

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206089Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 27, 2019

Requesting Office or Division: Division of Bone, Reproductive and Urologic Products (DBRUP)

Application Type and Number: NDA 206089

Product Name and Strength: Jatenzo (testosterone undecanoate) capsules
158 mg, 198 mg, 237 mg

Applicant/Sponsor Name: Clarus Therapeutics, Inc.

FDA Received Date: March 25, 2019

OSE RCM #: 2018-2148-1

DMEPA Safety Evaluator: Denise V. Baugh, PharmD, BCPS

Acting DMEPA Team Leader: Briana Rider, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the revised container labels for Jatenzo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made to add a linear barcode to the container labels^a and position the linear barcode vertically to facilitate scanning the product.^b

2 CONCLUSION

The revised container labels for Jatenzo are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Roule, J. Senior Regulatory Health Project Manager, Division of Bone, Reproductive, and Urologic Products (DBRUP), FDA. Email request sent on behalf of DMEPA. 2019 MAR 21.

^b Roule, J. Senior Regulatory Health Project Manager, Division of Bone, Reproductive, and Urologic Products (DBRUP), FDA. Email request sent on behalf of DMEPA. 2019 MAR 22.

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/

DENISE V BAUGH
03/27/2019 07:41:32 AM

BRIANA B RIDER
03/27/2019 09:34:25 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: March 22, 2019

To: Hylton Joffe, MD
Director
Division of Bone, Reproductive and Urologic Products (DBRUP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Kelly Jackson, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Jina Kwak, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): JATENZO (testosterone undecanoate)

Dosage Form and Route: capsule, for oral use

Application Type/Number: NDA 206089

Applicant: Clarus Therapeutics, Inc.

1 INTRODUCTION

On September 27, 2018, Clarus Therapeutics Inc. submitted for the Agency's review a resubmission to their New Drug Application (NDA) for JATENZO (testosterone undecanoate) capsules, for oral use. The application was originally submitted on January 3, 2014 and the Agency issued a Complete Response (CR) Letter on November 3, 2014. The Applicant resubmitted their NDA on June 22, 2017 and the Agency issued another Complete Response (CR) on March 22, 2018. The Applicant is seeking FDA approval for JATENZO for the proposed indication for testosterone replacement therapy (TRT) in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on October 1, 2018, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG), for JATENZO (testosterone undecanoate) capsule for oral use.

2 MATERIAL REVIEWED

- Draft JATENZO (testosterone undecanoate) MG received on September 27, 2018, and received by DMPP and OPDP on March 8, 2019.
- Draft JATENZO (testosterone undecanoate) Prescribing Information (PI) received on September 27, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 19, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/

KELLY D JACKSON
03/22/2019 09:17:07 AM

JINA KWAK
03/22/2019 09:27:21 AM

MARCIA B WILLIAMS
03/22/2019 10:15:10 AM

LASHAWN M GRIFFITHS
03/22/2019 10:16:30 AM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: March 13, 2019

To: Jeannie Roule
Regulatory Project Manager
Division of Bone, Reproductive and Urologic Products (DBRUP)

From: Jina Kwak, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 206089**
OPDP labeling comments for JATENZO™ (testosterone undecanoate) capsule, for oral use, CIII

In response to DBRUP's consult request dated October 1, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for JATENZO™ (testosterone undecanoate) capsule, for oral use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DBRUP (Jeannie Roule) on March 7, 2019 and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DBRUP (Jeannie Roule) on March 12, 2018 and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Jina Kwak: 301-796-4809; Jina.Kwak@fda.hhs.gov

31 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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/

JINA KWAK
03/13/2019 09:15:17 AM



MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 6, 2019

To: Hylton Joffe, M.D.
Division of Bone, Reproductive, and Urologic Products (DBRUP)

Through: Dominic Chiapperino, Ph.D., Director
Controlled Substance Staff (CSS)

From: Joshua Hunt, PharmD., Senior Regulatory Reviewer
Alicja Lerner, M.D., Medical Officer
Controlled Substance Staff (CSS)

Subject: Resubmission of NDA 206089 (associated with IND 78104)
Drug substance: testosterone undecanoate (proposed trade name: Jatenzo)
Route of Administration: oral
Sponsor: Clarus Therapeutics, Inc.

PDUFA Date: March 27, 2019

Materials

Reviewed: Sponsor *draft* labeling text, dated June 14, 2017 (EDR section 1.14.1.3)
Information Request (IR) response from Sponsor, dated December 7, 2018

I. Background

The Division of Bone, Reproductive, and Urologic Products (DBRUP, or the Division) sent a consult request to CSS on October 1, 2018, regarding NDA 206089. This is a 505(b)(1) application in its third review cycle. The application is resubmitted following a second-cycle Complete Response (CR) letter that the Sponsor received on March 22, 2018. The first CR was received by the Sponsor on November 3, 2014. Cardiovascular risk concerns over Phase 3 findings of increased systolic blood pressure, along with bioanalytical collection and dose titration issues have been discussed throughout the review of this NDA. The PDUFA date for this review cycle is March 27, 2019.

Alicja Lerner, M.D., CSS Medical Officer, previously provided a consult review for this NDA, dated October 23, 2014, during the initial NDA review cycle. CSS recommended that future consideration be given to the inclusion of abuse potential updates for Section 9 *Drug Abuse and Dependence* of the label. At the time, a Tracked Safety Issue (TSI) had been initiated, on March 19, 2014, with a goal to review current abuse and misuse information of all testosterone products along with additional epidemiological evidence.

The Division previously requested that CSS review the mostly recently proposed Package Insert (PI). Joshua Hunt, PharmD, CSS Senior Regulatory Reviewer, previously noted in a March 2, 2018 memo that the first CR re-submission included the updated *Section 9* labeling language, which was initially developed as part of the DBRUP/CSS led Tracked Safety Issue. Appendix 1 lists Section 9 of the proposed PI. These changes were agreed upon by all sponsors of approved testosterone products in August 2016, under the Agency's Safety Labeling Change (SLC) authorities provided in section 505(o)(4) of the FDCA.

II. CSS Conclusions

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

III. CSS Recommendations

We have no additional recommendations for the Sponsor at this time. We will remain engaged with the application review process, including labeling negotiations, as the March 27, 2019 PDUFA date approaches.

IV. Discussion

During this most recent submission, CSS sent an Information Request asking the Sponsor to provide the following information:

1. Provide narratives for all cases of depression, suicidality, aggression and anger.
2. Provide the following information on drug accountability:
 - Number of patients who did not return more than 10%, 20%, 30%, 40%, and 50% of the received oral TU capsules in the clinical studies.
 - Number of oral TU capsules that were not returned by individual patients who did not return more than 20%, 30%, 40%, and 50% of the received oral TU capsules.

The Sponsor's responsive data (provided December 7, 2018) showed that there were six AEs for depression, one case of suicidal ideation, one AE for aggression, and two AEs for anger during all clinical studies. The narratives of the six cases of depression further clarified that in four cases patients had a history of depression. These depression cases were mild-to-moderate in severity. Additionally, the suicidal ideation which occurred in one of the patients with worsening depression was described as mild.

The cases of anger and aggression were considered mild-to-moderate as well. Therefore, at this time, CSS concludes that there is not sufficient justification to recommend further changes in the testosterone label for Jatenzo at this time.

This IR request was based, in part, upon some unique AE findings observed in the recently approved Xyosted (testosterone enanthate) injection, NDA 209863. Xyosted includes the following statement in the *Warnings and Precautions* section of its label:

- Depression and suicidal ideation and behavior, including completed suicide, have occurred during clinical trials in patients treated with XYOSTED (5.16).

Appendix 1: Section 9 of Sponsor proposed Package Insert (PI)

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

JATENZO contains testosterone undecanoate, a prodrug of testosterone which is a Schedule III controlled substance as defined under the Anabolic Steroids Control Act.

9.2 Abuse

(b) (4)
Drug abuse is intentional non-therapeutic use of a drug, even once, for its rewarding psychological and physiological effects. Abuse and misuse of testosterone are seen in male and female adults and adolescents. Testosterone, often in combination with other anabolic androgenic steroids (AAS), and not obtained by prescription through a pharmacy, may be abused by athletes and bodybuilders. There have been reports of misuse by men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice.

Abuse-Related Adverse Reactions

Serious adverse reactions have been reported in individuals who abuse anabolic androgenic steroids and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression.

The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemias, testicular atrophy, subfertility, and infertility.

The following additional adverse reactions have been reported in women: hirsutism, virilization, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities.

The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty.

Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

9.3 Dependence

Behaviors Associated with Addiction

Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

- Taking greater dosages than prescribed
- Continued drug use despite medical and social problems due to drug use
- Spending significant time to obtain the drug when supplies of the drug are interrupted
- Giving a higher priority to drug use than other obligations
- Having difficulty in discontinuing the drug despite desires and attempts to do so
- Experiencing withdrawal symptoms upon abrupt discontinuation of use

Physical dependence is characterized by withdrawal symptoms after abrupt drug discontinuation or a significant dose reduction of a drug. Individuals taking suprathreshold doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism.

Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented.

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/

JOSHUA S HUNT
03/06/2019 02:13:34 PM

ALICJA LERNER
03/06/2019 02:42:14 PM

DOMINIC CHIAPPERINO
03/06/2019 02:46:53 PM



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 6, 2018

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

Through: Dominic Chiapperino, Ph.D., Acting Director
Controlled Substance Staff (CSS)

From: Joshua Hunt, PharmD, Senior Regulatory Reviewer
Controlled Substance Staff (CSS)

Subject: CSS review of NDA 206089 Complete Response (CR)
resubmission from Sponsor (associated with IND 78104)
Drug substance: testosterone undecanoate (proposed name:
Jatenzo)
Dosage/Route of administration: 158 mg, 198 mg and 237 mg
(twice daily), oral capsules
Proposed Indication: Testosterone replacement therapy in
hypogonadal men
Sponsor: Clarus Therapeutics Inc
555 Skokie Blvd Ste 340
Northbrook, IL 60062

Materials reviewed:

- 1) Sponsor *draft* labeling text dated October 2nd, 2017 (EDR section 1.14.1.3)

BACKGROUND

The Division of Bone, Reproductive and Urologic Products (DBRUP, or the Division) consulted CSS on June 26, 2017, regarding NDA 206089. This is a resubmission to a CR, which the Sponsor originally received back in November 2014. The Division requested that CSS review the mostly recently proposed Package Insert. This submission is a 505(b)(1) application and was re-submitted to the Agency on June 22, 2017. Subsequently, a public Advisory Committee (AC) Meeting was held by the Agency on January 9, 2018. A significant portion of the AC meeting discussions focused on cardiovascular risk and Phase 3 data that indicated an average increase of 5mm in daytime systolic blood pressure. Additional bioanalytical collection and dose titration issues were discussed as well. The AC meeting vote was 10-9 against approval.

Alicja Lerner, CSS Medical Officer, previously provided a consult review dated October 23, 2014, pertaining to the initial review cycle for this NDA. CSS recommended that future consideration be given to the inclusion of abuse potential updates for Section 9 *Drug Abuse and Dependence* of the labeling. At the time, a Tracked Safety Issue (TSI) had been initiated, on March 19, 2014, with a goal to review current abuse and misuse information of all testosterone products along with additional epidemiological evidence. In August 2016, a Safety Labeling Change (SLC) update requirement for Section 9 was sent to all sponsors of approved testosterone products. Upon resubmission, the Sponsor of this NDA (Clarus) did update Section 9 to reflect the labeling language already updated in the labeling of currently marketed testosterone products.

CONCLUSIONS:

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 canceled 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.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSHUA S HUNT
03/06/2018

DOMINIC CHIAPPERINO
03/06/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 26, 2018
Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products
Application Type and Number: NDA 206089
Product Name and Strength: Jatenzo^a (testosterone undecanoate) capsules
158 mg, 198 mg, 237 mg
Applicant/Sponsor Name: Clarus Therapeutics, Inc.
FDA Received Date: February 21, 2018
OSE RCM #: 2017-1235-1
DMEPA Safety Evaluator: Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader: Lolita G. White, PharmD

1 PURPOSE OF MEMO

The Division of Bone, Reproductive, and Urologic Products requested that we review the revised container labels and shipping labels for Jatenzo (testosterone undecanoate) capsules (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

2 CONCLUSION

The revised container label and shipping label for 'Jatenzo' is acceptable from a medication error perspective. We have no further recommendations at this time.

^a The proprietary name, Jatenzo was found to be conditionally approved (OSE Review # 2017-15895928 dated August 31, 2017).

^b Baugh, D. Label and Labeling Review for Jatenzo, testosterone undecanoate capsules (NDA 206089). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Oct 31. RCM No.: 2017-1235.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DENISE V BAUGH
02/26/2018

LOLITA G WHITE
02/27/2018

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: February 16, 2018

To: Jeannie Roule, Regulatory Project Manager
Division of Bone, Reproductive and Urologic Products (DBRUP)

From: Jina Kwak, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 206089
OPDP labeling comments on Testosterone Undecanoate

This memo is in response to DBRUP labeling consult request dated June 26, 2017. Due to outstanding deficiencies, DBRUP plans to issue a Complete Response letter. Therefore, OPDP defers comments on the proposed labeling at this time and request that DBRUP submit a new consult request during the subsequent review cycle.

If you have any questions, please contact Jina Kwak at (301) 796-4809 or jina.kwak@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JINA KWAK
02/16/2018

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

REVIEW DEFERRAL MEMORANDUM

Date: February 16, 2018

To: Hylton Joffe, MD
Director
**Division of Bone, Reproductive and Urologic Products
(DBRUP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, BSN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Medication Guide (MG)

Drug Name (established name): TRADENAME (testosterone undecanoate)

Dosage Form and Route: capsules for oral use CIII

Application Type/Number: NDA 206089

Applicant: Clarus Therapeutics, Inc.

1 INTRODUCTION

On June 22, 2017, Clarus Therapeutics (Clarus) submitted for the Agency's review a Class 2 resubmission of their proposed New Drug Application (NDA) 206089 for TRADENAME (testosterone undecanoate) capsules, for oral use, CIII, in response to a Complete Response (CR) Letter issued by the Agency on November 3, 2014. The Applicant originally submitted NDA 206089 to the Agency on January 3, 2014. On January 6, 2016, the Applicant submitted a Proposed Proprietary Name Request for "JATENZO", which was found to be conditionally acceptable by the Agency on May 19, 2016.

The proposed indication for TRADENAME (testosterone undecanoate) capsules is for 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)

On June 26, 2017, the Division of Bone, Reproductive and Urologic Products (DBRUP) requested the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for TRADENAME (testosterone undecanoate), capsules.

This memorandum documents the DMPP review deferral of the Applicant's proposed Medication Guide (MG) for TRADENAME (testosterone undecanoate), capsules.

2 CONCLUSIONS

Due to outstanding 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.

Please notify us if you have any questions.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TWANDA D SCALES
02/16/2018

LASHAWN M GRIFFITHS
02/16/2018

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 18, 2019
Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products
Application Type and Number: NDA 206089
Product Name and Strength: Jatenzo^a (testosterone undecanoate) capsules
158 mg, 198 mg, 237 mg
Applicant/Sponsor Name: Clarus Therapeutics, Inc.
FDA Received Date: September 27, 2018
OSE RCM #: 2018-2148
DMEPA Safety Evaluator: Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader: Lolita G. White, PharmD

1 PURPOSE OF MEMO

The Division of Bone, Reproductive, and Urologic Products requested that we review the revised container labels and shipping labels for Jatenzo (testosterone undecanoate) capsules (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

2 CONCLUSION

The revised container label and shipping label for 'Jatenzo' is acceptable from a medication error perspective. We have no further recommendations at this time.

^a The proprietary name, Jatenzo was found to be conditionally approved (OSE Review # 2017-15895928 dated August 31, 2017).

^b Baugh, D. Label and Labeling Review for Jatenzo, testosterone undecanoate capsules (NDA 206089). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Oct 31. RCM No.: 2017-1235.

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/

DENISE V BAUGH
01/18/2019 02:33:08 PM

LOLITA G WHITE
01/18/2019 05:22:01 PM

REVIEW MEMORANDUM

To: Jeannie Roule, MT
Project Manager
DBRUP/ODEII/OND/CDER

From: Eveline Arnold, Ph.D.
Scientific Reviewer
DCTD/OIR/CDRH

Subject: ICCR-2017-01901
Clarus JATENZO (oral testosterone undecanoate); use of NaF/EDTA tubes for measuring testosterone

Date: January 16, 2018

CDRH Review Summary:

CDER requested CDRH's feedback 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 used. Data are not available to resolve this difference.

Following review of the clinical studies as provided by CDER to CDRH, CDRH's remaining concerns are 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 to the review team. Information regarding suitable specimen collection and handling procedures is not available for serum or NaF-EDTA plasma specimens.

- Adequate and robust data demonstrating that the analytical test methods used to measure T in NaF/EDTA plasma are accurate and reliable are not yet available. 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 above in the sponsor's normal range data, assay matrix effects appear to be present between NaF-EDTA plasma and serum.

CDRH provided its comments to the draft presentations and FDA Backgrounder regarding the sponsor's proposal to use NaF/EDTA tubes to ensure the safe and effective dosing of oral testosterone undecanoate (TU) via e-mail to CDER. These are included as attachments to this memo.

A. GENERAL INFORMATION:

CDRH Review Team:

- Marianela Perez-Torres, Ph.D., MT, Chemistry Branch Chief, DCTD
- Courtney Lias, Ph.D., Division Director, DCTD
- Eveline Arnold, Ph.D., Scientific Reviewer, DCTD

Background:

CDRH received this consult request from CDER regarding the sponsor's proposal to use of NaF/EDTA tubes for the measurement of testosterone to adjust dosing of TU. CDER requested this consult request in preparation for the January 9, 2018 Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee¹.

Briefly, the sponsor (Clarus) proposed that TU is unstable in serum specimens and that TU may be converted to T in vitro when collected in serum collection tubes (the most commonly used specimen matrix for testosterone testing). This potential in vitro conversion may lead to overestimation of the circulating concentration of testosterone in the patient. The sponsor has proposed that using NaF/EDTA plasma will stabilize TU in the specimen and that this specimen type should be used for testosterone monitoring in patients taking TU. During review of the documents provided above, CDRH identified multiple deficiencies with the sponsor's studies on which they based the conclusion that NaF/EDTA will stabilize TU in the specimen.

B. DOCUMENTS REVIEWED

CDRH reviewed the following documents, provided by CDER:

¹ <https://www.fda.gov/AdvisoryCommittees/Calendar/ucm586362.htm>

- CLAR-15013 - Evaluation of Blood Collection Methodology Following Administration of A Single-Dose of An Oral Testosterone Undecanoate Formulation in Hypogonadal Men
- CLAR-15012 – A Phase 3, Randomized, Active-Controlled, Open-Label Study of The Safety and Efficacy of Oral Testosterone Undecanoate (TU) In Hypogonadal Men
- Sections: 8.3.3.1 Testosterone, 8.4.1.9 Comparing NaF-EDTA Plasma and Plain Serum Total T Results and Appendix A, Table A-6.
- CLAR-16014 - Comparison of Testosterone and Dihydrotestosterone Concentrations in Healthy Men When Blood Samples are Collected in Plain Tubes and in NaF-EDTA Tubes
- Package insert draft for JATENZOTM (testosterone undecanoate) for oral use –(10/2017)
- Clarus IR response dated October 30, 2017 (response to DBRUP IR dated October 3 and 11, 2017)
- DBRUP IR dated November 16, 2017
- Claurus IR response dated November 24, 2017 (response to DBRUP IR dated November 16, 2017)
- DBRUP IR dated December 5, 2017
- Clarus IR response dated December 18, 2017 (response to DBRUP IR dated December 5, 2017)
- FDA Advisory Committee Briefing Document – Bioanalysis Section
- FDA Clinical Pharmacology Presentation – Bioanalysis Section

C. REVIEW TIMELINE

During this consult request, CDRH attended the following meetings:

- November 28, 2017: Internal meeting with CDER; discuss sponsor’s response to IR letter
- December 4, 2017: NDA 206089, status meeting Oral TU, CLARUS
- December 4, 2017, AC Practice Session Clarus and (b) (4)
- December 11, 2017: AC Practice Session Clarus and (b) (4)
- December 18, 2017: AC Practice Session Clarus and (b) (4)
- December 20, 2017: AC Practice Session Clarus and (b) (4)
- December 21, 2017: AC Practice Session Clarus and (b) (4)
- January 3, 2018: AC Practice Session Clarus and (b) (4)
- January 9, 2018: Clarus, NDA 206089:Advisory Committee Meeting for Oral TU product

(b) (4)

D. REVIEW SUMMARY AND CONCLUSIONS:

Following review of the information from the sponsor provided by CDER, as well as the panel discussion during the January 9, 2018 Advisory Committee Meeting, CDRH concludes additional information is needed from the sponsor to support the claim that NaF/EDTA tubes need to be used to collect samples for measurement of testosterone for safe and effective dosing of TU.

E. RECOMMENDATION

CDRH recommends this inter-center consult request be closed. CDRH's comments are captured in attachments to this memo. Emails will be uploaded to CDRH's CTS (Center Tracking System) reference section.

