	27 (16.9)	91 (16.9)
Withdrawal of consent	25 (6.6)	15 (9.4)	40 (7.4)
Lost to follow-up	12 (3.2)	5 (3.1)	17 (3.2)
Adverse event	9 (2.4)	3 (1.9)	12 (2.2)
Protocol violation	5 (1.3)	2 (1.3)	7 (1.3)
Noncompliance with study drug	5 (1.3)	0	5 (0.9)
Hematocrit of >54%	5 (1.3)	0	5 (0.9)
Physician decision	2 (0.5)	1 (0.6)	3 (0.6)
Increase in PSA of >1.4 ng/mL	1 (0.3)	1 (0.6)	2 (0.4)

Source: From the Applicant's Table 5 in the ISS

[†] The oral TU exposure (n=377) was pooled from all phases 2 and 3 trials, and primarily came from two Phase 3 trials, the 4-month study CLAR-12011 and the 12-month study CLAR-09007 (see **Table 20** for details).

[‡] The T-gel exposure (n=160) is from the 12-month study CLAR-09007 and its extension study CLAR-12010. Study CLAR-12011 did not have a T-gel comparator arm.

Demographics and baseline characteristics:

The study population in all clinical trials was adult men having serum total T <300 ng/dL in the morning (before 10:00 am) on two repeated blood tests. Although a diagnosis of hypogonadism was required, there were no criteria requiring specific clinical signs and symptoms of hypogonadism for the subjects to enter the clinical trials. The mean baseline serum total T concentration was comparable between the oral TU and T-gel groups, 202 ±88 ng/dL and 201 ±82 ng/dL, respectively (**Table 19**). However, baseline serum T was >300 ng/dL in some subjects. For example, the maximum baseline serum T was 538 ng/dL in the oral TU group vs. 300 ng/dL in the T-gel. The number of enrolled subjects who had baseline serum T >300 ng/dL in the oral TU group was not reported.

Overall, the demographics and baseline characteristics were comparable between the oral TU and T-gel groups (**Table 19**), including mean age, race, BMI, and International Prostate Symptom Scores (IPSS). However, slightly fewer subjects in the oral TU group had “pre-diabetes”/diabetes mellitus and hypertension and used lipid-modifying agents compared to subjects in the T-gel group.

Table 19. Demographics and baseline characteristics in safety population
(From the Applicant's Table 6 in the ISS)

Characteristics	Oral TU N=377	T-gel N=160	Total N=537
Age (years)			
N	377	160	537
Mean (SD)	53.6 (11.3)	54.7 (11.2)	53.9 (11.3)
Median (min, max)	54 (20, 75)	57 (24, 74)	55 (20, 75)
Race, n (%)			
White	319 (84.6)	130 (81.3)	449 (83.6)
Black	40 (10.6)	23 (14.4)	63 (11.7)
Asian	14 (3.7)	6 (3.8)	20 (3.7)
Other	2 (0.5)	1 (0.6)	3 (0.6)
American Indian or Alaska Native	2 (0.5)	0	2 (0.4)
Ethnicity, n (%)			
Hispanic or Latino	50 (13.3)	18 (11.3)	68 (12.7)
Not Hispanic or Latino	327 (86.7)	142 (88.8)	469 (87.3)
BMI (kg/m²)			
N	375	160	535
Mean (SD)	30.2 (4.1)	29.9 (4.0)	30.08 (4.1)
Median (min, max)	30.2 (16.2, 54.5)	30.1 (19.9, 37.3)	30.2 (16.2, 54.5)
Total serum T (ng/dL) at Screening			
N	376	160	536
Mean (SD)	201.9 (87.8)	200.7 (81.8)	201.5 (85.9)
Median (min, max)	211.0 (2, 538)	224.5 (2, 300)	218.0 (2, 538)
Total IPSS at Screening			
N	375	159	534
Mean (SD)	5.1 (4.8)	5.9 (4.8)	5.3 (4.8)
Median (min, max)	4.0 (0, 18)	5.0 (0, 18)	4.0 (0, 18)
Baseline clinical characteristics			
Pre-diabetes mellitus (glucose: 100-125 mg/dL)	113 (30.0)	56 (35.0)	169 (31.5)
Diabetes mellitus (based on medical history)	69 (18.3)	32 (20.0)	101 (18.8)
Hypertension (based on medical history)	152 (40.3)	76 (47.5)	228 (42.5)
Use of statin, fibrate, omega-3 fatty acid, niacin	111 (29.4)	73 (45.6)	184 (34.3)

Dosage and duration of exposure:

Of a total of 377 subjects exposed to oral TU, 305 were from the two Phase 3 trials (including the 12-month extension trial) with a planned duration of treatment ranging from 4 to 24 months (Table 20).

Based on the latest update to the extension Phase 3 trial (CLAR-12010), submitted on July 18, 2014, a total of 69 subjects completed 2 years of treatment, and 79 subjects completed 1.5 years of treatment (Table 20)

Table 20. Safety database of Oral TU submitted in this NDA

Planned Duration	Actual Duration (Day) Mean±SD	Subjects		Oral TU Dose†		Protocol
		≥1 dose	Completed	Planned mg bid	Actual (mg/day) Mean±SD	
Phase 3 trials		305	246			
4 Months	105 ±25	144	246	100-250 mg	346.8±62.8	CLAR-12011
12 Months‡	322 ±99	161	129	100-300 mg	350.5±96.1	CLAR-09007
24 Months	702 ±85	86	69‡	100-300 mg	334.1±100.5	CLAR-12010
Phase 2 trials		72	67			
1 day	3*	12	12	100-200 mg		CLAR-07004
7 days	26.2±6.8*	29	24	200-300 mg		CLAR-08005
1 days	5*	16	16	300 mg		CLAR-09008
28 Days	32	15	15	200 mg		CLAR-09009
Total		377	313			

Source: Summarized from the Review of Individual Phase 3 trials in the Applicant's ISS

† The TU dose was based on T equivalents: 100 mg T = 158.3 mg TU

‡ Updated from the Applicant's July 18, 2014 submission: the extension study CLAR-12010 has been completed with the database locked on Jun 10, 2014 and 69 (80%) subjects in the oral TU group completed the Day 365 visit.

‡ Of 160 subjects who received ≥1 dose of Androgel 1% in the T-gel group, 133 (83% of 160) completed the 12-month study, 92 entered the 12-month extension (CLAR-12010), and 62 (66%) completed the extension.

* With multiple cross-over periods.

The majority of subjects in the Phase 3 trials received oral TU doses ranging between 100-200 mg *bid*. Few subjects were titrated upward to 250 mg (n=3) or 300 mg (n=4) during the 12-month Phase 3 trial (CLAR-09007). In the entire safety database, a small proportion of subjects received oral TU doses at 250 mg *bid* (n=10) or 300 mg *bid* (n=38) (Table 21).

Table 21. Exposure duration to oral TU doses in the safety population

	Daily Oral TU dose (divided to bid), mg/day					
	200 mg	300 mg	400 mg	500 mg	600 mg	TU+TE
Number of Subjects (n)	91	117	358	10	38	26
Dosing Duration (Day)						
Mean ±SD	104 ±137	55 ±57	137 ± 142	121 ±123	43 ±98	14 ±2
Median (min, max)	30 (1, 330)	42 (5, 314)	57 (1, 409)	70 (14, 299)	7 (7, 339)	14 (7, 15)

Source: From the Applicant's Table 8 in the ISS based on six completed trials

7.2.2 Explorations for Dose Response

The dose responses of oral TU were explored based on the final titrated dose (100-300 mg bid) at a visit, and the corresponding serum T exposure (C_{avg} and C_{max}) and safety parameters. As for most TRT therapy products, a titration regimen is needed for Rextoro and is based on the serum T concentration. In both phase 3 trials (CLAR-12011 and CLAR-09007), the serum T concentrations were dose-proportional to the oral TU doses (see the Clinical Pharmacology review for details). The assessed safety parameters (such as Hct/Hb, lipid profile, and prostate effects) appeared to be associated with the mean serum T concentrations (C_{avg}), especially when studies CLAR-09007 and CLAR-12011 were compared (ratio of C_{avg} between those: 1.5) and when oral TU and T-gel are compared in Study CLAR-0007 (ratio of T- C_{avg} between those: 1.3) (Table 9). However, the subsets of subjects received oral TU doses $>/< 200$ mg bid were generally too small and the serum T concentrations showed high variations, making it difficult to provide definitive conclusions from exposure-response and dose-response analyses.

7.2.3 Special Animal and/or In Vitro Testing

To address potential androgenic and non-androgenic effects of high TU and DHTU exposure from this product, the applicant conducted an animal toxicology study and three *in vitro* studies. As summarized in [4.3 Preclinical Pharmacology/Toxicology](#) of this review (also see the Pharm/Tox review for details), the binding affinity of TU and DHTU to androgenic receptor and some other receptors/enzymes were low. However, the potential pharmacological effects of TU and DHT remain unknown, including potential competition with T for binding to androgenic receptors (with potential impact on efficacy and safety). In addition, the screening studies were limited by the number of potential targets include in the assay kits.

7.2.4 Routine Clinical Testing

Safety assessments during the clinical trials included clinical AE monitoring, clinical laboratory tests, vital signs, physical examinations and prostate evaluation. The assessments occurred during periodic study site visits and also were based on subject self-reporting for AEs.

7.2.5 Metabolic, Clearance, and Interaction Workup

No particular metabolism, clearance and drug interactions of oral TU were conducted except for characterization of T and DHT converted from TU. The PK profile of serum TU and DHTU after a single dose of 100-200 mg TU were evaluated in a subset of subjects in Study CLAR-09007 (see Table 72, Table 73, Figure 19 and Figure 20). Although clearance of TU and DHTU from circulation appeared complete (back to baseline around 10-12 hours post dose), it is unclear whether these highly lipophilic molecules are sequestered in the extravascular tissues of the body, and if so, whether there is any further metabolism or binding to proteins.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The following are the clinical AEs typically reported for the T class and these were evaluated as part of routine safety monitoring during the studies, including clinical AE monitoring and related clinical laboratory testing. See [7.4.2 Laboratory Findings](#) of this review for detailed assessment of these AEs:

- Polycythemia and increase hematocrit/hemoglobin
- Prostate effects (including increased PSA, increased prostate volume and worsening BPH symptoms [IPSS])
- Increased blood pressure, including hypertension, and peripheral edema
- Lipid profile changes (particularly decreased HDL)

In addition, evidence for cardiovascular risk was evaluated by all relevant safety parameters in these studies.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during the clinical trials.

7.3.2 Nonfatal Serious Adverse Events

A total of 20 subjects (3.7% of 537) experienced at least one SAE in the overall safety database, consisting of the pooled six completed phases 2 and 3 trials (not including the extension study CLAR-12010), as summarized in **Table 22**. The overall incidence of SAEs appears comparable between the oral TU and T-gel groups (approximately 3.7% in each group).

The majority of SAEs in the oral TU group were reported from the Phase 3 trials, particularly from the long-term Phase 3 trials in which oral TU was concurrently compared with T-gel. The incidences of SAEs were higher in the oral TU group than in the T-gel groups. The overall SAE profile reported from the second 12 months of treatment (in CLAR-12010, completed on Jun 10, 2014) appears stable as compared to the first 12 months of treatment (in CLAR-12011), based on the Applicant's latest update (July 18, 2014).

The incidences of SAEs from the first 12 months of dosing (Study CLAR-09007) are:

- Oral TU (N=161): 6.8% (n=11)
- T-gel (N=160): 3.8% (n=6)

The incidences of SAEs from the second 12 months of dosing (Study CLAR-12010) are:

- Oral TU (N=86): 8.1% (n=7)
- T-gel (N=92): 6.5% (n=6)

The number and incidence of subjects experiencing CV SAEs pooled from the first 12-month study (CLAR-09007) and the second 12-month extension study (CLAR-12010, updated on July 18, 2014, not included in **Table 22**) are:

- Oral TU (N=161): 3.7% (n=6)
 - n=4 from Study CLAR-09007: acute MI (2), angina (1), and coronary artery disease (1)
 - n=2 from Study CLAR-12010: stroke (1) and angina (1)
- T-gel (N=160): 1.3% (n=2)
 - n=1 from Study CLAR09007: coronary artery disease (1)
 - n=1 from Study CLAR-12010: stroke (1)

The incidence of SAEs from the 4-month, single-arm, pivotal Phase 3 trial (Study CLAR-12011) was 1.4% (n=2: cerebrovascular accident, COPD).

All the SAEs had a temporal relationship to the study drug, although they were mostly confounded by underlying medical conditions and/or medications. Most of the SAEs were sporadically reported from various SOC, including sporadic cardiovascular SAEs. The two subjects experiencing acute MI in the oral TU groups (**Table 22**) were adjudicated by the investigators as being “related to study drug”.

[Reviewer’s Comment: The true causality of these two CV SAEs and the other SAEs is difficult to discern due to lack of blinding and a placebo-control in any study. Causality cannot be totally ruled out.]

Table 22. Serious adverse events in the safety database

Protocol/ Subject ID	SAE (Preferred term)	Study Day (Start/Stop)	Action taken with drug	Outcome
Oral TU: n=14 (3.71% of 377)				
08005/ (b) (6)	Osteomyelitis	14/ --	Drug withdrawn	Resolved
09007/ (b) (6)	Pneumonia	76/79	Drug interrupted	Resolved
	Acute MI	78/78	Drug interrupted	Resolved
09007/ (b) (6)	Osteoarthritis	240/267	Dose not changed	Resolved
	Arthralgia	319/322	Dose not changed	Resolved
09007/ (b) (6)	Sinusitis	94/105	Dose not changed	Resolved
09007/ (b) (6)	Gastroenteritis	173/174	Dose not changed	Resolved with sequelae
09007/ (b) (6)	Intervertebral disc degeneration	51/54	Drug interrupted	Resolved
	Basal cell carcinoma	343/	Dose not changed	Not resolved
09007/ (b) (6)	Angina pectoris	54/58	Dose not changed	Resolved
	Coronary artery disease	114/116	Dose not changed	Resolved
09007/ (b) (6)	Coronary artery disease	18/22	Drug withdrawn	Resolved
09007/ (b) (6)	Acute MI	114/117	Drug withdrawn	Resolved
09007/ (b) (6)	Urosepsis	306/311	Drug interrupted	Resolved with sequelae
09007/ (b) (6)	Epilepsy	15/20	Dose not changed	Resolved
	Musculoskeletal pain	103/106	Dose not changed	Resolved
	Lumbar spinal stenosis	236/240	Dose not changed	Resolved
	Spondylolisthesis		Dose not changed	Resolved
	Lumbar radiculopathy		Dose not changed	Resolved
	Nervous system disorder		Dose not changed	Resolved
09007/ (b) (6)	Hypoglycemia	226/308	Drug withdrawn	Resolved
12011/ (b) (6)	COPD	38/43	Dose not changed	Resolved
12011/ (b) (6)	Cerebrovascular accident	116/118	Dose not changed	Resolved with sequelae
T-gel: n=6 (3.75% of 160)				
09007/ (b) (6)	Appendicitis	95/97	Drug interrupted	Resolved
09007/ (b) (6)	Prostate cancer	134/235	Drug withdrawn	Resolved
09007/ (b) (6)	Aortic aneurysm	176/199	Dose not changed	Resolved
09007/ (b) (6)	Brachial plexus injury, Joint injury, Rhabdomyolysis	255	Dose not changed	Not resolved
09007/ (b) (6)	Appendicitis, Peritonitis	74/83	Drug interrupted	Resolved
09007/ (b) (6)	Coronary artery disease	48/49; 84/85	Dose not changed	Resolved

Source: from the applicant's Table 14 in ISS, not including the interim report of Study CLAR-12010 (submitted as 120-day safety update to the NDA).

7.3.3 Dropouts and/or Discontinuations

Approximately 3% (n=18) of subjects discontinued the study treatment due to AEs and this incidence was comparable between oral TU and T-gel groups based on pooled data: 3.4% (n=13) in the oral TU group and 3.1% (n=5) in the T-gel group. The common AEs causing discontinuation appeared to be AEs related to the T class. There were two discontinuations due to cardiovascular adverse events. The individual AEs leading to discontinuation are shown here:

- Oral TU (n=377): 3.4% [n=13: includes polycythemia (2), increased PSA (1), and hypoglycemia (2), acute MI (1), hypertension (1)]
- T-gel (n=160): 3.1% [n=5: includes increased PSA (1), rash (1)]

AE-related dose interruption of study treatment occurred in 3.4% (n=13) of subjects in the oral TU group and 3.1% (n=5) of subjects in the T-gel group. These AEs included polycythemia (n=2), acute myocardial infarction (n=1), and diarrhea (n=1) in the oral TU group, and benign prostatic hyperplasia (n=1), pollakiuria (n=1), and decreased urine flow (n=1) in the T-gel group.

7.3.4 Significant Adverse Events

Most AEs that emerged during the studies were mild or moderate in severity. A total of 21 (3.9%) subjects experienced severe AEs, and almost all were reported in the 12-month randomized Androgel-controlled study CLAR-09007. Only one subject had a severe AE in Study CLAR-12011 (worsening COPD) and only one subject had a severe AE in Study CLAR-08005 (osteomyelitis on right foot).

When comparing oral TU and T-gel groups in Study CLAR-09007, there were more subjects experiencing severe AEs in the oral TU group than in the T-gel group:

- Oral TU (N=161): 14.9% (n=24); the severe AEs were sporadically distributed under the following SOCs: musculoskeletal and connective tissue disorder (n=6), nervous system disorder (n=5), and infection and infestations (n=3). Possibly drug-related significant AEs (as per the investigators' judgment) included increased weight, hypertriglyceridemia and acute MI (SAE).
- T-gel (N=160): 8.1% (n=13); the severe AEs were mostly sporadically distributed under the following SOCs: infections and infestations (n=4), cardiac disorders (n=2) and injury (n=2). No significant AEs were considered related to the study drug as per the investigator's judgment.

7.3.5 Submission Specific Primary Safety Concerns

Although the overall safety profile of oral TU based on the submitted safety database (n=377 on oral TU) appears consistent with the T class and was comparable to T-gel in the 12-month randomized Androgel-controlled trial plus the 12-month extension, the differences between products in PK parameters (e.g. in DHT, TU, DHTU and SHBG concentrations) and the blood pressure increases from baseline were notable. The ultimate clinical impact of these differences is currently unclear.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Based on the pooled safety data, the overall incidence of subjects experiencing at least 1 AE was approximately 59% (of n=377) on oral TU and 63% (of n=160) on T-gel (**Table 23**). The duration of oral TU dosing in the safety database ranged from 1 day to 365 days.

When comparing Oral TU with T-gel in Studies CLAR-09007 and its extension CLAR-12010, the overall incidence of subjects with at least 1 AE was slightly higher in the oral TU group than in the T-gel group (**Table 23**):

- Incidence of all AEs in the first 12 months (CLAR-09007)
 - Oral TU (n=161): 68%
 - T-gel (n=160): 63%
- Incidence of all AEs in the second 12 months (CLAR-12010):
 - Oral TU (n=86): 44%
 - T-gel (n=92): 40%

Table 23. Overall AEs in the safety database

Subject with AE† n (%)	The first 12 months (CLAR-09007)			The second 12 months‡ (CLAR-12010)			4 Months (CLAR-12011)	All trials*
	Oral TU N=161	T-gel N=160	Total N=321	Oral TU N=86	T-gel N=92	Total N=178	Oral TU N=144	Oral TU N=377
Any AEs	110 (68.3)	100 (62.5)	210 (65.4)	38 (44.2)	37 (40.2)	75 (42.1)	70 (48.6)	211 (58.6)
SAEs	11 (6.8)	6 (3.8)	17 (5.3)	7 (8.1)	4 (4.3)	11 (6.2)	2 (1.4)	13 (3.4)
Drug-related AEs	53 (32.9)	36 (22.5)	89 (27.7)	11 (12.8)	13 (14.1)	24 (13.5)	33 (22.9)	103 (27.3)
Drug-related SAEs	2 (1.2)	0	2 (0.6)	0	1 (1.1)	1 (0.6)	0	3 (0.8)
AE-related dropout	8 (5.0)	5 (3.1)	8 (5.0)	1 (1.2)	6 (6.5)	7 (3.9)	3 (2.1)	13 (3.4)
Death	0	0	0	0	0	0	0	0

Source: From Applicant's Table 27 in Study CLAR-09007, Table 6 in Study CLAR-12010, Table 26 in CLAR-12011 and Table 10 in the ISS

† The drug-related AEs were based on the investigator's judgment

‡ based on the cut-off date Feb 5, 2014 of this ongoing extension study submitted with the 120-day safety update

* based on the six completed trials submitted to the original NDA

The AE profile for Oral TU in either short-term or long-term trials appeared consistent with the AE profile for T class. Although there were more SAEs and more AE-related drop-outs for oral TU compared with T-gel in Study CLAR-09007, the overall safety profiles appeared similar between oral TU and T-gel, as shown in Studies CLAR-09007 (12 months), CLAR-12011 (4 months), and when comparing the results from Studies CLAR-09007 (the first 12 months) and CLAR-12010 (extended 12 month).

In the T-gel controlled trials, slightly higher incidences of all AEs or individual AEs as compared to incidences reported in Study CLAR-12011 may be associated with the greater systemic T exposure (and perhaps also due to the increased DHT, TU, and DHTU exposures) from oral TU than from T-gel, as summarized in **Table 9**. The differences in incidences of AEs between CLAR-09007 and CLAR-12011 may also be related to differences in systemic exposure to TU and its metabolites (T, DHT, and DHTU).

The most commonly reported AES were in the following SOC: infections and infestations, gastrointestinal disorders, investigations, musculoskeletal and connective tissue disorders, nervous system disorders, respiratory disorders, and reproductive disorders (**Table 24**).

Table 24. Subjects experiencing any AEs by SOC in the safety database

SOC	Phase 3				Phase 2		Phases 2 & 3	
	Oral TU N=305		T-Gel N=160		Oral TU N=72		Oral TU N=377	
	n	%	n	%	n	%	n	%
Infections And Infestations	59	19.3	33	20.6	11	15.3	68	18.0
Gastrointestinal Disorders	47	15.4	19	11.9	12	16.7	55	14.6
Nervous System Disorders	28	9.2	13	8.1	17	23.6	41	10.9
General Disorders And Administration Site Conditions	30	9.8	8	5.0	10	13.9	37	9.8
Respiratory, Thoracic And Mediastinal Disorders	27	8.9	11	6.9	13	18.1	36	9.5
Musculoskeletal And Connective Tissue Disorders	29	9.5	17	10.6	8	11.1	35	9.3
Investigations	33	10.8	18	11.3	2	2.8	33	8.8
Reproductive System And Breast Disorders	32	10.5	14	8.8	2	2.8	33	8.8
Metabolism And Nutrition Disorders	21	6.9	8	5.0	4	5.6	24	6.4
Injury, Poisoning And Procedural Complications	22	7.2	9	5.6	1	1.4	23	6.1
Blood And Lymphatic System Disorders	19	6.2	9	5.6	2	2.8	21	5.6
Skin And Subcutaneous Tissue Disorders	17	5.6	14	8.8	3	4.2	20	5.3
Vascular Disorders	17	5.6	13	8.1	1	1.4	18	4.8
Psychiatric Disorders	16	5.2	10	6.3	2	2.8	17	4.5
Renal And Urinary Disorders	12	3.9	12	7.5	1	1.4	13	3.4
Cardiac Disorders	9	3.0	2	1.3		0.0	9	2.4
Neoplasms Benign, Malignant And Unspecified	7	2.3	2	1.3		0.0	7	1.9
Ear And Labyrinth Disorders	5	1.6	0	0.0	1	1.4	6	1.6
Eye Disorders	5	1.6	4	2.5	1	1.4	5	1.3
Endocrine Disorders	1	0.3	0	0.0		0.0	1	0.3
Hepatobiliary Disorders	1	0.3	1	0.6		0.0	1	0.3
Immune System Disorders	1	0.3	2	1.3		0.0	1	0.3

Source: From the Applicant's dataset "adae" in ISS, processed using JMP

The most commonly reported AEs (**Table 25**) experienced by $\geq 2\%$ of subjects (based on the oral TU group) were: upper respiratory tract infection (URI), polycythaemia, diarrhoea, nasopharyngitis, peripheral edema, prostatomegaly, hypertension, arthralgia, eructation, back pain and headache.

The incidence of cardiac disorder adverse events was approximately 3% with oral TU treatment versus 1.3% with T-gel treatment. Most of the CV events were reported from the 12-month study CLAR-09007, and included the following AEs, reported by not more than 2 subjects in either treatment group: coronary artery disease, palpitations, cardiac failure congestive, acute myocardial infarction and angina pectoris (**Table 25**).

Table 25. AEs reported by $\geq 1\%$ Subjects in the two Phase 3 trials

SOC/PT	CLAR-09007 & CLAR-12011		CLAR-12011		CLAR-09007			
	Oral TU N=305		Oral TU N=144		Oral TU N=161		T-Gel N=160	
	n	%	n	%	n	%	n	%
Blood And Lymphatic System Disorders	19	6.2	3	2.1	16	8.8	9	5.6
Polycythaemia	15	4.9	1	0.7	14	8.7	6	3.8
Cardiac Disorders	9	3.0	2	1.4	7	3.9	2	1.3
Coronary Artery Disease	3	1.0	0	0.0	3	1.9	1	0.6
Palpitations	3	1.0	1	0.7	2	1.2	0	0.0
Cardiac Failure Congestive	2	0.7	0	0.0	2	1.2	1	0.6
Acute Myocardial Infarction	2	0.7	0	0.0	2	1.2	0	0.0
Angina Pectoris	2	0.7	0	0.0	2	1.2	0	0.0
Gastrointestinal Disorders	47	15.4	21	14.6	26	14.4	19	11.9
Diarrhoea	14	4.6	5	3.5	9	5.6	3	1.9
Abdominal Discomfort	5	1.6	0	0.0	5	3.1	0	0.0
Eructation	7	2.3	3	2.1	4	2.5	0	0.0
Nausea	5	1.6	1	0.7	4	2.5	5	3.1
Vomiting	3	1.0	1	0.7	2	1.2	4	2.5
Gastroesophageal Reflux Disease	3	1.0	1	0.7	2	1.2	0	0.0
Abdominal Pain Upper	2	0.7	0	0.0	2	1.2	3	1.9
Toothache	2	0.7	0	0.0	2	1.2	3	1.9
Food Poisoning	2	0.7	0	0.0	2	1.2	1	0.6
Abdominal Pain	2	0.7	1	0.7	1	0.6	3	1.9
Haemorrhoids	3	1.0	3	2.1	0	0.0	1	0.6
Dyspepsia	5	1.6	5	3.5	0	0.0	0	0.0
General Disorders And Administration Site Conditions	30	9.8	11	7.6	19	10.5	8	5.0
Oedema Peripheral	13	4.2	4	2.8	9	5.6	2	1.3
Fatigue	3	1.0	1	0.7	2	1.2	1	0.6
Chest Pain	2	0.7	0	0.0	2	1.2	0	0.0
Pyrexia	0	0.0	0	0.0	0	0.0	3	1.9

SOC/PT	CLAR-09007 & CLAR-12011		CLAR-12011		CLAR-09007			
	Oral TU N=305		Oral TU N=144		Oral TU N=161		T-Gel N=160	
	n	%	n	%	n	%	n	%
Immune System Disorders	1	0.3	1	0.7	0	0.0	2	1.3
Seasonal Allergy	1	0.3	1	0.7	0	0.0	2	1.3
Infections And Infestations	59	19.3	17	11.8	42	23.2	33	20.6
Upper Respiratory Tract Infection	18	5.9	5	3.5	13	8.1	5	3.1
Nasopharyngitis	13	4.2	3	2.1	10	6.2	7	4.4
Sinusitis	5	1.6	0	0.0	5	3.1	5	3.1
Gastroenteritis Viral	5	1.6	0	0.0	5	3.1	2	1.3
Bronchitis	3	1.0	0	0.0	3	1.9	2	1.3
Lower Respiratory Tract Infection	3	1.0	1	0.7	2	1.2	1	0.6
Influenza	3	1.0	1	0.7	2	1.2	0	0.0
Pneumonia	2	0.7	0	0.0	2	1.2	0	0.0
Tooth Infection	1	0.3	0	0.0	1	0.6	3	1.9
Acute Sinusitis	0	0.0	0	0.0	0	0.0	3	1.9
Appendicitis	0	0.0	0	0.0	0	0.0	2	1.3
Cellulitis	0	0.0	0	0.0	0	0.0	2	1.3
Injury, Poisoning And Procedural Complications	22	7.2	4	2.8	18	9.9	9	5.6
Muscle Strain	3	1.0	1	0.7	2	1.2	1	0.6
Fall	2	0.7	0	0.0	2	1.2	0	0.0
Ligament Sprain	2	0.7	0	0.0	2	1.2	0	0.0
Arthropod Bite	1	0.3	0	0.0	1	0.6	2	1.3
Investigations	33	10.8	15	10.4	18	9.9	18	11.3
Prostatic Specific Antigen Increased	5	1.6	0	0.0	5	3.1	8	5.0
Blood Pressure Increased	4	1.3	1	0.7	3	1.9	1	0.6
Blood Creatinine Increased	5	1.6	3	2.1	2	1.2	2	1.3
Blood Glucose Increased	5	1.6	3	2.1	2	1.2	2	1.3
Weight Increased	4	1.3	2	1.4	2	1.2	1	0.6
Cardiac Murmur	2	0.7	0	0.0	2	1.2	1	0.6
Glomerular Filtration Rate Decreased	2	0.7	0	0.0	2	1.2	0	0.0
High Density Lipoprotein Decreased	3	1.0	2	1.4	1	0.6	1	0.6
Haematocrit Increased	3	1.0	3	2.1	0	0.0	0	0.0
Metabolism And Nutrition Disorders	21	6.9	9	6.3	12	6.6	8	5.0
Type 2 Diabetes Mellitus	3	1.0	1	0.7	2	1.2	1	0.6
Hypercholesterolaemia	2	0.7	0	0.0	2	1.2	1	0.6
Hyperkalaemia	2	0.7	0	0.0	2	1.2	0	0.0
Hypoglycaemia	2	0.7	0	0.0	2	1.2	0	0.0
Hyperglycaemia	1	0.3	0	0.0	2	1.2	0	0.0
Gout	3	1.0	3	2.1	0	0.0	2	1.3
Hyperlipidaemia	3	1.0	3	2.1	0	0.0	1	0.6

SOC/PT	CLAR-09007 & CLAR-12011		CLAR-12011		CLAR-09007			
	Oral TU N=305		Oral TU N=144		Oral TU N=161		T-Gel N=160	
	n	%	n	%	n	%	n	%
Hypertriglyceridaemia	3	1.0	3	2.1	0	0.0	0	0.0
Musculoskeletal And Connective Tissue Disorders	29	9.5	10	6.9	19	10.5	17	10.6
Back Pain	6	2.0	0	0.0	6	3.7	2	1.3
Arthralgia	7	2.3	2	1.4	5	3.1	6	3.8
Musculoskeletal Pain	4	1.3	2	1.4	2	1.2	1	0.6
Muscle Spasms	3	1.0	1	0.7	2	1.2	3	1.9
Intervertebral Disc Degeneration	2	0.7	0	0.0	2	1.2	0	0.0
Osteoarthritis	1	0.3	0	0.0	1	0.6	2	1.3
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	7	2.3	2	1.4	5	2.8	2	1.3
Basal Cell Carcinoma	3	1.0	1	0.7	2	1.2	0	0.0
Nervous System Disorders	28	9.2	12	8.3	16	8.8	13	8.1
Headache	6	2.0	2	1.4	4	2.5	5	3.1
Dizziness	4	1.3	0	0.0	4	2.5	2	1.3
Syncope	3	1.0	0	0.0	3	1.9	0	0.0
Radiculitis Lumbosacral	2	0.7	0	0.0	2	1.2	0	0.0
Psychiatric Disorders	16	5.2	5	3.5	11	6.1	10	6.3
Anxiety	2	0.7	0	0.0	2	1.2	2	1.3
Anger	2	0.7	0	0.0	2	1.2	0	0.0
Abnormal Dreams	1	0.3	1	0.7	0	0.0	3	1.9
Renal And Urinary Disorders	12	3.9	5	3.5	7	3.9	12	7.5
Nephrolithiasis	2	0.7	1	0.7	1	0.6	3	1.9
Haematuria	1	0.3	0	0.0	1	0.6	4	2.5
Pollakiuria	1	0.3	1	0.7	0	0.0	2	1.3
Reproductive System And Breast Disorders	32	10.5	10	6.9	22	12.2	14	8.8
Prostatomegaly	13	4.2	3	2.1	10	6.2	5	3.1
Prostatitis	5	1.6	1	0.7	4	2.5	2	1.3
Nipple Pain	3	1.0	0	0.0	3	1.9	2	1.3
Benign Prostatic Hyperplasia	2	0.7	1	0.7	1	0.6	3	1.9
Respiratory, Thoracic And Mediastinal Disorders	27	8.9	10	6.9	17	9.4	11	6.9
Cough	4	1.3	1	0.7	3	1.9	4	2.5
Nasal Congestion	3	1.0	1	0.7	2	1.2	2	1.3
Rhinitis Allergic	2	0.7	0	0.0	2	1.2	2	1.3
Asthma	2	0.7	0	0.0	2	1.2	0	0.0
Epistaxis	2	0.7	0	0.0	2	1.2	0	0.0
Sleep Apnoea Syndrome	0	0.0	0	0.0	0	0.0	3	1.9
Rhinorrhoea	3	1.0	3	2.1	0	0.0	0	0.0
Skin And Subcutaneous Tissue Disorders	17	5.6	4	2.8	13	7.2	14	8.8

SOC/PT	CLAR-09007 & CLAR-12011		CLAR-12011		CLAR-09007			
	Oral TU N=305		Oral TU N=144		Oral TU N=161		T-Gel N=160	
	n	%	n	%	n	%	n	%
Rash	2	0.7	0	0.0	2	1.2	2	1.3
Alopecia	2	0.7	0	0.0	2	1.2	1	0.6
Acne	2	0.7	1	0.7	1	0.6	4	2.5
Seborrhoea	0	0.0	0	0.0	0	0.0	2	1.3
Vascular Disorders	17	5.6	7	4.9	10	5.5	13	8.1
Hypertension	10	3.3	4	2.8	6	3.7	11	6.9
Hot Flush	3	1.0	1	0.7	2	1.2	0	0.0

Source: From the Applicant's dataset "adae" in ISS, processed using JMP

7.4.2 Laboratory Findings

Routine clinical laboratory tests were performed during the Phase 2 and 3 trials, and included several TRT-related safety parameters such as hemoglobin (Hb) and hematocrit (Hct), serum PSA, and serum lipid profile. Additional laboratory assessments including an assessment of selected CV biomarkers and T-related hormones. The following laboratory assessments come from the Phase 3 trials CLAR-09007 and CLAR-12011 at two major time-points (referred to as "primary post-baseline time-points") on Days 90 or 114 (corresponding to the time-point for the primary efficacy endpoint from Studies 09007 and CLAR-12011) and on Day 365 (for the long-term safety assessment from Study CLAR-09007).

The analysis and comparison between oral TU and T-gel were based on the safety population who had laboratory values at the evaluation time-points.

7.4.2.1 Hemoglobin (Hb) and Hematocrit (Hct):

The mean baseline Hb and Hct were within the normal range and comparable between the oral T and T-gel groups. Oral TU treatment increased Hct and Hb more than did T-gel during the head-to-head study, although the mean values were still within the normal range (**Table 26**).

- Mean Hct/Hb increase from baseline was larger for oral TU compared to T-gel (**Table 26**)
- Percentage of subjects with Hct/Hb shift from baseline normal to abnormal high was larger for oral TU compared to T-gel (**Table 27**)
- The mean increase from Day 90 or 114 to Day 365 was actually larger for T-gel compared to oral TU

Table 26. Mean changes in Hct and Hb in the safety database

Visit Day	Hemoglobin (g/dL)				Hematocrit (%)			
	Oral TU		T-gel		Oral TU		T-gel	
	Value (g/dL)	Change* (%)	Value (g/dL)	Change (%)	Value (%)	Change (%)	Value (g/dL)	Change (%)
Baseline								
N	376		160		376		160	
Mean±SD	14.7±1.0		14.6±1.0		44.0±2.8		43.9±2.6	
Day 90 or 114								
N	268	268	152	152	268	268	152	152
Mean±SD	15.3±1.4	3.8±7.4	14.7±1.2	0.2±6.3	47.2±3.9	6.3±7.7	44.5±3.5	1.3±6.6
Day 365								
N	128	128	131	131	128	128	131	131
Mean±SD	15.3±1.4	4.2±8.4	14.9±1.3	1.9±7.4	47.0±4.0	6.7±8.8	45.2±3.9	3.2±7.7

Source: From the Applicant's Tables 17 and 18 in ISS

* % change from baseline at the post-baseline time-points

Table 27. Hb/Hct shift from normal baseline to abnormal high in safety population

Visit Day	Hb Shift from Normal Baseline to Abnormal High				Hct Shift from Normal Baseline to Abnormal High			
	Oral TU N=377		T-gel N=160		Oral TU N=377		T-gel N=160	
	Normal Baseline n	Shift to High n (%)	Normal Baseline n	Shift to High n (%)	Normal Baseline n	Shift to High n (%)	Normal Baseline n	Shift to High n (%)
Day 90/114	261	31 (11.9%)	148	8 (5.4%)	241	40 (16.6%)	136	19 (14.0%)
Day 365	127	23 (18.1%)	127	17 (13.4%)	118	46 (39.0%)	118	26 (22.0%)

Source: from the applicant's Table 2.2.3.1 (for Hb) and Table 2.2.3.2 (for Hct) in the ISS

Incidence of polycythemia (as clinical AEs) or increased Hct/Hb (as clinical AEs)

In a total 24 subjects, polycythemia (n=21) or increased Hct/Hb (n=3) were reported as clinical AEs. The majority of the cases were from the oral TU group in Study CLAR-09007. The incidence of these AEs was higher in the oral TU group than in the T-gel group in both the safety database from Study CLAR-09007 only, and in the pooled safety database with CLAR-12011. However, the incidence from Study CLAR-12011 (lower dose titration than CLAR-09007) where only Oral TU was studied, was lower than the incidence for Oral TU in CLAR-09007, and appears comparable to T-gel in CLAR-09007, as follows:

- Oral TU (n=305): n=18 (5.9%) from pooled CLAR-09007 + CLAR-12011
- Oral TU (n=161): n=14 (8.7%) from CLAR-09007 only
- Oral TU (n=144): n=4 (2.8%) from CLAR-12011 only
- T-gel (n=160): n=6 (3.8%)

Subjects with at least one Hct value >54%

- Oral TU: 9.9% (n=16 of 161, Study 09007 only);
- T-gel: 3.1% (n=5 of 160)

7.4.2.2 Lipid profile

Serum lipids assessed during clinical trials included serum triglycerides (TG), total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Overall, all the tested lipids decreased from baseline over time in both oral TU and T-gel by either median or mean calculations except for the mean changes in TG and total cholesterol, which showed slight increases on Day 365 in both groups (similar) (**Table 28**). Of note, the inter-subject variations of all lipid measures were very high with a coefficient of variation (CV) ranging from 300% to 700%. Also of note, decrease in HDL is considered a clinically unfavorable, not a clinically favorable, direction of effect.

Table 28. Mean Changes in TG, total cholesterol and LDL from baseline in the pooled safety population

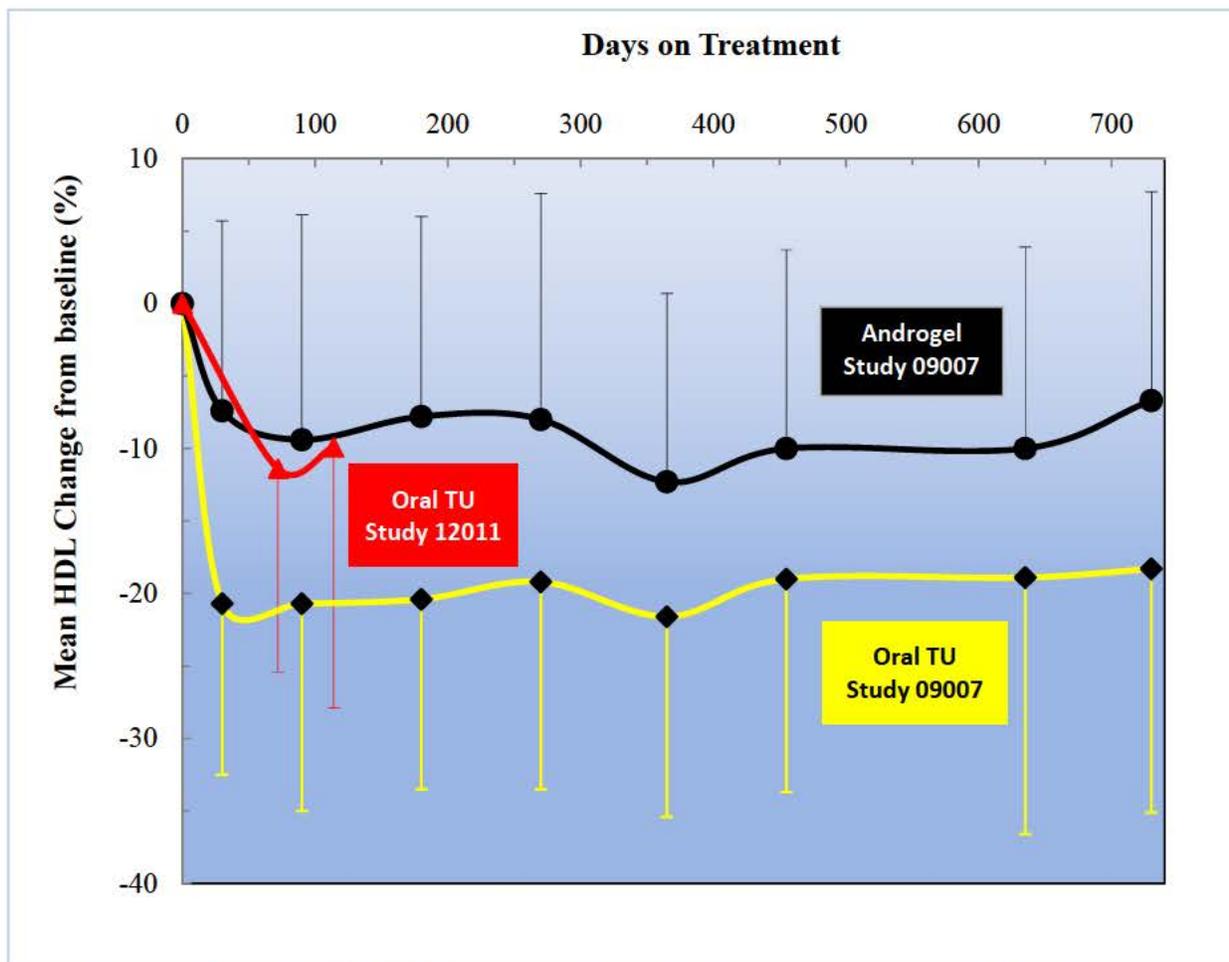
Visit Day	Triglyceride (mg/dL)		Total cholesterol (mg/dL)		LDL (mg/dL)	
	Oral TU N=377	T-gel N=160	Oral TU N=377	T-gel N=160	Oral TU N=377	T-gel N=160
Day 90 or 114	-5.4 (±35.8)	-1.8 (±40.9)	-6.8 (17.0)	-5.8 (13.1)	-0.5 (27.3)	-1.7 (21.6)
Day 365	4.7 (±55.5)	7.9 (±49.4)	-6.0 (18.3)	-3.0 (16.0)	1.3 (25.1)	1.8 (25.5)

Source: From Applicant's Tables 19, 20 and 22 in ISS

Serum HDL changes:

Serum HDL decreased from baseline more than the other three lipid parameters, with greater decreases in the oral TU group, at all time-points over 24 months of dosing compared to the T-gel group in Study CLAR-09007 and its extension CLAR-12010 (**Figure 3**). The HDL concentrations remained at stable low levels over the course of treatment in both groups. Since there was no off-drug monitoring, the reversibility of the HDL changes is unknown. The decreases and differences were also reflected in the HDL shift table, with more subjects in the oral TU group than in the T-gel group shifting from normal at baseline to abnormally low concentrations at all post-baseline time-points.

Figure 3. Mean serum HDL changes from baseline over 24 months in safety population



Source: From Applicant's Table 14.3.2.2.3b in Study CLAR-12010 submitted on July 18, 2014 and Table 14.3.2.2.3 in Study CLAR-09007. The data were from the subjects who received at least one dose of study drug and had HDL measure at the corresponding time-points. The coefficients of variations (CV) were 57-94% in the oral TU group and 105-215% in the T-gel group.

The HDL decreases in the oral TU group appear dose-related when comparing the two Phase 3 trials (Studies CLAR-09007 and CLAR-12011). On Day 90 or 114, the mean and median percentage of HDL decrease from baseline was about the same between the oral TU group in CLAR-12011 and the T-gel group in CLAR-09007. The corresponding C_{avg} of serum total T concentration was comparable between oral TU and T-gel in these two studies (Table 29). However, results from cross-study comparisons need to be interpreted cautiously.

Table 29. Comparison of the HDL decreases between the two Phase 3 trials

Visit Day	Study CLAR-12011		CLAR-09007			
	Oral TU, N=144		Oral TU, N=161		T-gel, N=160	
	Actual	Change	Actual	Change	Actual	Change
Baseline						
n	138		158		159	
Mean ±SD	44.3±10.1		48.7±11.9		51.2±12.9	
Median (min, max)	43 (28, 101)		47 (30, 94)		48 (29, 99)	
T-Cavg (ng/dL)†	246.5±84.8		209.0±108.4		218.9±103.7	
Day 90 or 114						
n	115	112	148	146	148	147
Mean ±SD	38.5±8.0	-9.9% ±18.1	38.0±8.6	-20.7% ±14.3	45.4±11.7	-9.4% ±15.5
Median (min, max)	37 (24,81)	-12.5% (-42.6, 92.9)	37 (22, 72)	-23.5% (-52.2, 18.4)	44 (23, 82)	-12.5% (-42.9, 75.6)
T-Cavg (ng/dL)†	422.3±171.3	175.8	628.3±342.8	419.3	485.0±220.1	266.1

Source: From Applicant's Table 32 in Study CLAR-12011, Table 34 in Study CLAR-09007 and Table 9 in this review

† The mean serum total T concentrations at the baseline (T-Cavg) and at Day 90 or 114 (average from on 24-hour PK)

Abnormal lipid changes meeting pre-specified criteria:

The incidence of abnormal lipids in subjects who had at least 1 value meeting the pre-specified criteria during Phase 2 and 3 trials are shown in Table 18. Compared to T-gel, Oral TU had a higher incidence of subjects meeting the low HDL criteria compared to T-gel in both the pooled database (all Phase 2 and 3 trials) and in Study CLAR-09007 alone (**Table 30**). When comparing oral TU and T-gel head-to-head (Study CLAR-09007), oral TU also had a higher incidence of patients meeting the pre-specified criteria for high LDL. The abnormal changes in other lipids meeting the pre-specified criteria appear comparable between oral TU and T-gel.

