ADVISORY COMMITTEE INDUSTRY BRIEFING DOCUMENT

Industry Presentation

Bone, Reproductive and Urologic Drugs Advisory Committee

Meeting on December 6, 2016

Available for Public Release

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

Secondary hypogonadism, also known as hypogonadotrophic hypogonadism, is defined by low serum testosterone concentrations in association with low or normal serum concentrations of luteinizing hormone. Men with secondary hypogonadism tend to be younger than men with primary testicular failure, and secondary hypogonadism is associated with co-morbidities, chronic disease, and certain medications.

Treatment with exogenous testosterone products leads to infertility and testicular atrophy and testosterone products have a history of misuse and abuse. Treatment with non-testosterone products designed to treat secondary hypogonadism may prevent these problems. This is of considerable importance to a younger population that may wish to maintain or improve fertility and testicular function and for men who are at increased risk for misuse or abuse of testosterone.

Approved and off-label approaches exist for the treatment of secondary hypogonadism while maintaining testicular function, including spermatogenesis. These include direct stimulation of testosterone production by the testicle and modulation of pituitary function with a selective estrogen receptor modulator or estrogen antagonist. Currently, impractical routes of administration or the lack of an FDA approved product for these conditions limit access to these treatments for men with secondary hypogonadism.

In this briefing document, industry sponsors of drugs intended to treat secondary hypogonadism present their perspective on appropriate clinical trial design features and primary clinical endpoints. The sponsors propose that:

1. For certain drugs, the primary endpoint should be serum testosterone levels alone, provided that the drug's purpose is to directly stimulate the testicle and that the active pharmaceutical ingredient is human chorionic gonadotropin (hCG) - a naturally occurring hormone that is currently approved for secondary hypogonadism and has been in clinical use for over 40 years.
2. In men with hypogonadotrophic hypogonadism causing oligozoospermia (impaired spermatogenesis) and resulting in male factor infertility, treatment should focus on improving sperm concentration. Unlike testosterone replacement, MSS-722, a selective estrogen receptor modulator, raises LH and FSH levels which improves spermatogenesis. A clinical trial design for men with hypogonadotrophic hypogonadism and oligozoospermia would utilize sperm concentration as a clinical efficacy endpoint and improvement in sperm concentration to normal as the clinical benefit.
3. For men who wish to maintain reproductive potential, and who are diagnosed with secondary hypogonadism (low testosterone and low or normal LH) associated with overweight and obesity, estrogen receptor antagonists, such as enclomiphene, may provide an alternative to off-label use of clomiphene (CLOMID). For drugs of this class, restoration of endogenous serum testosterone concentrations and maintenance of sperm concentrations in the normal range is an appropriate endpoint for clinical trials and clinically meaningful outcome for patients.

2. INTRODUCTION

The FDA has asked the Advisory Committee to:

> *…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.*

Three companies from Industry have collaborated to present Industry's recommendations for development of a product intended to treated men with secondary hypogonadism while preserving or improving testicular function. The participating companies are developing products from different drug classes and with different indications. The three companies are:

- MHB Labs Inc.
- Veru Healthcare
- Repros Therapeutics Inc.

This document provides background information on secondary hypogonadism as well as proposals for appropriate clinical trial design features and study endpoints for different approaches to treatment and different clinical indications.

3. SECONDARY HYPOGONADISM

3.1 Definition

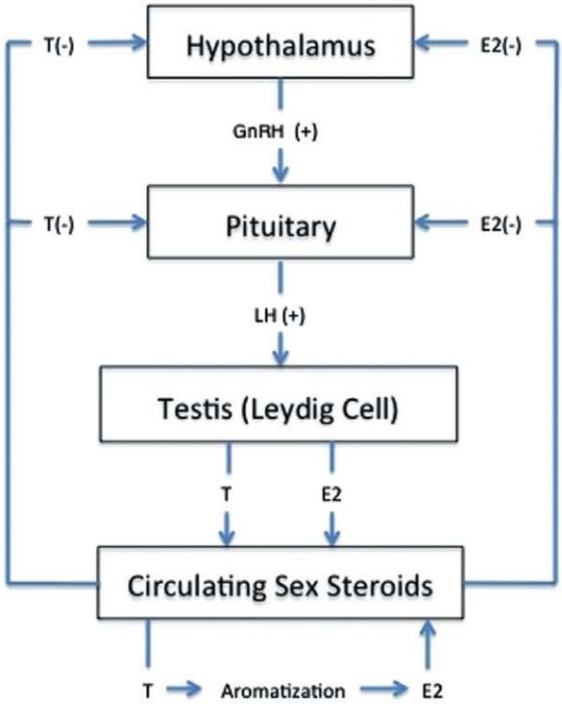
Hypogonadism is a medical disorder defined as low serum testosterone levels in conjunction with signs and symptoms of testosterone deficiency. Secondary hypogonadism refers to hypogonadism which occurs in association with low or normal levels of gonadotropins, whereas primary hypogonadism refers to hypogonadism in association with elevated gonadotropin levels. These terms reflect distinct underlying etiologies of hypogonadism. Primary hypogonadism is also known as primary testicular failure and results from impairments in testosterone production by the testicles. Secondary hypogonadism, also known as hypogonadotrophic hypogonadism or hypothalamic-pituitary failure, results from insufficient production of gonadotropins despite low testosterone levels (see Figure 1).

Luteinizing hormone (LH) is the gonadotropin that stimulates the Leydig cells of the testes to produce testosterone in the adult male. In prior studies, the appropriate LH cut-off levels to classify primary and secondary hypogonadism have been defined as 8.9 IU/L [Rochira, 2011], 9 IU/L [Guay, 2010] or as 9.4 IU/L [Tajar, 2010][Maseroli, 2015]. Hypogonadal men with LH levels below this cut-off are classified as having secondary hypogonadism. The sponsors propose using a LH cut-off of 9.4 IU/L.

3.2 Pathophysiology

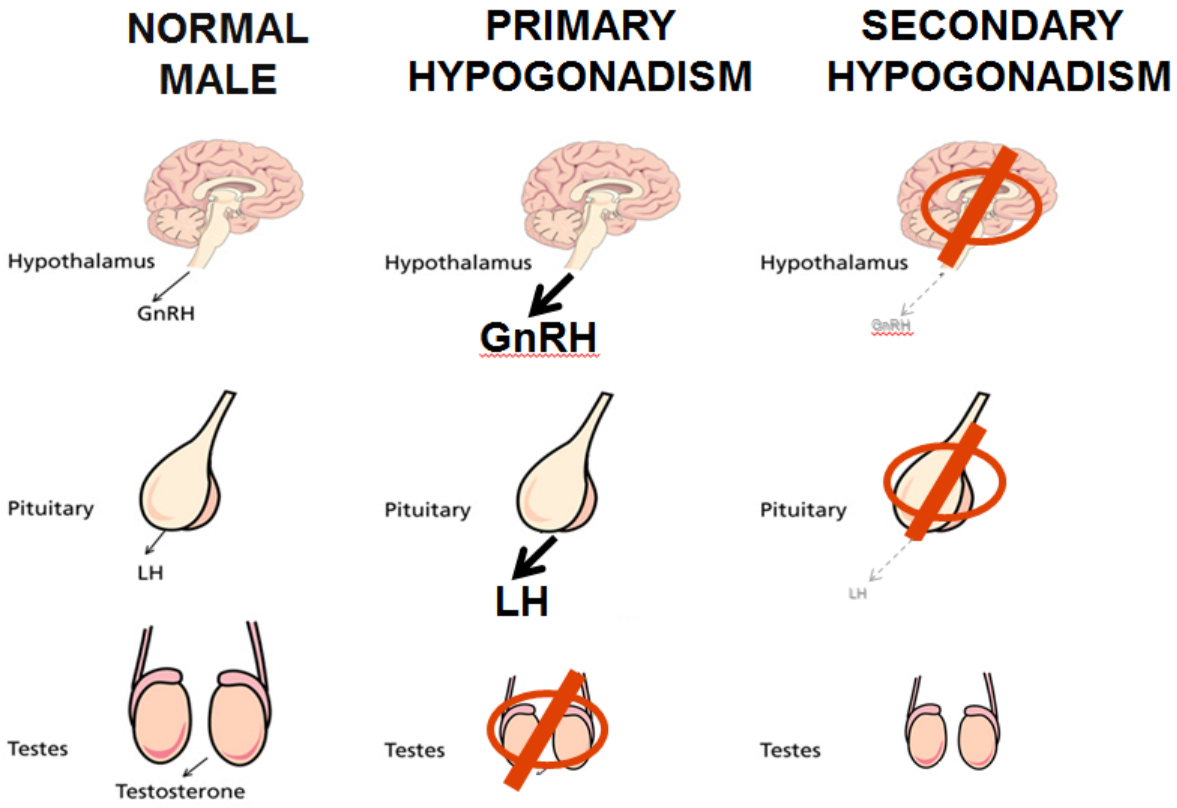
Under normal conditions, the Hypothalamic-Pituitary-Gonadal (HPG axis) regulates the production of testosterone. Gonadotropin releasing hormone (GnRH) is secreted by the hypothalamus, and stimulates secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH stimulates testosterone production by the Leydig cells which results in maturation of sperm in the testes. Circulating testosterone and estradiol provide negative feedback at the level of the hypothalamus and pituitary and act to decrease production of LH. Estradiol (E2) is produced largely from aromatization of T, with 10-20% of E2 directly produced by the Leydig cells of the testicle [Kacker, 2012]. Secondary hypogonadism occurs when LH levels are low or normal in the presence of testosterone deficiency.