APPEARS THIS WAY ON ORIGINAL



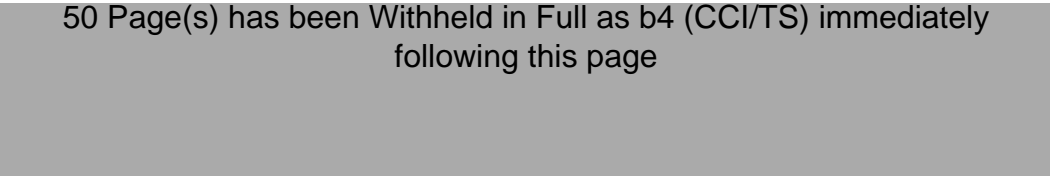
Eveline Arnold, Ph.D.
Scientific Reviewer
DCTD/OIR/CDRH

CC: Marianela Perez-Torres, Ph.D., MT
Chemistry Branch Chief
DCTD/OIR/CDRH

Attachments:

- Bioanalysis.CDRH.DCTD.Final.docx
- ClinPharm Slides for Clarus AC.CDRH.DCTD.pptx
- IR Letter December 18 2017.CDRH.DCTD.FINAL.docx
- RE_ICCR 2017-01901 DBRUP – IR questions, CDRH proposed questions attached.pdf

50 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEANNIE M ROULE
01/18/2018

Clinical Inspection Summary

Date	January 8, 2018
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Jeannie Roule, Regulatory Project Manager Mark Hirsch, M.D., Clinical Team Leader Roger Wiederhorn, M.D., Clinical Reviewer Division of Bone, Reproductive, and Urologic Products (DBRUP)
NDA #	206089
Applicant	Clarus Therapeutics, Inc.
Drug	Jatenzo (testosterone undecanoate)
NME	No
Review Priority	Priority Review
Proposed Indication	Testosterone replacement in adult males
Consultation Request Date	September 14, 2017
Summary Goal Date	January 30, 2018
Action Goal Date	March 22, 2018
PDUFA Date	March 22, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Belkoff, White, and Flippo were inspected in support of this NDA. The final classification of the inspections of all three sites was No Action Indicated (NAI).

For Protocol CLAR-15012, the primary efficacy measure was serum testosterone levels at Visit 7. Clinical investigators were blinded to the testosterone levels and were not provided unblinded results at the conclusion of the study. Therefore, there were no source documents at the sites to compare with the testosterone data line listings.

Otherwise, 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 indication.

2. BACKGROUND

The Applicant submitted this NDA to support the use of Jatenzo (testosterone undecanoate) for androgen replacement therapy in adult males.

Inspections were requested for the following protocol in support of this application:

Protocol CLAR-15012, “A Phase 3, Randomized, Active-controlled, Open Label Study of the Safety and Efficacy of Oral Testosterone Undecanoate (TU) in Hypogonadal Men”

This study involved 31 domestic sites randomizing 222 subjects.

The primary efficacy endpoint was the estimated proportion of subjects administered Jatenzo whose 24-hour testosterone Cavg at Visit 7 was within the eugonadal range (252 to 907 ng/dL).

Rationale for Site Selection

Dr. Belkoff’s, Flippo’s, and White’s clinical sites were chosen for inspection because each of these investigators enrolled a relatively large number of subjects.

3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (screened)	Inspection Dates	Classification
Site #109 Laurence Belkoff, M.D. Urologic Consultants of SE PA 1 Presidential Blvd Suite 100 Bala Cynwd, PA 19004-1015	CLAR-15012 Subjects: 30	20-27 Nov 2017	NAI
Site #104 Gregory Flippo, M.D. Alabama Clinical Therapeutics 52 Medical Park East Drive, Suite 202 Birmingham, AL 35235	CLAR-15012 Subjects: 32	23-26 Oct 2017	NAI
Site #122 Charles White, M.D. Coastal Clinical Research Inc. 100 Memorial Hospital Drive Annex Building, Suite 3B Mobile, Ala 36608-1185	CLAR-15012 Subjects: 31	16-19 Oct 2017	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

1. Laurence Belkoff, M.D.

At this site for Protocol CLAR-15012, 30 subjects were screened and 14 subjects were enrolled in the study, all of whom completed the study. The IRB approved all protocols, amendments, and the informed consent form prior to implementation of any study activities. All subjects signed and dated the consent forms prior to any study-related procedures.

The study records of the 14 subjects enrolled in the study were reviewed. Source documents were compared with the data listings. Records reviewed included, but were not limited to, IRB approvals, informed consent forms, Form FDA 1572s, principal investigator and sub-investigators' curriculum vitae and licensures, financial disclosure forms, training records, sponsor/CRO correspondence, delegation of authority logs, CRO monitor logs, subject medical records, physician progress notes, nursing notes, consultations, diagnostic procedure reports, laboratory results, protocol deviations, adverse events, subjects' meal diaries and psychosocial daily questionnaires, and study drug accountability and storage condition logs.

A Form FDA 483 was not issued at the conclusion of the inspection.

2. Gregory Flippo, M.D.

At this site for Protocol CLAR-15012, 32 subjects were screened and 12 subjects were enrolled in the study, all of whom completed the study. The IRB approved all protocols, amendments, and the informed consent form prior to implementation of any study activities. All 32 screened subjects signed and dated the consent forms prior to any study-related procedures.

The study records of the 12 subjects enrolled in the study were reviewed. Source documents were compared with the data listings. Records reviewed included, but were not limited to, IRB/ sponsor/monitor correspondence, financial disclosures, training documentation, delegation of authority logs, adverse event reports, concomitant medications, and investigational product accountability and storage.

A Form FDA 483 was not issued at the conclusion of the inspection.

3. Charles White, M.D.

At this site for Protocol CLAR-15012, 31 subjects were screened, 11 subjects were enrolled in the study, and 10 subjects completed the study. The IRB approved all protocols, amendments, and the informed consent form prior to implementation of any study activities. All 31 screened subjects signed and dated the consent forms prior to any study-related procedures.

The study records for the 11 subjects enrolled in the study were reviewed. Source documents were compared with the data listings. Records reviewed included, but were not limited to, IRB/sponsor/monitor correspondence, informed consent forms, financial disclosure forms, study worksheets, physical examinations, medical records, study assessments, questionnaires, subject diaries, adverse events, and test article accountability records.

A Form FDA 483 was not issued at the conclusion of the inspection.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm.\NDA 206089
DBRUP\Division Director\Hylton Joffe
DBRUP\Team Leader\Mark Hirsch
DBRUP\Medical Officer\Roger Wiederhorn
DBRUP\Project Manager\Jeannie Roule
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Phillip Kronstein
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analysts\Joseph Peacock\Yolanda Patague
OSI\Database Project Manager\Dana Walters

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROY A BLAY
01/09/2018

PHILLIP D KRONSTEIN
01/09/2018

LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 31, 2017
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products
Application Type and Number:	NDA 206089
Product Name and Strength:	Jatenzo*** ^a (testosterone undecanoate) Capsules 158 mg, 198 mg, 237 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Clarus Therapeutics, Inc.
Submission Date:	June 22, 2017 and October 3, 2017
OSE RCM #:	2017-1235
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lolita G. White, PharmD

^a The Proprietary Name, Jatenzo was found to be conditionally approved in (OSE Review# 2017-15895928 dated August 31, 2017)

1 REASON FOR REVIEW

The Division of Bone, Reproductive, and Urologic Products (DBRUP) has requested the Division of Medication Error Prevention and Analysis review the container label, carton labeling, and prescribing information (PI) for NDA 206089 for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the carton labeling, container label and Prescribing Information identified the following areas of concern which may contribute to medication errors with this product:

1. The package size is not included in the 'How Supplied/Storage and Handling' Section of the PI in accordance with 21 CFR 201.57(c)17.
2. The strength statement is not referenced properly on the container label.
3. The established name on the container label lacks prominence commensurate with the proprietary name.
4. The NDC number has not been provided on the container label for our review and comment.
5. The proposed color of the controlled substance symbol may lead to its misinterpretation or it may be overlooked.

We provide recommendations regarding these areas below in Section 4.1 and 4.2 to help minimize the potential for medication errors to occur with the use of the product.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the label and labeling which should be revised to help ensure the safe use of the product. We advise these recommendations are implemented prior to approval of this product.

Our recommendations can be found in section 4.1 for the Division and section 4.2 for Clarus Therapeutics, Inc below.

4.1 RECOMMENDATIONS FOR THE DIVISION

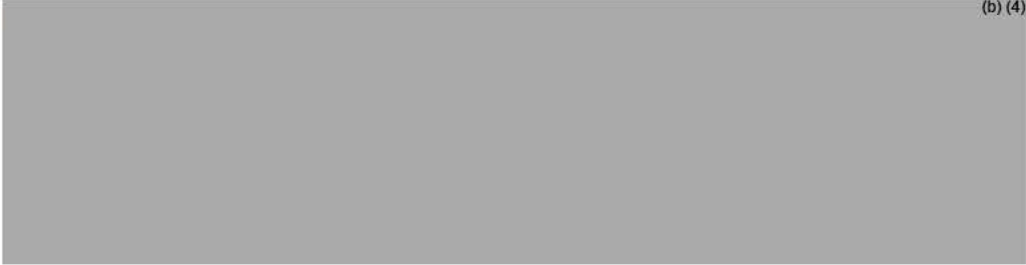
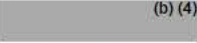
A. How Supplied/Storage and Handling

1. As currently presented, there is no package size configuration included in this section that assists practitioners in the prescribing process. Include this information in accordance with 21 CFR 201.57(c) 17.

4.2 RECOMMENDATIONS FOR CLARUS THERAPEUTICS, INC

We recommend implementation of the following prior to approval of this NDA:

A. Container Labels

1.  (b) (4)
2. The established name as proposed is presented in thin, closely spaced font – reducing its prominence relative to the proprietary name which is presented in large, bold letters. As such, the established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
3. We note that the container labels and shipping labels currently present the NDC placeholder numbers as  (b) (4). Provide the NDC number for the container label and shipping labeling for Agency review and ensure the NDC number assigned to the inner label (container) and the NDC number assigned to the outer labeling (shipping) are appropriate as per 21 CFR 207.33.

4. As presented, the controlled substance symbol (“CIII”) lacks prominence as described in 21 CFR 1302.04. Specifically, the CIII symbol is the same color as that of the proprietary name and may be misinterpreted. Revise the color of the CIII to improve the prominence of the symbol so that it is clear to the reader and less likely to be misinterpreted.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for 'Jatenzo' that Clarus Therapeutics, Inc. submitted on June 22, 2017.

Table 2. Relevant Product Information for Jatenzo	
Initial Approval Date	N/A
Active Ingredient	Testosterone undecanoate
Indication	Testosterone replacement therapy
Route of Administration	oral
Dosage Form	capsules
Strength	158 mg 198 mg, and 237 mg
Dose and Frequency	Starting dose is 237 mg orally twice daily with breakfast and dinner; minimum daily dose is 158 mg twice daily and the maximum daily dose is 396 mg twice daily
How Supplied	HDPE bottles
Storage	20°C to 25°C

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 26, 2017, we searched the L: drive and AIMS using the terms, 'Jatenzo', (b) (4), and '206089' to identify reviews previously performed by DMEPA. Our search identified one previous review^b. We note that some of our previous recommendations were included in the revisions to the container labels and carton labeling (submitted June 22, 2017) and we are not aware of the reasons for this partial implementation. As such, we are re-iterating those recommendations that were omitted in the revised labeling and we have one additional recommendation.

^b Fava W. Label, Labeling, and Packaging Review for (b) (4) NDA 206089. Silver Spring, MD: Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 September 5. RCM No.: 2014-679.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with post-market medication error data, we reviewed the following 'Jatenzo' labels and labeling submitted by Clarus Therapeutics, Inc. on June 22, 2017.

- Container label
- Shipping labeling
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

Container Label



^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DENISE V BAUGH
10/31/2017

LOLITA G WHITE
11/01/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Epidemiologist Study Comparison Review**

Date: April 10, 2015

Reviewers: Jana McAninch, M.D., M.P.H., M.S.
Division of Epidemiology II
Monique Falconer, M.D., M.S,
Division of Epidemiology II

Team Leader: Jie (Jenni) Li, PhD
Division of Epidemiology II

Deputy Division Director CDR David Moeny, M.P.H, R.Ph., USPHS
Division of Epidemiology II

Subject: Review of Shores et al. Observational Studies and Borst et al.
Meta-analysis: Association between Serum Dihydrotestosterone
Levels and Cardiovascular Events

Drug Name: Testosterone Undecanoate

Application Type/No. NDA #206089

Applicant/sponsor: Clarus Therapeutics

RCM # : 2015-2497

TABLE OF CONTENTS

LIST OF ABBREVIATIONS.....	3
EXECUTIVE SUMMARY	4
1 Introduction	5
1.1 Background and Regulatory History.....	5
1.2 Labeling.....	6
2 Methods and Materials	6
3 Results	7
3.1 Shores et al. Observational Studies	7
3.1.1 Summary of the Shores Studies	7
3.1.2 Exposures of interest.....	8
3.1.3 Outcomes	8
3.1.4 Covariates	8
3.1.5 Statistical Analyses	8
3.1.6 Study Results	8
3.1.7 Authors' Conclusions.....	10
3.1.8 DEPI Interpretation of the Shores et al. Studies Results	11
3.2 Borst et al. Meta-analyses	11
3.2.1 Study Design.....	11
3.2.2 Data Sources and Time Period.....	11
3.2.3 Selection Standards.....	12
3.2.4 Exposure/Intervention and Outcome	12
3.2.5 Covariates	12
3.2.6 Sample Size.....	12
3.2.7 Statistical Analysis.....	13
3.2.8 Study Results	13
3.2.9 Authors' Interpretation of Results	15
3.2.10 DEPI Interpretation of the Borst et al. Meta-analyses	16
4 Discussion.....	18
5 Conclusions	18
6 References	20
7 APPENDICES	25
7.1 Appendix A - Covariates Adjusted in Each Model by Study	25
7.2 Appendix B: Component Studies and Outcome Comparison among the Xu, Corona and Borst Meta-analyses	26
7.3 Appendix C: Component RCTs Included in the Borst Meta-analysis of TRT and CV AEs	28
7.4 Appendix D: Listing of CV events in RCTs selected for analysis of CV events (Four Oral TRT Trials Shaded).....	50
7.5 Appendix E: Characteristics of Testosterone Replacement Therapy (TRT) Trials Reporting Both Serum Testosterone and Dihydrotestosterone (DHT) Concentrations Before and After Treatment	53

LIST OF ABBREVIATIONS

AC	Advisory Committee
AE	Adverse event
CHF	Congestive heart failure
CHS	Cardiovascular Health Study
CI	Confidence interval
CV	Cardiovascular
CVD	Cardiovascular disease
DBRUP	Division of Bone, Reproductive and Urologic Products
DCRP	Division of Cardiovascular and Renal Products
DEPI	Division of Epidemiology
DHT	Dihydrotestosterone
DPV	Division of Pharmacovigilance
DSC	Drug Safety Communication
DVT	Deep vein thrombosis
FAERS	FDA Adverse Event Reporting Systems
FDA	Food and Drug Administration
HDL	High density lipoprotein
ICD-9	International Classification of Diseases, Version 9
IM	Intramuscular
MACE	Major Adverse Cardiac Events
MI	Myocardial infarction
NDA	New Drug Application
OR	Odds ratio
PBO	Placebo
PE	Pulmonary embolism
RCT	Randomized controlled trial
RR	Relative risk
SHBG	Sex hormone binding globulin
TU	Testosterone undecanoate
TSI	Tracked Safety Issue
TRT	Testosterone replacement therapy
U.S.	United States

EXECUTIVE SUMMARY

In November 2014, a New Drug Application (NDA #206809) for oral testosterone undecanoate (TU) received a Complete Response action. One of the major safety concerns identified for the product was that metabolism of oral TU leads to supraphysiologic levels of dihydrotestosterone (DHT). The clinical significance of the DHT changes on the risk of adverse cardiovascular (CV) events has not been well defined to date. Compared to Androgel, however, oral TU was associated with worse CV biomarkers. The Division of Bone, Reproductive, and Urologic Products (DBRUP) has asked the Division of Epidemiology II (DEPI) to review three publications on the association between DHT and CV risk and to comment on whether the evidence indicates that elevated DHT levels are associated with an increased risk of adverse CV outcomes. The purpose of this review is to describe and evaluate these publications--two observational cohort studies (Shores et al., 2014b; Shores et al., 2014a) and a meta-analysis (Borst et al., 2014a) - with respect to the evidence for an association between DHT levels and risk of adverse CV outcomes.

The Shores studies were retrospective cohort studies in older men. The studies found a non-linear (U-shaped) relationship between serum DHT levels and CV outcomes, with higher CV risks associated with the highest and lowest serum DHT concentrations. Borst et al. describe the results of two meta-analyses. In the first, the investigators found an elevated risk of broadly defined CV adverse events for the oral testosterone trials (relative risk [RR] 2.20, 95% confidence interval [CI] 1.45-3.35), but not for the trials using other routes of administration. In the second meta-analysis, using a different group of trials, they identified higher mean post-treatment serum DHT levels in the trials of oral and transdermal testosterone, compared to the intramuscular testosterone trials. They then superimposed the pooled serum DHT results onto Shores' results as a possible explanation for the meta-analysis findings, noting that the mean post-treatment DHT levels for the oral testosterone trials fall into the range of serum DHT levels associated with an increased risk of stroke in the Shores' study.

All three studies had major limitations. In the Shores studies, there was uncertainty in the risk estimates, particularly at the higher serum DHT levels due to the small sample size. Limitations of the Borst study included clinical heterogeneity, broad definition of CV endpoints, incomplete safety data reporting, lack of blinded ascertainment and adjudication of CV events, study arm imbalances in baseline CV risk and study retention, wide variation in baseline and post-treatment serum testosterone and DHT levels, and unclear timing of serum level measurement.

The Shores studies suggest a possible non-linear relationship between serum DHT levels and CV events; however, due to study limitations, the relationship remains uncertain. The Borst meta-analysis was not designed to directly answer the question of whether elevated DHT levels are associated with increased CV risk. The authors attempt to establish a link between oral testosterone, elevated post-treatment DHT, and CV risk through a series of inferences that are not supported by the data. Nonetheless, the Borst study does raise important unanswered questions about whether CV risk might vary by route of TRT and the authors propose a hypothesis as to why this could be biologically plausible. In designing safety studies to evaluate TRT and CV risk, possible differences in risk by route of administration should be considered and assessed. In addition, standardized measurement of pre- and post-treatment serum testosterone and DHT may help elucidate the complex relationship between testosterone, DHT and CV risk.

1 INTRODUCTION

1.1 BACKGROUND AND REGULATORY HISTORY

Testosterone is an androgen steroid hormone, secreted primarily by the testicles of males and the ovaries of females, although small amounts are also secreted by the adrenal glands. It is the principal male sex hormone and an anabolic steroid. In males, testosterone is key in the development of male reproductive tissues and promoting secondary sexual characteristics such as increased muscle, bone mass, and the growth of body hair.

Testosterone products have been approved in the U.S. since the 1950s to stimulate puberty, and for the treatment of primary hypogonadism and hypogonadotropic hypogonadism (congenital or acquired) in males. Testosterone products are approved as replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone, including congenital or acquired primary hypogonadism and hypogonadotropic hypogonadism. Safety and efficacy of testosterone products are not established in men with ‘age-related’ hypogonadism (2015 label updates).

FDA continues to evaluate the safety signal of increased risk of CV events associated with testosterone therapy suggested by several recent observational studies (Vigen et al., 2013; Finkle et al., 2014) and a meta-analysis of published trials (Xu, Freeman, Cowling, & Schooling, 2013). On September 17, an AC meeting was convened to discuss the benefits and risks associated with testosterone therapy and solicit advice to inform potential regulatory actions. The committee voted in favor of 1) labeling changes to clarify the indications for testosterone therapy and 2) requiring that industry conduct a large post-marketing safety in certain user populations study to evaluate the risk of CV events associated with testosterone.

In November 2014, an NDA for an oral TU product received a Complete Response action. One of the major safety concerns identified for the product is that metabolism of oral TU leads to supraphysiologic levels of DHT, which exerts more potent androgenic properties than testosterone, and elevated DHT:T ratio. The clinical significance of the DHT changes has not been well defined to date. Compared to Androgel, however, oral TU was associated with worse CV biomarkers, including increase in high-sensitivity C reactive protein, increase in blood pressure, larger decrease in HDL, and more polycythemia. DBRUP has asked DEPI to review three publications (Shores et al., 2014b; Shores et al., 2014a; Borst et al., 2014a) on the association between DHT and CV and, specifically, has asked DEPI to comment on whether elevated DHT levels are associated with an increased risk of adverse CV outcomes. The purpose of this review is to describe and critically evaluate these three publications with respect to the evidence of an association between DHT levels and increased risk of adverse CV outcomes.

1.2 LABELING

Language in the warnings and precautions sections of the current testosterone product labels varies but (as of March 13, 2015) includes the following statements, broadly related to the cardiac and vascular systems (none are boxed warnings):

- Edema: Edema, with or without congestive heart failure (CHF), may be a complication in patients with preexisting cardiac, renal, or hepatic disease.
- Lipids: Changes in serum lipid profile may require dose adjustment of lipid lowering drugs or discontinuation of testosterone therapy.
- Polycythemia: Increases in hematocrit, reflective of increases in red blood cell mass, may require discontinuation of testosterone.... An increase in red blood cell mass may increase the risk of thromboembolic events.
- Venous thromboembolism (VTE): VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), have been reported in patients using testosterone products. Evaluate patients with signs or symptoms consistent with DVT and PE.¹
- Sleep apnea: The treatment of hypogonadal men with testosterone products may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung disease.