A cross-study comparison of oral TU in Study CLAR-12011 with T-gel in Study CLAR-09007, showed that the incidence of patients meeting the pre-specified abnormal criteria for HDL and LDL appeared comparable between oral TU in Study CLAR-12011 and T-gel in Study CLAR-09007. The advantage of this comparison is that both groups had comparable T Cavg exposures although this comparison is limited because it is a cross-study comparison and also because of different durations of treatment.

Table 30. Abnormal lipid change based on pre-specified criteria

Lipid Parameter†	Pre-specified Abnormal Criteria	Oral TU				T-gel
		CLAR-09007 N=161 n (%)	CLAR-12011 N=144 n (%)	Phase II Trials N=72 n (%)	All Trials N=377 n (%)	CLAR-09007 N=160 n (%)
HDL	≤40 mg/dL & ≥33%↓ from baseline	52 (32%)	10 (6.9%)	9 (12.5)	71 (18.8%)	10 (6.3%)
LDL	≥160 mg/dL & ≥33%↑ from baseline	11 (6.8%)	2 (1.4%)	0	13 (3.4%)	6 (3.8%)
Total Cholesterol	≥240 mg/dL & ≥33%↑ from baseline	3 (1.9%)	0	0	3 (0.8%)	4 (2.5%)
Triglycerides	≥200 mg/dL & ≥33%↑ from baseline	32 (19.9%)	17 (11.8%)	11 (15.3%)	60 (15.9%)	37 (23.1%)

Source: Summarized from the Applicant’s Section 6.2.2 “Lipids” in ISS

† HDL: high-density lipoprotein; LDL: low-density lipoprotein; TC: total cholesterol; TG: triglyceride

7.4.2.3 Cholesterol efflux capacity of HDL:

The Applicant performed a sub-study of CLAR-09007 in 57 subjects to explore potential effects of oral TU compared to T-gel on cholesterol efflux (from macrophages in vitro), re-distribution of HDL particle sizes and some additional CV biomarkers including oxidized phospholipids (PC Ox-PL) and IgG Apolipoprotein B1 (IgG Apo-B1). These are exploratory CV biomarkers. It is not widely accepted that changes in these particular biomarkers lead to changes in CV outcomes.

Both oral TU and T-gel decreased cholesterol efflux capacity but with statistically significant greater decreases in the oral TU group over the 12 months of treatment than in the T-gel group. However, it appears that the HDL particles redistributed to smaller sizes (more anti-atherogenic HDL subclasses) in the oral TU group more than in the T-gel group. Other CV biomarkers appear either favorable to oral TU (Ox-PL) or no different from T-gel. In sum, these other CV biomarkers, present a conflicting pattern, with some favoring oral TU, others favoring T-gel, and some showing comparable changes for oral TU and T-gel.

7.4.2.4 Cardiovascular (CV) biomarkers:

Two major CV biomarkers, high-sensitivity C-reactive protein (hs-CRP) and lipoprotein-associated phospholipase A2 (Lp-PLA2), were assessed in the 12-month open-label, randomized, Androgel-controlled trial (CLAR-09007) and its 12-month extension trial (CLAR-12010). The measurements and analysis (change from baseline and responder analyses defined as >50% decrease from baseline) were pre-specified in both trial protocols. These are also exploratory CV biomarkers.

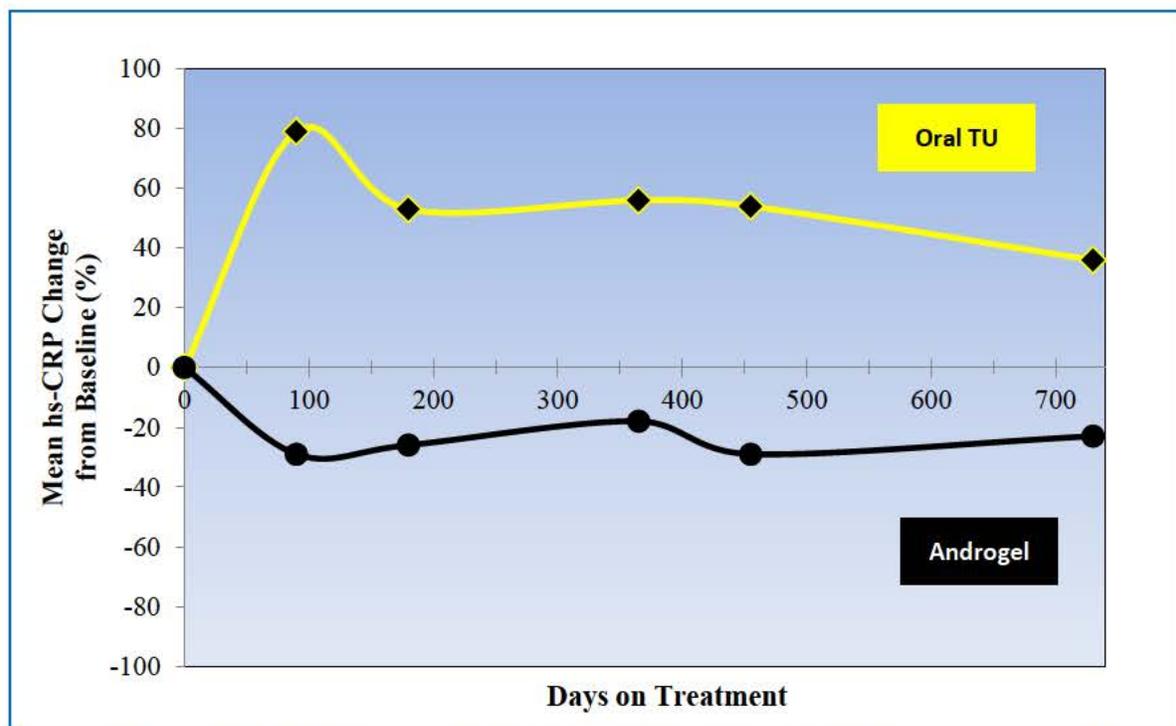
Overall, the oral TU treatment increased - but the T-gel treatment decreased - serum hs-CRP from baseline over the course of the 24 months (**Figure 4**) after excluding subjects with serum

hs-CRP >10 mg/L (as per the CDC/AHA’s recommendation because such high values are mostly related to acute inflammation). The differences between the oral TU and T-gel were statistically significant in the first 12-month study (CLAR-09007). **Figure 4** is based on the interim analysis data of Study CLAR-12010 submitted with the 120-day safety update to this NDA, except for the results at 730 days (Day 365 of CLAR-12010) which come from all subjects without any exclusion of subjects with serum hs-CRP >10 mg/L and is based on the Applicant’s updated submission after the 120-day SU.

The serum Lp-PLA2 slightly decreased from baseline in both treatment groups with less decreases in the oral TU group.

Consistently, the responder analyses (subjects with the pre-specified “worse” biomarkers) showed a higher incidence of subjects in the oral TU group compared to the T-gel group. The upper bound of the 95% CI for the “worse biomarkers” differences between the two groups was 17% on Day 365 in Study CLAR-09007 which was beyond the original pre-specified non-inferiority (NI) margin, 10%. See the Review of Individual Phase 3 Trials for details.

Figure 4. Serum hs-CRP change from baseline over 24 months of treatment in safety population



Source: From the **Table 100** “Excluding hs-CRP >10 mg/L” in the CLAR-12010 review and updated based on the Applicant’s submission of Aug 19, 2014. The data were from the subjects who received at least one dose of study drug, entered the extension study and had hs-CRP measures at the corresponding time-points in the Study CLAR-09007 (the first 12-month) and Study CALR-12010 (the second 12 months): n=82-63 on oral TU and n=85-55 on T-gel across time-points. Coefficient of variations (CV%) of the mean changes were 250-397% in the oral TU group and 362-583% in the T-gel group.

7.4.2.5 Liver tests:

Routine liver tests, including serum ALT, AST, bilirubin and alkaline phosphatase, were monitored during Phase 2 and 3 trials. Several subjects from Phase 3 trials had transient abnormal elevation of the tests, but there were no specific trends associated with oral TU or T-gel treatments.

- Oral TU: n=2 subjects with abnormal liver tests
 - Subject 09007/ (b) (6): ALT and AST >3x ULN with normal total bilirubin on Day 279 and resolved 2 weeks later while continuing oral TU treatment.
 - Subject 12011 (b) (6): AST >2x from baseline and 1x ULN without ALT and bilirubin elevation, resolved 4 days later.
- T-gel: n=1 subject with an abnormal liver test
 - Subject 09007/ (b) (6): ALT and AST >3x ULN on Day 30 and Day 269 without bilirubin elevation. Both resolved at next on-treatment visits.

7.4.2.6 Prostate-specific antigen

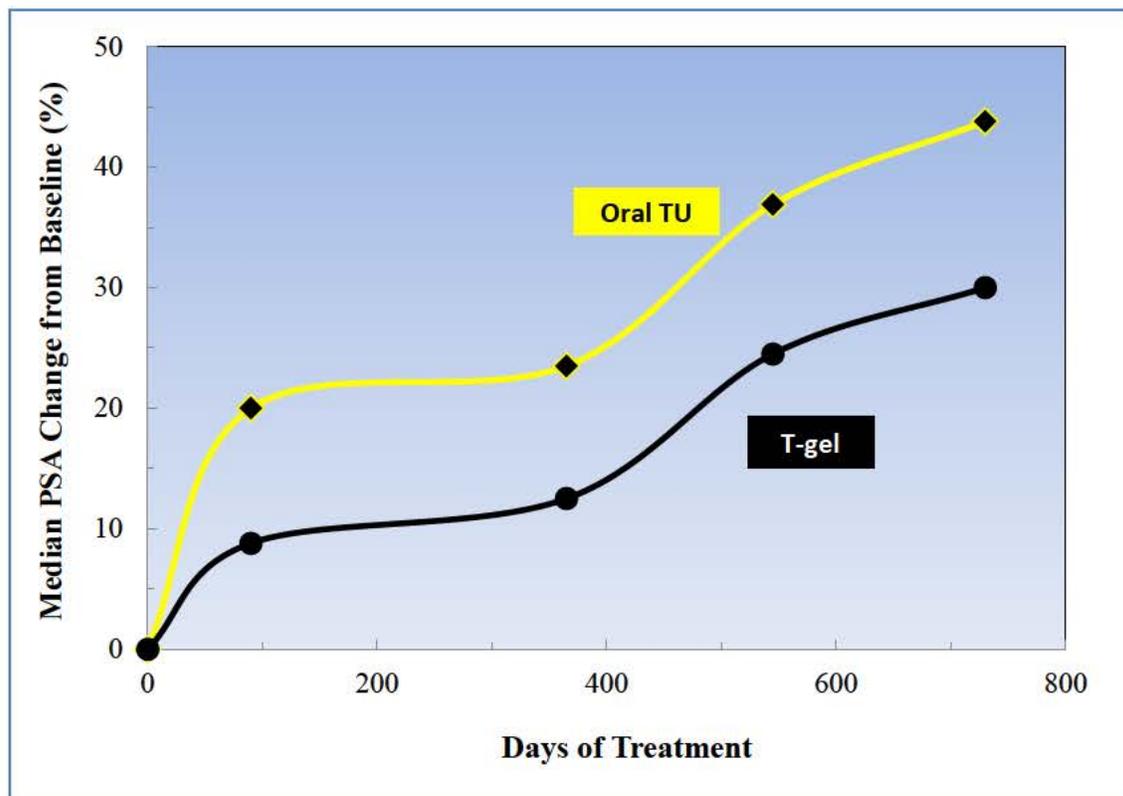
The serum prostate specific antigen (PSA) was monitored in the Phase 3 trials for up to 24 months on Day 90 or 114 (the primary endpoint time for CLAR-09007 and CLAR-12011, respectively), and on 365 days (CLAR-09007), 545 and 730 days (CLAR-12010). Due to high inter-subject variation in the PSA measures, the median values were used for comparisons between oral TU and T-gel, although both the mean and median analyses showed similar trends.

Median serum PSA

The median PSA increased from baseline in both treatment groups for up to 24 months of dosing (pooled from three Phase 3 trials), but with greater increases in the oral TU group (**Figure 5**). The median increases were <1.4 ng/ml across all time-points (the >1.4 ng/ml increase may be considered a clinically significant change).

The incidence of subjects with a serum PSA increased from baseline >1.4 ng/ml in the T-gel-controlled trials was similar (approximately 12%) between oral TU and T-gel over the 24 months of treatment. However, more subjects in the oral TU group during the 12-month extension experienced PSA increase >1.4 ng/ml compared to the T-gel group (**Table 31**).

Figure 5. Median Changes in serum PSA from baseline over 24 months of treatment in safety population†



Source: From Applicant’s Table 14.3.2.6b in Study CLAR-12010 updated on July 18, 2014 and Table 23 in ISS
† The subjects who received at least one dose of study drug and had PSA measures at the corresponding time-points in the Study CLAR-09007 (the first 12-month) and Study CALR-12010 (the second 12 months).

Table 31. Subjects with PSA increase by >1.4 ng/ml in Phase 3 trials

Phase 3 Trial	Planned Dosing duration	Oral TU		T-gel	
		N	n %	N	n %
CLAR-12011	4 months	144	1 (0.7%)		
CLAR-09007	12 months	161	12 (7.5%)	160	17 (10.6%)
CLAR-12010†	12 months	86	8 (9.3%)	92	3 (3.3%)

Source: From the Applicant’s clinical lab dataset “ADLB” of Studies CLAR-12011, CLAR-09007 and CLAR-12010

† The 12-month extension study from Study CLAR-09007. The table included the new cases from the interim report (about 30% subjects in the oral TU group completed Day 365 visit) submitted with the 120-day safety update on May 1, 2014.

Benign prostatic hyperplasia (BPH) as a clinical AE:

BPH was reported as a clinical AE sporadically across the trials.

- Oral TU: n=2 subjects (one each from CLAR-09007 and CLAR-12011)
- T-gel: n=3 subjects (all from CLAR-09007)

Prostate volume (PV):

The PV measured via trans-rectal ultrasound (TRUS) (in Study CLAR-09007 only) increased from baseline greater in the oral TU group than in the T-gel group. The difference was not statistically significant, likely due to high variability in the T-gel group on Day 365.

- PV at Baseline:
 - Oral TU: 29.3±14.2 ml
 - T-gel: 30.7±25.5 ml
- PV changes from baseline on Day 365:
 - Oral TU: 3.0±9.8 ml
 - T-gel: 1.8±26.4 ml

Incidence of prostatomegaly as a clinical AE:

The frequency of prostatomegaly reported as a clinical AE was similar between the two groups in the safety population (all trials). However, the majority of cases were reported from the 12-month T-gel controlled study (CLAR-09007), and the remaining few cases were from the 4-month study CLAR-12011 (n=3) and a phase 2 trial (CLAR-08005, n=1). In Study CLAR-09007, the incidence of prostatomegaly in the oral TU group was twice that reported in the T-gel group:

- Oral TU: 6.3% (10/160 subjects)
- T-gel: 3.1%, (5/160 subjects)

Two subjects in the oral TU group and one subject in the T-gel group in Study CLAR-09007 had PSA increased from baseline >1.4 ng/ml around the time of the prostatomegaly adverse event report.

5.4.2.7 T-related other hormones:

In addition to serum TU, T, DHT and DHT (already discussed), serum follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) and sex-hormone binding globulin (SHBG) concentrations were also monitored, mostly at the same time-points as for serum T evaluation during Phases 2 and 3 trials. The profile of changes for FSH, LH and estradiol associated with oral TU treatment appeared consistent with TRT and comparable to T-gel in the Androgel-controlled Phase 3 trial CLAR-09007. See the individual trial review of Study CLAR-09007 for details.

In the pivotal 4-month Phase 3 trial CLAR-12011, the serum SHBG concentration decreased from baseline at the end of treatment (Day 114) by approximately 35% following treatment with an oral TU dose of 200 mg bid for 42 days followed by titration.

In the supportive 12-month randomized, Androgel-controlled trial CLAR-09007, the serum SHBG concentrations decreased from baseline across all visits (over 12 month) by almost 50% on oral TU (at 200 mg bid followed by titration) vs. 5-12% on T-gel.

In the 4-week Phase 2 trial CLAR-09009, oral TU at 200 mg bid for 4 weeks decreased SHBG by approximately 38% from baseline without changes in serum albumin and serum total protein. This was the only clinical trial in the NDA submission that had an evaluation of serum albumin and total protein.

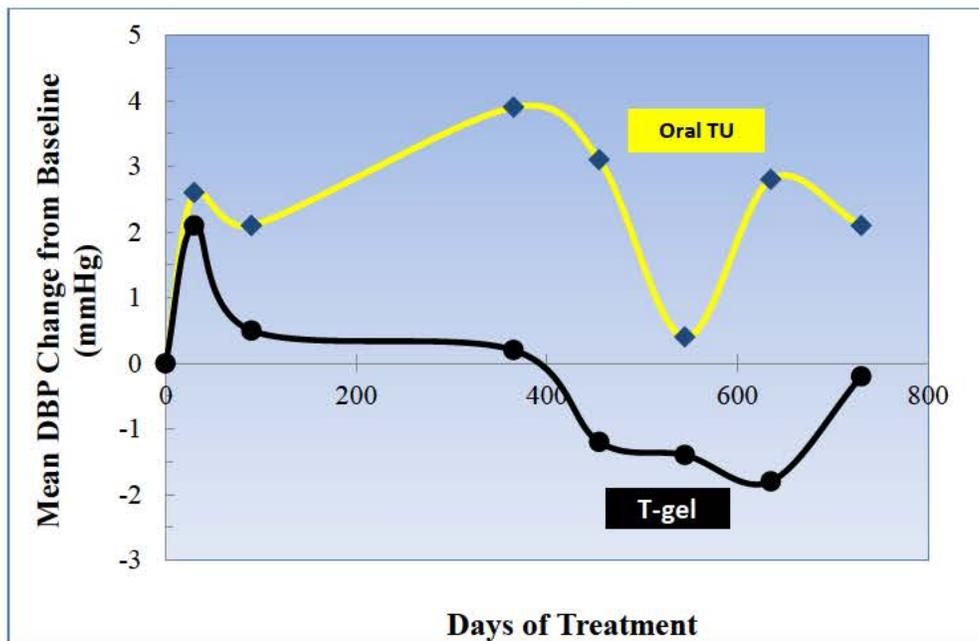
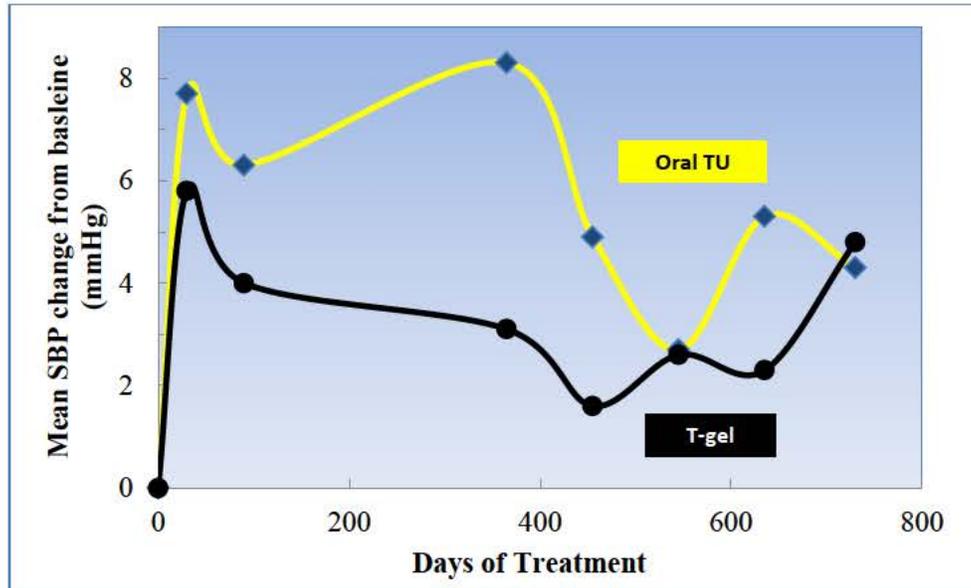
The reason for the greater decrease in the serum SHBG concentration associated with the oral T treatment compared to T-gel is unknown. SHBG production may be decreased and/or SHBG clearance may be increased. No corresponding decrease in the serum albumin and total protein was observed, speaking against a reduction in liver protein synthesis.

7.4.3 Vital Signs

Vital signs were monitored during Phases 2 and 3 trials. There were notable changes in blood pressure (BP). Although the BP values were highly variable across visits in all trials, there appeared to be a trend for increased mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) from baseline for both T products, greater with oral TU than with T-gel.

In the randomized, open-label Androgel-controlled Phase 3 trial and its extension (the first 12 month in Study CLAR-09007 and its 12-month extension in Study CLAR-12010), both oral TU and T-gel increased mean SBP and DBP, but there was a clearly greater increase in the oral TU group compared to the T-gel group over the course of the original 12 months (CLAR-09007) and the additional 12-month extension (CLAR-12010) (**Figure 6**). The greatest increases occurred 12 hours (vs. at 4 hours and check-in) after the morning dose across all visits in Studies CLAR-09007 and CLAR-12011 as summarized in **Table 32** (see the [Review of Individual Trial](#) for details).

Figure 6. Mean blood pressure change from baseline over 24 months in safety population†



Source: From Applicant's Tables 14.3.3.1 and 14.3.3.2 in Study CLAR-09007; and Tables 14.3.3.1, 14.3.3.2 and 14.3.3.3 in Study CLAR-12010

† The data from subjects who received at least one dose of study drug and had BP measures at the corresponding time-points. Data shown in the figures are from Hour 12, which was the time of maximum changes from baseline, followed by changes at Hour 4, then at Check-in.

Table 32. Mean blood pressure increase from baseline at 12 hours post-dose over 24 months in the Phase 3 trials

(The data represent a range of mean changes from baseline across all study visits)

Phase 3 trial	Exposure (Month)	Number of Subjects		SBP (mmHg) [†]		DBP (mmHg) [†]	
		Oral TU	T-gel	Oral TU	T-gel	Oral TU	T-gel
CLAR-12011	4	144	/	3.8 to 6.1	/	0.8 to 2	/
CLAR-09007	12	161	160	6.3 to 8.3	3.1 to 5.8	2.1 to 3.9	0.2 to 2.1
CLAR-12010 [‡]	24	86	82	2.7 to 11.5	1.6 to 5.9	0.4 to 1.4	-0.1 to -2.4

Source: from **Table 55**, **Table 81** and **Table 95** in the Review of Individual Phase 3 Trials

[†] The mean SBP/DBP increases from baseline at 12 hours post-AM dose (the time at which the greatest increase in both treatment groups was observed in all three trials, with lesser increases observed at the other two time-points post-AM dose: check-in and 4 hours post-dose)

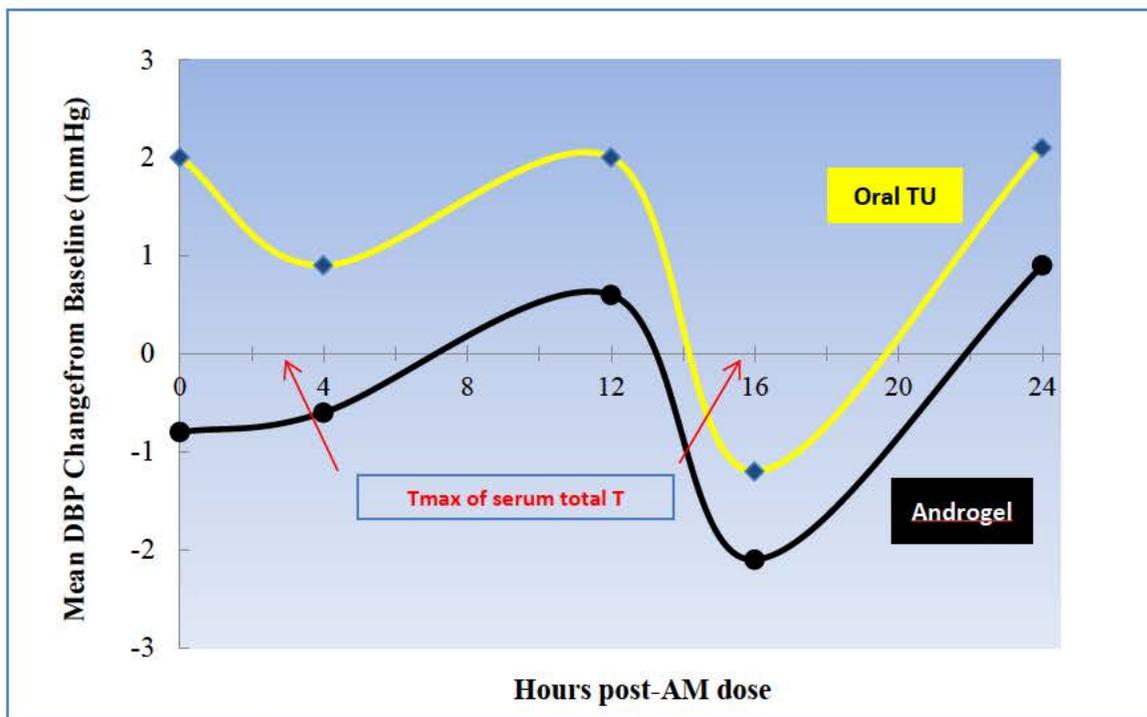
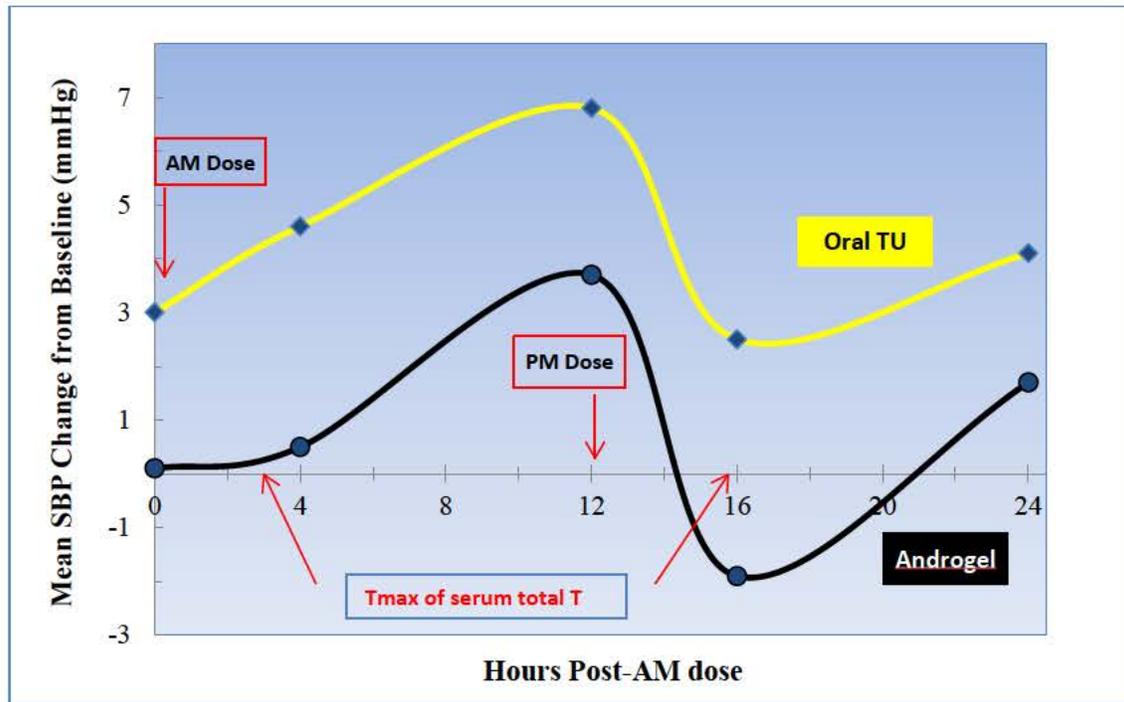
[‡] The data from CLAR-12010 (the 12-month extension to Study CLAR-09007), come from an interim report submitted with the 120-day safety update on May 1, 2014. In this study, the BP was measured at the check-in only.

In the Study CLAR-09007, BP was measured at Check-in, at 4 and 12 hours post-AM dose for all visits, and at additional time-points (16 and 24 hours post-AM dose, or 4 and 12 hours post-PM dose) for the Day 90/105 visit. At all visits, both mean SBP and mean DBP increased from baseline in both treatment groups and those increases appeared time-dependent in both groups, with the largest increase at 12 hours post-dose (either AM or PM), with smaller increases at 4 hours and at Check-in. The BP increase profile was not consistent with the PK profile of serum T and DHT; the largest BP increases were not at Tmax of serum T and DHT but at the trough times. In addition, the BP changes at the Check-in time, which should be at the end of a previous dose (approximately 12 hours post-PM oral TU dose before a visit), were lower than at the 12 hours post dose at a visit. The observed time-related BP changes appear consistent across all visits (**Figure 6**).

Figure 7 and **Table 33** show the mean BP changes from baseline (pre-dose) at check-in, at 4 hours, 12 hours, 16 hours and 24 hours after AM dosing on Day 90/105 in Study CLAR-09007. While a circadian fluctuation of systolic and diastolic BP was expected in both treatment groups (as reported in healthy young human subjects¹), greater increases in BP from baseline were observed across 24 hours in the oral TU group after both the AM and PM doses compared to the T-gel group.

¹ Degaute JP et al: Quantitative analysis of the 24-hour blood pressure and heart rate patterns in young men. *Hypertension* 18 (2): 199-210, 1991

Figure 7. Mean blood pressure change from baseline over 24 hours post dose on Day 90 in Study CLAR-09007



Source: From **Table 33** in safety population n=149 on oral TU and n=151 on Androgel

Table 33. Mean BP changes from baseline over 24 hours on Day 90 in Study 09007

BP Time (post-AM dose) [†]	SBP (mmHg)		DBP (mmHg)	
	Oral TU	T-gel	Orla TU	T-gel
Check-in	3.0±13.4	0.1±13.4	2.0±8.7	-0.8±9.7
4 hr	4.6±14.3	0.5±13.7	0.9±9.3	-0.6±9.4
12 hr	6.8±15.3	3.7±14.1	2.0±10.5	0.6±9.2
16 hr [†]	2.5±15.9	-1.9±15.2	-1.2±10.7	-2.1±10.2
24 hr [†]	4.1±14.0	1.7±14.5	2.1±9.6	0.9±10.5

Source: From the applicant's Aug-4-2014 update (Tables 14.3.3.2b and 14.3.3.1b).

[†] The time-points 16/24 hours post AM dose were 4/12 hours post-PM dose. The check-in time-point was approximately 12 hours post PM dose before the visit for oral TU group and 24 hours post dose for the T-gel group

In the pivotal, single-arm, open-label Phase 3 trial (CLAR-12011), there were still mean SBP and DBP increases from baseline with oral TU (e.g., systolic increases of 3.8 to 6.1 mmHg across visits), but these were smaller than in the previous Phase 3 trial, appearing to be in a similar range to that observed in the T-gel group in Study CLAR-09007 (**Table 32**).

It should be noted that the overall blood pressure changes observed in the oral TU group in Study CLAR-09007 appeared to be associated with higher systemic testosterone and/or DHT exposures compared to the T-gel group (**Table 9**). The blood pressure changes observed in Study CLAR-12011, where the testosterone exposures were lower than in the previous study, were smaller than the blood pressure changes observed in the previous study, and appeared similar to the blood pressure changes observed with T-gel in Study CLAR-09007. Conclusions from cross-study comparisons such as these should be viewed with caution.

Table 34 shows the blood pressure changes observed at check-in, Hour 4, and Hour 12 on Day 30 in Studies CLAR-09007 and CLAR-12011. **Table 34** also shows average serum T and DHT concentrations in these studies. These data appear to show a possible relationship between increase in blood pressure and systemic androgen exposure, but conclusions based upon such comparisons are limited by cross-study variations in blood pressure and in T and DHT exposure in both studies (**Table 34**). In addition, without a concurrent control (placebo and/or active), it is not possible to fully interpret the independent BP effects of oral TU or T-gel from these data.

Table 34. T and DHT exposure and BP changes on Day 30 at the same fixed oral TU dose between Study 09007 and Study 12011
(The data represent Mean±SD in safety population)

PK and BP	Study 09007		Study 12011
	Oral TU N=155	T-gel N=156	Oral TU N=133
T-Cavg (ng/dL)	606.8 ±299.3	378.7 ±155.7	509.2 ±222.1
DHT-Cavg (ng/dL)	123.6±67.0	61.5±42.5	106.7±68.1
<u>SBP Change</u>			
Check-in	3.0±11.9	1.9±13.9	0.5±13.7
4 hr	4.5±13.2	2.4±15.1	1.3±13.0
12 hr	8.1±13.9	5.6±16.5	6.0±13.9
<u>DBP Change</u>			
Check-in	2.3±8.2	0.9 ±9.1	0.2±9.3
4 hr	1.2±9.5	0.4±8.9	-0.6±10.1
12 hr	2.7±9.1	2.1±9.5	1.7±9.6

Source: The PK data were from the Study 09007 PK report (Tables 23 and 32) and the Study CLAR-12011 PK report (Tables 22 and 29); the BP data from the applicant's Aug-4-2014 update for Study 09007 (Tables 14.3.3.1b and 14.3.3.2b) and for Study 12011 (Tables 14.3.3.1b and 14.3.3.2b)

7.4.4 Electrocardiograms (ECGs)

ECG was not monitored in any clinical trials.

7.4.5 Special Safety Studies/Clinical Trials

No special safety study/clinical trials were submitted to this NDA.

7.4.6 Immunogenicity

No tests for immunogenicity were conducted during the clinical development program of oral TU. It appears no immunogenicity-related AEs and no laboratory abnormalities reflective of immunogenicity were reported in the clinical trials.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

All clinical trials were designed and conducted with a single-dose/arm for TU without parallel dose groups for TU. Subjects in all Phase 3 trials started with a fixed dose of oral TU at 200 mg

bid for 42 days followed by titration-up/down based on serum total T concentration (single time-point). The majority of subjects stayed at the initial dosage or titrated down to 150 or 100 mg bid. The subsets of each titrated doses were too small for meaningful dose-dependent AE analysis in each of the three Phase 3 trials.

The two Phase 3 trials, CLAR-12011 and CLAR-09007 (and its extension CLAR-12010), were conducted using different dosing titration regimens with a titration method in Study CLAR-09007 that led to higher serum T and DHT exposures (**Table 9**). The incidences of both total AEs and individual AEs were higher in Study CLAR-09007 compared to Study CLAR-12011 (see **Table 23** and also the individual trial reviews). The differences in incidences between the trials is likely a factor of differing androgen levels, but the duration of exposure to the study drug (4 months in CLAR-12011 vs. 12-24 months in CLAR-09007 and CLAR-12010) also plays some role.

7.5.2 Time Dependency for Adverse Events

While the total number of events tends to increase over time, the AE profile for oral TU appears consistent across various durations of exposure to oral TU, including the 4-month pivotal Phase 3 trial Study CLAR-12011, the 12 month T-gel-controlled trial Study CLAR-09007 and its additional 12 month extension Study CLAR-12010. Blood pressure continues to remain elevated and hematocrit appears to continue to increase over 24 months. Otherwise, no new safety signals were observed over long-term exposure for up to 24 months.

7.5.3 Drug-Demographic Interactions

The Applicant did not perform demographic subgroup analysis on the safety data. The safety database (n=377 on oral TU) was relatively too small for meaningful subgroup analysis.

7.5.4 Drug-Disease Interactions

The study population in the clinical development program had commonly-observed co-morbidities: diabetes mellitus (18.8%), “pre-diabetes” (31.5%), hypertension (42.5%), and hyperlipidemia or similar condition (34.3%). Although the total number of subjects exposed is relatively small, especially for the observation of serious cardiovascular adverse events, potential interactions of oral TU with these co-morbidities and associated medications should be covered by the overall safety profile.

However, underlying GI disorders were not reported in the submission, thus, the potential impact of underlying, co-morbid GI conditions on oral TU absorption and thus PK variations are unknown.

7.5.5 Drug-Drug Interactions

No specific drug-drug interactions (DDIs) were assessed in the clinical development program for oral TU. The drug is metabolized by widespread esterases and not by cytochrome P450 enzymes in the liver. As discussed in the above Drug-Disease Interaction section, the study population

was taking concomitant medications corresponding to the underlying medical conditions, and potential DDIs might be covered by the overall safety profile. The potential “class” DDIs for TRT products will eventually be listed in the proposed labeling. On additional concern might be the effect of oral TU on the absorption of concomitantly administered drugs. This concern should be addressed.

In two phase 3 trials, history of alcohol use was not uncommon: approximately 55% (n=169) were listed as “current” drinkers and 11% as “former” drinkers. With a fatty nature of this oral TU formulation, alcohol may potentially impact solubility of the oral TU formulation in the GI track and thus absorption. The alcohol PK interactions with the oral TU formulation were not assessed and are currently unknown. This concern should be addressed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Three subjects were diagnosed with a cancer in the safety database: 2 in the oral TU group (basal cell carcinoma and nasal cavity cancer) and 1 in the T-gel group (prostate cancer). Although they were considered not related to the study drug by the investigators, these events (except the nasal cancer, which was reported on Day 1 of dosing) were temporally related to the study drug and the causal relationship cannot be totally excluded.

- **Basal cell carcinoma** (Subject #09007/ (b) (6)) in the oral TU group from Study CLAR-09007: diagnosed on Day 343 after oral TU.
- **Nasal cavity cancer** (Subject #12011/ (b) (6)) from Study CLAR-12011: diagnosed on Day 1 of oral TU dosing.
- **Prostate cancer** (Subject #09007/ (b) (6)) in the T-gel group from Study CLAR-09007: diagnosed on Day 134. PSA value on Day 114 was 5.3 ng/mL (increased from baseline of 3.9 ng/ml) with positive biopsy on Day 130. Study drug was discontinued due to this event (on Day 139).

7.6.2 Human Reproduction and Pregnancy Data

No human reproductive assessments for oral TU capsules were conducted in males, and none were conducted in their spouses or female partners in the clinical development program. Pregnancy information of the subjects’ spouses or partners was not reported.

Reporting frequency of AEs under the Reproductive System and Breast Disorders SOC appears comparable between oral TU and T-gel, except for prostate events (discussed under other sections of this review). Most Repro AEs were reported in single subjects.

7.6.3 Pediatrics and Assessment of Effects on Growth

All clinical trials submitted in this NDA were conducted in adult men who had repeated serum testosterone concentrations that were low. No pediatric patients (<18 years old) were enrolled in any of clinical trials.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no overdose cases reported during the Phases 2 and 3 trials. Potential abuse and withdrawal associated with this product were not specifically assessed.

7.7 Additional Submissions / Safety Issues

At the time when the NDA was submitted, the 12-month extension trial, Study CLAR-12010, was ongoing. As agreed at the Pre-NDA meeting, the Applicant submitted the interim data, mostly summary tables of safety, in the 120-day Safety Update to this NDA. However, the safety data included only approximately 30% subjects in the oral TU group who completed the Day 365 visit, which was lower than the committed 50% during the Pre-NDA meeting. In response to the Division's request, the Applicant submitted additional safety data on July 18, 2014 (the database for Study CLAR-12010 was locked on Jun 10, 2014). Most of the safety data from both update submissions were accordingly incorporated in related sections of this review.

8 Postmarket Experience

There is no postmarket experience with this product, Rextoro, worldwide. However, an oral TU product, Andriol capsules, has been marketed in 80 countries, including Europe and Canada, for up to 30 years by a different pharmaceutical company. The Applicant provided a brief review of publicly available postmarketing experience with Andriol, including postmarketing surveillance reports and published studies based on postmarketing surveillance databases.

8.1 Comparison of PK profile with Andriol

It is important to note that the dosing regimen of Andriol that was used in those reports is different from the dosing regimen of the oral TU capsule submitted in this NDA. Based on the Product Monograph for Andriol (approved by Health Canada, Nov 15, 2011), the starting dose is 60-80 mg bid titrated to 20-60 mg bid, which is 4-5 times lower than Rextoro (200 mg bid in T equivalents, 317 mg TU bid). Correspondingly, the systemic exposure of T, TU and DHTU is lower for Andriol compared to Rextoro, based on cross-study comparison (**Table 35**).

Table 35. Cross-study PK comparisons between Rextoro and Andriol

Parameter	Rextoro†	Andriol‡	Difference (% of Andriol)
Labeling Dosage	200 mg bid	60-80 mg bid*	400-500%
Cavg (ng/dL) At single dose	(200 mg)	(50 mg)	400%
T (ng/dL)	520	175 ±37	300%
TU (ng/dl)	9200	1614 ±101	570%
DHTU (ng/dL)	6140	915 ±76	670%
Ratios (Cavg)			
TU/T	18	9	200%
DHTU/T	12	5	240%

† From the TU-PK subset (n=26) in Study CLAR-09007; see **Table 72** in this review for details. The Rextoro dosage is based on T equivalents (200 mg T = 317 mg TU)

‡ From a published study conducted in postmenopausal women by *Schnabel et al: Clin Endocrinol 66: 579-585, 2007*. The study dose of Andriol 50 mg T was converted from 80 mg TU. The Cavg at a regular meal (Meal C) was calculated from AUC divided by 24 hours (the 24-hr PK) and converted from the original “nmol/L” to “ng/dL” based on the molecular weight of 288.42 for T, 290.45 for DHT, 456.7 for TU and 458.7 for DHTU.

* The Andriol dosage is mg TU not T equivalents in the Product Monograph for Andriol approved by Health Canada (Nov 115, 2011).

8.2 Postmarketing surveillance reports:

The postmarketing surveillance reports included search/analysis of the WHO global individual case safety report database (VigiBase) and two published studies based on postmarketing surveillance database.

8.1.1 VigiBase postmarketing surveillance reports:

VigiBase is the WHO global individual case safety report database maintained by the Uppsala Monitoring Center (UMC) in Sweden, which consist of all spontaneous reports of adverse reactions received from member countries since 1968. As with any spontaneous report repository, the data in VigiBase has limitations such as insufficient information, under-reporting, multiple confounders, uncertain exposure, etc.

The Applicant searched the database using “testosterone undecanoate”, “suspected/interacting”, only oral administration, all reactions reported up to Nov 10, 2013. A total of 96 reports were identified from the database which covers the entire 30 years marketing experience of Andriol in 80 countries.

[Reviewer’s Comment: The low AE reporting frequency suggests significant under-reporting.]

The 96 cases were presented by MedDRA SOC. The top SOCs with at least 20 cases reported were: Skin and Subcutaneous Tissue disorders (n=25), General disorders and Administration Site conditions (n=22), Nervous System disorders (n=22) and Gastrointestinal disorders (n=21). The detailed preferred terms (PT) were not provided. As per the Applicant's brief summary, it appears that there were no specific clusters of PTs under any SOC. The following are selected SOCs with potentially clinically relevant PTS:

Cardiac disorders (n=5) and Vascular disorders (n=6):

- MI: n=3
- Coronary artery thrombosis: n=1
- Retinal artery thrombosis: n=1
- Thrombophlebitis or thrombosis: n=3

Hepatobiliary disorders (n=8):

- Hepatic function abnormal: n=2
- Jaundice: n=3
- Cholecystitis, cholestatic hepatitis, hepatocellular injury, and hyperbilirubinemia: n=1 each

Neoplasms (n=2):

- Adenocarcinoma: n=1
- Benign neoplasm of epididymis: n=1

Known T-related AEs:

- Polycythemia: n=3
- Increased PSA: n=1
- Prostatic disorder: n=1

8.1.2 GPRD-based epidemiology study (*Jick and Hagberg, 2013*)²:

This was a cohort study conducted in 5841 males who received at least one oral TU or injectable TU identified from GPRD (Jan 1991 to Oct 2009) with the objective to assess relative risks of hypertension, polycythemia and prostate conditions (prostate cancer, BPH and prostatism).

The average duration of follow-up was 7.3 years with 72% subjects on intramuscular (IM) injectable TU and 23% on Andriol. The dosage information for both TU formulations was not reported. Likely the dosing regimen of Andriol would follow the labeling recommended dose, titrated from 60-80 mg bid (*mg of TU but not T equivalents as per the Product Monograph dated Nov 15, 2011*). The baseline characteristics appeared comparable between the two cohorts in terms of smoking history, BMI, and history of CVD, hypertension, asthma/COPD and alcohol abuse; however, subjects in the oral TU cohort were older with less new users (17% vs. 74%).

² Jick SS and Hagberg W: The risk of adverse outcomes in association with use of testosterone products: a cohort study using the UK-based general practice research database. *Br J Clin Pharmacol* 75 (1): 260-270, 2013

Overall, both oral TU and injectable TU shared similar risks of hypertension, polycythemia, prostate cancer, BPH and prostatism, although there were purported statistically significant differences (95% CI excluded 1.0) in the relative risks of polycythemia and BPH (**Table 36**). The differences may be confounded by the unbalanced baseline and/or may have some relation to different systemic exposures to TU, T, DHT and DHTU that are associated with different formulations and dosing regimens.

However, this study is not properly designed to provide risk assessment for oral or injectable TU as compared to background for hypertension, polycythemia, prostate cancer, BPH and prostatism, the tested risks.

Table 36. Risks of oral TU and injectable TU in the GPRD cohort study

Risk	Crude Incidence (1000 patient-year)		RR [†] 95% CI
	Oral TU	Injectable TU	
Hypertension	12.3	14.4	0.8 (0.6, 1.2)
Polycythemia	1.2	10.1	0.13 (0.05, 0.35)
Prostate cancer	2.5	1.8	1.1 (0.7, 1.7)
BPH	4.1	2.1	1.5 (1.1, 2.2)
Prostatism	8.4	6.1	1.1 (0.8, 1.8)

Source: Summarized from the publication in *Br J Clin Pharmacol* 2013 by Jick and Hagberg⁶

[†] Adjusted relative risk (RR) of oral TU over injectable TU.

8.1.3 Austrian surveillance study (*Jungwirth et al 2007*)³

This was a survey study conducted in 43 centers in Austria in hypogonadal males who were treated with Andriol 80 mg bid for 3 months by their treating physicians. The primary objective was to assess improvement in androgen deficiency symptoms by the following questionnaires: ADAM (Androgen Deficiency in the Aging Male), AMS (Aging Males Symptoms) and SF-36. Another questionnaire on the treatment effects was administered by the treating physician, and as part of this additional questionnaire, information on serum T concentration and PSA was captured.

