Industry Presentation

U.S. Food and Drug Administration
Bone, Reproductive and Urologic Drugs
Advisory Committee
December 6, 2016
Meeting Objectives

- …discuss appropriate clinical trial design features, including acceptable endpoints for demonstrating clinical benefit, for drugs intended to treat secondary hypogonadism while preserving or improving testicular function, including spermatogenesis
Different Development Pathways

Three Sponsors:

- Different drug classes
- Different indications
- Different proposals

- **MHB Labs Inc.**
  - Human Chorionic Gonadotrophin for classical secondary hypogonadism

- **Veru Healthcare**
  - SERM for infertility

- **Repros Therapeutics Inc.**
  - Estrogen antagonist for obesity-associated secondary hypogonadism
Non Testosterone Therapies

- All 3 companies agree on the need for non-testosterone therapies
- First talk will be a general overview of secondary hypogonadism
- Talks by each sponsor on their drug class
# Presentation Agenda

<table>
<thead>
<tr>
<th>Session</th>
<th>Speaker</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
<td>Mike Wyllie, PhD</td>
<td>Managing Director, Global Pharma Consulting, Ltd.</td>
</tr>
<tr>
<td><strong>Treatment Considerations for Secondary Hypogonadism</strong></td>
<td>Mohit Khera, MD</td>
<td>Associate Professor of Urology, Baylor College of Medicine</td>
</tr>
<tr>
<td><strong>Sperm Concentration Endpoint for Fertility</strong></td>
<td>Edward Kim, MD</td>
<td>Professor of Surgery, University of Tennessee Graduate School of Medicine</td>
</tr>
<tr>
<td><strong>Human Chorionic Gonadotrophin</strong></td>
<td>Mohit Khera, MD</td>
<td>Associate Professor of Urology, Baylor College of Medicine</td>
</tr>
<tr>
<td><strong>Diagnostic Categories of Hypogonadism and Secondary Hypogonadal Population</strong></td>
<td>Frederick Wu, MD</td>
<td>Professor of Medicine and Endocrinology, University of Manchester</td>
</tr>
<tr>
<td><strong>Weight Associated, Secondary Hypogonadism: An Acquired Estrogen - Dependent Disorder</strong></td>
<td>Andrew McCullough, MD</td>
<td>Director of Male Sexual Health, Urology Dept., Lahey Health and Medical Center</td>
</tr>
<tr>
<td><strong>Conclusions</strong></td>
<td>Mike Wyllie, PhD</td>
<td>Managing Director, Global Pharma Consulting, Ltd.</td>
</tr>
</tbody>
</table>
# Presentation Agenda

<table>
<thead>
<tr>
<th>Section</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
<td>Mike Wyllie, PhD</td>
</tr>
<tr>
<td></td>
<td>Managing Director, Global Pharma Consulting, Ltd.</td>
</tr>
<tr>
<td><strong>Treatment Considerations for Secondary Hypogonadism</strong></td>
<td>Mohit Khera, MD</td>
</tr>
<tr>
<td></td>
<td>Associate Professor of Urology, Baylor College of Medicine</td>
</tr>
<tr>
<td><strong>Sperm Concentration Endpoint for Fertility</strong></td>
<td>Edward Kim, MD</td>
</tr>
<tr>
<td></td>
<td>Professor of Surgery, University of Tennessee Graduate School of Medicine</td>
</tr>
<tr>
<td><strong>Human Chorionic Gonadotrophin</strong></td>
<td>Mohit Khera, MD</td>
</tr>
<tr>
<td></td>
<td>Associate Professor of Urology, Baylor College of Medicine</td>
</tr>
<tr>
<td><strong>Diagnostic Categories of Hypogonadism and Secondary Hypogonadal Population</strong></td>
<td>Frederick Wu, MD</td>
</tr>
<tr>
<td></td>
<td>Professor of Medicine and Endocrinology, University of Manchester</td>
</tr>
<tr>
<td><strong>Weight Associated, Secondary Hypogonadism: An Acquired Estrogen - Dependent Disorder</strong></td>
<td>Andrew McCullough, MD</td>
</tr>
<tr>
<td></td>
<td>Director of Male Sexual Health, Urology Dept., Lahey Health and Medical Center</td>
</tr>
<tr>
<td><strong>Conclusions</strong></td>
<td>Mike Wyllie, PhD</td>
</tr>
<tr>
<td></td>
<td>Managing Director, Global Pharma Consulting, Ltd.</td>
</tr>
</tbody>
</table>
Treatment Considerations for Secondary Hypogonadism

Mohit Khera, M.D., M.B.A., M.P.H.
Associate Professor of Urology
Scott Department of Urology
Baylor College of Medicine
Houston, TX
Secondary Hypogonadism

- Secondary hypogonadism (hypogonadotrophic hypogonadism) is defined by low serum testosterone concentrations in association with low or normal serum concentrations of luteinizing hormone.
- Testosterone may be inappropriate for treatment of many cases of secondary hypogonadism.
- There is a clinical need for non-testosterone products to treat secondary hypogonadism.
Disadvantages with Testosterone Replacement