The testosterone cypionate injection label contains a contraindication for ‘patients with serious cardiac, hepatic, or renal disease.’ The testosterone enanthate injection label states “because androgens may alter serum cholesterol concentration, caution should be used when administering these drugs to patients with a history of myocardial infarction or coronary artery disease.” These testosterone injectable products were approved several decades ago, when standards and practices governing labeling differed from those of testosterone products approved more recently. FDA is currently updating labeling for all testosterone products to provide a warning on the potential CV risk associated with testosterone replacement therapy.

2 METHODS AND MATERIALS

For this review, DEPI evaluated the following publications:

1. Shores MM, Biggs ML, Arnold AM, Smith NL, Longstreth WT, Kizer JR, Hirsch CH, Cappola AR, Matsumoto AM. (2014) Testosterone, Dihydrotestosterone, and Incident Cardiovascular Disease and Mortality in the Cardiovascular Health Study. *J Clin Endocrinol Metab* 99, 2061-2068.

¹There is currently a separate Tracked Safety Issue (TSI) in process to harmonize the labels with regard to VTE risk. <http://www.fda.gov/drugs/drugsafety/ucm401746.htm>

2. Shores MM, Arnold AM, Biggs ML, Longstreth WT, Smith NL, Kizer JR, Cappola AR, Hirsch CH, Marck BT, Matsumoto AM. (2014) Testosterone, Dihydrotestosterone, and Incident Ischaemic Stroke in Men in the Cardiovascular Health Study. *Clinical Endocrinology* 81, 746-753.
3. Borst SE, Shuster JJ, Zou B, Ye F, Jia H, Wokhlu A, Yarrow JF. (2014) Cardiovascular risks and elevation of serum DHT vary by route of testosterone administration: a systematic review and meta-analysis. *BMC Medicine* 12: 211. (DOI: s12916-014-0211-5 [pii];10.1186/s12916-014-0211-5) and Additional Online Files 1-5.

The study methods and results are summarized for the two observational studies by Shores and the meta-analysis of RCTs by Borst, and the methodological considerations and study strengths and limitations are discussed. The meta-analysis is also discussed in the context of two previous DEPI reviews of meta-analyses examining the risk of CV events associated with TRT.^{2,3} An evaluation of the evidence for the relationship between DHT and CV risk is summarized.

The 2011 publication “Secondary use of randomized controlled trials to evaluate drug safety: a review of methodological considerations” (Hammad, Pinheiro, & Neyarapally, 2011) provided guidance for the meta-analysis review.

3 RESULTS

3.1 SHORES ET AL. OBSERVATIONAL STUDIES

3.1.1 Summary of the Shores Studies

Shores and colleagues published two cohort studies in 2014 evaluating the association between DHT and CV disease, mortality and incident ischemic stroke. Both studies used data from the CHS longitudinal study initiated in 1989 to identify risk factors for CV disease in older adults with prior CV diseases. Both studies included noninstitutionalized men over the age of 65 years who enrolled in the CHS study between 1989 to 1993, with clinical examinations between 1989 to 1999, and again in 2005. Men with no CV disease, stroke or prostate cancer as of the 1994 examination were excluded.

Both studies will be described and discussed together, as they mostly use the same study population and methods, but where there are differences in the studies, they will be described separately.

² McAninch, J. TSI #865; RCM# 2013-2704. “DEPI-II qualitative review of meta-analysis of randomized controlled trials of testosterone therapy and placebo.” July 31, 2014.

³ McAninch, J. TSI #865; RCM# 2013-2704. “DEPI Corona meta-analysis testosterone CV review FINAL.” December 10, 2014.

3.1.2 Exposures of interest

Each patient's serum DHT level was measured in 1994. One time samples were collected from the men in the study in 1994, and assays were done in duplicate and the average value used as the DHT level in this study analysis. Other hormones measured were total testosterone, and SHGB. The relationship between total and free DHT, the other hormones of interest, and the outcomes of interest were evaluated in the study.

3.1.3 Outcomes

The earlier published study (Shores et al., 2014b) evaluated the outcomes of CVD and all-cause mortality. The CVD outcome consisted of incident MI, incident stroke, and CV mortality. The later study (Shores et al., 2014a) evaluated incident ischemic stroke. All outcomes were ascertained using standardized algorithms, which used information from Medicaid, hospital records, death certificates, autopsy records and interviews with research subjects, relatives and attending physicians.

3.1.4 Covariates

In both studies, most of the covariates were measured at the 1994 baseline visit (unless otherwise noted). The demographic characteristics, age, race, educational level, smoking status, and alcohol intake were self-reported. Physical activity, weight, height, waist circumference and laboratory values were obtained in 1992–1993. Other covariates were systolic and diastolic blood pressure, atrial fibrillation, diabetes, insulin and fasting glucose levels, creatinine, HDL, total cholesterol and lipid-lowering, antihypertensive, antiplatelet and anticoagulation agents. Medication use was ascertained using a validated medication inventory.

3.1.5 Statistical Analyses

Patients were grouped by their 1994 baseline DHT level (<25ng/dL, 25-49, 50-74, and 75+). The study compared the risk of study outcomes between the groups. Cox proportional hazards regression models were used to estimate the relative risk of the outcomes associated with DHT. Time at risk was defined as the time between the 1994 examination (sera collection) and the incident outcome. The patients were not censored at death or loss-of-follow-up due to the lack of such information. Serial models were run to estimate the risk, controlling for different levels of confounding. **Appendix A** describes the confounders included in each model.

3.1.6 Study Results

There were 1,032 men in each of the studies. The mean age was 76 years (range 66-97), and the median follow-up in the studies was between 9-10 years. It appears that the same cohort of men was used in both studies (unconfirmed with the authors).

Higher risks for CVD were seen at the lowest (<25ng/dL: HR 1.70, 95% CI [1.26, 2.28]) and highest ($\geq$ 75ng/dL: HR 1.34, 95% CI [0.94, 1.89]) serum concentrations of DHT (Table 1). The risk was the lowest with the 50-74 levels. A non-linear relationship is depicted in Figure 1. The

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

risk estimates were less stable at the higher DHT serum concentrations due to the small sample size. Also, as more covariates were controlled in the models, there was a slight decrease in the hazard ratios.

Table 1: DHT and incident CVD

Concentration	No. of Events	Incidence per 1000	Hazard Ratio (95% Confidence Intervals)			
			Model 1 ^a	Model 2 ^a	Model 3 ^a	Model 4 ^a
DHT, ng/dL						
<25	84	63.2	1.70 (1.26-2.28)	1.52 (1.11-2.08)	1.44 (1.05-1.98)	1.48 (1.06-2.08)
25-49	209	46.7	1.35 (1.06-1.73)	1.32 (1.03-1.70)	1.31 (1.02-1.69)	1.30 (1.00-1.70)
50-74	95	36.3	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
≥75	48	51.0	1.34 (0.94-1.89)	1.36 (0.95-1.94)	1.30 (0.91-1.86)	1.42 (0.99-2.04)

Model 1 was adjusted for age, race, clinic site, smoking status (never, former, or current), and alcohol consumption
 Model 2 was additionally adjusted for hypertensive use, HDL cholesterol, BMI, and waist circumference
 Model 3 was additionally adjusted for diabetes status, a potential mediator of the association
 Model 4 a sensitivity analysis in which men who were treated with finasteride, which lowers DHT levels, were excluded from the analysis

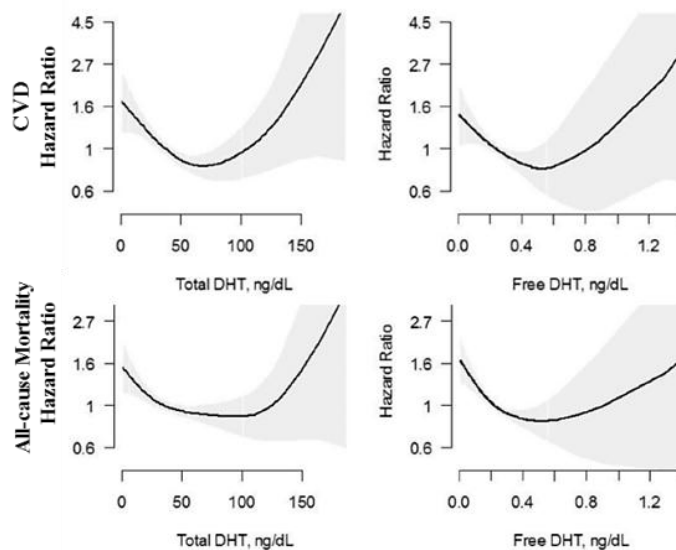


Figure 1: Spline regression graphs depicting the associations between continuous levels of total and free DHT and incident CVD (top 2 panels) and all-cause mortality (bottom 2 panels). The solid line represents the estimated hazard ratio, and the shaded area depicts the 95% confidence intervals. All models are adjusted for age.

Higher risks for ischemic stroke were seen at the lowest (<25ng/dL: HR 2.38, 95% CI [1.32, 4.29]) and higher (75-100 ng/dL: HR 2.13, 95% CI [1.00, 4.56]) serum concentrations of DHT (**Error! Reference source not found.**). The risk was the lowest with the 50-75 level. A non-linear relationship is depicted in (Figure 2) . The risk estimates were less stable at the

higher DHT serum concentrations. Also, as more covariates were added to the models, there was a slight decrease in the hazard ratios.

Table 2: DHT and ischemic stroke

DHT, ng/dl	N	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
<25	168	2.38 (1.32, 4.29)	2.05 (1.12, 3.75)	2.20 (1.18, 4.12)
25–50	487	1.63 (0.98, 2.72)	1.63 (0.98, 2.72)	1.67 (0.99, 2.83)
50–75	279	1.00 (reference)	1.00 (reference)	1.00 (reference)
75–100	71	2.13 (1.00, 4.56)	2.45 (1.13, 5.27)	2.45 (1.09, 5.50)
>100	27	1.47 (0.44, 4.98)	1.60 (0.47, 5.42)	1.89 (0.55, 6.53)
P-value*		0.004	0.018	0.006

*Based on a likelihood ratio test of linear and quadratic terms.

Model 1: Adjusted for age

Model 2: Adjusted for age, ever smoked, pack-years (ln), systolic blood pressure, antihypertensive medications, diabetes and atrial fibrillation. Model 3: Adjusted for age, ever smoked, pack-years (ln), systolic blood pressure, antihypertensive medications, atrial fibrillation, total and HDL cholesterol, lipid-lowering medications, high creatinine, fasting glucose (ln) and use of insulin or oral hypoglycaemic medications.

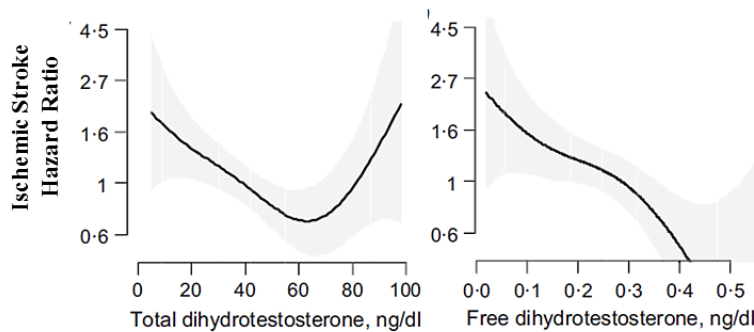


Figure 2: Spline regression graphs depicting the association of ischemic stroke risk with total DHT (ng/dl) (left panel) and free DHT (ng/dl) (right panel). (adapted from study report)

3.1.7 Authors' Conclusions

The authors concluded that the association between DHT and ischemic stroke is non-linear, in which the optimal DHT level is associated with the lowest risk, and a higher or lower level DHT with an elevated risk. The authors also concluded that the DHT was associated with incident CVD and all-cause mortality. However, the authors believe additional studies are needed to confirm these associations.

3.1.8 DEPI Interpretation of the Shores et al. Studies Results

The study results are suggestive of a non-linear relationship between DHT and CV events. However, there are limitations to consider in interpreting these results. For example, the study was done in only older men (average 76.5 years old) with prior CV diseases, so it might be difficult to extrapolate the results to other age groups.

Also, only a single DHT measurement was taken from the men in 1994, but of note, a sub-study of 74 men with repeated measurements suggested that a single measurement might be representative. Further, only the baseline measure in 1994 was used to group patients by DHT level, not taking into account the changing level of DHT during the study follow-up period between 1994 and 2005. The control of confounding is limited; it is uncertain that the risk difference in CVD is solely or partially attributable to the 1994 baseline measure of DHT.

It is unknown how many patients were lost to follow-up during the study. In addition, in the study of incident stroke, smaller study population sizes at the lower and higher DHT serum concentrations produced risk estimates with wider confidence intervals that include the null, so there is uncertainty in the risk for ischemic stroke at the lower and higher DHT levels. For the risk for CVD, there is the same uncertainty with the estimates with the higher DHT levels due to small sample size and wide CIs.

3.2 BORST ET AL. META-ANALYSES

3.2.1 Study Design

This publication describes two separate meta-analyses. The first was a systematic review and meta-analysis of RCTs, examining CV risk associated with TRT. The second was a meta-analysis of clinical trials (placebo-controlled or not) that reported both serum testosterone and DHT levels before starting TRT and at the end of the trial. The first meta analysis found a significantly increased risk of CV adverse events only with oral TRT. The investigators then conducted the secondary meta analysis to generate mean pre- and post-treatment DHT levels by testosterone formulation. The DHT values were then superimposed on the Shores data to demonstrate that the oral formulations, on average, raise DHT levels into a range associated with an increased risk of stroke in the Shores study.

The investigators state that they followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and disclose no competing interests. There is no reference to a published protocol.

3.2.2 Data Sources and Time Period

Two study investigators independently searched PubMed for English language publications up to May 31, 2014, using the following search terms (“testosterone” or

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

“androgen”) and (random*) and trial”. An additional search was conducted using the search terms “testosterone” and “clinical trials”. Studies were limited to men. The reviewers also searched the World Health Organization International Clinical Trials Registry and conducted a manual search of bibliographies. The investigators also sought clarification from study authors concerning events by study arm.

For the second meta analysis, to identify studies reporting serum testosterone and DHT elevation, the investigators performed a supplemental search of all TRT clinical trials in men, using the terms “testosterone” and “DHT” and (“injection” or “gel” or “patch” or “oral”).

3.2.3 Selection Standards

For the first meta analysis, of TRT and CV risk, the investigators selected only placebo-controlled RCTs that reported CV AEs by study arm. RCTs less than twelve weeks treatment duration were excluded. Duplicate studies using the same trial participants were excluded, based on authorship, study description, number of participants, and participant characteristics.

For the second meta analysis, of serum testosterone and DHT elevation, the investigators selected any TRT trial that reported both serum testosterone and DHT, before and after treatment, regardless of study duration or whether the study was blinded. Duplicates were removed as described above, and one study was excluded because DHT was measured by immunoassay, a technique that has been shown to be invalid.

3.2.4 Exposure/Intervention and Outcome

The intervention was defined as testosterone therapy. Formulation/route, dose, and duration of therapy were documented.

The primary outcome was composite CV events, defined as anything reported as such by the original study. In cases where the investigators received a table of all AEs from study authors, two investigators, including one cardiologist, identified CV AEs using the ICD-9 codes I00 to I99: Diseases of the circulatory system.

The secondary outcome was elevation of serum testosterone and DHT following TRT administration by different routes (intramuscular, transdermal, or oral).

3.2.5 Covariates

The analyses were stratified by route of administration.

3.2.6 Sample Size

Out of an initial 2,313 publications screened, the final sample size for the TRT and CV risk analysis included 35 trials with 3,703 men. Of the 35 trials, 16 administered TRT intramuscularly, 15 transdermally, and 4 orally. A total of 131 CV AEs were reported

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

among the 2,114 men receiving TRT and 87 CV AEs were reported among the 1,589 men receiving placebo.

For the second meta-analysis examining the effect of route of administration on serum testosterone and DHT, the final sample included 31 trials (1,176 men) out of an initial 419 publications screened.

3.2.7 Statistical Analysis

For the TRT and CV risk analysis, the investigators employed a sample-size weighted random effects method designed for low event-rate meta-analysis.

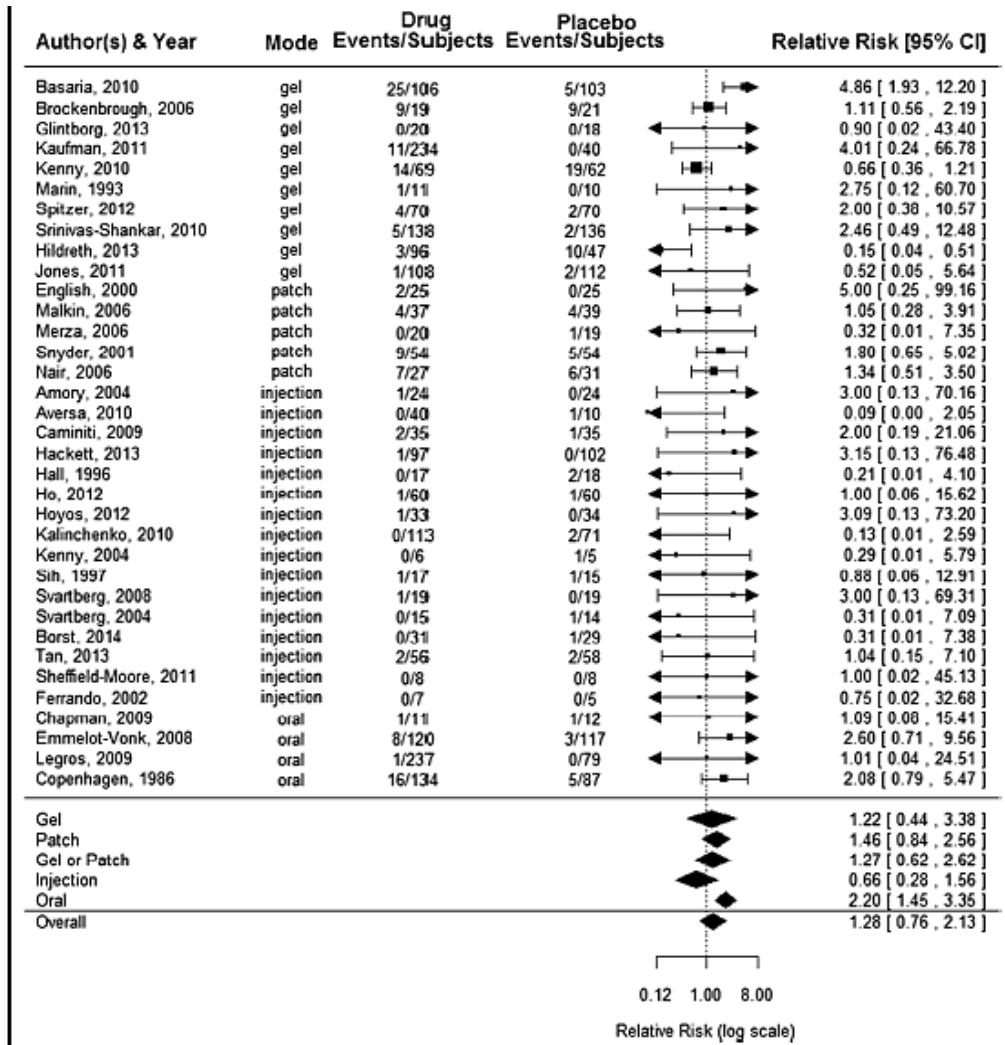
To generate pooled mean pre- and post-treatment serum levels in the second meta analysis, the investigators used a minor modification of the patient weighted random effects method, using the t-distribution rather than the normal approximation. Means were sample weighted, and individual study pre-post changes were analyzed rather than the ratio of summary pre and post estimates.

3.2.8 Study Results

3.2.8.1 TRT and CV Adverse Event Analysis

As shown in Figure 3, among patients receiving any form of TRT, the estimated relative risk for CV AEs was 1.28 (95% CI 0.76 to 2.13). CV AE rates varied by mode of TRT administration: oral TRT was associated with a significantly increased incidence of CV events (RR 2.20, 95% CI 1.45 to 3.35), while neither intramuscular TRT (RR 0.66, 95% CI 0.28 to 1.56) nor transdermal TRT (RR 1.27, 95% CI 0.62 to 2.62) significantly affected the risk of CV events.

Figure 3: Forest plot of placebo-controlled RCTs examining the pooled effect of TRT on CV AEs, overall and by TRT administration route.



Source: Borst et al. 2014, Figure 2

Borst et al. also re-analyzed trial-level data from the studies included in the previous meta-analysis by Xu et al. using the same method employed in the above analysis and obtained a relative risk for CV AEs that was similar to the pooled OR obtained by Xu et al. but not statistically significant (RR 1.59, 95% CI 0.90 to 2.57).

Appendix B provides a comparison of the component trials included Borst’s TRT and CV AE analysis to those included in previously reviewed meta-analyses by Xu et al. and Corona et al. The Borst analysis includes all trials that were part of Xu’s study, plus one of the seven additional trials included by Corona et al., and seven other RCTs, only four of which contributed events to the analysis. **Appendix C** provides descriptions of the

individual component trials contributing data to this analysis,⁴ and **Appendix D** provides a description of all CV AEs included in the Borst analysis.