A total of 189 patients and 185 doctors completed the survey forms. The mean age of patients was 54.7±12.3 years with mean dosing duration of 13.9±2.2 weeks. Serum testosterone level increased from baseline by >50%. Treatment improved symptoms on the ADAM and AMS scales, whereas no changes were observed on the SF-36. There were no significant effects on serum PSA levels. The authors concluded that short-term treatment with oral testosterone undecanoate in a clinical practice setting improved late-onset hypogonadism symptoms in aging men with low testosterone levels. No safety assessments except serum PSA were performed.

³ Jungwirth A et al: Clinical experience with Andriol1 Testocaps1 – The first Austrian surveillance study on the treatment of late-onset hypogonadism. *Aging Male* 10(4): 183-187, 2007

9 Appendices

9.1 Literature Review of oral TU safety

As per the Division’s request during the pre-NDA meeting, the Applicant conducted a literature search and review of published clinical studies on oral TU, focusing on the safety results. The following review is based on the Applicant’s literature summary submitted to the original NDA.

9.1.1 Literature search method:

- Literature source: MEDLINE, EMBASE, BIOSIS Previews, Current Contents Search, Derwent Drug File and Reference lists of retrieved studies and review articles
- The search terms: “testosterone undecanoate”, “oral administration” and its synonyms both as index terms and as keywords in the title and abstract.
- The search covering period: 1970 to 2013

9.1.2 Literature search outcome:

Out of 152 citations captured by the search, the Applicant identified a total of 34 publications that contained safety information on oral TU in males. The 34 studies published between 1980 and 2013 and were categorized to the following 4 types based on the study designs (**Table 37**).

- Randomized, double-blind, placebo-controlled trials (R/DB/PC)
- Randomized, open-label controlled trials (R/OL/CT)
- Open-label uncontrolled trials (OL/unCT)
- Postmarketing surveillance studies (PMSS), including studies based on the postmarketing experience with Andriol (an oral TU product that has been marketed in >80 countries for >30 years outside the US)

Table 37. Published studies on oral TU safety
(From the Applicant’s summary in ISS)

Study Type†	Number of Studies	Publication Year	Oral TU Exposure	Number of Male Subjects
R/DB/PC	12	1980-2010	40-120 mg bid x 1-12 months	585
R/OL/CT	7	1988-2013	10-120 mg bid x 1-24 months	202
OL/unCT	13	1981-2003	40-80 mg bid x 1 month-10 yrs	644‡
PMSS	1	2013	GPRD (Jan 1991-Oct-2009); Mean follow-up 7.3-yr after 1 st Rx; unknown dosage	1329 (oral TU) 4190 (IM TU) 322 (both)
	1	2007	Austrian survey 80 mg bid x 3 months	374
	1	2013	VigiBase (unknown dosage)	96

† R: Randomized; DB: double-blinded; PC: placebo-controlled; OL: open-label; CT: controlled; unCT: uncontrolled; PMSS: postmarketing surveillance studies (reviewed under [5 Postmarket Experience](#))

‡ Including n=33 hypogonadal males aged 15-62 years who received oral TU 80-200 mg/day for up to 10 years.

9.1.3 Safety evaluation:

Study population:

The majority of study subjects in the published studies were adult hypogonadal males and/or elderly males.

Extent of exposure:

In the 32 controlled and uncontrolled clinical studies, a total of 1388 male subjects were treated with oral TU 20-240 mg/day (mostly 10-120 mg bid) for up to 24 months (Table 37).

- N=33 received oral TU 80-200 mg/day x10 years
- N=124 received oral TU 20-40 mg/day x24 months
- N=287 received oral TU 80-240 mg/day x12 months
- N=411 received oral TU 80-160 mg/day x6 months

Safety evaluation and discussion:

The safety monitoring included AE reports and certain clinical laboratory tests, but reporting of the safety data were highly variable in details across studies. The overall AE profile, including laboratory abnormalities reported in those clinical studies appear consistent with the TRT class except for some non-specific gastrointestinal disorders, Effects on Hct/Hb, prostate, lipid profile and the cardiovascular system were reported. One patient in the oral TU group in the 12-month randomized, placebo-controlled study developed prostate cancer about 320 days after oral TU 80 mg/day which was judged by the authors as “possible related to study drug”. In another randomized placebo-controlled trial, two subjects in the placebo group developed prostate cancer.

However, the oral TU doses reported in all published studies was much lower than Rextoro’s dosage in the Applicant’s proposed labeling. The dosages for Andriol used in those studies was mostly 40-80 mg bid in TU, not T equivalents, while dosage for Rextoro trials and in the proposed labeling was 200 mg bid T equivalent or 317 mg TU bid. The systemic exposure of TU and its metabolites were much higher for Rextoro than for Andriol based on the labeled recommended doses. Thus, the safety profile of oral TU in the literature is not entirely applicable to Rextoro.

9.2 Literature review of DHT and DHT/T ratio

To support risk assessment of the supraphysiological DHT concentrations that resulted from Rextoro, the Applicant performed a literature search and review for the following safety assessments:

- The safety of short-/long-term exposure to high DHT concentrations or DHT/T ratios on the prostate
- The impact of circulating DHT or DHT/T ratio on intra-prostatic DHT and DHT/T
- The impact of circulating DHT on cardiovascular safety, and other non-prostatic safety.

The literature search method was not provided in the original NDA submission. In response to the Division's request, the Applicant submitted "Methods to identify credible information sources regarding risk(s) associated with elevated serum DHT" on April 18, 2014. The following review is based on this updated information and the Applicant's literature summary submitted in the original NDA.

9.2.1 Literature search method:

- Literature database: PubMed and ClinicalTrials.gov
- Search terms: DHT and related safety concerns (such as prostate disease, cardiovascular risk, Hct, lipids) and drugs (Andriol and TRT)

9.2.2 Literature search outcome:

Of >1000 abstracts identified from PubMed, 190 abstracts were considered relevant and published in the English language and 58 of them were ultimately referenced in the Applicant's literature review. The detailed study designs were not summarized in the submission.

9.2.3 DHT concentration and DHT/T ratios

The Applicant summarized the DHT concentrations and DHT/T ratios from 10 published studies. Some values appear estimated from the publication figures because no data summary was provided in the original study reports.

As per the Applicant's summary, both serum DHT concentration and DHT/T ratios increased from baseline in subjects who received all TRT products. According to the Sponsor, the values appeared comparable between Rextoro and T-gel or Andriol. However, this observation is limited by the cross-study comparisons (because of differences in study design and conduct). In the head-to-head comparison trial Study CLAR-09007 (where T exposures were higher with oral TU than T-gel), the mean serum DHT concentrations and DHT/T ratios were constantly higher in the oral TU group than in the T-gel group across all visits over the dosing course of 12 months (**Table 67**). The DHT levels and DHT/T ratios from the T-gel group in this study were lower than DHT levels and DHT/T ratios in any reports referenced by the Applicant, suggesting cross-study variations.

The Applicant's assessment of the literature is summarized as follows:

- In the T-gel studies,
 - Serum DHT concentrations: 130-210 ng/dL
 - Serum DHT/T ratios: 0.25-0.30
- In the oral TU studies (Andriol),
 - Serum DHT concentrations: 90-93 ng/dl
 - Serum DHT/T ratios: 0.4-0.5
- In the DHT-gel studies,
 - DHT concentrations: 244-732 ng/dL (dependent on dosage)
 - DHT/T ratios: 1.4-12.2

[Reviewer’s Comments: Pharmacologically, the DHT that results from oral TU is contributed from metabolic pathways involving both T and DHTU, while non-TU products produce DHT only from T. Thus, a higher DHT concentrations following oral TU administration is expected. It is well known that DHT has greater androgenic potency than T. Adequately controlling or “replacing” DHT concentration is important for both efficacy and safety of this product.]

9.2.4 Potential risks of the elevated DHT and DHT/T ratios

In the literature summary that was provided, the Applicant stated their opinion that elevated serum DHT concentrations, particularly from exposure to DHT-gel products, appears not to confer increased prostate or non-prostate risks in hypogonadal males.

As summarized in **Table 38**, five published randomized, double-blind, placebo-controlled trials on DHT-gel were discussed in the Applicant’s literature review. The study population was mostly healthy adult males, with 232 men on DHT-gel (145 healthy males and 87 hypogonadal males) and 192 men on placebo who received at least one dose. The DHT-gel dose ranged from 35 to 250 mg/day for up to 24 months across the studies. A total of 207 subjects completed their studies. The primary objective in those studies was to assess effectiveness of DHT-gel for male hypogonadism. The potential prostate and non-prostate adverse effects were a part of the routine safety evaluation, including AE monitoring and clinical laboratory tests.

The DHT-gel treatment increased serum DHT 5-10 fold above baseline and the mean serum DHT concentrations reached 3-9x upper limit of normal (ULN), and DHT/T ratios increased by 10-30 times from baseline.

Adverse effects on prostate:

Prostate evaluation was performed routinely during those placebo-controlled studies, including serum PSA, prostate volume (TRUS or DRE) and IPSS scores. The Applicant did not observe trends of increase in the prostate volume or in IPSS scores associated with short-term and long-term DHT-gel treatments. However, long-term exposure to DHT-gel tended to increase the mean serum PSA with more DHT-treated subjects experiencing increased PSA from baseline compared to the placebo group.

In addition, the Applicant observed no apparent relationships between intra-prostatic DHT and DHT/T ratios and circulating T and DHT levels. The Applicant asserted that the literature suggests that intra-prostatic DHT levels are primarily controlled by intra-prostatic factors rather than by systemic T and DHT levels.

There was very limited literature information in the submission in order to conduct risk assessment of long-term exposure to T and DHT associated with prostate cancers. According to the Applicant, a large placebo-controlled trial, entitled *Reduction by Dutasteride of Prostate Cancer Events (REDUCE)* trial⁴, showed no relationship between circulating levels of DHT or T and the risk of prostate cancer. However, that conclusion was based on baseline T and DHT

⁴ Muller RL et al: Serum Testosterone and Dihydrotestosterone and Prostate Cancer Risk in the Placebo Arm of the Reduction by Dutasteride of Prostate Cancer Events Trial. *Eur Urol* 62: 757-764, 2012

levels (low vs. normal) not through exogenous exposure to any T or DHT products; therefore, that study results and conclusions are not directly applicable to supraphysiological DHT exposure.

Table 38. Randomized placebo-controlled studies of transdermal DHT-gel from literature
(Based on the literature submitted by the Applicant)

Duration of Dosing (Month)	Subject†	DHT-gel dose	Serum level in the DHT-gel group‡			Overview of Reported Safety	Reference
			DHT (ng/dL)	T (ng/dL)	DHT/T ratio		
1	Healthy male 35-55 yrs N=12D N=15P	70mg/day	7x Base: 35	decreased Base: 440	NA	No change in clinical labs, No difference in intra-prostate DHT, PSA, PV and androgen-related gene expression	Page et al: <i>J Clin Endocrinol Metab</i> 96: 430-437, 2011
3	Healthy male >60 yrs; N=18D N=19P	70 mg qd	490-534 Base: 41	144-210 Base: 432	2.4-3.7 Base: 0.09	No adverse effects on prostate and cardiovascular system; Increased Hct/Hb (in normal range);	Ly et al: <i>J Clin Endocrinol Metab</i> 86: 4078-4088, 2001
6	Healthy male 50-70 yrs; N=60D N=60P	125-250 mg/day	238 Base: 44	170 Base: 464	1.4 Base: 0.09	No adverse effects on prostate; no changes on lipids; increased Hct/Hb	Kunelius et al: <i>J Clin Endocrinol Metab</i> 87: 1467-1472, 2002
6	Hypogonadal male, 55-80 yrs; N=43D N=44D N=41P	35mg/day 70mg/day	244-300 Base: NA	106-124 Base: 226-231	2.3-2.4 Base: NA	2 deaths (unrelated), n=15 SAEs (2 related: prostate cancer and one increased PSA); no effects on prostate volume but increased PSA (3.4% on DHT-gel vs. 0% on placebo); increased Hct/Hb and polycythemia; no effects on BP	A Phase 2 trial from <i>Ascend Therapeutics, Inc.</i> IND?
24	Healthy male without prostate disease >50 yrs; N=55D N=58P	70mg/day	730 Base: 64	69 Base: 490	10.5 Base: 0.1	Slightly increased PSA & prostate volume; no changes on lipids; increased Hct >50%; increased serum creatinine; SAEs: DVT, PE, pericarditis and atrial fibrillation	Idan et al: <i>Ann Intern Med</i> 153:621-632, 2010

† D: DHT-gel, P: placebo

‡ Serum DHT and T were stable over the course of treatment; Base: baseline; NA: not available

Non-prostate adverse effects

Non-prostate adverse effects of supraphysiological DHT exposures were monitored during the DHT-gel studies through capture of routine clinical AEs and clinical laboratory evaluations, including serum lipid profile, CV biomarkers, and Hct/Hb.

Clinical AEs, including Cardiovascular (CV) AEs: CV-related SAEs were sporadically reported, including pericarditis, atrial fibrillation, pulmonary embolism (PE), deep vein thrombosis (DVT), unstable angina, arterial stenosis, and coronary blockage. Although these SAEs were considered not related to the study drug by the investigators, the studies were too small for causality adjudication.

The Applicant points out that in one case-control study, a high DHT level (around ULN) actually showed a lower association (a lower risk) with claudication than a lower DHT level. The

Applicant conjectures that this might be related to a vasodilatory effect of DHT-gel that was observed in another clinical study. The Applicant also points to a cardiac stress study in eugonadal males with coronary artery disease who has been treated with DHT-gel (32 mg/day for 3 months) in which improved left ventricular function was observed.

[Reviewer's Comments: The data on CV risk and DHT is very limited and is inconclusive.]

CV biomarkers: The Applicant purports that in one, randomized, double-blind, placebo-controlled study, hs-CRP, ICAM-1 and VACM-1, showed no changes after 3 months of DHT-gel (70 mg/day) as compared to placebo.

Lipid profile: The Applicant purports that treatment with DHT-gel resulted in no changes in the lipid profile, including HDL, in most of the cited studies, following up to 24 months of exposure.

Hct/Hb: The Applicant observed that treatment with DHT-gel clearly resulted in increased Hct/Hb and polycythemia as observed in several placebo-controlled studies. The incidences of increased Hct/Hb or polycythemia appear time-dependent, with greater incidences in studies of long-term DHT exposure (such as 24 months).

Relevance to the oral TU product:

Although the Applicant believes that supraphysiological DHT exposure from DHT-gel treatment in the published clinical studies cited in the submission appears not to have caused serious adverse reactions in both prostate and non-prostate organ systems, the studies were too small, particularly for long-term exposure studies, and were not specifically designed for the risk assessment. For the proposed oral TU product, Rextoro, in this NDA, the high circulating DHT exposure (>1 x ULN for the labeling dosing regimen) together with high systemic TU and DHTU exposure may pose different risks than DHT-gel alone, as shown in the literature.

There is a clear association of increased Hb/Hct with increasing androgen exposure, including exposure to DHT, and this adverse effect appears to worsen with long-term exposure.

The intra-prostate DHT independency of the circulating DHT from DHT-gel products may also not fully apply to the oral TU treatment in hypogonadal males. Both TU and its major metabolite (in terms of AUC) DHTU were highly lipophilic and hypothetically they may be sequestered in the prostate and converted there to DHT.

[Reviewer's Comment: Overall, potential risks of the high systemic DHT, DHTU and TU exposures associated with chronic use of oral TU needs further assessment in the target population.]

9.3 Labeling Recommendations

No formal labeling review was conducted during this review cycle due to the CR action.

9.4 Advisory Committee Meeting

An joint meeting of “**The Bone, Reproductive and Urologic Drugs Advisory Committee and The Drug Safety and Risk Management Advisory Committee**” was held on September 18, 2014. The questions to the committees for discussion and voting are summarized in **Table 39**. The majority of members concluded that both efficacy and safety evidence of this product has not been adequately established.

Table 39. Questions for the AC discussion and voting

Question to AC	Voting Result		
	Yes	No	Abstain
1. VOTE: Is there sufficient evidence to conclude that oral testosterone undecanoate is effective as testosterone replacement therapy? <i>Please provide a rationale for your vote.</i>	8	12	1
2. DISCUSSION: Discuss whether the safety of oral testosterone undecanoate has been adequately characterized. If additional safety data are needed, discuss the type(s) of data that are needed and whether these data should be obtained pre-approval or whether these data can be obtained post-approval.	2	18†	1
3. VOTE: Is the overall benefit/risk profile of oral testosterone undecanoate acceptable to support approval of this product for testosterone replacement therapy? <i>Please provide a rationale for your vote.</i>	3	18	0

† Majority of members commented that the safety of oral TU had not been adequately characterized..

9.5 Clinical Investigator Financial Disclosure (Using the Recommended Review Template)

Application Number: **NDA206-089**

Submission Date(s): **Jan 3, 2014**

Applicant: **Clarus Therapeutics Inc.**

Product: **Rextoro capsules (oral testosterone undecanoate)**

Reviewer: **Jin Chen, MD, PhD**

Date of Review: **Mar 4, 2014**

Covered Clinical Study (Name and/or Number) **Two phase 3 trials:
CLAR-09007 and CLAR-12011**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 267 (148 in CLAR-09007 and 119 in CLAR-12011)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2 investigators at Site (b) (6) of CLAR-09007 (b) (6) and 1 investigator at Site (b) (6) of CLAR-12011 (b) (6)		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

[Reviewer's Comment: See Section [3.3 Financial Disclosures above](#) for a detailed summary and discussion.]

9.6 Individual Trial Review

9.6.1 CLAR-12011 (4-month pivotal Phase 3 trial)

Title: “Open-label study of the safety and efficacy of Oral testosterone undecanoate (TU) in hypogonadal men”

Study location: 27 sites in US (24 sites enrolled ≥ 1 subject)
Study duration: Feb 8, 2013 to July 29, 2013
Study indication: Testosterone replacement therapy in the treatment of male hypogonadism
GCP compliance: Yes
Central Lab: (b) (4)

Objective:

Primary: To determine the efficacy of oral TU in hypogonadal males based on the percentage of treated subjects with 24-hour average serum T concentration (C_{avg}) within the normal range

Secondary:

- To determine the percentage of treated subjects with maximum T concentrations (C_{max}): ≤ 1500 ng/dL, >1800 to ≤ 2500 ng/dL, and >2500 ng/dL
- To assess the effectiveness of dose titration at steady-state, if needed, based upon a single serum T sample obtained at 3-5 hours post-AM dose on Day 30 (± 3 days) and on Day 72 (± 3 days)
- To define the safety profile of the oral TU product for up to ~ 114 days of continuous therapy based on: clinical adverse events, clinical chemistry and hematology (specifically serum lipid concentrations, Hb/Hct); and PSA

9.6.1.1 Study design and conduct:

This was an open-label, single-arm, dose-titration study in hypogonadal males. The duration of treatment was 4 months.

The overall study design was similar to Study CLAR-09007 except that this study included a single-arm with no comparator, had a less aggressive dose titration regimen for TU, and had a shorter duration of treatment (4 vs. 12 months). The study schedule and assessments are summarized in **Table 40**.

Table 40. Study schedule and assessment of CLAR-12011
(From the Applicant's Table 2 in Study CLAR-12011)

Study Days	Screening	Treatment					
	Days -21 to 0 (Weeks -3 to 0) Screening Visit	Days 0 Visit 1	Days 30 (±3 days) Visit 2	Day 42 (±3 days) Visit 3	Day 72 (±3 days) Visit 4	Day 84 (±3 days) Visit 5	Day 114 (±3 days) Visit 6
Informed consent	+						
Medical history	+						
Initial review of concomitant medications	+						
Physical examination with DRE	+						+
Serum total testosterone (T) [2 samples drawn at 1 hr (± 10 minutes) apart between 6:00 and 10:00 AM]	+						
Pre-dose T, free T, DHT, E2 [2 samples drawn 1 hr (± 10 minutes) apart between 6:00 and 10:00 AM for serum T; one sample for free T, DHT, and E2]		+					
Brief physical – vital signs (obtain vital signs, AEs and changes in concomitant medications)			+		+		
Eligibility labs (non-fasting) - PSA, hemoglobin and hematocrit, AST, ALT, ALP, serum bilirubin and creatinine, and dipstick U/A. HbA1c for diabetic subjects only	+						
Abbreviated safety labs (fasting) ^a		+					
Complete safety labs (fasting) (± 3 days for all visits)					+		+
SHBG		+					+
LH and FSH		+					
PSA	+						+
AUA/I-PSS	+						+
Study drug dispensed		+		+		+	
Dose titration (based on single sample drawn 3-5 hrs post dose at previous visit)				+		+	
Serial sampling ^b (24 hrs; over-night stay) total T, free T, DHT, E2, LH, and FSH							+
Serial sampling ^c (12 hrs post AM dose) total T, free T, DHT			+		+		
Adverse event monitoring, review of concomitant medications							→

DRE = digital rectal examination; T = testosterone; DHT = dihydrotestosterone; E2 = estradiol; hs-CRP = high sensitivity C-reactive protein; SHBG = sex hormone binding globulin; LH = luteinizing hormone; FSH = follicle-stimulating hormone; PSA = prostate-specific antigen; AUA/I-PSS = American Urological Association/International Prostate Symptom Score; AEs = adverse events; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; U/A = urinalysis; HbA1c = glycosylated hemoglobin

^aChemistry panel (sodium, potassium, chloride, bicarbonate, glucose, calcium), lipids (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides [TG]), complete blood count

^b30 minutes and 0 hr pre-dose, and 1, 2, 3-5, 6, 8, and 12 hrs post AM dose and 1, 2, 3-5, 6, 8, and 12 hrs post PM dose (e.g., 7:30 AM, 8:00, 9:05, 10:05, 11:05 - 1:05 PM, 2:05, 4:05, 8:05, 9:05, 10:05, 11:05 - 1:05 AM, 2:05, 4:05, and 8:05 AM)

^c30 minutes and 0 hr pre-dose, and 1, 2, 3-5, 6, 8, and 12 hrs post AM dose (e.g., 7:30 AM, 8:00, 9:05, 10:05, 11:05-1:05 PM, 2:05, 4:05, and 8:05 PM)

NOTE: Additional serum was collected, frozen, and stored on Days 0 and 114 for potential future testosterone metabolite and/or lipid-related analyses.

Treatment:

- Initial dose: 200 mg bid within 15 min after a meal
- Titration: dose titrated up or down by an increment of 50 mg based on serum total T concentration at **3-5 hours (C3-5) post-AM dose**; up to 2 dose titrations allowed, on Days 42 and/or Day 84 when serum total T fell outside the range of 250-700 ng/dL (**Figure 8**)
- Maximum dose: 300 mg bid
- Rationale for the dosage and titration regimen: Dosage and titration regimen based on the results (serum T-Cavg and Cmax) from Study CLAR-09007 (see the review of Study CLAR-09007 for details)

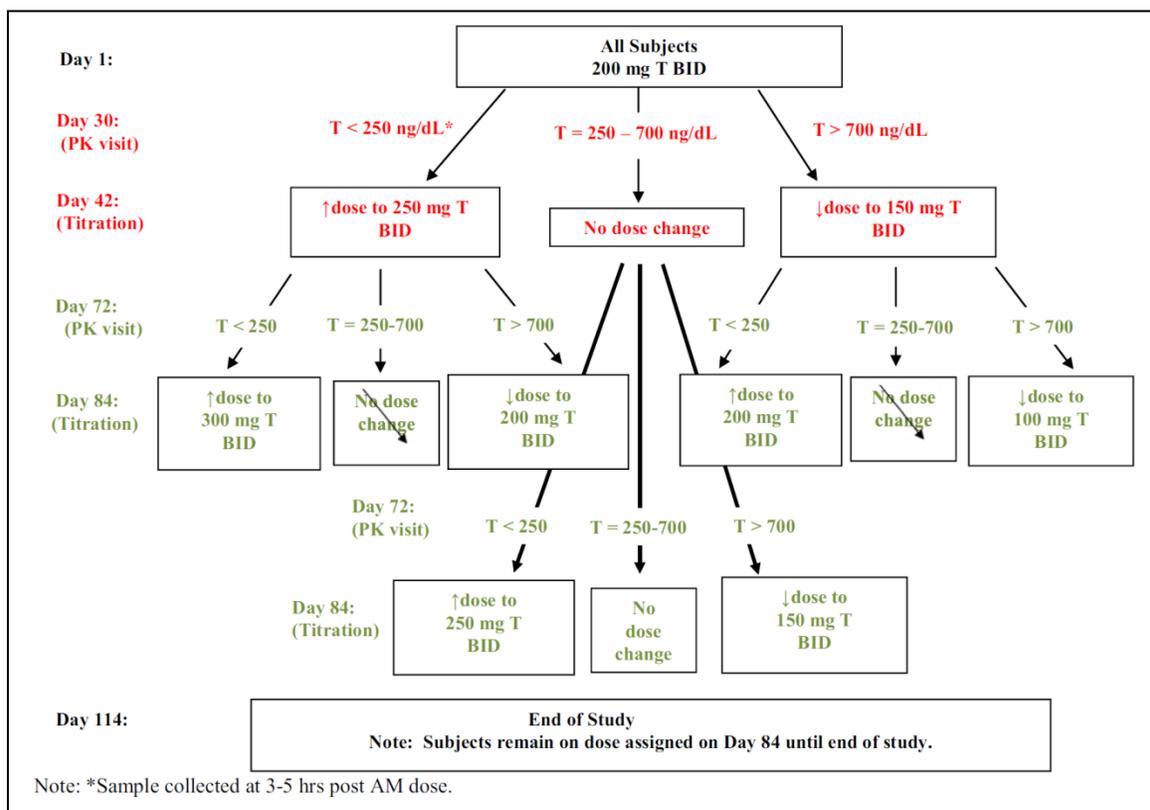
Visit schedule:

- Six on-treatment visits: on Days 0, 30, 42, 72, 84 and 114 (visits 1-6) with window ± 3 days
- Single PK sample for serum total T: on Days 30 and 72 (3-5 hours post-AM dose)
- Dose adjustment possible on Day 42: based on the Day 30 serum total T concentration
- Dose adjustment possible on Day 84: based on the Day 72 serum total T concentration

Assessments:

- Full PK evaluation:
 - 24-hour full PK (post-AM/PM doses) assessment on Day 114: serum total T, free T, DHT, E2, LH and FSH
 - 12-hour full PK (post-AM dose) assessments on Days 30 and 72: serum total T, free T and DHT only
- Single blood sample at 3-5 hours post-AM dose on Days 30 and 72 for serum total T concentration, used to determine need for dose titration on Day 42 and 84
- Efficacy assessments: no clinical efficacy parameters were measured
- Safety assessments:
 - Collection of clinical adverse events
 - Vital signs and body weight assessments on Days 30, 72 and 114
 - Physical examination at screening and on Day 114
 - Clinical chemistry and hematology (particularly lipids, Hb/Hct, and PSA) at screening and on Days 0, 30, 72 and 114
 - International Prostate Symptom Score (IPSS scores) at screening and on Day 114

Figure 8. Dose titration of oral TU in Study CLAR-12011



Source: From the Applicant's Figure 1 in the Study CLAR-12011 report

9.6.1.2 Statistical and analytical plans:

The statistical analysis plan (SAP) was finalized on Aug 7, 2013, after the study was terminated on July 29, 2013 and prior to database lock.

Sample size:

A total of 148 hypogonadal males were enrolled in order that at least 90 would complete through Day 114 (final) visit, with the following assumptions:

- ≥75% of subjects achieve a Cavg within the normal range for serum total T based on an earlier Phase 2 study (in which approximately 86% of subjects achieved this Cavg)
- Using one-sample model: 2-sided test, $\alpha = 0.05$, power = 0.85, with p (success) = 86% and $p_0 = 75\%$; ≥90 completers needed on Day 114
- Approximately 25% dropout rate prior to Day 114.

Analysis populations:

- Efficacy Population: Subjects who completed Visit 6 (Day 114) with sufficient PK data to calculate serum T Cavg; this population served as the basis for the primary analysis of efficacy.
- Safety Population: All subjects who received at least one dose of the study drug
- Pharmacokinetic Population: All subjects who had sufficient data points to calculate at least one PK parameter

Primary endpoint and analysis:

- The proportion (%) of subjects whose Cavg-24 (based on the 24-hr PK on Day 114) was within the range of 300-1000 ng/dL
- The 95% CI for the proportion (%) of subjects with Cavg-24 between 300-1000 ng/dL
- **Primary endpoint:** The trial will “win” on the primary efficacy endpoint if $\geq 75\%$ of subjects have serum total T Cavg-24h within the normal range 300-1000 ng/dL on Day 114 in the efficacy population with a lower bound of the associated 95% confidence interval $\geq 65\%$.
- Additional assessment: Proportion (%) of subjects whose Cavg-24 (based on the 24-hr PK on Day 114) was:
 - Cavg-24 < 300 ng/dL
 - Cavg-24 > 1000 ng/dL
 - *Post-hoc* sensitivity analyses of the primary endpoint were performed in the safety population and PK population with LOCF and WCS imputations for subjects with missing data on Day 114.

Secondary analysis:

- The frequencies (%) of subjects whose Cmax, based on the 24-hr PK on Day 114, were: ≤ 1500 ng/dL, > 1800 to ≤ 2500 ng/dL, and > 2500 ng/dL.
- Other PK parameters for serum T, including: Tmax, AUC0-24, and AUC0-12.
- PK parameters (Cmax, Tmax, AUC0-24, AUC0-12, and Cavg) for serum free T and serum DHT:
 - Post-AM dose on Days 30 and 72
 - Post-AM and -PM doses on Day 114
- PK parameters (AUC0-24 and Cavg) for estradiol (E2) on Day 114
- AUC for DHT/T ratios

Normal values of the tested hormones:

The normal ranges of test hormones referenced for this and other Phase 3 trials in this NDA were from the (b) (4) (Table 41), which was a central lab for all Phase 3 trials.

Table 41. Normal range of tested hormones in eugonadal males
(From Applicant's Table in the CLAR-12011 Report)

Hormone	Units	Normal Range	
		Lower Bound	Upper Bound
Total Testosterone (T)	ng/dL	300	1000
Free Testosterone (Free T)	ng/dL	3.66	16.62
Dihydrotestosterone (DHT)	ng/dL	13.69	76.88
DHT/T	ratio	0.0356	0.114
Estradiol (E2)	pg/mL	7.5	30.6
Follicle Stimulating Hormone (FSH)	mIU/mL	1.4	9.5
Luteinizing Hormone (LH)	mIU/mL	1.3	8.1
Sex Hormone Binding Globulin (SHBG)	nmol/L	10.78	46.62

Note: referenced from

(b) (4)

Study subject:

The same criteria as described in Study CLAR-09007 were used for the subject selection (see review of Study CLAR-009007 for details).

The key inclusion criteria:

- 1) Male 18-75 years of age
- 2) Two repeated serum total T concentrations \leq 300 mg/dL [signs and symptoms of hypogonadism were not required]

The key exclusion criteria

- IPSS \geq 19 points
- Serum PSA $>$ 3.9 ng/ml
- Body mass index (BMI) \geq 38 kg/m²
- Diabetes with HbA1c $>$ 9.5%
- Polycythemia or Hct $<$ 35% or $>$ 48%
- History of prostate cancer or breast cancer

Subjects with **confirmed Hct $>$ 54%** (by re-test) would be withdrawn from the study (Investigator could have advised the subject to undergo phlebotomy prior to making decision regarding withdrawal)

Protocol amendments

No amendments were made to the original protocol dated Dec 17, 2013 during the study conduct.

9.6.1.3 Subject disposition:

A total of 148 subjects were enrolled with the following disposition (**Table 42**):

- 144 received ≥ 1 doses (Safety population)
- 133 had sufficient PK data to calculate at least one PK parameter (PK population)
- 116 completed Visit 6 with sufficient PK data to calculate Cavg (Efficacy population)

Table 42. Subject disposition in Study CLAR-12011

Disposition	Oral TU N=148 n (%)
Safety Analysis Set	144 (97.3)
PK Analysis Set	133 (89.9)
Efficacy Analysis Set	116 (78.4)
Subjects Who Completed Study	117 (81.3)
Subjects Who Discontinued Study	27 (18.8)
Adverse Event	3 (2.1)
Lost to Follow-Up	5 (3.5)
Non-Compliance with Study Drug	2 (1.4)
Protocol Violation	1 (0.7)
Withdrawal of Consent	8 (5.6)
Hematocrit of > 54%	3 (2.1)
Other	5 (3.5)

Source: From the Applicant's Table 3 in Study CLAR-12011

Safety analysis set: all subjects who received at least one dose of the study drug.

PK analysis set: all subjects who had sufficient data points to calculate at least one PK parameter.

Efficacy analysis: all subjects who completed Day 144 visit with sufficient PK data for primary efficacy analysis.

The dropout rate on Day 114 was 18.8%, mainly due to withdrawal of consent and loss to follow-up. A total of 3 subjects (2.1%) discontinued due to an adverse event.

Protocol deviations:

Protocol deviations during the study were not summarized by the Applicant; instead they were presented in a Listing table. The Applicant stated "None of the (protocol) deviations affected the analyses".

9.6.1.4 Demographic and baseline characteristics:

The mean ages of the safety population was 54.8 (± 10.6) years with a mean BMI of 29.9 (± 3.9) kg/m². The majority of subjects were White (79.2%), followed by Black or African American (10.4%) and Asian (9%). Approximately, half of the participants had “pre-diabetes”, diabetes or hypertension (**Table 43**).

Medical history:

The Applicant did not summarize the medical history of the subjects in the study report, instead the Applicant referenced the Listings tables. These were analyzed by the reviewer.

Concomitant medications:

In the Safety population, approximately 83% subjects took at least one concomitant medication during the study. The most frequently used concomitant medications by class, as summarized below, was consistent with the underlying medical conditions in the study population.

- lipid-modifying agents (39.6%)
- vitamins (36.1%)
- agents acting on the renin-angiotensin system (33.3%)
- anti-thrombotic agents (26.4%)
- anti-inflammatory and anti-rheumatic products (25.7%)

Treatment compliance:

Compliance to study medication was assessed based on amount dispensed, amount returned, and amount lost/destroyed. The overall compliance rate was approximately 96% (± 15.1) with mean total daily oral TU dose of 347 mg (± 62.8).

Table 43. Demographics and baseline characteristics in the safety population

Characteristic	Oral TU N=144
Age (years)	
Mean ±SD	54.8 ±10.6
Median (Min, Max)	55.5 (27, 75)
Race, n (%)	
American Indian or Alaska Native	1 (0.7)
Asian	13 (9.0)
Black or African American	15 (10.4)
White	114 (79.2)
Other	1 (0.7)
Ethnicity, n (%)	
Hispanic or Latino	19 (13.2)
Not Hispanic or Latino	125 (86.8)
Height (cm)	
Mean ±SD	177.4 ±7.9
Median (Min, Max)	177.8 (154.9, 198.1)
Weight (kg)	
Mean ±SD	94.2 ±15.2
Median (Min, Max)	92.3 (56.0, 134.0)
BMI (kg/m²)	
Mean ±SD	29.9 ±3.9
Median (Min, Max)	29.6 (19.3, 37.7)
Baseline Characteristics, n (%)	
Pre-Diabetic (Glucose of 100-125 mg/dL)	45 (31.3)
Diabetes Mellitus	25 (17.4)
Hypertensive	65 (45.1)
Statin, Fibrate, Omega-3 FA, or Niacin Use	54 (37.5)

Source: From the Applicant's Table 4 in Study CLAR-12011 report

9.6.1.5 Primary endpoint

Primary analysis:

For the primary analysis, efficacy is demonstrated if the proportion of subjects with serum total T-Cavg-24hr within the normal range (300-1000 ng/dL) on Day 114 is at least 75% and the lower bound of the 95% confidence interval for this proportion is at least 65%. This primary analysis was conducted in those subjects who had serum total T-Cavg-24hr data on Day 114. Based on this analysis, the percentage of subjects with a serum total T-Cavg-24hr within the normal range on Day 114 was 75.0% (87 of 116 subjects) with a corresponding 95% confidence interval of 66.1% to 82.6% (Table 44).

The majority of subjects who did not have Cavg within the normal range (n=42) had serum T-Cavg-24hr <300 ng/dL (n=40) rather serum T Cavg >1000 ng/dL (n=2).

Table 44. Primary endpoint analyses in Study CLAR-12011

Analysis	Analysis Population [†] (N)	Subjects with normal T-Cavg-24h* % (n)	95% CI
Pre-specified primary analysis			
Completer	E 116	75.0% (87)	66.1%, 82.6%
Post-hoc sensitivity analyses[‡]			
LOCF	S 144	70.8% (102)	62.7%, 78.1%
WCS	S 144	60.4% (87)	51.9%, 68.5%

Source: Applicant's Table 7; the analyses are confirmed by the statistical review team

* T-Cavg-24hr: time-weighted average concentration over 24 hours on Day 114;

The normal serum total T: 300- 1000 ng/dl

[†] E - Efficacy Population: subjects with sufficient PK data on Day 114

S - Safety Population: subjects received ≥1 dose during the study

[‡] LOCF: last observation carried forward

WCS: the worst case scenario, all subjects with missing data on Day 114 considered treatment failure

Post-hoc sensitivity analyses:

Although the pre-specified primary efficacy analysis met the criteria for demonstration of efficacy, the analysis did not include 19.4% of subjects who did not have serum total T-Cavg-24hr data on Day 114 and who took at least one dose of oral TU. Given that this is a single, open-label pivotal study without a concurrent control group for a testosterone product with a new route of administration, post-hoc sensitivity analyses were conducted to assess the impact of missing data on the consistency of the results by using all subjects who took study treatment.

These *post-hoc* sensitivity analyses were performed using all 144 subjects who took at least one dose of oral TU and accounted for missing data in various ways. One approach used last

observation carried forward (LOCF), including baseline. Another approach used the worst case scenario (WCS), that is, subjects with missing data were considered failures.

The worst case scenario (WCS) is a conservative approach because it assumes that all missing data were below the threshold for success even though there may be other reasons for the missing data that are unrelated to efficacy. The LOCF approach is not as conservative as the worst case scenario because 17 of the 28 subjects did have post baseline data and 11 subjects did not have any post-baseline data even though they took study product (range of days that the product was taken: 4 to 60 days).

For the LOCF analysis, the percentage of subjects with a serum total T-Cavg-24hr within the normal range on Day 114 was 70.8% (102 of 144 subjects) with a 95% confidence interval of 62.7% to 78.1%. For the WCS analysis, the percentage of subjects with a serum total T-Cavg-24 within the normal range on Day 114 was 60.4% (87 of 144 subjects) with a 95% confidence interval of 51.9% to 68.5%. Both sensitivity analyses did not meet the thresholds for efficacy (Table 44).

9.6.1.6 Secondary endpoints

Serum T Cmax on Day 114:

The proportions of subjects with T Cmax <1500 ng/dL met the threshold requirements on Day 114. Less than 5% of subjects were supposed to have T Cmax >1800 to ≤2500 ng/dL; 6% of subjects had a T Cmax in that range. No subjects were supposed to have T Cmax >2500 ng/dL; however, there were four subjects in this study who had Cmax >2500 ng/dL (Table 45).

Table 45. Serum total T Cmax on Day 114
(From the Applicant's Table 9 in Study CLAR-12011)

Cmax (ng/dL)	Oral TU (N=116) n (%)	Threshold
<1500	95 (81.9%)	>85%
>1500-1800	10 (8.6%)	<10%
>1800-2500	7 (6.0%)	<5%
>2500	4 (3.4%)	0%

In those 4 cases, the serum T Cmax>2500 ng/dL was transient, resulting from a single assay on Day 114 (except in the case of 514-003, in which there were two consecutive assays showing T concentration >2500 ng/dL), as shown in the serum T profile of those 4 individual subjects (Figure 9). One subject (#514-003) was suspected to have taken a double dose. The high Cmax in these 4 cases was not associated with any serious AEs in all four subjects, as per the Applicant's narrative summary (Table 46).

Figure 9. Serum T profile of four subjects with C_{max}>2500 ng/dL on Day 114
(From the Applicant's Figure 3 in Study CLAR-12011)

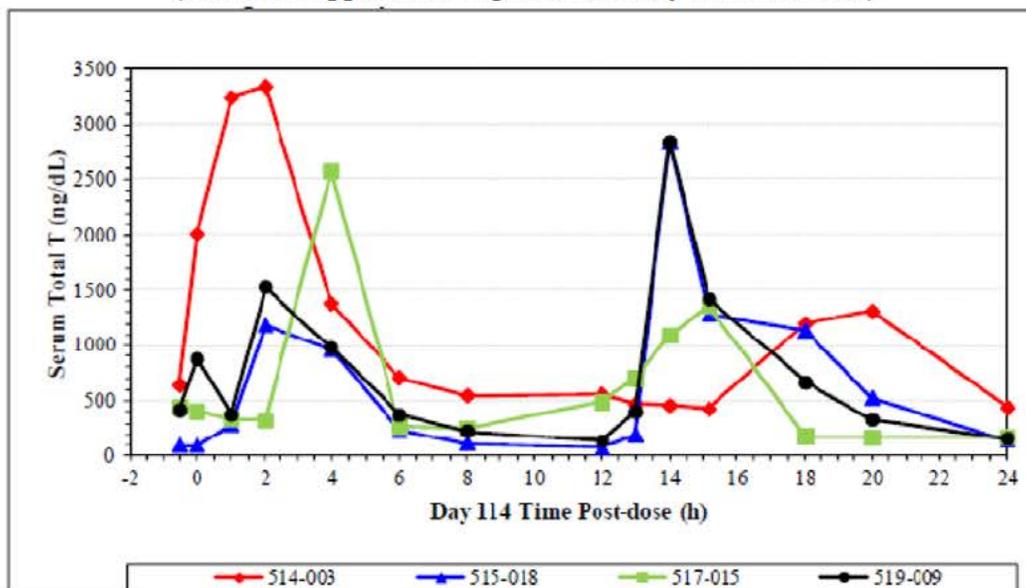


Table 46. Narrative summary of subjects with serum T C_{max}>2500 ng/dL on day 114
(From the Applicant's narratives in Study CLAR-12011)

Subject ID	Age & ethnic	C _{max} (ng/dL)	Exposure (mg, Day) [†]	AEs	Medical History	Concomitant medications	Remark [‡]
(b) (6)	56, white	3340	Day 114 (2 hrs post-AM) 150 mg bid	Hip arthralgia on Day 30	BMI 35, hypogonadism, depression, bipolar disorder	Ambien, acetaminophen /hydrocodone	Day 114 C3-5 post-AM 1380 ng/dL; (suspected double dose as per Applicant)
	46, white	2838	Day 114 (2 hr post-PM) 200 mg bid	Head injury (mild) on Day 38	BMI 27. Hypogonadism, asthma, back pain	naproxen	Day 114 C3-5 post-PM 1290 ng/dL
	54, white	2570	Day 114 (post-AM) 150 mg bid	None	BMI 27, hypogonadism, coronary artery disease, s/p stent placement and MI, high cholesterol, hypertension	metoprolol, clopidogrel and simvastatin	Day 114 C _{max} <1500 post-PM dose
	52, white	2840	Day 114 (2 hr post-PM) 200 mg bid	nasal congestion (moderate severity) on Day 21	BMI 37, hypogonadism, tinnitus, GERD, high cholesterol, erectile dysfunction, decreased libido, rash to Androderm and seasonal allergies	simvastatin, omeprazole and aspirin	Day 114 C3-5 = 1420 ng/dL post-PM dose

[†] The oral TU dose at the time of C_{max} measurement and duration of dosing

[‡] C3-5: the serum total T concentration at 3-5 hours post-AM dose (a single PK sample)

PK profile of serum total T:

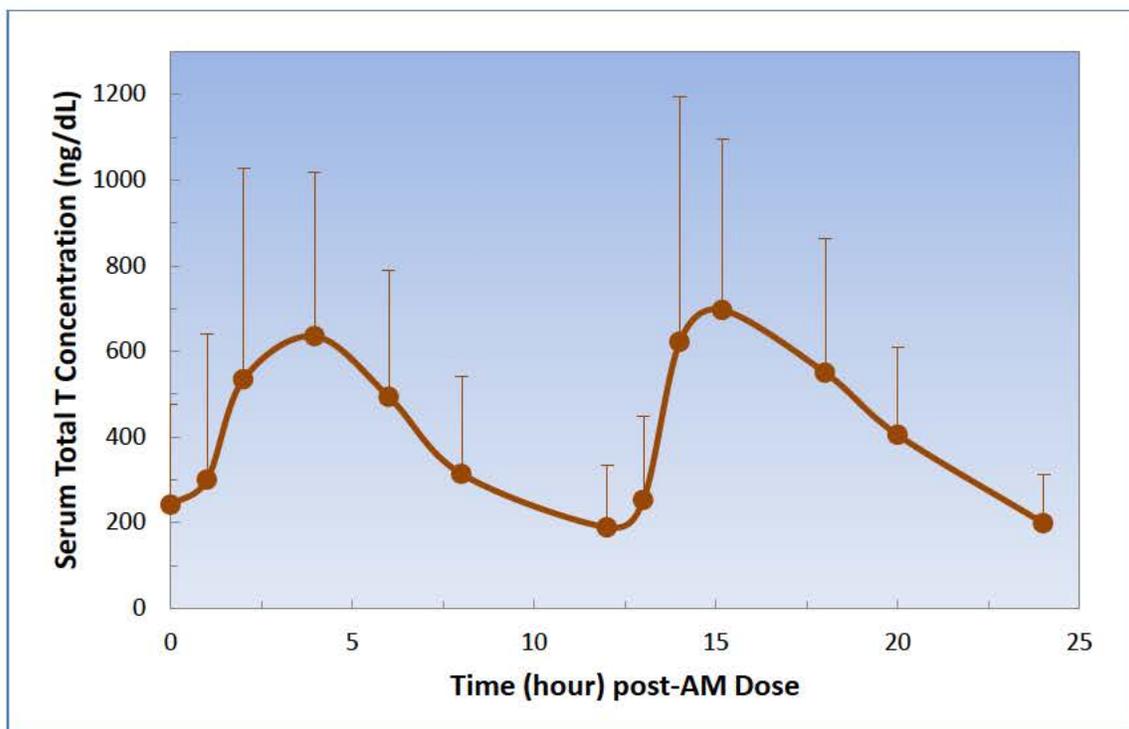
The average overall PK parameters for serum total T from the three full PK evaluations (conducted for 12 hours on Days 30 and 72 and for 24 hours in Day 114) appear comparable (see the Clinical Pharmacology review for details), as summarized below and in **Table 47**:

- C_{max} : 928 to 1107 ng/dL
- T_{max} : 4-4.5 hours post-AM or -PM dose
- AUC_{12-hrs} : 4763-6111 ng/h/dL
- $C_{avg\ 24-hrs}$: 422-509 ng/dL
- C_{min} (pre-dose): 189-272 ng/dL
- C_{min} (12 hours post-dose and prior to next dose): 189-213 ng/dL

The systemic T exposure was slightly higher on Day 30 which was likely attributed to the fixed starting dose of 200 mg bid during the first 30 days in all subjects. The majority of subjects titrated down to 150 mg or 100 mg bid after Day 30

On Day 114, the PK profile of serum total T appears comparable between the post-AM and post-PM doses (**Figure 10**), but the average C_{max} and C_{avg} from the post-PM dose were approximately 29% and 23% greater, respectively, compared to the post-AM dose.