• Suppresses testicular androgen production
• Suppresses spermatogenesis and can cause infertility
• Risks associated with abuse and dependence (FDA MedWatch)
• Topical T formulations have risk of transference to children and women
Non-Testosterone Treatments for Secondary Hypogonadism

• Non-testosterone approaches:
  1. Direct stimulation of testicular Leydig cells
  2. Modulation of pituitary function by estrogen receptor antagonists
  3. Selective estrogen receptor modulators (SERMs) for infertility

• Advantages of non-testosterone formulations:
  1. Maintenance or improvement in spermatogenesis
  2. Preservation of testicular volume
  3. Decreased potential for misuse/abuse
  4. Decreased potential for accidental transference
Hypothalamus

Anterior Pituitary

Sertoli Cells

Leydig Cell

Germinal Epithelium

FSH

LH

Direct Stimulation

Estrogen

Testosterone → Estrogen

Inhibin

SERMs

Estrogen Receptor Antagonists
Direct Stimulation of Testicular Leydig Cells

• Goal: directly stimulate LH receptors on testicular Leydig cells to produce testosterone

• Human chorionic gonadotropin (hCG) directly binds LH receptors in the testis and stimulates Leydig cell production of testosterone

• hCG has been shown to be an effective treatment for restoring serum testosterone levels to the normal range

• hCG has long been used for the treatment of male infertility
Estrogen Receptor Antagonists

- Estrogen receptor antagonists block estrogen receptors in the hypothalamus and pituitary
- Block the normal negative feedback of circulating estradiol
- Result: increase in LH secretion which leads to increased testosterone production
Selective Estrogen Receptor Modulators (SERMs)

- SERMs competitively bind to estrogen receptors on the hypothalamus and pituitary gland.
- SERMs differ from pure estrogen receptor agonists and antagonists is that their action is different in various tissues.
- In the brain SERMs act as antagonists.
- Results:
  - Increase in LH secretion which leads to increased testosterone production.
  - Some studies have found improvement in sperm production¹.

¹El Sheikh et al Andrology. 2015 Sep;3(5):864-7
Advantages of Treating Secondary Hypogonadism with Non-Testosterone Formulations
Maintenance or Improvement in Spermatogenesis
Studies in Male Contraception: Testosterone

• 271 men received 200 mg TE weekly
• 157 (65%) azoospermic at 6 months
  • Mean time to azoospermia 120 days
• Recovery follow-up (n=230: 85%)
  • 84% to $\geq 20$ million/mL (median 3.7 months)
  • Only 46% able to return to baseline sperm density at an average of 6.7 months

Preservation of Testicular Volume

Effect of Exogenous Testosterone on Testis Size

• 39 hypogonadal men treated with testosterone enanthate (200mg) weekly or bimonthly for 4 months

• 54% of men had testicular atrophy at 4 months
  • Weekly TRT - 19% loss in testicular volume
  • Bimonthly TRT - 16% loss in testicular volume

• Of 46% of men that did not experience testicular atrophy, up to 12 additional weeks of TRT resulted in 23% loss in testicular volume in 76% of these men

• Decrease in testicular volume was directly related to decrease in sperm count

Decreased Potential for Misuse and Abuse of Testosterone Therapy

• Non-testosterone formulations rely solely on the testicles’ ability to produce testosterone

• Non-testosterone formulations are unlikely to achieve supraphysiologic levels of serum testosterone as seen with exogenous testosterone formulations
Decreased Risk of Transference

- Topical testosterone products contain a black box warning regarding the risk of transference.
- Non-testosterone formulations would not carry this same risk.

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE
See full prescribing information for complete boxed warning.

- Virilization has been reported in children who were secondarily exposed to testosterone gel. (5.2, 6.2)
- Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel. (2.2, 5.2)
- Healthcare providers should advise patients to strictly adhere to recommended instructions for use. (2.2, 5.2, 17)
## Aspects of Testosterone and Non-Testosterone Products

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Testosterone Formulations</th>
<th>Non-Testosterone Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restore serum testosterone</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Spermatogenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suppress</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Maintain/Restore</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Restore</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Intra-testicular testosterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suppress</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Maintain/Restore</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Restore</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Aspects of Testosterone and Non-Testosterone Products

<table>
<thead>
<tr>
<th></th>
<th>Testosterone Formulations</th>
<th>Non-Testosterone Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suppress</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Maintain</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Restore</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Transference risk</td>
<td>Yes*</td>
<td>No</td>
</tr>
</tbody>
</table>

*Topical testosterone formulations
<table>
<thead>
<tr>
<th>Presentation Agenda</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Treatment Considerations for Secondary Hypogonadism</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Sperm Concentration Endpoint for Fertility</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Human Chorionic Gonadotrophin</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Diagnostic Categories of Hypogonadism and Secondary Hypogonadal Population</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Weight Associated, Secondary Hypogonadism: An Acquired Estrogen - Dependent Disorder</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Conclusions</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Sperm concentration is an acceptable endpoint for demonstrating clinical benefit in men who have oligozoospermia (impaired spermatogenesis) and hypogonadotropic hypogonadism as a cause of male infertility

Edward D. Kim, M.D.
Professor of Surgery/Division of Urology
University of Tennessee Graduate School of Medicine
Knoxville, TN
Definition of Hypogonadism: Endocrine Society Guidelines

“A clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis.”

