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Division of Documents Management
U.S. Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Clarus Therapeutics, Inc. ("Clarus" or "Petitioner") submits this Citizen Petition under Sections 505(b), 505(j), and 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and in accordance with the Food and Drug Administration's ("FDA's" or the "Agency's") implementing regulation set forth at 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs establish clear, written guidance regarding the safety and efficacy standards required for oral testosterone-ester prodrugs as testosterone ("T") replacement therapy for adult men with a deficiency or absence of endogenous T. Furthermore, until requested action is taken, FDA should not approve any pending NDA for an oral T-ester to treat male hypogonadism that fails to meet the standards for approval set forth in this petition.

A. Action Requested:

Petitioner requests that FDA issue written guidance regarding the specific criteria that oral T-ester prodrugs must meet regarding:

> **(a)** Primary efficacy [historically defined/applied by FDA as average T levels (i.e., C_{avg})] in the eugonadal range in 75% of treated hypogonadal men with a lower bound of the 95% confidence interval of 65%. Furthermore, for phase 3 efficacy studies of oral T-esters (or any T-replacement product in this day and age), FDA should ensure that circulating T is measured by validated assay [preferably by liquid chromatography dual mass spectrometry (LC/MS-MS)] that meets, for example, the standards established by the Centers for Disease Control and Prevention's Hormone Standardization Project (CDC-HoSt Program)[1].
>
> **(b)** Secondary efficacy [historically defined/applied by FDA as peak T levels (i.e., C_{max})] falling within the criteria used by FDA for the past 10 years but never codified in written guidance.

[1] See Appendix A. The objective of the Centers for Disease Control and Prevention's Hormone Standardization Project (CDC-HoSt Program) is to improve diagnosis, treatment, and prevention of diseases and disorders through the standardization of testosterone measurements.

These C_{max} criteria/targets for T products (after dose adjustment) are: ≥85% of men with T C_{max} < 1500 ng/dL; ≤ 5% of men with T C_{max} between 1800-2500 ng/dL; and no men with T C_{max} > 2500 ng/dL;

(c) Dose titration instructions in product labeling based on phase 3 study(ies) wherein the T concentration from a single status blood sample (and not T C_{avg}) is used to guide dose adjustment(s) thus mimicking 'real world' clinical practice;

(d) Concordance, defined as the extent of agreement between a decision to adjust dose (up or down) when a single circulating T concentration in response to an oral T-ester dose remains in the hypogonadal (i.e., <300 ng/dL) or supraphysiological range (i.e., > 1000 ng/dL) and the desired outcome of that decision (i.e., circulating T level in the eugonadal range between 300 and 1000 ng/dL);

(e) Food effect given the lipophilic nature of T-esters and the potential for differences in bioavailability based on meal composition and each specific oral T-ester formulation); and

(f) Characterization of post-collection conversion of specific T-ester to T in blood drawn from men treated with oral T-ester to assess clinical T response. Prospective studies are essential to define the extent of post-collection conversion on T pharmacokinetic parameters [most notably, AUC, Cavg and Cmax for T and for T-ester(s)] and determine how such conversion will be prospectively factored into the design of phase 3 efficacy studies to avoid over-estimates of circulating T levels that can significantly bias efficacy results and, in a real world clinical setting, lead to erroneous dose adjustment decisions for T-esters products.

Petitioner further requests that FDA refuse to approve any New Drug Application ("NDA") or Abbreviated New Drug Application ("ANDA") seeking approval to market an oral T-ester product (or combination of T-esters) for the treatment of male hypogonadism unless the sponsor(s) of such application(s) have met criteria set forth in written guidance from FDA relative to above and that FDA assess/approve oral T-ester NDAs on the basis of efficacy that is consistent with FDA approval precedent for T replacement drug products.[2, 3]

B. STATEMENT OF GROUNDS

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[2] Petitioner acknowledges that FDA has historically considered failure to achieve certain efficacy targets as 'review issues' and appropriately so within justifiable limits. However, in the case of T replacement products the FDA has not to our knowledge approved any T replacement product in the past 10+ years that failed to achieve primary efficacy (as defined herein) nor has approval been granted for a product that fails to achieve close (albeit imperfect) alignment to secondary efficacy (i.e., C_{max}) targets.

[3] It is noteworthy that the oral T-ester developed by Petitioner and approved by FDA—namely, JATENZO® (testosterone undecanoate) Capsules; NDA 206089, approved on March 27, 2019—has been granted a 3-year period of market exclusivity by FDA. It is the Petitioner's position that the scope of this exclusivity will block full FDA approval of oral TU products under development (either pre- or post-NDA submission) for use as T-replacement in hypogonadal men until March 27, 2022. Most notable in this regard is NDA 208088 currently under review by FDA for an oral T-ester product for T-replacement therapy in hypogonadal men. Based on public information disseminated by the sponsor of this NDA (i.e., Lipocine, Inc.), the PDUFA target for this pending application is November 9, 2019.

