Establishing Effectiveness for Drugs Intended to Treat Male Hypogonadotropic Hypogonadism Attributed to Nonstructural Disorders

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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TABLE OF CONTENTS

Establishing Effectiveness for Drugs Intended to Treat Male Hypogonadotropic Hypogonadism Attributed to Nonstructural Disorders Guidance for Industry[1]

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I. INTRODUCTION

- This guidance provides recommendations for establishing clinical effectiveness for drugs intended to treat male hypogonadotropic hypogonadism associated with obesity and other conditions that do not cause structural disorders of the hypothalamus or pituitary gland. These drugs should both increase serum testosterone concentrations and improve how patients feel, function, or survive.

- This guidance incorporates advice the FDA received at a December 2014 advisory committee meeting on the appropriate indicated population for testosterone therapy[2] and a December 2016 advisory committee meeting on hypogonadotropic hypogonadism.[3]

- This guidance does not address the development of drugs to treat specific conditions associated with male hypogonadotropic hypogonadism (e.g., weight management in patients with obesity).

[1] This guidance has been prepared by the Division of Bone, Reproductive, and Urologic Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] See the FDA's archived 2014 Meeting Materials, Drug Safety and Risk Management Advisory Committee web page at https://wayback.archive-it.org/7993/20161022142708/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm380883.htm.

[3] See Meeting Materials on the FDA's December 6, 2016: Meeting of the Bone, Reproductive, and Urologic Drugs Advisory Committee web page at https://www.fda.gov/AdvisoryCommittees/Calendar/ucm522253.htm.

- In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

- Male hypogonadism is characterized by serum testosterone concentrations below the lower limit of the normal range for young, healthy men with associated symptoms (e.g., reduced libido) or signs (e.g., loss of muscle mass with reduced muscle strength).

- Hypogonadism is classified as hypogonadotropic when serum gonadotropin concentrations are normal or low despite low serum testosterone concentrations.

- Men with classic hypogonadotropic hypogonadism have low serum testosterone because of intrinsic damage to the hypothalamus or pituitary gland caused by well-recognized conditions, including congenital disorders that affect sexual development or puberty (e.g., Kallmann syndrome) or following pituitary resection.

  - These men are clearly testosterone deficient; testosterone replacement therapy is the standard of care for these men when they have no desire for near-term fertility.

  - A sponsor can establish effectiveness of a testosterone drug for use in these patients by showing the drug reliably increases serum testosterone concentrations to within the normal range for young, healthy men. The design features of such trials are well established and not covered in this guidance.

- Some men who have had normal puberty and sexual development are subsequently diagnosed with hypogonadotropic hypogonadism associated with obesity or other acquired conditions in the absence of intrinsic damage to the hypothalamus or pituitary.

  - Although these men have serum testosterone concentrations below the lower limit of the normal range for young, healthy men, the associated symptoms often experienced in this population (e.g., low energy, depressed mood) are nonspecific and cannot definitively be attributed to the low testosterone concentrations. In addition, it is unclear whether these testosterone concentrations—in the absence of intrinsic damage to the hypothalamus and pituitary gland—are inappropriately low and whether increasing testosterone concentrations in these men confers clinical benefit.

  - For these reasons, serum testosterone is not a validated surrogate endpoint for establishing efficacy in these patients, and sponsors should show that an increase in serum testosterone translates into improvement in how patients feel, function, or survive. The key design features of such trials are discussed below.

III. CLINICAL TRIAL DESIGN FEATURES—KEY CONSIDERATIONS

A. Enrollment Criteria

- The trial population should have clinical and laboratory evidence of hypogonadotropic hypogonadism, including the following:
  - Low serum total testosterone concentrations in the morning on at least two occasions separated by at least 3 days, assessed using a validated assay
  - Low free testosterone concentrations in the morning on at least two occasions separated by at least 3 days using a validated assay (if there are sex-hormone binding globulin abnormalities)
  - Serum gonadotropins (follicle stimulating hormone and luteinizing hormone) that do not exceed the upper limit of the reference range
  - Symptoms or signs that the drug is intended to target
  - Normal serum prolactin concentration
  - Normal thyroid function tests (with or without thyroid hormone supplementation)
- The patients enrolled in the trial should have no intrinsic damage to their hypothalamus, pituitary glands, and testes, but the trial population should be well defined with regard to the underlying associated condition, symptoms, and signs.

B. Efficacy Endpoints

- Randomized, double-blind, placebo-controlled trials should show that the drug increases serum testosterone and provides clinically meaningful improvement in at least one symptom or sign of hypogonadism.
  - For example, a responder could be a patient who has normalized testosterone concentrations (based on pharmacokinetic sampling) and also has clinically meaningful improvement in the targeted symptoms or signs.
- Patient-reported outcome (PRO) instruments may play a central role in establishing efficacy because they provide direct evidence of how patients feel or function.

  - Sponsors should use well-defined and reliable instruments that take into account the recommendations in the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.[4]

  - Currently, the FDA is not aware of PRO instruments shown to be adequate for regulatory use to assess improvement in hypogonadal symptoms or signs. We are open to evaluating existing or modified PRO instruments assessing the important disease-related symptoms or signs in men with hypogonadism.

  - The FDA encourages development of a publicly available, fit-for-purpose PRO instrument that can be used across multiple drug development programs.[5]

- The FDA does not consider improvement in biomarkers (e.g., changes in muscle mass) that are not established surrogate endpoints[6] for how patients feel, function or survive to be sufficient for establishing evidence of clinical benefit.

- Depending on the mechanism of action, the drug could worsen or improve or have no effect on spermatogenesis.

  - For drugs that improve spermatogenesis, sponsors could establish efficacy by showing improved fertility outcomes (e.g., pregnancy in the partner). Changes in semen parameters (e.g., sperm count) alone are not sufficient for establishing efficacy because of the following:

    - The intent of the drug is to improve fertility in these men

    - Sperm count is only one measure of normal spermatogenesis

    - Improvement in semen parameters does not ensure fertility

  - For drugs that do not show an effect on spermatogenesis (or that show an adverse effect on spermatogenesis), sponsors could establish efficacy by showing improvement in other hypogonadal symptoms or signs.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[5] See the guidance for industry and FDA staff *Qualification Process for Drug Development Tools*.

[6] Established surrogate endpoints can be used to support marketing approval of a drug in a defined context without the need for additional studies to demonstrate the clinical benefit directly.