Figure 10. Serum total T profile following oral TU on Day 114



Source: From the Applicant's Table A-1 in the Study CLAR-12011 PK report. Data were Mean \pm SD of serum total T concentrations following final titrated doses of oral TU on Day 114 in efficacy population.

Table 47. PK profile of serum total T over 114 days in PK population

PK Visit	PK Parameter†	Units	N	Mean	SD
Day 30 AM	Cmax	ng/dL	133	1106.5	707.9
	Tmax	hour		4.1	1.8
	AUC-12 hrs	ng.h/dL		6110.5	2665.0
	Cavg-12 hrs	ng/dL		509.2	222.1
	Cpre	ng/dL		267.9	164.8
	C12	ng/dL		203.3	125.5
Day 72 AM	Cmax	ng/dL	130	928.4	514.2
	Tmax	hour		4.5	2.0
	AUC-12 hrs	ng.h/dL		5455.1	2306.6
	Cavg-12 hrs	ng/dL		454.6	192.2
	Cpre	ng/dL		271.5	218.8
	C12	ng/dL		213.3	164.7
Day 114 AM	Cmax	ng/dL	116	826.6	504.5
	Tmax	hour		4.2	2.3
	AUC-12 hrs	ng.h/dL		4763.2	2350.3
	Cavg-12 hrs	ng/dL		397.5	197.5
	Cpre	ng/dL		251.5	199.6
	C12	ng/dL		189.3	143.3
Day 114 PM	Cmax	ng/dL	116	920.2	526.8
	Tmax‡	hour		16.4	2.2
	AUC-12 hrs	ng.h/dL		5371.5	2170.0
	Cavg-12 hrs	ng/dL		448.1	180.9
	Cpre	ng/dL		189.3	143.3
	C12	ng/dL		198.8	114.7
Day 114 (Full)	Cmax	ng/dL	116	1061.7	581.13
	Tmax	hour		10.8	6.1
	AUC-24 hrs	ng.h/dL		10134.7	4111.1
	Cavg-24 hrs	ng/dL		422.3	171.3
	Cpre	ng/dL		251.5	199.6
	C12	ng/dL		198.8	114.7

Source: From the Applicant's Tables 3 and 22 in Study CLAR-12011 report

† Cpre: serum T concentration at the pre-dose; C12: serum T concentration at 12 hours post-dose and prior to the next dose

‡ Tmax was the time to the highest serum T concentration during the 24-hours. The actual Tmax post PM dose was approximately 4 hours (**Figure 10**)

Duration of serum T within the normal range:

The mean duration of serum T within the normal range was 51% of the treatment day on Day 114; 44% of time the serum T concentration was <300 ng/dL and 5% of the time, it was >1000 ng/dL (**Table 48**).

The Applicant believes that “*T effects do not necessarily require the serum T concentration to be in the eugonadal range for the entire dosing interval*” with the following justifications/rationales:

- In eugonadal males there is diurnal variability in serum T concentration with values below the normal range
- DHT concentrations rise subsequent to rises in T concentrations as demonstrated by concentration-time profiles and the serum DHT PK profile was in the upper half of the normal range, or above the normal range, on Day 114.
- PD effects of oral TU were comparable between this study and Study CLAR-09007.
- The half-life of T and DHT in tissues may be longer than the serum half-life.
- In vitro evidence suggests that androgen receptor occupancy is prolonged.
- AEs associated with androgen withdrawal were not frequently reported in subjects treated with oral TU.

[*Reviewer’s Comments: PD parameters were not assessed in this study. The other Applicant’s rationales are considered reasonable, though theoretical in large part.*]

Table 48. Duration of serum T total concentrations on Day 114 within or outside the normal range
(From the Applicant’s Table 11 in Study CLAR-12011)

Serum Total T (ng/dL)	Efficacy Population				Population with normal T Cavg			
	N	Mean	SD	95% CI	N	Mean	SD	95% CI
300-1000	116	50.7%	21.51%	46.7%, 54.6%	87	57.9%	18.20%	54.1%, 61.7%
<300	116	43.9%	24.19%	39.5%, 48.3%	87	35.9%	18.69%	32.0%, 39.8%
>1000	116	5.4%	9.49%	3.7%, 7.1%	87	6.2%	8.66%	4.4%, 8.0%

Note: The percentage of the day (24 hours on Day 114)

Subgroup analysis of T Cavg:

The subgroup analyses of serum total T Cavg by age, body weight, BMI and race/ethnicity showed that subjects with age >65 years, BMI ≥ 30 kg/m² or body weight >93 kg appear slightly less likely to reach the normal range of serum T (**Table 49**). Also, slightly lower proportions of Blacks and Hispanic/Latinos achieved normal T values compared to Whites or non-Hispanics. However, the subgroup analyses by age, race and ethnicity are limited by the small size of the subsets for age >65 years old, Blacks and Hispanics.

Table 49. Subgroup analysis of serum T Cavg

Subgroup	N	Cavg 300-100 ng/dL		Cavg >1000 or <300 ng/dL	
		N (%)	95% CI	N (%)	95% CI
Age					
≤ 65 years	97	73 (75.3%)	65.5%, 83.5%	24 (24.7%)	16.5%, 34.5%
> 65 years	19	14 (73.7%)	48.8%, 90.9%	5 (26.3%)	9.2%, 51.2%
Baseline weight					
≤ 93 kg	58	45 (77.6%)	64.7%, 87.5%	13 (22.4%)	12.5%, 35.3%
> 93 kg	58	42 (72.4%)	59.1%, 83.3%	16 (27.6%)	16.7%, 40.9%
Baseline BMI					
< 30 kg/m ²	60	47 (78.3%)	65.8%, 87.9%	13 (21.7%)	12.1%, 34.2%
≥ 30 kg/m ²	56	40 (71.4%)	57.8%, 82.7%	16 (28.6%)	17.3%, 42.2%
Race					
Black	12	8 (66.7%)	34.9%, 90.1%	4 (33.3%)	9.9%, 65.1%
White	95	70 (73.7%)	63.6%, 82.2%	25 (26.3%)	17.8%, 36.4%
Other	9	9 (100.0%)	66.4%, 100.0%	0	0.00%, 33.6%
Ethnicity					
Hispanic/Latino	16	11 (68.8%)	41.3%, 89.0%	5 (31.3%)	11.0%, 58.7%
Non-Hispanic/Latino	100	76 (76.0%)	66.4%, 84.0%	24 (24.0%)	16.0%, 33.6%

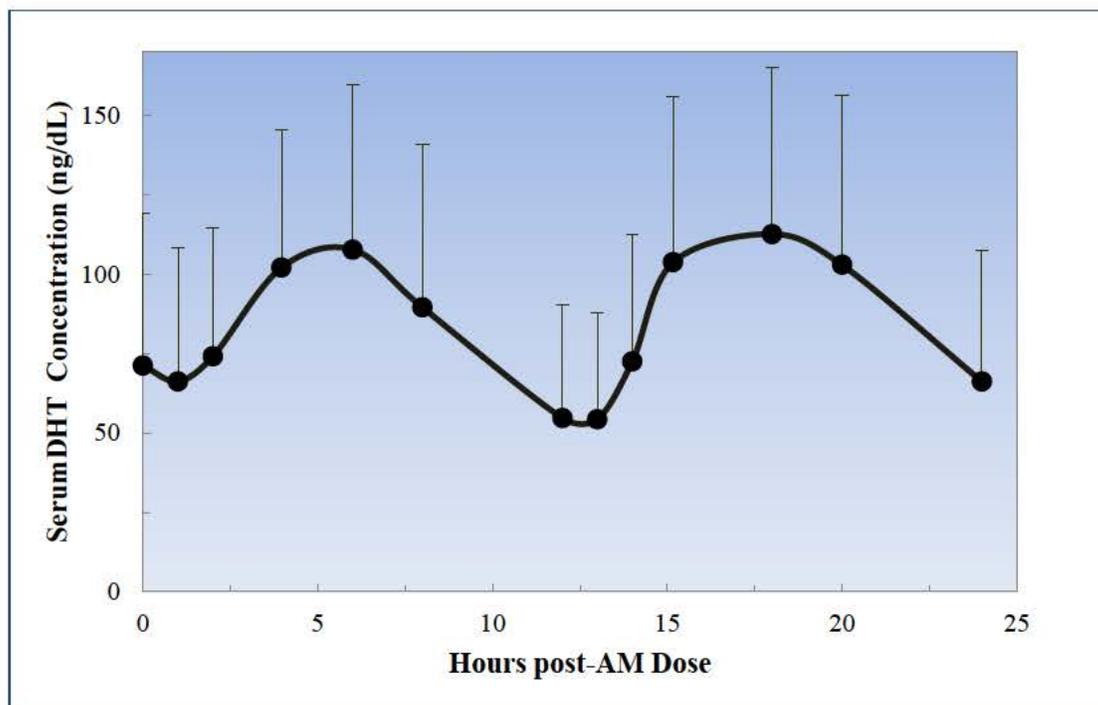
Source: From the Applicant's Table 18 in Study CLAR-12011 report

[Reviewer's Comments: *Although the sample size is small (n=28), it is notable that the product clearly failed to meet the success thresholds in Black and Hispanic subjects, an important subgroup.*]

DHT and DHT/T ratios:

The mean baseline DHT concentration was approximately 18 ng/dL, near the lower limit of normal (13.69-76.88 ng/dL). The serum DHT profile after oral TU were similar in shape to the serum T profile with T_{max} delayed approximately 0.3-1.4 hours compared to T (**Figure 11**). The mean serum DHT concentration after the fixed dose of 200 mg bid for 30 days was 137.1 ng/dL (**Table 50**), approximately 1.8-fold the upper limit of normal. The mean serum DHT concentration on Day 114 was lower but was still 1.1-fold above the upper limit of normal.

Figure 11. Serum DHT profile following oral TU on Day 114



Source: From the Applicant's Table 28 in the Study CLAR-12011 PK report. Data were Mean \pm SD of serum DHT concentrations following final titrated doses of oral TU on Day 114 in efficacy population.

PK parameters of serum DHT: In the 3 full PK evaluation periods (conducted for 12 hours on Days 30 and 72, and for 24 hours on Day 114), the mean DHT C_{avg}, C_{max} and AUC were higher on Day 30 than on Days 72 and 114 (**Table 50**).

- DHT C_{baseline}: 17.8 \pm 8.6 ng/dL
- DHT C_{avg}: 84-87 ng/dL on Days 72 and 114 vs. 137 ng/dL on Day 30
- DHT C_{max}: 142-148 ng/dL on Days 72 and 114 vs. 209 ng/dL on Day 30
- DHT C₁₂ (concentration 12 hours post dose): 55-64 ng/dL on Days 72 and 114 vs. 86 ng/dL on Day 30

The higher DHT exposure on Day 30 as compared to the other visits was likely due to the fixed starting dose of 200 mg bid for the first 30 days in all subjects. Approximately 66% of subjects were titrated down to 150 mg bid on Day 72, and by the end of study (Day 114 visit), 58% subjects were on 150 mg bid and 28% of subjects were on 100 mg bid.

[Reviewer's Comments: It is notable that mean serum DHT concentration is above the upper limit of normal on Day 114, subsequent to all titration.]

DHT/T ratios: The DHT/T ratios of AUC ranged from 0.22 to 0.29 in the 3 full PK evaluations (Days 30, 72 and 114) and there were no time-dependent changes (**Table 50**). The baseline DHT/T ratio was 0.076 \pm 0.034.

Table 50. PK parameters of serum DHT and DHT/T ratios in PK population

PK Visit	PK Parameter	Units	N	Mean	SD
Day 114 (Full)	Cpre	ng/dL	116	75.5	50.8
	C24	ng/dL		66.2	41.4
	Cmax	ng/dL		147.5	59.7
	Tmax	hour		12.095	6.8
	AUC	ng.h/dL		2084.7	864.8
	Cavg	ng/dL		86.9	36.0
	DHT/T	ratio		0.22	0.086
Day 30 AM	Cpre	ng/dL	133	106.7	68.1
	C12	ng/dL		86.2	55.0
	Cmax	ng/dL		209.2	106.22
	Tmax	hour		4.4	2.3
	AUC	ng.h/dL		1641.5	785.4
	Cavg	ng/dL		137.1	65.8
	DHT/T	ratio		0.29	0.15
Day 72 AM	Cpre	ng/dL	130	80.1	54.7
	C12	ng/dL		64.3	41.6
	Cmax	ng/dL		142.0	63.9
	Tmax	hour		5.2	2.4
	AUC	ng.h/dL		1145.3	550.5
	Cavg	ng/dL		95.6	46.0
	DHT/T	ratio		0.22	0.08
Day 114 AM	Cpre	ng/dL	116	75.5	80.8
	C12	ng/dL		54.7	35.8
	Cmax	ng/dL		127.1	58.0
	Tmax	hour		4.7	2.6
	AUC	ng.h/dL		1007.7	446.7
	Cavg	ng/dL		84.1	37.3
	DHT/T	ratio		0.23	0.09
Day 114 PM	Cpre	ng/dL	116	54.7	35.8
	C12	ng/dL		66.2	41.4
	Cmax	ng/dL		133.8	55.3
	Tmax	hour		17.8	2.6
	AUC	ng.h/dL		1077.0	463.4
	Cavg	ng/dL		89.4	38.4
	DHT/T	ratio		0.21	0.09

Source: From the Applicant's Table 12 and 29 in Study CLAR-12011 report

Note: the baseline DHT was 17.8±8.6 ng/dL and baseline DHT/T ratio was 0.076 ±0.034

[Reviewer's Comments: *The mean average and mean maximum DHT concentrations on Day 114 are above the upper limit of normal of 76.88. The mean DHT/T concentration ratio (>0.20) also appears to be supraphysiological as the reported normal range was 0.11. The clinical impact of these DHT results is not definitively known, but they do raise some degree of concern.]*

Free T and Free T/T ratios:

The mean serum free T: The mean serum free T increased from the lower limit of normal (LLN) at baseline to the middle of the normal range (3.7-16.6 ng/dL) across the three PK visits (on Days 30, 72 and 114):

- Baseline: 3.8 ng/dL
- C12: 3.8-4.4 ng/dL
- Cpre: 5.3-6.3 ng/dL
- Cavg: 8.4-12.6 ng/dL

The mean free T/T ratios: The mean free T/total T ratios increased from a baseline of 1.6% to 2.2-2.4% across the three PK visits (on Days 30, 72 and 114). The ratios appeared consistent with a wide range of T Cavg levels.

Sex Hormone Binding Globulin (SHBG):

Serum SHBG concentration was measured at baseline and on Day 114. The mean SHBG concentration decreased from baseline (34.5 nM) to Day 114 (22.4 nM) by approximately 35%, but still remained within the normal range (10.8-46.6 nM). The SBHG decrease appears dose-related (**Figure 12**).

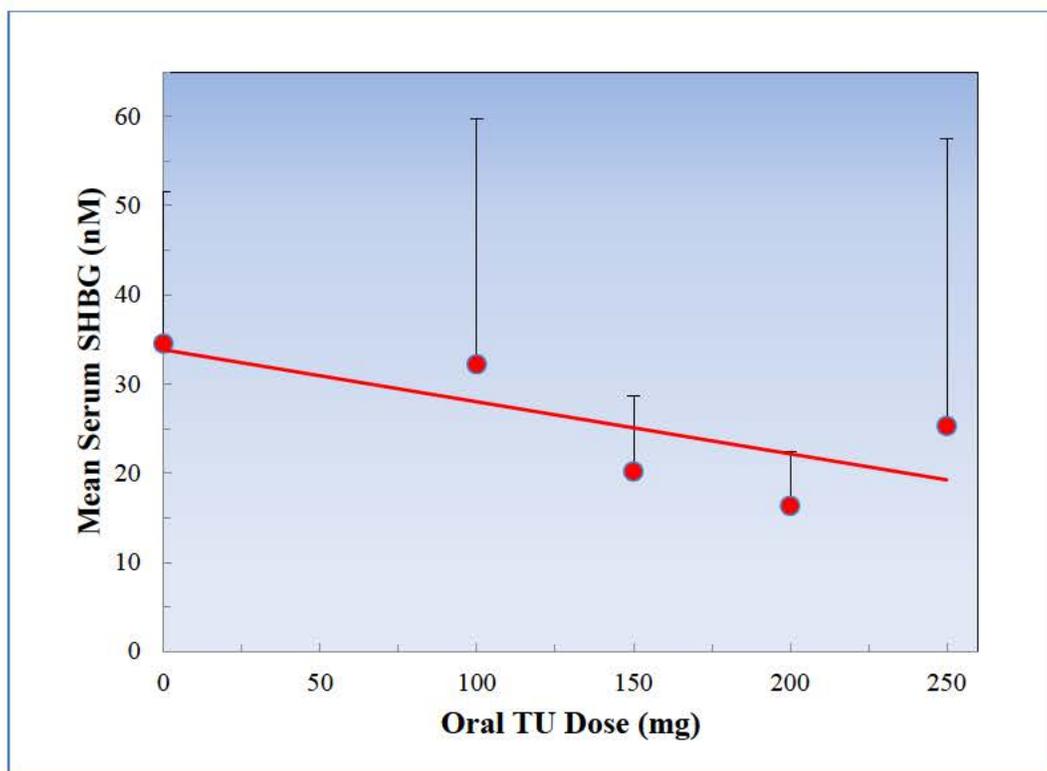


Figure 12. Serum SHBG decreases over various dose level of oral TU

Oral TU Dose (mg)	0	100	150	200	250
Safety population	142	28	58	28	4

[Reviewer’s Comments: The reason for the 35% decrease from baseline in mean SHBG remains unclear. The decrease may reflect decreased production of this protein in the liver and/or increased clearance of this protein.]

9.6.1.7 Other hormones:

Full PK of serum estradiol (E2, including E2/T ratios), FSH and LH were evaluated on day 114. Changes from baseline in serum estradiol appear consistent with T replacement therapy.

- Mean serum E2 increased from baseline on Day 114 by approximately 50-60% with fluctuation during the 24-hour monitoring but remained within the normal range (7.5-30.6 pg/ml)
- E2/T ratios decreased from 8.4×10^3 at baseline to 5.8×10^3 post-PM dose on Day 114.
- Serum FSH decreased from 7 mIU/ml at baseline to 2 mIU/ml (Cavg) on Day 114 without fluctuation (**Table 51**).
- Serum LH decreased from 4.7 mIU/ml at baseline to 1.2 mIU/ml (Cavg) on Day 114 without fluctuation (**Table 51**).

Table 51. PK parameters of serum FSH and LH
(From the Applicant’s tables 16 and 17 in Study CLAR-12011)

PK Parameter	Units	N	FSH		LH	
			Mean	SD	Mean	SD
Cmax	mIU/mL	116	2.40	6.50	1.87	3.66
Tmax	hour	116	6.21	7.56	6.54	7.90
AUC	mIU.h/mL	116	48.25	140.04	28.31	68.60
Cavg	mIU/mL	116	2.01	5.84	1.18	2.86
Fluct Index	ratio	116	0.58	0.89	0.96	1.25
C-baseline	mIU/mL	144	7.00	9.14	4.70	5.06

Dose adjustment during the study:

Nearly 50% of subjects had no dose adjustment on the two titration days (Days 42 and 84) (**Table 52**). Of those who had their dose changed, the majority were titrated down to 150 mg bid or 100 mg bid from the initial 30-day fixed dose of 200 mg bid. No subject was titrated upward to 300 mg bid (**Table 53**).

The serum T concentrations appear dose-proportional when comparing Cmax and Cavg between the Day 30 PK profile (at the fixed dose of 200 mg bid) with the Day 114 PK (final titrated dose, 100 to 250 mg bid). Most subjects with dose down-titration were likely to have lower serum T and DHT concentrations on Days 72 and 114 as compared to concentrations on Day 30.

Table 52. Dose titration on Days 42 and 84 in the safety population

Titration Day	Oral TU N=144 n (%)
Day 42	
Titrated Up	2 (1.4)
Titrated Down	67 (46.5)
Remaining Unchanged	63 (43.8)
Day 84	
Titrated Up	5 (3.5)
Titrated Down	55 (38.2)
Remaining Unchanged	68 (47.2)

Source: From the Applicant's Table 25 in Study CLAR-12011 report

Table 53. Number (percentage) of subjects on a given dose on Days 0, 30, 72 and 114 of the study

Visit	100 mg BID	150 mg BID	200 mg BID	250 mg BID	All Doses
Day 0	0	0	144 (100%)	0	144
Day 30	0	0	133 (100%)	0	133
Day 72	0	66 (51%)	62 (48%)	2 (1.5%)	130
Day 114	28 (24%)	58 (50%)	27 (23%)	4 (3%)	117

Source: From the Applicant's Table 19 in Study CLAR-12011 report

[Reviewer's Comments: The majority of patients required dose down titration during the study, suggesting that the starting dose of 200 mg BID is too high.]

Relationship of C3-5 with Cavg, Cmax and Tmax:

A single blood sample for serum total T concentration at 3-5 hours (C3-5) post-dose was used as a surrogate for Cavg when making dose titration decisions in this study and (b) (4)

The time-point for C3-5 appears consistent with the mean Tmax of serum T, which is approximately 4 hours. Regression analysis showed a strong correlation of Cavg and Cmax with the C3-5 (see the PK review for details).

9.6.1.8 Safety evaluation

Extent of exposure:

In this study, a total of 144 subjects received at least one dose of oral TU with mean dosing duration of 104.8 (± 25.3) days. The treatment compliance was approximately 96% with the mean daily dose of 346.8 (± 62.8) mg. The majority of subjects were taking a dose of 100 to 150 mg bid at the end of the study (**Table 52** and **Table 53**); the mean daily dosage was not provided in the study report.

Adverse events:

Overall, the AE profile was consistent with the T class. The frequency of AE reports was lower in this study compared to in Study CLAR-09007, which may be attributed by less aggressive dose titration and thus lower overall systemic exposure to T, TU and testosterone-related metabolites. [See the integrated Review of Safety for more detailed comparisons].

A total of 70 subjects (49%) experienced at least one treatment-emergent adverse event (TEAE) during the 114 days of treatment, including two subjects with a SAE and three who discontinued due to an AE.

Serious AEs:

The two subjects who experienced an SAE are summarized below. The SAEs were temporally related to the oral TU treatment but confounded by underlying medical conditions (medical history and concomitant medications):

Subject # (b) (6): A 58-year-old white male reported severe chronic obstructive pulmonary disease (COPD) after approximately one month on the study drug. The subject's medical history included COPD, asthma, bronchitis, and pneumonia with concomitant medications such as albuterol, lisinopril, Dry Eye Refresh liquid gel, diazepam, melatonin, vitamin D, etodolac, tizanidine, Vicodin, Zantac, Motrin, and Symbicort. The patient withdrew from the study and recovered after being hospitalized for one week.

Subject # (b) (6): A 74-year old white male experienced vertigo on Day 110 which was relieved without treatment. He was diagnosed with a moderate stroke on imaging work-up that was done on Days 114 (MRI) and 116 (cerebral angiogram and CT scan) to determine the etiology of the vertigo. The patient was hospitalized for 2 days and discharged in a stable condition. The oral TU dose was titrated down to 150 mg bid at the first titration and remained 150 mg BID until the end of study (Day 114). The patient's medical history included hypertension and previous TIA. He was taking anti-hypertensive therapy. The patient's BP at screening was 135/79 mmHg and his BMI was 26.6 kg/m². During the study, his systolic BP ranged from 129 to 162 mmHg and his diastolic BP from 72 to 83 mmHg. The patient's Hct and Hb increased during the study (hematocrit increased from 46.9% to 54.7%), with slightly decreased HDL and slightly increased LDL; the serum total T was in the normal range after dose down-titration (**Table 54**).

Table 54. Laboratory and PK parameters of Subject (b) (6) with SAE (stroke)

Visit Day	Cholesterol (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)	Hct (%)	Hb (g/dL)	Serum Total T (ng/dL)	
							Cmax	Cavg
Screening	164	97	42	173	46.9	15.6		275
Day 30							1550	840
Day 72	162	111	39	142	52.6	18.1	753	477
Day 114	155	101	38	111	54.7	18.4	698	369

Source: Summarized from the Applicant's SAE narratives in Study CLAR-12011 report

Vital signs:

Vital signs were measured at baseline and on Days 30, 72 and 114 (at the time of check-in, and 4 and 12 hours post-AM dose) and at the time of early withdrawal (once). The Applicant concluded the changes in vital signs that occurred in subjects over 4 months of treatment were minor and were not considered clinically significant.

However, both systolic and diastolic blood pressure increased from baseline across the three visits (on Days 30, 72 and 114), particularly at 12 hours post-AM dose (**Table 55**). Over all study visits, the increase from baseline at that hour was between 3.8 and 6.1 mmHg for systolic blood pressure and between 0.8 and 2 mmHg for diastolic blood pressure. BP increases were also observed in the first Phase 2 study, Study CLAR-09007, although the increases in this study were of a lower magnitude compared to the previous Phase 3 study, perhaps due to lower overall T exposure associated with a less aggressive dose titration regimen.

Prostate evaluation:

Prostate examinations and evaluations were conducted at baseline and end of treatment, including serum PSA, IPSS score and DRE. Oral TU slightly increased PSA and IPSS score over the 4 months of treatment with two subjects developing an enlarged prostate on physical examination. The prostate effects appear consistent with the TRT class.

Serum PSA:

- Mean PSA baseline: 1.1 ±0.8 ng/ml
- Mean PSA at Day 114: 1.3±1.4 ng/ml
- Mean increase from baseline at Day 114: 0.3±1.2 (or 35%±95)
- Median increase from baseline at Day 114: 0.1 (or 14%)

IPSS scores:

- Mean baseline: 5.2 ±4.5
- Mean increase from baseline at Day 114: 0.8±4.5
- Median increase from baseline at Day 114: 0

DRE for prostate:

Two subjects had mildly enlarged prostates at the end of treatment that were considered related to the study drug by the investigators. One of these subjects also had an increase in the IPSS score and serum PSA.

Table 55. Mean blood pressure changes during the study

Visit Day and time for BP recording	N	Systolic BP (mmHg)			Diastolic BP (mmHg)		
		Mean	SD	Min, Max	Mean	SD	Min, Max
Baseline	144	128.8	12.6	97, 158	80.0	8.8	48, 102
Day 30							
Check-in	134	129.5	14.2	100, 179	80.5	8.1	60, 104
4 hrs post-AM dose	133	130.2	13.1	108, 180	79.7	8.0	60, 100
12 hrs post-AM dose (Change from baseline)	133	134.9 (+6.1)	15.0	108, 185	82.0 (+2)	8.0	64, 110
Day 72							
Check-in	130	126.9	13.7	100, 171	78.8	8.3	54, 102
4 hrs post-AM dose	130	129.0	13.3	100, 173	78.6	8.3	58, 104
12 hrs post-AM dose (Change from baseline)	130	132.6 (+3.8)	12.6	104, 166	81.2 (+1.2)	8.4	64, 108
Day 114							
Check-in	119	128.9	15.2	100, 188	80.5	9.2	60, 106
4 hrs post-AM dose	118	130.0	13.6	102, 166	79.5	8.6	60, 98
12 hrs post-AM dose (Change from baseline)	117	132.7 (+3.9)	14.3	91, 174	80.8 (+0.8)	9.2	62, 115
Early withdrawal	14	131.0	12.1	103, 148	75.0	6.6	66, 86

Source: From the Applicant's Tables 14.3.3.1 and Table 14.3.3.2 in Study CLAR-12011 report

9.6.2 CLAR-09007 (12-month “supportive” Phase 3 trial)

Title: “Phase III, Active-Controlled, Safety and Efficacy Trial of Oral Testosterone Undecanoate (TU) in Hypogonadal Men”

[The following clinical review is based on the Applicant’s updated CSR submitted on March 28, 20140.]

Study location: 36 sites (30 sites enrolled ≥ 1 subject: 25 in US and 5 in Germany)
Study duration: July 30, 2011 to April 11, 2013
Study indication: Male hypogonadism
GCP compliance: Yes
Central Lab: (b) (4)

Study objective:

Primary objective: To determine the efficacy of oral TU in hypogonadal males based on the percentage of subjects with 24-hour serum T average (Cavg) within the normal range (300-1000 ng/dL)

In addition, to determine the percentage of subjects with a serum T Cmax:

- ≤ 1500 ng/dL
- >1500 to ≤ 1800 ng/dL
- >1800 to ≤ 2500 ng/dL, and
- >2500 ng/dL

Secondary objectives:

- To assess the effectiveness of dose titration based on serum T obtained at 4-6 hours post AM dose
- To confirm efficacy (consistency of serum T concentrations) for up to 365 days
- To define the safety profile of oral TU for up to 365 days compared with T-gel, based upon:
 - Clinical chemistry and hematology – specifically, serum lipid concentrations and hemoglobin (Hb)/hematocrit (Hct) levels
 - Cardiovascular (CV) biomarkers, with non-inferiority analyses for Lp-PLA2 and hs-CRP
- Prostate volume
- To determine the effect of Oral TU compared with T-gel on:
 - lean body mass and bone density
 - sexual function parameters (sexual desire, sexual enjoyment, sexual performance, sexual activity, and positive and negative sexual moods)
 - general well-being

Exploratory objective: for all study subjects

- Changes in lipoprotein(a) (Lp[a]) and apolipoprotein A1 (ApoA1)
 - Relatedness of relevant hematology and lipid parameters and CV biomarkers to both $T_{Cmax} > 1500$ ng/dL and $C_{avg} > 1000$ ng/dL
 - Relatedness of adverse events (AEs) and serious adverse events (SAEs) to a $T_{Cmax} > 1500$ ng/dL
 - Determination of whether serum T or its primary metabolites such as DHT and E2 were the primary drivers of change (if any) in aforementioned safety parameters
- **Exploratory objective:** for subgroup (n=30/arm)
 - Cholesterol efflux (*in vitro* macrophage model)
 - HDL particle number and composition
 - Serum phospholipase A2 (sPLA2)
 - Oxidized phospholipids (PC ox-PL)
 - IgG and IgM apolipoprotein B1 (ApoB1) immune complexes, and IgG and IgM antibodies to malonylaldehyde oxidized LDL, and LDL fractionation for total and small LDL particle concentration and phenotype (by ion mobility).

9.6.2.1 Study design and conduct:

This was a 12-month, randomized, open-label, 2-arm, active (Androgel) controlled study with the following procedures (**Table 56**).

Eligible hypogonadal males were randomized in a 1:1 ratio to two arms (n≈150/arm): oral TU or T-gel. There were seven on-treatment visits: Visit 1 (Day 0 or 1 for randomization, baseline assessment and first dose), Visit 2 (Day 30), Visit 3 (Day 42), Visit 4 (Day 90/105), Visit 5 (Day 180), Visit 6 (Day 270) and Visit 7 (Day 365).

Treatment and dose titration:

- Initial fixed starting doses (x 42 days):
 - Oral TU: 200 mg (T equivalents) bid, 30 min after a regular meal
 - T-gel: 5 g Androgel 1% once daily (consistent with the Androgel labeling)
- Dose titration on Days 42, 74, 180 and 270:
 - Titrations on Days 42 and 74: based on serum T level at 4-6 hours post-AM dose on Days 30 and 60, respectively
 - Dose titration up or down with an increment of 50 mg for TU (**Figure 13**) or 2.5 g for T-gel (**Figure 14**)
 - Subjects with serum T level > 1800 ng/dL (repeated) were to be discontinued from the treatment on Day 90 (or on Day 105 for subjects who underwent titration on Day 74)
- Maintenance dose continues from Day 91 (or Day 106) through Day 365 (referred to as Period #3 for safety follow-up), unless requiring further titration or discontinuation:
 - Days 180 and 270: Serum T level evaluation and possible dose titration (**Figure 15**)
 - Subjects with serum T level > 1500 ng/dL (repeated) at an oral TU dose of 100 mg bid or a T-gel dose of 5 g daily were to be discontinued.

Table 56. Study Schedule and Assessment
 (From the Applicant's Table 2 of CLAR-09007 report)

Study Days (Weeks)	Screening		Treatment Period 1	Treatment Period 2	Treatment Period 3 (Safety Follow-Up)	
	Days -35 to 0 (Weeks -5 to 0)		Days 0-42 (Weeks 1-6) (Month 0-1.5)	Days 42-90/105 ^c (Weeks 7-12) (Months 1.5-3)	Days 91/106-180 (Weeks 13-24) (Months 4-6)	Days 181-365 (Weeks 25-52) (Months 7-12)
Treatment	Visit 1	Visit 2	Initial Dose	Dose Titration to Maintenance Dose ^a	Maintenance Dose	Maintenance Dose
Dosing Regimen			Days 1-42	Days 42-90	Days 91-180	Days 181-365
Consent	+					
Medical history	+					
Urine drug screen		+				
Physical examination with DRE		+		Day 90-91 or 105-106	Day 180	Final Visit – Day 365
Serum total testosterone (T) between 6:00 and 10:00 AM	+	+				
Pre-dose T, free T, DHT, E2 (2 samples drawn 30 minutes apart between 6:00 and 10:00 AM)			Day 0 or 1			
Brief physical – obtain AEs and changes in concomitant medications)			Day 0 or 1			Day 270
Vital Signs		+	Day 0 or 1, Day 30	Day 90 or 105		Day 270, Day 365
Safety laboratory assessments (<i>fasting</i>) (± 3 days for all visits)		+	Day 30	Day 90- 91 or 105-106	Day 180	Day 270 and Final Visit – Day 365
CV biomarkers (hs-CRP and Lp-PLA ₂)			Day 0 or 1	Day 90 or 105	Day 180	Day 365
SHBG		+	Day 30	Day 90 or 105	Day 180	Day 270 and Final Visit – Day 365
LH and FSH		+	Day 30		Day 180	Day 270 and Final Visit – Day 365
PSA		+		Day 90 or 105	Day 180	Day 270 and Final Visit – Day 365
AUA/ I-PSS		+		Day 90 or 105		Day 365
Single serum T sample 4-6 hours post AM dose				Day 60 ^a	Day 180	Day 270
Dose titration (based on single sample) ^a				Day 42 (± 3 days) Day 74 (± 3 days)	Day 192 (± 3 days) Day 204 (± 3 days)	Day 282 (± 3 days) Day 294 (± 3 days)
Serial sampling ^b (24 hours overnight stay) total T, free T, DHT, E2, LH, and FSH				Day 90-91 or 105-106 (± 3 days)		
Serial sampling ^c (12 hours post AM dose) total T, free T, DHT, E2			Day 30 ^c (± 3 days)			Final Visit – Day 365 (± 7 days)
Limited serial sampling TU ^e (in subset of ~40 subjects only)				Day 90 or 105		
Adverse event monitoring	→					
Transrectal prostate ultrasound (TRUS)			Day 0 (± 3 days)			Final Visit – Day 365 (± 3 days)
Psychosexual questionnaire (Completed daily for 7 days preceding visit)			Days 0 and 30	Day 90 or 105	Day 180	Day 270 and Final Visit – Day 365
DEXA scan (Body composition and bone mineral density) ^d			Day 0 (± 3 days)		Day 180 (± 3 days)	Final Visit – Day 365 (± 3 days)
Validated well-being questionnaire (SF-36)			Day 0	Day 90 or 105	Day 180	Day 270 and Final Visit – Day 365

DRE = digital rectal examination; T = testosterone; DHT = dihydrotestosterone; E2 = estradiol; hs-CRP = high sensitivity C-reactive protein; Lp-PLA₂= lipoprotein-associated phospholipase A2; SHBG = sex hormone binding globulin; LH = luteinizing hormone; FSH = follicle-stimulating hormone; PSA = prostate specific antigen; AUA/I-PSS = American Urological Association/International Prostate Symptom Score; DEXA = dual-energy x-ray absorptiometry; SF-36 = Short Form Health Survey Version 36.

^aDay 105 was only for subjects in the Oral TU group who had been titrated both on Day 42 and Day 74.

^bDoses were titrated, if needed, based upon serum T at 4-6 hours post AM dose. Only those subjects whose dose was titrated on Day 42 (±3 days) returned on Day 60 (± 3 days) for a single sample at 4-6 hours post AM dose with additional titration on Day 74 (± 3 days) if needed. It was permitted that additional titration may occur following Days 180 and 270.

^c30 minutes and 0 minutes pre-dose, and 1.5, 3, 4-6, 8, and 12 hours post AM dose and 1.5, 3, 4-6, 8, and 12 hours post PM dose (e.g., 7:30 AM, 8:00, 9:30, 11:00, 12:00 - 2:00 PM, 4:00, 8:00, 9:30, 11:00, 12:00 - 2:00 AM, 4:00, and 8:00 AM).

^e30 minutes and 0 minutes pre-dose, and 1.5, 3, 4-6, 8, and 12 hours post AM dose (e.g., 7:30 AM, 8:00, 9:30, 11:00, 12:00 - 2:00 PM, 4:00, and 8:00 PM).

^dAt German sites, DEXA scans were only scheduled at Day 0 and Day 365.

Figure 13. Dose Titration of Oral TU
(From the Applicant's Figure 1 of CLAR-09007 Report)

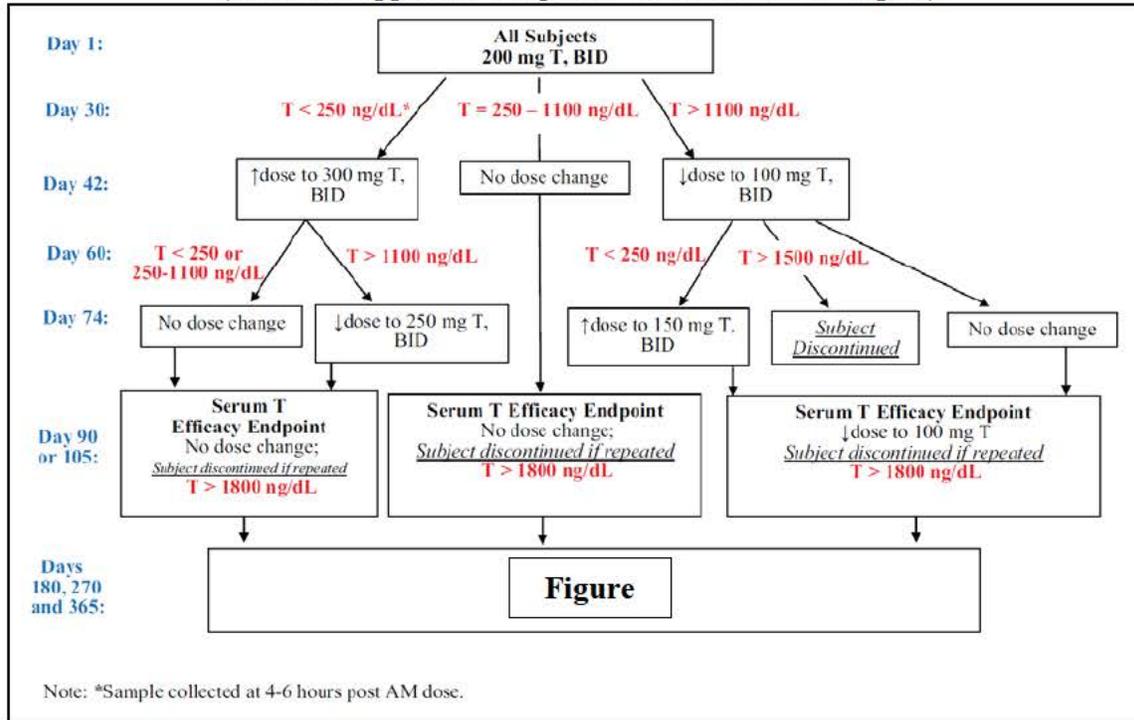


Figure 14. Dose titration of T-Gel
(From the Applicant's Figure 2 of CLAR-09007 Report)

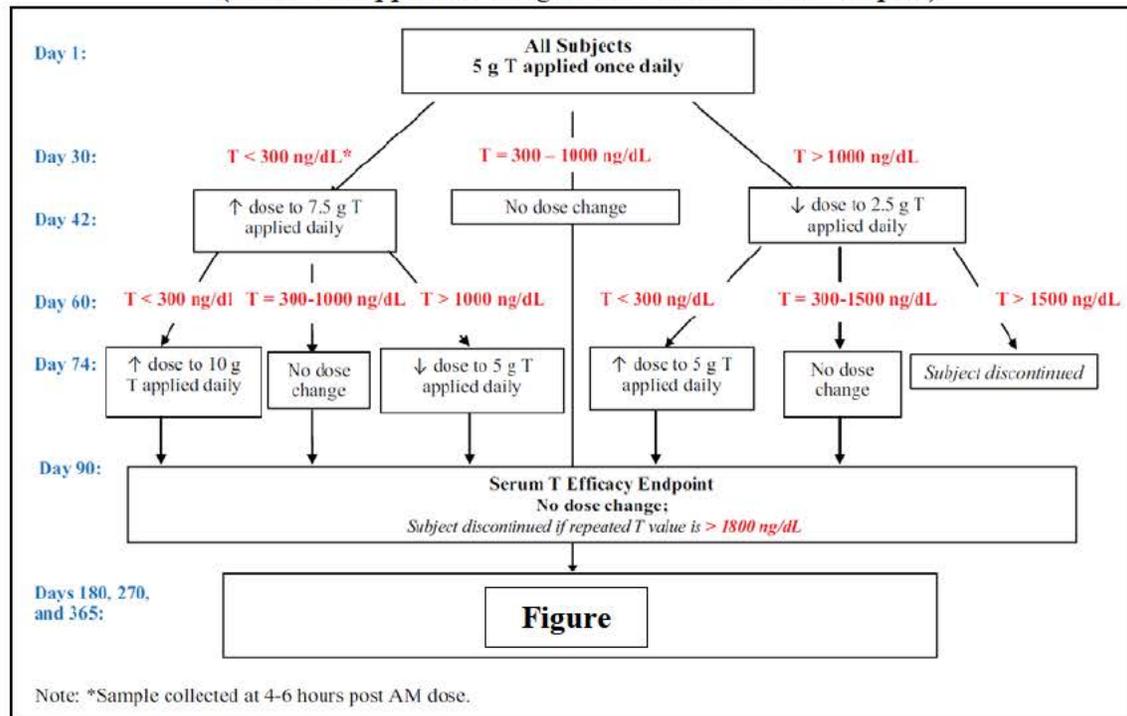
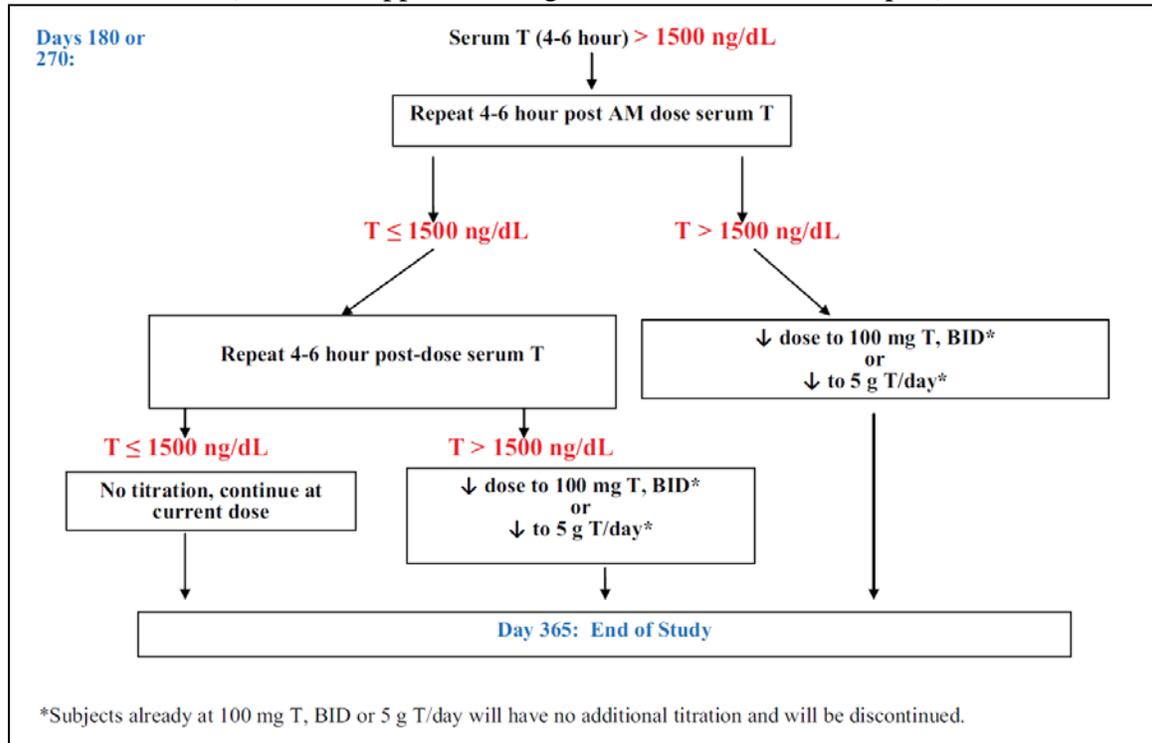


Figure 15. Dose titration of oral TU and T-Gel for Days 180-365
(From the Applicant's Figure 3 of CLAR-09007 Report)



Full PK evaluation:

- 24 hour PK (12 hours post AM dose and 12 hours post PM dose) on Day 90 (or Day 105) for serum total T, free T, DHT, E2, LH and FSH
- 12-hour PK (12 hours post AM dose) on Day 30 and Day 365 (±3) for serum total T, free T, DHT, E2, LH and FSH
- 12-hour PK (12 hours post AM dose) on Day 90/105 in a subset of subjects (n≈40) for serum TU and DHTU
- DHT/T ratios of AUC from full PK on Days 30, 90/105 and 365

Efficacy assessments:

- Primary efficacy: Serum total T Cavg and Cmax following approximately 12 weeks of continuous therapy with Oral TU, derived from the 24-hour serum total T levels on Day 90/105
- Secondary efficacy:
 - All other PK evaluations (as listed above), including single PK sample 4-6 hours post AM dose
 - Psychosexual questionnaire (includes assessments of sexual desire, sexual enjoyment, sexual performance, sexual activity score, and positive and negative sexual moods) completed daily for the 7 days preceding visits on Visit 1 (Day 0 or 1), Visit 2 (Day 30), Visit 4 (Day 90 or 105), Visit 5 (Day 180), Visit 6 (Day 270), unscheduled visit, and Visit 7 (Day 365) or upon early withdrawal.

