Treating Secondary Hypogonadism While Preserving or Improving Testicular Function

Opening Remarks

Bone, Reproductive, and Urologic Drugs Advisory Committee Meeting

December 6, 2016

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Outline

• Objectives and scope of this meeting
• Background
• Agenda
• Discussion and voting questions
Objectives and Scope

• To identify appropriate clinical trial design features for drugs proposed to treat secondary hypogonadism while preserving or improving testicular function

• A major goal is to identify acceptable endpoints for demonstrating clinical benefit for these drugs

• To ensure appropriate expertise, the committee includes urologists, endocrinologists, and experts in fertility, obesity, and patient-reported outcomes
Objectives and Scope (cont.)

• Products investigated in this drug space include:
  – Estrogen agonists/antagonists (e.g., clomiphene citrate)
  – Aromatase inhibitors
  – Gonadotropin receptor agonists
  – **NOT** testosterones (which can suppress spermatogenesis)

• These drugs have important side effects, but safety profiles for individual drugs are not the focus today

• The goal today is to obtain input on how to establish substantial evidence of effectiveness (clinical benefit)
Pertinent Developments with Testosterone Therapies

• In 2014, an FDA advisory committee discussed the appropriate indicated population for testosterone

• The meeting focused on “age-related hypogonadism” because of this widespread use of testosterone

• The committee overwhelmingly concluded that:
  – Efficacy and safety of testosterone have not been established for “age-related hypogonadism”
  – Available evidence supports an indication for testosterone only in men with “classic” hypogonadism
Pertinent Developments with Testosterone Therapies (cont.)

• The committee stated that clinical endpoints (not only serum testosterone concentrations) are needed to support an indication for “age-related hypogonadism”

• FDA believes this paradigm applies to all scenarios that do not reflect “classic” hypogonadism, including
  – Hypogonadism associated with obesity
  – Products that are not testosterone
Treating Secondary Hypogonadism While Improving Testicular Function

• FDA has approved drugs that raise sperm concentrations above a threshold (e.g., 1 million/mL) in azoospermic men with secondary hypogonadism
  – Is this approach still reasonable given existing assisted reproductive technologies (e.g., ICSI)?
  – What about other semen parameters?
  – When should the endpoint be pregnancy in the partner?
  – Is the same approach appropriate for azoo- and oligospermia?
  – Is the same approach appropriate for “classic” hypogonadism and for those who do not have “classic” hypogonadism?

ICSI = intracytoplasmic sperm injection
Treating Secondary Hypogonadism While Improving Testicular Function: FDA Perspective

• For a Proposed Indication Relating Only to Fertility
  – Would need to use an acceptable endpoint for fertility
  – Do not need to show improvement on other hypogonadal symptom(s) or sign(s)
  – Such drugs would be approved for shorter-term use with discontinuation when fertility is no longer desired

• For a Proposed Broader Hypogonadism Indication
  – Other endpoints would also be needed
Men Without “Classic” Hypogonadism (e.g., Hypogonadism Associated with Obesity)

• Raising serum testosterone does not establish clinical benefit
  – A product must improve hypogonadal symptom(s) or sign(s), otherwise the need for therapy is not established

• Preserving testicular function does not – by itself or with serum testosterone – establish clinical benefit
  – If a product improves hypogonadal symptom(s) or sign(s) then also preserving testicular function can be important, but discussion is needed on how to define and assess preservation
Agenda

- Presentations, with opportunities to ask questions
  1. Sergio Oehninger, M.D., Ph.D. (Guest Speaker) (40 minutes)
     - Director, Division of Reproductive Endocrinology and Fertility
       The Jones Institute for Reproductive Medicine
     - Professor and Vice Chair, Department of Obstetrics and Gynecology
       Eastern Virginia Medical School
  2. Collaborative presentation by three drug companies (1 hour)
  3. FDA (40 minutes)
     - Open public hearing
     - Committee discussion and voting
Discussion and Voting Questions
Discussion Question 1

• For drugs intended to treat secondary hypogonadism while preserving existing testicular function (e.g., maintenance of sperm parameters or demonstration of continued fertility), discuss:
  
a. The patient population that should be enrolled in clinical trials

b. How preservation of testicular function should be defined and assessed

c. Acceptable endpoints for demonstrating clinical benefit for men with classic hypogonadism and for those who do not have classic hypogonadism

d. Other trial design features that should be considered
Discussion Question 2

• For drugs intended to treat secondary hypogonadism while improving testicular function (e.g., improved sperm parameters or amelioration of infertility), discuss:

  a. The patient population that should be enrolled in clinical trials

  b. How improvement in testicular function should be defined and assessed

  c. Acceptable endpoints for demonstrating clinical benefit for men with classic hypogonadism and for those who do not have classic hypogonadism

  d. Other trial design features that should be considered
Voting Question 1

• For products intended to treat men with hypogonadism attributed to obesity, is raising serum testosterone concentrations into the normal range for young, healthy eugonadal men and preservation of spermatogenesis, as assessed by maintenance of sperm concentrations, sufficient for establishing evidence of clinical benefit?