3.2.8.2 Route of TRT administration and elevation of serum testosterone and DHT

As shown in Table 3 from the second meta analysis, transdermal TRT elevated DHT to a significantly greater degree (5.46-fold) than intramuscular TRT (2.20-fold). Only four eligible oral TRT studies were identified, and the data were deemed insufficient for statistical analysis. However, oral TRT appeared to produce increases in serum DHT levels that were similar to that of transdermal TRT and greater than with the intramuscular route. Timing of post-treatment serum testosterone and DHT measurement, particularly in relation to the final dose, was not specified for the various regimens. Characteristics of the TRT trials included in this analysis are shown in **Appendix E**.

Table 3: Change in serum testosterone and dihydrotestosterone (DHT) when assessed by testosterone replacement therapy (TRT) administration route

Route of administration	Number of studies	Testosterone			DHT		
		Pre-treatment T (nmol/L) (95% CI)	Post-treatment T (nmol/L) (95% CI)	Pre-Post treatment fold increase in T (95% CI)	Pre-treatment DHT (nmol/L) (95% CI)	Post-treatment DHT (nmol/L) (95% CI)	Pre-Post treatment fold increase in DHT (95% CI)
Intramuscular	8	9.27 (5.68 to 12.85)	23.11 (15.38 to 34.72)	2.91 (2.19 to 3.86)	1.02 (0.69 to 1.34)	1.62 (1.2 to 2.19)	2.20 (1.74 to 2.77)
Transdermal (patch and gel)	20	7.28 (6.09 to 8.42)	16.69 (12.62 to 21.98)	2.53 (1.83 to 3.50)	0.99 (0.78 to 1.20)	3.43 (2.37 to 4.98)	5.46 (4.51 to 6.60)
Gel	13	8.90 (7.67 to 10.13)	18.3 (15.18 to 23.12)	1.98 (1.70 to 2.30)	1.19 (0.93 to 1.46)	3.81 (2.57 to 5.63)	5.12 (4.07 to 6.45)
Patch	7	4.20 (2.78 to 5.23)	9.73 (4.01 to 23.62)	4.43 (2.99 to 6.54)	0.62 (0.36 to 0.88)	2.16 (0.68 to 6.87)	6.61 (3.08 to 14.16)
Oral ^a	4	6.66 (1.05, 2.9, 5.6, 4.1)	21.88 (59.2, 57.0, 7.6, 14.96)	2.80 (4.20, 2.20, 1.4, 3.6)	0.90 (1.1, 1.8, 0.30, 0.41)	3.92 (9.89, 3.30, 1.13, 1.35)	4.46 (9.0, 1.8, 3.8, 3.3)

^aEffects of oral TRT on T and DHT concentrations were not statistically analyzed because only four studies were identified that met our *a priori* inclusionary criteria, which resulted in sufficient data. For oral studies, the mean and individual values for each of the four studies are listed. Transdermal (patch or gel) TRT produces a greater elevation of serum DHT than intramuscular TRT. Means are adjusted for sample size.

Source: Borst et al., 2014, Table 3

3.2.9 Authors' Interpretation of Results

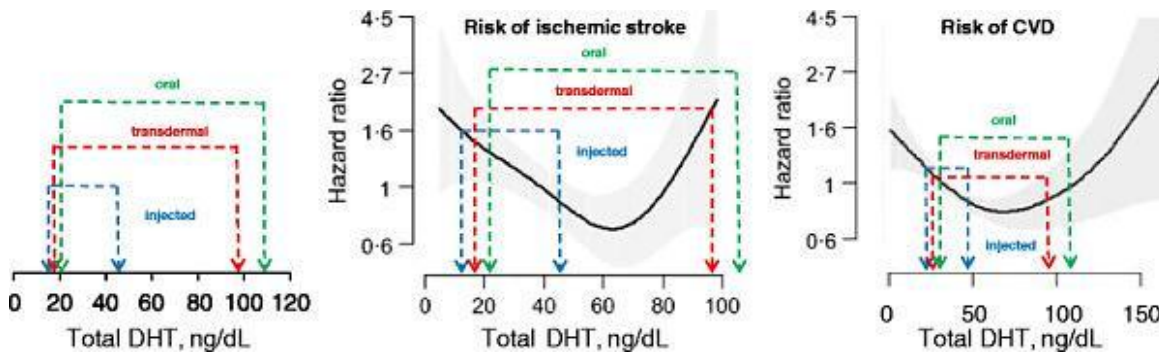
Borst et al. conclude that no significant increase in CV AE risk was found among studies of various TRT administration routes when analyzed together. When analyzed by mode of administration, only oral TRT was associated with significantly elevated risk of CV AEs when compared with placebo. The second meta analysis suggests that oral and transdermal administration of TRT were associated with greater DHT elevations than was intramuscular TRT administration.

The authors postulate that the greater elevation of DHT seen with oral or transdermal TRT may be due to the high expression of 5-alpha reductase in skin and liver compared to skeletal muscle. They then describe findings from the two observational studies by

⁴ The three trials with 0 events were not reviewed in detail.

Shores which suggest a non-linear relationship between serum DHT and CVD or stroke, with higher or lower DHT levels associated with an elevated CVD or stroke risk, as shown in Figure 4. Borst et al. superimposed their pre- and post-TRT serum DHT values from the meta analysis onto the Shores data, as shown in Figure 4, to suggest that, unlike intramuscular TRT, oral and transdermal TRT increase serum DHT into a range that is associated with unchanged CVD risk but increased risk of ischemic stroke.

Figure 4: Comparison of DHT levels after testosterone treatment with DHT levels that are associated with CV disease risk



Comparison of DHT levels after testosterone treatment with DHT levels that are associated with CV disease risk. Left panel. Testosterone-induced elevation of DHT in the eight RCTs of testosterone injection, twenty RCTs of transdermal administration and four RCTs of oral testosterone administration shown in Table 2. Transdermal administration causes a greater elevation of serum DHT. **Center panel.** Data from panel 1 is overlaid on observational data from Shores *et al.* showing the relationship between serum DHT and 10 year risk of incident ischemic stroke in older men. The solid line represents the estimated hazard ratio (HR) and the shaded area depicts the 95% confidence interval. All models are adjusted for age (reprinted with permission from Shores *et al. Clin Endocrinol (Oxf)* 2014. doi: 10.1111/cen.12452 [22]). **Right panel.** Data from panel 1 is overlaid on observational data from Shores *et al.* showing the relationship between serum DHT and incident CV disease risk. The solid line represents the estimated hazard ratio (HR) and the shaded area depicts the 95% confidence intervals. All models are adjusted for age. (Reprinted with permission from Shores *et al. J Clin Endocrinol Metab* 2014, **99**:2061-2068. [23]). DHT, dihydrotestosterone; RCT, randomized controlled trial.

Source: Borst et al. 2014, Figure 4

3.2.10 DEPI Interpretation of the Borst et al. Meta-analyses

An examination of the four component RCTs included in the meta-analysis of oral TRT and CV AEs raises serious questions about the validity and generalizability of the results. First, the trial contributing the greatest number of CV events to the oral TRT analysis—16 of the 26 events in the TRT arm—was a study in hospitalized alcoholic men with advanced cirrhosis (Copenhagen Study Group, 1986). This population would be expected to have hemodynamic, coagulation, and metabolic derangements that make it virtually impossible to generalize results to the general population of men taking oral TRT. Moreover, 12 of the 16 CV events in the TRT arm and five in the placebo arm were deaths from bleeding esophageal varices, a phenomenon occurring almost exclusively in the setting of severe liver disease and resulting from physiologic mechanisms that are quite different from those involved in CV events such as AMI and ischemic stroke. The other trial contributing a large proportion of events—eight in the TRT and three in the placebo arm—provided only aggregate numbers of “CV

complaints” with no further details on the nature of these complaints (Emmelot-Vonk et al., 2008). The largest of the oral TRT trials (Legros et al., 2009) reported only deaths and did not provide any further information on other CV events that may have occurred during the trial, although the paper mentions 19 other patients with “serious AEs” not further classified. In total, the four oral testosterone trials reported three cases of MACE⁵ in the TRT arm and one MACE in the placebo arm. Because of the extreme heterogeneity in study populations and CV outcomes, as well as the incomplete description of adverse events in two of the larger trials of the oral products, the elevated pooled CV risk identified in Borst’s meta-analysis of these four trials lacks credibility.

Furthermore, although the Borst meta-analysis of TRT (oral and other formulations) and CV AE risk employs different statistical models and stratifies by route of administration, it is, on the whole, quite similar to the previously reviewed meta-analysis by Xu et al. (Xu et al., 2013) and suffers from the same serious limitations described in detail in the DEPI review of this study.⁶ In addition to the clinical heterogeneity, overly broad definition of CV endpoints, and incomplete safety data reporting noted above, these limitations include lack of blinded ascertainment and adjudication of CV events, unknown impact of trial selection, and study arm imbalances in baseline CV risk and study retention.

Borst et al. then conducted a second meta-analysis of pre- and post-TRT serum testosterone and DHT levels by testosterone formulation. These results were difficult to interpret for a number of reasons. First, baseline serum testosterone levels varied considerably across trials, even across trials using the same route of TRT administration (Appendix E), and dose and frequency of administration were not consistent across studies using the same route of administration. Trial duration for the pre-post testosterone and DHT studies ranged from a single dose to 7 years. Finally, several different types of assays were used in the included trials, and the timing of serum testosterone and DHT measurement, particularly post-treatment, was not clear. The impact of these various factors on the relative effect of the drugs on serum testosterone and DHT levels is unclear. It also should be noted that DHT levels were generally not measured in the RCTs included in the meta-analysis of TRT and CV risk. Nor was CV risk assessed in the analysis of trials measuring pre- and post-treatment testosterone and DHT levels. Due to the lack of patient-level data and the use of two different groups of trials, one cannot determine from these data whether individuals, or even groups of individuals, with greater increases in DHT or higher post-treatment levels of DHT have an increased risk of CV events.

⁵ Defined as acute myocardial infarction, ischemic stroke, or cardiovascular death.

⁶ RCM #2013-2704. McAninch J., “OSE.DEPI Xu meta-analysis review final.” July 31, 2014.

4 DISCUSSION

The objective of the Shores studies was to evaluate the relationship between serum DHT levels and CVD, including ischemic stroke, and the results suggest a possible non-linear, U-shaped relationship between serum DHT levels and CVD, albeit with considerable uncertainty around the CV risk estimates at higher DHT levels. The Borst study was designed to examine the CV risk associated with various TRT formulations, and this meta-analysis found a significantly increased risk of CV adverse events only with oral TRT. The investigators then conducted a secondary meta-analysis to examine differential elevation of testosterone and DHT based on route of TRT administration. The mean pre- and post-treatment DHT levels generated by this second meta-analysis were then applied to the figures presented in the Shore's study to suggest that the increased CV risk seen with oral TRT formulations might be because oral formulations, on average, raise DHT levels into a range associated with an increased risk of stroke in the Shores study.

Aside from the serious limitations of Borst's two meta-analyses described in the previous section, this logic of superimposing the DHT values onto Shore's study figures is problematic. First, none of the CV AEs described in the oral TRT trials were documented to be strokes (see Appendix D). Second, the oral TRT data were deemed insufficient for statistical analysis due to small sample size. Third, two of the four oral TRT trials actually had mean post-treatment DHT levels *below* that of the mean levels for the intramuscular trials (Table 3) and below levels where the risk of stroke starts to increase. Third, oral and transdermal TRT increased serum DHT to similar levels, yet the meta-analysis of transdermal TRT RCTs did not show a significant increase in CV risk (Figure 3).

Finally, it is inappropriate to apply the CV risk estimates from the Shores studies to Borst's second meta-analysis given the substantial differences in the study populations. In the Shores studies, the study population were older men (mean age 76.5 years) with higher CV risk. The authors did not specify if any of these men might have been on TRT. The Borst meta-analysis was comprised of clinical trials of mostly middle-aged men treated with TRT.

5 CONCLUSIONS

The Shores studies suggest a possible non-linear relationship between serum DHT levels and CV events; however, due to study limitations, the relationship remains uncertain and requires additional studies to confirm the association. The Borst meta-analysis was not designed to directly answer the question of whether elevated levels of DHT are associated with increased CV risk. The authors attempt to establish a link between oral testosterone, elevated post-treatment DHT levels, and CV risk through a series of inferences that DEPI does not find to be supported by the data, both because of serious

limitations in the meta-analyses themselves and because of problems arising from an attempt to superimpose data from one study onto those of a completely different study. Nonetheless, the Borst study does raise important questions about whether CV risk might vary by route of testosterone administration, and the authors propose an intriguing hypothesis as to why this could be plausible. However, the study itself was unable to answer either of these questions. In designing safety studies to evaluate the association between TRT and CV risk, possible differences in risk based on route of administration should be considered and assessed. In addition, standardized measurement of pre- and post-treatment serum testosterone and DHT may help elucidate the relationship between testosterone, DHT and CV risk.

6 REFERENCES

- Amory, J. K., Watts, N. B., Easley, K. A., Sutton, P. R., Anawalt, B. D., Matsumoto, A. M. et al. (2004). Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol.Metab.*, 89, 503-510.
- Aversa, A., Bruzziches, R., Francomano, D., Rosano, G., Isidori, A. M., Lenzi, A. et al. (2010). Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *J Sex Med*, 7, 3495-3503.
- Basaria, S., Coviello, A. D., Travison, T. G., Storer, T. W., Farwell, W. R., Jette, A. M. et al. (2010). Adverse events associated with testosterone administration. *N Engl J Med*, 363, 109-122.
- Borst, S. E., Shuster, J. J., Zou, B., Ye, F., Jia, H., Wokhlu, A. et al. (2014a). Cardiovascular risks and elevation of serum DHT vary by route of testosterone administration: a systematic review and meta-analysis. *BMC Med*, 12, 211.
- Borst, S. E., Yarrow, J. F., Conover, C. F., Nseyo, U., Meuleman, J. R., Lipinska, J. A. et al. (2014b). Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial. *Am J Physiol Endocrinol.Metab.*, 306, E433-E442.
- Brockenbrough, A. T., Dittrich, M. O., Page, S. T., Smith, T., Stivelman, J. C., & Bremner, W. J. (2006). Transdermal androgen therapy to augment EPO in the treatment of anemia of chronic renal disease. *Am J Kidney.Dis*, 47, 251-262.
- Caminiti, G., Volterrani, M., Iellamo, F., Marazzi, G., Massaro, R., Miceli, M. et al. (2009). Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol.*, 54, 919-927.
- Chapman, I. M., Visvanathan, R., Hammond, A. J., Morley, J. E., Field, J. B., Tai, K. et al. (2009). Effect of testosterone and a nutritional supplement, alone and in combination, on hospital admissions in undernourished older men and women. *Am J Clin Nutr.*, 89, 880-889.

Copenhagen Study Group (1986). Testosterone treatment of men with alcoholic cirrhosis: a double-blind study. The Copenhagen Study Group for Liver Diseases. *Hepatology*, 6, 807-813.

Emmelot-Vonk, M. H., Verhaar, H. J., Nakhai Pour, H. R., Aleman, A., Lock, T. M., Bosch, J. L. et al. (2008). Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. *JAMA*, 299, 39-52.

English, K. M., Steeds, R. P., Jones, T. H., Diver, M. J., & Channer, K. S. (2000). Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. *Circulation*, 102, 1906-1911.

Finkle, W. D., Greenland, S., Ridgeway, G. K., Adams, J. L., Frasco, M. A., Cook, M. B. et al. (2014). Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One*, 9, e85805.

Hackett, G., Cole, N., Bhartia, M., Kennedy, D., Raju, J., & Wilkinson, P. (2013). Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes. *J Sex Med*, 10, 1612-1627.

Hackett, G., Cole, N., Bhartia, M., Kennedy, D., Raju, J., Wilkinson, P. et al. (2014). The response to testosterone undecanoate in men with type 2 diabetes is dependent on achieving threshold serum levels (the BLAST study). *Int J Clin Pract.*, 68, 203-215.

Hall, G. M., Larbre, J. P., Spector, T. D., Perry, L. A., & Da Silva, J. A. (1996). A randomized trial of testosterone therapy in males with rheumatoid arthritis. *Br J Rheumatol.*, 35, 568-573.

Hammad, T. A., Pinheiro, S. P., & Neyarapally, G. A. (2011). Secondary use of randomized controlled trials to evaluate drug safety: a review of methodological considerations. *Clin Trials*, 8, 559-570.

Ho, C. C., Tong, S. F., Low, W. Y., Ng, C. J., Khoo, E. M., Lee, V. K. et al. (2012). A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptoms scale. *BJU.Int*, 110, 260-265.

Hoyos, C. M., Yee, B. J., Phillips, C. L., Machan, E. A., Grunstein, R. R., & Liu, P. Y. (2012). Body compositional and cardiometabolic effects of testosterone therapy in obese men with severe obstructive sleep apnoea: a randomised placebo-controlled trial. *Eur J Endocrinol.*, *167*, 531-541.

Jones, T. H., Arver, S., Behre, H. M., Buvat, J., Meuleman, E., Moncada, I. et al. (2011). Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care*, *34*, 828-837.

Kalinchenko, S. Y., Tishova, Y. A., Mskhalaya, G. J., Gooren, L. J., Giltay, E. J., & Saad, F. (2010). Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. *Clin Endocrinol.(Oxf.)*, *73*, 602-612.

Kaufman, J. M., Miller, M. G., Garwin, J. L., Fitzpatrick, S., McWhirter, C., & Brennan, J. J. (2011). Efficacy and safety study of 1.62% testosterone gel for the treatment of hypogonadal men. *J Sex Med*, *8*, 2079-2089.

Kenny, A. M., Fabregas, G., Song, C., Biskup, B., & Bellantonio, S. (2004). Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. *J Gerontol.A Biol Sci Med Sci*, *59*, 75-78.

Kenny, A. M., Kleppinger, A., Annis, K., Rathier, M., Browner, B., Judge, J. O. et al. (2010). Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. *J Am Geriatr.Soc*, *58*, 1134-1143.

Legros, J. J., Meuleman, E. J., Elbers, J. M., Geurts, T. B., Kaspers, M. J., & Bouloux, P. M. (2009). Oral testosterone replacement in symptomatic late-onset hypogonadism: effects on rating scales and general safety in a randomized, placebo-controlled study. *Eur J Endocrinol.*, *160*, 821-831.

Malkin, C. J., Pugh, P. J., West, J. N., van Beek, E. J., Jones, T. H., & Channer, K. S. (2006). Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. *Eur Heart J*, *27*, 57-64.

Marin, P., Holmang, S., Gustafsson, C., Jonsson, L., Kvist, H., Elander, A. et al. (1993). Androgen treatment of abdominally obese men. *Obes.Res*, *1*, 245-251.
[30].UNIQUEID DOI>

Merza, Z., Blumsohn, A., Mah, P. M., Meads, D. M., McKenna, S. P., Wylie, K. et al. (2006). Double-blind placebo-controlled study of testosterone patch therapy on bone turnover in men with borderline hypogonadism. *Int J Androl.*, 29, 381-391.

Nair, K. S., Rizza, R. A., O'Brien, P., Dhatariya, K., Short, K. R., Nehra, A. et al. (2006). DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med*, 355, 1647-1659.

Shores, M. M., Arnold, A. M., Biggs, M. L., Longstreth, W. T., Jr., Smith, N. L., Kizer, J. R. et al. (2014a). Testosterone and dihydrotestosterone and incident ischaemic stroke in men in the Cardiovascular Health Study. *Clin Endocrinol.(Oxf.)*, 81, 746-753.

Shores, M. M., Biggs, M. L., Arnold, A. M., Smith, N. L., Longstreth, W. T., Jr., Kizer, J. R. et al. (2014b). Testosterone, dihydrotestosterone, and incident cardiovascular disease and mortality in the cardiovascular health study. *J Clin Endocrinol.Metab.*, 99, 2061-2068.

Sih, R., Morley, J. E., Kaiser, F. E., Perry, H. M., III, Patrick, P., & Ross, C. (1997). Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *J Clin Endocrinol.Metab.*, 82, 1661-1667.

Snyder, P. J., Peachey, H., Berlin, J. A., Rader, D., Usher, D., Loh, L. et al. (2001). Effect of transdermal testosterone treatment on serum lipid and apolipoprotein levels in men more than 65 years of age. *Am J Med*, 111, 255-260.

Spitzer, M., Basaria, S., Travison, T. G., Davda, M. N., Paley, A., Cohen, B. et al. (2012). Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. *Ann Intern Med*, 157, 681-691.

Srinivas-Shankar, U., Roberts, S. A., Connolly, M. J., O'Connell, M. D., Adams, J. E., Oldham, J. A. et al. (2010). Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol.Metab.*, 95, 639-650.

Svartberg, J., Aasebo, U., Hjalmsen, A., Sundsfjord, J., & Jorde, R. (2004). Testosterone treatment improves body composition and sexual function in men with COPD, in a 6-month randomized controlled trial. *Respir Med*, 98, 906-913.

Svartberg, J., Agledahl, I., Figenschau, Y., Sildnes, T., Waterloo, K., & Jorde, R. (2008). Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. *Int J Impot.Res*, 20, 378-387.

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

Tan, W. S., Low, W. Y., Ng, C. J., Tan, W. K., Tong, S. F., Ho, C. et al. (2013). Efficacy and safety of long-acting intramuscular testosterone undecanoate in aging men: a randomised controlled study. *BJU Int*, *111*, 1130-1140.

Vigen, R., O'Donnell, C. I., Baron, A. E., Grunwald, G. K., Maddox, T. M., Bradley, S. M. et al. (2013). Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*, *310*, 1829-1836.

Xu, L., Freeman, G., Cowling, B. J., & Schooling, C. M. (2013). Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med*, *11*, 108.