At its core, the purpose of this petition for FDA is to establish written guidance regarding the safety and efficacy requirements for oral T-ester products developed for the treatment of male hypogonadism. The first ever U. S. oral T-ester product indicated for T-replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous T (namely, JATENZO®) was approved by FDA on March 27, 2019. In light of the FDA-mandated development requirements for this product and the associated 'learnings' by both FDA and the Petitioner along the way, written guidance is necessary to ensure that sponsors of oral T-ester products in development are provided consistent advice regarding clinical development programs for oral T-ester and that NDAs are reviewed in a consistent manner to avoid 'arbitrary' decisions by FDA in its review process. This is particularly critical in light of the unique challenges oral T-esters present from a drug development perspective (compared to non-oral T replacement products) given their chemical nature. These include:

(a) formulation development (T-esters are highly lipophilic and challenging to formulate);

(b) inherent bioavailability challenges due to the lipophilic nature of T-ester prodrugs;

(c) route of absorption (i.e., intestinal lymphatic v. portal circulation);

(d) food effect [e.g., effect of food and/or dietary fat content of a meal on both T-ester and T pharmacokinetics (PK)];

(e) PK profiles (e.g., classic trough-peak-trough profiles for each dosing interval, typically, 12 hours) compared to other approved T-replacement products (e.g., topical T-gel formulations);

(f) inherent individual differences in T-ester absorption and conversion (via endogenous esterases) to T as a result of intra-patient variability;

(g) identification of a single status blood sample after oral T-ester dosing on which to assess efficacy [i.e., single T value reflects average circulating T concentration (C_{avg})] and directs dose adjustment (if any);

(h) achieving primary (T C_{avg}) and secondary efficacy [peak circulating T concentrations (C_{max})] in close alignment with FDA targets (that have not been codified in official FDA 'guidance' but have been used for at least the past 10 years as an essential efficacy standard for T-replacement products);

(i) demonstration of 'acceptable' concordance between single serum T status samples and subsequent dose-adjustment decision(s) (i.e., what is the magnitude of agreement between a single T value that should reflect C_{avg} and the outcome of a dose adjustment decision based on this single T value); and

(j) the post collection conversion of T-esters in blood drawn from men treated with such prodrugs thus leading to inaccurate measurement (i.e. overestimation) of the actual T concentration at the time the blood sample was collected.

Each of these factors will not be addressed in this section of the petition. Rather, emphasis is placed on those most critical from the perspective of demonstrating efficacy and guiding (via product labeling)

how oral T-esters are used by health care professionals in real world clinical practice to treat male hypogonadism.

Primary Efficacy (T C_{avg}):

Available public information from FDA regarding the primary and secondary efficacy criteria for T replacement products (e.g., Medical Reviews of new drug applications for T products) indicates that FDA established efficacy 'targets' in about 2010 and has consistently applied these targets to NDAs submitted for all T products since that time – regardless of the route of delivery (see Table 1). Specifically, for the primary efficacy endpoint, phase 3 trials of T-replacement products must demonstrate that the product achieves a T C_{avg} within the eugonadal range (typically, 300-1000 ng/dL) for at least 75% of subjects and that the lower bound of the corresponding 95% confidence interval for this point estimate is at least 65%. Testosterone C_{avg} is a time-averaged calculation that divides total exposure (area under the concentration-time curve or AUC, based on pharmacokinetic sampling over 24 hours) by 24 and the 75% efficacy applies to subjects at the final PK visit – typically after up to two opportunities for dose adjustment. To the Petitioner's knowledge, FDA has not granted approval to any T replacement product since 2010 that has not met this standard and, in fact, has applied this standard to results of sensitivity analyses of efficacy data that precisely reached the 75% threshold and used the outcome of these sensitivity analyses to, in part, deny NDA approval (see Appendix B).[4]

Despite the fact that FDA has established a primary efficacy threshold for T replacement products, it has not been scientifically justified and memorialized in written guidance. Nor has FDA clearly set forth which patient population is to be used when calculating efficacy. For example, how should the intent-to-treat (ITT) population be defined? Petitioner recommends that the ITT be comprised of those patients who actually received at least one dose of the oral T-ester and that this study population be used for determination of efficacy. FDA should also require specific sensitivity analyses around efficacy to further support efficacy. FDA should also make clear in written guidance how missing data are to be handled – particularly in light of the fact that efficacy for all T-replacement products is dependent on carefully designed clinical studies in which T C_{avg} serves as the primary efficacy endpoint.

[4] In a Phase 3 study of Petitioner's oral TU product, the per protocol primary efficacy endpoint of ≥ 75% of men with a serum T Cavg was exactly achieved (i.e., 75.0%). *Post hoc* sensitivity analyses by FDA indicated success rates of <75% -- a factor FDA used to, in part, to deny approval of the NDA. See Appendix B, also see Appendix M, pages 196-199.