Figure 1. The Hypothalamic-Pituitary-Gonadal (HPG) Axis



The differences in pathophysiology of primary and secondary hypogonadism, as compared to the normal state are illustrated in Figure 2 below.

Figure 2. Pathophysiology of Primary and Secondary Hypogonadism



3.3 Epidemiology

3.3.1 Prevalence

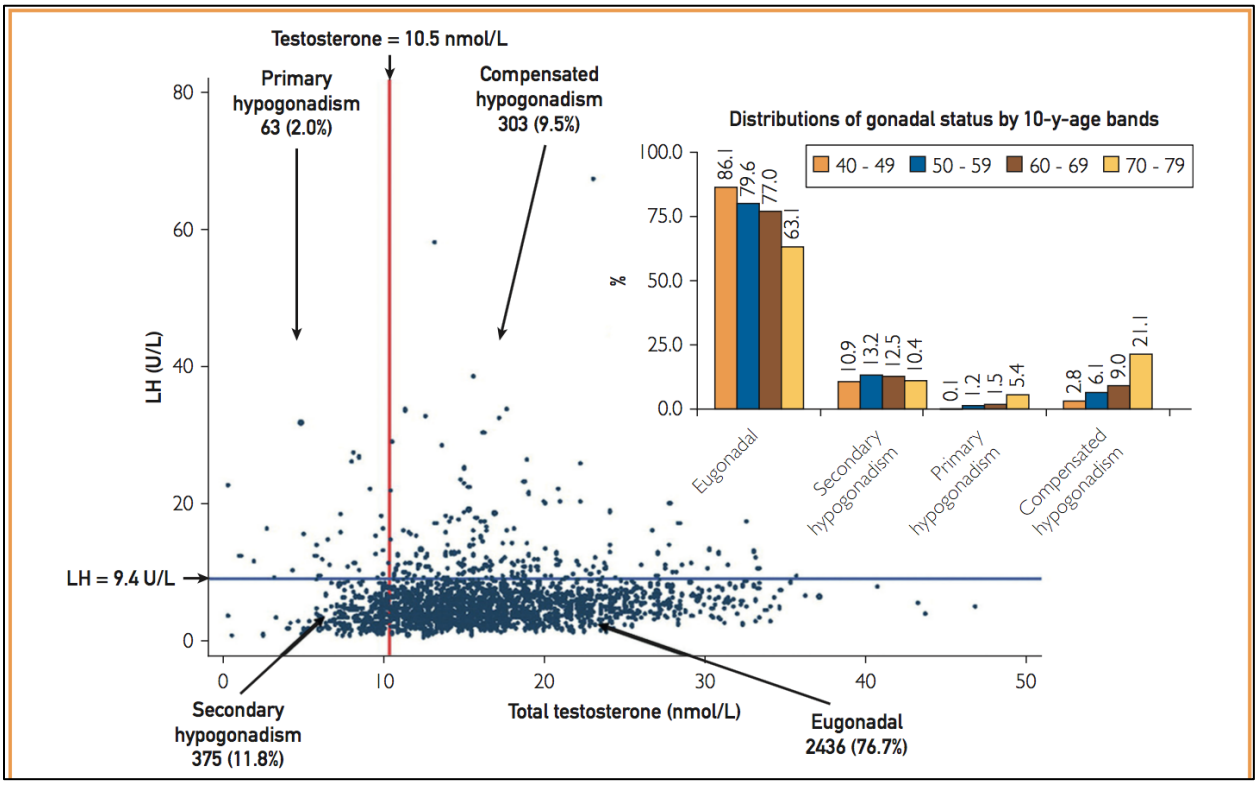
The overall prevalence of hypogonadism has been reported as 5.6%, although there was no distinction between primary and secondary hypogonadism [Araujo, 2007]. Three studies have reported on the prevalence of secondary hypogonadism. Among 438 men in the European Male Aging Study with serum testosterone levels under 300ng/dL, 85.5% were classified as having secondary hypogonadism on the basis of LH levels under 9.4 IU/L [Tajar, 2010] (see Figure 3). Similarly, in hypogonadal men from an overlapping cohort of European men with erectile dysfunction, the rate of secondary hypogonadism was 87.1% [Maseroli, 2015]. In a separate US-based cohort of men seeking care for sexual dysfunction, 83.8% of 359 hypogonadal men had secondary hypogonadism [Guay, 2010].

3.3.2 Secondary Hypogonadism and Age

Several studies have shown modest increases in the rate of overall hypogonadism with age, with the largest increase in older age groups [Arajou, 2004; Arajou, 2007]. However, the relationship between aging and secondary hypogonadism is less clear. Younger men are far more likely to have secondary rather than primary hypogonadism. The population-based European Male Aging

Study examined the rate of primary and secondary hypogonadism along with age and comorbidities among 3,369 men selected from 8 European countries [Tajar, 2010]. Among hypogonadal men, the majority under 60 years of age had secondary hypogonadism (see Figure 3 below). Similar trends were observed for a clinical population of 990 men in the US [Guay, 2010]. In this cohort, 86.3% of men aged 40-60 had secondary hypogonadism, but only 44.4% of men over age 70 had secondary hypogonadism. This observation that younger men with hypogonadism are likely to have secondary hypogonadism has important clinical implications. Compared to older men, younger men may be more likely to wish to maintain fertility. In some cases, they may also have potentially reversible causes of hypogonadism.

Figure 3. Testosterone and LH Levels in Primary and Secondary Hypogonadism



Subgroups of men by gonadal status and by decade of age from the European Male Ageing Study (EMAS) [Tajar, 2010]

3.3.3 Secondary Hypogonadism is Associated with Co-morbidities, Chronic Disease States, and Medications

Several studies have linked hypogonadism with obesity, insulin resistance, and metabolic disease [Ding, 2006]. In the EMAS, the presence of a BMI over 30 kg/m^2 was significantly associated with the presence of secondary hypogonadism [Tajar, 2010]. In a related cohort, most men with secondary hypogonadism had metabolic disease and BMI over 30 kg/m^2 [Maseroli, 2015]. Longitudinal data from the EMAS shows that obese men who lost >15% of their body weight had significant increases in serum testosterone levels. For these men, serum LH levels increased on average, but this did not reach statistical significance [Camacho, 2013]. Current physiologic

understanding supports a complex and bidirectional relationship between metabolic dysfunction and hypogonadism, with studies alternatively suggesting that insulin resistance reduces testosterone secretion and that testosterone deficiency directly affects metabolic pathways leading to insulin resistance [Pitteloud[a], 2005; Pitteloud[b], 2005].

Secondary hypogonadism can also occur in non-obese men and may be related to several other chronic illnesses and clinical situations, such as hypertension, tobacco abuse, sleep apnea and work stress [Guay, 2010], athletic overtraining [Barron, 1985], acute burns [Vogel, 1985], head trauma [Woolf, 1986], military combat situations [Rose, 1969], chronic obstructive pulmonary disease [Bhasin, 2006], [Mousavi 2012], HIV [Rochira, 2011] and drugs including opioids [Vescovi, 1985], and corticosteroids [Yeap, 2016].

