Robert E. Dudley, PhD
President & CEO
Clarus Therapeutics, Inc.
555 Skokie Boulevard, Suite 340
Northbrook, IL 60062

Re: Docket No. FDA-2019-P-4644

FEB 27 2020

Dear Dr. Dudley:

This letter responds to the citizen petition submitted to the Food and Drug Administration (FDA or Agency) by Clarus Therapeutics, Inc. (Clarus), and received on October 2, 2019 (Petition). In the Petition, Clarus requests that FDA:

1. Issue "clear, written guidance regarding the safety and efficacy standards required for oral testosterone-ester [(T-ester)] prodrugs as testosterone ('T') replacement therapy for adult men with a deficiency or absence of endogenous T"[1] as outlined in the Petition; and "[r]efuse 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 [. . .]."[2]
2. Furthermore, Clarus requests FDA not to approve "any pending [new drug application (NDA)] for an oral T-ester to treat male hypogonadism that fails to meet the standards for approval set forth in [the] petition," 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."[3]

We have carefully considered your Petition. For the reasons explained below, your Petition is denied.

I. BACKGROUND

A. Oral T-ester Replacement Therapy

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic,

[1] Petition at 1.

[2] Id. at 2.

[3] Id. 1-2

chest and axillary hair; laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution. Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter syndrome or Leydig cell aplasia, whereas secondary hypogonadism (also known as hypogonadotropic hypogonadism) is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (i.e. follicle-stimulating hormone, luteinizing hormone).[4]

Testosterone replacement therapy (TRT) is the current standard of care for hypogonadal adult male patients with primary or secondary hypogonadism due to certain structural or genetic conditions. Jatenzo (testosterone undecanoate) capsules for oral use are FDA-approved as oral TRT in adult males for conditions associated with a deficiency or absence of endogenous T due to certain genetic or structural conditions.[5]

Clarus is the holder of NDA 206089 for Jatenzo. Jatenzo capsules are available in 158 milligrams (mg), 198 mg, and 237 mg. Jatenzo oral capsules were approved on March 27, 2019, and qualified for 3-year marketing exclusivity that expires on March 27, 2022.[6]

B. Statutory and Regulatory Background

The Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations require that an applicant seeking to market a new drug submit an application to FDA for review and approval.[7] To be approved, an NDA submitted under section 505(b) of the FD&C Act must, among other things, be supported by investigations showing the drug product to be safe and effective for its intended use(s).[8] Section 505(c)(1)(A) of the FD&C Act states that FDA will "approve the application if [FDA] . . . finds that none of the grounds for denying approval specified in [section 505(d) of the FD&C Act] applies." Section 505(d) of the FD&C Act and FDA's regulation in 21 CFR 314.125(b) include grounds for refusing to approve an application. For example, FDA will refuse to approve an application if adequate tests do not show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling.[9] FDA will also refuse to approve an application if the applicant fails to provide substantial evidence of effectiveness.[10] As stated in section 505(d) of the FD&C Act, "substantial evidence" means:

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[4] See Drugs@FDA: FDA-Approved Drugs; Jatenzo Prescribing Information (March 2019), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206089s000lbl.pdf.

[5] See id.

[6] See Orange Book (https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm); search results for "Jatenzo" (last visited Dec. 20, 2019). The use code listed in the Orange Book is U-2507 "Method of treating testosterone deficiency."

[7] Section 505(a) of the FD&C Act (21 U.S.C. 355(a)) and 21 CFR part 314.

[8] Section 505(b)(1) of the FD&C Act.

[9] Section 505(d)(2) of the FD&C Act; 21 CFR 314.125(b)(3).

[10] Section 505(d)(5) of the FD&C Act; 21 CFR 314.125(b)(5).

> . . . evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

The characteristics of adequate and well-controlled clinical investigations are described in FDA's regulation in 21 CFR 314.126. FDA's guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) outlines the Agency's current thinking on acceptable approaches to meeting these statutory and regulatory requirements.[11]

Efficacy endpoints are measures intended to reflect the effects of a drug. They include assessment of clinical events (e.g., mortality, stroke, pulmonary exacerbation, venous thromboembolism); patient symptoms (e.g., pain, dyspnea, depression); measures of function (e.g., ability to walk or exercise); or a surrogate of these events or symptoms.[12] Demonstrating statistical significance on clinical trial endpoints alone, however, is insufficient. An applicant must also show that the drug provides a therapeutic, or clinically meaningful, benefit.[13] In analyzing whether a drug meets the standard for approval, FDA conducts a benefit-risk assessment. That assessment:

> takes into account the extensive evidence of safety and effectiveness submitted by a sponsor . . . as well as many other factors affecting the benefit-risk assessment . . . . This assessment [inevitably] involves both quantitative analyses and a subjective qualitative weighing of evidence.[14]

Key considerations of benefit "include the results of the clinical trials and the clinical meaning of primary and secondary endpoints, as well as appropriate analyses of subpopulations."[15] Key considerations of risk "include the adequacy of the safety database, the severity and reversibility

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[11] Available at https://www.fda.gov/media/71655/download. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[12] See, e.g., the FDA draft guidance for industry *Multiple Endpoints in Clinical Trials* (January 2017) at 2, available at https://www.fda.gov/media/102657/download. When final, this guidance will represent FDA's current thinking on this topic.

[13] See, e.g., *Warner Lambert Co. v. Heckler*, 787 F.2d 147 (3d Cir. 1986). See also FDA's guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (January 2017), available at https://www.fda.gov/media/71655/download.

[14] See *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision Making, Draft PDUFA V Implementation Plan—February 2013, Fiscal Years 2013-2017* at 1, available at http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf.

[15] Id.

of adverse events, and the potential for sub-optimal management in the post-market setting that may be of concern."[16]

C. FDA Guidance Documents

FDA guidance documents, including those containing product-specific recommendations, are not binding,[17] except in certain limited circumstances defined by statute.[18] FDA's guidance documents describe the Agency's current thinking on a topic and should only be viewed as recommendations, unless specific regulatory or statutory requirements are cited.[19] FDA is not required to issue a product-specific guidance to approve a drug application.[20] Even if FDA issues guidance, regulated parties can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.[21] The Agency recognizes that an approach other than that recommended in a guidance may support a drug approval, and the Agency considers such an approach if the data provided in the individual application provide an appropriate scientific basis.[22]

D. Section 505(q) of the FD&C Act

Section 505(q) of the FD&C Act was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85, 121 Stat. 823) and was amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144, 126 Stat. 993), which was signed into law on July 9, 2012. Section 505(q) of the FD&C Act, as originally added by FDAAA, applies to certain citizen petitions and petitions for stay of Agency action that request that the Agency take any form of action relating to a pending application submitted under 505(b)(2) or (j) of the FD&C Act and governs the manner in which these petitions are treated.

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[16] Id.

[17] See § 10.115(d) (21 CFR 10.115(d)) ("Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA").

[18] See, e.g., section 745A(a)(1) of the FD&C Act.

[19] See § 10.115.

[20] We note that the Petition refers to ANDAs in addition to NDAs. The ANDA approval process is set forth in section 505(j) of the FD&C Act. To obtain approval, an ANDA applicant is not required to submit evidence establishing the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the "listed drug" referenced by the ANDA (the "reference listed drug" or RLD) is safe and effective. Section 505(j) of the FD&C Act, together with its implementing regulations, generally requires that an ANDA must contain, among other things, information to demonstrate that the proposed drug product and the applicable RLD are the same with respect to active ingredient(s), dosage form, route of administration, strength, previously approved conditions of use, and, with certain exceptions, labeling; to demonstrate that the proposed product is bioequivalent to the RLD; and to ensure the product's identity, strength, quality, and purity. See section 505(j)(2)(A) and 505(j)(4) of the FD&C Act, 21 CFR 314.94, 21 CFR 320.21(b) and 21 CFR 314.127. FDA is not required to issue a product-specific guidance to approve either an NDA or ANDA.