Table 1: FDA Use of C_{avg} and C_{max} Efficacy Targets for Evaluation of Approved T Replacement Products Since 2010

Approved Drug	Year	$C_{avg} \geq 75\%$[a]	C_{max} Targets[b]	Source
Tlando®	2019	✓	✓	FDA Briefing Document BRUDAC Advisory Committee Meeting January 10, 2018 (see Appendix C)
Jatenzo®	2019	✓	✓	FDA Briefing Document BRUDAC Advisory Committee Meeting January 9, 2018 (see Appendix D)
Xyosted®	2018	✓	✓	CDER Clinical Review September 25, 2018 (see Appendix E)
Aveed®	2014	✓	✓	CDER Clinical Review February 21, 2014 (See Appendix F)
Natesto®	2014	✓	✓	CDER Clinical Review May 20, 2014 (See Appendix G)
Vogelxo®	2014	✓	✓	CDER Clinical Review August 12, 2013 (see Appendix H)
AndroGel® 1.62%	2011	✓	✓	CDER Clinical Review April 19, 2011 (See Appendix I)
Axiron®	2010	✓	✓	CDER Clinical Review November 19, 2010 (See Appendix J)
Fortesta®	2010	✓	✓	CDER Clinical Review December 1, 2010 (See Appendix K)

[a] Lower limit of 95% confidence limit ≥ 65%

[b] C_{max} targets set/used by FDA are: C_{max} ≤1500 ng/dL in at least 85% of subjects; C_{max} between 1800 and 2500 ng/dL in not more than 5% of subjects; and C_{max} >2500 ng/dL in no subject.

Secondary Efficacy (T C_{max}):

FDA has also established, but not set forth in written guidance, the secondary efficacy targets used in its review of T-replacements products -- namely those defined by peak concentrations of T or C_{max}. Nor has the FDA set forth the complete rationale for assessing T C_{max}, including the scientific basis for establishing the current targets and what latitude around these targets is permissible. As was the case for primary efficacy, secondary efficacy targets for T replacement products were established in about 2010 and have been applied to all NDAs submitted for T replacement products since that time. Specifically, the secondary T C_{max} endpoints are as follows: a) C_{max} ≤1500 ng/dL in at least 85% of subjects; b) C_{max} between 1800 and 2500 ng/dL in not more than 5% of subjects; and c) C_{max} >2500 ng/dL in no subject. Public statements by FDA in 2014 about the importance of T C_{max} outliers in response to an oral T-ester product under review indicate that T C_{max} is considered to be a critical secondary efficacy criterion that should be met: "*In determining the need for a critical secondary endpoint, C_{max} outliers, the underlying premise was that excessive testosterone, excessive outside of the normal range does not meet the primary efficacy endpoint of [T][5] repletion to the normal range.*"[6]

[5] Clarification added

[6] Transcript from Joint Meeting of Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Sfety and Risk Management Advisory Committee (DSaRM), September 17, 2014, 7:58 a.m. to 5:04 p.m. (see Appendix L, pages 96, 211).

FDA further addressed the specific issue of C_{max} outliers being an efficacy issue when it responded to a question from a panel member of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) that was evaluating an oral T-ester product. Specifically, BRUDAC member Dr. Herring said *"I have a question about what's included in efficacy. Are also the endpoints of C_{max} over 1800 and 2500 [ng/dL][7] included in efficacy, or is it safety?"* In response, Dr. Hylton Joffe (Director of DBRUP) stated, *"I would say that's efficacy. Those are secondary endpoints. So I would like at the totality of those data, the primary endpoints and the secondary endpoints, and say, is there enough there to say that this will work reasonably for people who need testosterone replacement therapy."*[8] A similar comment about the importance of C_{max} was made by Dr. Mark Hirsch (Team Leader, DBRUP) immediately prior to a BRUDAC vote regarding approvability of an oral T-ester product that failed to meet the C_{max} targets, *"To be clear, the C-average responder rate is the primary endpoint, and we consider the C_{max} outlier criteria to be a critical secondary efficacy endpoint."*[9]

To avoid arbitrary assessment of C_{max} targets, Petitioner submits that FDA should apply the current C_{max} secondary efficacy standard to all T products in a manner consistent with past precedent unless and until FDA can provide a sound, data-driven basis for not doing so. To date, FDA has not approved any T replacement product whose T C_{max} profile was not closely aligned with FDA targets. Presumably FDA has a sound scientific basis for its position, one that is supported by clinical data and not mere conjecture/ hypotheses or safety data from small clinical data sets. However, FDA has never provided its rationale for T C_{max} targets in a guidance document. This very point has been raised both internally within FDA and by a member of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) when considering an oral T-ester product. For example. in response to an appeal filed by Petitioner regarding FDA's decision not to approve its oral T-ester NDA for JATENZO, Amy Egan, MD (then Deputy Director of the Office of Drug Evaluation III) stated in her letter denying the appeal: *"I agree that the scientific rationale behind the C_{max} thresholds has not been explained in Guidance and I would urge DBRUP to do so....These are the thresholds that have been part of the basis for approval for all testosterone products for at least the last 12 years, and you were well aware of them throughout your clinical development program."* A similar theme was summarized by Dr. Lewis (Committee Chairperson) at the BRUDAC meeting held to review the NDA for the oral TU product Tlando®: *"So in terms of the C_{max} or maximal testosterone concentration.....a greater understanding of how the C_{max} was chosen [by FDA][10] in terms of its physiologic or clinical significance."*

From the Petitioner's vantage point—having spent considerable time and effort to successfully develop an oral T-ester product that achieved close alignment with the C_{max} standard set by FDA (thus demonstrating that it is indeed possible for an oral T-ester product to achieve this standard)—there are two principle issues with C_{max} outliers.