  – If you voted “no,” describe what endpoints would be needed to provide sufficient evidence of clinical benefit for such products.

  – If you voted “yes,” specify how preservation of spermatogenesis should be defined based on sperm concentrations, and provide an explanation for your definition.
Voting Question 2

• For products intended to treat men with classic secondary hypogonadism and azoospermia or oligospermia, is raising sperm concentration above a specific threshold sufficient evidence of clinical benefit?

  a) Yes, but only for azoospermia
  b) Yes, but only for oligospermia
  c) Yes, for azoospermia and oligospermia
  d) No

Include rationale for your answer.

  – If you voted “no,” describe what endpoint(s) would be needed to provide sufficient evidence of clinical benefit for such products.

  – If you voted “yes,” (chose a, b, or c), specify the threshold for sperm concentration that should be exceeded to establish evidence of clinical benefit and explain why you selected that threshold.
Voting Question 3

• For products intended to treat men with secondary hypogonadism and azoospermia or oligospermia, but who do not have classic hypogonadism, is raising sperm concentration above a specific threshold sufficient evidence of clinical benefit?

  a) Yes, but only for azoospermia
  b) Yes, but only for oligospermia
  c) Yes, for azoospermia and oligospermia
  d) No

Include rationale for your answer.

  – If you voted “no,” describe what endpoint(s) would be needed to provide sufficient evidence of clinical benefit for such products.

  – If you voted “yes,” (chose a, b, or c), specify the threshold for sperm concentration that should be exceeded to establish evidence of clinical benefit and explain why you selected that threshold.
FDA Clinical Perspective on Development of Non-Testosterone Products to Treat Male Secondary Hypogonadism

Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) Meeting
December 6, 2016

Olivia J. Easley, M.D.
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Male Hypogonadism

Low serum testosterone (T) + symptoms/signs

Primary – high FSH, LH
- Congenital
- Acquired

Secondary – low or normal FSH, LH
- Congenital
- Acquired

FSH=follicle stimulating hormone; LH=luteinizing hormone
Diagnostic Criteria for Hypogonadism

• Morning serum total testosterone below the lower limit of normal (typically <300 ng/dL) on two separate occasions

• Consistent signs and symptoms (e.g., incomplete sexual development, decreased libido, gynecomastia)
“Classic” Hypogonadism

• **Classic hypogonadism** – caused by intrinsic pathology of the hypothalamic pituitary testicular (HPT) axis due to specific, well-recognized medical conditions, such as
  – Klinefelter syndrome
  – Kallmann syndrome
  – Pituitary tumor/resection

• Testosterone replacement is necessary in these men for development or maintenance of secondary sexual characteristics
“Non-classic” Hypogonadism

• Low testosterone and associated symptoms (that may or may not be related to the low testosterone) in men with other conditions

• Examples include
  – Age-associated hypogonadism
  – Hypogonadism attributed to obesity

• There is no definitive evidence that raising testosterone in these men leads to clinical benefit and is safe
Treatment of Hypogonadism in Clinical Practice

Address reversible causes

Desires fertility in short or intermediate term?

no

Testosterone replacement therapy (TRT)
FDA Approval Paradigm for Testosterone Replacement Therapy

• A typical phase 3 trial
  – Enrolls “hypogonadal” men with confirmed morning serum testosterone <300 ng/dL
  – Is designed to show the product can reasonably increase serum testosterone into the normal range for young, healthy, eugonadal men
  – Does not provide substantial evidence of improvement in hypogonadal signs or symptoms

• Current paradigm cannot establish efficacy or safety in men without “classic” hypogonadism
FDA Approved Use of Testosterone

Indication:

- Drug X is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:
  - **Primary hypogonadism (congenital or acquired):** testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter Syndrome, chemotherapy, or toxic damage from alcohol or heavy metals.
  - **Hypogonadotrophic hypogonadism (congenital or acquired):** idiopathie gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.
Limitation of use:

- Safety and efficacy of Drug X in men with “age-related hypogonadism” have not been established.
Treatment in Clinical Practice of Hypogonadal Men Desiring Fertility

Exogenous testosterone

Treatment in Clinical Practice of Hypogonadal Men Desiring Fertility

Address reversible causes

Desires fertility in short or intermediate term?