- DEXA scan for body composition and bone mineral density (BMD) assessments at baseline, Day 180 and Day 365, except at German study sites, where DEXA conducted only at baseline and on Day 365
- SF-36 at baseline, Days 90/105, 180, 270 and 365 or upon early withdrawal

Safety assessments:

- Physical examination, vital signs and AEs (coded by MedDRA 15.1)
- Clinical laboratory (hematology, chemistry, urinalysis)
- CV biomarkers: hs-CRP, Lp-PLA2, Lp(a), and ApoA1 on baseline, Days 90/105, 180 and 365
- Other hormone measures: LH, FSH, E2, and SHBG
- Prostate evaluation:
 - DRE with physical exam at baseline, Day 90/105, 180 and 365
 - Transrectal ultrasound for prostate volume (reviewed by a central reader) at baseline and Day 365
 - PSA and AUA/IPSS at baseline, Days 90/105, 270 (PSA only), and 365

Statistical analysis plan (SAP):

- Sample size determination: $n \approx 150$ /arm based on the following assumptions:
 - Dropout rate: 25%
 - Non-inferiority (NI) between groups will be demonstrated for CV biomarkers (based upon 20% NI margin, 80% power, and 5% α)
 - 75% of subjects will have a final serum T Cavg 300-1000 ng/dL with the lower limit of a 95% CI restricted to $\geq 65\%$
- Analysis populations:
 - ITT population: All randomized subjects
 - Efficacy population: Randomized subjects with sufficient PK data on Day 90/105.
 - Safety population: Randomized subjects receiving ≥ 1 dose of study drug
 - PK population: Randomized subjects with sufficient data to calculate ≥ 1 PK parameter on Day 90/105.
- Missing data:
 - No imputation for missing data or dropouts for efficacy analysis
 - Only actual measurements at each visit were used to summarize efficacy and safety results
 - *Post-hoc* sensitivity analyses of subjects with normal T-Cavg-24hr were performed in the safety population and PK population with LOCF and WCS imputation for subjects with missing data on Day 90/105
- Baseline definition:
 - The measures at pre-dose date (Day 0 or 1) for efficacy analysis
 - The last non-missing measurement prior to the first dose for safety analysis
- Primary analysis: the serum total T on Day 90/105 in the efficacy population:
 - The percentage of subjects with 24-hour serum T Cavg (ng/dl) of 300-1000 ng/dL on Day 90/105; 95% CI for the percentage with Cavg between 300-100 ng/dl; the target

- for success for the primary endpoint: $\geq 75\%$ of subjects with Cavg between 300-1000 ng/dl and a lower bound of the associated 95% CI of $\geq 65\%$.
- The percentage of subjects (and 95% CI) with Cmax (ng/dl) ≤ 1500 , >1800 to 2500 and >2500 ng/dL.
 - Secondary analysis: PK parameters of serum T and other hormones at different time-points in the PK population
 - Safety analyses:
 - Pre-specified non-inferiority (NI) analysis of CV biomarkers (hs-CRP and Lp-PLA2) with pre-specified NI margin of 20% for the upper bound of the 95% CI of difference between the two treatment groups
 - Subgroup analysis by T Cavg ($>$ and ≤ 1500 ng/dl) on most clinically relevant safety measures (such as Hct, PSA, CV biomarkers, prostate volume and IPSS)
 - Sub-study (n=57): cholesterol efflux assay

Study subject:

A total of 325 subjects (planned for 300) were enrolled with the following selection criteria:

Inclusion criteria:

- 1) Male, age 18-75 years, with hypogonadism as defined by a total serum T of ≤ 300 ng/dL in the morning before 10:00 AM on two occasions within two weeks (on separate days)
- 2) Naïve to androgen-replacement therapy (or washout required), willing to temporarily cease current T treatment, or were not taking T treatment in order to participate in the study. Subjects were required to remain off all forms of T except for study medication throughout the entire study.
- 3) If on replacement therapy for hypopituitarism or multiple endocrine deficiencies, the subject was required to be on stable doses of thyroid hormone and adrenal replacement hormones for at least 14 days prior to enrollment.

Exclusion criteria:

- 1) Oral, topical (e.g., gel or patch) or buccal T therapy within the previous one week, or intramuscular T injection of short acting duration within the previous four weeks.
- 2) Significant intercurrent disease of any type, in particular liver, kidney, uncontrolled or poorly controlled heart disease including hypertension, congestive heart failure (CHF), or coronary artery disease, or psychiatric illness.
- 3) Subjects with recent (within three months) history of stroke, not including transient ischemic attack.
- 4) Untreated, severe obstructive sleep apnea.
- 5) Serum ALT or AST $>2x$ ULN, serum bilirubin > 2.0 mg/dL and serum creatinine > 2.0 mg/dL
- 6) Hematocrit $< 35\%$.
- 7) Known clinical polycythemia or hematocrit $> 48\%$.
- 8) Diabetic subjects with HbA1c $> 9\%$.
- 9) Body mass index (BMI) > 38 kg/m².
- 10) Stable doses of lipid-lowering medication for <3 months.
- 11) Stable doses of oral medication for diabetes for < 2 months.

- 12) Abnormal prostate digital rectal examination (DRE) (palpable nodule[s]), elevated PSA (serum PSA > 4 ng/mL), AUA/IPSS score \geq 19 points, and/or history of prostate cancer.
- 13) History of breast cancer.
- 14) History of abnormal bleeding tendencies or thrombophlebitis unrelated to venipuncture or intravenous cannulation within the previous two years.
- 15) Use of dietary supplement saw palmetto or phytoestrogens and use of any dietary supplements that may increase serum T, such as androstenedione or dehydroepiandrosterone (DHEA), within the previous four weeks.
- 16) Known malabsorption syndrome and/or current treatment with oral lipase inhibitor (e.g., orlistat [Xenical]) and bile acid-binding resins (e.g., cholestyramine [Questran], colestipol [Colestid]).
- 17) Smokers who were unable to refrain from smoking during the confinement periods as required by the individual study site.
- 18) History of abuse of alcohol (i.e., > 21 drinks/week) or any drug substance within the previous two years.
- 19) Poor compliers or those unlikely to keep clinic appointments.
- 20) Receipt of any drug as part of a research study within 30 days of initial dose administration in this study.
- 21) Blood donation (usually 550 mL) within the 12-week period before the initial study dose.
- 22) Current use of antiandrogens, estrogens, potent oral CYP3A4 inducers (e.g., barbiturates, glucocorticoids [pharmacologic doses of glucocorticoids for replacement therapy were not exclusionary]) and potent CYP3A4 inhibitors (e.g., human immunodeficiency virus [HIV] antivirals [indinavir, nelfinavir, ritonavir, saquinavir, delaviridine], amiodarone, ciprofloxacin, ketoconazole). (Note: Short-term ciprofloxacin administration completed more than seven days prior to study visits was not exclusionary during the study.)

Study drug and treatment:

- Oral TU: 158.3 mg TU capsules (equivalent to 100 mg T) and 237.5 mg TU capsules (equivalent to 150 mg T), starting at 200 mg BID with possible down-titration to 150 mg or 100 mg bid, or up-titration to 250 mg or 300 mg BID taken with a regular, unrestricted diet. See **Figure 13** and Figure 15 for detailed titration regimen of oral TU.
- T-gel: 1% AndroGel, starting at 5 g qd with possible down-titration to 2.5 g, or up-titration to 7.5 or 10 g, topically applied to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. See **Figure 14** and **Figure 15** for detailed titration regimen of T-gel

Dose selection:

- The dosing regimen of oral TU dose selection was based on two Phase 2 studies (CLAR-08005 and CLAR-09009), including the decision to utilize a single serum sample for serum T monitoring and dose titration purposes (4-6 hour post AM dose). See the Clinical Pharmacology review for details.
- The dosing regimen of T-gel was consistent with the approved AndroGel labeling

Concomitant medication:

- Allowed concomitant medications as listed in the subject selection criteria.
- No dose change in any concomitant medication allowed, specifically lipid lowering medication modifications during the first 90 days of the study
- Prohibited all forms of T replacement therapies and any dietary supplements that may increase serum T such as androstenedione or DHEA

Treatment compliance:

Compliance of subjects on the study drugs was assessed based on amount dispensed, amount returned and amount lost/destroyed, and time of exposure to treatment.

Stopping criteria:

- Total serum T >1500 ng/dl (repeated tests) when dose had already been titrated down to minimum (100 mg BID for oral TU or 2.5 g qd for T-Gel).
- Intolerable/unacceptable adverse experiences;
- Major violation or deviation of study protocol procedures;
- Hematocrit > 54% (confirmed by re-test, may advise to undergo phlebotomy)
- Non-compliance with protocol;
- PSA increase of > 1.4 ng/mL;
- Unwilling to proceed and/or consent withdrawn;
- In the Investigator's judgment for the subject's best interest (e.g., abnormal serum lipids requiring change during the first 90 days of the study in concomitant drug specifically designed for lipid modification); or
- The need to take medication that could have interfered with study measurements

[Reviewer's Comments: Overall, the study design and conduct are consistent with the latest version of the study protocol (version #5, dated July 25, 2012) and are traditional for development of drugs for the proposed indication. While specific clinical signs and symptoms of male hypogonadism were not required in the subject selection criteria, subjects had a history of hypogonadism, in the opinion of the investigator.]

Amendments to the protocol:

Four amendments to the original protocol (finalized on Mar 10, 2011) during the study. The study began with the 1st amendment (protocol version #2, dated Jun 9, 2011). Most of the amendments involved clarifications to the protocol and appeared unlikely to compromise the quality of the study. The following were some key changes:

- Amendment #1 (June 9, 2011):
 - A second titration would be scheduled, if needed, after ~4 weeks of treatment at the titrated dose (i.e., at steady-state after titration).

- Total body composition and bone density assessment procedures were modified to reflect that at selected sites outside of the U.S., DEXA scans may be scheduled at Days 0 and 365 only
- Text was added to note that at selected sites, additional serum samples from a single time point on Days 0, 90, 180 and/or 365 would be frozen and held for potential future analyses (e.g., HDL function, inflammatory markers, and/or adipokines).
- Amendment #2 (Sep 26, 2011)
 - (b) (4) was added to the list of Central Laboratories
 - Guidance for referral and potential discontinuation was added regarding subjects with a PSA increase of > 1.4 ng/mL
- Amendment #3 (Jan 27, 2012)
 - Exclusion criteria for BMI increased from 36 to 38 kg/m²
 - Exclusion criteria for CYP3A4 inducers and inhibitors change to “potent” only, because TU avoids first pass hepatic metabolism.
- Amendment #4 (July 25, 2012)
 - The titration threshold was lowered from 1800 ng/dL to 1500 ng/dL.
 - Hct levels > 54% were to be resampled; if levels were still > 54% subjects were not allowed to have their Oral TU dose adjusted downward and were required to be discontinued from the study or undergo phlebotomy and continue to be monitored.

Changes to the SAP:

- Minor changes to the planned analyses after database lock and after the final SAP, including unlocking the database one time to re-activate concomitant medications and AE eCRF pages.
- Additional *post-hoc* non-inferiority analysis of hs-CRP (by excluding hs-CRP >10 mg/L), which appears reasonable (see the CV biomarker analysis for details).

9.6.2.2 Subject disposition

Subject disposition: Of a total of 325 subjects enrolled and randomized, 321 received study drug and overall dropout rates were approximately 6.5% on Day 90 and 18.4% on Day 365. The most common reasons for dropouts were withdrawal of consent (8.3%), lost to follow-up (3.7%) and AEs (3.4%). The disposition of subjects appears balanced between the two treatment groups (**Table 57**).

Table 57. Subject disposition in CLAR-09007

Disposition†	Oral TU n (%)	T-gel n (%)	Total n (%)
Subjects Randomized (ITT)	162 (100)	163 (100)	325 (100)
Safety Population	161 (99.4)	160 (98.2)	321 (98.8)
PK Population	158 (97.5)	157 (96.3)	315 (96.9)
Efficacy Population	146 (90.1)		146 (44.9)
Completers at Day 365	129 (79.6)	133 (81.6)	262 (80.6)
Dropout (Days 0-365)	33 (20.4)	30 (18.4)	63 (19.4)
Withdrawal of Consent	12 (7.4)	15 (9.2)	27 (8.3)
Adverse Event	7 (4.3)	4 (2.5)	11 (3.4)
Lost to Follow-Up	7 (4.3)	5 (3.1)	12 (3.7)
Non-compliance with Study Drug	3 (1.9)	0	3 (0.9)
Protocol Violation	0	1 (0.6)	1 (0.3)
Hematocrit of > 54%	2 (1.2)	0	2 (0.6)
Other	2 (1.2)	5 (3.1)	7 (2.2)

Source: From the Applicant's Table 3 in the Study CLAR-09007 report

† The analysis population was re-defined as follows:

- **Intent-to-treat (ITT) population:** all randomized subjects irrespective of any deviation from the protocol or premature discontinuation, which was the basis to calculate percentages of other analysis populations.
- **Safety population:** all randomized subjects who received ≥ 1 dose of the study drug; the actual treatment defined the treatment group assignment.
- **PK population:** all randomized subjects who had sufficient data points to calculate at least one PK parameter.
- **Efficacy population (for primary efficacy analysis):** all subjects randomized to the Oral TU and completed Visit 4 (day 90) with sufficient PK data to calculate serum T Cavg.

Protocol deviations: The Applicant stated “None of the deviation affected the analyses”. A summary of protocol deviations was not provided, instead the Applicant referenced the subject listing table (61 pages). Overall, review of the listings seems consistent with the Applicant’s conclusion.

Demographics and baseline characteristics: The mean age was 55 years, most men were White (84%) and the mean BMI was 30 kg/m². Approximately half of the subjects had “pre-diabetes”, diabetes or hypertension (**Table 58**). The Applicant did not present the results from laboratory parameters in the demographics section, but stated that the demographics and baseline characteristics were balanced between the two groups.

Table 58. Demographics of subjects in ITT population

Characteristic	Oral TU (N = 161)	T-gel (N = 160)	Total (N = 321)
Age (years)			
Mean ±SD	55.0 ±11.1	54.7 ±11.2	54.9 ±11.1
Range	20-75	24-74	20-75
Race, n (%)			
White	141 (87.6)	128 (80.0)	269 (83.8)
Black or African American	18 (11.2)	23 (14.4)	41 (12.8)
Asian	0	5 (3.1)	5 (1.6)
Other	2 (1.2)	4 (2.5)	6 (1.9)
BMI (kg/m ²)			
Mean ±SD	30.0 ±3.9	29.9 ±4.0	30.0 ±3.9
Range	17.1 - 38.5	19.6 - 37.4	17.1 - 38.5
Baseline characteristics, n (%)			
Pre-Diabetic (Glucose 100-125 mg/dL)	62 (38.5)	56 (35.0)	118 (36.8)
Diabetes Mellitus	31 (19.3)	32 (20.0)	63 (19.6)
Hypertensive	66 (41.0)	76 (47.5)	142 (44.2)
Statin, Fibrate, Omega-3 FA, or Niacin Use	67 (41.6)	73 (45.6)	140 (43.6)

Source: From the Applicant's Table 4 of the Study CLAR-09007 report

Medical history and Concomitant medications: The Applicant did not provide a summary of medical history but did provide the concomitant medications (by ≥5% subjects).

[Reviewer's Comments: *The concomitant medication profile suggests a prevalent history of cardiovascular disorders.*]

Approximately 83% of subjects took ≥1 concomitant medication; lipid modifying agents (45%) were most commonly used, followed by anti-hypertensives (35% on renin-angiotensin agents, 18% beta-blockers and 14% calcium channel blockers). Overall, the concomitant medication uses were comparable between the two groups, except slightly less subjects in the oral TU group than in T-gel were on the following therapies:

- Statin: 35% vs. 42%
- Psychoanaleptics (such as trazodone, sertraline and amphetamine): 20% vs. 26%

Treatment Compliance:

The compliance evaluation was based on amount of study medication dispensed, amount returned, and amount lost/destroyed during the study. Overall, compliance was comparable

between the two groups, with slightly higher compliance with oral TU (95%) than with T-gel (92%).

9.6.2.3 Primary efficacy analyses:

Primary endpoint:

Cavg-24hr of serum total T on Day 90/105:

Primary analysis: Efficacy is demonstrated if the proportion of subjects with serum total T-Cavg-24hr within the normal range (300-1000 ng/dL) on Day 90/105 is at least 75% and the lower bound of the 95% confidence interval for this proportion is at least 65%. This primary analysis was conducted in those subjects who had serum total T-Cavg-24hr data on Day 90/105. Based on this analysis, the percentage of oral TU subjects with a serum total T-Cavg-24hr within the normal range on Day 90/105 was 83.6% (122 of 146 subjects) with a corresponding 95% confidence interval of 75.6% to 89.2% (**Table 59**). In the T-gel group, the percentage of subjects with a serum total T-Cavg-24hr within the normal range on Day 90/105 was 79.2% (118 of 149 subjects) with a 95% confidence interval of 71.8% to 85.4% (**Table 59**).

Table 59. Primary endpoint analyses in Study CLAR-09007

Analysis	Oral TU			T-gel		
	Analysis Population [†] (N)	Subject with Normal T-C _{avg} [*] n (%)	95% CI	Analysis Population (N)	Subject with Normal T-C _{avg} [*] n (%)	95% CI
Pre-specified primary analysis						
Completer	E 146	122 (83.6%)	75.6%, 89.2%	E 149	118 (79.2%)	71.8%, 85.4%
Post-hoc sensitivity analyses[‡]						
LOCF	S 161	133 (82.6%)	75.9%, 88.1%	S 160	NA	NA
WCS	S 144	122 (75.8%)	68.4%, 82.2%	S 160	NA	NA

Source: From applicant Table 6 and the analyses were confirmed by the statistical review team.

* T-Cavg-24hr: time-weighted average concentration over 24 hours on Day 90/105

The normal serum total T: 300-1000 ng/dl.

† E - Efficacy Population: subjects with sufficient PK data on Day 90/105

S - Safety Population: subjects received ≥1 dose during the study

‡ LOCF: last observation carried forward;

WCS: the worst case scenario, all subjects with missing data on Day 114 considered treatment failure

NA: Not available (the sensitivity analyses were not performed for the T-gel group)

Post-hoc sensitivity analysis: The pre-specified primary analysis did not include 9.3% of subjects who did not have serum total T Cavg-24hr data on Day 90/105 and who took at least one dose of oral TU. A *post-hoc* sensitivity analysis based on LOCF, including baseline, using all 161 subjects who took at least one dose of oral TU was conducted to determine the impact of missing

data. This sensitivity analysis gave results similar to the pre-specified primary efficacy analysis (Table 59).

C_{max} of serum total T on Day 90/105:

The percentage of subjects with T C_{max} >2500 ng/dL was approximately 14% (n=20) in the oral TU group (Table 60), which significantly exceeds the Agency’s pre-specified criteria of zero (threshold) and poses a potential safety risk. The mean T C_{max} for oral TU on Day 90/105 was about 2-fold the mean T C_{max} for T-gel (1676 vs. 818 ng/dL).

Table 60. Percentage of subjects with serum T C_{max} in pre-specified range on Day 90/105

C_{max} (ng/dL)	Oral TU N = 146	T-gel N=149	FDA Threshold
≤1500	86 (58.9%)	138 (92.6%)	≥85%
>1800 - 2500	19 (13.0%)	6 (4.0%)	<5%
>2500	20 (13.7%)	1 (0.7%)	0%

Source: From the Applicant’s Table 7 of CLAR-0907 Report and the dataset “PK_T”

In those subjects with T C_{max}>2500 ng/dl, the supraphysiological exposure appeared sporadic and transient; none of the evaluable subjects had T C_{max} >2500 ng/dL on more than two occasions and only 3 subjects had 2 excursions >2500 ng/dL.

PK profile of serum total T:

The PK profile of serum T from oral TU appeared comparable across the three full PK evaluation visits (Days 30, 90 and 365), but different from T-gel (Figure 16) due to differences in formulation (T-ester vs. T), administration route (oral vs. topical) and dosing regimen (bid vs. qd).

In the 24-hour full PK on Day 90 (the pre-specified landmark for the primary endpoint), the mean AUC, C_{max} and C_{avg} of serum T in the oral TU group were higher than those reported for the T-gel group at both post-AM and post-PM doses or their combination (Table 61).

In the oral TU group, the mean AUC, C_{max} and C_{avg} of serum T from the post-PM PK were slightly higher than the same parameters from the post-AM PK, with a mean increase of 12%, 15% and 11%, respectively. The differences between AM and PM may be due to the different fat compositions between breakfast and dinner meals (e.g., higher fat composition in the dinner meal).

For oral TU, the mean T_{max} of the post-PM PK was similar to that of the post-AM PK, and appeared to occur at around 3- 4 hours after each dose (Figure 16).

Table 61. PK profile of serum total testosterone on Day 90

Dose Time	Oral TU N=146-147†				T-Gel N=149-150‡			
	Tmax (hour)	Cmax (ng/dL)	Cavg (ng/dL)	AUCt (ng.h/dL)	Tmax (hour)	Cmax (ng/dL)	Cavg (ng/dL)	AUCt (ng.h/dL)
AM	3.8±1.9	1227.5 ±1054.6	592.2 ±398.6	7106.5 ±4783.1	5.5±3.7	685.4 ±414.1	478.4 ±235.0	5740.3 ±2820.4
PM	16.3±2.1*	1413.7 ±1222.0	661.3 ±398.7	7935.7 ±4784.1	18.2±3.7	703.5 ±405.3	488.5 ±251.3	5862.6 ±3015.9
Full	10.2±6.3	1676.0 ±1408.5	628.3 ±342.8	15079.9 ±8226.4	12.6±7.9	817.5 ±480.5	485.0±2 20.1	11641.0 ±5282.4

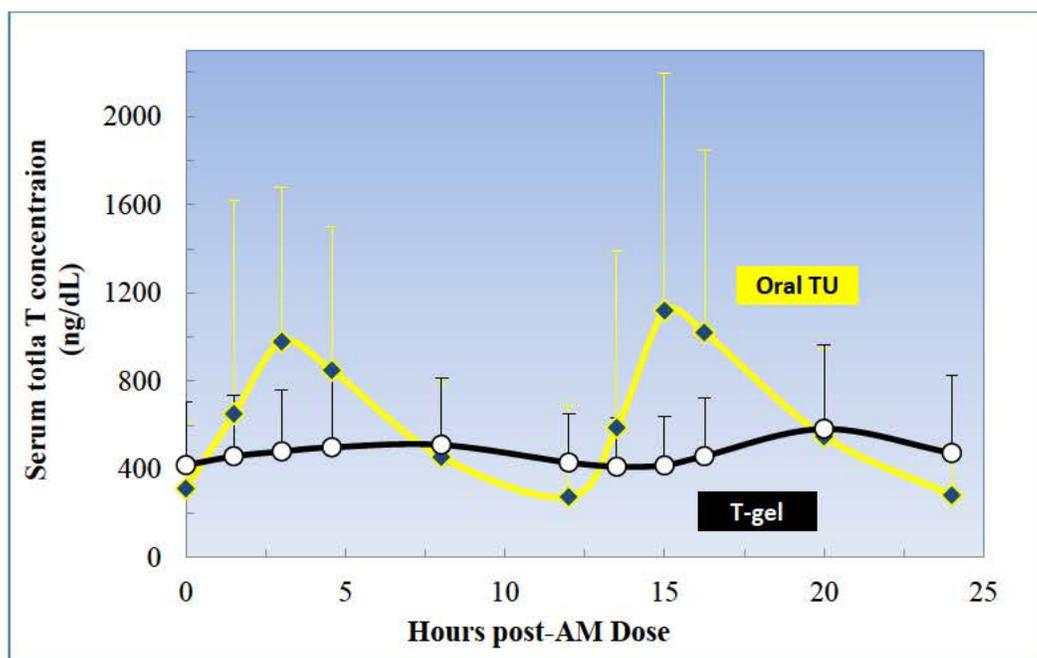
Source: From the Applicant's Table 23 of the CLAR-09007 Report

† N=147 for the post-AM and post-PM PK and n=146 for the combined AM and PM (Full)

‡ N=150 for the post-AM and post-PM PK and n=149 for the combined AM and PM (Full)

* The Tmax was approximately at Hour 16 post-AM dose but at Hour 4 post-PM dose (see Figure 16)

Figure 16. Serum total T profile following oral TU and T-gel on Day 90/105



Source: From the Applicant's Table 18 in the Study CLAR-09007 PK report. Data were Mean±SD of serum DHT concentrations at final titrated doses on Day 90/105 in efficacy population.

Cmin (pre-dose and 12 hours post-dose):

The Cmin at trough post-AM or post-PM oral TU dose on Day 90/105 ranged from below the lower limit of normal to near 300 ng/dL, while in the T-gel groups, the serum T was maintained at a level above 400 ng/dL for the entire 24 hours. The same trends in Cmin were observed at the other PK visits (on Days 30 and 365).

- Serum T Cpre (pre-AM dose) on Day 90/105:
 - Oral TU: 326.1±270.3 ng/dL

- T-gel: 437.5±262.7 ng/dL
- Serum T C12 (12 hours post-AM dose) on 90/105:
 - Oral TU: 274.1±420.5 ng/dL
 - T-gel: 430.1±223.0 ng/dL

Time course of serum total T over 12 months:

Based on the 12-hour full PK evaluations of serum total T on Days 30, 90 and 365 after oral TU treatment, the overall PK parameters including C_{max}, C_{avg}, AUC and T_{max} were comparable and constant across the three time-points post-AM dose, on Days 30, 90 and 365.

- T_{max} was about 4 hours post-AM dose at all three full PK time-points, which was consistent with the timing for the single time-point T C4-6
- C_{avg} of serum total T at the three full PK visits was about 40-50% of C_{max}

Baseline serum total T concentrations at the screening visit and on Day 0 (prior to any dose) were comparable between the two groups. However, the T concentration at 0.5 hours prior to dosing (“pre-dose”) at each time-point was lower in the oral TU than in the T-gel group (**Table 62**), which is likely due to the differences in formulation and dosing regimen.

Table 62. Serum total T concentration at baseline and pre-dose

PK Day	Oral TU		T-gel	
	n	Mean±SD (ng/dL)	n	Mean±SD (ng/dL)
Screen	162	184.4±88.5	163	194.0±78.9
Day 0	161	208.1±108.4	158	220.0±100.5
Day 30	155	323.7±231.2	155	418.7±292.9
Day 90	149	341.5±274.0	150	455.4±264.8
Day 365	128	287.2±210.8	133	454.9±243.7

Source: From the Applicant’s Table 18 of the CLAR-09007 PK report
The PK sample was collected at -0.5 hour prior to dosing

The mean duration of serum total T within the normal range on Day 90/105:

The mean duration of serum total T concentration within the normal range was shorter with oral TU than with T-gel during the 24 hours on Day 90/105 (**Table 63**). The duration maintaining the serum total T concentrations within the normal range was approximately 14 hours for oral TU and 17 hours for T-gel.

The Applicant stated that the shorter duration of time within normal range for oral TU vs T-gel was due to the differing dosing regimens and is not inconsistent with the diurnal variability in T concentrations.

Table 63. Duration (% of 24-hour) of serum total T within the normal range on Day 90/105

T Concentration (ng/dL)	Oral TU N=146	T-Gel N=149
<i>C (any time-point)</i> Mean±SD (95% CI)	56.8±16.8 (54.1-59.5)	72.3±29.2 (67.6-77.0)
<i>Cavg</i> Mean±SD (95% CI)	60.5±14.3 (58.0-63.1)	84.7±16.6 (81.7-87.7)

Source: From the Applicant's Table 2 in the End of Text Tables of CLAR-09007 PK Report

[Reviewer's Comments: Although the Applicant's explanation appears reasonable, it is unknown whether the shorter duration of time within the normal range and/or the fluctuation of serum T concentration will impact the clinical outcomes that may be expected from oral TU. The Applicant stated the results of clinical PD assessments in this study (e.g., body mass parameters, bone mineral density, libido) were comparable between the two products; however, the treatments and assessments were not blinded.]

Concentration-time profile of serum total T:

The mean serum T concentration-time profile on Days 30, 90/105 and 365 for oral TU, at a starting dose of 200 mg bid titratable to a maximum of 300 mg bid or to a minimum of 100 mg bid, showed considerable variability. **Table 64** and **Figure 17** do not show a clear relationship between serum T concentration and TU dose level or duration of oral TU treatment. The dose level used for this analysis is the dose being taken at the time of the primary efficacy assessment on Day 90/105 (**Table 64**).

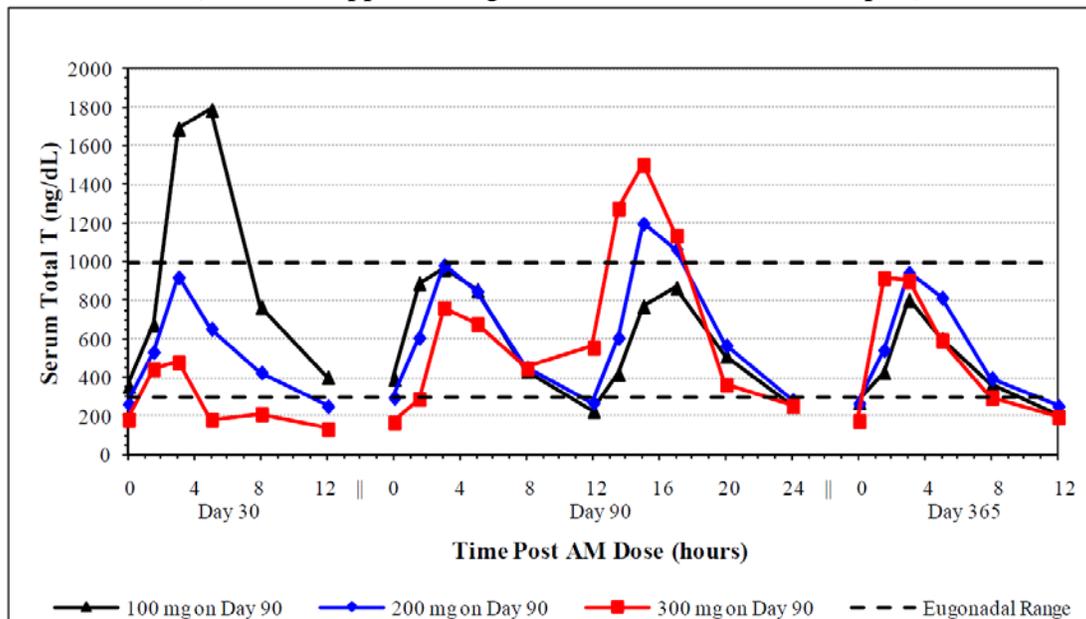
Table 64. Time-averaged serum total T concentration (Cavg) at the final dose on Day 90/105 and Day 365 in the efficacy population

PK Day and Cavg†	Oral TU dosage				
	100 mg bid	150 mg bid	200 mg bid	250 mg bid	300 mg bid
Day 90/105 N=145					
n (%)	27 (18.6%)	6 (4.1%)	105 (72.4%)	4 (2.8%)	4 (2.8%)
Cavg	589.6 ±487.6	581.9 ±175.1	638.2 ±307.2	689.9 ±308.8	637.8 ±415.7
Day 365 N=127					
n (%)	26 (20.5%)	5 (3.9%)	89 (70.0%)	3 (2.4%)	4 (3.1%)
Cavg	451.4 ±194.6	469.3 ±174.1	551.6 ±220.8	471.6 ±178.7	500.7 ±245.1

Source: From the Applicant's Table 24 in the CLAR-09007 PK report

† Cavg (ng/dL): based on the 24-hour PK on Day 90/105

Figure 17. Mean serum T concentration-time profile at various oral TU dose levels
(From the Applicant Figure 1 of CLAR-09007 PK report)



Source: Table 21

Subgroup analysis of serum T Cavg:

The subgroup analyses of T Cavg on Day 90/105 by demographics in the oral TU group (Table 65) showed that the proportions of subjects with serum T Cavg in the normal range were lower with age >65 years, body weight ≤93 kg or BMI <30 kg/m² compared to age ≤65 years, body weight >93 kg, or BMI ≥30 kg/m². Black and Hispanic subjects had slightly greater success rates compared to White and non-Hispanic subjects, respectively, however, size of the subset was too small to allow for definitive conclusions.

9.6.2.4 Serum DHT and DHT/T ratios:

Full PK of serum DHT was evaluated on Days 30, 90 and 365 with the same sample collection time-points as for the serum total T. DHT/T ratios were calculated at the three PK time-points as well as on Days 180 and 270 (albeit based upon single PK time-points on Days 180 and 270). Increases in serum DHT and the DHT/T ratios were higher in the oral TU group compared to the T-gel group, based upon AUC and Cavg (Table 67), Cmax (Table 69) and C4-6 (Table 71). Overall, the DHT/T ratios were higher with oral TU than T-gel across all time-points based on AUC, Cavg, Cmax and C4-6.

**Table 65. Subgroup analysis of Serum T Cavg within normal range on Day 90/105
In the oral TU group by demographics in efficacy population**

Subgroup	Efficacy Population	Subjects with T-Cavg 300-1000 ng/dL		
		n	%	95% CI
Age (year)				
≤65	123	105	85.4	77.9%, 91.1%
>65	23	17	73.9	51.6%, 89.8%
Body Weight (kg)				
≤93	74	57	77.0	65.8%, 86.0%
>93	72	65	90.3	81.0%, 96.0%
BMI (kg/m²)				
<30	73	58	79.5	68.4%, 88.0%
≥30	73	64	87.7	77.9%, 94.2%
Race				
Black	17	15	88.2	63.6%, 98.5%
White	129	107	82.9	75.3%, 89.0%
Ethnicity				
Hispanic	16	14	87.5	61.7%, 98.5%
Non-Hispanic	130	108	83.1	75.5%, 89.1%

Source: Table 23 of Study CLAR-09007 report

PK parameters of DHT on Day 90:

The 24-hour full PK on Day 90 showed oral TU increased the serum DHT by approximately 56% more for Cav_g, and by 83% more for C_{max} compared to T-gel (**Table 66**). For oral TU, the average and maximum serum DHT concentrations were 1.6-fold and 3-fold above the upper limit of normal, respectively. The DHT/T ratios were greater for oral TU compared to T-gel: 0.2 for oral TU vs. 0.16 for T-gel based on both AUC and Cav_g.

Table 66. Serum DHT, T and DHT/T ratio from 24-hour PK on Day 90

PK Parameter	Serum DHT†		Serum T		DHT/T Ratio‡	
	Oral TU N=145	T-Gel N=148	Oral TU N=146	T-Gel N=149	Oral TU	T-Gel
AUCt (ng.h/dL)	2994.7 ±1766.4	1916.9 ±1108.6	15079.9 ±8226.4	11641.0 ±5282.4	0.20	0.16
Cavg (ng/dL)	124.8 ±73.6	79.9 ±46.2	628.3 ±342.8	485.0 ±220.1	0.20	0.16
Cmax (ng/dL)	228.0 ±137.3	124.6 ±73.8	1676.0 ±1408.5	817.5 ±480.5	0.14	0.15
Tmax (hr)	12.2 ±6.9	12.0 ±8.3	10.2 ±6.3	12.6 ±7.9		

Source: From the Applicant's Tables 23 and 32 in Study CLAR-09007

† Normal serum DHT concentration: 13.7-76.9 ng/dL and normal serum DHT/T ratio: 0.036-0.114
(normal reference values derived from the central lab at (b) (4))

‡ Calculation based on the mean values of each PK parameter

Time-course of DHT and DHT/T ratios:

The oral TU treatment had constantly higher DHT and DHT/T ratios (based on AUC and Cavg) from Day 30 to Day 365, although there was no time-related increase during this period in either treatment group (Table 67).

Table 67. Time-course of serum total T, DHT and DHT/T ratios

PK Day†	Oral TU				T-gel			
	n	DHT (ng/dL)	T (ng/dL)	DHT/T Ratio‡	n	DHT (ng/dL)	T (ng/dL)	DHT/T Ratio‡
0	162	16.8 ±10.8	209.0 ±108.4	0.11 ±0.18	160	16.7 ±11.7	218.9 ±103.7	0.10 ±0.09
30	155	123.6 ±67.0	606.8 ±299.3	0.21 ±0.078	156	61.5 ±42.5	378.7 ±155.7	0.16 ±0.062
90	147	121.1 ±80.4	592.2 ±398.6	0.22 ±0.094	150	80.4 ±48.8	478.4 ±235.0	0.17 ±0.073
90F	145	124.8 ±73.6	628.3 ±342.8	0.21 ±0.090	148	79.9 ±46.2	485.0 ±220.1	0.17 ±0.067
365	127	117.7 ±64.0	524.4 ±215.2	0.24 ±0.114	131	69.1 ±33.0	424.7 ±177.5	0.17 ±0.070

Source: From the Applicant's Tables 23, 32, B-1, B-2, B-21 and B22 of the CLAR-09007 PK Report

† Serum DHT and total T (Cavg) from the 12-hour full PK (post-AM) on Days 30, 90 and 365, except Day 90F from the 24-hour full PK (post-AM and post-PM on Day 90); the difference in DHT/T ratios on Day 90F between oral TU and T-gel was statistically significant (P<0.001 by t-test). Day 0 was the baseline.

‡ The DHT/T ratios (based on AUC) were expressed as Mean±SD.

Dose-response of DHT/T ratios:

For both oral TU and T-gel, serum DHT concentrations and DHT/T ratios (based on AUC and Cavg) were elevated during treatment throughout the course of the study, although there was no dose-related increase in either treatment group (**Table 68**). However, the small size of the subgroups that were titrated to doses higher or lower than 200 mg bid for oral TU and 50 mg for T-gel (2-20%) precluded meaningful subgroup analyses. The majority of subjects (>70%) did not undergo dose titration during the study.

Table 68. Serum DHT/T ratios (Cavg) at highest maintenance doses of oral TU

PK Day	TU Dose (mg)	Subject N	DHT Cavg (ng/dL)		DHT/T Ratio	
			Mean	SD	Mean	SD
Day 0/1	0	145	16.27	10.79	0.12	0.19
Day 30	200	142	124.70	67.41	0.21	0.08
Day 90	100	27	133.70	105.74	0.25	0.13
	150	6	140.96	49.36	0.25	0.07
	200	104	121.74	66.31	0.20	0.07
	250	4	125.09	45.21	0.19	0.05
	300	4	118.90	66.70	0.23	0.14
Day 365	100	26	114.85	53.72	0.28	0.13
	150	5	109.98	62.60	0.22	0.05
	200	89	120.17	68.80	0.23	0.11
	250	3	91.51	37.54	0.22	0.14
	300	4	109.23	42.31	0.25	0.16

Source: From the Applicant's Table 33 of the CLAR-09007 PK Report

DHT Change from baseline and normal range:

The mean baseline serum DHT and DHT/T ratios were within the normal ranges (the reference from the central lab for this study: DHT 13.7-76.9 ng/dL and DHT/T ratio 0.036-0.114) and were comparable between the two treatment groups. However, on Day 30, the DHT/T ratios increased by 75% in the oral TU group (**Table 66**) and by 60% with T-gel (**Table 69**).

Table 69. DHT/T ratios of Cavg at highest maintenance doses of T-gel

PK Day	T-Gel Dose (mg)	Subject N	DHT Cavg (ng/dL)		DHT/T Ratio	
			Mean	SD	Mean	SD
Day 0/1	0	147	16.18	9.47	0.10	0.10
Day 30	50	147	61.84	43.11	0.16	0.06
Day 90	25	1	78.03	NE	0.15	NE
	50	86	80.63	51.73	0.16	0.07
	75	42	84.20	40.84	0.17	0.06
	100	19	66.95	27.70	0.17	0.06
Day 365	25	1	82.46	NE	0.16	NE
	50	76	68.99	34.51	0.17	0.07
	75	40	66.28	26.73	0.18	0.07
	100	15	76.65	40.77	0.17	0.05

Source: From the Applicant's Table 33 of the CLAR-09007 PK Report

Point estimate (Cmax and C4-6) of DHT and DHT/T ratios:

The Cmax and C4-6 (4-6 hours post dose) of serum DHT were consistently increased from baseline at all measured post-treatment time-points in both treatment groups. However, Cmax and C4-6 for DHT were approximately 2.5x and 2x ULN (upper limit of normal of DHT: 76.9 ng/dL) with oral TU, respectively, and approximately 1x the ULN with T-gel (Table 70 and Table 71). The DHT/T ratios based on Cmax and C4-6 were similar between the two groups, which may be explained by the delayed onset of the PK profile for DHT relative to that of T due to the slow metabolic conversion of T to DHT.

Table 70. Cmax of serum DHT

PK Day	Oral TU				T-gel			
	n	DHT (ng/dL)	T (ng/dL)	Ratio	n	DHT (ng/dL)	T (ng/dL)	Ratio
30	155	195.8 ±129.4	1261.4 ±785.0	0.16	156	82.0 ±56.8	532.8 ±255.1	0.15
90	147	189.8 ±133.0	1227.5 ±1054.7	0.15	150	107.5 ±65.5	685.4 ±414.1	0.16
365	277	187.5 ±132.4	1099.7 ±648.4	0.17	131	91.6 ±43.0	581.7 ±275.6	0.16

Source: From the Applicant's Tables 23 and 32 of the CLAR-09007 PK Report

The Cmax of DHT and T was Mean±SD; the Ratios (DHT/T) were calculated based on the mean values of Cmax.

Table 71. C4-6 of serum DHT concentration (4-6 hours post-AM dose)

PK Day	Oral TU				T-Gel			
	n	DHT (ng/dL)	T (ng/dL)	DHT/T Ratio	n	DHT (ng/dL)	T (ng/dL)	DHT/T Ratio
0	161	16.5±10.4	208.1±108.4	0.08	158	16.9±11.7	220.0±100.5	0.08
30	158	156.9±91.9	874.5±590.2	0.18	156	62.7±48.9	376.0±179.6	0.17
60	45	135.5±98.3	751.9±702.2	0.18	67	79.9±54.4	441.2±270.4	0.18
90	149	150.4±97.5	849.1±649.8	0.18	151	81.1±53.4	499.1±339.0	0.16
180	139	152.8±121.9	781.5±654.7	0.20	142	102.8±78.2	581.5±404.0	0.18
270	132	163.6±111.1	734.6±437.2	0.22	138	102.3±76.0	509.0±273.2	0.20
365	128	146.8±87.3	754.7±481.5	0.19	132	71.1±35.1	431.8±220.9	0.16

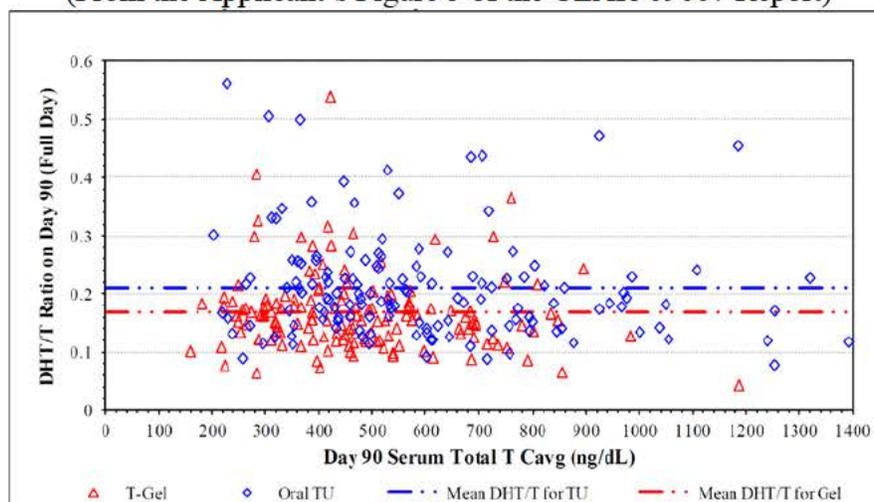
Source: From the Applicant's Table 18 and Table 31 of the CLAR-09007 PK Report

Note: DHT and T concentrations were based on the PK sample at 4-6 hours post-AM dose (C4-6) from the Applicant's Table 31 for serum DHT and Table 18 for serum T of the CLAR-09007 PK Report. The DHT/T ratios were calculated based on the Applicant's mean C4-6 values of DHT and T.

The distribution of DHT/T ratios over T Cavg:

A greater percentage of subjects in the oral TU group had high DHT/T ratios compared to the percentage of subjects in the T-gel group with high DHT/T ratios (**Figure 18**), a result which may be explained by the overall increased total T Cavg in the oral TU group. However, the distribution of DHT/T ratio over a range of T-Cavg appeared to overlap between the two treatment groups (see **Figure 18**).

Figure 18. Relationship of DHT/T ratios with T Cavg-24hr on Day 90
(From the Applicant's Figure 5 of the CLAR-09007 Report)



Source: Appendix D, Listing D-14 and Listing D-19

[Reviewer’s Comments: Overall, serum DHT concentrations and DHT/T concentrations were greater in the oral TU group compared to the T-gel group. Although this difference might be explained by increased overall T exposure in the oral TU group compared to T-gel, there may be other reasons for this difference related to differing routes of administration and formulations.]

9.6.2.5 Serum TU and DHTU:

The 12-hour full PK of serum TU and DHTU were evaluated in a subset of subjects (n=26 from three study sites) on Day 90 post-AM dose of oral TU.

Overall, systemic exposures following a dose of 200 mg (n=21) on Day 90 was approximately 20 times for serum TU and 12 times for serum DHTU compared to serum total T based on AUC; and 34 times for serum TU and 14 times for serum DHTU based on C_{max} (**Table 72**). The PK profiles showed no accumulation of TU or DHTU.

[Reviewer’s Comments: However, the Applicant did not provide any information about the clearance pathway(s) of the circulating TU and DHTU, the two highly lipophilic molecules.]