Androgen abuse also has a well-documented suppressive effect on both LH and testosterone production. In many cases, suppression of LH production can persist for 2 years or longer after cessation of androgen abuse [Garevik, 2011].

3.4 Clinical Presentation and Considerations for Treatment

Both primary and secondary hypogonadism share a set of signs and symptoms. The most common symptoms are reduced libido, sexual dysfunction, fatigue, depressive symptoms and infertility. Signs may include reduced muscle mass/strength, decreased bone mineral density and anemia.

However, an important difference between primary and secondary hypogonadism is the younger age of the latter population [Guay, 2010 and Tajar, 2010]. For younger men maintenance of testicular function, including fertility, may be an important consideration in deciding whether and how to treat.

Certain clinical conditions deserve special consideration since they may be chronic or lifelong and occur in men who are at elevated risk for misuse or abuse of medication. Opioid addiction affects approximately 2.5 million adults in the US and 3-4% of the adult population has been prescribed long-term opioid therapy [Volkow, 2016]. Avoidance of the potential for medication misuse is an important consideration for these men, along with men who have a history of anabolic steroid abuse or are otherwise at elevated risk for misuse of controlled substances.

4. ADVANTAGES OF TREATING SECONDARY HYPOGONADISM WITH NON-TESTOSTERONE FORMULATIONS

Treatment of hypogonadism by administering testosterone can lead to normalization of serum testosterone levels and ameliorate symptoms of testosterone deficiency. However, testosterone therapy is inappropriate treatment for several groups of patients with secondary hypogonadism, including those who wish to maintain fertility or testicular volume and for patients who have a history of medication abuse.

Exogenous administration of testosterone produces a suppression of hypothalamic-pituitary activity and a suppression of LH levels. Without LH stimulation of Leydig cells, intra-testicular testosterone production is suppressed so that spermatogenesis is impaired and the germ cell population of the testicle is reduced. This can lead to loss of fertility and reduced testicular volume. While 84% men will recover from suppressed spermatogenesis after cessation of exogenous testosterone, 54% will not achieve full recovery to baseline sperm density [WHO task force, 1990]. Similarly, testicular production of testosterone will often return after cessation of exogenous testosterone use. However, the time required for testosterone production to return is variable, with some men taking years to recover to normal serum testosterone levels [Garevik, 2011].

Several effective non-testosterone treatments exist for secondary hypogonadism, including human chorionic gonadotropin (hCG) and estrogen modulators such as clomiphene, but only hCG is approved in the US. In this section the rationale for use of one of these treatments instead of testosterone for the treatment of men with secondary hypogonadism is discussed.

4.1 Preservation or Restoration of Testicular Volume

Testosterone treatments are known to cause testicular atrophy [AndroGel 1.62% USPI]. Strategies to treat secondary hypogonadism without use of testosterone preserve or restore testicular volume. Clinical trial data from studies comparing enclomiphene to topical testosterone and placebo showed that testosterone reduced testicular volume whereas low dose (12.5 mg/day) enclomiphene had no effect and 25 mg/day increased testicular volume [Sorokin, 2016].

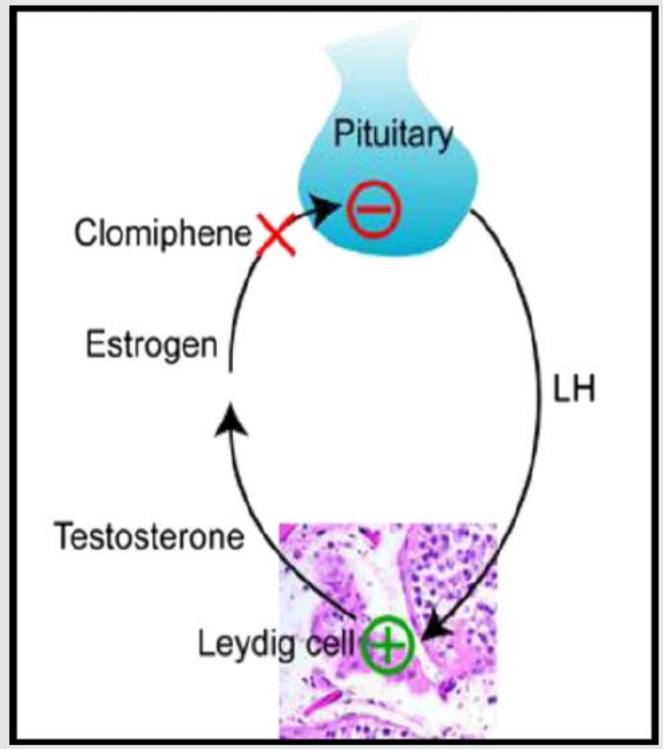
4.2 Maintenance or Improvement in Spermatogenesis

As reflected in the labeling for testosterone replacement therapy (TRT) products and the medical literature [Kim, 2013], exogenous testosterone can suppress spermatogenesis to the point of azoospermia. In two WHO studies of testosterone injections as a possible male contraceptive, it was found that after completion of a year long duration of suppressed spermatogenesis with periodic testosterone injections, sperm densities returned to baseline in only 46% and 34% of subjects. The median times to return to baseline levels were 6.7 months and 7.25 months, respectively [WHO Task Force, 1990 and 1996].

Drugs in several therapeutic classes, which either maintain or improve spermatogenesis, have been studied as possible treatments for low testosterone and secondary hypogonadism.

Clomiphene (CLOMID), a mixture of isomers enclomiphene and zuclomiphene, acts by blocking estrogen suppression of the hypothalamic-pituitary axis, as shown in Figure 4 below.

Figure 4. Action of Clomiphene on the HPG Axis



Clomiphene citrate works by blocking estrogen at the pituitary. The pituitary sees less estrogen and makes more LH. More LH means that the Leydig cells in the testes make more testosterone. [Kim, 2013]

Enclomiphene, the purified trans-isomer found in clomiphene, is being investigated as a treatment for secondary hypogonadism in men. This drug has no effect on spermatogenesis, in contrast to topical testosterone which results in marked suppression of spermatogenesis [Kim, 2016]. Data from this study are provided in Section 5.3.3 Estrogen Antagonists as Treatment for Secondary Hypogonadism.

4.3 Decreased Potential for Misuse and Accidental Transfer

Anabolic-androgenic steroid abuse occurs among athletes, but is actually more common among body builders that want to enhance their masculine image [Pope, 2014]. Although other drugs are used for performance enhancement, anabolic androgenic steroids, especially testosterone are the most common [Pope, 2014]. Suppression of spermatogenesis and loss of fertility due to androgen abuse have been clearly described [Ramasamy, 2015]. There are many other undesirable consequences associated with testosterone abuse, including detrimental effects on the heart, liver, kidney and brain in addition to suppression of the hypothalamic-gonadal axis with consequent suppression of spermatogenesis and testicular atrophy [Pope, 2014]. The hormonal suppression following steroid abuse has been reported to last at least several years after cessation of drug use [Rasmussen, 2016]. Suppression of testicular function occurs even when testosterone is administered at doses resulting in normal plasma concentrations.

SERMs and hCG are not testosterone, rather, they restore or enhance testosterone production by normal physiologic processes. Although the possibility that bodybuilders and some athletes may use these drugs in an attempt to mitigate testosterone induced hypogonadism or increase serum testosterone, these experiments are unlikely to result in consistent supra-therapeutic serum testosterone concentrations, that is, above the upper level of normal.

Accidental transfer to women and children is a concern worthy of a black box warning for topical testosterone products. With oral or injectable products this is not an issue.

4.4 Comparison of Exogenous Testosterone to Non-Testosterone Products

A brief summary of attributes associated with testosterone replacement therapy compared to non-testosterone is shown in Table 1. Further information on these treatment modalities is presented later.