Abnormal sperm concentration is an important criterion for the presence of hypogonadism in infertile men

Definition of Infertility:
American Society of Reproductive Medicine

“The inability to achieve a pregnancy through natural means after 1 year.“

- The male factor is contributory to 50% of infertile couples.
- Hypogonadotrophic hypogonadism with oligozoospermia is a cause of 0.6-2% male infertility: an estimated 16,000-56,000 men per year.

Practice Committee ASRM, 2004.
“Semen analysis is the cornerstone of the laboratory evaluation of the infertile male and helps to define the severity of the male factor.”\(^1\)

Sperm concentration reflects sperm production and is widely used for decision-making:
- Referral for evaluation
- Treatment choices
  - Drugs
  - Procedures

1. Practice Committee ASRM, 2012
Improvement in sperm concentration $\geq 15$ million/mL is an acceptable measure of clinical benefit.

Oligozoospermia (<15 million sperm/mL) correlates with reduced fertility in the male.
- 95% of fertile men had a sperm concentration of ≥15 million/mL
- Clinical relevance—Data were obtained from fertile men

Hypogonadism is defined as an abnormal number of spermatozoa and a diminished production of testosterone, not by the inability to initiate a pregnancy.

Sperm Concentration Influences Time to Pregnancy

## Comparison of Concentration vs TMSC

<table>
<thead>
<tr>
<th>Sperm Concentration</th>
<th>Total Motile Sperm Count (TMSC)</th>
</tr>
</thead>
</table>
| ≥15 million sperm/ml | • <1-5 million/ml, <5 million/ml overall  
|                     | • >1 million/ml (IMC) for IUI  
|                     | • 5-10 million/ml for IUI  
|                     | • Pre-wash vs post-wash |
| WHO, 5th edition    | Variety of non-validated publications |
| Spontaneous pregnancy | Artificial pregnancy |
| Guidelines utilize for clinical decision-making | Not used by Guidelines |
MSS-722: A fixed combination of trans- and cis-clomiphene isomers (SERM)

- Clomiphene citrate demonstrates improvement in sperm concentration.¹
  - However, no established dose, dose schedule, or appropriate patient population
  - May account for inconsistent clinical results

- The most appropriate patient population for treatment with MSS-722 that may demonstrate consistent efficacy:
  - Men with oligozoospermia and secondary hypogonadism as a cause of male infertility

Clinical Trial Design: MSS-722

Men who have oligozoospermia (≤15 million/mL) and secondary hypogonadism as cause for male infertility

Randomized, placebo-controlled, 5 month study

Proportion of men who achieve a sperm concentration of >15 million/mL is clinical benefit
Patient Population and Assessment of Clinical Benefit

- Evaluation
  - Semen analysis
  - Male factor infertility
  - Endocrine evaluation

- Sperm concentration < 15 million/mL
- Low to low-normal LH

Secondary hypogonadism with oligozoospermia

Treat with product for 2 cycles

- Clinical benefit
  - Nonoligozoospermia
  - Sperm concentration > 15 million/mL

- Failure
  - Impaired spermatogenesis: Oligozoospermia
  - Sperm concentration < 15 million/mL

Go to other therapies including assisted reproductive procedures
Summary

- Definition of hypogonadism includes failure to produce a normal number of spermatozoa.

- Sperm concentration is the cornerstone of the evaluation of the infertile male and helps to define the severity of the male factor.
  - WHO 5th edition defines ≤15 million sperm/mL as the lower reference range (impaired spermatogenesis)

- MSS-722 will study men with oligozoospermia (≤15 million/mL) and hypogonadotrophic hypogonadism as a cause of male infertility.
  - Primary endpoint is sperm concentration
  - Clinical benefit is improvement of sperm concentration (>15 million/mL). Non-responders may need aggressive therapies such as ART.
# Presentation Agenda

| Introduction | Mike Wyllie, PhD  
Manager, Global Pharma Consulting, Ltd. |
|-------------|--------------------------------------------------|
| Treatment Considerations for Secondary Hypogonadism | Mohit Khera, MD  
Associate Professor of Urology, Baylor College of Medicine |
| Sperm Concentration Endpoint for Fertility | Edward Kim, MD  
Professor of Urology, University of Tennessee Graduate School of Medicine |
| Human Chorionic Gonadotrophin | Mohit Khera, MD  
Associate Professor of Urology, Baylor College of Medicine |
| Diagnostic Categories of Hypogonadism and Secondary Hypogonadal Population | Frederick Wu, MD  
Professor of Medicine and Endocrinology, University of Manchester |
| Weight Associated, Secondary Hypogonadism: An Acquired Estrogen - Dependent Disorder | Andrew McCullough, MD  
Director of Male Sexual Health, Urology Dept., Lahey Health and Medical Center |
| Conclusions | Mike Wyllie, PhD  
Manager, Global Pharma Consulting, Ltd. |
Human Chorionic Gonadotropin for the Treatment of Secondary Hypogonadism