First, high C_{max} values may have a significant effect on individual patient T C_{avg} by skewing the T C_{avg} to a higher value. Thus, for an oral T-ester product with a significant number of C_{max} outliers, it is possible

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[7] Units added

[8] Transcript from Joint Meeting of Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM), September 18, 2014, 7:58 a.m. to 5:04 p.m. (see Appendix M, pages 237-238).

[9] Transcript from Joint Meeting of Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM), September 18, 2014, 7:58 a.m. to 5:04 p.m.; page 238 (see Appendix M, page 238).

[10] Clarification added

that the minimum requisite T C_{avg} target set by FDA of 75% was achieved when this may not have been the case in the absence of there being a significant number of T C_{max} excursions outside the targets set by FDA. This is consistent with FDA's stated view above that a high degree of T C_{max} outliers does not reflect physiological T replacement – the clinical goal of T replacement therapy.

Second, as FDA has opined in public statements, high T C_{max} values raise potential safety concerns.[11] And while we and others have not identified a specific safety signal in this regard, it is logical to think high T C_{max} outliers pose some degree of risk and hence FDA's adoption of C_{max} targets that have been consistently applied in its review of all T replacement product for the past decade.[12]

In the absence of unequivocal clinical data to the contrary, the Petitioner submits that the current T C_{max} standard should continue to be consistently applied to all T products in development (NDA or ANDA) and that arbitrary decisions in this regard be avoided. At the same time, FDA should establish written guidance that sets forth the rationale for T C_{max} outlier targets and provide some level of guidance beyond 'this will be a review issue' for the degree of variance permitted.[13] For example, is alignment within some percentage of the target permissible? If so, what is this percentage? One approach would be for FDA to establish a 95% confidence interval for T C_{max} outliers that must be achieved — much like the approach FDA has taken for primary efficacy based on T C_{avg}. In addition, in its review of oral T-ester product applications where T C_{max} outliers are far from alignment with FDA targets, Sponsors should be required to demonstrate (by appropriate analyses) that the pattern of T C_{max} outliers does not unacceptably and systematically bias the T C_{avg} used to support primary efficacy.

Dose Titration:

FDA should publish guidance regarding how to establish dose adjustment algorithms based on individual T response to oral T-ester products. This is critically important to guide use of such products in real-world clinical medicine. At the same time, there should be unequivocal 'stopping rules' for oral T-ester products that cannot be dose-adjusted when individual patient T C_{avg} is below the lower or above the upper limit of the eugonadal T range (typically 300 – 1000 ng/dL).

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[11] In considering an NDA submitted for an oral T-undecanoate product (namely, Tlando), FDA stated in its Briefing Book issued in advance of a BRUDAC meeting held on January 10, 2018, the following about Cmax outliers relative to Tlando, *"As noted, previously trials for testosterone therapies have three standard secondary endpoints to assess for unacceptably high maximal exposures to testosterone that could potentially raise safety concerns. In the new trial that tested 225 mg twice daily, none of these three targets were met. We will seek the advisory committee's input on the relevance of these findings to the safe* [emphasis added] *use of Tlando."* (See Appendix C, page 7).

[12] Remarks made by the Sponsor of an NDA for a T-ester product (i.e., Tlando®) being considered by the BRUDAC suggested that C_{max} targets were established by FDA for transdermal T products – the implication being that they should not form the basis of an efficacy analysis for an oral T-ester product (See Appendix N, page 47). Petitioner has found no evidence to support this contention. To the contrary, if this were the case, these C_{max} targets would not have been secondary efficacy requirements for non-transdermal T products (including oral T-esters) and, based on Medical Reviews published by FDA for all T products approved since about 2010, this is clearly not the case. (See Appendices C-K).

[13] When asked a question by a BRUDAC panel member regarding the approval of any T product in whom the T C_{max} did exceed 2500 ng/dL, FDA responded, *"In terms of how hard an endpoint are those three categories, they are per protocol. You are supposed to make them by strict per-protocol definitions. And they didn't make them here"* [referring to the oral TU product REXTORO that was under development by Petitioner]. *But having said that, there's always allowance for a little bit of a review issue. How much did they fail by? Was it a very, very transient, supratherapeutic concentration? I can't recall offhand if we've ever approved a drug that has failed on the three C_{max} criteria, but I do think there is room to analyze how bad that failure was."* (See Appendix M, page 195).