Table 1. Aspects of Testosterone and Non-Testosterone Products

	TRT-topical	TRT-injection	SERMs-oral	Estrogen Receptor Antagonist-oral	hCG-injection
Restore serum testosterone	Yes	Yes	Yes	Yes	Yes
Restore testicular testosterone	No	No	Yes	Yes	Yes
Spermatogenesis					
Suppress	Yes	Yes	No	No	No
Maintain	No	No	Yes	Yes	Yes
Restore	No	No	Yes	Yes	Yes
Intra-testicular testosterone					
Suppress	Yes	Yes	No	No	No
Maintain	No	No	Yes	Yes	Yes
Restore	No	No	Yes	Yes	Yes
Testicular volume					
Suppress	Yes	Yes	No	No	No
Maintain	No	No	Yes	Yes	Yes
Restore	No	No	Yes	Yes	Yes
Transfer risk	Yes	No	No	No	No
Easily achieve supra-therapeutic testosterone levels	Yes	Yes	No	No	No

5. APPROACHES TO TREATMENT OF SECONDARY HYPOGONADISM

5.1. Direct Stimulation of Testicular Leydig Cells

5.1.1 Physiology

In adult males, LH is the gonadotropin that stimulates testosterone production by testicular Leydig cells. In secondary hypogonadism, LH levels are insufficient leading to testosterone deficiency. One approach to treatment of secondary hypogonadism is to directly stimulate LH receptors on testicular Leydig cells to produce testosterone.

Human chorionic gonadotropin (hCG) is well known to stimulate the Leydig cells of the testes and can be administered to treat secondary hypogonadism. hCG is a naturally occurring glycoprotein which is normally produced in very small concentrations by syncytiotrophoblast cells in normal adult male testicles. However, hCG seen is best known as a hormone produced by the placenta and exists in high concentrations in the serum of pregnant women, in the fetal circulation, and in the amniotic fluid. [Cole, 2009]. Among several other physiologic roles, hCG is believed to stimulate the fetal testes to produce testosterone during a critical period of sexual development known as the masculinizing programming window. hCG binds to LH receptors on Leydig cells in both adult and fetal testes to stimulate production of testosterone. [Scott, 2009].

5.1.2 Clinical Use

Pharmaceutical preparations of hCG can be used to treat secondary hypogonadism in adults. Administration hCG at levels as low as 125 IU/L is enough to stimulate intra-testicular testosterone production [Roth, 2010]. Treatment with higher doses of hCG can maintain testosterone levels in the normal range for men with secondary hypogonadism and pharmaceutical preparations of hCG have carried FDA approval for treatment of selected cases of secondary hypogonadism since 1973. hCG is also approved for the treatment of prepubertal cryptorchidism not due to an anatomic obstruction and for the induction of ovulation in anovulatory women.

In clinical practice, there is a decades-long history of use of hCG to treat men with infertility associated with sperm abnormalities (reduced sperm concentration, motility, and/or morphology) associated with low serum testosterone associated with low or normal LH concentrations (secondary hypogonadism). hCG has been used singly or in combination with FSH to successfully restore fertility in men with azoospermia. In addition, hCG has been shown to be effective treatment for men with symptoms of secondary hypogonadism by restoring serum testosterone to the normal range.

5.2. Selective Estrogen Receptor Modulators for Infertility

5.2.1 Oligozoospermia (impaired spermatogenesis) as a Symptom of Secondary Hypogonadism (Hypogonadotropic hypogonadism) in Men who have Male Factor Infertility

Clinical hypogonadism is a disorder associated with a deficiency or absence of endogenous testosterone plus clinical signs and symptoms. Asymptomatic men are men who have low testosterone levels without symptoms, are not classified as clinically hypogonadal and should not be treated.

Clinical hypogonadism is caused by inadequate gonadal function and is classified as primary, secondary or mixed. Primary hypogonadism occurs when the testicle is intrinsically poorly functioning and incapable of producing both testosterone and sperm. Primary testicular failure results in low testosterone levels, impairment of spermatogenesis, and elevated gonadotropin (LH and FSH) levels. Secondary hypogonadism is also referred to as hypogonadotropic hypogonadism and occurs when there are central defects of the hypothalamus or pituitary. Men who have secondary hypogonadism have testicular failure because of inadequate gonadotropic stimulation. These men have impairment of spermatogenesis, low testosterone and low or low normal gonadotropin levels [Rambhatla, 2016] [Bhasin, 2010]. The term Mixed hypogonadism results from a combination of primary and secondary causes. Men who have secondary hypogonadism may also have intrinsically poorly functioning testicles. These men present with low testosterone levels, low to normal LH levels, but have an elevated FSH levels [Kaminetsky 2013].

The current definition of infertility according to the American Society for Reproductive Medicine is the inability to achieve a pregnancy through natural means after 1 year [Practice Committee ASRM, 2004]. The male factor is contributory to 50% of infertile couples [Mosher, 1991]. Hypogonadotropic hypogonadism is a cause of male infertility. The Endocrine Society Guidelines state “Hypogonadism in men is 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" [Bhasin, 2010]. The production of spermatozoa is known as spermatogenesis, a process that is dependent on intra-testicular testosterone concentration. Impaired spermatogenesis is an important criterion for hypogonadism [Bhasin, 2010].

Only a small subset of infertile men present with both abnormally low sperm concentration and testosterone levels. In the United States, 0.6-2% of cases of male factor infertility are caused by hypogonadotropic hypogonadism [Damani, 2008; Chudnovsky, 2007; de Kretser, 1997]. Based on the estimated prevalence of hypogonadotropic hypogonadism as a cause of male infertility, and the estimated number of men that sought testing for infertility, the estimated size of the population affected by male infertility caused by hypogonadotropic hypogonadism ranges from 38,833 – 129,443 in the adult population. In a recent study from Europe in a population of over 1,000 infertile men, 43% of men who were hypogonadal, having a testosterone <300 ng/dL, also had oligozoospermia (sperm concentration of <15 million/mL). [Ventimiglia, 2016] If these

data are extrapolated to the US, the estimated prevalence of hypogonadotropic hypogonadism associated with oligozoospermia in the infertile male population is 16,698-55,660.

Table 2. Relative Frequency of Conditions Associated with Male Infertility

Condition	Frequency (%)
Idiopathic	38.9
Varicocele (medium to large)	25
Varicocele (small)	15.3
Cryptorchidism	6.4
Possible obstruction	4.5
Epididymal or vas obstruction	4.1
Klinefelter's syndrome	1.9
Mumps orchitis	1.6
Hypogonadotropic hypogonadism	0.6
Nonmotile sperm	0.6
Irradiation/chemotherapy	0.5
Coital disorders	0.5
Androgen resistance	0.1
Total	100

From Damani, M, Shaban, S. Medical Treatment of Male Infertility. In The Global Library of Women's Medicine. *(ISSN: 1756-2228)* 2008; DOI 10.3843/GLOWM.10334. [Damani 2008]

5.2.2 Testosterone Therapy is Inappropriate for the Treatment of Impaired Spermatogenesis and Secondary Hypogonadism

Testosterone replacement therapy inhibits spermatogenesis [Ko, 2012; Kim, 2016]. Administration of exogenous testosterone suppresses secretion of LH and FSH from the pituitary which results in lower intra-testicular testosterone production, thereby inhibiting sperm production (spermatogenesis) [Covielllo, 2005; Huhtaniemi, 2015; Bouloux, 2003]. In the FDA Prescribing Information for testosterone therapies it is noted that "Exogenous administration of androgens may lead to azoospermia [AndroGel 1.62% Prescribing Information].

The WHO evaluated the contraceptive effects of testosterone-induced azoospermia in normal men. Recovery of spermatogenesis was assessed after 12 months of weekly intramuscular testosterone injections. After testosterone injections were stopped, the median time to reestablish

baseline sperm concentration was 6.7 months [WHO task force, 1990]. The study demonstrated that recovery of spermatogenesis after short-term testosterone supplementation is not immediate and can take as long as a year to revert back to baseline levels [WHO, 1990].

Effects of cessation of long-term testosterone replacement therapy on spermatogenesis and endogenous testosterone production have not been adequately studied, especially in men with pre-existing low testosterone levels and impaired spermatogenesis. In some men it appears that the suppression of LH and FSH by testosterone replacement may lead to long term negative effects on Leydig cells and suppression of spermatogenesis [Crosnoe, 2013]. Accordingly, men who have hypogonadotropic hypogonadism and oligozoospermia and wish to be fertile should not be treated by exogenous testosterone replacement.