[21] See § 10.115(d)(2).

[22] Similarly, the Agency's rejection of a particular alternative approach proposed by an applicant (e.g., a proposal not to conduct certain recommended studies) reflects a conclusion that the proposed approach is not adequately supported as a scientific matter, not that FDA is applying the recommendation as a *binding* requirement.

Among other things, section 505(q)(1)(F) of the FD&C Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, the Agency must take final Agency action on a petition not later than 150 days after the date on which the petition is submitted. The 150-day period is not to be extended for any reason.

II. DISCUSSION

A. Product-Specific Guidance

The Petition requests that FDA issue "clear, written guidance regarding the safety and efficacy standards required for oral [T-ester] prodrugs as testosterone ('T') replacement therapy for adult men with a deficiency or absence of endogenous T,"[23] and "[r]efuse to approve any [NDA] or [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 [. . .]."[24]

You state that "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-esters and that NDAs are reviewed in a consistent manner to avoid 'arbitrary' decisions by FDA in its review process."[25] We disagree that a guidance document is necessary to ensure consistent advice. The Petition does not provide evidence that sponsors or applicants have been provided inconsistent advice or that the Agency has made "arbitrary" decisions. To the contrary, the Petition acknowledges that FDA consistently applies accepted scientific standards to T replacement products.[26]

As described above, FDA will only approve an application after determining that the drug product meets the statutory standards set forth in section 505 of the FD&C Act and FDA's implementing regulations.[27] Although the statutory standards apply to all new drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards.[28] Accordingly, the Agency is required to exercise its scientific judgment to determine the kind and quantity of data and information an

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[23] Petition at 1.

[24] Id. at 2.

[25] Petition at 3.

[26] Petition at 4 ("FDA has not granted approval to any T replacement product since 2010 that has not met this [primary efficacy] standard"). Petition at 5 ("[S]econdary 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"). Petition at 6 ("To date, FDA has not approved any T replacement product whose T C_{max} [maximum plasma concentration] profile was not closely aligned with FDA targets").

[27] See, e.g., 21 CFR part 314.

[28] See 21 CFR 314.105(c).

applicant is required to provide to support a drug application, and these views are publicly available through guidance documents, recommendations, and other statements of policy.[29]

Your Petition refers to "FDA-mandated development requirements"[30] and asks that certain criteria for oral T replacement products be "codified" in written guidance.[31] As a general matter, FDA guidance is not *codified* like a statute or regulation. Guidance documents do not establish legally enforceable rights or responsibilities or *FDA-mandated* requirements.[32] FDA guidance is not binding on FDA or any applicant and reflects the Agency's current thinking on a topic.[33] Thus, even if FDA were to issue a product-specific guidance document on oral T-ester drug products, the Agency recognizes that an approach other than that recommended in a guidance may support a drug approval and the Agency considers such an approach if the data provided in the individual application provide an appropriate scientific basis.[34]

At this time, the Agency declines to issue a product-specific guidance on oral T-ester drug products. FDA is not required to issue a product-specific guidance to approve a drug application and has decided that issuing a product-specific guidance document on oral T-ester drug products would be an unnecessary use of the Agency's limited resources. For these reasons, your request that FDA issue product-specific guidance on oral T-ester drug products is denied. In addition, for the reason discussed above regarding the non-binding nature of guidance, your request that FDA refuse to approve an NDA or ANDA for an oral T-ester drug product for the treatment of male hypogonadism unless the application meets criteria set forth in written guidance from FDA is also denied.