Yes

Primary hypogonadism: donor sperm, assisted reproductive technology (ART), adoption

Secondary hypogonadism: urinary human chorionic gonadotropin (hCG) +/- follicle stimulating hormone (FSH)
Treatment Options for Hypogonadal Men Desiring Fertility

• hCG
  – Pharmacologic activity nearly identical to luteinizing hormone (LH)
  – Available since 1930s and approved for “selected cases of hypogonadotrophic hypogonadism in males”
  – Used to simultaneously raise testosterone and stimulate spermatogenesis

• Recombinant FSH (e.g., Follistim, Gonal-F)
  – Approved since 2000 for induction of spermatogenesis in men with hypogonadotrophic hypogonadism
  – Shown in open-label trials to increase the percentage of azoospermic men achieving a sperm concentration ≥1 million/mL
Assisted Reproductive Technology for Treatment of Male Infertility

- Intrauterine insemination – mild male infertility (total motile sperm count >5 million/ejaculate)
- *In vitro* fertilization (IVF)
- Intracytoplasmic sperm injection (ICSI) – moderate-to-severe male factor infertility, including severe oligospermia
Non-Testosterone Alternatives to Treating Male Secondary Hypogonadism

• Interest in products that either preserve or improve fertility

• Candidate drug classes:
  – Gonadotropins (expensive, no available oral formulations)
  – Estrogen receptor agonists/antagonists
  – Aromatase Inhibitors
Estrogen Receptor Agonist/Antagonists

- Blocks negative feedback of estradiol at hypothalamus and pituitary
- Increases LH/FSH → increases endogenous testosterone production
- May not suppress spermatogenesis
- Require intact hypothalamic-pituitary-testicular axis
Clomiphene Citrate

- Approved for treatment of ovulatory dysfunction in women desiring pregnancy
- Investigated as testosterone alternative and treatment for infertility
- Majority of published trials uncontrolled, small, short duration in men with hypogonadism associated with age or obesity
- Appears to increase serum testosterone to some extent but no definitive evidence this leads to clinical benefit
- Raised sperm concentration in one small study involving three men with hypogonadotrophic hypogonadism and azoo- or oligospermia
Enclomiphene Citrate

• Isomer of clomiphene citrate

• Two published trials in obese men with secondary hypogonadism (testosterone <300 ng/dL) and baseline sperm concentration >15 million/mL compared enclomiphene to placebo and to exogenous testosterone in increasing testosterone and maintaining sperm concentration

• Composite efficacy endpoint -- the percentage of men with normal serum testosterone AND sperm concentration >10 million/mL at 16 weeks
Enclomiphene Citrate (continued)

• So, intent is to raise serum testosterone and maintain sperm in obese men with secondary hypogonadism:
  – No definitive evidence that raising testosterone in these men leads to clinical benefit
  – Sperm concentrations are only one marker of normal spermatogenesis and do not assure fertility; the clinical utility of thresholds (e.g., >10 million/mL) is unclear
  – “Maintaining” sperm at or near pre-treatment levels – even if shown to be meaningful – is not relevant if the therapy has not been shown to provide clinical benefit for the condition being treated (hypogonadism) – otherwise why should patients receive the therapy in the first place?
Aromatase Inhibitors

- Include tamoxifen, letrozole
- Approved for treatment of breast cancer
- Decrease estradiol $\rightarrow$ less negative feedback at pituitary $\rightarrow$ increases FSH and LH $\rightarrow$ increases testosterone
- Studied primarily in men with hypogonadism attributed to obesity
- Small, open-label trials show that testosterone is increased and estradiol is decreased
FDA PERSPECTIVE AND REGULATORY CHALLENGES
Treating “Non-Classic” Secondary Hypogonadism (e.g., Associated with Obesity) While Preserving Testicular Function

• The clinical benefit of raising testosterone in this patient population has not been established - one approach could be to show that the product improves sign(s) or symptom(s) of hypogonadism, but challenges include:
  – Many signs and symptoms are non-specific
  – Currently no patient reported outcome measure to assess hypogonadal symptoms meets FDA validation criteria
• If the goal is to also “maintain testicular function”
  – How should this be defined and assessed?
  – Note that “maintaining testicular function” is not treating the underlying condition (hypogonadism) and cannot establish that increasing testosterone in these patients leads to clinical benefit
Treating Secondary Hypogonadism While Improving Testicular Function

• Can clinical benefit be established based on raising testosterone and increasing sperm concentrations above a specific threshold? If no, what endpoints should be required? If yes, what threshold should be used?