The proportion of serum TU and available metabolites based on AUC, by ng/dL and nM:

- Serum TU: 58% and 56%
- Serum DHTU: 39% and 38%
- Serum T: 3.3% and 5.1%
- Serum DHT: 0.6% and 0.9%

Table 72. Serum TU/T, DHTU/TU and DHTU/DHT ratios at oral TU dose of 200 mg

PK Parameter	Serum Measure Mean (SD)				Ratios Mean (SD)			
	TU	T	DHT	DHTU	TU/T	DHTU/ DHT	DHTU/ TU	DHT/T
AUC (ng.h/ml)	1103.5 (722.3)	62.6 (41.6)	10.9 (4.9)	736.9 (455.9)	19.2 (9.3)	75.6 (50.0)	0.7 (0.4)	0.2 (0.1)
C _{max} (ng/ml)	329.2 (194.2)	10.9 (8.3)	1.5 (0.8)	147.3 (105.2)	34.2 (15.9)	122.4 (98.6)	0.5 (0.4)	0.2 (0.1)
C _{avg} (ng/ml)	92.0 (60.2)	5.2 (3.5)	0.9 (0.4)	61.4 (38.0)	19.2 (9.3)	75.6 (50.0)	0.7 (0.4)	0.2 (0.1)

Source: analyzed by the statistical reviewer Dr. Sonia Castillo based on the Applicant’s datasets “PK_TU”, “PK_DHTU”, “PK_T” and PK_DHT” submitted with the CLAR-09007 report; n=21 on 200 mg on Day 90 for 12-hour full PK

PK profile of serum TU and TU/T ratios

The mean Tmax of serum TU was 2.6 hours (**Table 73**), approximately 1.2 hours earlier than the Tmax of serum T (3.8 hours), which is consistent with the metabolic conversion of TU to T. The TU Cmax and AUC appeared not dose proportional between 100 mg and 200 mg, which may be related to capacity of absorption of TU and/or to a very small number of subjects who were titrated to the lower doses, limiting definitive conclusions from the analysis of these data.

The mean TU/T ratio was approximately 19.2 based on AUC in “ng.h/ml” (**Table 72**) and approximately 11 based upon molar units “nmol.h/ml” (molecular weight is 288.42 for T, 456.70 for TU). The time-concentration profile of serum TU was persistently high up to 8 hours post dosing. The serum TU concentration returned close to baseline at the end of the dosing interval (**Figure 19**).

Table 73. PK profile of serum TU on Day 90 (12-hour post-AM dose)

Dose (mg)	Subject N	Baseline (ng/ml)	Cmax (ng/ml)	Tmax (hour)	AUCt (ng.h/ml)	CL/F (L/h)
100	4	6.5 ±5.8	396.8 ±239.1	2.3±0.9	872.9 ±199.1	188.3 ±40.36
150	1	0.5	327.0	1.5	642.8	369.5
200	21	23.0 ±49.2	329.2 ±194.2	2.7±2.3	1103.5 ±722.3	375.6 ±185.4
All	26	19.6 ±44.6	339.5 ±194.0	2.6 ±2.1	1050.3 ±660.5	346.5 ±180.1

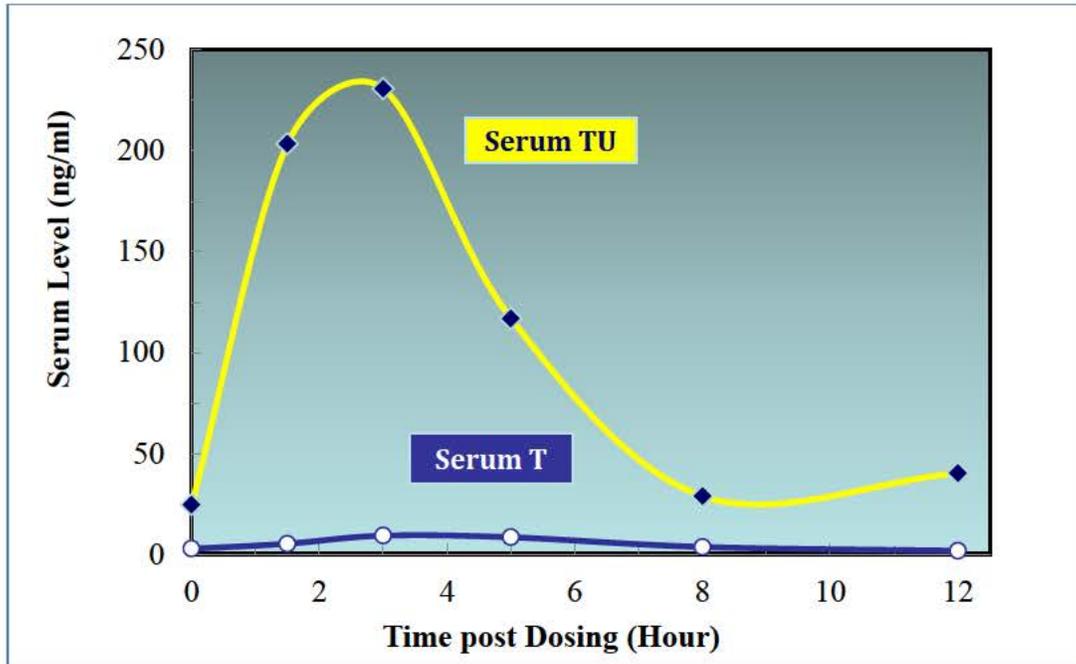
Source: From the Applicant’s Table 46 of the CLAR-09007 PK Report

Profile of serum DHTU and DHTU/DHT ratios:

The mean Tmax of serum DHTU was 3.5 hours, approximately 1 hour later than the TU-Tmax (2.6 hours) as expected for metabolic conversion. The AUC and Cmax of DHTU were approximately 76 and 122 times higher than serum DHT, respectively (**Table 72**). Serum DHTU concentrations declined to baseline at the end of the dosing interval, 12 hours post-dosing (**Figure 20**).

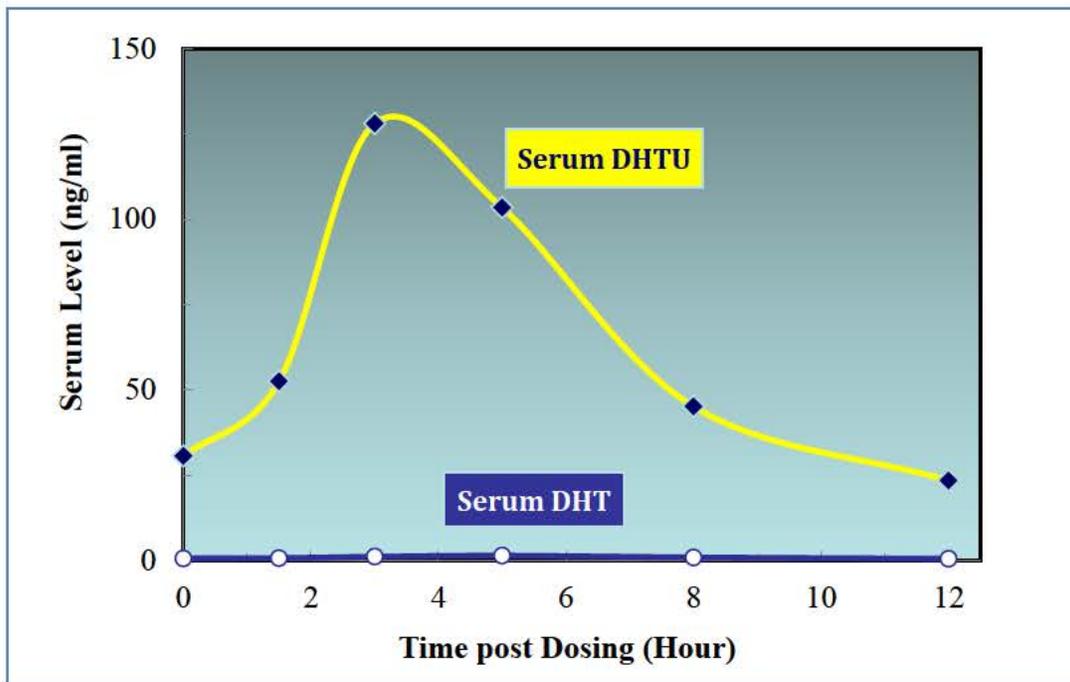
[Reviewer’s comments: The PK profiles of both serum TU and DHTU show a complete clearance of TU and DHT from the circulation. However, the Applicant’s conclusion of “no accumulation of TU and DHTU with chronic dosing” may be inaccurate because of lacking information on the clearance pathway of TU and DHTU from extra-vascular tissues.]

Figure 19. PK profile of serum TU and total T following 200 mg oral TU on Day 90



Source: From the Applicant's datasets "PK_TU" and "PK_T" of Study CLAR-09007 with 12-hour full PK on Day 90 in n=21

Figure 20. PK profile of serum DHTU and DHT following 200 mg oral TU on Day 90



Source: From the Applicant's datasets "PK_DHTU" and "PK_DHT" of Study CLAR-09007 with 12-hour full PK on Day 90 in n=21

9.6.2.6 Serum free T, SHBG, estrogen, FSH and LH

Free serum T:

In CLAR-09007, the full PK of serum free T was evaluated at the three time-points, on Days 30, 90 and 365.

- Serum free T concentrations:
 - The baseline serum free T was comparable between oral TU and T-gel, reported as 3.0-3.2 ng/dL, which is below the lower limit of normal (normal range: 3.7-16.2 ng/dL)
 - The mean free T C_{avg} increased from baseline in the both treatment groups, but with a larger increase observed in the oral TU group (12-14 ng/dL) than in T-gel group (5-8 ng/dL).
- Serum free T/total T ratios:
 - The baseline free T/total T ratio was 1.4%, similar between the two treatment groups.
 - The free T/total T ratio (based on AUC) increased from baseline in both groups, but with a larger increase observed in the oral TU group (2.1-2.4%) than in the T-gel group (1.5-1.8%), and the difference was statistically significant. There was approximately 70% greater free T concentrations in the oral TU group compared to T-gel.
 - The free T/total T ratios appeared stable over the 12 months of the study in both treatment groups, with a slight increase observed on Day 365.

[Reviewer's Comments: The Applicant stated the difference in free T profile between groups was partially due to the relatively lower SHBG concentration in the oral TU group (SHBG decreased from baseline by 43-49% in the oral TU group vs. 5-12% reduction in SHBG on T-gel). Another reason for the difference between groups may be greater overall testosterone exposure in the oral TU group, although factors related to different routes of administration and different formulations may also be involved. See the following section for details on SHBG.]

Sex Hormone Binding Globulin (SHBG):

Serum SHBG was evaluated at screening (baseline) and pre-dose on Days 30, 90, 180, 270 and 365.

- At baseline, SHBG was comparable between the two treatment groups, reported as approximately 34-35 nM (normal SHBG range: 10.8-46.6 nM).
- Serum SHBG concentration declined in both treatment groups, starting on the first testing day (Day 30) and remained at the lower levels over the course of the 12-month dosing period (**Table 74** and **Figure 21**). A markedly greater reduction in SHBG was observed in the oral TU group (43-49% reduction) compared to the T-gel group (5-12% reduction).
- In Study CLAR-12011, SHBG decreased from baseline by approximately 35% on Day 114 (**Figure 21**).

[Reviewer’s Comments: The clinical significance of the difference between groups is not known. The SHBG decrease with oral TU appears dose-related by cross-study comparison with Study 12011.]

Table 74. Serum SHBG concentration over 12 months of treatment

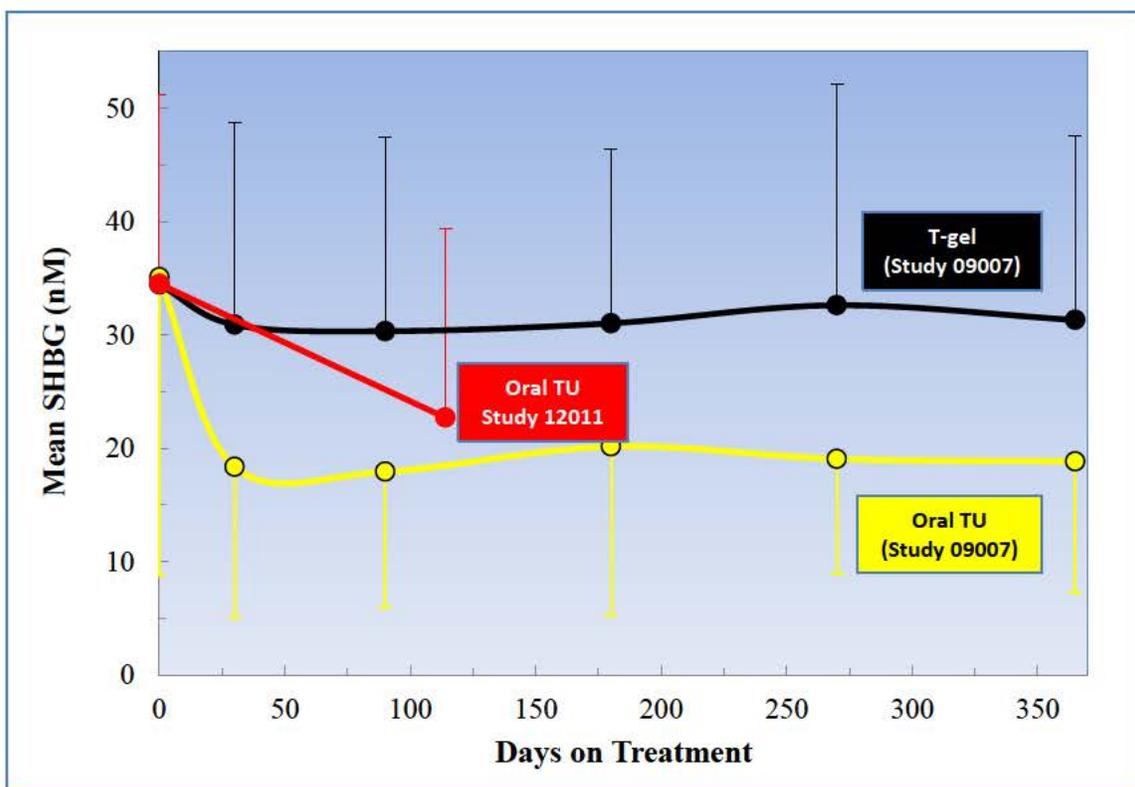
PK Day	Oral TU			T-gel		
	n	SHBG† (nM)	Decrease‡ (%)	n	SHBG† (nM)	Decrease‡ (%)
0	160	35.1±26.3	0	162	34.5±24.3	0
30	155	18.4±13.3	47.6	155	30.9±17.8	10.3
90	149	17.9±11.9	48.9	150	30.3±17.1	12.0
180	129	20.2±14.9	42.5	125	31.0±15.4	9.9
270	127	19.1±10.2	45.7	133	32.6±19.5	5.3
365	128	18.9±11.6	46.3	133	31.3±16.2	9.1

Source: From Applicant’s Table 37 of Study CLAR-09007

† SHBG concentration expressed as mean±SD

‡ The % decrease from baseline: calculated using the mean values of SHBG concentrations.

Figure 21. Serum SHBG profile over 12 months of treatment in safety population



Source: From the Applicant’s Table 37 in Study CLAR-09007 report and Table 14 in Study CLAR-12011 report; also see **Table 74** in this review

Estradiol (E2):

In Study CLAR-09007, the full PK of serum estradiol (E2) was evaluated on Days 30, 90 and 365.

Serum E2 concentration:

- The baseline serum E2 concentrations were comparable between the two treatment groups: reported as 22-25 pg/mL. The estradiol concentrations were within the normal range for serum E2 (7.5-30.6 pg/mL).
- Over 12-month dosing, the mean serum E2 (C_{avg}) increased by approximately 9-36% in the oral TU group (27-33 pg/mL) vs. an increase of 8-28% in the T-gel group (24-31 pg/mL), with the lowest increase observed on Day 365 (by 8-9%).
- The steady-state level of serum E2 (C_{ss}) was 35-42 pg/mL on oral TU and 31-39 pg/mL on T-gel

Serum E2/T ratios:

- At baseline, E2/T ratios were comparable between the two treatment groups: reported as 36-39 ($\times 10^{-3}$) with high variability (400-600% CV).
- On Days 30, 90 and 365, the E2/T ratios (based upon AUC from post-AM PK) decreased to and were maintained at 5.9-6.3 ($\times 10^{-3}$) in the oral TU group, and to 6.1-7.6 ($\times 10^{-3}$) in the T-gel group, with no systematic changes related to dosage, serum total T level, and dosing duration in either treatment group.

Serum FSH and LH:

Serum FSH and LH were evaluated at baseline, and pre-dose on Days 30, 180, 270 and 365 and via 24-hour full PK on Day 90.

Serum FSH:

- The mean baseline FSH concentrations were 8-11 mIU/ml, near the upper limit of normal (the normal FSH range: 1.4-9.5 mIU/ml), and comparable between the two groups.
- Serum FSH declined by Day 30 (the first testing time-point post dosing) to 1.6-3.6 mIU/ml on oral TU and to 4.5-6.0 mIU/ml on T-gel, and was maintained at the low levels for the remaining of the study.
- The mean FSH concentrations were within the normal range in both treatment groups on all PK clinic visits, with the FSH concentration observed to be closer to the lower limit of normal for the oral TU treatment
- In the 24-hour full PK on Day 90, the mean C_{max}, AUC and C_{avg} of serum FSH were approximately 2.7 times lower for oral TU than for T-gel.
- FSH concentration had no fluctuation with serum T over the dosing intervals and during the 24-hour full PK observation on Day 90.

Serum LH:

- The mean baseline LH concentrations were 5-6 mIU/mL, near the upper limit of the normal (normal range: 1.3-8.1 mIU/mL), and comparable between the two treatment groups.

- Serum LH declined by Day 30 (the first test time-point post dosing) to 2-4 mIU/ml on oral TU and 3-4 mIU/ml on T-gel, and was maintained at the low levels for the remaining of the study.
- The mean LH concentrations were within the normal range in both treatment groups on all PK clinic visits, and closer to the lower limit of normal for the oral TU treatment.
- In the 24-hour full PK on Day 90, the mean C_{max}, AUC and C_{avg} of serum LH were approximately 2 times lower for oral TU than T-gel.
- LH concentration had no fluctuation with changes in serum T over the dosing intervals and during the 24-hour full PK observation on Day 90.

[Reviewer's Comments: Serum FSH and LH declined greater in the oral TU group than in the T-gel group was consistent with higher serum T and DHT concentration resulted from the oral TU treatment.]

9.6.2.7 Clinical benefit measures

Psychosexual Questionnaire:

Psychosexual subjective rating questionnaires (sexual desire, sexual enjoyment, sexual performance, sexual activity score, and positive and negative sexual moods) were completed for 7 days prior to visits at baseline (Day 0/1) and on-treatment (Days 30, 90/105, 180, 270 and 365). Overall, all measures assessed in these questionnaires were improved very slightly in both treatment groups from baseline throughout the 12-month treatment period but without time-dependent improvement. There were no statistically significant differences in any measure between the two groups.

Short Form Health Survey-36:

The Short Form-36 assesses general well-being and was administered at baseline and on Days 90/105, 180, 270 and 365. The mean changes in the questionnaire parameters from baseline at all time-points were very slightly improved in both treatment groups. Overall, the oral TU group had greater mean improvements than T-gel with statistical significance in changes from baseline for certain questions and/or at certain time-points.

Bone Mineral Density and Total Body Composition:

DEXA scans to assess bone mineral density (BMD) of spine and hip, and body composition (lean and fat) were performed at baseline and on Days 180 (though not for the German study sites) and 365, or upon early withdrawal.

- Spine and hip BMD showed slight improvement from baseline in both treatment groups. The BMD improvements appeared time-dependent from Day 180 to Day 356, and oral TU showed greater improvement from baseline in hip BMD at both time-points.
- Body composition (lean and fat) showed slight improvement from baseline in both treatment groups. The improvements were time-dependent from Day 180 to Day 356,

and oral TU showed greater changes from baseline in both measurements at both time-points as compared to T-gel.

9.6.2.8 Extent of Exposure:

Mean duration of exposure:

- Oral TU (n=161): 322 ±99 days
- T-gel (n=160): 334 ±86 days

Titrated dosage:

The majority of subjects remained on the starting dose, 200 mg bid for oral TU and 5 g for T-gel at each visit (**Table 64**). In the oral TU group, approximately 72% subjects on Day 90/105 and 70% on Day 365 were at the stable dose of 200 mg bid and only approximately 6% of subjects titrated up to 250 mg or 300 mg on Day 90 and Day 365.

The mean total daily dose:

- Oral TU (n=161): 350.5 ±96.1 mg/day (in divided doses)
- T-gel (n=160): 5.6 ±1.6 g/day

9.6.2.9 Adverse events:

The overall incidence of any adverse event (AE) was 68% (n=110) on oral TU and 63% (n=100) on T-gel. However, the incidence of serious treatment emergent AEs (TEAEs) was greater in the oral TU group (6.8%) than in the T-gel group (3.8%) [see the *SAE review* for details].

Overall, most AEs reported with oral TU appear consistent with the T class and were comparable to the AEs reported with T-gel. The following AEs were reported at a higher incidence in the oral TU group than in the T-gel group (**Table 75**), some of which may be due to higher systemic exposure of T from the oral TU; the GI disorder imbalance may be related to the different routes of administration.

- Polycythemia: 8.7% vs. 3.8%
- Upper respiratory tract infection (URI): 8.1% vs. 3.1%
- GI disorders (abdominal discomfort, diarrhea, eructation): >2-times greater
- Peripheral edema: >2-times greater
- Prostate enlargement and prostatitis: >2-times greater

Polycythemia resolved in 6 of 14 subjects (43%) who reported polycythemia in the oral TU group vs. 5 of 6 subjects (83%) in the T-gel group. Two oral TU subjects withdrew from the study due to polycythemia vs no T-gel subject. These results are also shown herein:

- In the oral TU group: n=14 with polycythemia AE (2 withdrawals)
 - N=6 unresolved (1 withdrawal)
 - N=8 resolved (1 withdrawal)
- In the T-gel group: n=6 with polycythemia AE (no withdrawals)

- N=5 resolved
- N=1 unresolved

Table 75. Treatment-Emergent AEs in $\geq 2\%$ Subjects in the Safety Population

Preferred Term	Oral TU N=161		T-gel N=160		Total N=321	
	n	%	n	%	n	%
Polycythemia	14	8.7	6	3.8	20	6.2
Upper respiratory tract infection	13	8.1	5	3.1	18	5.6
Nasopharyngitis	10	6.2	7	4.4	17	5.3
Prostatomegaly	10	6.2	5	3.1	15	4.7
Diarrhoea	9	5.6	3	1.9	12	3.7
Edema peripheral	9	5.6	2	1.3	11	3.4
Back pain	6	3.7	2	1.3	8	2.5
Hypertension	6	3.7	11	6.9	17	5.3
Abdominal discomfort	5	3.1	0	0.0	5	1.6
Arthralgia	5	3.1	6	3.8	11	3.4
Gastroenteritis viral	5	3.1	2	1.3	7	2.2
Prostatic specific antigen increased	5	3.1	8	5.0	13	4.0
Sinusitis	5	3.1	5	3.1	10	3.1
Dizziness	4	2.5	2	1.3	6	1.9
Eructation	4	2.5	0	0.0	4	1.2
Headache	4	2.5	5	3.1	9	2.8
Nausea	4	2.5	5	3.1	9	2.8
Prostatitis	4	2.5	2	1.3	6	1.9
Cough	3	1.9	4	2.5	7	2.2
Vomiting	2	1.2	4	2.5	6	1.9

Source: MAED analysis of the Applicant's datasets *adae* and *addm* of Study CLAR-09007

Subgroup analysis of AEs by T-Cmax:

Approximately 46% of subjects in the oral TU group and 14% subjects in the T-gel who experienced any AEs had a T-Cmax >1500 ng/dL (**Table 76**). AEs of note in this analysis included: polycythemia, PSA increase, nipple pain, and GI disorders.

Table 76. Subjects with AEs related to T-Cmax>1500 mg/dL in safety population

PT	Oral TU		T-gel	
	Subject with AE n	Subject with AE & T-Cmax>1500 ng/dL n (%)	Subject with AE n	Subject with AE & T-Cmax>1500 ng/dL n (%)
Any AEs	110	50 (45.5%)	100	14 (14%)
Polycythemia	14	6 (43%)	6	1 (17%)
Upper respiratory tract infection	13	5 (38%)	5	0
Nasopharyngitis	10	2 (20%)	7	0
Prostate enlargement	10	6 (60%)	5	1 (20%)
Diarrhea	9	5 (56%)	3	0
Edema peripheral	9	3 (33%)	2	0
Back pain	6	1 (17%)	2	0
Hypertension	6	0	11	2 (18%)
Abdominal discomfort	5	4 (80%)	0	0
Arthralgia	5	1 (20%)	6	1 (17%)
Gastroenteritis viral	5	0	2	1 (50%)
Increased PSA	5	2 (40%)	8	0
Sinusitis	5	1 (20%)	5	0
Dizziness	4	3 (75%)	2	1 (50%)
Eructation	4	2 (50%)	0	0
Headache	4	1 (25%)	5	0
Nausea	4	1 (25%)	5	0
Prostatitis	4	1 (25%)	2	0
Cough	3	1 (33%)	4	0
Vomiting	2	1 (50%)	4	0

Source: From the Applicant's Table 14.3.1.1.7a and datasets *adae* and *PK_T* of Study CLAR-09007

Death and SAEs:

There were no deaths in the study. A total 17 subjects experienced a SAE with a greater incidence in the oral TU group (6.8%, n=11) compared to the T-gel group (3.8%, n=6) (Table 77). Most of the SAEs were sporadically reported under different system organ classes (SOCs), with the exception of slightly more cases clustered in the Cardiac disorders SOC.

In addition, more subjects with any SAE in the oral TU group also had T-Cmax >1500 ng/dL (n=6 of 11; 55%) than in the T-gel group (n=1 of 6; 17%).

Table 77. Serious Treatment-Emergent Adverse Events in Safety Population
(From Applicant's Table 30 of CLAR-09007 report)

System Organ Class Preferred Term, n (%)	Oral TU (N = 161)	Transdermal T-gel (N = 160)	Total (N = 321)
Subjects with any serious TEAE	11 (6.8)	6 (3.8)	17 (5.3)
Cardiac disorders	4 (2.5)	1 (0.6)	5 (1.6)
Acute myocardial infarction	2 (1.2)	0	2 (0.6)
Angina pectoris	1 (0.6)	0	1 (0.3)
Coronary artery disease	2 (1.2)	1 (0.6)	3 (0.9)
Infections and infestations	4 (2.5)	2 (1.3)	6 (1.9)
Appendicitis	0	2 (1.3)	2 (0.6)
Gastroenteritis	1 (0.6)	0	1 (0.3)
Peritonitis	0	1 (0.6)	1 (0.3)
Pneumonia	1 (0.6)	0	1 (0.3)
Sinusitis	1 (0.6)	0	1 (0.3)
Urosepsis	1 (0.6)	0	1 (0.3)
Injury, poisoning and procedural complications	0	1 (0.6)	1 (0.3)
Brachial plexus injury	0	1 (0.6)	1 (0.3)
Joint injury	0	1 (0.6)	1 (0.3)
Metabolism and nutrition disorders	1 (0.6)	0	1 (0.3)
Hypoglycaemia	1 (0.6)	0	1 (0.3)
Musculoskeletal and connective tissue disorders	3 (1.9)	1 (0.6)	4 (1.2)
Arthralgia	1 (0.6)	0	1 (0.3)
Intervertebral disc degeneration	1 (0.6)	0	1 (0.3)
Lumbar spinal stenosis	1 (0.6)	0	1 (0.3)
Musculoskeletal pain	1 (0.6)	0	1 (0.3)
Osteoarthritis	1 (0.6)	0	1 (0.3)
Rhabdomyolysis	0	1 (0.6)	1 (0.3)
Spondylolisthesis	1 (0.6)	0	1 (0.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.6)	1 (0.6)	2 (0.6)
Basal cell carcinoma	1 (0.6)	0	1 (0.3)
Prostate cancer	0	1 (0.6)	1 (0.3)
Nervous system disorders	1 (0.6)	0	1 (0.3)
Epilepsy	1 (0.6)	0	1 (0.3)
Lumbar radiculopathy	1 (0.6)	0	1 (0.3)
Nervous system disorder	1 (0.6)	0	1 (0.3)
Vascular disorders	0	1 (0.6)	1 (0.3)
Aortic aneurysm	0	1 (0.6)	1 (0.3)

The incidence of SAEs reported in the Cardiac disorders SOC was 2.5% (n=4) in the oral TU group and 0.6% (n=1) in the T-gel group. These SAEs included: acute MI (n=2), angina (n=1) and coronary artery disease (n=3) (**Table 78**). According to the narratives of these SAE cases, as summarized in **Table 79**, in all 5 cases, underlying cardiovascular conditions were reported to be present.

Table 78. Serious Cardiovascular Adverse Events during the 12-month treatment

	Oral TU (n=161)	T-gel (n=160)
<i>Total Cardiac SAEs</i>	4 (2.5%)	1 (0.6%)
Acute MI	2 (1.2%)	0
Angina pectoris	1 (0.6%)	0
Coronary artery disease	2 (1.2%)	1 (0.6%)
Exposure		
Dose	200 mg bid	5 g qd
Days (Mean ±SD)	322 ±99	334 ±86
Serum T Cmax >1500 ng/dL†	2	1

Source: From the Applicant's Table 13 in CLAR-09007 report

† One case in the oral TU group had no PK data available because the event occurred prior to Day 30 (the first scheduled full PK evaluation), see narrative summary of the 5 cases in Table 79 for details.

Table 79. Narrative summary of subjects with CV SAEs in Study CLAR-09007

Subject ID	Age & ethnic	C _{max} †	Exposure (mg, days)†	AEs	Medical History	Concomitant Medications
(b) (6)	57, white	Day 30: 559 ng/dL Day 91: 4280 ng/dL in AM 7650 ng/dL in PM	Oral TU 200 mg x 365 days (interrupted Day 76-81 due to event)	Day 76: Non-ST elevation MI	BMI=34, hypogonadism, hypercholesterolemia, diabetes type 2, diabetic neuropathy, and sleep apnea	Related to the underlying medical history
	65, white	Day 30: 1345 ng/dL Day 90: 490 ng/dL	Oral TU 200mg x30days then 100 mg x365 days	Days 54 and 114: Chest pain, abnormal stress test and coronary angiography	BMI=33, hypogonadism, hypertension, hyperlipidemia, type 2 diabetes, DVT, gout, and metabolic syndrome	Related to the underlying medical history; angioplasty/stents related to the events
	74, white	Not available (AE occurred prior to the Day 30 full PK)	Oral TU 200 mg x19 days (discont due to the event)	Day 18: Chest pain, positive PET/stress test and coronary angiography	BMI=31, hypogonadism, hypertension, hyperlipidemia, type 2 diabetes, obesity, ED, former smoker, currently drinks alcohol; 3-week chest pain history	Related to the underlying medical history; coronary artery stents
	74, white	Day 90: 1995 ng/dL Day 120:1640 ng/dL Day 123: 96 ng/dL (2 days after discontinuing)	Oral TU 200 mg x121 days	Day 113: non-ST elevation MI	BMI=32, hypogonadism, hypertension, hyperlipidemia, sick sinus syndrome (with pacemaker), intermittent pedal edema, sleep apnea, hypothyroidism, chronic intermittent hyponatremia, acute renal failure, BPH, and former heavy user of alcohol and tobacco	Related to the underlying medical history; on TRT prior to the study
	49, white	Day 93: 1990 ng/dL	T-Gel 5 g for unknown days	Abnormal coronary angiography (planned procedure due to suspected coronary heart disease)	BMI=33, hypogonadism, diabetes, recurrent thrombosis in the upper arm, activated protein C (APC) resistance, and psoriatic arthritis	Related to the underlying medical history; angioplasty/stents

Source: Summarized from the Applicant's Narratives of SAEs in the Study CLAR-09007

† AM: post-AM dose PK; PM: post-PM dose PK

AE-related dropouts:

A total of 13 subjects dropped out due to AEs, with a slightly higher dropout rate in the oral TU group (5%, n=8) than in the T-gel group (3%, n=5). All were single cases sporadically distributed across different SOCs, except for the following AEs: polycythemia (n=2 on oral TU), and hypoglycemia (n=2 on oral TU) (**Table 80**).

There were three dropouts due to AEs in the oral TU group (37.5%, 3/8), one each due to polycythemia, acute MI, and hypoglycemia, in which the discontinued subject had a T-C_{max} > 1500 ng/dL, while no dropout due to an AE from the T-gel group had a T C_{max} > 1500 ng/dL.

AE-related dose adjustment or interruption:

A total of 12 subjects in the oral TU group and 7 subjects in the T-gel group had dose adjustment or dose interruption due to AEs during the study. Except for two subjects in each group with severe AEs, both considered by the investigators to be not related to study drug, all other AEs were mild to moderate in severity. Two subjects in the oral TU group experienced moderate polycythemia.

Table 80. Discontinuations due to AEs in the safety population
(From the Applicant's Table 31 of Study CLAR-09007)

SOC/PT n (%)	Oral TU N=161	T-gel N=160	Total N=321
All AE-related discontinuation	8 (5.0)	5 (3.1)	13 (4.0)
Blood and lymphatic system disorders	2 (1.2)	0	2 (0.6)
Polycythaemia	2 (1.2)	0	2 (0.6)
Cardiac disorders	2 (1.2)	0	2 (0.6)
Acute myocardial infarction	1 (0.6)	0	1 (0.3)
Coronary artery disease	1 (0.6)	0	1 (0.3)
General disorders and administration site conditions	1 (0.6)	0	1 (0.3)
Chest pain	1 (0.6)	0	1 (0.3)
Injury, poisoning and procedural complications	0	1 (0.6)	1 (0.3)
Arthropod bite	0	1 (0.6)	1 (0.3)
Investigations	1 (0.6)	1 (0.6)	2 (0.6)
Prostatic specific antigen increased	1 (0.6)	1 (0.6)	2 (0.6)
Metabolism and nutrition disorders	2 (1.2)	0	2 (0.6)
Hypoglycaemia	2 (1.2)	0	2 (0.6)
Musculoskeletal and connective tissue disorders	0	1 (0.6)	1 (0.3)
Arthralgia	0	1 (0.6)	1 (0.3)
Neoplasms benign, malignant and unspecified	0	1 (0.6)	1 (0.3)
Prostate cancer	0	1 (0.6)	1 (0.3)
Thyroid neoplasm	0	1 (0.6)	1 (0.3)
Reproductive system and breast disorders	1 (0.6)	0	1 (0.3)
Prostatic disorder	1 (0.6)	0	1 (0.3)
Skin and subcutaneous tissue disorders	0	1 (0.6)	1 (0.3)
Rash	0	1 (0.6)	1 (0.3)

9.6.2.10 Vital signs and physical examination:

Vital signs: Routine vital signs were recorded at screening, baseline and on Days 30, 90/105, 270 and 365.

[Reviewer’s Comments: The Applicant concluded “changes in vital signs that occurred in subjects in both treatment groups were minor and not considered clinically significant.” The study report contained a brief summary of blood pressure (BP) and pulse rate. The reviewer conducted additional analyses based upon the submitted vital signs data.]

BP was measured at the time of check-in, and 4 and 12 hours post-AM dosing for all visits, with additional BP checks at 16 and 24 hours post-AM dosing on Day 90. The mean systolic BP (SBP) and diastolic BP (DBP) increased from baseline at the majority of time-points across all visits in both groups, particularly at the 12 hours post-AM dose assessment (**Table 81**). The oral TU group had larger increases than the T-gel group for all visits. The largest increases were observed at the 12 hours post-AM dose on Days 90 and 365. Over all study visits, the mean maximum SBP increase from baseline ranged from 6.3-8.3 mmHg on oral TU vs. 3.1-5.8 mmHg on T-gel, and the mean maximum DBP increases ranged from 2.1-3.9 mmHg on oral TU vs. 0.2-2.1 on T-gel.

Table 81. Mean BP changes during 12 months of treatment in safety population

Visit Day and BP time	Systolic BP (mmHg)				Diastolic BP (mmHg)			
	Oral TU, n=161		T-gel, n=160		Oral TU, n=161		T-gel, n=160	
	Mean	Change	Mean	Change	Mean	Change	Mean	Change
Baseline								
Pre-dose	127.5		128.1		78.8		79.5	
Day 30								
Check-in	130.2	2.7	130.2	2.1	81.0	2.2	80.4	0.9
4-hr	131.7	4.2	130.7	2.6	79.9	1.1	79.9	0.4
12-hr	135.2	7.7	133.9	5.8	81.4	2.6	81.6	2.1
Day 90								
Check-in	130.1	2.6	128.5	0.4	80.8	2.0	78.5	-1.0
4-hr	131.6	4.1	128.9	0.8	79.8	1.0	78.8	-0.7
12-hr	133.8	6.3	132.1	4.0	80.9	2.1	80	0.5
16-hr	129.6	2.1	126.5	-1.6	77.8	-1.0	77.3	-2.2
24-hr	131.1	3.6	130.1	2.0	81.0	2.2	80.3	0.8
Day 365								
Check-in	132.6	5.1	130.0	1.9	82.4	3.6	80.2	0.7
4-hr	133.0	5.5	129.7	1.6	81.0	2.2	78.7	-0.8
12-hr	135.8	8.3	131.2	3.1	82.7	3.9	79.7	0.2

Source: From the Applicant’s Tables 14.3.3.1 and 14.3.3.2 in Study CLAR-09007

Note: The mean absolute change from baseline. The data were from subjects who had BP measures at the corresponding time-points.

[Reviewer's Comments: *The mean systolic and diastolic BP slightly increased in both groups across all visits with greater increase in the oral TU group. Interestingly, the incidence of hypertension reported as an AE during the 12-month study was actually lower in the oral TU group (3.7%, n=6) as compared to in the T-gel group (6.9%, n=11), as summarized in the common AE table (Table 75).]*

Physical examination (PE): PE, including a digital rectal examination (DRE), was performed at Screening, and on Days 90/105, 180 and 365. There were no clinically significant findings over the course of the 12-month treatment in either group.

9.6.2.11 Clinical laboratory:

Clinical laboratory evaluations (hematology, biochemistry and urinalysis) were conducted at baseline and on-treatment visits (on Days 30, 90/105, 180, 270 and 365). The results are summarized below.

Laboratory parameters: Laboratory parameters assessed included:

- Hematology: Hb/Hct, RBC count, WBC count
- Biochemistry: serum lipids, serum electrolytes, liver and renal function
- Specific tests: serum PSA, cardiovascular (CV) biomarkers
- Urinalysis: only at screening

Analysis of laboratory data: The analysis of lab data focused on changes from baseline at each visit, and included:

- Analyses of T-related parameters: Hct/Hb, serum lipids, serum PSA, CV biomarkers
- Subgroup analyses by serum T levels (Cmax >1500 ng/dL and Cavg >1000 ng/dL)
- Comparison between the oral TU and T-gel groups

Liver tests: No clinically significant changes in serum ALT, AST, ALP and total bilirubin were observed except in one subject (# (b) (6) from oral TU group), in whom serum ALT and AST were 2.5x and 3.4x ULN, respectively, with a normal total bilirubin on Day 270. On Day 365, the patient's serum ALT and AST returned to 1.8x and 2.6x ULN, respectively.

[Reviewer's Comments: *No other clinical information was provided. The Applicant concluded that the increases in serum transaminases in this subject were not clinically significant.]*

Renal function: No clinically significant changes in renal lab tests were observed, except in five subjects who experienced increases in serum creatinine levels that may be clinically significant, as follows:

- Oral TU Group: n=3
 - Subject (b) (6): serum creatinine increased from 1.1 mg/dL to 1.6 mg/dL on Day 180 and subject withdrew from study
 - Subject (b) (6): serum creatinine increased from 1.2 to 1.5 mg/dL on Day 270 and subsequently decreased to 1.2 mg/dL on Day 356
 - Subject (b) (6): serum creatinine increased from 1.5 to 1.7 mg/dL on Day 30 and decreased to 1.6 mg/dL on Day 365

- T-gel: n=2 at screening only (1.7 mg/dL and 2 mg/dL), without further increases during the treatment.

9.6.2.12 Hematology results:

Overall, oral TU was associated with a larger increase in hematocrit (Hct) from baseline compared to T-gel, with a larger number of subjects experiencing a Hct>54%. Increases in Hct appeared to be slightly associated with T-Cmax>1500 ng/dL, particularly on Day 90.

- Baseline Hct: comparable between Oral TU (44.1% ±2.5) and T-gel (43.9% ±2.6)
- Change (%) from baseline at Days 90/105 and 365: larger increases in the oral TU group compared to T-gel group:
 - On Day 90/105: 4.9% (±7.8) vs. 1.3% (±26.4)
 - On Day 365: 6.8% (±8.9) vs. 3.2% (±7.6)
 - Mean Hct values within the normal range in both groups from Days 30-365
- Subjects with shifts in Hct from normal at baseline to high on Day 365:
 - Oral TU: 39%
 - T-gel: 22%
- Subjects with at least one Hct value >54% (from the applicant's clinical lab dataset "ADLB"):
 - Oral TU: 9.9% (n=16 of 161)
 - T-gel: 3.1% (n=5 of 160)
- Subjects with at least one Hct value > 54% who underwent phlebotomy
 - Oral TU: n=4
 - T-gel: n=7 (this number reported by the Sponsor is higher than the 5 total patients on T-gel who were reported to have Hct >54%)

9.6.2.13 Lipid profiles

Triglycerides (TG):

- The median baseline serum TG was within the normal range (<199 mg/dL) and comparable between the two groups:
 - Oral TU: 137.5 mg/dL
 - T-gel: 144.0 mg/dL
- Median change from baseline on Day 90/105: comparable between the two groups
 - Oral TU: -16.0 mg/dL
 - T-gel: -15.0 mg/dL
- Median change from baseline on Day 365:
 - Oral TU: -7.0 mg/dL
 - T-gel: 0 mg/dL
- The mean TG change: not related to Cmax ≤ vs. >1500 ng/dL, or Cavg >1000 ng/dL
- TG level shift from baseline normal to post-dosing high or baseline high to post-dosing normal:
 - Majority of subjects (approximately 90%) remained normal across all visits and this finding was comparable between the two groups

- Approximately 35-40% subjects with a high baseline shifted to normal on Day 365 and this finding was comparable between the two groups

Total cholesterol:

Total cholesterol: In both oral TU and T-gel groups, serum total cholesterol decreased slightly over the course of treatment and this finding appeared comparable between groups.

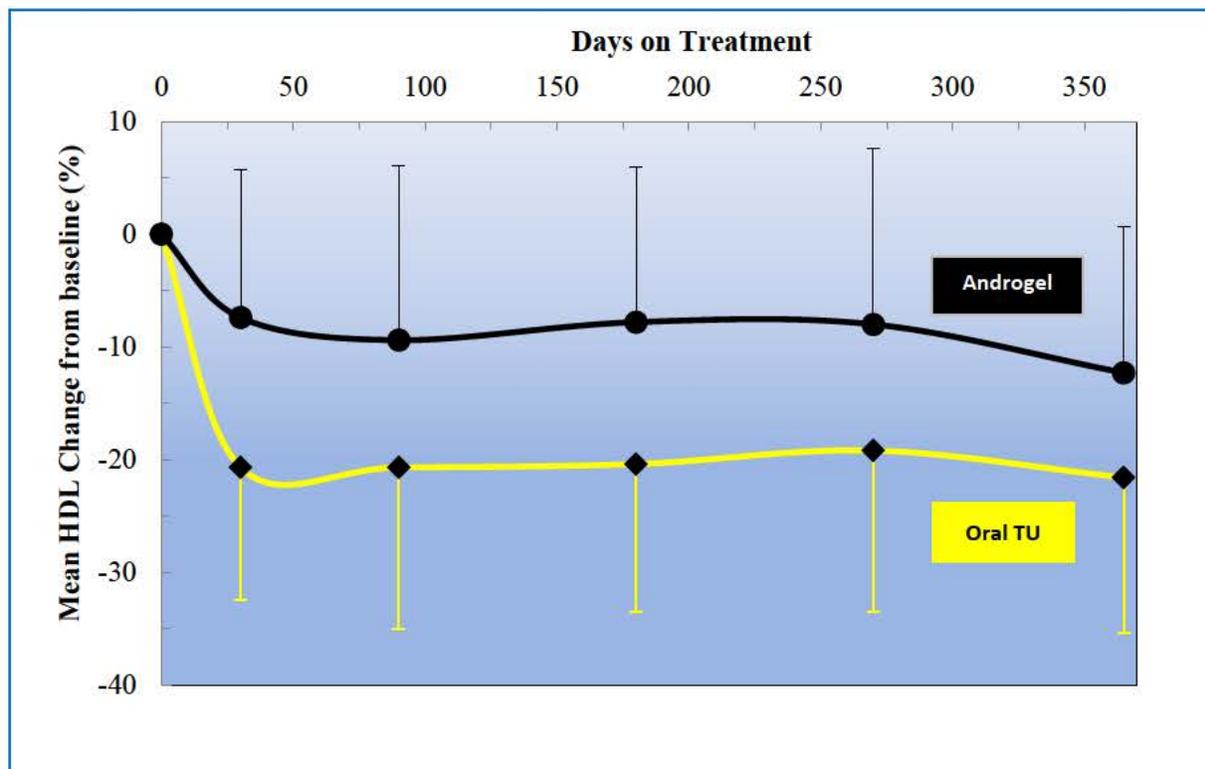
- Median baseline total cholesterol: 181 mg/dL (within normal range <200 mg/dL) and comparable between the two groups.
- Median change from baseline: slightly greater in the oral TU group
 - On Day 90/105: - 15.8 mg/dL on oral TU vs. - 10 mg/dL on T-gel
 - On Day 365: - 14 mg/dL on oral TU vs. - 8 mg /dL on T-gel
- Subgroup analysis by T-Cmax in the oral TU group: slightly greater decrease with T-Cmax>1500 ng/dL compared to Cmax≤1500 ng/dL
- Shift from “high” at baseline to “normal” post dosing on Day 365: 33% on oral TU and 47% on T-gel

High-density Lipoprotein (HDL):

In both oral TU and T-gel groups, serum HDL decreased over the 12-month dosing, with a greater decrease on oral TU as compared to T-gel, starting on Day 30 (the first testing time-point) (**Figure 22**).

- Median baseline HDL was comparable between oral TU (47 mg/dL) and T-gel (48 mg/dL)
- Median change from baseline
 - On Day 90: - 24% on oral TU vs. - 13% on T-gel
 - On Day 365: - 25% on oral TU vs. - 13% on T-gel
- Subgroup analysis by T-Cmax for the oral TU group: similar decreases from baseline between the group with Cmax>1500 ng/dL and those with Cmax≤1500 ng/dL
- Subgroup analysis by T-Cavg: too few subjects with Cavg >1000 ng/dL precludes meaningful analysis
- Shift from baseline normal to post-dosing low on Day 365: 57% on oral TU and 32% on T-gel

Figure 22. Mean serum HDL change from baseline over the 12-month treatment in safety population



Source: From the Applicant's Table 14.3.2.2.3 of Study CLAR-09007. The coefficient of variation was 55-64% in the oral TU group and 105-195% in the T-gel group across time-points.