Mohit Khera, M.D., M.B.A., M.P.H.
Associate Professor of Urology
Scott Department of Urology
Baylor College of Medicine
Houston, TX
Human Chorionic Gonadotrophin (hCG)

- Naturally occurring hormone
- Only currently approved drug for secondary hypogonadism
- Clinical experience and regulatory approval >40y
- Acts directly on Leydig cells of testes to increase endogenous production of T
- New formulations in development
Physiology of hCG

• Best known as serum marker for pregnancy
• Produced by syncytiotrophoblast cells found in placenta and in gonads
• hCG mimics actions of LH to stimulate endogenous testosterone production
• Binds to same receptor as LH on fetal and adult testicular Leydig cells
Clinical Uses of hCG

- Best-known as fertility treatment to induce spermatogenesis in azoospermic men with secondary hypogonadism
- Frequently used as treatment to stimulate testosterone production in men with secondary hypogonadism
- Preservation of fertility in men undergoing testosterone therapy
- Pediatric use for cryptorchidism
- Ovulation induction in women
hCG and Testosterone

**Liu et al, JCEM, 2002:**
- Double-blind Randomized Controlled Trial: 40 men with androgen deficiency treated with hCG injections twice weekly or placebo
- Stable increase in serum testosterone levels within the normal range after 3 months of treatment

**Roth et al, JCEM, 2010:**
- 37 healthy men received a GnRH antagonist and were treated with low doses of hCG daily or Testosterone gel for 10 days
- Dose-response relationship between hCG and serum testosterone levels

Linear dose response relationship between low-dose hCG and serum T
Adapted from Roth et al, JCEM, 2010

Recovery of Spermatogenesis and hCG

• hCG alone or in conjunction with human menopausal gonadotropin (hMG) or recombinant human follicle stimulating hormone (r-hFSH) can restore spermatogenesis in some men with azoospermia and secondary hypogonadism¹

• hCG therapy alone can maintain sperm production for up to two years in previously azoospermic men²

hCG Preserves Fertility and Intra-Testicular Testosterone Production in Men on Testosterone Therapy

- 26 men treated with daily TRT gel or weekly T injections
- HCG 500 IU every other day
- Follow-up 6.2 months
- After 6 months, there was only a slight decline in sperm density and motility (p>0.05)

Coviello et al. J Clin Endocrinol Metab, 90(5):2595-2602, 2005

- 29 normal healthy fertile men
- Randomized to receive testosterone enanthate 200mg per week plus hCG at a doses of 0, 125, 250, or 500IU twice weekly
- Despite supraphysiologic doses of T, high levels of intra-testicular testosterone were maintained with administration of low-dose hCG
Currently Approved Indications for hCG

• Secondary hypogonadism

  “Selected cases of hypogonadotrophic hypogonadism in males”

• Cryptorchidism not due to obstruction

• Induction of ovulation for female infertility
Clinical Need for New hCG Formulations

- Current formulations are inconvenient:
  - Reconstitution of lyophilized powder
  - Refrigeration required after reconstitution
  - Self-injections 2-3x per week

- Inconvenience is a challenge for patient care
  - Treatment initiation
  - Compliance
  - Persistence

- Clinical need for more convenient formulations
  - Longer duration of action
  - Greater stability
Trial Endpoints for New hCG Formulations

• An extended release hCG formulation in development is expected to follow current hCG indications

FDA Briefing Document:
• Recognizes hCG as effective for men with classical secondary hypogonadism
• FDA Approval Paradigm for TRT is “acceptable for patients with classic hypogonadism, because replacing testosterone in these patients is clearly necessary for the development and/or maintenance of secondary sexual characteristics.”

• New hCG formulations would follow the FDA Approval Paradigm for TRT

Well-Recognized Medical Causes of Secondary Hypogonadism

- Pituitary tumors or infiltrative disease
- Hyperprolactinemia
- Pituitary injury (traumatic or iatrogenic Injury from Surgery)
- Exogenous steroid use
- Chronic opioid therapy/dependence
- Certain recognized chronic systemic illness (HIV, cirrhosis, chronic renal failure)
Clinical Trial Design Features

Same inclusion/exclusion criteria as for T products plus low or normal LH

Trial design should demonstrate that new hCG formulations achieve key pharmacokinetic endpoints used for T products

Additional indications beyond classical secondary hypogonadism (e.g. preservation or improvement of spermatogenesis) would require additional clinical endpoints