First, FDA should require that T is assayed by validated methods [e.g., liquid chromatography dual mass spectrometry – arguably the gold standard for T assay in clinical research] and in the most appropriate matrix (e.g., see section below regarding post collection conversion of T-ester to T). Moreover, FDA should affirm that calculation of T C_{avg} is based on full 24-hr PK profiles to establish the most accurate T C_{avg} on which primary efficacy is assessed. This is only logical given the fact that efficacy based on C_{avg} should be based on the most complete pharmacokinetic (PK) profile reasonably possible in a clinical trial setting.

Second, for all oral T-ester products, a single status time point should be derived that correlates closely with C_{avg} and informs healthcare providers who treat hypogonadal men with oral T-ester products when, after the morning T-ester dose, their patient(s) should have blood drawn for assay of T concentration. This approach was communicated to Petitioner by FDA in light of FDA's conclusion that a single time point-based titration scheme is necessary to support product labeling (see Appendices W and ZZ) and guide healthcare provider's use of an oral T-ester in real-world clinical settings where T status based on a single blood sample is the clinical practice norm.

Third, the proposed dose titration algorithm must be prospectively evaluated in a phase 3 clinical trial of each particular T-ester product (or one containing a combination of T-esters). This is especially important for an oral T-ester product that has a composition different from one already approved by FDA since it is almost certain that different oral-T ester formulations built around the same T-ester will exhibit different bioavailability and PK profiles for both the T-ester and T.[14]

[14] One need only consider the differences in lipophilicity between oral T-esters used in current T-ester products and those under development to appreciate that each T-ester (or combination thereof) developed as a T-replacement product will have a unique formulation. Moreover, this unique formulation will result in product-specific differences in T and T-ester PK parameters (e.g., C_{avg} and C_{max}) that will have downstream effects relative to food effect, efficacy, and concordance. Factors such as drug solubility in intestinal fluids, drug dispersion in intestinal spaces, drug interaction with carrier and transport macromolecules, drug translocation through or across cellular structures, drug movement and stability in circulating fluids such as plasma, lymph, serum and blood (both in terms of extent of interaction and the rates of interaction; i.e., the kinetics of drug movement, metabolism and interaction with patient physiology) play a role in how each T-ester affects PK parameters. Therefore, oral T-esters as a general drug class to do not lend themselves to development under 505(j) (i.e., as ANDA products).

Concordance:

FDA should set an explicit target (i.e., percent with defined lower bound of the 95% confidence interval) for acceptable overall (i.e., total) concordance between the decision to adjust the oral T-ester dose (on the basis of a single serum T concentration) and the clinical outcome of that decision (namely, a serum T in the male eugonadal range) at each dose titration point (typically two in studies of T-replacement products).

When comparing the outcome of titration decisions based on C_{avg} with the status sample time point proposed for use in a real world clinical setting, for example C_x (where x represents the hour after the morning dose when a status PK sample is collected for T assay), it is useful to use a 3x3 concordance table where the table's cell boundaries are the lower and upper titration boundaries for the particular oral T-ester. In such a 3×3 concordance table (see Table 2 below), concordance occurs when the dose-titration decision is the same regardless of whether it is based on C_x or C_{avg}, and falls in the shaded cells which are on the diagonal of the 3×3 table. However, even in the off-diagonal cells, many of the titration decisions are appropriate. These off-diagonal cases represent situations where the dose-titration decision based on C_x is different than that based on C_{avg}, but the outcome of the C_x-based decision results in a T-ester dose that should yield a C_{avg} in the eugonadal range (i.e., 'effective concordance'). Although not all patients whose C_x and C_{avg} place them in off-diagonal cells will be titrated into the eugonadal range, most will be.

Table 2: Example of 3 x 3 Concordance Table for Dose Adjustable Oral T-Ester Products

Titration Boundaries		C_{avg}		
		< XXX ng/dL	**XXX - YYY ng/dL**	**> ZZZ ng/dL**
C_x	**< XXX ng/dL Increase dose (maximum xx%)**	Concordant	Patients with $C_{avg} \leq$ XXX ng/dL remain in eugonadal range after dose titration	Discordant
	XXX - YYY ng/dL No dose change	Patients with $C_{avg} \geq$ XXX ng/dL are in eugonadal range	Concordant	Discordant[a]
	> ZZZ ng/dL Decrease dose (maximum xx%)	Discordant[a]	All patients remain in eugonadal range despite decrease in dose	Concordant

Abbreviations: C_x = concentration x hours after morning dose; C_{avg} = average observed T concentration over 24 hours; XXX, YYY and ZZZ concentrations of T are oral T-ester-specific based on PK modeling and simulation of actual serum T PK data from men dosed with a particular T-ester; xx% represents the maximum increase or decrease in oral T-ester dose for each dose adjustment.