• Should other semen parameters be assessed?
Limitations of Semen Analysis in Assessing Testicular Function

• Analysis does not definitively distinguish fertile from infertile men
• Extensive overlap between fertile and infertile men in sperm concentration, motility and morphology
• Other factors may affect male fertility that are not detectable on standard semen analysis
  – Oxidative stress
  – Sperm DNA fragmentation
Treating Secondary Hypogonadism While Improving Testicular Function

• Sperm concentrations do not guarantee fertility. Are fertility outcomes needed? For classic hypogonadism, could fertility outcomes feasibly be obtained given the smaller numbers of such patients?

• Should the same approach be applied to azoospermic men and oligospermic men? Should oligospermic men have a diagnosis of infertility at baseline?

• Should the same approach be applied for “classic” hypogonadism as for “non-classic” hypogonadism?
References


4 – Nguyen, CP, et. al. Testosterone and “Age-Related Hypogonadism” – FDA Concerns. NEJM 2015; 373: 689-691.


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REGULATORY APPROACH TO CLINICAL OUTCOME ASSESSMENT REVIEW FOR DRUG DEVELOPMENT

BONE, REPRODUCTIVE AND UROLOGIC DRUGS ADVISORY COMMITTEE (BRUDAC) MEETING DECEMBER 06, 2016

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www.fda.gov
"... the FDA is working to give patients a greater voice in medical product development and evaluation.

Success in these efforts could lead to tremendous advances in the understanding of health, disease, diagnosis, treatment, and recovery, ultimately transforming patients’ experience of health care by enabling physicians to tailor care to an individual’s specific needs and preferences.

Including clinical outcomes that are meaningful to patients can profoundly influence drug development by ensuring the patient voice is captured."

Hunter NL, O’Callaghan KM, Califf RM. JAMA 2015
Integrating Patients into the Drug Development Process

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Pre-Clinical</th>
<th>Clinical (Phase I –III)</th>
<th>Pre-Launch &amp; Approval</th>
<th>Post-Approval</th>
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- Patient-informed needs
- Patient-informed Clinical Trial Design
- Patient-Reported Outcomes
- Communicating Benefit-Risk to Patients
- Patient-Centered Outcomes
Purpose of an Outcome Assessment

• To determine whether or not a drug has been shown to provide **clinical benefit** to patients
  – A **positive clinically meaningful effect** of an intervention on how an individual *feels, functions,* or *survives*

• A conclusion of clinical benefit is described in labeling in terms of the concept of interest (outcome) measured
Types of Outcome Assessments

- **Clinical Outcome Assessments (COAs)**
  - Performance Outcomes (PerfOs)
  - Clinician-reported Outcomes (ClinROs)
  - Observer-reported Outcomes (ObsROs)
  - Patient-reported Outcomes (PROs)

- **Surrogates**
  - Often a biomarker* that is intended as a substitute for how a patient feels, functions, or survives

*Biomarker: a physiologic, pathologic, or anatomic characteristic that is objectively measured and evaluated as an indicator of some normal or abnormal biologic function, process or response to a therapeutic intervention
“Feels, Functions, or Survives”

• General reasons for a patient to want to take a drug would be:
  – *Improved survival*
  – Resulted in a benefit that was detectable by the patient (improvement in symptoms, improvement in functional capacity)
  – *Decreased probability* of developing an undesirable complication (e.g., stroke)
1. Understanding the Disease or Condition

- Natural history
- Patient subpopulations
- Real-world clinical practice
- Patient/caregiver perspectives

2. Conceptualizing Clinical Benefit

- Identify measurement concepts (clinically important outcomes)
- Define context of use
- Determine planned endpoints
- Select clinical outcome assessment type

3. Selecting/Developing the COA

- Search for existing COA
- Modify an existing COA
- Develop a COA de novo
Development Process for a Clinical Outcome Assessment

**SPOKE I**
Identify Context of Use and Concept of Interest
- Outline hypothesized concepts and potential claims
- Determine intended population
- Determine intended application/characteristics (type of scores, mode and frequency of administration)
- Perform literature/expert review
- Develop hypothesized conceptual framework
- Position assessment within a preliminary endpoint model
- Document context of use and concept of interest