Low-density Lipoprotein (LDL):

In both the oral TU and T-gel group, serum LDL decreased slightly from baseline during the 12-month dosing period and this finding appeared comparable between groups.

- Median baseline LDL was identical between the two groups, 102 mg/dL, slightly above the normal range (<100 mg/dL)
- Median change from baseline:
 - On Day 90: -4 mg/dL on oral TU and -3 mg/dL on T-gel
 - On Day 365: -2 mg/dL on oral TU and 0 on T-gel
- Subgroup analysis by T-Cmax on the oral TU group: similar between the group with T-Cmax >1500 ng/dL and those ≤1500 ng/dL
- Shift from baseline high to post-dosing normal on Day 365: 19% on oral TU and 27% on T-gel

[Reviewer's Comments: Whether the observed effects on serum lipids are clinically meaningful is not known. The increased reduction in serum HDL in the oral TU group compared to the T-gel group is notable.]

9.6.2.14 Prostate effects

Prostate evaluation in this study included: prostate symptom score (by IPSS questionnaire), prostate volume (by TRUS), and prostate specific antigen (PAS).

IPSS score:

- Mean baseline IPSS score: 5.9±5.2 on oral TU vs. 5.9±4.8 on T-gel (both in mild severity category)
- Day 90/105: minimal change from baseline: -0.1 points on oral TU -0.4 points on T-gel
- Day 365: minimal change from baseline: +0.5 on oral TU vs. +0.4 on T-gel
- Subgroup analysis by T-Cmax >1500 vs. ≤1500 ng/dL for the oral TU group: no effects on Day 90, but greater increase in IPSS score on Day 395 with Cmax>1500 ng/dL
- IPSS score change in subjects with BPH history: as per medical history dataset (*admh*), a total of 28 subjects reported BPH at baseline (n=16 on oral TU and n=12 on T-gel). Of these, a total of 16 and 22 subjects had IPSS score available on Days 90 and 365, respectively. Except one subject in the oral TU group, all subjects have T-Cmax <1500 ng/dL and T-Cavg <1000 ng/dL. Overall, there was no trend in IPSS scores either increased or decreased in both groups.

Prostate volume (PV, ml):

- Mean baseline PV: 29.3±14.2 mL on oral TU vs. 30.7 ±25.5 mL on T-gel
- On Day 365: the mean change from baseline: +3.0 ±9.8 mL on oral TU vs. +1.8 ±26.4 mL on T-gel
- Subjects with BPH: more BPH subjects in the oral TU group (82%) had PV increase from baseline than BPH subjects in the T-gel group (57%) (**Table 82**). The PV increases were highly variable from 16% to 65%.

Table 82. Prostate volume change on Day 365 in subjects with BPH

Change from baseline	Oral TU n=11	T-gel n=7
No change	1	0
Increase, n (%)	9 (82%)	4 (57%)
Decrease, n (%)	1	3

Source: summarized from the Applicant datasets *ADMH* and *ADTRUS* of study CLAR-09007

Prostate specific antigen (PSA):

- Mean baseline PSA: 0.79 ng/ml on oral TU vs. 0.76 ng/ml on T-gel
- Median change from baseline: slightly greater in the oral TU group than T-gel:
 - Day 90: +0.21 ng/ml vs. +0.07 ng/ml
 - Day 365: +0.15 ng/ml vs. +0.1 ng/ml
- Subgroup analysis by T-Cmax>1500 ng/dL in the oral TU group:
 - Day 90: similar between >1500 and <1500 ng/dL

- Day 365: greater change from baseline with T-Cmax >1500 ng/dL: +0.29 vs. +0.12 ng/ml
- Subjects with at least one PSA increase by >1.4 ng/ml (possibly clinically meaningful):
 - Oral TU: n=12 (3 confirmed as per the Applicant)
 - T-gel: n=16 (7 confirmed as per the Applicant)
- Prostate biopsy was undertaken for increased PSA in 8 subjects (5 on oral TU and 3 on T-gel): all prostate biopsies were negative except for one subject in the T-gel group who was diagnosed with prostate cancer (in this subject, serum PSA increased from a baseline of 3.9 ng/ml to 15.8 ng/ml on Day 90).

9.6.2.15 Cardiovascular (CV) biomarkers

Four CV biomarkers were evaluated during the course of the 12-month treatment period and the additional 12-month extension study, as pre-specified, including: hs-CRP, Lp-PLA2, Lp(a), and ApoA1. These biomarkers were assessed at baseline, and on Days 90/105, 180 and 365. The hs-CRP and Lp-PLA2 were considered as the major CV biomarkers. CRP and Lp-PLA2 were pre-specified for non-inferiority comparison between oral TU and T-gel.

High sensitivity C-reactive protein (hs-CRP):

An increase in hs-CRP suggests increased CV risk. Serum hs-CRP increased from baseline in the oral TU group but decreased in the T-gel group on both Days 90 and 365. The Applicant's comparison between the two groups on Days 90 and 365 showed a statistically significant difference when subjects with a markedly high hs-CRP (>10 mg/L) were excluded (**Table 83**). The exclusion of hs-CRP value >10 mg/L was based on CDC and AHA's recommendation⁵ because such a high hs-CRP level is possibly related to acute inflammation.

The hs-CRP changes was similar in subjects with T-Cmax >1500 ng/dL and those with T-Cmax ≤1500 ng/dL.

⁵ Pearson TA et al: Markers of Inflammation and Cardiovascular Disease Application to Clinical and Public Health Practice A Statement for Healthcare Professionals From the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 107: 499-511, 2003

Table 83. Serum hs-CRP concentration in safety population (primary analysis)

Visit Day	Including all hs-CRP data				Excluding hs-CRP>10 mg/L			
	Oral TU		T-gel		Oral TU		T-gel	
	Actual	Change (%)	Actual	Change (%)	Actual	Change (%)	Actual	Change (%)
Baseline								
N	161		157		153		146	
Mean±SD	2.7 ±5.5		3.7±7.4		1.7 ±1.6		2.2 ±2.0	
Day 90								
N	146	146	146	145	140	134	136	130
Mean±SD	3.1 ±5.3	+70 ±172	3.1±4.4	-56 ±278	2.2 ±1.9	+66 ±165†	2.1 ±1.8	-39 ±159
Day 365								
N	123	123	130	130	117	112	124	118
Mean±SD	3.1 ±5.3	+84 ±326	3.2 ±10.3	-47 ±268	2.1 ±2.0	+53 ±193†	1.9 ±1.6	-17 ±77

Source: From Applicant Tables 39 and Table 14.3.2.5.1c in Study CLAR-09007

† p<0.005 for the differences between oral TU and T-gel by repeat measure ANOVA. The mean % change from baseline was disproportional to the mean absolute change from baseline due to high inter-subject variation.

Lipoprotein-Associated Phospholipase A2 (Lp-PLA2):

A reduction in Lp-PLA2 suggests decreased CV risk. The serum Lp-PLA2 concentration decreased from baseline during the 12-month treatment in both groups, with slightly less decrease in the oral TU group. Comparisons for this biomarker did not reveal a statistically significant difference between groups.

- Mean baseline:
 - Oral TU: 320.1 ±81.4 ng/ml
 - T-gel: 312.6 ±85.7 ng/ml
- Day 90 mean change from baseline:
 - Oral TU: -10% (±27)
 - T-gel: -5% (±32)
- Day 365 mean change from baseline:
 - Oral TU: -11% (±23)
 - T-gel: -8% (±32)
- Subgroup analysis by T-Cmax>1500 ng/dL in the oral TU group: subjects with T-Cmax>1500 ng/dL had less decrease Lp-PLA2 from baseline than those with T-Cmax≤1500 ng/dL.

Lipoprotein A [Lp(a)]:

Lp(a) has been associated with increased CV risk, with elevated Lp(a) suggesting increased CV risk. In both oral TU and T-gel groups, serum Lp(a) decreased during the 12 months of treatment. Comparisons between groups showed greater decreases in the oral TU group than T-gel.

Apolipoprotein A1 (ApoA1):

ApoA1 is the main constituent of HDL. In both oral TU and T-gel groups, ApoA1 decreased with larger decreases in the oral TU group compared to the T-gel group. The difference between groups appeared statistically significant, and is consistent with the change from baseline in serum HDL concentration (see the above HDL review for details).

9.6.2.16 Non-inferiority analysis of CV biomarkers:

Non-inferiority (NI) comparison of change in the two major CV biomarkers (hs-CRP and Lp-PLA2) between oral TU and T-gel was one of secondary objectives in the Study CLAR-09007 and the NI design was pre-specified in the original protocol (dated March 10, 2011). The NI margin was amended in the latest (5th version) protocol (dated July 25, 2012) and in the final SAP (dated July 15, 2013).

The sample size estimate for this study was based on the NI analysis with an original NI margin of 10% set for the upper bound of 95% CI for the difference between oral TU and T-gel), thus expecting n=112 (completers) per arm at the end of 12-month treatment with the following assumptions:

- NI margin: 10% maximum negative difference between oral TU and T-gel
- Power: 80%
- Type-I error (α): 5%
- Pooled variability: 30%

The NI margin was changed, without FDA agreement, from the original “no more than 10% worse” to “no more than 20% worse” on July 25, 2012 (in the most recent protocol, version #5 and in the final SAP dated July 15, 2013) (**Table 84**). The duration of this study (first and last observation) was July 30, 2011 to April 11, 2013; and the NI margin was amended approximately 12 months after the study was initiated.

[Reviewer’s Comments: The Applicant explained that the NI margin was changed prior to the delivery of all serum samples to the central laboratory that was responsible for CV biomarker assays and therefore, before any analyses had been conducted.]

Table 84. Applicant's amendment on the NI Margin
(From Applicant's protocol versions 1-5 and final SAP)

Original NI margin (Protocol versions 1-4, dated March 10, 2011 to Jan 27, 2012)
Under these assumptions, a total of 224 subjects (112/treatment group) will be required. That is, a total of 224 subjects will provide approximately 80% power to reject the null hypothesis that oral TU is inferior to T-gel (i.e., oral TU has more than a 10% greater negative effect on the CV biomarker than T-gel) in favor of non-inferiority (i.e., the effect of oral TU on the CV biomarker is no more than 10% worse than that of T-gel) using a one-sided t-test at the 5% significance level. Because the safety question raised by FDA is whether oral TU results in a worse effect (i.e., uni-directional) on the CV inflammatory biomarker, a one-sided test is justified. To account for 25% attrition over the 12 month safety period (estimated worst case), a total of 150 subjects/group should be randomized.
Amended NI Margin (Most recent protocol, version-5, dated July 25, 2012 and the final SAP dated July 15, 2013)
Under these assumptions, a total of 224 subjects (112/treatment group) will be required. That is, a total of 224 subjects will provide approximately 80% power to reject the null hypothesis that oral TU is inferior to T-gel (i.e., oral TU has more than a 10% greater negative effect on the CV biomarker than T-gel) in favor of non-inferiority (i.e., the effect of oral TU on the CV biomarker is no more than 20% worse than that of T-gel) using a one-sided t-test at the 5% significance level. Because the safety question raised by FDA is whether oral TU results in a worse effect (i.e., uni-directional) on the CV inflammatory biomarker, a one-sided test is justified. To account for 25% attrition over the 12 month safety period (estimated worst case), a total of 150 subjects/group should be randomized.

The Applicant's non-inferiority analysis involved first defining a subject with "worsened" CV biomarkers. Thus, definitions for "worse" required classification of low, average and high risks:

- Classification of the CV risk based on hs-CRP and Lp-PLA2:
 - **hs-CRP** (Pearson TA et al 2003)⁶:
 - Low risk: <1 mg/L
 - Average risk: 1-3 mg/L
 - High risk: >3 mg/L
 - **Lp-PLA2** (Corson et al 2008)⁷
 - Low risk: < 200 ng/mL
 - Moderate risk: 200-235 ng/mL
 - High risk: >235 ng/mL
- Definition of a "worse" case, in which a subject's CV biomarkers got "worse":

⁶ Pearson TA et al: Markers of Inflammation and Cardiovascular Disease Application to Clinical and Public Health Practice A Statement for Healthcare Professionals From the Centers for Disease Control and Prevention and the American Heart Association *Circulation* 107:499-511, 2003

⁷ Corson MA et al: Review of the Evidence for the Clinical Utility of Lipoprotein-Associated Phospholipase A2 as a Cardiovascular Risk Marker. *Am J Cardiol* 101[suppl]:41F-50F, 2008

- Any shift to increased risk category, i.e., low to average (moderate), low to high, or average (moderate) to high, **and**
- A numeric increase in the biomarker itself of >50%
- Definition of “not worse” case:
 - No change or any decrease in risk category, i.e., average (moderate) to low, high to average (moderate), or high to low, without regard to numeric change in the biomarkers
 - Any increase in risk category, i.e., low to average (moderate), low to high, or average (moderate) to high, **and** a numeric increase in the biomarker itself of ≤50%
- Analysis:
 - ITT population (all randomized population): n=161 (oral TU) and n=160 (T-gel)
 - The proportion of subjects scored as “WORSE” was compared between oral TU and T-gel. A 95% CI and p-value were calculated by Fisher’s exact test
 - Non-inferiority would be established if the upper and lower bounds of the 95% CI for the difference in “worse” proportions were < 20% and <0%, respectively (based on Sponsor’s revised NI margin, without FDA agreement).
- The non-inferiority analysis result (**Table 85**):
 - There was a numerically higher proportion of subjects with “worse” CV biomarkers in the oral TU group (21.6%) than in the T-gel group (16.7%)
 - The upper and lower bounds of the 95% CI for the difference (4.9%) of oral TU over T-gel was within the Sponsor’s “pre-specified” NI margin (without FDA agreement): <20% and <0%, respectively
 - Applicant’s Conclusion: “non-inferiority (was shown) for oral TU compared to transdermal T-Gel in prediction of CV risk based on the composite reclassification of risk based on these two biomarkers”

Table 85. Applicant’s non-inferiority analysis of CV biomarkers
(From the Applicant’s Table 41 of Study CLAR-09007)

Crude Counts for Risk Classification ¹	Day 365		Total Both Groups	P-value ³
	Oral TU (N = 161) n (%)	Transdermal T-gel (N = 160) n (%)		
Worse	27 (21.6)	22 (16.7)	49	
Not Worse	98 (78.4)	110 (83.3)	208	
Proportion Worsening Point Estimate (95% CIs)	0.216 (0.147, 0.298)	0.167 (0.107, 0.241)		0.3432
Difference in point estimate (Oral TU- T-gel) (95% CIs) = 0.049 (-0.074, 0.171) ²				

Source: Post-text Table 14.3.2.5.6.

¹For Lp-PLA₂ or hs-CRP, any increase in risk classification, i.e., low to moderate, low to high, or moderate to high and a numeric increase > 50% were scored as "WORSE"; No change or any decrease in risk classification, i.e., moderate to low, high to moderate or high to low, without regard to numeric change were scored for either as "NOT WORSE"; Any increase in risk classification, i.e., low to moderate, low to high, or moderate to high and a numeric increase < 50% were scored for either as "NOT WORSE". The non-inferiority analysis was based on both biomarkers (hs-CRP and Lp-PLA₂). If a subject was "WORSE" on either or both biomarkers, the subject was scored as "WORSE". Percentages in all calculations are based on the subjects with no missing values in either baseline or Day 365.

²A value of < 0.20 (20%) for the upper boundary of the confidence interval was consistent with "Non-Inferiority".

³P-value was from Fisher Exact Test.

The Agency conducted a *post-hoc* non-inferiority re-analysis (by the Statistical review team):

- FDA’s Re-Analysis method (modified from the Applicant’s):
 - Definition of a “worse” case: change from baseline in the biomarker itself by >50% for either biomarker
 - Use of the evaluable population instead of the safety population
 - Use of an additional time-point (Days 365 and the 12-month extension)
 - Subgroup analysis by each of the biomarkers (hs-CRP and Lp-PLA2)
 - Exploration of shift trends between “worse” and “not worse” across visits

FDA Re-Analysis results: generally consistent (in the same direction) with the Applicant’s analysis but with a worse outcome in the oral TU group than in T-gel, as compared to the Applicant’s analysis (**Table 86** and **Table 87**)

- Greater frequency of “worse” biomarkers in both groups
- Greater differences were observed between oral TU and T-gel
- In the evaluable population analysis, the upper bounds of the 95% CI on Days 90 and 365 were >15%
- In the 24-month completer analysis, the upper bounds of the 95% CI for the difference between groups were 30-40% at all time-points.
- Majority of “worse” cases in both groups were due to “worse” hs-CRP

[Reviewer’s Comments: The re-analysis of the 24-month data (based on an incomplete study report for CLAR-12010) is limited by the small subgroups and the high variation of hs-CRP measures. With the exploratory nature of the CV biomarkers, the clinical significance of the differences between groups in the CV biomarkers is currently unknown.]

Table 86. Agency’s non-inferiority analysis of “Worse” CV biomarkers in evaluable population

Visit Day	Oral TU		T-gel		Difference (Oral TU vs. T-gel)	95% C.I.
	N	Frequency n (%)	N	Frequency n (%)		
Day 90	148	54 (36.5)	144	45 (31.2)	5.2%	(-5.6%, 16.0%)
Day 365	125	39 (31.2)	132	33 (25.0)	6.2%	(-4.8%, 17.2%)

Note: Subjects with “worse” CV biomarkers (hs-CRP and/or Lp-PLA2) was defined as changed from baseline >50%; “Evaluable Population” was subjects with hs-CRP and/or Lp-PLA2 data at the each time-point.

Table 87. Agency’s non-inferiority analysis of “Worse” CV biomarkers in 24-month completers

Visit Day†	Oral TU N=31 n (%)	T-gel N=28 n (%)	Difference	95% CI‡
Day 90	14 (45.2)	4 (14.3)	30.9%	7.1%, 52.4%
Day 180	13 (41.9)	8 (28.6)	13.4%	-12.4%, 37.5%
Day 365	11 (35.5)	6 (21.4)	14.1%	-9.8%, 36.9%
Day 455	12 (38.7)	6 (21.4)	17.3%	-7.0%, 40.1%
Day 730	9 (29.0)	6 (21.4)	7.6%	-15.7%, 30.0%

The 24-month completers were subjects who completed the 12-month extension (Study 12010) by February 5, 2014 based on the Applicant’s 120-day safety update submission.

† Days 90-365 from Study CLAR-09007 and Days 455-730 from the extension study (CLAR-12010); for each time point, those subjects who had at least one CV biomarker value were used.

‡ 95% confidence interval (CI) was based on exact methods

9.6.2.17 HDL-Mediated cholesterol efflux

The Applicant conducted a sub-study in 57 subjects who were selected from three study sites to primarily explore effects of oral TU on HDL-mediated cholesterol efflux (CE) compared to T-gel. The rationale for this sub-study was that the literature suggests there is an inverse correlation between cholesterol efflux and coronary artery disease and this inverse correlation is independent of total HDL.

HDL particle fractionation and other CV biomarkers were also evaluated in the same sub-study.

[Reviewer’s Comments: Like many of the other CV biomarkers, HDL-mediated CE is exploratory and its relationship to CV risk is controversial. The results from this sub-study should be interpreted with caution. No detailed study design and experimental procedure on the CE assay were provided in the sub-study report.]

According to the Protocol addendum to CLAR-09007 (version #2) dated June 9, 2011, a total of 57 subjects who were selected from three study sites were randomized to two groups, oral TU (n=28) and T-gel (n=29), as in the main study of CLAR-09007. There were no additional visits or assessments except that additional blood volume was collected at four scheduled visits (on Days 0, 90, 180 and 365). Cholesterol efflux mediated by HDL contained in the serum sample was assayed in vitro using a macrophage cell line J774 loaded with radiolabeled cholesterol. HDL and LDL particle fractionation was analyzed using ion mobility.

The following is a brief summary of results from the CE and HDL particle fractionation assays. The more detailed results from this sub-study were reviewed by the Clinical Pharmacology reviewer.

CE capacity:

Both oral TU and T-gel treatments decreased the CE capacity from baseline but a greater decrease was observed in the oral TU group across all three visit days (**Table 88**). The differences in the cholesterol efflux decrease between the two groups were statistically significant ($p=0.034$ by ANOVA). The mean decreases from baseline observed in the oral TU group, but not observed in the T-gel group, were approximately 1-SD across all time-points. According to a published case-controlled study in the literature, CE increase by one SD is associated with a meaningful decrease in CV risk⁸.

Table 88. Cholesterol efflux capacity *in vitro*

Visit Day	Oral TU			Change†	T-gel			Change†
	N	Mean	SD		N	Mean	SD	
0	28	5.88	0.97	0	29	5.98	0.86	0
90	26	4.93	0.56	0.95	28	5.59	0.76	0.39
180	25	5.10	0.82	0.78	28	5.49	0.84	0.46
365	25	5.05	0.84	0.83	29	5.73	0.78	0.25

Source: From Applicant's Table 5a in the sub-study of CLAR-09007

† Change from baseline (Day 0), the differences between oral TU and T-gel were statistically significant by ANOVA test ($P=0.034$).

HDL particle sizes:

Both oral TU and T-gel treatments shifted HDL particles toward the smaller sizes across three visits with a slightly greater shift observed in the oral TU group. The differences in the small HDL particle concentration were not statistically significant between the two groups.

9.6.2.18 Regression analysis of T-derived hormones and specific safety parameters:

The Applicant performed a *post-hoc* stepwise regression analysis to evaluate the effects of T, DHT, DHT/T ratio, and E2 on Hct, HDL, PSA, prostate volume, hs-CRP, and Lp-PLA2. The changes from baseline to Days 90 and 365 from both oral TU and T-gel groups were used. All hormone variables left in the model were significant at the 0.15 significance level.

On Day 90:

- No hormone parameters appeared to have an effect on Hct levels. There was a significant relationship between treatment and Hct ($p < 0.0001$).

⁸ Khara AV et al: Cholesterol Efflux Capacity, High-Density Lipoprotein Function, and Atherosclerosis. *N Engl J Med* 364 (2): 127-35, 2011

- DHT/T ratio ($p = 0.0978$) and E2 ($p = 0.0262$) had an effect on HDL. There was a significant relationship between treatment and HDL ($p < 0.0001$).
- No hormone parameters appeared to have an effect on PSA. There was a significant relationship between treatment and PSA ($p = 0.121$) levels.

On Day 365:

- Only serum T appeared to have a significant relationship with Hct levels ($p = 0.0905$). There was a significant relationship between treatment group and Hct ($p = 0.0031$).
- Only DHT/T ratio appeared to have a significant relationship with HDL ($p = 0.0386$). Treatment group appeared to have a significant relationship with HDL ($p < 0.0001$).
- There was no significant relationship between PSA and treatment groups ($p = 0.4586$); only E2 appeared to correlate with PSA ($p = 0.0313$); there was no significant relationship between treatment group and prostate volume ($p = 0.5674$) and none of the hormone parameters was related to prostate volume.

[Reviewer's Comments: The regression modeling analysis was not pre-specified and all variables included in the analysis had high variability. Some outcomes of this analysis appeared inconsistent with known pathophysiologic relationships (e.g., no relationship between serum T and DHT with PSA and prostate volume).]

9.6.3 CLAR-12010 (12-month extension of CLAR-09007)

Title: “Phase IV, open-label study of oral testosterone undecanoate in hypogonadal men”

Study CLAR-12010 was a 12-month extension of Study CLAR-09007 (the duration of CLAR-09007 was July 30, 2011 to April 11, 2013). The study’s primary objective was a long-term safety evaluation of oral TU compared to T-gel without full PK evaluation. There were three time-points of single PK samples at 4-6 hours post-dose (C4-6 hr assessment on extension days 0, 180 and 365) for the purpose of determining the need for dose adjustment.

Interim data were submitted in the 120-day Safety Update on May 1, 2014, and included a brief summary of an interim safety analysis from this extension study. This submission strategy had been agreed upon by the Division during the Pre-NDA meeting.

The 120-day safety update included:

- The database snapshot date:
 - Overall safety: February 5, 2014
 - SAE reports: up to March 26, 2014
 - PK data (single time-point): March 20, 2014
- The finalized SAP (version 1.0) dated Jan 29, 2014 (prior to the 120-day database snapshot)
- Safety data from all subjects who completed Day 90, Day 180, and Day 270 visits:
 - TEAEs: all AEs with an onset date on or after the first dose of study drug in the extension study
 - Selected clinical lab parameters: hematocrit (Hct), hemoglobin (Hb), triglycerides (TG), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and prostate-specific antigen (PSA)
 - Cardiovascular (CV) biomarkers: high-sensitivity C-reactive protein (hs-CRP) and lipoprotein-associated phospholipase A2 (Lp-PLA2)
 - Plots of the safety response: change from baselines in Hct, PSA, hs-CRP, and Lp-PLA2 versus time on treatment, dose and exposure level (DHT/T ratios), using primary baseline (first dose date of the extension study) and secondary baseline (the first dose date of Study CLAR-09007)

[Reviewer’s Comments: According to the Applicant, the safety data were not “fully verified”.]

- The following data were not submitted with the 120-day safety update:
 - Protocol deviations
 - Individual patient medical history
 - Compliance with study drug

Objectives:

Primary objective: To define the long-term safety profile of oral TU compared with transdermal T-gel based on clinical chemistry and hematology (specifically lipids, Hb, and Hct), CV biomarkers, and prostate volume

Secondary objective: To measure serum testosterone concentrations for subjects receiving oral TU treatment under conditions of real-life use

9.6.3.1 Study design and conduct:

The study maintained the original open-label, randomized, active-controlled design from Study CLAR-09007 (**Figure 23** and **Table 89**)

- Subjects were those who had completed 12 months of treatment in Study CLAR-09007 at the US study sites and who were willing to enter this extension study.
- Subjects maintained the randomized treatment assignment at the conclusion of Study CLAR-09007 (Day 365):
 - Oral TU: 100-300 mg bid
 - T-gel (AndroGel 1%): 2.5-10 g qd
- Dose titration in the extension study was based on serum total T concentration 4-6 hours (C4-6) post dose on Day 0 (Day 365 of study CLAR-09007), Day 180 and Day 365 (**Figure 23**)
- Safety assessment took place every 3 months (study site visit)
- Analysis populations:
 - ITT analysis set: all subjects who completed Study CLAR-09007 and who were enrolled into this extension study, irrespective of any deviation from the protocol or premature discontinuation
 - Safety analysis set: all subjects who received at least 1 dose of study drug during the extension study

Single time-point PK (C4-6):

- Serum total T concentration at 4-6 hours post-AM dose on Days 0, 180, and 365. If applicable, additional samples were taken at unscheduled visits following dose titration.
- Serum DHT concentration on Days 90, 180, 270, and 365 at 4-6 hours post-AM dose (Days 180 and 365)

Safety assessments:

- Clinical labs (hematology and chemistry) in a fasting state on Days 0, 90, 270, and 365; and additional Hb and Hct on Day 180.
- CV biomarkers: hs-CRP and Lp-PLA2 on Days 0, 90, and 365.
- Prostate evaluation:
 - PSA on Days 0, 180, and 365.
 - Prostate volume (by TRUS) on Days 0 and 365
 - IPSS questionnaire on Days 0, 180, and 365.
- Physical examination (PE):
 - Full PE with a digital rectal examination (DRE) on Days 0 and 365
 - Brief PE to assess vital signs, AEs, and changes in concomitant medications on Days 90, 180, and 270.
- Vital signs at all visits, any unscheduled visits and early withdrawal
- AEs and concomitant medications throughout the study

Figure 23. Dose Titration for subjects entering Study CLAR-12010
(From the Applicant's Figures 1 and 2 of the 120-day safety update)

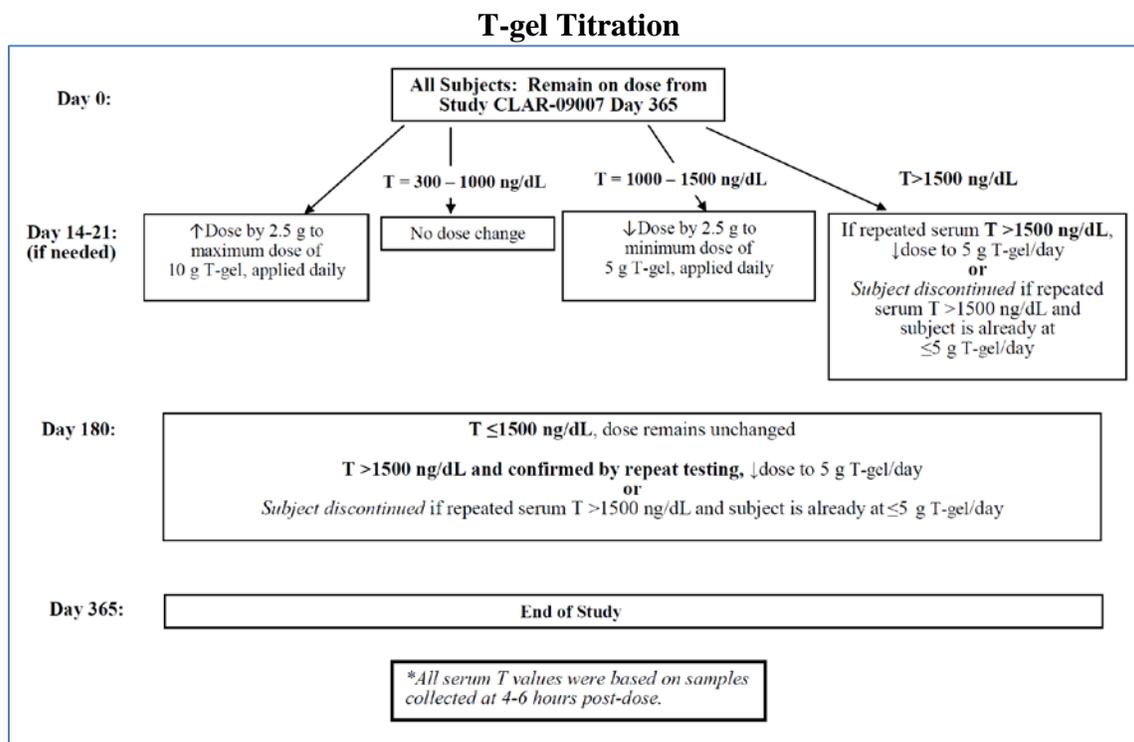
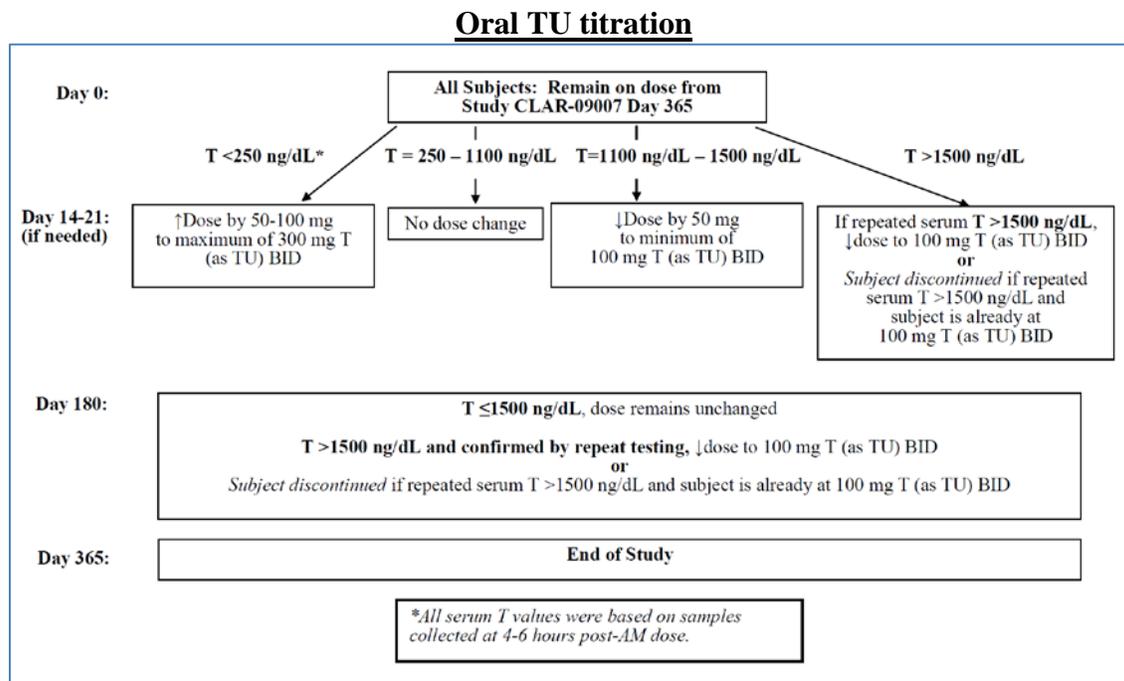


Table 89. Schedule of assessment in Study CLAR-12010
(From Applicant’s Table 1 of the 120-day safety update)

Assessment	Visit 1 Day 0 (Baseline values from CLAR-09007 Day 365)	Visit 1.1 Day 14-21 Dose Titration Visit (if needed)	Visit 2 Day 90 (±5) (Month 15 of continuous T treatment)	Visit 3 Day 180 (±5) (Month 18 of continuous T treatment)	Visit 4 Day 270 (±5) (Month 21 of continuous T treatment)	Visit 5² Day 365 (±5) (Month 24 of continuous T treatment)
Daily dosing regimen						
Consent ¹	+					
Brief physical examination (obtain vital signs, AEs and changes in concomitant medications)			+	+	+	
Physical examination with DRE	+					+
Safety labs—fasting (±5 days for all visits) (clinical chemistry, lipids, and hematology)	+		+	Hb and Hct only	+	+
CV biomarkers (hs-CRP and Lp-PLA ₂)	+		+			+
PSA	+			+		+
Single serum T (4-6 hours post-dose)	+			+		+
Single serum DHT			+	+	+	+
Dose titration, if needed		+ ³		+ ⁴		
Prostate ultrasound	+					+
Adverse event monitoring						
Concomitant medication recording						
AUA/IPSS questionnaire	+			+		+

Abbreviations: AE=adverse event; AUA/IPSS=American Urological Association/International Prostate Symptom Score; CV=cardiovascular; DHT=dihydrotestosterone; DRE=digital rectal exam; Hb=hemoglobin; Hct=hematocrit; hs-CRP=high-sensitivity C-reactive protein; Lp-PLA₂=lipoprotein-associated phospholipase A₂; PSA=prostate-specific antigen; T=testosterone

¹ Consent was obtained on Day 0 (i.e., Day 365 of Study CLAR-09007).

² Subjects withdrawn/terminated/discontinued prior to completion of the study were to have all assessments scheduled for Visit 5 at their final visit.

³ Visit 1.1 was to occur for subjects requiring dose titration based on the 4-6 hour post-dose sample on Day 365 of Study CLAR-09007.

⁴ Doses were to be titrated, if needed, based upon serum T at 4-6 hours post-dose on Day 180. Dose titration was to occur within 14 days of receipt of serum T level confirming need for titration.

Source: [Appendix 16.1.1](#)

Statistical and Analytical Plan:

- Continuous data: summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum [Min], and maximum [Max]), and, if relevant, 95% confidence intervals (CI)
- Categorical data: described using frequencies and percentages, with percentages based on the frequencies of subjects in the analysis set for whom there were non-missing data, unless otherwise specified.
- No imputation for missing data unless otherwise stated
- Baselines for calculation of change from baseline:
 - Primary baseline: the last non-missing measurement obtained prior to the first dose date in the extension study
 - Secondary baseline: the last non-missing measurement obtained before or on the first dose date of Study CLAR-09007, for additional analyses of change from baseline in selected clinical laboratory parameters and in CV biomarkers
- Classified the selected clinical laboratory results as below, within or above the reference range and compared by three-by-three shift tables (baseline vs. follow-up visits) based on primary and secondary baselines

Protocol amendments:

There were two protocol amendments and one SAP update during the study. The following are key changes summarized from the report.

Protocol amendment #1: dated Aug 28, 2012

- Changed the serum T concentration limit for mandating dose titration or discontinuation from 1800 ng/dL to 1500 ng/dL
- Clarified subjects entering the extension study within 14 days of completing Study CLAR-09007
- Clarified that subjects with Hct >54% needed to have confirmation by re-test and that the Investigator may advise these subjects to donate blood (phlebotomy) prior to making a decision regarding subject withdrawal.

Protocol amendment #2: dated Oct 18, 2012:

- Included blood collection for serum DHT periodically during the study.
- Included comparisons between treatment groups for critical safety parameters under the statistical section

SAP changes: for the 120-day safety update

- An additional TEAE analysis for a combined TEAE incidence including CLAR-09007
- Summary statistics tables of CV biomarker data for hs-CRP and Lp-PLA2
- Summary statistics tables for IPSS results
- Plots of the safety response (change from primary and secondary baselines in Hct, PSA, hs-CRP, and Lp-PLA2) to time on treatment, study drug dose, and exposure level (based on DHT/T ratios)
- Summary statistics tables for T, DHT, and DHT/T data

9.6.3.2 Subject disposition:

A total of 182 subjects (from 23 US sites) who completed the 12-month study in the CLAR-09007 entered into the 12-month extension study CLAR-12010 (**Table 90**).

- Oral TU: n=88
- T-gel: n=94

Subject disposition at the date of database snapshot (Feb 5, 2014):

- Completed Day 270 visit: 79.1%
 - Oral TU: 86.4% (n=76)
 - T-gel: 72.3% (n=68)
- Completed Day 365 visit: 27.5%
 - Oral TU: 29.5% (n=26)
 - T-gel: 25.5% (n=24)
- Overall dropout rate: 22.5% (n=41)
 - Oral TU: 17% (n=15)
 - T-gel: 27.7% (n=26)

[Reviewer's Comments: The Applicant committed at the Pre-NDA meeting to submit the safety summary from this study at the 120-day safety update with at least 50% of subjects having completed Day 365. Only 27.5% of subjects had actually completed through Day 365.]

Demographic and baseline characteristics:

The demographics and baseline characteristics were comparable between the two treatment groups and were similar to the profiles observed in Study CLAR-09007.

Concomitant medications:

The overall profile of concomitant medication used during the extension study was similar to what was observed in the first 12 months (in Study CLAR-09007). The majority of subjects took at least one concomitant medication with slightly fewer subjects taking concomitant medication in the oral TU group (88%) than in the T-gel group (94%).

- Oral TU > T-gel in the following medications:
 - Anti-thrombotic agents (aspirin): 33% vs. 25%
 - Calcium channel blockers: 16% vs. 13%
 - Psycholeptics: 24% vs. 20%
- Oral TU < T-gel in the following medications:
 - Beta-blockers: 19% vs. 23%
 - Diuretics: 6% vs. 13%
 - Lipid-modifying agents: 47% vs. 53%
 - Urologicals: 17% vs. 22%
 - Psychoanaleptics: 20% vs. 27%

Table 90. Subject disposition at the Database snapshot date

Subject Disposition	Oral TU n (%)	T-gel n (%)	Total n (%)
Subjects Enrolled to the Extension (ITT set)	88 (100)	94 (100)	182 (100)
Subjects Received ≥1 Dose (Safety set)	86 (97.7)	92 (97.9)	178 (97.8)
Subjects Completed Visit	26 (29.5)	24 (25.5)	50 (27.5)
Visit 2 (Day 90)	81 (92.0)	82 (87.2)	163 (89.6)
Visit 3 (Day 180)	79 (89.8)	75 (79.8)	154 (84.6)
Visit 4 (Day 270)	76 (86.4)	68 (72.3)	144 (79.1)
Visit 5 (Day 365)	26 (29.5)	24 (25.5)	50 (27.5)
Subjects Continuing in the Study	47 (53.4)	44 (46.8)	91 (50.0)
Dropouts	15 (17.0)	26 (27.7)	41 (22.5)
Withdrawal of Consent	3 (3.4)	8 (8.5)	11 (6.0)
Increase in PSA of >1.4 ng/mL	4 (4.5)	3 (3.2)	7 (3.8)
Lost to Follow-Up	1 (1.1)	6 (6.4)	7 (3.8)
Other*	2 (2.3)	4 (4.3)	6 (3.3)
Adverse Event	0	3 (3.2)	3 (1.6)
Hematocrit of >54%	1 (1.1)	1 (1.1)	2 (1.1)
Non-Compliance with Study Drug	2 (2.3)	0	2 (1.1)
Protocol Violation	1 (1.1)	0	1 (0.5)
Missing	1 (1.1)	1 (1.1)	2 (1.1)

Source: From the Applicant's Table 2 of the Study CLAR-12010 summary at the 120-day safety update

* The "other" included unrelated surgery, fatigue, PSA of 4.3 ng/mL, nontherapeutic testosterone levels (2 subjects), and polycythemia.

9.6.3.3 Extent of exposure:

The median duration of exposure was similar between treatment groups, approximately 9 months from the first dose date of the extension study or 21 months from the initiation of Study CLAR-09007 (Table 91).

- Based on the primary baseline (the first dose date of Study CLAR-12010): 9 months
 - Oral TU: 276.5 days with mean daily dose of 334 mg
 - T-gel: 270.5 days with mean daily dose of 6.1 g
- Based on secondary baseline (the first dose date of Study CLAR-09007): 21 months
 - Oral TU: 643.5 days
 - T-gel: 636.0 days

Table 91. Extent of exposure at the database snapshot date in the safety population

Exposure	Oral TU N=86	T-gel N=90
<i>Total Duration (days) based on Primary Baseline†</i>		
Mean ±SD	286.5 ±83.9	256.3 ±96.0
Median	276.5	270.5
Min, Max	6.0, 380.0	2.0, 381.0
<i>Total duration (days) based on Secondary Baseline‡</i>		
Mean ±SD	654.8 ±85.8	625.0 ±98.9
Median	643.5	636.0
Min, Max	376.0, 782.0	373.0, 778.0
<i>Average Total Daily Dose based on Primary Baseline*</i>		
n	85	89
Mean ±SD	334.1 ±100.5 mg/day	6.1 ±2.2 g/day
Median	358.0	6.2
Min, Max	102.4, 589.7	0.0, 10.7

Source: From the Applicant's Table 5 and post-text Tables 14.3.1.3a, 14.3.1.3b, and 14.3.1.4

† The total number of days a subject took the study drug was calculated from: Last dose date in the extension study – First dose date in the extension study + 1

‡ The total number of days a subject took the study drug was calculated from: Last dose date in the extension study – First dose date in Study CLAR-09007 + 1

* Average total daily dose (mg in T equivalents): based on average dose and time exposure (days) for each subject from the first dose date in the extension study to the last dose date in the extension study.

9.6.3.4 Adverse events:

The treatment-emergent adverse events (TEAEs) reported during the extension treatment were all AEs with an onset date on or after the first dose of study drug in the extension study.

The overall incidence of TEAEs was slightly greater in the oral TU group (44%) than in the T-gel group (40%). However, the overall incidences of TEAEs in both groups were approximately 20% lower than those observed during the first 12-month study (CLAR-09007), although the incidence of SAEs appear similar between the first and second 12 months of treatment (**Table 92**).

Table 92. Summary of TEAEs up to 24 months in the safety population

Subject with AE† n (%)	The first 12 months (CLAR-09007)			The second 12 months (CLAR-12010)		
	Oral TU N=161	T-gel N=160	Total N=321	Oral TU N=86	T-gel N=92	Total N=178
Any TEAE	110 (68.3)	100 (62.5)	210 (65.4)	38 (44.2)	37 (40.2)	75 (42.1)
Any serious TEAE	11 (6.8)	6 (3.8)	17 (5.3)	7 (8.1)	4 (4.3)	11 (6.2)
Any treatment-related TEAE‡	53 (32.9)	36 (22.5)	89 (27.7)	11 (12.8)	13 (14.1)	24 (13.5)
Any serious treatment-related TEAE‡	2 (1.2)	0	2 (0.6)	0	1 (1.1)	1 (0.6)
Any TEAE-related dropout	8 (5.0)	5 (3.1)	8 (5.0)	1 (1.2)	6 (6.5)	7 (3.9)
Any TEAE leading to death	0	0	0	0	0	0

Source: From the Applicant's Table 27 of Study CLAR-09007 and Table 6 of Study CLAR-12010

† AEs were coded using MedDRA Version 15.1; TEAEs included all AEs with an onset date on or after the first dose of study drug in the extension study.

‡ The Applicant defined "treatment-related TEAEs" as those events with an investigator's judgment of causality as possibly related, probably related, definitely related, or missing.

Overall, the AE profile in both the first and second 12 months of this investigation appears consistent with the T class and similar between the first and second 12 months in both treatment groups (**Table 93**).

The incidences of all AEs and TRT-related AEs decreased in the second 12 months in both treatment groups but a slightly higher incidence persisted in the oral TU group. There were no new AEs clustered under certain SOCs during the second 12 months of treatment.

The following are notable observations from the AE data in the extension study:

- There was a higher incidence of the following AEs over 24 months in the oral TU group vs. T-gel
 - Polycythemia
 - GI disorder (abdominal discomfort, diarrhea)
 - Peripheral edema
 - Upper respiratory infection
 - Prostate enlargement
- AEs coded as "hypertension" were greater in incidence for T-gel vs oral TU
- Incidence of TRT- and other drug-related AEs that decreased >3% during the 2nd 12 months compared with the 1st 12 months in the oral TU group:
 - Prostate enlargement: decreased from 5.6% to 1.2%
 - Peripheral edema: decreased from 5.6% to 0%
 - Polycythemia: decreased from 8.1% to 4.7%
 - Diarrhea and abdominal discomfort: decreased from 5.6% and 3.1% to 0%
- Incidence of AEs with no known relatedness to TRT that decreased >3% during the 2nd 12 months compared with the 1st 12 months in the oral TU group:
 - Upper respiratory infection (URI): decreased from 6.8% to 1.2%
 - Nasopharyngitis: decreased from 6.2% to 0%

- Incidence of AEs that reduced by >3% during the second 12 months in the T-gel group:
 - Hypertension: reduced from 6.9% to 3.3%
 - Nasopharyngitis: reduced from 4.4% to 1.1%
 - Sinusitis: reduced from 3.1% to 0

[Reviewer's Comments: Comparisons between the first 12 months of treatment (Study CLAR-09007) and the second 12 months of treatment (Study CLAR-12010) should be interpreted with caution because only a subset of completers from the first 12 month study (non-randomly) entered the extension study and considerably fewer patients contributed data during the 12 month extension.]