Note: *Concordance*: When the titration decision based on C_x or C_{avg} is the same. *Off-Diagonal Titration Decision*: When the titration decision based on C_x results in an oral T-ester dose that will generate a C_{avg} in the eugonadal range.

[a] Although some cases may have effective off-diagonal titrations, these cases are rare and not material to the calculation of **Total Concordance = Effective + Concordant** (denoted in table as cells bounded by the thick black line).

Effective off-diagonal titration can be estimated if the following criteria are established of a particular oral T-ester. First, testosterone exposure in response to a particular T-ester should ideally be dose proportional thus making it possible to predict the change in C_{avg} with change in oral T-ester dose.

Second, the titration boundaries (i.e., a serum T range on a decision is made to adjust the oral T-ester dose must be established (also unique for each oral T-ester) and shown to effectively guide dose adjustments based on the span of adjustments enabled by the particular strengths of the T-ester. Practically speaking, this means that the titration boundaries are likely to fall within or close to the eugonadal T boundaries (i.e, 300 to 1000 ng/dL). Furthermore, the eugonadal range is wide (3.5 fold) compared to the magnitude of the largest dose increment or decrement of a particular T-ester. Consequently, the dose increments/decrements employed for a particular oral T-ester should allow movement within the eugonadal range (e. g., increasing the dose of a patient with a C_{avg} of <300 ng/dL by, for example 33%) will raise the C_{avg} to a maximum of YYY ng/dL [XXX × 1.33]). Similarly, when titration decisions based on C_x are different from those based on C_{avg}, the outcome will often be a C_{avg} in the eugonadal range. For example, when a patient's C_x is less than 300 ng/dL (indicating a dose increase is required), but whose C_{avg} is actually 600 ng/dL (indicating no titration), the impact of titrating based on C_x is that the C_{avg} will increase but remain in the eugonadal range. In the current example, the largest dose increase of 33% will raise the C_{avg} to 798 ng/dL. Therefore, despite titration based on C_x (that was not closely aligned with the actual C_{avg}), this patient's C_{avg} did not rise above the upper boundary of the eugonadal range. Thus, the titration decision based on C_x is *effectively concordant* with that based on C_{avg}, since both titration decisions will result in a patient with a C_{avg} in the eugonadal range. Therefore, when comparing the effectiveness of dose-titration decisions based on C_x and C_{avg}, both concordance (on-diagonal agreement between C_x and C_{avg}) and effective off-diagonal concordance (i. e., effective concordance) must be considered and yield the following equation: Total Concordance = Concordance + Effective Concordance.

FDA should establish a minimum Total Concordance requirement for dose-adjustable oral T-ester products that is <u>at least</u> equal to the minimum serum T C_{avg} efficacy target used by FDA for the last decade in its review of T-replacement products, namely ≥75% with a lower bound of the 95% confidence interval of ≥ 65%. However, because concordance reflects clinical decisions to up or down titrate an oral T-ester dose and can result in prolonged periods of time when patients remain hypogonadal or have serum T concentrations that are too high (thus posing a potential safety risk), Petitioner recommends that the minimal standard for Total Concordance be set at ≥85% with a lower bound of the 95% CI of 75%.

<u>Food Effect</u>:

Due to a high degree of lipophilicity[15], T-esters are essentially treated by the body as a fat and their absorption following oral administration (almost exclusively via the intestinal lymphatic pathway) may be affected by the fat content of a concomitant meal. An early formulation of oral TU developed in the 1970's outside of the U. S. required co-administration with a fatty meal to foster adequate bioavailability. This resulted in a significant food effect and a high level of intra- and inter-patient variability in circulating T response. To overcome the need for a high fat meal and reduce the magnitude of food on T-ester bioavailability, current-day formulations of T-esters often employ oral self-emulsifying drug delivery systems (SEDDS). These unique T-ester-specific formulations enable the solubilization of the highly lipophilic T-ester(s) and foster creation of T-ester containing micelles when the SEDDS formulation is dispersed in the aqueous environment of the gut. T-ester containing micelles are absorbed in a manner identical to fat-containing micelles generated in the small intestine in response to dietary fat (i.e, by the intestinal lymphatic pathway).

[15] Lipophilicity of T-esters is a direct function of fatty-acid chain length; the longer the length the more lipophilic the T-ester and thus the more hydrophobic.

Of the T-esters developed or under current development, TU is the most fully characterized relative to food effect and this level of understanding can only be attained by clinical evaluation of food effect for each oral T-ester formulation.[16,17,18] Because minor changes in the composition of an oral T-ester formulation may change how such a formulation functions to raise circulating T-ester and T levels (by, for example, changing the degree of T-ester solubility in the gut, or affecting the type and size of micelle formation, thereby affecting T systemic bioavailability), FDA should establish written guidance that describes how each T-ester formulation that is not an exact compositional match to an oral T-ester formulation approved by FDA under an NDA must address the food effect issue. That is, FDA should not permit the approval of an ANDA for any oral T-ester product in the absence of an appropriately designed food effect study. Data from this study should be factored into subsequent clinical studies required by FDA to demonstrate efficacy.