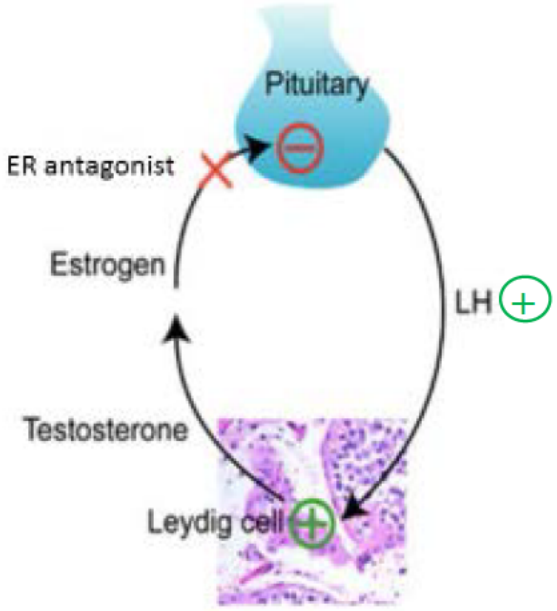
5.3. Modulation of Pituitary Function by Estrogen Receptor Antagonists

5.3.1 Estrogen's Role in the Hypothalamic-Pituitary-Testicular Axis

Both estrogen and testosterone provide negative feedback to the HP axis. In secondary hypogonadal men, high estrogen suppresses HP responsiveness in the secondary hypogonadal male with subsequent suppression of LH, which in turn leads to diminished testosterone production by the testes.

This hypothesis is supported by an increase in pituitary secretion of LH when an estrogen antagonist is administered to the secondary hypogonadal men. Figure 5 below illustrates the mechanism of action of an estrogen receptor (ER) antagonist, which is blockade of the estrogen receptors in the hypothalamus and the pituitary. When exogenous testosterone is given to men with low testosterone, it further suppresses the hypothalamic-pituitary axis and consequently decreases LH production.

Figure 5. Mechanism of Action of an Estrogen Receptor Antagonist



5.3.2 The Role of Obesity in Secondary Hypogonadism

In contrast to primary hypogonadism, which is usually age-related, a common etiology of secondary hypogonadism is overweight and obesity. Figure 6 and Figure 7 below are based on a publication by Tajar [Tajar, 2010]. The p-values reflect the difference in responses compared to those of eugonadal men. These data clearly show that obesity (high BMI) is the major risk factor for secondary hypogonadism in contrast to primary hypogonadism, for which age is a major risk factor. This dichotomy between primary and secondary hypogonadism is also evident in symptoms. Erectile dysfunction is a major symptom of primary, but not secondary hypogonadism. Low vigorous activity, likely a reflection of low energy, is a major symptom of secondary hypogonadism, although poor morning erections also tend to be reported more often than by eugonadal men.

Figure 6. Risk Factors and Symptoms of Primary Hypogonadism [Tajar, 2010]

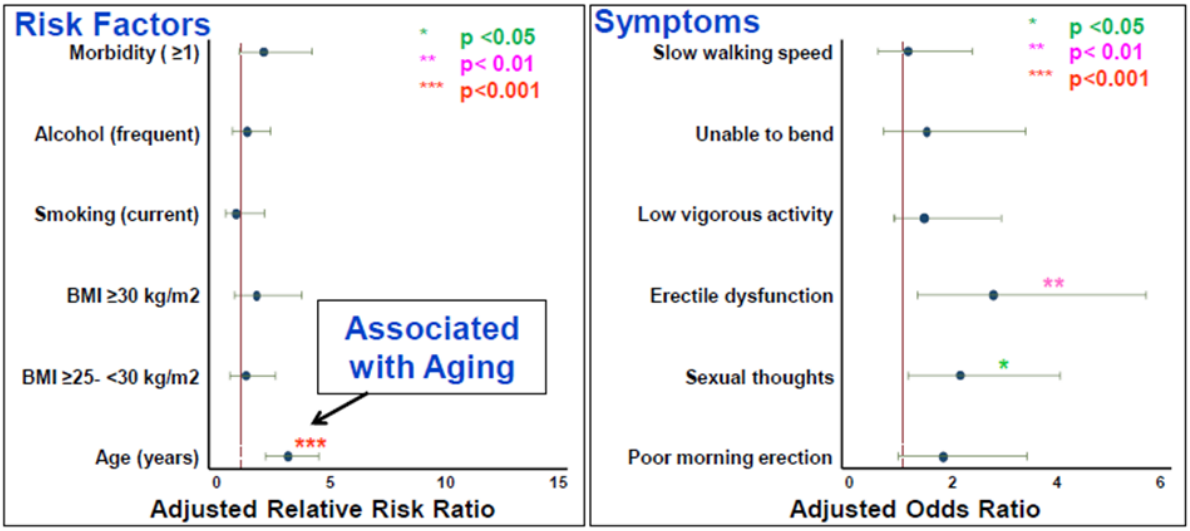
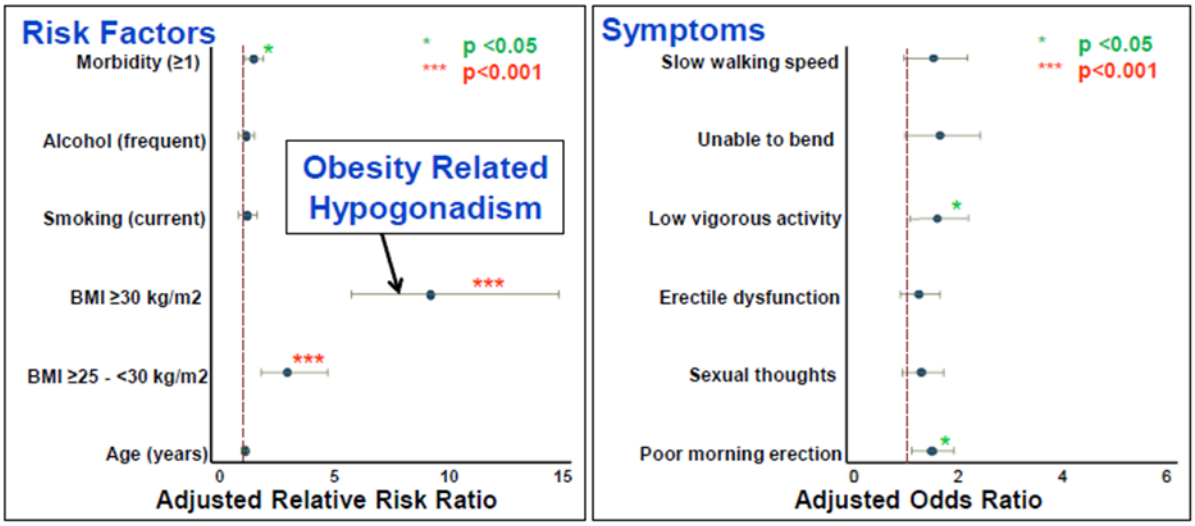
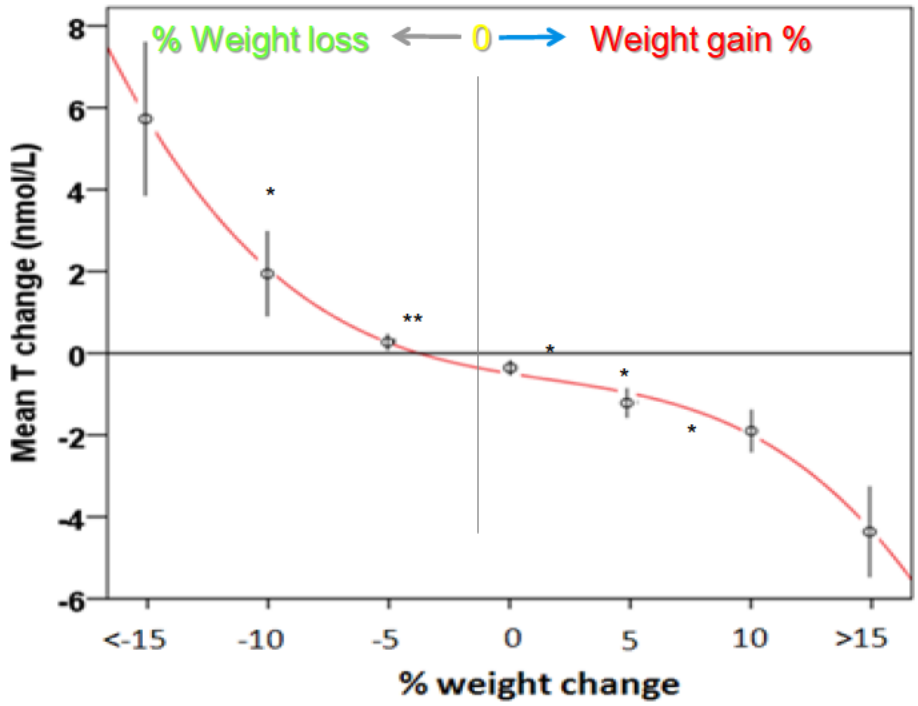


Figure 7. Risk Factors and Symptoms of Secondary Hypogonadism [Tajar, 2010]



Not only is serum testosterone directly related to weight, this relationship is dynamic in that changes in testosterone inversely correlate with changes in weight. Figure 8 below is based on the EMAS [Camacho, 2013]. The greater the weight change, in either direction, the greater the change in serum testosterone concentration in the opposite direction.