<table>
<thead>
<tr>
<th>Key Pharmacokinetic Endpoints for T products</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 75% of subjects are to achieve an average serum testosterone concentration ($C_{avg}$) within the normal range with the lower bound of the associated 95% confidence interval at least 65%.</td>
</tr>
<tr>
<td>The maximum serum testosterone concentration ($C_{max}$) is to be ≤1500 ng/dL in at least 85% of subjects</td>
</tr>
<tr>
<td>Testosterone $C_{max}$ is to be between 1800 and 2500 ng/dL in not more than 5% of subjects</td>
</tr>
<tr>
<td>Testosterone $C_{max}$ is to be &gt;2500 ng/dL in no subject</td>
</tr>
</tbody>
</table>
# Trial Endpoints for hCG Formulations

<table>
<thead>
<tr>
<th>Indication</th>
<th>Intended Population</th>
<th>Trial Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical secondary hypogonadism</td>
<td>Men with classical secondary hypogonadism</td>
<td>Serum T levels alone</td>
</tr>
<tr>
<td>Preservation of fertility</td>
<td>Men on TRT wishing to preserve fertility</td>
<td>Serum T plus sperm concentration</td>
</tr>
<tr>
<td>Treatment of infertility</td>
<td>Men with azoospermia or oligospermia (concentration &lt;15M/ml)</td>
<td>Serum T plus sperm concentration</td>
</tr>
</tbody>
</table>
## Presentation Agenda

<table>
<thead>
<tr>
<th>Section</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
<td>Mike Wyllie, PhD</td>
</tr>
<tr>
<td></td>
<td>Managing Director, Global Pharma Consulting, Ltd.</td>
</tr>
<tr>
<td><strong>Treatment Considerations for Secondary Hypogonadism</strong></td>
<td>Mohit Khera, MD</td>
</tr>
<tr>
<td></td>
<td>Associate Professor of Urology, Baylor College of Medicine</td>
</tr>
<tr>
<td><strong>Sperm Concentration Endpoint for Fertility</strong></td>
<td>Edward Kim, MD</td>
</tr>
<tr>
<td></td>
<td>Associate Professor of Urology, Baylor College of Medicine</td>
</tr>
<tr>
<td><strong>Human Chorionic Gonadotrophin</strong></td>
<td>Mohit Khera, MD</td>
</tr>
<tr>
<td></td>
<td>Associate Professor of Urology, Baylor College of Medicine</td>
</tr>
<tr>
<td><strong>Diagnostic Categories of Hypogonadism and Secondary Hypogonadal Population</strong></td>
<td>Frederick Wu, MD</td>
</tr>
<tr>
<td></td>
<td>Professor of Medicine and Endocrinology, University of Manchester</td>
</tr>
<tr>
<td><strong>Weight Associated, Secondary Hypogonadism: An Acquired Estrogen - Dependent Disorder</strong></td>
<td>Andrew McCullough, MD</td>
</tr>
<tr>
<td></td>
<td>Director of Male Sexual Health, Urology Dept., Lahey Health and Medical Center</td>
</tr>
<tr>
<td><strong>Conclusions</strong></td>
<td>Mike Wyllie, PhD</td>
</tr>
<tr>
<td></td>
<td>Managing Director, Global Pharma Consulting, Ltd.</td>
</tr>
</tbody>
</table>
Diagnostic Categories of Hypogonadism and the Secondary Hypogondal Population

Frederick C.W. Wu
Professor of Medicine & Endocrinology
University of Manchester, U.K.
Mechanisms Controlling Testicular Functions

Hypothalamus → Pituitary
- GnRH
  → LH, FSH
  → Testis
    - Leydig cells
    - Sertoli cells
      - Testosterone (T)
      - Spermatogenesis

Estradiol (E₂)
- DHT
- T

Androgen Effects
- Fertility
NORMAL MALE

Hypothalamus

GnRH

Pituitary

LH

Testes

Testosterone

PRIMARY HYPOGONADISM

Hypothalamus

GnRH

Pituitary

LH

Testes

SECONDARY HYPOGONADISM

Hypothalamus

GnRH

Pituitary

LH

Testes
Categorizing Gonadal Status by Testosterone and LH

Primary ‘Hypogonadism’
Low T, high LH
n=52 (1.7%)

Compensated ‘Hypogonadism’
Normal T, high LH

Secondary ‘Hypogonadism’
Low T, normal/low LH
n=318 (10.4%)

Eugonadal
Normal T and LH

n = 3219
40 – 80 yr

Exclusions (n = 150) Known pituitary/testicular diseases and current medications affecting pituitary, testicular function or metabolism of T

EMAS Tajar, JCEM 2010
Hypogonadism

- Primary
  - Klinefelter’s syndrome
  - Cryptorchidism
  - Chemotherapy
  - Orchitis
  - Injury
  - Surgery
  - Torsion

- Secondary
  - Kallmann’s syndrome
  - Pituitary tumors
  - Hypothalamic lesions
  - Opiates
  - Anabolic steroids
  - Overweight/Obesity
Increasing BMI is associated with progressively lower total testosterone levels, independent of age.

Increasing age is associated with progressively higher LH levels, independent of BMI, but SHBG shows the effects of increasing age as well as BMI.