Post-collection Conversion of Specific T-ester to T:[19]

The potential for T-esters to hydrolyze in the presence of nonspecific esterases in recently collected blood samples from men treated with oral T-esters poses an important issue that must be addressed during oral T-ester clinical development.

The biochemistry of post-collection T-ester conversion to T is simple: T-ester prodrugs [from those first introduced in the U. S. market in parenteral forms (e. g., T-enanthate; T-cypionate and, more recently TU) to an oral TU product approved by the FDA in March of 2019 (i.e., JATENZO®)], all require the activity of endogenous non-specific esterases to free T from its ester linked side chain at the C-17 position on the T molecule. Although the extent of such post-collection conversion was first thought to be low/insignificant [see Wang et al, 2008[20] and retraction of such findings for TU (see Wang et al 2018)[21]], post-collection conversion of TU to T in men treated with oral TU has now been definitively

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[16] Bagchus, W.M., Hust, R., Maris, F., Schnabel, P.G. and Houwing, N.S. (2003). Important effect of food on the bioavailability of oral testosterone undecanoate. *Pharmacotherapy, 23*: 319–325. (See Appendix O)

[17] Schnabel, P.G., Bagchus, W., Lasst, H., Thomsen, T. and Geurts, T.B.P. (2007). The effect of food composition on serum testosterone levels after oral administration of Andriol® Testocaps®. Clin. Endocrinol. 66: 579-585. (See Appendix P)

[18] Yin, A.Y., Htun, M., Swerdloff, R.S., Diaz-Arjonilla, M., Dudley, R.E., Faulkner, S., Bross, R., Leung, A., Baravarian, S., Hull, L., Longstreth, J., Kulback, S., Flippo, G. and Wang, C. Re-examination of Pharmacokinetics of Oral Testosterone Undecanoate in Hypogonadal Men with a New Self-Emulsifying Formulation. *J. Andrology* 33: 190-201. (See Appendix Q)

[19] Petitioner raised this issue with FDA on 26 September 2017 due to concerns that FDA did not seemingly recognize the importance of this issue and thus was not requiring the Sponsor of another oral TU NDA to prospectively address the impact of post-collection conversion of TU to T on phase 3 efficacy data. In response, FDA recommended Petitioner submit its concern via a Citizen Petition (see FDA letter for 10 October 2017). Clarus decided at that time that it would take a 'wait-and-see approach'. Now, however, in light of the fact that this issue has been thoroughly reviewed by FDA in its review of the Petitioner's NDA for JATENZO and found to have scientific/regulatory merit, Petitioner has included this issue (along with several other science-based issues) in this Citizen Petition. (see Appendix R)

[20] Wang, C., Shiraishia, S., Leung, A., Baravarian, S., Hull, L., Goha, V., Lee, P.W.N., and Swerdloff, R.S. (2008). Validation of a testosterone and dihydrotestosterone liquid chromatography tandem mass spectrometry assay: Interference and comparison with established methods. *Steroids* 73: 1345-1352. (See Appendix S)

[21] Wang, C., Shiraishia, S., Leung, A., Baravarian, S., Hull, L., Goha, V., Lee, P.W.N., and Swerdloff, R.S. (2019). Corrigendum to "Validation of a testosterone and dihydrotestosterone liquid chromatography tandem mass spectrometry assay: Interference and comparison with established methods" [Steroids Volume 73, Issue 13, 12

shown to be clinically relevant in terms of both speed and extent (e.g., >15% for TU to T conversion, exclusive of potential further overestimation due to inherent intra-assay variability) [see Ceponis et al 2018 (Appendix U)]. Specifically, unless steps are taken to substantially block esterase activity in blood samples containing T-esters, T-prodrugs will convert, *ex vivo* to T. The clinical implications of such a conversion are obvious.

First, in response to oral-T esters, accurate measurement of circulating levels of T may be compromised (i.e., artifactually elevated). And because demonstration of primary efficacy for T replacement products rests solely on attainment of an FDA-mandated PK target (specifically, the percentage of men that achieve average T levels in the eugonadal range), it is critically important that the data on which efficacy is based does, in fact, reflect what occurred in the body of men dosed with oral TU and not what happened in the blood collection tube into which a sample was collected for T assay. Thus, it is necessary to prevent or to account for T-ester post-collection conversion in order to accurately quantify T concentrations in patients enrolled in clinical studies designed to evaluate the efficacy and safety of oral T-esters.