7 APPENDICES

7.1 APPENDIX A - COVARIATES ADJUSTED IN EACH MODEL BY STUDY

Study	Model 1	Model 2	Model 3	Model 4	Sensitivity
DHT and CVD and mortality	Age, race, clinic site, smoking status, alcohol intake	Added antihypertensives, HDL, TC, BMI, WC	Added diabetes	Model 2 covariates plus SHBG	Excluded men with finasteride use
DHT and ischemic stroke	Age	Age, SBP, antihypertensives, AF, diabetes, ln pack years	Added lipid lowering drugs, HDL, TC, high creatinine	-	Excluded men with finasteride use

AF atrial fibrillation, BMI body mass index, HDL high density lipoprotein, ln natural log, SBP systolic blood pressure, SHBG sex hormone binding globulin, TC total cholesterol, WC waist circumference

7.2 APPENDIX B: COMPONENT STUDIES AND OUTCOME COMPARISON AMONG THE XU, CORONA AND BORST META-ANALYSES

Author, year	Included in Xu meta-analysis	Included in Corona meta-analysis*	Included in Borst meta-analysis	Were # CREs counted same in all three meta-analyses? If no: # of TRT/PBO CREs counted in each study	Explanation of discrepancy among meta-analyses
Copenhagen Study Group, 1986	√	√	√	yes	
Hall <i>et al.</i> , 1996	√	√	√	yes	
Sih <i>et al.</i> , 1997	√	√	√	yes	
English <i>et al.</i> , 2000	√	√	√	yes	
Amory <i>et al.</i> , 2004	√	√	√	No: Corona: 2/0 Xu: 1/0 Borst: 1/0	Corona cites 1 stroke and 1 arrhythmia, but cannot find documentation of the arrhythmia in the article. Does not affect MACE analysis.
Kenny <i>et al.</i> , 2004	√	√	√	yes	
Svartberg <i>et al.</i> , 2004	√	√	√	yes	
Brockenbrough <i>et al.</i> , 2006	√	√	√	yes	
Malkin <i>et al.</i> , 2006	√	√	√	No: Corona: 5/6 Xu: 4/4 Borst: 4/4	Corona counted 2 presyncope events, one in each arm, and a sudden death in PBO arm as CREs. Xu and Borst did not include these.
Merza <i>et al.</i> , 2006	√	√	√	yes	
Nair <i>et al.</i> , 2006	√	√	√	yes	
Emmelot-Vonk <i>et al.</i> , 2008	√	√	√	No: Corona: 7/3 Xu: 8/3 Borst: 8/3	Xu and Borst include 1 man in TRT group who withdrew before 3 month visit for CV complaint, but was not included in authors' total number for "CV complaints"
Svartberg <i>et al.</i> , 2008	√	√	√	yes	
Caminiti <i>et al.</i> , 2009	√	√	√	yes	
Chapman <i>et al.</i> , 2009	√	√	√	No: Corona: 1/0 Xu: 1/1 Borst: 1/1	Appears to be an inconsistency in Corona paper—1 MI in PBO group counted as MACE but not CRE
Legros <i>et al.</i> , 2009	√	√	√	yes	
Aversa <i>et al.</i> , 2010 (1)	√	√	√	yes	
Basaria <i>et al.</i> , 2010	√	√	√	yes	
Kalinchenko <i>et al.</i> , 2010	√	√	√	yes	
Srinivas-Shankar <i>et al.</i> , 2010	√	√	√	yes	
Ho <i>et al.</i> , 2011	√	√	√	No: Corona: 2/2 Xu: 1/1 Borst: 1/1	Xu and Borst did not count 1 "chest pain" in each group, reason unclear
Hoyos <i>et al.</i> , 2012	√	√	√	yes	

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

Jones <i>et al.</i> , 2011	√	√	√	yes	
Kaufman <i>et al.</i> , 2011	√	√	√	No: Corona: 17/2 Xu: 11/0 Borst: 11/0	Corona counts events listed in text with implied treatment arm (17/2) while Xu and Borst only include events listed in AE table (11/0).
Marin <i>et al.</i> , 1993	√		√	Xu: 1/0 Borst: 1/0	
(Snyder <i>et al.</i> , 2001)	√		√	Xu: 9/5 Borst: 9/5	
Spitzer <i>et al.</i> , 2012	√		√	yes	
(Snyder <i>et al.</i> , 1999)		√		Corona: 9/5	
Seidman <i>et al.</i> , 2001		√		Corona: 0/1	
Steidle <i>et al.</i> , 2003		√		Corona: 2/0	
Okun <i>et al.</i> , 2006		√		Corona: 1/2	
Aversa <i>et al.</i> , 2010 (2)		√		Corona: 0/1	Appears to be overlap in study population with Aversa, 2010 (1)—MACE event in PBO group here and in that study may have been same event but counted twice
Behre <i>et al.</i> , 2012		√		Corona: Only included trial in MACE analysis figure -- 1 coronary artery disease death and one DVT in TRT group not counted in overall CREs—unclear why	
Hildreth <i>et al.</i> , 2013		√	√	Corona: 4/11 Borst: 3/10	Unclear origin of additional events in Corona analysis
NCT00957528		√		Corona: 1/1	
(Ferrando <i>et al.</i> , 2002)			√	Borst: 0 events	
Kenny <i>et al.</i> , 2010			√	Borst: 14/19	CV AE table supplied to Borst by authors on request
(Sheffiedl-Moore <i>et al.</i> , 2011)			√	Borst: 0 events	
(Glintborg <i>et al.</i> , 2013)			√	Borst: 0 events	
Hackett <i>et al.</i> , 2013			√	Borst: 1/0	
Tan <i>et al.</i> , 2013			√	Borst: 2/2	
Borst <i>et al.</i> , 2014			√	Borst: 0/1	

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

7.3 APPENDIX C: COMPONENT RCTs INCLUDED IN THE BORST META-ANALYSIS OF TRT AND CV AEs

Key: AE=adverse event; BPH=benign prostatic hypertrophy; CA=cancer; CABG=coronary artery bypass graft; CHF=congestive heart failure; CVA=cerebrovascular accident; ESRD=End stage renal disease ; HCT=hematocrit; HGB=hemoglobin; HTN=hypertension; LTFU=loss to follow-up; MI=myocardial infarction; NYHA=New York Heart Association; NR=not reported; NS=non-significant; PBO=placebo; PSA=prostate-specific antigen; PVD=peripheral vascular disease; T=testosterone; TRT=treatment

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
1. Amory, 2004 2. U.S. 3. Not stated	1. 36 months 2. T enanthate 200mg IM every 2wks (Potential for dose-reduction of T for hct>52%)	1. TRT n=24; PBO n=24 2. IC: 65+ years and total T <12.1 nmol/l 3. EC: severe illness, use of anabolic steroids, antiandrogens, glucocorticoids, bisphosphonates, diuretics, calcitonin, seizure meds, warfarin; Paget's disease; smoking or heavy alcohol use, sleep apnea, hematocrit>48%; total cholesterol>300mg/dl; abnormal kidney, liver, thyroid, adrenal, or pituitary function; regular exercise >3x/week; prostate CA/nodule or PSA>4.0 or Prostate Symptoms Score>8; elevated urinary post-void residual, abnormal transrectal ultrasound 4. Mean age 71 (range 65-83)	Any serious adverse CV, cerebrovascular, or pulmonary events 1. No 2. NR	1 cerebral hemorrhage in testosterone-only arm	1. Relatively low CV risk except older age. Important CV risk factors excluded: smoking, use of diuretics (would exclude many w/ HTN), total chol>300 2. BMI (27-28), age (71) balanced, but most CV risk factors unknown 3. 29% discontinuation rate, study arm not specified. Telephone f/u conducted for men who discontinued prematurely	Older, but generally healthy population. <u>Strengths:</u> 1. Long trial duration <u>Limitations:</u> 1. 29% discontinuation rate. Only 2 lost to follow-up, but unclear whether non-prostate outcomes were assessed in follow-up calls. Arm-specific number of drop-outs not specified 2. CV/safety outcomes not prespecified; unclear if blinded
1. Aversa, 2010 2. Italy 3. Not stated	1. 12-months (with 12 month open-label extension) 2. T undecanoate	1. TRT n=40; PBO n=10 2. IC: 45-65 years old with metabolic syndrome and/or Type 2 diabetes AND total serum T	Only adverse events related to withdrawals appear to have	1 acute MI in PBO group	1. Enriched for cardiac risk factors due to diabetes and/or metabolic syndrome, but younger age group	Younger group, but enriched for CV risk factors

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
	(TU) 1000mg q 12 weeks	level <3.0 ng/ml or calculated free T levels <250 pmol/L AND ≥ 2 symptoms of hypogonadism 3. EC: Androgen therapy or anabolic steroid use; history of prostate or breast CA; drug or alcohol abuse; history of tumors, blood coagulation irregularities; symptomatic obstructive sleep apnea; HCT≥52%; elevated PSA or abnormal digital rectal exam; use of 5-alpha-reductase inhibitors; uncontrolled endocrine disorder including HbA1c ≥ 9; NYHA class III or IV heart failure; hepatic or renal insufficiency; severe neurological and psychiatric disease; requiring or undergoing fertility treatment. 4. Mean age 57	been reported. 1. No 2. NR		2. No major CV risk imbalances noted: Age (57-58), smokers (20%), BMI (30-31), DM (30%), antihypertensive (60-65%), statin (20-25%), and metformin (37-40%) were fairly balanced 3. Four patients discontinued (8%) --3 in T group due to HCT>52% and the one MI in placebo group.	<u>Strengths:</u> Long trial duration. <u>Limitations:</u> 1. Overall adverse event count and discontinuation rate not clear. Only adverse events related to withdrawals noted. 2. Unclear how adverse events were monitored during open-label extension 3. CV/safety outcomes not prespecified; unclear if blinded
1. Basaria, 2010 2. U.S. 3. Testosterone and placebo gel provided by Auxilium. Various consulting fees and grant support from Auxilium and other pharmaceutical companies.	1. 6 months 2. 100mg topical testosterone gel daily (potential dose adjustment at 2 weeks)	1. TRT n=106; PBO n=103 2. IC: 65+ years, community-dwelling with mobility limitations, total serum T 3.5-12.1 nmol/l or free serum T <50pg/ml 3. EC: Uncontrolled HTN, unstable angina, MI within 3 months, NYHA class III or IV CHF, active cancer, severe lower urinary tract symptoms, untreated severe sleep apnea, glucocorticoid or anabolic steroid therapy, HbA1c>8.5%, HCT>48%, PSA>4ng/ml, BMI > 40	Data and safety monitoring board reviewed serious adverse events as they occurred and cumulative adverse events q 6 months. 1. Yes 2. Yes	<u>Testosterone Group:</u> • Acute coronary syndrome and chest pain • Syncope (2) • Myocardial infarction (2) • Angioplasty and coronary artery bypass • Peripheral edema (5) • Ectopy on ECG • Left ventricular strain pattern	1. High prevalence of chronic disease, pre-existing CV disease, and CV risk factors 2. Stratified by age (65-75 and 75+) before randomization. Balanced for age (74), BMI (30). Imbalance for race (more blacks in T group). Higher % with dx hyperlipidemia on statin in T group (p 0.03). NS higher proportion with pre-existing CVD in T group (53% vs 47% in PBO group). Balanced for other CV risk factors (DM, BP, obesity, smoking) and Framingham risk score -22 in T group v.s 21 in	Elderly frail group, high prevalence of pre-existing CV disease and risk factors <u>Strengths:</u> 1. Exhaustive reporting of CV-related events. 2. Attempt to verify CV-related events through medical record review and exam <u>Limitations:</u> 1. Randomization failure?

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
		4. Mean age 74		during exercise testing • ST-segment depression during exercise testing • Elevated BP (2) • Atrial fibrillation with CHF exacerbation and hospitalization • Stroke • Elevated BP and atrial fibrillation • Tachycardia with fatigue • Death, suspected myocardial infarction • Congestive heart failure exacerbation <u>Placebo group:</u> • Syncope resulting in hospitalization • Tachycardia • Elevated BP • Arrhythmia – ectopy noted on ECG before exercise testing	placebo (p=0.31) 3. Study stopped early due to increased CV-related adverse events in treatment group. Adherence > 90% both groups	Multiple imbalances in CV risk factors (but perhaps not enough to account for large imbalance in CV outcomes) 2. CV events very broadly defined, unclear whether some were CV-related at all 3. Early stopping may exaggerate magnitude of difference in CV events in TRT vs. PBO groups. 4. Unclear if results generalizable to group expected to use T.

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
				Carotid bruit and carotid-artery plaque identified on ultra-sonography		
1. Borst, 2014 2. U.S. 3. Yes—Merck grant	1. 12 months 2. 125 mg/wk TE IM (additional PBO and TRT groups were also treated with 5mg/day finasteride)	1. n=16 PBO, 14 TRT (without finasteride); 13 PBO, 17 TRT (with finasteride) 2. IC: Men aged ≥60 years with serum total T ≤300 ng/dl or BioT ≤70 ng/dl. 3. EC: Failed Min-Cog test, hx prostate or breast CA, severe BPH, AUA/IPSS score ≥25, class 3 or 4 CHF, sleep apnea, Hct>49%, PSA≥2.6ng/ml, BMI>35, orthopedic limitations precluding strength testing, recieved T within 4 wks 4. Mean age 70.8 years (PBO and 69.2 years (TRT)	1. No 2. No	Not clearly stated, appears to have been unpublished data available to author	1. Appear to be at average risk but little info 2. BMI balanced, no other CV risk info 3. 50% discontinuation in TRT group, 25% discontinuation in PBO	<u>Limitations:</u> 1. High discontinuation rate 2. Very small study 3. Little info on cardiac risk factors 4. CV event not included in published paper

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
1. Brockenbrough, 2006 2. U.S. 3. Yes (Auxilium)	1. 6 months 2. 100 mg topical T gel daily	1. TRT n=19; PBO n=21 2. IC: Male 18+ years old; hemodialysis-dependent ESRD; total T $\leq$ 10.4 nmol/L; anemia requiring rHuEPO for $\geq$ 3 months. 3. EC: T therapy within 6 months; use of anabolic supplements or medications that interfere with T; PSA > 4ng/m; prostate CA, bilateral nephrectomy, liver failure, HIV, substance abuse, life expectancy < 6 months, home dialysis, or weight > 300 lbs; non-English-speaking; recent investigational study drug use; allergy/hypersensitivity to T gel components. 4. Mean age = 53 years (PBO), 59 (TRT)	Adverse events reported in detail on case-report forms throughout the study. 1. No 2. NR	<u>Withdrawals</u> 3 withdrawals due to CV death in TRT group 1 withdrawal due to stroke death in PBO group - Withdrawals due to prolonged hospitalization in both groups—reason not specified. <u>Adverse events:</u> - Access thrombosis: 6 PBO, 2 TRT - Cardiac disorders: 3 PBO, 7 TRT	1. Likely enriched for CV risk due to ESRD (suggesting high prevalence of DM and HTN, although prevalence of baseline comorbidities not reported) 2. Some group imbalances: mean age older (59 vs. 53, p=0.25), mean time on dialysis longer (44 vs. 32 months, p=0.49), baseline rHuEPO dose lower, and DHT and estradiol levels higher (p=0.02 and 0.01, respectively) in TRT group. 3. 45% discontinuation at 6 months. 71% of study attrition in TRT group was in first 3 months, compared to 30% in PBO group. Monthly drug compliance better in TRT group (76-94%) than PBO group (61-84%)	Younger group, but likely enriched for CV risk factors due to ESRD, which is associated with high prevalence of HTN and diabetes <u>Strengths:</u> 1. Systematic collection of adverse event and withdrawal data <u>Limitations:</u> 1. "Cardiac disorders" not further specified. 2. High discontinuation rate (45%), with earlier discontinuation in TRT group. 3. Prevalence of baseline comorbidities and CV risk factors not reported
1. Caminiti, 2009 2. Italy 3. No	1. 12 weeks 2. 1000 mg T undecanoate IM at 6 and 12 weeks	1. TRT n=35, PBO n=35 2. IC: Elderly males with symptomatic CHF (NYHA class II or III), LVEF<40%; clinical stable without CHF hospitalization past 3 months 3. EC: Unstable angina or recent acute MI, history of severe liver or kidney disease, uncontrolled hypertension, significant pulmonary disease, HCT>50%,	Patients followed clinically every month. Echo and exercise ECG at baseline and end of study 1. No 2. NR	Worsening CHF in 2 TRT patients (1 requiring hospitalization) and 1 PBO patient No side effect requiring discontinuation of treatment occurred, and there were no deaths.	1. Elderly, pre-existing CHF suggests high baseline risk for CV-related events. Most were on beta-blockers, ACE-I, statin, and anti-platelets 2. TRT group slightly older (median age 71 vs. 69, NS). Comorbidities and CV risk factors were fairly balanced. 3. 9% discontinuation overall—4 discontinued in TRT group, 2	Enriched population: Elderly with stable pre-existing cardiac disease. Hypogonadism not required for study inclusion. <u>Limitations:</u> 1. Short study duration 2. Unclear whether all CV adverse effects were reported or only those related to CHF

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
		prostate CA, PSA>3ng/ml, severe lower urinary tract symptoms, vascular or other disease of lower extremities that could prevent a symptom limited exercise test 4. Median age 70 years; (range 66-76)			in placebo, all "unrelated to treatment"	exacerbation
1. Chapman, 2009 2. Australia 3. Yes, Supported by Organon	1. 1 year 2. Oral T undecanoate 80 mg BID (Dose adjusted for HCT>54% or elevated PSA) Active placebo: nutritional supplement	1. TRT n=6 PBO n=6 years (men and women but only data for men described here) 2. IC: Age ≥ 65, community dwelling, undernourished (Mini Nutritional Assessment score <24 and BMI <22 or self-reported weight loss ≥7.5% in past 3 months) 3. EC: Inability to comply, cognitive impairment, HCT>50%, history of prostate CA, elevated PSA, abnormal prostate exam, breast CA, depression, CHF NYHA class III or IV, abnormal LFTs, predicted death within 1 year, any androgen therapy past 4 months 4. Mean age in men: 74 (TRT), 78 (PBO)	Hospitalizations reported by patients, confirmed by GP and, where possible, hospital records. Phone calls every 2-4 weeks, and home visits q 1-2 months, where adverse events occurrence was actively sought. 1. No 2. NR	1 MI in nutritional supplement only group (PBO) 1 MI death in T group (known heart disease) and no CV deaths in PBO group	1. Co-morbidities and CV risk factors not specified. 2. PBO group older (NS). Co-morbidities and CV risk factors not reported by study group 3. 35% reduced or discontinued treatment (men and women combined, study arm not specified) Adherence 83% overall while on treatment.	Frail elderly, but prevalence of CV risk factors and comorbidities not clear. Hypogonadism not required for study inclusion. <u>Strengths:</u> 1. Attempt to verify hospitalizations 2. Long study duration <u>Limitations:</u> 1. Unclear whether TRT MI death in study the same that the author reported? 2. Extremely small sample 3. Gender and study arm specific discontinuation not reported. 4. Limited generalizability: elderly frail/malnourished.
1. Copenhagen	1. 36 months	1. TRT n=134; PBO n=87	Clinical	<u>Deaths in TRT group</u>	1. Comorbidities other than	Younger group, all with

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
study, 1986 2. Denmark 3. Not stated	intervention but only 8 to 62 months follow-up (median 28 months) due to death and early stopping of study 2. Micronized-free T 200mg orally TID	2. IC: Hospitalized men with >50gm/day ethanol consumption for ≥ 2 years and recent diagnosis of cirrhosis without other known cause 3. EC: Unable to cooperate, HbsAg+, malignancy, Klinefelter's syndrome, recent treatment with anabolic-androgenic steroids 4. Mean age 53 (range 24-79)	assessment at entry and during follow-up. 1. No 2. Outcome assessors blinded, but not clear if cause of death determination was blinded	12 bleeding esophageal varices 1 acute MI 1 hepatic vein and 2 portal vein thrombosis <u>Deaths in PBO group</u> 5 bleeding esophageal varices 1 patient in TRT group discontinued due to acute MI, unclear if this was same patient who died from acute MI In 12% (TRT) and 18% (PBO), cause of death was unknown.	liver-related were not specified. CV risk factors not reported. 2. Unknown how well groups balanced in CV risk factors 3. 11% (TRT) and 9% (PBO) discontinuation rate. Study stopped early because of increased mortality seen at provisional comparison based on 184 patients.	advanced alcoholic liver disease. Hypogonadism not required for study inclusion. <u>Strengths:</u> 1. Long study duration (but highly variable length of follow-up) with reasonably good retention rate <u>Limitations:</u> 1. Very limited generalizability—all patients with alcoholic cirrhosis, likely to have atypical baseline hematologic and coagulation parameters. 2. Only deaths reported. Unclear if other CV-related events occurred, and unclear if cause of death was determined by blinded assessor. 3. Baseline androgen status and CV risk factors not described
1. Emmelot-Vonk, 2008 2. Netherlands 3. No (trial medication provided by Organon)	1. 6 months 2. 80mg T undecenoate orally BID	1. TRT n=120; PBO n=117 2. IC: Aged 60-80 years, T level <13.7nmol/L (50% percentile) 3. EC: MI or CVA past 6 months, symptomatic CHF; malignancy past 5 years or history of hormone-dependent tumor,	AEs information sought by questioning and examining patients 1. AEs and serious AEs were	"CV complaints:" 7 (6%) in TRT group, 3 (3%) in PBO group 5 serious AEs in TRT group, 10 in PBO group: 5 planned hospitalization, additional	1. Half with prior CV disease, including MI (>6 months prior), angina, HTN, or stroke. Diabetes and symptomatic CHF excluded. HTN not well-controlled—mean baseline SBP > 150 2. 17.5% smokers in TRT vs.	Older group, with high prevalence of pre-existing CV disease (including HTN), but diabetes and CHF excluded. <u>Strengths:</u>

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
		serious liver/renal disease, HCT $\geq$ 50%, epilepsy, migraine $>$ 1/month, diabetes, fasting glucose $>$ 6.9mmol/L, corticosteroid use past 6 months (except short courses or inhaled), use of testosterone/androgens, history of prostate hyperplasia, elevated PSA 4. Mean age 67	prespecified 2. Outcome assessor blinded	hospitalizations “not related to the study medication,” and 2 prostate CA	12.8% in PBO group. Mean SBP and DBP higher in TRT group. 3. 13% (TRT) and 12% (PBO) discontinuation rate . 7 in each group with no follow-up. Adherence: $>$ 90% of patients used at least 80% of medication. Blinding was effective.	1. AEs and serious AEs prespecified and ascertainment blinded 2. More broadly generalizable group than many other studies. <u>Limitations:</u> No detail given about nature of “CV complaints,” whether any verification was done, or which hospitalizations were CV-related
1. English, 2000 2. UK 3. Not stated (SKB provided patches)	1. 12 weeks 2. 5mg topical T nightly (two 2.5mg transdermal patches)	1. TRT n=25; PBO n=25 2. IC: Coronary artery disease ($>$ 70% stenosis of a major coronary artery by angiography, previous proven MI, or typical angina symptoms and a “double positive” [$>$ 1mm downsloping ST-segment depression with chest pain on exercise stress test] 3. EC: Elevated PSA or other contraindication to androgen therapy, left main (or equivalent stenosis), coronary or cerebrovascular event 4. Mean age 62	1. Only the treadmill results were prespecified 2. Treadmill analysis was blinded, not clear if adverse event assessment was blinded	1 patient in TRT group had MI (while awaiting coronary revascularization) 2 patients withdrawn from TRT arm: 1 with MI, one with elective coronary angioplasty	1. High risk population with known coronary artery disease 2. Baseline imbalances, with more PBO patients with HTN, DM, family history, current smoking (16 vs. 4%), hypercholesterolemia, use of ACE, diuretic, and Nicorandil (an anti-anginal), baseline time to 1mm ST-segment depressions 3. 12% discontinuation from TRT arm, for MI, skin irritation, and early coronary angioplasty	Younger group but highly enriched, all with pre-existing CV disease. Hypogonadism not required for study inclusion. <u>Limitations:</u> 1. Failed randomization with regard to risk of CV event? (apparent higher risk in PBO group) 2. Short trial duration 3. Unclear whether MI noted in safety section and in withdrawal description was same event
1. Hackett, 2014	1. 30 weeks plus 12 month open label	1. TRT n=97; PBO n=102	1. No	(Per Borst, table of adverse events	1. Elevated CV risk due to diabetes.	All patients with T2 diabetes, so at elevated CV risk.