**SPOKE II**
Draft Instrument & Evaluate Content Validity
- Obtain patient or other reporter input
- Generate new items
- Select recall period, response options and format
- Select mode/method of administration/data collection
- Conduct cognitive interviewing
- Pilot test draft instrument
- Finalize instrument content, format and scoring rule
- Document content validity

**SPOKE III**
Cross-Sectional Evaluation of Other Measurement Properties
- Assess score reliability (test-retest or inter-rater) and construct validity
- Establish administration procedures & training materials
- Document measure development
- Prepare user manual

**SPOKE IV**
Longitudinal Evaluation of Measurement Properties/Interpretation Methods
- Assess ability to detect change and construct validity
- Identify responder definition(s)
- Provide guidelines for interpretation of treatment benefit and relationship to claim
- Document all results
- Update user manual

**SPOKE V**
Modify Instrument
- Identify a new context of use
- Change wording of items, response options, recall period, or mode/method of administration/data collection
- Translate and culturally adapt
- Evaluate modifications using spokes I – IV
- Document all changes
Clinical Outcome Assessment Review

- Was the instrument appropriately used in the trial?
- Was the instrument developed in the studied population?
- Does the instrument measure what it is supposed to measure?
- Is the instrument reliable?
- Does the instrument measure what is important to the patient?
- Did one question drive the result?
- What does a score improvement of 2-points mean?
- Is the instrument sensitive to detect change over time?

If there are multiple concepts/domains being measured, do they overlap?
FDA PRO Guidance (2009)

- Defines **good measurement principles** to consider for “well-defined and reliable” (21 CFR 314.126) PRO measures intended to provide evidence of clinical benefit
  - Goal: Avoid labeling statements that may be false or misleading

- All clinical outcome assessments can benefit from the good measurement principles described within the guidance

- Provides **optimal approach** to PRO development; flexibility and judgment needed to meet practical demands
Good Measurement Principles

• The assessment is appropriate for its context of use.
• The assessment directly/indirectly measures the most important concepts to the patient for that disease.
• The assessment’s content/concepts are well-defined.
• The assessment can generate consistent and reproducible data.
• The assessment can measure what it is supposed to measure.
• The assessment is sensitive to detect change whether it is improvement or deterioration.
• The assessment’s score change is interpretable and reflective of meaningful changes.
Case Example

- Symptomatic secondary hypogonadism in adult males

Symptoms that might be explored:
- Reduced sexual desire (libido) and activity

Context of Use
Male adults (>18y) with symptomatic secondary hypogonadism

Clinical Benefit
Resolution of clinical signs and symptoms

Concept of Interest
Severity of Hypogonadism Symptoms

Clinical Outcome Assessment
Symptoms: Patient-reported symptom tool

Endpoint
Symptoms: Score change from baseline
Considerations for Using COAs in Secondary Hypogonadism

• Potential trial endpoints
  – Endpoints related to sign/symptom improvement
  – Endpoints related to physical functioning

• Measuring sign/symptom improvement
  – Prioritize concepts to include core signs and symptoms
  – Enrich trial with symptomatic patients
  – Sufficient symptom score at enrollment

• Measuring functional improvement
  – Prioritize concepts to include core aspects of functioning attributed to disease
  – Sufficient functional impact score at enrollment
Pathways for FDA Review & Advice: Clinical Outcome Assessments

1. IND/NDA/BLA Pathway
   - Within an individual drug development program
   - Investigational New Drug (IND) submissions to FDA
   - Potential to result in labeling claims

2. DDT COA Qualification Pathway
   - Outside of an individual drug development program
   - Development of novel COAs for use in multiple drug development programs
   - Potential to result in qualification of COA

3. Critical Path Innovation Meetings Pathway
   - Outside of an individual drug development program
   - Potential for general CDER advice on specific methodology or technology (e.g., COA) in early development stages

DDT = Drug Development Tool; COA = Clinical Outcome Assessment; PRO = Patient-Reported Outcome
NDA = New Drug Application; BLA = Biologics Licensing Application
Helpful Links

• FDA’s Patient-Reported Outcome (PRO) Guidance for Industry:

• FDA’s DDT Qualification Program Guidance for Industry:

• FDA’s DDT Clinical Outcome Assessment Qualification Program webpage:
    • Includes Roadmap and Wheel and Spokes diagrams