Figure 8. Changes in Testosterone Levels with Changes in Weight



[Camacho, 2013]

The effects of obesity on testosterone levels have been reported since the late 70's [Glass, 1977]. By the early 90's Vermeulen reported [Vermeulen, 1993] a significant negative correlation between free testosterone and BMI and a significant positive correlation between estradiol and BMI. He further notes, "Whereas LH pulse frequency was similar in the obese and control subjects, mean diurnal LH levels, mean diurnal pulse amplitude, and the sum of all diurnal LH pulse amplitudes and secretory masses were significantly lower in the obese than in controls."

By 2008 Pitteloud showed that, "1) T and E2 have independent effects on LH. 2). Inhibition of LH by T requires aromatization for its pituitary, but not hypothalamic effects. 3) E2 negative feedback on LH occurs at the hypothalamus" [Pitteloud, 2008].

5.3.3 Estrogen Antagonists as Treatment for Secondary Hypogonadism

Restoration of serum testosterone into the normal range, while preserving spermatogenesis, would provide appropriate treatment for men with obesity-related secondary hypogonadism. Use of SERMs was under investigation as treatments of hypogonadism during the 1990's. Most notable was the series of published studies conducted by Guay [Guay, 1995] in which he demonstrated that the SERM, clomiphene, a mixture of zu- and en-clomiphene, was able to significantly raise LH, FSH and testosterone levels in hypogonadal men, compared to placebo. Presumably these men were secondary hypogonadal.

Although it is not the intent to review the clinical development and regulatory history of enclomiphene, discussion of some key events and decisions can provide background into why Repros Therapeutic Inc, the Sponsor, is of the opinion that restoration of serum testosterone into

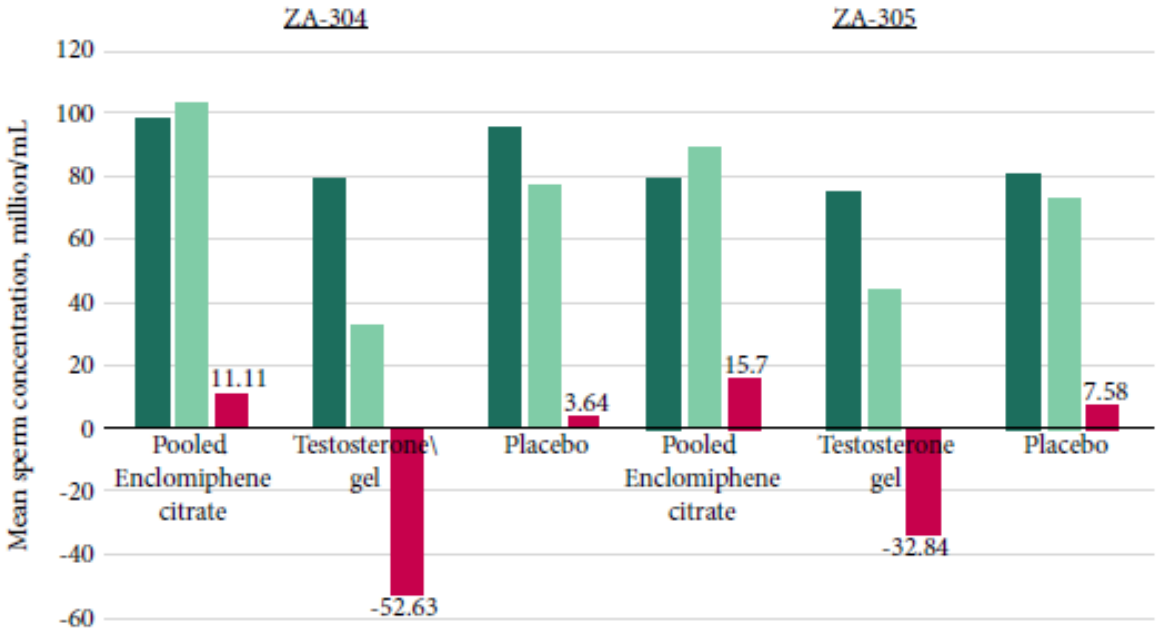
the normal range, while preserving spermatogenesis is an appropriate treatment for men with obesity related secondary hypogonadism. Repros currently has an NDA on file with the Division of Bone, Reproductive and Urologic Products. Since the IND was first opened in 2002, the Sponsor has only studied secondary hypogonadal men using LH and morning testosterone as biochemical markers for the disorder. Many of the studies included topical testosterone as an active comparator since it was gaining wide acceptance as a hormone replacement. Studies conducted by others, incorporating hormone replacement strategies, did not differentiate between primary and secondary hypogonadism.

Starting in 2013, Repros began to publish its clinical findings. In the first study conducted by the sponsor under the IND, for which an end of Phase 2 meeting was held with FDA in 2004, Wiehle *et al* observed increased secretions of both LH and FSH and resultant testosterone normalization and preservation of sperm concentration in men administered enclomiphene [Wiehle, 2014]. Men administered topical testosterone, on the other hand, exhibited significant reduction of both LH and FSH as their testosterone levels increased due to the exogenous replacement treatment.

Repros conducted a larger comparative study that noted the same phenomenon. In a meeting held with the FDA in 2007 the Sponsor suggested that there was a distinct possibility that secondary hypogonadal men may experience significant suppression of the HPG axis via administration of exogenous testosterone. The FDA agreed that the Sponsor could conduct a small comparator study of enclomiphene versus a topical testosterone product to assess the effects on spermatogenesis. The suppressive effects of hormone replacement on the HPG axis were observed, as predicted, and later published by Kaminetsky et al, in the Journal of Sexual Medicine, 2013 [Kaminetsky, 2013].

This study led to an agreement with the FDA in 2010 that preserving spermatogenesis was a worthy clinical benefit in treating the secondary hypogonadal male for his low testosterone state. Several studies ensued, including the latest two pivotal studies, ZA-304 and ZA-305 [Kim, 2016]. Both studies demonstrated that treatment with enclomiphene had no negative effect upon spermatogenesis, while exogenous testosterone led to marked suppression of sperm concentration. Figure 9 below is from this publication.

Figure 9. Mean Sperm Concentration (million/mL) in ZA-304 and ZA-305 at Baseline and 16 weeks and the Percentage Change Seen from Baseline to 16 weeks



Note: Pooled Enclomiphene citrate (Pool of 12.5 mg and 25 mg doses). Dark green=before treatment, light green=after treatment, red=%change from baseline. [Kim, 2016]

In these studies reported by Kim, subjects were required to exhibit sperm concentrations ≥15 million/ml (WHO standard for the lower bound of the 95% confidence interval of normal male sperm concentrations), low or normal LH (<9.4 IU/L), and confirmed morning testosterone of ≤300 ng/dL at baseline.

In summary, estrogen receptor antagonists, in particular enclomiphene, have been shown to restore serum testosterone not only to normal serum levels, but to maintain spermatogenesis in overweight or obese men. This is an important and clinically relevant consideration for men seeking and receiving treatment for secondary hypogonadism who wish to preserve their reproductive potential.

6 CONSIDERATIONS FOR THE DESIGN OF CLINICAL STUDIES IN THE TREATMENT OF SECONDARY HYPOGONADISM

This section provides proposals for appropriate clinical trial design features and study endpoints for different approaches to treatment and different clinical indications.

6.1. Direct Stimulation of Testosterone Production by the Testicle

6.1.1 Existing FDA Approval and History of Clinical Use

Human Chorionic Gonadotropin (hCG) is the only currently approved product for secondary hypogonadism. HCG is a naturally occurring hormone which acts to stimulate the Leydig cells of the testicle to produce testosterone.