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
2. UK 3. No	phase 2. TU 1000mg IM q 6 weeks x 3	2. IC: Men with diagnosed type II DM, 18-80 years with total T 8.1-12 nmol/l or free T 0.181-0.25 nmol/l (mild group) or total T <8.0 nmol/l or free T <0.18 nmol/l (severe group) with symptoms of hypogonadism 3. EC: Frailty, or serious comorbid conditions, hx of T replacement, prostate, breast or hepatic CA, abnormal DRE, severe BPH or PSA>4 or HCT>54%. 4. Mean age 61.6 years	2. Not stated	provided upon request)	2. TRT group older, higher BP, but BMI, cholesterol similar. CV and DM medications similar. 3. 96% completed 30-week trial	<u>Strengths:</u> Has some info on baseline CV risk—fairly balanced 2. Comprehensive table of AEs provided to Borst <u>Limitations:</u> 1. Table of AEs not available for review 2. CV events not prespecified or adjudicated. 3. Some imbalance in mean age
1. Hall, 1996 2. UK 3. Yes, supported by Schering Healthcare.	1. 9 months 2. 250 mg T enanthate IM monthly, increased after 6 months to q 2 weeks	1. TRT n=17, PBO n=18 2. IC: Receiving stable dose of routine anti-rheumatic therapy 3. EC: Contraindications to T 4. Median age 62 (range 34-79)	CV-related adverse events noted only as reason for withdrawal 1. No 2. NR	1 cerebrovascular accident and 1 hypertension in PBO arm	1. 89% current or ex-smokers. Otherwise, baseline CV risk not well characterized. 2. TRT group was older (NS, mean 64 vs. 59 yrs) and lower weight (p=0.05) 3. 12% discontinuation from TRT arm for osteomyelitis, pneumonia; 17% discontinuation from PBO arm, due to HTN, moved, cerebrovascular accident	Younger group, all with rheumatoid arthritis. High prevalence past/current smoking. Hypogonadism not required for study inclusion. <u>Strengths:</u> Relatively long study duration <u>Limitations:</u> 1. Only AEs resulting in withdrawal were described 2. Very small sample size 3. Limited generalizability—only rheumatoid arthritis patients

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
1. Hildreth, 2013 2. U.S. 3. Industry support limited to provision of study drug and matching placebo	1. 12 months 2. T gel 5 mg/day, titrated every 2 weeks to achieve T level of 400-550 ng/dL	1. TRT n=96; PBO n=47 2. IC: Community-dwelling men ≥60 years old with total T 200-350 ng/dL, stable medication regimen for ≥3 months, BMI <35, stable weight x 6 months, MMSE score ≥24. 3. EC: Evidence of active coronary disease on graded maximal exercise test; exercise-limiting conditions, abnormal DRE or prostate ultrasound, high PSA, AUA prostate symptoms score ≥20, history prostate/breast CA, uncontrolled HTN or DM, untreated dyslipidemia, HCT >52%, use of androgenic steroids or other drugs affecting T levels, other clinically important illnesses or conditions that could affect outcome measures. 4. Mean age 66.5 years each group	Serious adverse events (subject sought medical attention) were categorized into CV and non-CV based on review of adverse event reports and medical records by 2 study physicians blinded to treatment assignment 1. No 2. Yes	Only serious adverse events listed <u>TRT group:</u> 1 acute coronary syndrome (MACE) 2 syncope/presyncope <u>PBO group:</u> 3 acute coronary syndrome (MACE) 4 arrhythmia 1 aortic aneurysm 2 syncope/presyncope 1 death in PBO group—not specified whether was CV-related	1. BP well controlled, fasting glucose normal, lipid profiles good; mean number of chronic conditions <1 2. No notable imbalances 3. 14% discontinuation with LTFU overall—no major imbalance between groups. Treatment adherence similar among groups, 85-88%	Unusually healthy group of older men without pre-existing coronary disease <u>Strengths:</u> 1. Serious CV events were verified through medical record review by 2 blinded physicians 2. Long study duration with fairly good/balanced retention <u>Limitations:</u> 1. Limited generalizability due to many exclusion criteria, unusually healthy cohort

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
1. Ho, 2011 2. Malaysia 3. Yes, supported by Bayer Schering	1. 48 weeks 2. T undecanoate 1000mg IM at weeks 0, 6, 18, 30, and 48	1. TRT n=60; PBO n=60 2. IC: Age 40-70 years, total T <12 nmol/L and total Aging Male Symptoms (AMS) score ≥ 27 , PSA <4ng/ml 3. EC: HbA1c >8%, clinical hypo or hyperthyroidism; HCT >55%, prostate or male mammary CA, liver tumors, other significant medical conditions (American Society of Anaesthetists score >3), psychosis, schizophrenia, or manic depression, or sleep apnea, hypersensitivity to active substance or on medication interfering with T metabolism or recent T treatment 4. Mean age 53 (range 40-70)	Safety monitored by scheduled assessment and self-report of adverse events. 1. No 2. Unblinded: codes were revealed when a serious adverse event occurred	<u>TRT group:</u> 1 death (MI) 1 withdrawal for chest pain <u>PBO group:</u> 1 death (MI) 1 withdrawal for chest pain Both patients with MI had history of ischemic heart disease. Both chest pain withdrawals refused further investigation	1. Relatively younger and lower risk group for CV events (significant medical conditions excluded) 2. Baseline CV risks were somewhat unbalanced with TRT group having higher baseline risk: heavier, more HTN and higher BP at baseline, higher diabetes prevalence, more history of coronary artery disease, AMS score higher (NS) 3. 7% (TRT) and 4% (PBO) discontinuation rate	Overall, younger and healthier group. <u>Strengths:</u> Relatively long study duration <u>Limitations:</u> 1. Randomization failure?—groups not well balanced for risk factors. 2. Only deaths and withdrawals described, not other AEs, and no adjudication or medical verification of cause of “chest pain”
1. Hoyos, 2012 2. Australia 3. Yes, Bayer Schering	1. 18 weeks 2. T undecanoate 1000 mg at 0, 6, and 12 weeks All underwent weight loss program	1. TRT n=33; PBO n=34 2. IC: Aged 18+ years, male, BMI >30kg/m ² , and apnea hypopnea index >10. 3. EC: uncontrolled concurrent medical or psychiatric illness, CPAP need or more severe sleep apnea, medication altering androgen action sleep or body weight, contraindications to T or injection, desire for paternity next 12 months or in sport banning testosterone, HCT > 52%, PSA, > 4 ng/ml, in another drug trial past 30 days	Clinical assessments at 0, 6, 12, 18 weeks. Safety follow-up visit at 26 weeks. 1. No 2. “Randomization code not broken until all data were collected and database locked.”	1 cardiac event in TRT group, 0 in PBO group	1. Pre-existing CV disease in 3 participants (2 in PBO, 1 in TRT) 2. CV/metabolic risk factors well balanced except waist circumference (significantly higher in PBO group) 3. 21% (TRT) and 18% (PBO) discontinuation rate. Only 1 withdrawal for AE in each group.	Younger, healthier group with lower baseline CV risk. Hypogonadism not required for study inclusion. <u>Strengths:</u> Maintained blinding <u>Limitations:</u> 1. “Cardiac event” not specified or verified

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
		4. Mean age 48 (TRT), 49 (PBO)				
1. Jones, 2011 2. Europe (multiple countries) 3. Yes, sponsored and funded by ProStrakan.	1. 6 months (+ 6 months open label extension) 2. 60mg T gel topically (2% gel) daily	1. TRT n=108, PBO n=112 2. IC: Men aged 40+ years with total T ≤ 11 nmol/L or free T ≤ 255 pmol/L, 2+ symptoms of hypogonadism, and Type 2 diabetes and/or metabolic syndrome 3. EC: T treatment past 6 months, hormone therapy past 3 months, prostate/breast CA, abnormal prostate exam, severe BPH or elevated PSA. 4. Mean age: 60	AEs elicited each visit by a “non-leading question” 1. No 2. “All individuals involved in monitoring, data management, or other study aspects were blinded to treatment”	CV AEs occurred more commonly with PBO than TRT (10.7% vs. 4.6% p=0.095) 1 CV death (PBO)	1. Elevated CV risk due to DM and metabolic syndrome 2. Groups balanced for reported cardiac risk factors 3. 29% discontinuation from RCT phase, not broken out by study arm. “Safety population comprised all randomized patients who received ≥ 1 dose of study medication.” Nine patients lost to follow-up.. 18 withdrawals due to AEs in TRT group and 12 in PBO group. Substantial cross-over occurred (protocol violations in 125 participants)	Younger group but enriched for CV risk <u>Strengths:</u> Larger study, groups balanced for reported CV risk factors <u>Limitations:</u> 1. CV AEs not further specified 2. High drop out and cross-over rate could create bias. Unclear what drug was actually being taken among those with CV-related AEs. 3. AE numbers not given, only %’s—numbers back-calculated by Xu.
1. Kalinchenko, 2010 2. Russia 3. Yes, supported by Bayer Schering	1. 30 weeks 2. 1000 mg T IM at 0, 6, and 18 weeks All received diet and physical activity education	1. TRT n=113, PBO n=71 2. IC: Men aged 35-70 years with metabolic syndrome and total T <12.0 nmol or free T <225 pmol. 3. EC: participation in another clinical study, incapable of consenting or complying, serious organic or mental disease, known or suspected prostate/breast CA, hepatic tumors or disease, renal disease, HCT>55%, hypersensitivity to study drug.	Safety data based on reasons for discontinuation of intervention 1. No 2. NR	1 angina case and 1 MI death in PBO group	1. Relatively high risk for CV disease due to metabolic syndrome. 23-25% current smokers, 28-34% T2DM, 86-89% on BP lowering drugs 2. Baseline characteristics balanced. 3. 7% (TRT) and 8% (PBO) discontinuation rate. 1 LTFU in TRT group	Relatively high-risk group but unknown prevalence of pre-existing CV disease <u>Strengths:</u> Good retention <u>Limitations:</u> No detail on CV-related outcomes or whether there were

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
		4. Mean age 51.6 (TRT), 52.8 (PBO)				other CV AEs in those not discontinuing treatment
1. Kaufman, 2011 2. U.S. 3. Yes, funded by Abbott	1. 182 days 2. Topical T gel: 1.25, 2.5, 3.75, and 5g daily Dose adjustments on days 14, 28, and 42.	1. TRT n=214; PBO n=37 2. IC: Men ages 18-80 years with total T <300 ng/dL and BMI between 18 and 40 kg/m ² 3. Impaired liver function, prostate symptoms, PSA > 2.5 ng/ml, abnormal prostate exam, untreated prolactinoma, known or suspected prostate or breast CA, eczema, psoriasis, sleep apnea, multiple sclerosis, skin disease, heart failure, HCT>48% or HGB >16 g/dL. 4. Mean age 53.5 (TRT) and 55.5 (PBO)	ADs and vital signs recorded throughout study. ECGs at baseline and day 182. 1. No 2. NR	19 CV-related events were recorded in 23 patients: <u>TRT group:</u> cardiac failure congestive, cardiomyopathy, myocardial infarction, palpitations, tachycardia, chest pain, edema peripheral, pitting edema, BP decreased, BP increased, ultrasound Doppler abnormal, joint effusion, dizziness, syncope vasovagal, hypertension, malignant hypertension, and phlebitis <u>PBO group:</u> presyncope, nocturia Table notes 11 vascular treatment emergent AEs and 6 HTN cases in TRT group, 0 in PBO group	1. Low-risk group except mean BMI>30. 2. Mean BP balanced at baseline. No information on other CV risk factors. 3. 28% (TRT) and 30% (PBO) discontinuation; 25 withdrawals due to AE in TRT group (most for PSA increases). 5 LTFU in TRT group and 2 in PBO group. Subjects included in the safety sample were those allocated to treatment having at least one dose of study medication	Hypogonadal but otherwise healthy men. Younger group. <u>Limitations:</u> 1. High number of discontinuations in both groups. 2. Difficult to be confident actual number of CREs—discrepancies between text and tables. Xu used conservative estimate (from table). Text implies that other CREs occurred in both the TRT and PBO groups, but not entirely clear. Author did not respond to inquiries. 3. No relation described between dose and CV-related AEs.

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
				Text notes severe TEAEs in 11/234 subjects the TRT group and none in the PBO group—list MI and tachycardia. 16 different severe TEAEs are listed.		
1. Kenny, 2004 2. U.S. 3. No	1. 12 weeks 2. 200 mg T enanthate IM every 3 weeks	1. TRT n=6; PBO n=5 2. IC: Men aged 65+ years with bioavailable T level <128 ng/dl and mild-moderate cognitive impairment 3. EC: History of prostate CA, nodule or elevated PSA, HGB.16.5 gm/dL, vitamin E use 4. Mean age 81 (TRT); 78 (PBO)	Safety ascertainment not specified 1. No 2. No	1 cerebral vascular accident in PBO group	1. 2 with history of heart disease in TRT group, 1 in PBO group, 2 in each group on cholesterol-lowering therapy; 1 with HTN in TRT group, 2 in PBO group 2. Very small sample, groups not entirely balanced in cardiac history and risk factors. 3. No discontinuations	Very elderly, with cognitive decline <u>Limitations:</u> 1. Extremely small sample 2. Short duration
1. Kenny, 2010 2. U.S. 3. No	1. 16 months 2. 5mg/day Androgel 1%	1. TRT n=69; PBO n=62 2. Men 60+ years with at least one of five frailty criteria and BMD T-score hip < -2.0. 3. EC: PSA>6.5 or hix prostate CA, bone metabolism disease, hx pituitary disease, sleep apnea, heavy alcohol use, use of androgen or estrogen in preceding year, use of calcitonin or bisphosphanates, metastatic or advanced CA, current chemo or	Safety ascertainment not specified 1. No 2. No	(Per Borst, table of AEs provided upon request) Withdrawals: <u>TRT:</u> 1 CHF 1 leaky valve 3 deceased (no further detail) <u>PBO:</u> 1 open heart surgery 1 MI	1.15% with HTN, 16% (TRT) and 22% (PBO) with CAD 2. Baseline CAD prevalence higher in PBO group (p 0.15) 3. 32% withdrawal in TRT group, 44% in PBO group at 16 months. Overall adherence 54% at 12 months, 56% at 16 months.	Older, frail men. <u>Strengths:</u> Long study duration <u>Limitations:</u> 1. High discontinuation rate, with some imbalance by study arm 2. More with baseline coronary disease in PBO group (but not statistically significant)

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
		radiation tx., advanced liver or renal disease, Hgb>16.5 g/dL.		1 aneurysm 1 CHF 7 deceased (no further detail)		
1. Legros, 2009 2. 14 European countries 3. Yes, Schering-Plough	1. 12 months 2. 80, 160, or 240 mg/day oral T undecanoate	1. TRT n=78 (80mg), 82 (160mg), 77 (240mg); PBO n=79 2. IC: Men age 50+ years, BMI between 18 and 34 kg/m ² with symptoms of androgen deficiency (ADAM questionnaire) and free T <0.26 nmol/L 3. EC: Prostate/breast CA, abnormal prostate exam, lower urinary tract symptoms, PSA >4 ng/ml, cause of androgen deficiency other than aging, androgen/anabolic steroid treatment past 2 years, hyperprolactinemia or treatment with prolactin-lowering drugs, history polycythemia or HCT>50%, severe sleep apnea, uncontrolled HTN, insulin-dependent DM, clinically significant baseline lab values, untreated endocrine disorders, liver or renal disease, psychiatric disease, history or presence of other disorders such as clinically significant CV, cerebrovascular, or hematological disorders which could compromise participation, medication that could interfere with T 4. Mean age 58.7	Follow-up included questioning patients about adverse events, and exam—unclear frequency 1. No 2. NR	1 TRT group death due to arrhythmia and hypertrophic cardiomyopathy (not related to study drug as judged by investigator) 1 TRT group death 3 months after end of treatment due to cardiac arrest (not related to study drug as judged by investigator) 19 other patients with “serious AEs” not otherwise specified (2 in placebo group)—higher proportion in TRT group	1. Apparently healthy group based on exclusion criteria but no information on baseline CV risk factors. 2. Groups balanced in general but minimal info on CV risk factors 3. 25% discontinuation rate without marked difference between groups in rate or reason for discontinuation.	Younger group, many exclusions suggest healthier participants <u>Strengths:</u> 1. Large study of long duration 2. Fairly broadly generalizable to younger, healthier populations (although non-US) <u>Limitations:</u> 1. Only deaths reported by treatment group. Higher proportion of serious AEs in TRT group compared to PBO not further specified whether any were CV-related. 2. Fairly high discontinuation rate (but balanced) 3. Minimal information on baseline CV risk of group
1. Malkin, 2006	1. 12 months	1. TRT n=37, PBO n=39	Safety monitoring	TRT group:	1. Elevated cardiac risk due to	All patients with stable CHF—

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
2. UK 3. No (patches provided by Watson)	2. 5mg transdermal T patch daily	2. IC: Ambulatory males aged 18+ years with stable CHF >6 months and impaired exercise tolerance and at least moderate LV systolic dysfunction on echo. 3. EC: Use of sex hormones, abnormal PSA, exercise limitation due to non-cardiac cause, malignancy. 4. Mean age 63.1 (TRT), 64.9 (PBO)	plan not described 1. No 2. No	1 stroke 1 unstable angina 1 presyncope 2 exacerbation CHF <u>PBO group:</u> 2 new arrhythmia 1 sudden death 1 presyncope 2 exacerbation CHF	CHF 2. Randomization stratified by ischemic vs. non-ischemic etiology of heart failure—balanced across groups. Mean resting pulse higher in TRT group, otherwise fairly balanced. More smokers (10) in TRT group than PBO (6) but NS. Slightly more DM in PBO group (8 vs.5), also NS. 3. 49% (TRT) and 41% (PBO) discontinuation	elevated risk for CV events Most participants without hypogonadism: only 24% with baseline T below normal range <u>Limitations:</u> 1. No significant change in either HCT or PSA—lower dose? 2. Very high drop-out rate—many due to skin reactions.
1. Marin, 1993 2. Europe (country?) 3. Yes, Besins-Iscovesco	1. 9 months 2. Testogel 125 mg topically daily ; second group with 125 mg dihydrotestosterone topically daily	1. 31 men total (3 groups) 2. IC: Men >40 years and abdominally obese (waist-hip ratio>0.9), BMI <35 kg/m ² , total T < 20nmol/L and <2 kg weight change in past 2 months. 3. EC: Prostate enlargement and/or elevated PSA. Clinical DM or HTN requiring drug treatment, suspected alcohol abuse 4. Mean ages: 56.7 (TRT 1), 57.8 (TRT 2), 58.5 (PBO)	Monthly history and physicals 1. No 2. No	1 splanchnic venous thrombosis in TRT group (had had similar problems prior to study)	1. DM and HTN excluded but all with increased waist-hip ratio, increasing CV risk 2. TRT groups were slightly heavier than PBO but slightly younger. No major imbalances. 3. 4 discontinued, 3 for “occupational reasons”	Younger group with abdominal obesity, but major risk factors of DM and HTN excluded, others not described. Low-normal baseline T levels included. <u>Limitations:</u> 1. Very small sample 2. Only withdrawals were noted, not all AEs.
1. Merza, 2006 2. UK 3. Yes, Ferring Pharmaceuticals	1. 6 months (with 6 month open label extension) 2. 5mg/day transdermal patch	1. TRT n=20; PBO n=19 2. IC: Men >40 years with total testosterone <10nmol/L presenting to a male sexual dysfunction clinic	Baseline and f/u visits at 1, 3, 6, 9, 12 months with exam and labs. 1. No	1 patient withdrawal in PBO group due to angina	1. Younger group, DM and uncontrolled HTN or cardiac disease excluded. Other CV risk factors not described. 2. TRT group older, other risk factors not described	Younger, apparently healthier group. Little information on CV risk factors but DM and uncontrolled HTN excluded. <u>Limitations:</u>