Table 93. TEAEs occurred in ≥2% subjects over 24 months in safety population

SOC/PT† n (%)	Oral TU			T-gel		
	1 st 12M N=161	2 nd 12M N=86	Combined N=161	1 st 12M N=160	2 nd 12M N=92	Combined N=160
Any TEAE	110 (68.3)	38 (44.2)	116 (72.0)	100 (62.5)	37 (40.2)	107 (66.9)
Blood and lymphatic system disorders	14 (8.7)	5 (5.8)	17 (10.6)	9 (5.6)	4 (4.3)	10 (6.3)
Polycythemia	13 (8.1)	4 (4.7)	15 (9.3)	6 (3.8)	4 (4.3)	8 (5.0)
Gastrointestinal disorders	26 (16.1)	3 (3.5)	28 (17.4)	18 (11.3)	4 (4.3)	20 (12.5)
Abdominal discomfort	5 (3.1)	0	5 (3.1)	0	0	0
Diarrhea	9 (5.6)	0	9 (5.6)	3 (1.9)	0	3 (1.9)
Eructation	4 (2.5)	0	4 (2.5)	0	0	0
Nausea	4 (2.5)	0	4 (2.5)	4 (2.5)	0	4 (2.5)
General disorders and administration site conditions	17 (10.6)	2 (2.3)	19 (11.8)	6 (3.8)	3 (3.3)	9 (5.6)
Edema peripheral	9 (5.6)	0	9 (5.6)	2 (1.3)	0	2 (1.3)
Fatigue	2 (1.2)	1 (1.2)	4 (2.5) ^b	0	1 (1.1)	1 (0.6)
Immune system disorders	0	2 (2.3)	2 (1.2)	2 (1.3)	0	3 (1.9)
Seasonal allergy	0	2 (2.3)	2 (1.2)	2 (1.3)	0	2 (1.3)
Infections and infestations	39 (24.2)	13 (15.1)	45 (28.0)	32 (20.0)	9 (9.8)	38 (23.8)
Bronchitis	3 (1.9)	3 (3.5)	6 (3.7)	2 (1.3)	4 (4.3)	5 (3.1)
Gastroenteritis viral	4 (2.5)	0	4 (2.5)	2 (1.3)	0	2 (1.3)
Nasopharyngitis	10 (6.2)	0	10 (6.2)	7 (4.4)	1 (1.1)	8 (5.0)
Sinusitis	5 (3.1)	3 (3.5)	7 (4.3)	5 (3.1)	0	5 (3.1)
Tooth infection	1 (0.6)	0	1 (0.6)	3 (1.9)	1 (1.1)	4 (2.5)
Upper respiratory tract infection	11 (6.8)	1 (1.2)	12 (7.5)	4 (2.5)	0	4 (2.5)
Investigations	17 (10.6)	3 (3.5)	20 (12.4)	16 (10.0)	4 (4.3)	20 (12.5)
PSA increased‡	5 (3.1)	2 (2.3)	7 (4.3)	8 (5.0)	2 (2.2)	10 (6.3)

SOC/PT† n (%)	Oral TU			T-gel		
	1 st 12M N=161	2 nd 12M N=86	Combined N=161	1 st 12M N=160	2 nd 12M N=92	Combined N=160
Musculoskeletal and connective tissue disorders	17 (10.6)	2 (2.3)	20 (12.4)	17 (10.6)	9 (9.8)	24 (15.0)
Arthralgia	4 (2.5)	0	4 (2.5)	6 (3.8)	2 (2.2)	8 (5.0)
Back pain	4 (2.5)	1 (1.2)	6 (3.7) ^c	2 (1.3)	1 (1.1)	3 (1.9)
Intervertebral disc protrusion	0	0	0	0	2 (2.2)	2 (1.3)
Muscle spasms	2 (1.2)	0	2 (1.2)	3 (1.9)	1 (1.1)	4 (2.5)
Nervous system disorders	16 (9.9)	5 (5.8)	22 (13.7)	13 (8.1)	7 (7.6)	19 (11.9)
Dizziness	4 (2.5)	1 (1.2)	5 (3.1)	2 (1.3)	1 (1.1)	3 (1.9)
Headache	4 (2.5)	1 (1.2)	6 (3.7)	5 (3.1)	1 (1.1)	6 (3.8)
Psychiatric disorders	11 (6.8)	4 (4.7)	16 (9.9)	10 (6.3)	1 (1.1)	11 (6.9)
Depression	1 (0.6)	2 (2.3)	3 (1.9)	0	0	0
Reproductive system and breast disorders	21 (13.0)	3 (3.5)	24 (14.9)	14 (8.8)	2 (2.2)	16 (10.0)
Prostatitis	4 (2.5)	0	4 (2.5)	2 (1.3)	1 (1.1)	3 (1.9)
Prostatomegaly	9 (5.6)	1 (1.2)	10 (6.2)	5 (3.1)	1 (1.1)	6 (3.8)
Respiratory, thoracic, and mediastinal disorders	14 (8.7)	0	14 (8.7)	11 (6.9)	2 (2.2)	12 (7.5)
Cough	3 (1.9)	0	3 (1.9)	4 (2.5)	1 (1.1)	5 (3.1)
Sleep apnea syndrome	0	0	0	3 (1.9)	1 (1.1)	4 (2.5)
Skin and subcutaneous tissue disorders	11 (6.8)	3 (3.5)	12 (7.5)	13 (8.1)	2 (2.2)	14 (8.8)
Acne	1 (0.6)	0	1 (0.6)	4 (2.5)	0	4 (2.5)
Rash	2 (1.2)	2 (2.3)	4 (2.5)	2 (1.3)	2 (2.2)	3 (1.9)
Vascular disorders	10 (6.2)	2 (2.3)	12 (7.5)	13 (8.1)	4 (4.3)	17 (10.6)
Hypertension	6 (3.7)	2 (2.3)	8 (5.0)	11 (6.9)	3 (3.3)	14 (8.8)
Uncoded SOC	0	7 (8.1)	8 (5.0)	0	5 (5.4)	6 (3.8)
Uncoded preferred term	0	7 (8.1)	8 (5.0)	0	5 (5.4)	6 (3.8)

Source: From the Applicant's Table 7 of Study CLAR-12010

Note: The first 12 months (1st 12M) was from the base study (CLAR-09007) and the second 12 months (2nd 12M) from the extension study (CLAR-12010)

† AEs were coded using MedDRA Version 15.1. TEAEs in the 2nd 12 months included all AEs with an onset date on or after the first dose of study drug in the extension study. TEAEs in the 1st 12 months (base) and combined groups included all AEs with an onset date on or after the first dose of study drug in Study CLAR-09007.

‡ Included 3 subjects with uncoded PSA increased in the 2nd 12-month (Study CLAR-12010), n=1 on oral TU and n=2 on T-gel.

9.6.3.5 Serious AEs:

As of the cut-off date (Mar 26, 2014) for SAE reports for the 120-day safety update, three more subjects in the oral TU group (8.1%, n=7) than in the T-gel group (4.3%, n=4) had experienced an SAE, as listed in **Table 94**.

Those SAEs were mostly single events sporadically reported under various SOCs. As per the investigators' judgment, the cerebrovascular accident in the oral TU group and prostate adenocarcinoma in the T-gel group were the only SAEs considered related to study drug.

Discontinuations due to AEs or AEs requiring dose adjustment:

- AE-related dropouts (**Table 92**):
 - Oral TU (1.2%): n=1 (increased PSA)
 - T-gel (6.5%): n=6 (n=2 polycythemia, n=1 cerebrovascular accident, n=1 atrial fibrillation and ejection fraction decreased, n=1 nocturia and pollakiuria, and n=1 rash)
- AE-related dose adjustment:
 - Oral TU: n=4 (n=1 each of polycythemia, rash, hematospermia and Prinzmetal's angina)
 - T-gel: n=0

Table 94. Serious ARs reported during the extension study
(From the Applicant's Table 9 in Study CLAR-12010)

Subject ID	Preferred Term	Start/ Stop Date	Start/ Stop Study Day ^a	Relationship to Study Treatment/ Severity	Reason for Serious ^b	Action Taken with Study Drug	Outcome
Treatment: Oral TU							
(b) (6)	Cerebrovascular accident	(b) (6)	NA	Related/ Severe	5	Interrupted	Not resolved
	Abdominal pain		NA	NA/ Severe	5	Dose not changed	Resolved
	Hip surgery		NA	Unrelated/ Severe	5	Drug withdrawn	Not resolved
	Syncope		85	Unrelated/ Moderate	6	Dose not changed	Not resolved
	Prinzmetal angina		117/ 119	Unrelated/ Severe	5	Interrupted	Resolved
	Osteoarthritis (requiring hip replacement)		--	Unrelated/ Moderate	5	--	Resolved
	Neck injury		NA	Unrelated/ Moderate	5	Dose not changed	Resolved
Treatment: Transdermal T-gel							
(b) (6)	Gastric ulcer hemorrhage	(b) (6)	246/ 246	Unrelated/ Severe	5	Dose not changed	Resolved
	Adenocarcinoma of the prostate ^c		409/	Related/ Severe	6	Dose not changed	Not resolved
	Sepsis		410/ 413	Unrelated/ Severe	5	Dose not changed	Resolved
	Duodenal ulcer hemorrhage		21/ 22	Unrelated/ Severe	5	Dose not changed	Resolved
	Cerebrovascular accident		264/ 269	Unrelated/ Severe	3, 5	Drug withdrawn	Resolved

Abbreviations: NA=not available; TU=testosterone undecanoate

Note: This table includes all SAEs reported through 26 March 2014, the final date for SAE inclusion in this 120-day safety update.

^a Study day is relative to the first day of study treatment in the extension study.

^b 1=persistent or significant disability/incapacity; 2=congenital anomaly or birth defect; 3=life-threatening; 4=results in death; 5=requires or prolongs hospitalization; 6=other medically important serious event.

^c This subject had an event that was reported past the database snapshot date. Information is from the early safety report.

^d Subject 112-005 was enrolled in the extension study, but did not receive study drug. He entered the study on 02 January 2013 and discontinued the study on 25 March 2013 without any record of drug exposure.

^e This event was uncoded in the post-text TEAE tables; reported term is used here.

Source: [Post-text Table 14.3.1.1.9](#), Safety Database for Study CLAR-12010

9.6.3.6 Vital signs:

Vital signs pre-specified in the study protocol included blood pressure and pulse rate, which were measured at check-in on Days 90, 180, 270 and 365. Both mean systolic and diastolic BPs increased in the oral TU group in a similar trend, though of a lesser magnitude, as observed in

the first 12 months. T-gel also showed increased mean systolic BP, but to less of a degree than oral TU. Of note, the mean diastolic BP in the T-gel group actually decreased from baseline at all visits (**Table 95**).

The range of mean systolic BP change from baseline across visits was:

- Oral TU: +2.7 to +11.5 mmHg
- T-gel: +1.6 to +5.9 mmHg

The range of mean diastolic BP increase from baseline across visits was:

- Oral TU: +0.4 to +1.4 mmHg
- T-gel: -0.1 to -2.4 mmHg

Mean heart rate remained steady within normal variations across all visits and were comparable between the two treatment groups.

Table 95. Changes in blood pressure and pulse rate from baseline during the 12-month extension study in safety population

Visit Day†	Systolic BP (mmHg)				Diastolic BP (mmHg)				Pulse rate			
	Oral TU N=86		T-gel N=92		Oral TU N=86		T-gel N=92		Oral TU N=86		T-gel N=92	
	Mean	Change	Mean	Change	Mean	Change	Mean	Change	Mean	Change	Mean	Change
Baseline-1	127.5	0	128.1	0	78.8	0	79.5	0	70.3	0	69.9	0
Baseline-2	137.7	10.2	132.2	4.1	82.9	4.1	79.4	-0.1	73.9	3.6	73.5	3.6
Day 90	132.4	4.9	129.7	1.6	81.9	3.1	78.3	-1.2	70.8	0.5	70.0	0.1
Day 180	130.2	2.7	130.7	2.6	79.2	0.4	78.1	-1.4	71.8	1.5	70.6	0.7
Day 270	132.8	5.3	130.2	2.1	81.9	3.1	77.5	-2.0	70.1	-0.2	68.6	-1.3
Day 365	132.4	4.9	131.6	3.5	80.1	1.3	77.1	-2.4	70.5	0.2	66.5	-3.4

Source: From the Applicant's Table 14.3.3.1, Table 14.3.3.2 and Table 14.3.3.3 in Study CLAR-12010.

The changes from baseline at each visit were calculated by "mean post-baseline – mean baseline" because the mean changes from baseline in BP and pulse rate were not available in the submission.

† Baseline-1 was defined as Day 0 of Study CLAR-09007 and Baseline-2 as the day when entered the CLAR-12010 extension study (equal to Day 365 of CLAR-09007). The data at each visit were from subjects who entered the extension treatment, received at least one dose of study drug and had BP measures at the corresponding time-points. Coefficient of variation (CV) for the mean SBP and DBP was about 10-15%.

9.6.3.6 Prostate safety

Prostate-related AEs:

A total 4 subjects from each group had prostate-associated TEAEs, including: BPH, increased PSA (by >1.4 ng/ml), prostate enlargement and prostatitis. Those AEs are generally known to be related to TRT and were considered by the investigator as at least possibly related to study drug.

Prostate specific antigen (PSA):

Serum PSA was measured on Days 180 and 365. The median PSA increased in both treatment groups, with slightly greater increase in the oral TU group (**Table 96**), although the mean changes from baseline were comparable between the two groups but with high variations (the coefficient of variation ranged from 147% to 179%). Slightly more subjects in the oral TU group had PSA increase by >1.4 ng/ml (a possibly clinically relevant increase) from the pre-dose baseline during the extension study compared with the T-gel group (**Table 97**).

Overall, the serum PSA changes during the 12-month extension treatment appear similar to the changes observed in first 12-month study.

[Reviewer’s Comments: Only 30% of subjects from the oral TU group have completed the Day 365 visit, which renders unstable data for that time-point. In addition, the serum T and DHT concentrations appear lower compared with the first 12 months (see the T and DHT section). These factors may have mitigated a demonstration of drug-related effects on PSA.]

Table 96. Serum PSA changes during the extension study in the safety population

Visit Day†	Oral TU			T-gel		
	N	Median Change %	Mean Change (±SD) %	N	Median Change %	Mean Change (±SD) %
Baseline-1	85	0	0	91	0	
Baseline-2	86	23.5	50±91	92	11.2	55±206
Day 180	79	36.9	67±104	74	24.5	65±171
Day 365	30	49.5	85±110	25	39.3	114±262

Source: From Applicant’s Table 23 in Study CLAR-12010

† Baseline-1: measurements on Day 0 of Study CLAR-09007; and Baseline-2: Day 0 of the extension study (CLAR-12010) which was equal to Day 365 of Study CLAR-09007. The baseline-1 was used for the median and mean % changes from baseline at each visit .

Table 97. PSA increase >1.4 ng/ml during extension period in safety population

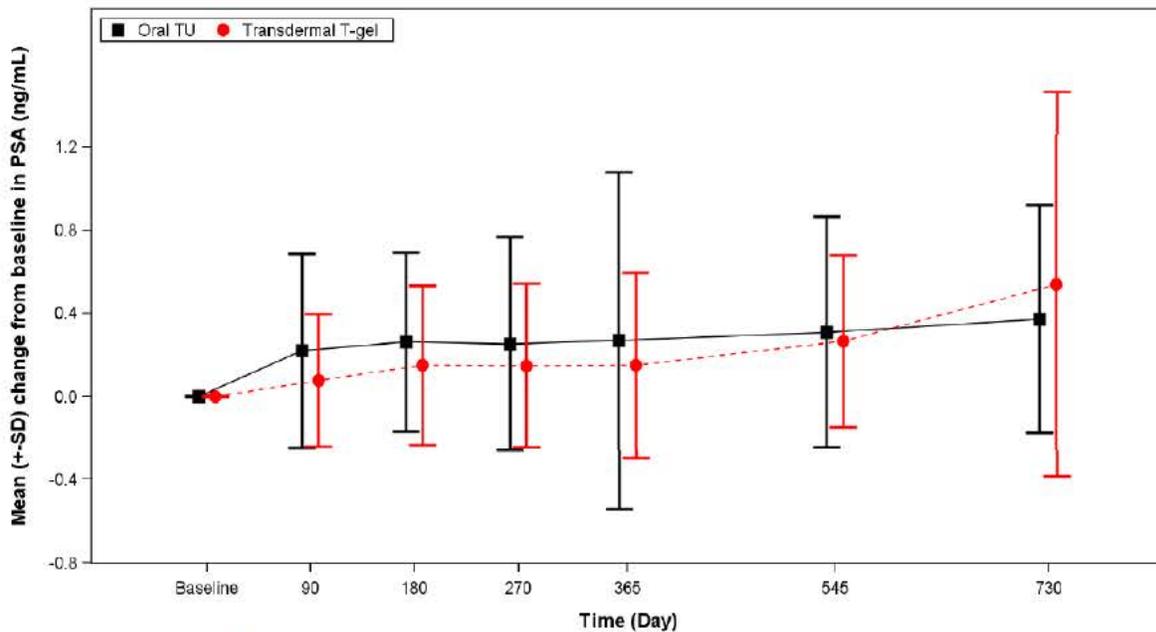
PSA Increase by >1.4 ng/ml	Oral TU N=86		T-gel N=92	
	n	%	n	%
From Study 09007 baseline	5	5.8	3	3.3
From extension baseline	0	0	2	2.2
Dropout	4	4.7	3	3.3

Source: From the Applicant's Tables 14.3.7b, 14.3.7a and Table 14.1.2; the data were based on 34% subjects in the oral TU group and 26% subjects in the T-gel group who completed the Day 365 visit

Mean change in PSA over 24 months:

The mean increase in PSA from the Study 09007 baseline were consistently slightly higher in the oral TU group than in the T-gel group over the two 12-month periods, except on Day 365 of the second 12 month period (**Figure 24**), which may be due to the small number of subjects who completed Day 365.

Figure 24. Mean PSA change (±SD) from baseline over 24 months in safety population



Source: From the Applicant's Figure 4 in Study CLAR-12010. The data were from subjects who entered the extension treatment, received at least one dose of study drug and had PSA measure at the corresponding time-points. For the first 12-month data (Study CLAR-09007), only subjects who entered the extension study are included in the analysis.

Prostate volume (PV):

Prostate was assessed using a transrectal ultrasound examination (TRUS) and a digital rectal examination (DRE) on Days 0 and 365. No PV data were provided in the 120-day safety update submission.

IPSS scores:

The IPSS was assessed on Days 180 and 365. Overall, the mean score was similar to the baseline of the extension study with stable or slight increases from the pre-dose baseline in Study CLAR-09007 in the oral TU group, but slight decreases from the baseline in the T-gel group (**Table 95**).

Three subjects on oral TU but none on T-gel had a shift to increased IPSS severity during the extension study. The IPSS scores in these three subjects increased from moderate (8-19) at the baseline (prior to the extension study) to severe (20, 22, 26).

Table 98. Mean change in the IPSS scores during the 12-month extension study

Visit Day [†]	Oral TU			T-gel		
	N	Mean±SD	Change [‡]	N	Mean±SD	Change [‡]
Baseline-1	86	6.1±5.3	0	92	6.0±4.6	0
Baseline-2	86	6.5±6.0	0.4±4.0	92	6.5±5.4	0.5±4.4
Day 180	77	6.0±5.9	0	75	5.9±4.8	-0.1
Day 365	30	7.3±5.4	0.7	26	5.7±4.0	-0.9

Source: From the Applicant's Table 22 in Study CLAR-12010

[†] Baseline-1: measurements on Day 0 of Study CLAR-09007; and Baseline-2: Day 0 of the extension study (CLAR-12010) which was equal to Day 365 of Study CLAR-09007

[‡] The mean change from pre-dose baseline (Baseline-1)

9.6.3.7 Cardiovascular safety

CV-associated TEAEs:

A total of 7 subjects in the oral TU group and 9 subjects in the T-gel group experienced CV AEs (**Table 99**). Three AEs in 3 subjects in the oral TU group were coded as SAEs (one each of cerebrovascular accident, syncope, and Prinzmetal's angina) and one AE in 1 subject in the T-gel group (cerebrovascular accident). These were included in the above "SAEs" section.

Table 99. CV-associated AEs in the extension study

SOC/PT <i>n</i> (%)	Oral TU (N=86)	T-gel (N=92)	Total (N=178)
Any CV AEs	7	9	16
Cardiac disorders			
Atrial fibrillation	0	1 (1.1)	1 (0.6)
Prinzmetal angina	1 (1.2)	0	1 (0.6)
Tachycardia	1 (1.2)	0	1 (0.6)
Investigations			
Blood pressure increased	1 (1.2)	1 (1.1)	2 (1.1)
Ejection fraction decreased	0	1 (1.1)	1 (0.6)
Heart rate increased	0	1 (1.1)	1 (0.6)
Nervous system disorders			
Cerebrovascular accident	1 (1.2)	1 (1.1)	2 (1.1)
Syncope	1 (1.2)	0	1 (0.6)
Vascular disorders			
Hypertension	2 (2.3)	3 (3.3)	5 (2.8)
Venous insufficiency	0	1 (1.1)	1 (0.6)

Source: From the Applicant's Table 13 of Study CLAR-12010

CV biomarkers and non-inferiority analysis:

The two major CV biomarkers, hs-CRP and Lp-PLA2, were evaluated on Days 90 and 365 during the extension study. The overall profile of the changes from baseline in both biomarkers during the 12 month extension appears similar to the changes observed in the first 12 months, with more unfavorable (worse) trends in the oral TU group compared to T-gel across most visits (**Table 100**).

Analysis was conducted by excluding hs-CRP >10 mg/L (based on the CDC/AHA's recommendation) and this showed the same trends as the primary analysis, but as expected, smaller variations.

The mean values of Lp-PLA2 decreased from baseline across 24 months in both treatment groups in the safety population who entered to the extension study. The changes appear comparable between the two groups.

The Applicant did not plan and did not perform non-inferiority analysis of the CV biomarkers for the extension study.

Using the same modified statistical methodology that was used for the first 12-month data as described in the review of Study CLAR-09007, the statistical reviewers performed a post-hoc non-inferiority analysis of hs-CRP and Lp-PLA2 in the safety population who completed Day

365 visit (n=31 on oral TU and n=28 on T-gel). As summarized in (Table 87), the proportion of subjects with “worse” CV biomarkers was higher in the oral TU group than in the T-gel group, on Day 90, and the difference was statistically significant. Based on the analysis excluding subjects with hs-CRP changes > 10 mg/L, there was no evidence that the CV biomarkers were getting further worse over time.

Table 100. Serum hs-CRP profile over 24 months in safety population who entered the extension study

Visit Day	Including all hs-CRP data				Excluding hs-CRP>10 mg/L			
	Oral TU		T-gel		Oral TU		T-gel	
	Actual	Change [†] (%)	Actual	Change [†] (%)	Actual	Change [†] (%)	Actual	Change [†] (%)
Baseline[†]								
N	86		92		82		85	
Mean±SD	2.6±4.2	0	4.3±9.2	0	1.9±1.7	0	2.2±1.9	0
Day 90								
N	83	87	87	87	79	75	81	77
Mean±SD	3.6±6.6	+87±213	3.1±4.2	-58±324	2.4±2.1	+79±205	2.0±1.7	-29±128
Day 180								
N	86	86	91	91	82	78	83	80
Mean±SD	2.9±3.4	+56±125	3.6±5.6	-80±405	2.3±2.0	+53±118	2.2±1.8	-26±94
Day 365								
N	85	85	91	91	82	78	85	80
Mean±SD	2.9±4.9	+65±245	3.8±12.3	-61±317	2.1±2.0	+56±221	2.0±1.6	-18±80
Day 455								
N	80	80	82	82	76	72	75	72
Mean±SD	3.1±4.9	+77±217	4.2±8.0	+101±429	2.1±1.8	+54±135	2.2±1.9	-29±121
Day 730								
N	31	31	28	28	65	63	57	55
Mean±SD	2.2±3.4	+97±460	2.6±3.5	+18±86	1.9±1.8	36±143	2.1±2.0	-23±134

Source: From Applicant’s Table 24 of CLAR-12010; the Day 730 data with excluding hs-CRP>10 mg/ml was updated based on the Applicant’s submission of Aug 19, 2014

[†] The Pre-dose baseline: the last non-missing measurement before or on the first dose date of Study CLAR-09007

[‡] The mean percentage change from the pre-dose baseline (Study CLAR-09007). The mean % change from baseline were disproportional to the mean absolute change from baseline due to high inter-subject variations.

9.6.3.8 Hb/Hct effects

Hct and Hb were measured on Days 90, 180, 270 and 365. Overall, the mean increases in Hct/Hb and shifts from baseline during the 12-month extension were greater in the oral TU group than in the T-gel group. The increase in Hct and Hb appears not time-dependent throughout the 12-month extension period and findings were comparable to the first 12-month treatment.

Mean increase in Hb and Hct from baseline:

The mean increases in Hb (Table 101) and Hct (Table 102) from the pre-dose baseline (prior to Study CLAR-09007) were greater in the oral TU groups than in the T-gel group across all visits during the extension study. The small mean increases from baseline were approximately two times larger with oral TU vs with T-gel. Compared with the first 12 months (CLAR-09007, Day 365), the mean Hb/Hct increases were similar to or very slightly greater in both groups at the end of the second 12 months (CLAR-12010).

Table 101. Change in Hb during the 12-month extension study
(From the Applicant's Table 15 in Study CLAR-12010)

Visit Day†	Oral TU			T-gel		
	N	Mean±SD	Change‡	N	Mean±SD	Change‡
Baseline-1	86	14.8±1.0	0	92	14.6±0.9	0
Baseline-2	86	15.4±1.5	+4.3 (±8.9)	92	14.8±1.3	+1.4 (±7.3)
Day 90	80	15.4±1.3	+5.4 (±8.4)	82	14.9 ±1.2	+2.9 (±7.4)
Day 180	79	15.5±1.4	+5.4 (±8.2)	75	14.8 ±1.3	+2.0 (±8.1)
Day 270	75	15.7±1.5	+6.7 (±8.8)	67	14.8±1.5	+1.9 (±10.0)
Day 365	32	15.6±1.6	+6.6 (±9.9)	26	14.9±1.8	+3.0 (±14.0)

† Baseline-1: measurements on Day 0 of Study CLAR-09007; and Baseline-2: Day 0 of the extension study (CLAR-12010) which was equal to Day 365 of Study CLAR-09007

‡ The mean change from pre-dose baseline (Baseline-1)

Table 102. Change in Hct during the 12-month extensions study
(From the Applicant's Table 16 in Study CLAR-12010)

Visit Day†	Oral TU			T-gel		
	N	Mean±SD	Change‡	N	Mean±SD	Change‡
Baseline-1	86	44.3±2.3	0	92	44.0±2.5	0
Baseline-2	86	46.6±3.7	+5.3 (±7.7)	92	44.9±3.9	+2.1 (±7.6)
Day 90	80	47.2±3.5	+6.6 (±7.7)	82	45.5±3.8	+3.8 (±7.3)
Day 180	79	47.2±3.8	+6.2 (±8.0)	75	45.2±4.3	+2.9 (±8.1)
Day 270	75	47.1±3.9	+6.6 (±8.3)	67	44.7±4.7	+1.9 (±10.1)
Day 365	32	46.8±4.2	+6.2 (±9.5)	26	44.6±5.3	+2.8 (±13.3)

† Baseline-1: measurements on Day 0 of Study CLAR-09007; and Baseline-2: Day 0 of the extension study (CLAR-12010) which was equal to Day 365 of Study CLAR-09007

‡ The mean change from pre-dose baseline (Baseline-1)

Subjects with confirmed Hct >54%:

The proportion of subjects with confirmed Hct >54% in both treatment groups was slightly higher in the extension period than in the first 12 months. The reporting frequency of Hct >54% across all visits appears comparable between the two treatment groups (**Table 103**).

Table 103. Subjects with confirmed Hct ≥54% during the extension study

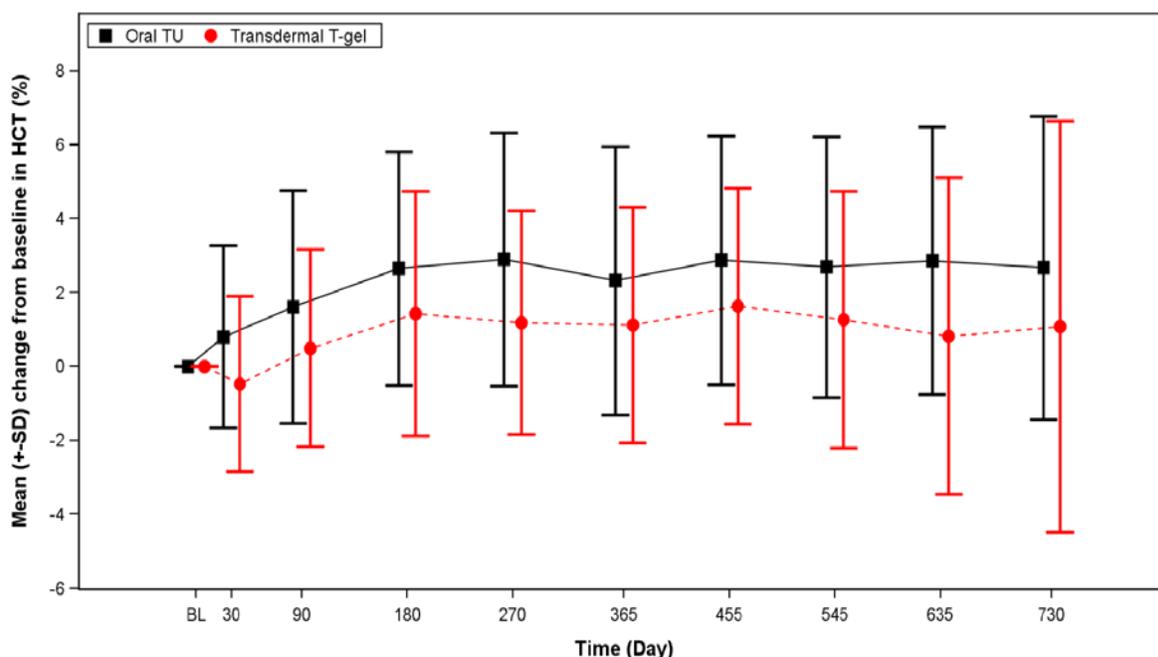
Visit Day	First 12 months (CLAR-09007)		Second 12 months (CLAR-12010)	
	Oral TU N=161	T-gel N=160	Oral TU N=86	T-gel N=92
Baseline	0	0	0	1
Day 30	1	0		
Day 90	3	1	2	1
Day 180	4	2	1	1
Day 270	0	1	3	1
Day 365	4	1	1	1
Total	4 (2.5%)	1 (0.6%)	3 (3.5%)	3 (3.3%)
Withdrawal due to Hct >54%	2	0	1	1

Source: From Applicant's Tables 14.3.6 in Study CLAR-12010 and 14.3.7 in Study CLAR-09007. The data were from subjects with a confirmed Hematocrit value >54% at any visit during the study. Subjects with more than one occurrence are counted once.

Mean Hct increase over 24 months:

The mean increases in Hct over the two 12-months period were consistently higher in the oral TU group than in the T-gel group (**Figure 25**).

Figure 25. Mean Hct changes from baseline over 24 months in safety population



Source: From the Applicant's Figure 3 in Study CLAR-12010. The data were from all subjects who entered the extension treatment and received at least one dose of study drug and had a Hct measure at the corresponding time-points. For the first 12-month data (Study CLAR-09007), only subjects who entered the extension study are included in the analysis.

9.6.3.9 Lipid profile:

The serum lipid profile, including triglyceride (TG), total cholesterol, LDL and HDL were monitored at extension baseline (Day 365 of CLAR-09007), and on extension days 90, 270 and 365. Overall, the lipid profile during the extension was consistent with the first 12-month study. The lipids maintained at the decreased levels across all visits during the 12-month extension and were comparable between oral TU and T-gel, except for HDL (Table 104 and Table 105).

Triglycerides (TG):

Mean and median TG decreases from baseline during the extension study in both groups were similar to the first 12 months, with slightly greater decrease in the oral TU groups (the mean or median changes from pre-dose baseline) than in the T-gel group (Table 104).

It appears that more subjects shifted from a high pre-dose baseline TG to a normal level than from a normal baseline TG to a high level in both groups. The shifts were similar between the two groups.

For subjects with high TG values at the pre-dose baseline that remained high in subsequent visits, none of the high triglyceride values were considered clinically significant by the investigator.

Total cholesterol:

Mean and median total cholesterol decreased from the pre-dose baseline during the extension period with slightly greater decrease in the oral TU group than in the T-gel group. The magnitude of the decrease was similar between the two 12 month periods.

Most subjects in the normal baseline remained in the normal range over the course of the two 12-month periods, with slightly favorable to the oral TU groups.

None of the high total cholesterol experienced by subjects was considered clinically significant by the Investigator.

Low-density Lipoprotein (LDL):

The LDL levels in both treatment groups remained relatively unchanged over both the first and second 12 months with a slight decrease on Days 270 and 365 in the oral TU group but not in the T-gel group.

Most subjects in the normal baseline remained in the normal range over the course of the extension study. None of the abnormal LDL experienced by subjects was considered clinically significant by the Investigator.

High-density Lipoprotein (HDL):

As in the first 12 months, the median HDL remained decreased from pre-dose baseline in both groups during the extension period with greater decrease in the oral TU groups. The HDL changes appear stabilized with no further decrease during the extension (**Table 105**).

The median HDL decreased from pre-dose baseline by 24-25% on oral TU vs. 13% on T-gel during the first 12 months, and by 18-26% on oral TU and 5-14% on T-gel across different visits during the second 12 months.

Overall, more subjects with normal HDL at the pre-dose baseline changed to below the normal during the extension study in the oral TU group vs T-gel:

- On extension day 90: 44% on oral TU vs. 20% on T-gel
- On extension day 270: 46% on oral TU vs. 26% on T-gel

The shift profile was consistent with the observation during the first 12 months of treatment (Study CLAR-09007), as shown in percentage of subjects with change from normal baseline to below normal on Day 365: 57% on oral TU vs. 32% on T-gel.

Table 104. Changes in serum lipid profile during the 12-month extension
(From the Applicant’s Tables 18, 19, 20 and 21 in Study CLAR-12010)

Visit Day†	Safety Population		Triglyceride (mg/dL)				Total Cholesterol (mg/dL)				LDL (mg/dL)			
	Oral TU N=86	T-gel N=92	Oral TU		T-gel		Oral TU		T-gel		Oral TU		T-gel	
			Median	Change‡	Median	Change	Median	Change	Median	Change	Median	Change	Median	Change
Baseline-1	85	91	145.0	0	139	0	181.0	0	181.4	0	101.0	0	95.0	0
Baseline-2	86	91	127.5	-7.3	132.0	-5.9	166.0	-9.1	162.0	-5.1	99.0	-1.6	94.0	0
Day 90	80	81	134.0	-12.7	129.0	-10.1	176.0	-9.5	173.0	-4.4	106.0	+0.5	104.0	+4.8
Day 270	74	66	139.0	-10.5	116.0	-13.4	168.0	-12.2	173.0	-5.2	92.0	-5.9	98.0	0
Day 365	32	26	122.5	-5.4	110.5	-19.8	164.5	-8.2	169.0	1.0	99.0	-7.5	103.5	+4.8

Note: The median values are summarized in the table due to high inter-subject variations; the median and mean values were in the same directions of oral TU vs, T-gel.
† Baseline-1: measurements on Day 0 of Study CLAR-09007; and Baseline-2: Day 0 of the extension study (CLAR-12010) which was equal to Day 365 of Study CLAR-09007; ‡ The median change (%) from pre-dose baseline (Baseline-1).

Table 105. Change in serum HDL during the 12-month extension study
(From the Applicant’s Table 20 in Study CLAR-12010)

Visit Day†	Oral TU, n=86				T-gel, n=92			
	N	Median	Min, Max	Median Change (%)	N	Median	Min, Max	Median Change (%)
Baseline-1	85	47.0	32, 94	0	91	48.0	29, 87	0
Baseline-2	86	37.0	24, 79	-25.5	92	41.5	24, 80	-14.0
Day 90	80	39.0	24, 92	-21.4	82	44.0	29, 80	-7.1
Day 270	75	37.0	20, 81	-22.0	67	44.0	26, 85	-12.3
Day 365	32	38.5	25, 84	-17.7	26	45.0	27, 72	-5.0

See the footnote under **Table 104**

9.6.3.10 Hepatic and renal effects:

Liver effect test:

One subject in the oral TU group had serum ALT 5x ULN (8x baseline) on Day 266, but without changes in serum AST or total bilirubin, and the elevation decreased to near baseline with continued dosing.

Renal function:

Two subjects in the T-gel group had serum creatinine levels which were considered clinically significant by the investigator.

9.6.3.11 DHT and DHT/T ratios:

Serum total T and DHT concentrations were measured with a single PK sample at 4-6 hours (C4-6) post-dose on Days 0, 90, 180, 270 and 365. The cut-off date for the PK data was March 20, 2014, which included >75% of Day 365 visit values.

Serum T concentrations: The mean serum total T concentrations across all four visits decreased and were highly variable in the oral TU group while T concentrations remained stable in the T-gel group as compared with the mean values at the beginning of the extension study (**Table 106**). Of note, on extension days 90 and 270, the mean serum total T concentrations in the TU group appeared to drop to hypogonadal levels (196 ng/dL and 268 ng/dL, respectively) with correspondingly lower serum DHT concentrations (compared to other visits).

Table 106. Mean serum T and DHT concentrations and DHT/T ratios during 12-month extension study

Visit Day†	Safety Population‡		T (ng/dL)		DHT (ng/dL)		DHT/T Ratio	
	Oral TU	T-gel	Oral TU	T-gel	Oral TU	T-gel	Oral TU	T-gel
Baseline-1	84, 84	86, 86	207.2±102.5	220.7±98.2	16.2±11.6	15.9±9.3	0.11±0.20)	0.10±0.10
Baseline-2	84, 84	86, 86	696.9±371.6	449.0±214.9	140.3±73.2	72.0±37.5	0.23±0.13	0.17±0.08
Day 90	62, 60	62, 57	196.2±125.8	445.1±268.6	66.4±50.7	70.6±44.1	0.36±0.22	0.17±0.06
Day 180	79, 78	75, 74	632.1±366.2	519.1±259.7	101.9±48.3	86.7±49.2	0.18±0.08	0.18±0.07
Day 270	69, 68	63, 62	268.0±187.9	469.1±280.9	69.2±43.0	84.2±60.8	0.30±0.16	0.18±0.08
Day 365	72, 71	66, 66	442.0±386.8	446.4±272.5	78.2±55.6	79.2±61.5	0.22±0.14	0.18±0.08

Source: Applicant's Tables 14.2.1b, 14.2.2a and 14.2.3b; the PK blood samples were collected at 4-6 hours (C4-6) post-AM dose as specified in the protocol.

† Baseline-1: measurements on Day 0 of Study CLAR-09007; and Baseline-2: Day 0 of the extension study (CLAR-12010) which was equal to Day 365 of Study CLAR-09007

‡ The first number was the subjects for serum total T and the second number was the subjects for serum DHT and DHT/T.

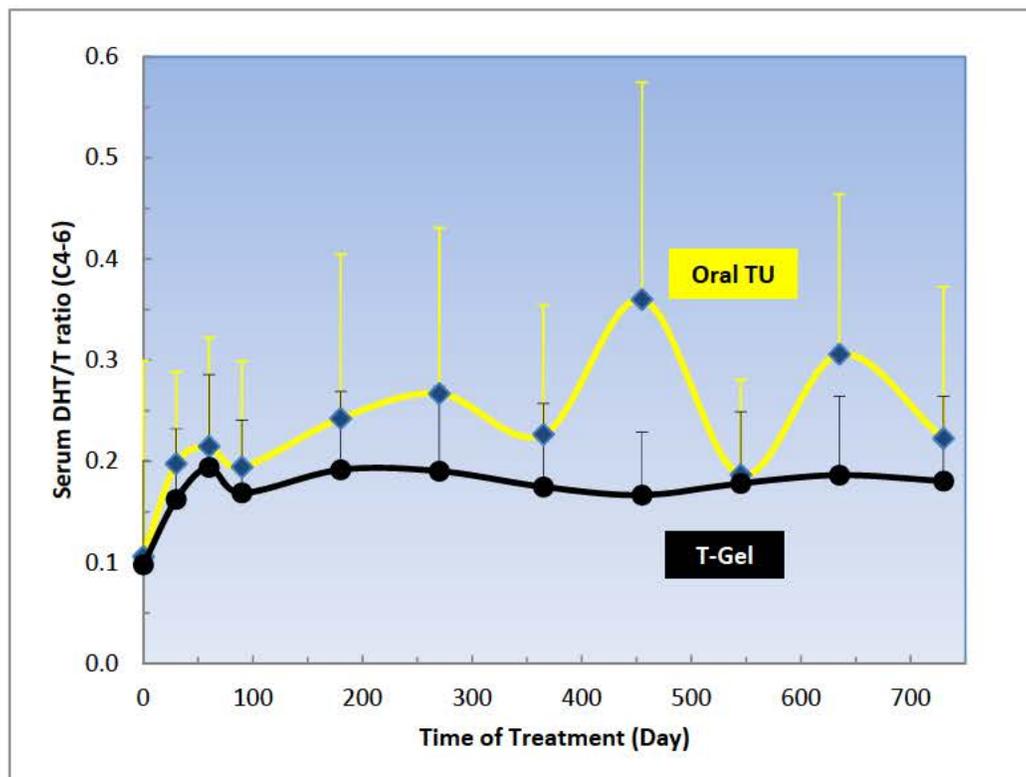
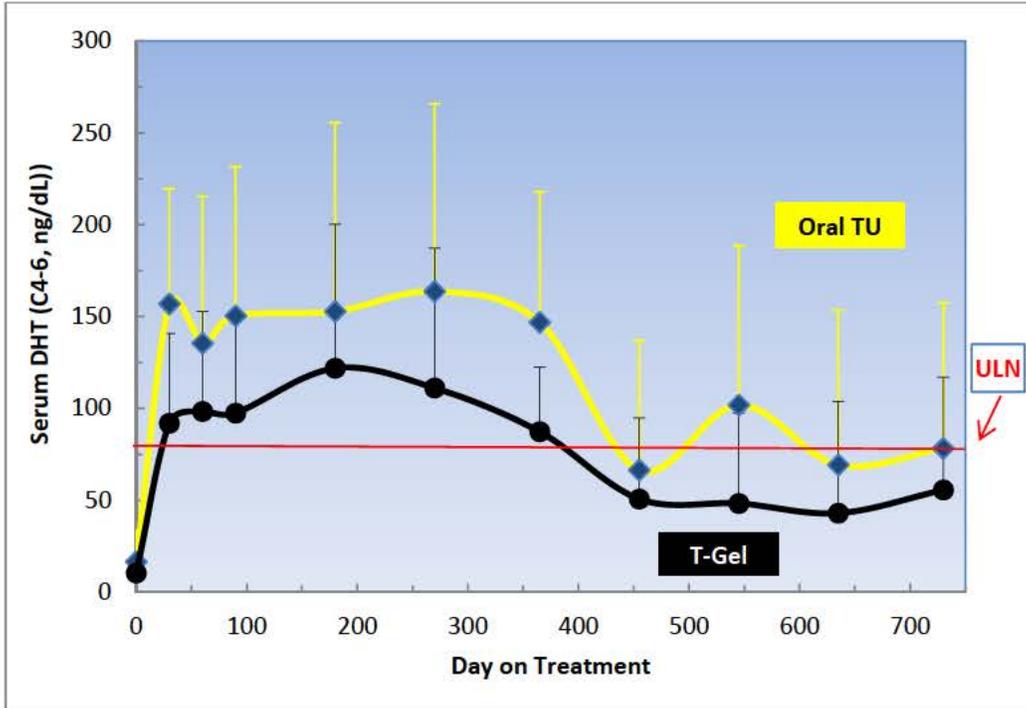
[Reviewer's Comments: The Applicant explained that on Days 90 and 270 "the sample draw times were not pre-specified, so T concentrations at these visits cannot be meaningfully compared to the C4-6 values".]

Serum DHT concentrations: The DHT concentrations decreased from the baseline of the extension study across all visits in the oral TU group while DHT concentrations remained stable in the T-gel group. The differences between oral TU and T-gel became smaller and even turned in the opposite direction on Days 90, 270 and 365 (**Table 106** and **Figure 26**).

Serum DHT/T ratios: Overall the DHT/T ratios in the oral TU groups were still higher than in the T-gel group across all visits except on Day 180 (**Table 106** and **Figure 26**). But the ratios across visits were highly variable in the oral TU groups.

[Reviewer's Comments: The single PK blood samples at 4-6 hours post-AM dose were pre-specified in the protocol for serum total T concentration on Days 180 and 365, but not for T concentration samples on Days 90 and 270. It is not clear whether the lower single draw T and DHT concentrations observed on Days 90 and 270 reflect sampling error, reduced product efficacy, decreased patient compliance with study medication, or overall less strict study monitoring. Therefore, it appears prudent to avoid drawing definitive conclusions from the T and DHT concentrations data from days 90 and 270 of this extension study.]

Figure 26. Serum DHT/T ratio profile over the 24 months of dose



Source: From the applicant's dataset "PK_DHT_T" submitted on July 18, 2014 update to Study 12010. Data were Mean+SD of serum DHT/T ratios at 4-6 hours post-AM dose of oral TU and T-gel from subjects who entered the extension study and had serum DHT and T measures (n=85 on oral TU and n=86 on T-gel).

9.6.3.12 Regression analysis of DHT/T ratios over selected safety parameters

The Applicant performed regression analysis of DHT/T ratios versus changes from baseline (initial and extension) in Hct, PSA, hs-CRP and Lp-PLA2. According to the Applicant, these analyses showed “no strong relationship” between DHT/T ratios and these parameters.

9.6.3.13 Additional Safety Information Submitted by Applicant

The following comment on Study CLAR-12010 was conveyed to the Applicant during the review cycle:

The total number of subjects who received testosterone undecanoate capsules in the entire drug development program and in the Phase 3 studies is small (n=377 and n=305, respectively). The total number of subjects who received testosterone undecanoate capsules for at least 12 months and 24 months is also relatively small (n=161 subjects and n=88 subjects, respectively). In order to provide more support for the long-term safety of testosterone undecanoate capsules, submit safety data from any additional subjects who have received testosterone undecanoate capsules for at least 180 and 365 days in Study CLAR-12010.

On July 18, 2014, the Applicant submitted a response to the request. The Applicant notified the Division that Study CLAR-12010 has completed with database lock on Jun 10, 2014. The response included updated tables and datasets.

Of 88 subjects in the oral TU group who has entered into the 12-month extension study,

- N=79 completed Day 180
- N=69 completed Day 365

Dose, exposure and compliance in these subjects were not provided. The Applicant further stated that safety profile in these subjects was consistent with that described in the information provided in 120-Day safety update submission and that “no new safety signals” have been identified during the second year of dosing.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIN CHEN
10/24/2014

MARK S HIRSCH
10/24/2014
I concur.