In a Federal Register Notice dated September 17, 1970, the Commissioner of Food and Drugs reported that a hCG preparation called Riogan (NDA 2-811) was regarded as effective in selected cases of male hypogonadism secondary to pituitary failure. Since then, several hCG product labels have included, among other uses, approval for "selected cases of hypogonadotrophic hypogonadism". The most recently approved label revision is dated 4/17/2011 for Human Chorionic Gonadotropin for Injection, USP, 10,000 Units/vial under NDA 17016, Novarel® for Ferring. Approvals for these various hCG products have all been based on biochemical testosterone response alone.

hCG has now been in continuous clinical use for over 40 years. Men with secondary hypogonadism may be treated with hCG in order to normalize testosterone levels, prevent physiological and psychologic sequelae of hypogonadism, and, in some cases, restore fertility. Dosage regimens vary in clinical and research studies, but are generally within the approved dosage range that appears on hCG product labels, ie, 500 to 4000 IU administered two to three times per week. Maximum testosterone levels are limited by Leydig cell capacity so that supratherapeutic testosterone levels are difficult to achieve and hCG has limited potential for overdosing [Handelsman, 2009]. Administration of hCG reliably leads to increased serum testosterone levels for a variety of clinical situations including younger men with a history of anabolic steroid abuse [Rahnema, 2014] or congenital secondary hypogonadism [Young, 2003] and for older men with hypogonadism [Liu, 2002][Vignera, 2016].

The adverse effects associated with hCG overlap with the adverse effects associated with administration of testosterone. Both treatment approaches can lead to polycythemia (increase in hematocrit), acne, oily skin, nipple sensitivity, gynecomastia, and fluid retention. In contrast to exogenous testosterone products, administration of hCG preserves or improves endogenous testosterone production and fertility. Since the original approval, the FDA has added a warning that anaphylactic reactions to urinary derived hCG have been reported.

6.1.2 New Product Opportunities

hCG has several advantages over exogenous testosterone preparations for the treatment of secondary hypogonadism, particularly in young men of reproductive age. However, its use is limited primarily by its inconvenience. Treatment with hCG typically involves three injections

per week. In addition, currently approved preparations of hCG require reconstitution, refrigeration, and self- administration of the product. These features promote poor compliance and premature discontinuation of an effective therapy. In these cases, men may turn to exogenous testosterone products or off-label therapies that are more convenient and practical.

New approaches to the administration and delivery of hCG are needed in order to make hCG therapy available and practical for men with secondary hypogonadism. Such approaches may provide for convenient administration of hCG by reducing the need for frequent injections or by improving drug stability and storage. Other opportunities may involve the development of novel therapeutics which use hCG or LH moieties to directly stimulate testosterone production by the testicle.

6.1.3 Appropriate Clinical Trial Design Features for New Drugs

New drugs based on hCG for secondary hypogonadism deserve special consideration by the agency due to: 1) the prior approval of hCG for the condition; 2) clinical use of hCG for over 40 years with continued evidence supporting efficacy and the absence of serious adverse events; and 3) the fact that hCG is a naturally occurring hormone. The specific regulatory requirements for approval of any new treatment clearly depend on the specific treatment approach.

However, certain reasonable clinical trial requirements can be applied to most drugs that directly stimulate testicular Leydig cells, particularly for those in which the active pharmaceutical ingredient is clinically indistinct from currently approved forms of hCG.

1) The primary endpoint should be serum testosterone levels. General guidelines for target testosterone levels as proposed for exogenous testosterone formulations are reasonable for hCG products, including 85% of treated individuals falling within the normal range, and avoidance of excessively high levels in more than a specified percentage of men. Studies should demonstrate safety and efficacy in achieving these endpoints in affected populations defined by the same inclusion and exclusion criteria used for testosterone products, plus LH levels less than 9.4 IU.
2) We agree with current labeling on testosterone product regarding Limitations of Use and believe similar Limitations of Use would be appropriate for hCG products. Additional Limitation of Use specific to hCG should also be included, in particular a warning against use for weight loss.

6.2. Male Infertility

For men who have oligozoospermia (impaired spermatogenesis) and hypogonadotropic hypogonadism as a cause for male factor infertility, sperm concentration is a valid clinical efficacy endpoint and improvement in sperm concentration is a clinical benefit.

The semen analysis has become the key clinical laboratory assessment of male factor infertility and remains the main determinant for referrals to infertility clinics nationwide [Murray, 2012]. The American Society of Reproductive Medicine (ASRM) Practice Committee indicates that "Semen analysis is the cornerstone of the laboratory evaluation of the infertile male and helps to define the severity of the male factor" [Practice Committee ASRM, 2012]. Sabanegh states in Campbell's Urology that "Semen analysis is one of the most important predictors in determining the fertility potential of a man" [Sabanegh, 2011]. Reference intervals for values of semen parameters from a fertile population provide data from which a prognosis of fertility or diagnosis of infertility can be determined [Cooper, 2010].

According to the WHO manual (Cooper et al, 2010), semen quality is accepted as a validated measure of male fecundity in clinical andrology, male fertility, reproductive toxicology, epidemiology and pregnancy risk assessments. As an example of the clinical utility of sperm concentration, the ASRM/American Urological Association (AUA) use sperm concentration as the basis for genetic testing: "Karyotyping and genetic counseling should be offered to all patients with nonobstructive azoospermia and severe oligospermia (<5 million sperm/mL)" [ASRM Practice Committee, 2012]. As another example of the ASRM/AUA recommendations, "an initial endocrine evaluation should include at least a serum testosterone and FSH. It should be performed if there is: (1) an abnormally low sperm concentration, especially if less than 10 million/mL; (2) impaired sexual function; or (3) other clinical findings suggestive of a specific endocrinopathy."

Oligozoospermia is impaired sperm production (spermatogenesis) and is defined by WHO as the concentration of spermatozoa below the lower reference limit (sperm concentration of <15 million sperm/ml) [Cooper, 2010]). Oligozoospermia equates with reduced fertility in the male. For the WHO, 5th edition, men whose partners had a time to pregnancy of <12 months were chosen as the reference group from which the reference values for human semen from fertile men were determined [Cooper, 2010]. Semen samples from over 4500 men in 14 countries on four continents were obtained from fertile men, men of unknown fertility status and men selected as normozoospermic. This methodology was determined to be an acceptable analysis for determination of a normal reference range with an outcome of spontaneous pregnancy.

It should be noted that the WHO manual does not reference total motile sperm count as a clinically useful assessment of fertility, as there is no consensus in the published literature or by scientific societies as to what constitutes a normal total motile sperm count [Hamilton, 2015]. It should also be noted that a treatment for a subpopulation of men with hypogonadism with oligozoospermia should not be measured by a women's outcome, but rather by the improvement in sperm concentration. Analysis of pregnancy rate would result in the introduction of variables that would 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. Accordingly, sperm concentration is the most useful quantifiable clinical measure of male factor fertility [Sabanegh, 2011].

Table 3. Lower Reference Limits (5th centiles and their 95% confidence intervals) for Semen Characteristics

Parameter	Lower reference limit
Semen volume (ml)	1.5 (1.4–1.7)
Total sperm number (10^6 per ejaculate)	39 (33–46)
Sperm concentration (10^6 per ml)	15 (12–16)
Total motility (PR + NP, %)	40 (38–42)
Progressive motility (PR, %)	32 (31–34)
Vitality (live spermatozoa, %)	58 (55–63)
Sperm morphology (normal forms, %)	4 (3.0–4.0)

WHO laboratory manual for the Examination and processing of human semen, 5th edition, 2010, page 238.

6.2.1 Potential Clinical Trial Design for the Development of Products for the Treatment of Oligozoospermia (impaired spermatogenesis) in Men with Hypogonadotropic Hypogonadism as a Cause for Male Factor Infertility.

The intended treatment population is the subset of men with hypogonadotrophic hypogonadism that present with oligozoospermia as a cause for male factor infertility during an evaluation for infertility. The intended treatment population is **not** men who have primary hypogonadism (intrinsic testicular failure) or men who have hypogonadotrophic hypogonadism with sperm concentrations of ≥15 million/mL and male factor infertility.