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
		3. Prostate/breast CA, BPH, PSA>2.5, uncontrolled HTN, DM, uncontrolled cardiac disease, renal failure, liver disease, HCT>50%, history of aggressive behavior, alcohol or drug abuse, anticoagulant therapy, testosterone replacement 4. Mean age 63 (TRT) and 59.7 (PBO)	2. NR		3. In RCT phase, 1 PBO withdrawal. in open-label extension, 3 TRT and 1 PBO withdrawal due to elevated HCT and 1 TRT and 2 PBO withdrawals with no specific cause	1. Only withdrawal information given. 2. Small study, with little description of baseline CV risk factors.
1. Nair, 2006 2. U.S. 3. No, but various consultant fees etc.	1. 2 years 2. 5 mg transdermal T patch daily	1. TRT n=30; PBO n=31 (only men included) 2. IC: Age 60+ years, bioavailable testosterone < 3.6 nmol/L and DHEA level < 2.6 micromol/L 3. EC: Clinically important coexisting illnesses or conditions that could have an effect on outcomes measures, elevated PSA or abnormal prostate exam. 4. Mean age 66.2 (TRT), 67.1 (PBO)	"Adverse effects were assessed" 1. No 2. No	5 CV AEs in testosterone group, 5 in PBO group.	1. Older men, but many co-existing illnesses and conditions appear to have been excluded. 2. Groups fairly well balanced for age, BMI, lipids, fasting glucose 3. 10% (TRT) and 0% (PBO) discontinuation 3 LTFU in TRT group, 1 in PBO group. 24/30 completed on protocol in TRT group and 28/31 in PBO group	Generally healthy older men with low or low-normal testosterone. <u>Strengths:</u> 1. Long duration 2. Tables of adverse events included <u>Limitations:</u> 1. Exclusion criteria not clearly elucidated. 2. Details of CV AEs not provided 3. Fairly high proportion of discontinuation and treatment cross-overs
1. Sih, 1997 2. U.S.	1. 12 months 2. 200 mg T cypionate IM q 14-	1. TRT n=17, PBO n=15 2. IC: Men 50+ years; community dwelling; Mini mental status	Not specified. 1. No	1 TRT group withdrawal for uncontrolled A fib with CHF	1. Medical conditions (TRT/PBO): HTN 4/2, DM 2/1, hypercholesterolemia 2/1, atrial fib 2/0, depression 2/0, s/p	Older group, with fairly low prevalence of CV-related disease and risk factors.

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
3. Funding source not stated	17 days	exam score >23; normal liver function tests, PSA, HCT; bound testosterone level ≤ 60 ng/dL. 3. EC: Significant prostate disease, COPD, CHF or angina 4. Mean age 65 (TRT), 68 (PBO)	2. NR	1 PBO group withdrawal due to stroke	CABG no angina 0/1, on aspirin 7/4. TRT group slightly older. 2. Low numbers, but slightly more TRT than PBO with HTN, DM, A fib. 3. TRT group: 14/15 completed 6 months, 12/15 completed 12 months; 1 LTFU before 6 month eval and 3 withdrawals for HCT >51% PBO group: 14/17 completed 6 months, 10/17 completed 12 months. 1 LTFU before 3 month eval, 1 LTFU before 9 month eval.	<u>Limitations:</u> 1. Very small study 2. Only AEs associated with withdrawals reported
1. Snyder, 2001 2. U.S. 3. Not stated. ALZA Corp. provided testosterone patches.	1. 36 months 2. Testoderm scrotal patch 6mg/day	1. TRT n=54; PBO n=54 2. IC: Men >65 years with baseline T <16.5 nmol/L 3. EC: Diseases or medication known to cause hypogonadism or that testosterone could exacerbate such as prostate CA or BPH. 4. Mean age: 73 both groups	Obtained history of clinically apparent CV events q 6 months and confirmed events with hospital records: events included MI, CABG, arrhythmia, and vascular events such as stroke and peripheral embolism 1. Yes 2. NR	<u>Testosterone-treated group:</u> 2 MI 2 CABG 3 arrhythmia 2 other vascular events TOTAL 9 <u>PBO-treated group:</u> 1 MI 2 CABG 1 arrhythmia	1. No major diseases as part of IC but EC also not extensive--not clear what co-morbidities were present in study population or by study arm 2. LDL higher in PBO group (NS). Age balanced. 3. 7% (TRT) and 15% (PBO) discontinuation	Older men with low-normal testosterone. <u>Strengths:</u> CV events were specifically sought, prespecified and verified through medical records, but not clear whether blinded. <u>Limitations:</u> 1. Inclusion and exclusion criteria not specifically listed. Baseline CV risk and health status of study population not

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
				1 other vascular event TOTAL 5 RR 1.8 (0.7-5.0)		clear. 2. Some difference in discontinuation rate—possibly informative censoring
1. Spitzer, 2012 2. U.S. 3. No	1. 14 weeks 2. T 1% gel 10 g, increased to 15 mg after 2 weeks if serum T <17.35 nmol/L (all participants also got sildenafil)	1. TRT n=70, PBO n=70 2. IC: Men aged 40-70 years, erectile dysfunction, serum T <11.45 nmol/L or free T <50 pg/mL 3 EC: Prostate /breast CA, penile abnormalities, lower urinary tract symptoms, untreated sleep apnea, major psychiatric disease, HCT >50%, elevated creatinine or PSA, HbA1C ≥ 8.5%, BP> 160/100, MIR or stroke in past 6 months, uncontrolled heart failure, using androgens or nitrates 4. Mean age 55.1 (TRT), 54.6 (PBO)	Adverse events were ascertained at each visit. 1. No 2. "Investigators and study staff did not have access to the randomization table"	4 (6%) with CV AE in TRT group, 2 (3%) in PBO group	1. 21-22% with DM, 40-45% with HTN, 46-50% with CV disease, mean BMI 32. 2. Groups fairly balanced. TRT with NS higher proportion with CV disease and HTN. 3. 14% (TRT) and 17% (PBO) discontinuation; with 5 LTFU (TRT) and 11 LTFU (PBO). Adherence 90% TRT, 89% PBO	Younger men, but with high baseline risk for CV event (half with pre-existing CV disease) Trial was of sildenafil and testosterone combined or sildenafil alone. <u>Limitations:</u> 1. Short trial duration 2. No detail given on CV AEs 3. Both TRT and PBO groups received drug that also has CV effects.
1. Srinivas-Shankar, 2010 2. U.K. 3. Yes, funded by Bayer Schering	1. 6 months 2. 50mg/day 1% transdermal T gel. Dose adjusted at 3 months.	1. TRT n=138, PBO n=136 2. IC: Men aged 65+ years, community-dwelling, meeting 1+ criteria for frailty and T ≤12 nmol/L 3. EC: Prostate CA, BPH, high PSA, chronic renal impairment or active liver disease, moderate-severe PVD, CHF (NYHA class	1. No 2. "Monitoring clinician" remained blinded	<u>TRT group</u> 1 pulmonary embolism 1 heart failure 1 abdominal aneurysm 1 constrictive pericarditis <u>PBO group</u> 1 acute MI	1. Average of 2.5-2.6 comorbidities, not otherwise specified 2. Age, weight, BMI, frailty scores, cholesterol levels balanced 3. 11% discontinuation overall, study arm not specified. Compliance assessed by self-	Frail and "intermediate frail" elderly men with low to borderline-low testosterone. <u>Strengths:</u> 1. Large study, with good balance of comorbidities in study arms 2. Maintained blinding of monitoring physicians 3. Assessed medication

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
		>1), angina requiring nitrates >once a week, untreated sleep apnea, major psychiatric illness, medications interfering with sex steroid metabolism, stroke with persistent weakness, active muscle/joint disease, cognitive impairment. 4. Mean age 74 (both groups)		1 death from ruptured AAA	report. Over 85% used more than 95% of study medication, with no significant differences between groups	compliance—no major imbalances 4. Long study duration, with reasonable retention <u>Limitations:</u> 1. No detail on discontinuations by study arm 2. Limited description of CV risk factors
1. Svartberg, 2004 2. Norway 3. No	1. 26 weeks 2. 250 mg T enanthate IM q 4 weeks	1. TRT n=15; PBO n=14 2. IC: Men aged 54-75 years with moderate-severe COPD, stable medical condition 3. EC: Asthma, malignancies, cardiac impairment, hepatic or endocrine disease 4. Mean age 64.5 (TRT, range 54-74); 67.5 (PBO, range 56-75)	Potential adverse events were recorded every fourth week. 1. No 2. NR	1 PBO patient died of probable MI (sudden death).	1. High prevalence past/current smoking due to COPD but active cardiac and endocrine disease excluded. 2. Control group slightly older (NS) and higher BMI (NS). Smoking balanced. Other CV risk factors not described. 3. All completed to week 12, 7% discontinuation by week 26, study arm not specified	Men without known pre-existing CV disease but at elevated risk due to heavy smoking history (COPD). Hypogonadism not required for study inclusion. High baseline T levels (low T not a criterion for study inclusion) <u>Limitations:</u> 1. Very small sample 2. Limited description of CV risk factors 3. Limited generalizability—only men with COPD included
1. Svartberg, 2008 2. Norway 3. Yes, Bayer Schering	1. 1 year 2. 1000mg T undecanoate at 0, 6, 16, 28, and 40 weeks	1. TRT n=19; PBO n=19 2. IC: Men aged 60-80 with testosterone $\leq$ 11.1 nmol/L 3. EC: Malignancy, unstable ischemic or congestive heart	Exams at baseline and 1 year 1. No 2. NR	1 death from cardiac arrhythmia in TRT group	1. 18-22% smokers, 4/19 (TRT) and 5/19 (PBO) with coronary heart disease, 1 in each group with T2DM, 4/19 (TRT) and 7/19 (PBO) with HTN 2. Groups fairly balanced for	Older group, but fairly low prevalence of coronary heart disease, DM, HTN, and smoking. <u>Strengths:</u>

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

1. Author, year 2. Setting 3. Industry funding?	1. Duration 2. Drug formulation, dose, route	Participants: 1. Sample size 2. Inclusion criteria (IC) 3. Exclusion criteria (EC) 4. Mean age 5. Initial T level	Ascertainment of CV-related events 1. Pre-specified? 2. Blinded?	CV-safety results	Methodological considerations: 1. Baseline CV risk status of participants 2. Randomization/balance of CV risk factors across study arms 3. Discontinuation, adherence, and loss to follow-up	DEPI Comments, Strengths/Limitations
		disease, epilepsy, migraine, HCT>50% or HGB >17gm/100ml, PSA>4, creatinine>130mmol/L, ALT >100 U/>, allergy to study medication, warfarin treatment, participation in other studies. 4. Mean age 69 both groups			CV risk factors. 3. 1 withdrawal without reason from each study arm and 1 cardiac death in TRT group	Long study duration <u>Limitations:</u> 1. Very small sample, but groups fairly well balanced for CV risk factors 2. Only deaths reported, unclear if other CREs occurred
1. Tan, 2013 2. UK, Malaysia 3. Yes, Bayer Schering supported	1. 48 weeks 2. T undecanoate 1000 mg IM	1. TRT n=60, PBO n=60 2. IC: Total T ≤ 12 nmol/L X 2, at least mild symptoms of hypogonadism, PSA <4 ng/mL 3. EC: Uncontrolled DM, hypo/hyperthyroidism, Hct > 55%, prostate CA or CA of mammary gland, history of liver tumours, other significant medical or psychological conditions, medications that interfere with T metabolism, sleep apnea or T treatment within 6 months 4. Median age: 53.1 years (PBO), 53.8 years (TRT)	1. No 2. No	TRT group: 1 death from MI, 1 withdrawal due to chest pain PBO group: 1 death from MI, 1 withdrawal due to chest pain	1. Significant medical conditions excluded, including CV disease and uncontrolled DM. 2 BMI, waist circumference, and DBP significantly higher in TRT arm 3. 56/60 TRT and 58/60 PBO completed study	Average risk middle-aged men <u>Strengths:</u> Moderately long study duration with good retention <u>Limitations:</u> 1. Significant imbalances in baseline CV risk factors

Abbreviations: AE=adverse event; BPH=benign prostatic hypertrophy; CA=cancer; CABG=coronary artery bypass graft; CHF=congestive heart failure; CVA=cerebrovascular accident; ESRD=End stage renal disease ; HCT=hematocrit; HGB=hemoglobin; HTN=hypertension; LTFU=loss to follow-up; MI=myocardial infarction; NYHA=New York Heart Association; NR=not reported; NS=non-significant; PBO=placebo; PSA=prostate-specific antigen; PVD=peripheral vascular disease; T=testosterone; TRT= testosterone replacement therapy

References: (Amory et al., 2004; Aversa et al., 2010; Basaria et al., 2010; Borst et al., 2014b; Brockenbrough et al., 2006; Caminiti et al., 2009; Chapman et al., 2009; 1986; Emmelot-Vonk et al., 2008; English, Steeds, Jones, Diver, & Channer, 2000; Hackett et al., 2014; Hall, Larbre, Spector, Perry, & Da Silva, 1996; Ho et al., 2012; Hoyos et al., 2012; Jones et al., 2011; Kalinchenko et al., 2010; Kaufman et al., 2011; Kenny, Fabregas, Song, Biskup, & Bellantonio, 2004; Kenny

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

et al., 2010; Legros et al., 2009; Malkin et al., 2006; Marin et al., 1993; Merza et al., 2006; Nair et al., 2006; Sih et al., 1997; Snyder et al., 2001; Spitzer et al., 2012; Srinivas-Shankar et al., 2010; Svartberg, Aasebo, Hjalmsen, Sundsfjord, & Jorde, 2004; Svartberg et al., 2008; Tan et al., 2013;).

7.4 APPENDIX D: LISTING OF CV EVENTS IN RCTs SELECTED FOR ANALYSIS OF CV EVENTS (FOUR ORAL TRT TRIALS SHADED)

	Event	T	P	Comments T= testosterone treated group, P = placebo (Oral TRT trials shaded)
Amory 2004	cerebral hemorrhage	1	0	
Aversa 2010	acute myocardial infarction	0	1	
Borst 2014	syncope due to bradycardia	0	1	
Caminiti 2009	worsening of heart failure – hospitalization	1	1	
	worsening of heart failure – no hospitalization	1	0	
Ferrando 2002	none	0	0	Authors confirmed to Borst et al that no CV events occurred
Hackett 2013	Worsening of atrial fibrillation	1	0	Authors supplied events table to Borst et al.
Hall 1996	hypertension	0	1	
	cerebrovascular accident	0	1	
Ho 2011	died of myocardial infarction	1	1	
Hoyos 2012	unspecified CV event	1	0	
Kalinchenko 2010	angina	0	1	
	died of myocardial infarction	0	1	
Kenny 2004	cerebrovascular accident	0	1	
Sih 1997	atrial fibrillation with congestive heart failure	0	1	
	stroke	0	1	
Svartberg 2004	death due to probable myocardial infarction	0	1	
Svartberg 2008	death due to cardiac arrhythmia	1	0	
Sheffield-Moore 2011	none	0	0	Authors confirmed to Borst et al that no CV events occurred
Tan 2013	Myocardial infarction	2	2	
Basaria 2010	acute coronary syndrome and chest pain	2	0	Several subjects had CV events of procedures that were attributed to prior conditions and were not counted.
	syncope	2	1	
	myocardial infarction	2	0	
	angioplasty and coronary artery bypass	1	0	
	peripheral edema	5	0	
	ectopy on ECG	1	0	
	left ventricular strain pattern during exercise test	1	0	
	ST segment depression during exercise testing	1	0	
	hypertension and atrial fibrillation	1	0	
	hypertension	2	1	
	chest pain	1	0	
	atrial fibrillation	2	0	
	stroke	1	0	
	tachycardia with fatigue	1	0	
	tachycardia	0	1	
death of suspected myocardial infarction	1	0		
exacerbation of heart failure	1	0		
arrhythmia and ectopy on ECG before exercise test	0	1		
carotid bruit and plaque identified by ultrasound	0	1		
Brockenbrough 2006	CV events involving death	3	1	CV death in the P group was from stroke
	CV events not involving death	4	2	
	access thrombosis	2	6	

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

	Event	T	P	Comments T= testosterone treated group, P = placebo (Oral TRT trials shaded)
Glintborg 2013	none	0	0	Authors confirmed to Borst et al that no CV events occurred
Hildreth 2013	Acute coronary syndrome Arrhythmia Aortic aneurysm Syncope/presyncope	1 0 0 2	3 4 1 2	
Jones 2011	died of myocardial infarction unspecified CV events	0 5	1 11	Unspecified CV events are not given as a number but may be inferred from percentages reported.
Kaufman 2011	died of myocardial infarction unspecified CV events	1 10	0 0	
Kenny 2010	cerebrovascular accident shortness of breath death due to CAD and alcohol chest pain acute myocardial infarction coronary bypass surgery diaphoresis and disorientation death – unexplained MI with coronary bypass surgery death due to cerebrovascular accident heart failure exacerbation of heart failure syncope angioplasty death due to arrhythmia transient ischemic attack ECG suggest leaky heart valve ascending aortic aneurysm death due to transient ischemic attack and infection admission for chest tightness	1 1 1 0 0 2 0 0 0 1 2 1 2 1 0 1 0 0 0 0 1	3 1 0 2 2 1 1 1 0 2 0 1 0 1 0 1 1 1 1	CV adverse event table supplied by authors to Borst et al.
Marin 1993	splanchnic venous thrombosis	1	0	Identification of treatment arm supplied by authors to Xu et al.
Spitzer 2012	CV events requiring hospitalization CV events not requiring hospitalization	1 3	0 0	
Srinivas-Shankar	acute myocardial infarction death due to ruptured aneurysm angina pulmonary embolism died of constrictive pericarditis abdominal aneurism with surgery heart failure	0 0 1 1 1 1 1	1 1 0 0 0 0 0	
English 2000	myocardial infarction (MI) early elective coronary angioplasty MI while awaiting coronary revascularization	1 1 1	0 0 0	1 st 2 events are listed as withdrawals; the 3 rd event is listed under “Safety” and is assumed to be one of the 1 st two events.