Free testosterone shows progressively lower levels with increasing BMI as well as increasing age.
BMI and Age: Different Effects on Hormones

With obesity, LH does not respond to the progressive fall in testosterone – functional hypothalamic/pituitary suppression.
Risk Factors for Secondary Hypogonadism

- Age (yrs)
- BMI ≥ 25 - <30 kg/m²
- BMI ≥ 30 kg/m²
- Smoking (current)
- Alcohol (frequent)
- Co-morbidity (≥1)

**Adjusted Relative Risk Ratio**

EMAS Tajar, JCEM 2010

- ***** p<0.0001**
- *** p<0.05**

**Obesity Related Hypogonadism**
Obesity Precedes the Development of Secondary Hypogonadism

Potential Predictors of Incident Secondary Hypogonadism (n = 140)

- Current smokers
- Alcohol ≥5 drinks/wk
- ≥1 comorbidity
- BMI 25-30 kg/m²
- BMI ≥30 kg/m²
- Age 60-69 yr
- Age ≥ 70 yr
- Age 50-59 yr
- Low grade education
- Medium grade education
- PASE ≤78
- Chronic widespread pain
- Have partner not live together
- Not have a partner

Follow-up of 2268 Eugondal Men for 4.3 yrs

Odds Ratio (95% CI)

EMAS Rastrelli JCEM 2015

OR = 2.86

*** p<0.0001
US Prevalence of Obesity-Related Secondary Hypogonadism

US men 18-64 yr

BM I >30
35%

T <300 ng/dl
LH <9.5 U/L
23%

Symptomatic and seeking treatment
17%

98.5 million
34.5 million
7.9 million
1.3 million

Estimates of secondary hypogonadism based on % prevalence in EMAS (Tajar et al 2010; Rastrelli et al 2015)
Symptoms and Signs of Hypogonadism

**More Specific**
- Reduced libido
- Decreased spontaneous erections
- Infertility
- Gynecomastia
- Loss of body hair
- Reduced testes volume
- Hot flushes
- Low bone density & increased fractures

**Less Specific**
- Decreased energy
- Decreased motivation
- Decreased mood
- Reduced muscle bulk
- Decreased physical strength & function
- Increased body fat & insulin
- Decreased concentration

Endocrine Society Guidelines (Bhasin et al 2010)
We recommend that symptomatic men who have unequivocally low total and/or free testosterone levels that are assayed on at least 2 samples drawn before 10am should be considered for TRT.

But how appropriate is T therapy in younger patient with secondary hypogonadism who wish to have children?

AACE/ACE Position Statement 2015,
Endocrine Practice, Vol 21 (9) September 2015
Mechanisms Controlling Testicular Function

Hypothalamus

Pituitary

GnRH

LH

FSH

Estradiol (E₂)

DHT

Testis

Leydig cells

Testosterone (T)

Sertoli cells

Spermatogenesis

Androgen Effects

Fertility
Exogenous Testosterone for Secondary Hypogonadism

Exogenous Testosterone Suppresses the HPG Axis

Hypothalamus

Pituitary

GnRH

LH

FSH

Testis

Leydig cells

Sertoli cells

Testosterone (T)

Spermatogenesis

Estradiol (E₂)

DHT

Androgen Effects

Fertility
Exogenous Testosterone for Secondary Hypogonadism

Exogenous Testosterone Suppresses the HPG Axis

Exogenous Testosterone will further suppress the dormant HPG-axis, compromise fertility and prevent recovery.

Androgen Effects
Conclusions

- *Secondary Hypogonadism* associated with *obesity* is a *reversible* functional suppression of hypothalamic/pituitary function
  - Well characterized, diagnosable

- Current treatment guidelines recommend TRT, not optimal for these men

- Strategies to reverse gonadotrophin suppression, and encourage recovery of *endogenous* T safely, *and* preserve spermatogenesis, are preferable to *exogenous* T in the treatment of men with secondary hypogonadism
## Presentation Agenda

<table>
<thead>
<tr>
<th>Session</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>Mike Wyllie, PhD&lt;br&gt;<em>Managing Director, Global Pharma Consulting, Ltd.</em></td>
</tr>
<tr>
<td>Treatment Considerations for Secondary Hypogonadism</td>
<td>Mohit Khera, MD&lt;br&gt;<em>Associate Professor of Urology, Baylor College of Medicine</em></td>
</tr>
<tr>
<td>Sperm Concentration Endpoint for Fertility</td>
<td>Edward Kim, MD&lt;br&gt;<em>Professor of Surgery, University of Tennessee Graduate School of Medicine</em></td>
</tr>
<tr>
<td>Sperm Concentration Endpoint for Infertility</td>
<td>Mohit Khera, MD&lt;br&gt;<em>Associate Professor of Urology, Baylor College of Medicine</em></td>
</tr>
<tr>
<td>Diagnostic Categories of Hypogonadism and Secondary Hypogonadal Population</td>
<td>Frederick Wu, MD&lt;br&gt;<em>Professor of Medicine and Endocrinology, University of Manchester</em></td>
</tr>
<tr>
<td>Weight Associated, Secondary Hypogonadism: An Acquired Estrogen-Dependent Disorder</td>
<td>Andrew McCullough, MD&lt;br&gt;<em>Director of Male Sexual Health, Urology Dept., Lahey Health and Medical Center</em></td>
</tr>
<tr>
<td>Conclusions</td>
<td>Mike Wyllie, PhD&lt;br&gt;<em>Managing Director, Global Pharma Consulting, Ltd.</em></td>
</tr>
</tbody>
</table>
Weight Associated Secondary Hypogonadism