B. FDA Approval of NDAs that Meet the Standards in the Petition and on the Basis of Efficacy that is Consistent with FDA Approval Precedent

Clarus also requests FDA not to approve "any pending NDA for an oral T-ester to treat male hypogonadism that fails to meet the standards for approval set forth in [the] petition," 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."[35]

Section 505(q)(1)(F) of the FD&C Act requires the Agency to take final Agency action on a petition subject to 505(q) within 150 days of submission. Therefore, we must take action on your Petition at this time, but we deny without comment the specific requests in your Petition

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[29] Id.

[30] Petition at 3.

[31] Petition at 1, 3.

[32] § 10.115(d).

[33] Id.

[34] Similarly, the Agency's rejection of a particular alternative approach proposed by an applicant (e.g., a proposal not to conduct certain recommended studies) reflects a conclusion that the proposed approach is not adequately supported as a scientific matter, not that FDA is applying the recommendation as a *binding* requirement.

[35] Petition at 1-2.

regarding how FDA should review and make approval decisions on any pending or future oral T-ester products. FDA has made no final determination on whether to approve or not approve any oral T-ester product other than Jatenzo for TRT. FDA's consideration of any currently pending or future applications for oral T-ester products will necessarily be informed by our decisions on the nature of the data and information regarding the approvability of such applications.

The FD&C Act and FDA regulations establish procedural protections for applicants in the context of application review. Section 505 of the FD&C Act and FDA's regulations in 21 CFR part 314 describe certain procedures by which FDA reviews an application and notifies an applicant if it determines that an application is approved[36] or may not be approved,[37] or identifies the deficiencies in the application and the steps an applicant may take to respond to the deficiencies.[38] In addition, the statute and regulations describe procedures under which an applicant whose application the Agency has found does not meet the requirements for approval may challenge the Agency's determination.[39] Under such procedures, applicants receive notice of an opportunity for a hearing on whether the application is approvable, with a specific time frame and process if the applicant requests such a hearing.[40] These procedures ensure that applicants have an adequate opportunity to challenge a finding by the Agency that a product does not meet the requirements for approval.

There is no evidence that by enacting section 505(q) of the FD&C Act, Congress intended to bypass the application review process or to lessen an applicant's procedural rights by requiring that the Agency make decisions that constitute final Agency action regarding the approvability of applications outside of the process established under the FD&C Act and FDA regulations.[41] Therefore, we do not interpret section 505(q) of the FD&C Act to require that the Agency render a final Agency decision within the 150-day statutory deadline on the approvability of any pending or future application for an oral t-ester product when a final decision on the approvability of such products has not yet been made.[42] Accordingly, we are denying without

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[36] See 21 CFR 314.105.

[37] See sections 505(c), (d), & (j) of the FD&C Act; 21 CFR 314.125 & 314.127.

[38] See 21 CFR 314.110.

[39] See sections 505(c)(1)(B) & 505(j)(5)(E) of the FD&C Act; 21 CFR 314.103.

[40] Id.

[41] In other citizen petition responses, we have responded to requests related to general standards for approval (e.g., bioequivalence criteria for generic drug products) that may pertain to one or more pending drug applications without commenting on the approvability of any particular aspect of a specific pending application. We believe that this approach of describing our general policies or standards for approval of a drug application (beyond the descriptions provided in this response) would not be appropriate in this case because, as stated, our review of a given application would inform our decisions regarding the sufficiency of the data and information needed for approval. We will continue to evaluate each citizen petition on a case-by-case basis on the appropriateness of responding to requests regarding any pending application.

[42] Under applicable statutory and regulatory provisions, we are generally prohibited from disclosing any determinations regarding the receipt or approvability of any pending application before we have reached a final decision on whether to approve or not approve the application. See, e.g., 21 CFR 314.430.

comment your additional requests regarding how FDA should review and make approval decisions on any pending or future oral T-ester products.

III. CONCLUSION

For the reasons described in this response, the Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research