Second, because the extent and peak effect of T-ester to T conversion is directly proportional to the levels of circulating T-esters, comprehensive PK sampling in hypogonadal men treated with the particular T-ester(s) or combinations thereof are needed prior to the conduct of phase 3 studies on which clinical efficacy is to be based.[22] In other words, FDA should require the prospective understanding of the impact of T-ester to T conversion in blood samples collected prior to centrifugation (the process that stops all conversion) with these learnings being prospectively integrated into the study design of the pivotal phase 3 study(ies). The reverse path should not be adopted by FDA as acceptable since data from such a study are seriously flawed (i.e., there is no way to know whether the T concentrations measured in the study reflect those actually in the circulation at the time a blood sample was drawn because blood samples were not collected in a controlled fashion). Accordingly, these data cannot be 'rescued' by *post-hoc* analyses. It should be unacceptable for a Sponsor of a phase 3 study of any T-ester product to 'back calculate' the magnitude of the effect of post-collection conversion of T-ester to T based on studies conducted after the pivotal phase 3 study was conducted. For example, if a sponsor discovers that data upon which a decision was made not to account for post-collection conversion of a T-ester to T was in error [see, for example, Wang et al 2019 Corrigendum (Appendix T) retracting observation that TU to T conversion does not occur], then a new phase 3 study should be required to accurately measure T and demonstrate efficacy in contrast to trying to 'fix' the problem, *post hoc.*

This is not to say such retrospective analyses would not shed valuable light on the observed T response; they would. For example, such *post hoc* analyses can be used to verify the accuracy of T concentrations measured in the pivotal study and confirm efficacy. But such analyses should not be utilized by FDA as the basis on which to assess efficacy and judge approvability. Instead, in this example, FDA should require a new phase 3 study that prospectively addresses the impact of T-ester to T conversion and thus leads to accurate determination of T pharmacokinetics and appropriate dose titration in the first place.

December 2008, Pages 1345-1352]. *Steroids* 135:108. (See Appendix T)

[22] A corollary to this is that any *in vitro* study of oral TU to T conversion must be evaluated over the range of TU concentrations observed in men exposed to the TU dose(s) expected to be used in the phase 3 clinical study (and thus translated into dosing instructions for product labeling) and not at artifactually low TU concentrations that would grossly underestimate (i.e., hide) the true magnitude of conversion.

Recent history shows that this is precisely the approach that the Petitioner took during its development of an oral TU formulation for the treatment of men with T deficiency, with concurrence of the FDA. In this case, the Petitioner alerted FDA that post-collection conversion of TU to T was a real and important phenomenon that must be controlled for in phase 3 clinical development. In a meeting with FDA in which the topic was discussed[23], FDA concurred and agreed with Petitioner's plan to collect blood in tubes containing NaF-EDTA (an esterase inhibitor) and held on ice prior to centrifugation, a process that halts the TU to T conversion process. Studies conducted before initiation of the pivotal phase 3 efficacy trial demonstrated that TU to T conversion was essentially nil using this approach. To be transparent, use of NaF-EDTA tubes presented other challenges (e.g., matrix effect) when T was assayed by LC/MS-MS, but these factors were known and accounted for by Petitioner prior to conduct of the pivotal study of oral TU. Therefore, the T assay results used for the assessment of efficacy were accurate. And this was confirmed in *post-hoc* analyses based on further clinical data that was requested by FDA. The key point is that oral TU efficacy was prospectively demonstrated on the basis of accurate T measurements and prospectively defined analyses, and then further supported by additional confirmatory *post-hoc* analyses that were requested by FDA—not the reverse.[24]

C. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31.

D. ECONOMIC IMPACT

Petitioner will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b).

E. CERTIFCATIONS

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

Petitioner makes the following certification pursuant to FDC Act § 505(q)(l)(H): I certify that, to the best of my knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: October 26, 2012[25]; April 15,

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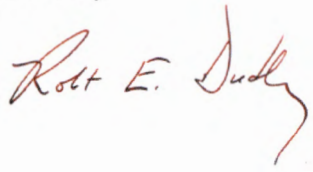
[23] Advice/Information request from FDA to Petitioner on December 22, 2016 (See Appendix ZZZ).

[24] Details of these *post-hoc* analyses are not necessary for the purposes of this Petition. Suffice to say FDA required an additional study wherein blood was collected from men dosed with oral TU into various blood collection tubes held at various conditions. These data were then used to calculate 'correction factors' for TU to T conversion in various matrices (e.g., plasma, NaF-EDTA plasma, serum) and ultimately to confirm the efficacy observed in the pivotal oral TU study conducted by Petitioner.

[25] Email correspondence between FDA and Clarus on October 26, 2010 at 2:26PM EST (See Appendix V).

2016[26]; October 28, 2016[27]; November 3, 2014[28]; and March 6, 2015[29]. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Clarus Therapeutics, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Sincerely,



Robert E. Dudley, PhD
President & CEO

[26] Advice Letter to Petitioner from FDA Division of Bone, Reproductive and Urologic Products (See Appendix W)
[27] FDA correspondence to Petitioner (See Appendix X).
[28] FDA correspondence to Petitioner (See Appendix Y).
[29] Endocrine Society abstract (LBF-019) regarding importance of proper blood collection for T assays in men treated with oral T-undecanoate to avoid post-collection conversion of TU to T in blood sample (See Appendix Z).