An acquired – estrogen dependent disorder

Andrew McCullough, MD

Lahey Hospital and Medical Center
Weight Related Secondary Hypogonadism
Reversible with Weight Loss

Camacho et al. European Journal of Endocrinology 2013

Mean (SEM) Testosterone Changes Related Weight Change

% Weight loss

% weight change

% Weight loss

Weight gain %

Camacho 2013
Obesity and Estrogen in Secondary Hypogonadism

- Obesity
  - Increases aromatase expression giving relative estrogen excess
  - Decreases pituitary LH release (Vermeulen 1993)
- Anti-estrogens and aromatase inhibitors increase both LH and testosterone
- Estrogen antagonism: mechanistically rational approach in obese men
Anti-estrogen and Topical Testosterone Effects on LH

- Anti-estrogen blocks estradiol, raising LH
- Pulsatile behavior of LH enhanced
- Topical testosterone suppresses LH

Wiehle 2013
Effects on Testosterone and LH

**Testosterone**

- **Mean Morning T (ng/dL)**
  - **Enclomiphene T**
  - **Androgel T**

- **Baseline** vs. **End of Study**

- **Enclomiphene T** vs. **AndroGel**
  - p = 0.0007

**LH**

- **Median LH (mIU/mL)**
  - **Enclomiphene LH**
  - **Androgel LH**

- **Enclomiphene LH** vs. **AndroGel**
  - p < 0.0001

Adapted from Kim 2016
Effect on Sperm Concentration

Median Percent Change from Baseline in Sperm Count

- Enclomiphene: 12.6
- AndroGel: -52.8
- Placebo: -1.3

vs. Enclomiphene
p < 0.0001

Pivotal Studies of Enclomiphene; Adapted from Kim 2016
Change in Testicular Volume by Orchidometry

Mean Percent Change in Testicular Volume Measured by Orchiometry

- Enclomiphene
  - 6.0
  - n = 85
  - vs. Enclomiphene, p = 0.0005

- AndroGel
  - -4.5
  - n = 84

- Placebo
  - 8.2
  - n = 86
  - vs. Enclomiphene, p = 0.7900

Pivotal Studies of Enclomiphene
Recommended Phase 3 Study

- **Indication:** Overweight/obese men with secondary hypogonadism who wish to maintain spermatogenesis

- **Population**
  - BMI > 25
  - Confirmed morning T < 300 ng/dL
  - LH ≤ 9.4 mIU/mL
  - Confirmed sperm concentration > 15 M/mL

- **Study Design**
  - Randomized Placebo Controlled
  - 12 weeks
Co-Primary Endpoints

- Responder analysis composite endpoint
  - Percent with normal morning T and sperm concentration > 15 M/mL

- Non-inferiority compared to placebo
  - Percent with end of study sperm concentration < 15 M/mL
Conclusions

- Secondary hypogonadism is highly prevalent in obese men
  - Can be accurately diagnosed via morning T and LH
- Anti-estrogens:
  - Maintain diurnal rhythm
  - Effective in normalizing testosterone
  - Preserve spermatogenesis, an important clinical benefit
- Testosterone replacement is detrimental:
  - To the pituitary gonadal axis
  - To spermatogenesis
- Many men are concerned about maintaining spermatogenesis
- Treatment modalities restoring T rather than replacing T need to be available
- It is time to change the paradigm for the treatment of hypogonadism
## Presentation Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
<td>Mike Wyllie, PhD</td>
</tr>
<tr>
<td><strong>Managing Director, Global Pharma Consulting, Ltd.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment Considerations for Secondary Hypogonadism</strong></td>
<td>Mohit Khera, MD</td>
</tr>
<tr>
<td><strong>Associate Professor of Urology, Baylor College of Medicine</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Sperm Concentration Endpoint for Fertility</strong></td>
<td>Edward Kim, MD</td>
</tr>
<tr>
<td><strong>Professor of Surgery, University of Tennessee Graduate School of Medicine</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Sperm Concentration Endpoint for Infertility</strong></td>
<td>Mohit Khera, MD</td>
</tr>
<tr>
<td><strong>Associate Professor of Urology, Baylor College of Medicine</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Diagnostic Categories of Hypogonadism and Secondary Hypogonadal Population</strong></td>
<td>Frederick Wu, MD</td>
</tr>
<tr>
<td><strong>Professor of Medicine and Endocrinology, University of Manchester</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Weight Associated, Secondary Hypogonadism: An Acquired Estrogen-Dependent Disorder</strong></td>
<td>Andrew McCullough, MD</td>
</tr>
<tr>
<td><strong>Director of Male Sexual Health, Urology Dept., Lahey Health and Medical Center</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Conclusions</strong></td>
<td>Mike Wyllie, PhD</td>
</tr>
<tr>
<td><strong>Managing Director, Global Pharma Consulting, Ltd.</strong></td>
<td></td>
</tr>
</tbody>
</table>
Secondary Hypogonadism: Myths and Reality