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

	Event	T	P	Comments T= testosterone treated group, P = placebo (Oral TRT trials shaded)
Malkin 2006	arrhythmia stroke unstable angina hospitalized	0 1 1 2	2 0 0 2	
Merza 2005	angina	0	1	
Nair 2006	ascending aorta dilation CAD stent placement chest pain coronary artery bypass graft coronary artery disease ventricular ectopic beats hypotension phlebitis triple bypass surgery	1 0 0 1 2 1 0 1 1	2 1 1 0 0 0 1 1 0	
Snyder 2001	myocardial infarction coronary bypass graft surgery arrhythmia vascular events	2 2 3 2	1 2 1 1	
Chapman 2009	death from myocardial infarction hospitalization for myocardial infarction	1 0	0 1	1 chest pain in P group not counted
Copenhagen study 1986	death from bleeding esophageal varices death from acute myocardial infarction thrombosis	12 1 3	5 0 0	
Emmelot-Vonk 2008	CV complaints	8	3	
Legros 2009	death from arrhythmia and cardiac enlargement	1	0	

Source: Borst et al., 2014, Additional Online File 3

7.5 APPENDIX E: CHARACTERISTICS OF TESTOSTERONE REPLACEMENT THERAPY (TRT) TRIALS REPORTING BOTH SERUM TESTOSTERONE AND DIHYDROTESTOSTERONE (DHT) CONCENTRATIONS BEFORE AND AFTER TREATMENT

Author/Year	Study type	Mode	Dose	Duration	Age	Subjects in TRT group	Serum T at entry	Health status
Amory 2004 [32]	RCT	i.m.	100 mg TE/week	36 months	71 ± 4 (SD)	24	302 ± 48 (SD) ng/dL	hypogonadal
Arver 1997 [65]	open-label	i.m.	266 mg TE/26 days	3 weeks	58 ± 10 (SD)	27	121 ± 100 (SD) ng/dL	hypogonadal
Bhasin 2012 [66]	RCT	i.m.	125 mg TE/week	5 months	40 ± 7 (SD)	12	519 ng/dL (mean)	eugonadal
Borst 2014 [34]	RCT	i.m.	125 mg TE/week	12 months	69.2 ± 8.0 (SD)	31	264 ± 92 (SD) ng/dL	hypogonadal
Lakshman 2010 [67]	RCT	i.m.	125 mg TE/week	5 months	65.6 ± 4.3 (SD)	11	581 ± 168 (SD) ng/dL	eugonadal
Raynaud 2008 [68]	open-label	i.m.	250 mg TE/3 weeks	12 months	41.8 ± 12.4 (SD)	32	43 ng/dL (mean)	hypogonadal
Shubert 2003 [69]	open-label	i.m.	250 mg TE/3 weeks	12 months	31.9 ± 2.5 (SD)	14	63.6 ng/dL ±14 (SD)	hypogonadal
Wang 2010 [70]	open-label	i.m.	750 mg TU/4 to 10 weeks	21 months	>18	117	320 ng/dL ±111 (SD)	low normal T
Brockenbrough 2006 [48]	RCT	gel	10 mg T/day	6 months	58.9 ± 14.9 (SD)	19	218 ± 64 (SD) ng/dL	hypogonadal, renal disease
Cherrier 2003 [71]	RCT	gel	50-100 mg T/day	6 months	34 to 70	12	320 ± 90 (SD) ng/dL	low normal T
Chiang 2007 [72]	RCT	gel	50 mg T/day	3 months	20 to 75	17	213 ± 158 (SD) ng/dL	hypogonadal
Dean 2004 [73]	open-label	gel	50 mg T/day	9 months	58.5 (mean)	257	247 ng/dL (mean)	hypogonadal
Di Luigi 2012 [74]	open-label	gel	50 mg T/day	1.25 month	31.3 ± 7.5 (SD)	10	72 ng/dL (mean)	hypogonadal
Juang 2014 [75]	RCT	gel	100 mg T/day	3.5 months	24 to 51	14	302 ± 37 (SD) ng/dL	hypogonadal, osteoporosis
Kenny 2010 [53]	RCT	gel	50 mg T/day	12 months	79.9 ± 7.3 (SD)	69	380 ± 179 (SD) ng/dL	eugonadal, osteoporosis
Marin 1993 [54]	RCT	gel	125 mg T/day	9 months	56.7 ± 2.2 (SD)	10	455 ± 23 (SD) ng/dL	eugonadal, obese
Mazer 2005 [76]	RCT	gel	59 mg/day	2 weeks	52.4 ± 12.2 (SD)	28	226 ± 110 (SD) ng/dL	hypogonadal
Page 2011 [77]	RCT	gel	75 mg T/day	6 months	>50	27	204 ng/dL (mean)	hypogonadal, BPH
Swerdloff 2000 [78]	open-label	gel	100 mg T/day	3 months	51.3 (mean)	76	280 ng/dL (mean)	hypogonadal
Wang 2000 [79]	no placebo group	gel	100 mg T/day	2 weeks	26 to 59	10	179 ± 41 (SD) ng/dL	hypogonadal
Wang 2011 [80]	open-label	gel	60 mg T/day	4 months	51.5 ± 12.7 (SD)	135	215 ± 84 (SD) ng/dL	hypogonadal
Ahmed 1988 [81]	no placebo group	patch	15 mg T/day	6 to 8 weeks	34 to 54	5	45 ± 12 (SD) ng/dL	hypogonadal
Bals-Pratch 1988 [82]	not stated	patch	10 to 15 mg T/day	14 months	31 to 37	7	189 ng/dL (mean)	hypogonadal
Behre 1999 [83]	open-label	patch	2.4 to 3.6 mg T/day	7 years	35.9 ± 9.8 (SD)	11	147 ± 37 (SD) ng/dL	hypogonadal
Cunningham 1989 [84]	placebo-controlled	patch	15 mg T/day	8 weeks	33 to 66	12	43 ± 11 (SD) ng/dL	hypogonadal
Mazer 2005 [76]	open-label	patch	5 mg T/day	2 weeks	28 to 71	28	215 ± 110 (SD) ng/dL	hypogonadal

RCM# 2015-2497 DEPI review of serum dihydrotestosterone levels and the risk for cardiovascular events

Meikle 1992 [85]	not stated	patch	12.6 mg T/day	single dose	24 to 66 40.7 ± 10.5 (SD)	6	161 ± 27 (SD) ng/dL	hypogonadal
Raynaud 2008 [68]	open-label	patch	2.5 mg T/day	12 months		131	43 ng/dL (mean)	hypogonadal
Franchimont 1978 [86]		oral	120 to 240 mg TU/day	9 weeks	16 to 51	10	120 ng/dL (mean)	hypogonadal
Roth 2011 [87]	open-label	oral	400 mg TU/day	1 day	18 to 52	11	405 ± 14 (SD) ng/dL	eugonadal
Schubert 2003 [69]	open-label	oral	160 mg TU/day	12 months	34.5 ± 3.9 (SD)	13	63.6 ng/dL ± 14 (SD)	hypogonadal
Van Coevorden 1986 [88]	RCT	oral	240 mg TU/day	12 weeks	40 ± 11 (SD)	19	161 ± 86 (SD) ng/dL	hypogonadal, renal insufficiency

Source: Borst et al., 2014, Table 2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANA K MCANINCH
04/10/2015

MONIQUE FALCONER
04/10/2015

JIE J LI
04/10/2015

DAVID G MOENY
04/10/2015

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: October 29, 2014

TO: Hylton V. Joffe, MD
Director,
Division of Bone, Reproductive, and Urologic Products
Office of New Drugs

FROM: Young Moon Choi, Ph.D.
Pharmacologist,
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR covering NDA 206089 Testosterone
Undecanoate Oral Capsules, sponsored by Clarus
Therapeutics, Inc.

This review is an addendum to the DBGLPC (OSI) inspection review dated August 08, 2014 in DARRTS. This addendum includes review of inspections of the clinical portions of the following safety and efficacy study as requested by the Division of Bone, Reproductive, and Urologic products:

Study #: CLAR-12011
Study Title: "Phase III, open-label study of the safety and efficacy of oral Testosterone Undecanoate (TU) in hypogonadal men"

FDA inspection was conducted at the following two sites:

Site 1: Tower Urology, Tower Research Institute
Los Angeles, CA 90048

Site 2: University Urology Associates, New York, NY

FDA investigator Iram Hassan (ORA, New York District office) conducted inspection at University Urology Associates from September 8 to 18, 2014 and Ms. Donna Tartaglino Besone (ORA, Los Angeles District office) conducted inspection at Tower Urology from October 8 to 23, 2014.

The audits included a review of the organization, a thorough examination of study records, informed consent, protocol compliance, IRB approval, facilities, test article accountability, and interviews and discussions with the firm's management and staff.

Following the inspections at the above sites, no objectionable conditions were observed, and no Form FDA-483 was issued.

However, there was one discussion item at Tower Urology, regarding unreported protocol deviation for subject (b) (6). This subject had high levels of testosterone (1320 ng/dL) and hematocrit (> 54%) at visit 4. The subject was not given a decreased dose according to the protocol after visit 4, and he was ultimately terminated from the study after visit 5 because of the hematocrit > 54 %. This observation is unlikely to impact the quality and integrity of the overall study data.

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 Agency review.

Young Moon Choi, Ph.D.
Jyoti B. Patel, Ph.D.
Pharmacologist,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

Final Classifications:

NAI: Tower Urology, Tower Research Institute, Los Angeles, CA
NAI: University Urology Associates, New York, NY

Page 3 - NDA 206089 Testosterone Undecanoate Oral Capsules,
sponsored by Clarus Therapeutics, Inc.

CC:

OSI/DBGLPC/Taylor/Haidar/Bonapace/Dasgupta/Skelly/Choi/patel
OSI/DBGLPC/Dejernett/Johnson
OSI/DBGLPC/Fenty-Stewart/Nkah
CDER/DBRUP/Joffe
CDER/OCB/DCP-3/Al Habet/Ahn/Roule
ORA/LOS-DO/Tartaglino Besone
ORA/NY-DO/ Hassan

Draft: YMC 10/10/2014

Edit: JBP 10/27/2014; SHH 10/29/2014; WHT 10/29/2014

Files # BE6684

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/Tower Urology, Tower Urology Institute, Los Angeles, CA /
University Urology Associates, New York, NY

FACTS: 8755458

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JYOTI B PATEL

10/30/2014

Signing for Dr. Young Moon Choi as well

SAM H HAIDAR

10/31/2014

WILLIAM H TAYLOR

10/31/2014



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: Oct 23, 2014

To: Hylton V. Joffe, M.D., Director
Division of Bone, Reproductive and Urologic Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

From: Jovita Randall-Thompson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: **NDA 206089**
Name: (b)(4) (testosterone undecanoate (TU) oral capsules)
Indication: 1. Primary hypogonadism (congenital or acquired);
2. Hypogonadotropic hypogonadism (congenital or acquired)
Dosage: Two immediate release 158.3 mg (100 mg of testosterone) or
237.5 mg (150 mg of testosterone) TU capsules taken twice-daily,
maximum single dose of 475 mg TU; dose titrated in 50 mg of testosterone
increments based on total serum testosterone concentration

Company: Clarus Therapeutics, Inc.

Materials reviewed:

- NDA 206089/in EDR dated Jan 3 2014 and Amendment dated March 28 2014
- Lerner, Alicja_CSS review_NDA 22219 Aveed dated Jan 24 2014 (in DARRTS)
- Documentation for DBRUP for proposed label changes for section 9 and TSI (3/9/2014) related to all testosterone products

Table of Contents

I. BACKGROUND	2
II. CONCLUSIONS	3
III. RECOMMENDATIONS	3

I. Background

This memorandum responds to a consult from the Division of Bone, Reproductive and Urologic Products (DBRUP) requesting the Controlled Substance Staff (CSS) to review a label for the new investigational drug (NDA) (b) (4) (NDA 206089, submitted January 3, 2014). (b) (4) is an oral testosterone undecanoate (TU) product submitted by Clarus Therapeutics, Inc. under section 505(b)(2) of the Federal Food, Drug & Cosmetic Act. of the Federal Food, Drug & Cosmetic Act referencing the Monograph of Product for Andriol (by Merck Inc.), a drug marketed outside the US for more than 30 years (as stated in the NDA by Clarus) and not yet approved by FDA for marketing in the United States.

(b) (4) proposed indication is for the treatment of:

- 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.
- Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.

The initial submission contained only pharmacokinetic data (PK). In response to the Division's (DBRUP) request for additional efficacy information the Sponsor submitted an amendment to the NDA on March 28, 2014. The amendment provided new clinical study reports for studies CLAR-09007 and CLAR-1200 that included clinical efficacy data (see Clarus' cover letter dated March 28, 2014, in EDR).

(b) (4) was studied in six clinical trials (4 Phase II, 2 Phase III). The Sponsor asserts that Phase III trials demonstrate that when administered twice-daily (b) (4) effectively replaces serum T levels into the eugonadal range Cavg (300- 1000 ng/dL). The clinical development program also includes one ongoing, long-term safety study of this oral TU in hypogonadal men. Four of the 6 completed studies (Studies CLAR-07004, CLAR-08005, CLAR-09008, and CLAR-09009) were Phase 2 pharmacokinetic (PK) studies. The other two completed studies (Studies CLAR-09007 and CLAR-12011) were Phase 3 dose-titration studies that assessed efficacy based on PK evaluations. The long-term safety study (CLAR-12010) is a one-year extension of treatment available to subjects in the U.S. who completed Study CLAR-09007.

CSS reviewed the information submitted in the current NDA application from an abuse perspective and has reviewed the Sponsor's proposed 9.0 section of the label on abuse and dependence. On the bases of this review, we provide the following conclusions and recommendations.

II. Conclusions

1. Section **9 Drug Abuse and Dependence** of the label for (b)(4) NDA 206089 does not provide the consumers (physicians and patients) current information related to abuse/misuse of this drug, or provide updated safety data related to abuse, misuse, overdose, dependency and withdrawal symptoms.
2. 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.
3. All product-related label issues a for (b)(4) NDA 206089 label were discussed in the CSS review for a similar product, Aveed NDA 22219 (Dr. Alicja Lerner, Jan 24 2014, Aveed, NDA 22219 in DARRTS).

III. Recommendations

1. 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 reported by Tracked Safety Information (TSI) that was initiated on March 19 2014. The TSI goal is to review current abuse and misuse information of all testosterone products.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALICJA LERNER
10/23/2014

JOVITA F RANDALL-THOMPSON
10/23/2014

MICHAEL KLEIN
10/24/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 22, 2014

To: Jeannie Roule
Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products (DBRUP)

From: Trung-Hieu Brian Tran, PharmD, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA: 206089**
[REDACTED] (b) (4) (oral testosterone)

OPDP acknowledges receipt of your March 31, 2014, consult request regarding the Package Insert (PI), Patient Package Insert (PPI), and Carton/Container Labeling for [REDACTED] (b) (4) (oral testosterone) [REDACTED] (b) (4). Reference is made to an October 21, 2014, email from DBRUP that informed OPDP that DBRUP will take a Complete Response action on this product. For this reason, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DBRUP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Trung-Hieu Brian Tran, (240) 402-0281, or trung-hieu.tran@fda.hhs.gov.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TRUNG-HIEU B TRAN
10/22/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

REVIEW DEFERRAL MEMORANDUM

Date: October 22, 2014

To: Hylton Joffe, MD
Director
Division of Bone, Reproductive, and Urologic Products (DBRUP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Robin Duer, MBA, BSN, RN
Team Leader (Acting), Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Medication Guide (MG)

Drug Name (established name): (b) (4) (testosterone undecanoate)

Dosage Form and Route: Capsules, for oral use

Application Type/Number: NDA 206-089

Applicant: Clarus Therapeutics

1 INTRODUCTION

On January 03, 2014, Clarus Therapeutics submitted for the Agency's review a New Drug Application (NDA-206089) for [REDACTED]^{(b)(4)} (testosterone undecanoate) capsules, for oral use, indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. On March 31, 2014, the Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for [REDACTED]^{(b)(4)} (testosterone undecanoate) capsules, for oral use.

This memorandum documents the DMPP review deferral of the Applicant's proposed MG for [REDACTED]^{(b)(4)} (testosterone undecanoate), capsules, for oral use.

2 CONCLUSIONS

Due to outstanding clinical and clinical pharmacology 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.

Please notify us if you have any questions.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHAWNA L HUTCHINS
10/22/2014

ROBIN E DUER
10/22/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: September 5, 2014

Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products (DBRUP)

Application Type and Number: NDA 206089

Product Name and Strength: (b) (4) (testosterone undecanoate) Capsules, 158 mg and 237 mg

Product Type: Single Ingredient

Rx or OTC: Rx

Applicant/Sponsor Name: Clarus Therapeutics

Submission Date: January 3, 2014

OSE RCM #: 2014-679

DMEPA Primary Reviewer: Walter Fava, RPh., MEd., Safety Evaluator

DMEPA Team Leader: Tingting Gao, PharmD., Acting Team Leader

1 REASON FOR REVIEW

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that we review the (b) (4) (Testosterone Undecanoate) labels and labeling submitted on January 3, 2014, for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is seeking approval for two product strengths, a 158 mg and a 237 mg softgel capsule. These strengths represent testosterone undecanoate. We reviewed the container labels and the Prescribing Information and we note that dosage and administration section of the Prescribing Information references the (b) (4)

This does not align with the revised 158 mg and 237 mg testosterone undecanoate product strengths stated on the currently proposed container labels. Therefore, we provide recommendations that the strength presentation be revised throughout the labels and labeling, (b) (4) to minimize the risk of confusion that may lead to dosing errors.

Additionally, we determined that the container labels can be revised to improve the readability of the proprietary name, and we also provide additional recommendations to minimize the risk of wrong strength selection errors, which include more clearly differentiating the appearance of the principal display panels for each strength and avoid assigning NDC product codes that are numerically similar or identical.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the Full Prescribing Information, container labels, and carton labeling should be revised to clearly convey the amount of testosterone being provided from each softgel capsule of testosterone undecanoate. Additionally, the proposed container label can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product to mitigate any confusion. We provide recommendations in section 4.1 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information and Full Prescribing Information

1. Dosage and Administration

- a. Revise the starting dose statement to read: [REDACTED] (b) (4)
- b. Revise the dose adjustment information to align with the proposed strengths of the 158 mg and 237 mg [REDACTED] (b) (4) capsules.

2. Dosage Forms and Strengths

- a. Revise the strength statement to read: [REDACTED] (b) (4)

3. How Supplied/Storage and Handling

- a. Revise the statement, [REDACTED] (b) (4)
- b. Include information regarding to the package size configuration (i.e. Bottle of 120).

4.2 RECOMMENDATIONS FOR CLARUS THERAPEUTICS

A. Container Labels



2. Revise the presentation of the proprietary name from all-capital letters to title case letters (e.g. (b) (4)) to improve readability. We recommend capitalizing only the first letter in the proprietary name because words written in all-capital letters are less legible than words written in mixed case letters.
3. Consider changing the color scheme of the 158 mg strength statement (b) (4) color) to a color that is different from the color used for the proprietary name. The use of the same (b) (4) color font for the proprietary name and one of the product's strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors.
4. We note that the container labels currently present the NDC numbers as 'XXXXX-XXX-XX'. Please provide the actual NDC on the container labels if known and avoid assigning product codes that are numerically similar or identical to minimize the risk of wrong strength selection errors per FDA Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (page 14).
5. We note that you provided the shipping labels for each strength of (b) (4) however, you did not provide individual carton labeling. If the containers will be packaged in cartons, we recommend that you apply the same recommendations provided above to the carton labeling. Furthermore, we recommend including the Controlled Substance designation, CIII, on the shipping label along with the statement, 'Rx Only'.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for (b) (4) that Clarus Therapeutics submitted on January 3, 2014.

Table 2. Relevant Product Information for (b) (4)	
Initial Approval Date	N/A
Active Ingredient	Testosterone Undecanoate
Indication	Replacement therapy in males with primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired)
Route of Administration	Oral
Dosage Form	(b) (4) capsules
Strength	158 mg and 237 mg
Dose and Frequency	Starting dose is 316 mg testosterone undecanoate which is equivalent to 200 mg testosterone taken orally twice daily in the morning and the evening with food. Dose adjustments are based on serum testosterone concentrations at least 7 days after starting treatment.
How Supplied/Container Closure	Containers with child resistant closures. Bottles of 120 soft gelatin capsules.
Storage	(b) (4)

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on August 22, 2014 using the terms, (b) (4) to identify reviews previously performed by DMEPA.

C.2 Results

Our search did not identified any relevant reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following (b) (4) labels and labeling submitted by Clarus Therapeutics on April 21, 2014.

- Container label
- Shipping labels
- Prescribing Information (no image)

G.2 Label and Labeling Images

Container Labels



¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WALTER L FAVA
09/05/2014

TINGTING N GAO
09/05/2014

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: August 8, 2014

TO: Hylton V. Joffe, MD
Director
Division of Bone, Reproductive, and Urologic Products

FROM: Young Moon Choi, Ph.D.
Pharmacologist
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR covering NDA 206-089 Testosterone
Undecanoate Oral Capsules, sponsored by Clarus
Therapeutics, Inc.

At the request of the Division of Bone, Reproductive, and Urologic Products (DBRUP), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections for clinical and analytical portions of the following studies submitted to NDA 206-089.

Study CLAR-12011: "Phase III, Open-Label Study of the Safety and Efficacy of Oral Testosterone Undecanoate (TU) in Hypogonadal Men"

Study CLAR-09007: "Phase III, Active-Controlled, Safety and Efficacy Trial of Oral Testosterone Undecanoate (TU) in Hypogonadal Men"

ORA investigator Truong (Andy) Nguyen (Los Angeles District Office) audited the clinical portion of Study CLAR-09007, and OSI scientist Young Moon Choi audited the analytical portions of

both Study CLAR-09007 and Study CLAR-12011 at (b) (4)

(b) (4) The audits included a review of the organization, a thorough examination of study records, facilities and equipment, and interviews and discussions with s management an he inspections started on (b) (4) and closed on (b) (4)

During the inspection at (b) (4) no objectionable conditions were observed. At the conclusion of inspection, no Form FDA-483 was issued.

The audits of the clinical portions of Study CLAR-12011 at the following two sites will be conducted during August and September 2014:

Tower Urology, Tower Research Institute
Los Angeles, CA

University Urology Associates
New York, NY

The outcomes of these inspections will be reported to DBRUP as soon as the results are shared with OSI/DBGLPC.

Conclusion:

Following the inspections, this DBGLPC reviewer concludes that clinical and bioanalytical data from (b) (4) are acceptable for further Agency review.

Young Moon Choi, Ph.D.
Pharmacologist
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

Final Classification:

NAI:

(b) (4)

CC:

OSI/DBGLPC/Taylor/Haidar/Bonapace/Dasgupta/Skelly/Choi/
OSI/DBGLPC/Dejernett/Johnson
OSI/DBGLPC/Fenti-Stewart/Nhik
CDER/DBRUP/Joffe
CDER/OCP/DCO-3/Al Habet/Ahn/Roule
ORA/LOS-DO/Nyuen/Hall

Draft: YMC 8/6/2014

Edit: MFS 8/7/2014; SHH 8/8/2014

Files # BE6684

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Labora lytical
Sites/ (b) (4)

Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Labora nical
Sites/ (b) (4)

FACTS: (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YOUNG M CHOI
08/08/2014

WILLIAM H TAYLOR
08/08/2014

SAM H HAIDAR
08/08/2014