...What it is not:

- Idiopathic
- Age-related
- Associated with a unique symptom
- Undiagnosable
- Only of concern to the next generation
Secondary Hypogonadism: Myths and Reality

What it is:
- Often seen and diagnosable by clinicians
- Definable
- Commonly body mass dependent
- Often estrogen dependent
- In need of effective therapy particularly in men wishing to preserve or improve fertility
- In need of definition of track for regulatory approval
Back up slides
“The results (for TMSC) indicate a lack of prospective studies, a lack of standardization in semen testing methodology and a huge heterogeneity of patient groups and IUI treatment strategies.”
Total Motile Sperm Count (TMSC)

- A single, non-validated study
- TMSC <1 and 1-5 million/ml had lower spontaneous pregnancy rate

- Motility is not a direct measure of spermatogenesis.
- There is no consensus regarding a normal TMSC.
Sperm Concentration Directs Decision-Making—Evidence Based Medicine

“Semen analysis is the cornerstone of the laboratory evaluation of the infertile male and helps to define the severity of the male factor.”

Decision-making relies on sperm concentration

1. Practice Committee ASRM, 2012
Isn’t pregnancy outcome the best predictor of a fertility treatment?

- Real-world biology is complicated.
- Analysis of pregnancy rates results in the introduction of female factors (age, female pathology, treatment biases) that confound interpretation of effects of a drug on spermatogenesis.
- Hypogonadism is defined as an abnormal number of spermatozoa and a diminished production of testosterone, not by the inability to initiate a pregnancy.
Distribution of Sperm Concentration at Baseline

**ZA-304**

- **Number of Subjects per Interval**
  - Mean Sperm Concentration (10^6/mL)
  - Range: <15, 25, 35, 45, 55, 65, 75, 85, 95, 100, 150, 200, 250, >250

**ZA-305**

- **Number of Subjects per Interval**
  - Mean Sperm Concentration (10^6/mL)
  - Range: <15, 25, 35, 45, 55, 65, 75, 85, 95, 100, 150, 200, 250, >250

*Pivotal Studies of Enclomiphene*
## Baseline Signs and Symptoms

<table>
<thead>
<tr>
<th>Baseline Sign/Symptom</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue/Lack of Energy</td>
<td>48 (96%)</td>
</tr>
<tr>
<td>Depression, Irritability, Lack of Focus</td>
<td>37 (74%)</td>
</tr>
<tr>
<td>Poor Libido</td>
<td>29 (58%)</td>
</tr>
<tr>
<td>Muscle Weakness</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>Erectile Dysfunction</td>
<td>14 (28%)</td>
</tr>
<tr>
<td>Hair Loss</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Poor Bone Mass</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

Enclomiphene Study ZA-205 in Obese Men
Endometrial Edema/Epithelial Hyperplasia of Mucosa or Glands in Ovariectomized Mice

Ovariectomized Mice Study Xenometrics 11829
Dilation of Lumen and/or Endometrial Glands in Ovariectomized Mice
Men (n=39) eugonadal at baseline who developed secondary hypogonadism (low tT & low fT) at follow-up have new or worsened sexual, physical and psychological symptoms.

Referent: men eugonadal at baseline and follow-up (n=1909)

a, p<0.05, b, p<0.01 c, p<0.001
Men (n=102) eugonadal at baseline who developed ‘secondary hypogonadism’ (low tT & normal fT) at follow-up have no new or worsened symptoms

Referent: men eugonadal at baseline and follow-up (n=1909)
Clomiphene

\[ R = (C_2H_5)_2NCH_2CH_2 \]

**Enclomiphene**

- **Trans** (60%)
- **Cis** (40%)

**Zu-clomiphene**
Bone Mineral Density
ZA-303

Median % Change in BMD

- Total Hip
  - Enclomiphene 12.5 mg: 0.1
  - Enclomiphene 25 mg: 0.0
  - Placebo: -0.1
  - p=0.0043

- Femoral Neck
  - Enclomiphene 12.5 mg: 0.0
  - Enclomiphene 25 mg: 0.0
  - Placebo: -0.1
  - p=0.2671

- L2-L4 Spine
  - Enclomiphene 12.5 mg: -0.2
  - Enclomiphene 25 mg: 0.0
  - Placebo: 0.0
  - p=0.3905

Sample sizes:
- Total Hip: n=117 85 99
- Femoral Neck: n=117 85 100
- L2-L4 Spine: n=118 88 98