Selective Estrogen Receptor Modulators (SERMs) by stimulating endogenous testosterone production may improve spermatogenesis as assessed by sperm concentration.

Current FDA approved treatments for men who have hypogonadotropic hypogonadism and male factor infertility are HCG and FSH injections. There are no FDA approved oral therapies for male infertility. CLOMID (clomiphene citrate) 50mg tablet is FDA approved and indicated "for the treatment of ovulatory dysfunction in women desiring pregnancy." Clomiphene citrate has been commonly used off-label as a medical therapy for idiopathic male factor infertility [Chehab, 2015] [Chua, 2013].

Clomiphene citrate is a selective estrogen receptor modulator which as a class of drugs competitively binds to estrogen receptors on the hypothalamus and pituitary gland. As a result, the pituitary sees less estrogen, and in response, secretes LH and FSH. LH stimulates testosterone production by Leydig cells and FSH supports Sertoli cells activities and spermatogenesis in the testes. Clomiphene is not effective in raising serum testosterone levels

when LH and FSH levels are already elevated, as seen in primary testicular failure [Whitten, 2006].

Clomiphene has not been studied for regulatory approval for the indication of hypogonadotropic hypogonadism and oligozoospermia; therefore, there is no established dose or schedule for efficacy or safety. Clomiphene has been used empirically to treat idiopathic male infertility without specifically targeting men with hypogonadotropic hypogonadism and oligozoospermia [Roth, 2013] [Bridges, 2015] [Chua, 2013]. In these studies, clomiphene has generally demonstrated the ability to improve sperm quality and sperm counts in infertile men and result in higher pregnancy rates. Clomiphene appears to be well tolerated in men with doses as high as 400 mg/day and up to 3 years of use [Roth, 2013] [Chua, 2013] [Bridges, 2015] [Patel, 2015] [Allag, 1979]. However, the efficacy results for individual patients have been inconsistent from study to study for several reasons: the form of clomiphene used (CLOMID or clomiphene generics contain varying ratios of the trans- and cis-isomers), different doses given, various dosing schedules followed, poorly designed clinical trials, and different populations of male factor infertility studied. However, in a meta-analysis from 2013, Chua et al reported that in 11 randomized controlled trials of good methodological quality, a statistically significant increase in sperm concentration (WMD 5.24; 95% CI 2.12, 88.37; p = 0.001) and per cent sperm motility (WMD 4.55; 95% CI 0.73, 8.37; p = 0.03) were reported [Chua, 2013].

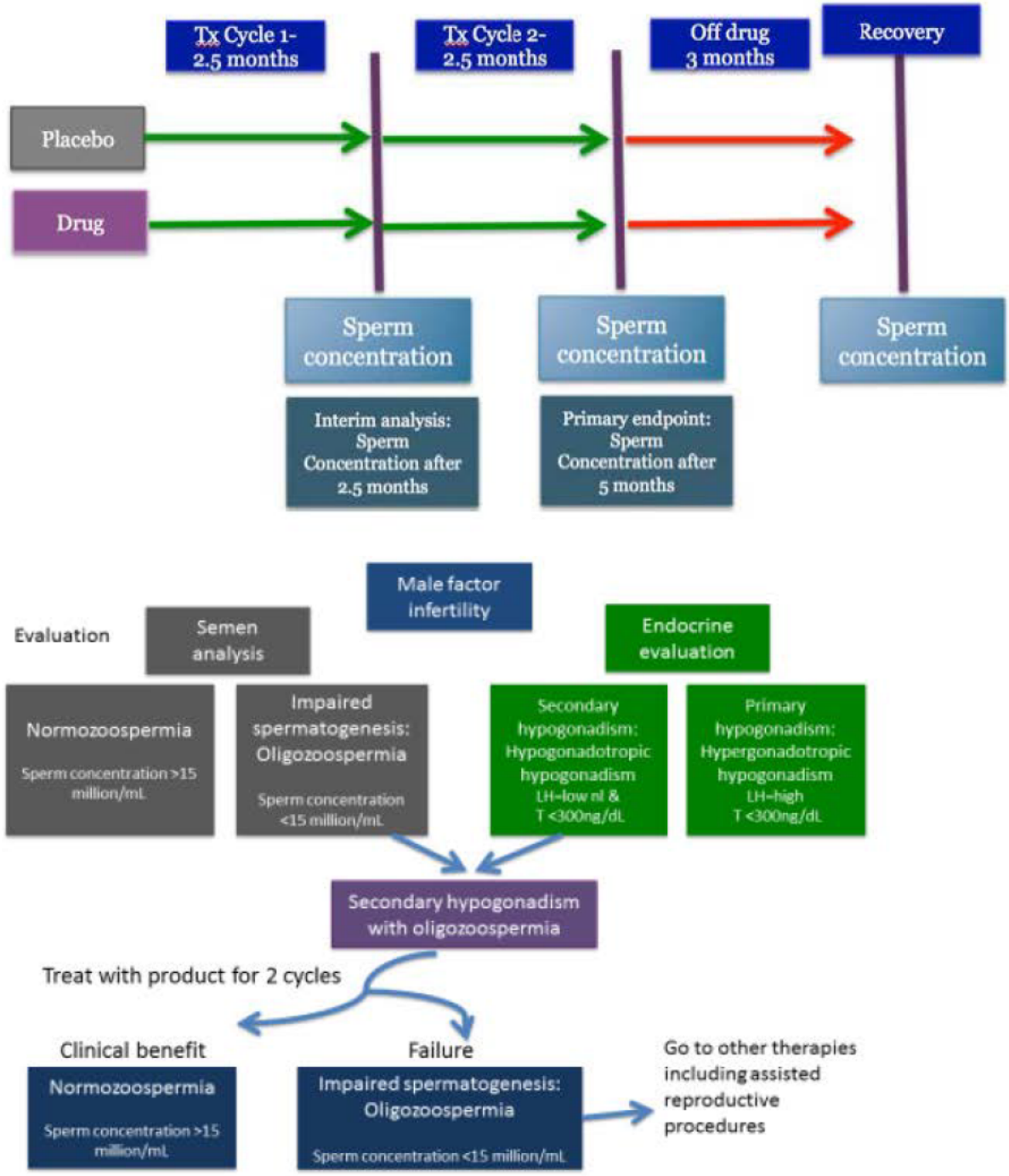
MSS-722, a proprietary specific fixed combination of trans- and cis-clomiphene isomers oral tablet, is being developed by Veru Healthcare for the treatment for the oligozoospermia as a cause for male factor infertility in men who have secondary hypogonadism. MSS-722 will not be appropriate for men with primary hypogonadism or hypogonadotropic hypogonadism due to pituitary-hypothalamic injury (from tumors, trauma, or radiation) because a functional, but under stimulated anterior pituitary is required for physiologic effect.

6.2.2 Schematic Design

The clinical trial should be randomized, double-blind, and placebo controlled. Patients eligible for the trials must have male factor infertility, as they were not able to achieve pregnancy for at least 1 year, have hypogonadotropic hypogonadism (LH low to low-normal and testosterone levels of <300 ng/dL), and oligozoospermia (sperm concentration ≤ 15 million sperm/mL based on WHO 2010 definition). Eligible patients will be randomized to receive either investigational drug or placebo. A ***cycle*** of treatment is 2.5 months which represents the approximate time required for the entire process of spermatogenesis from immature to mature sperm [Sabanegh, 2011]. Sperm concentration will be measured after each cycle up to 2 cycles of treatment. The primary efficacy endpoint will be sperm concentration after 2 cycles (5 months total time). The primary efficacy endpoint is the percentage of men who have normal sperm concentration (sperm concentration >15 million/mL) by 2 cycles of treatment in the drug versus the placebo group (responder's analysis). After 2 cycles of treatment, men who remain oligozoospermic will be referred to their fertility expert for other possible treatments including assisted reproductive procedures. Sperm concentration will be determined after a 3-month recovery phase off drug to assess the durability of treatment. Secondary endpoints would include total motility sperm count, semen volume, sperm morphology and safety.

The expectation is that this product would be used for the acute treatment (≤ 5 months) of oligozoospermia in men with hypogonadotropic hypogonadism as a cause of male factor infertility. Testosterone levels are not intended to be an endpoint of study.

Figure 10. Clinical Trial Design for the Treatment of Oligozoospermia in Men with Secondary Hypogonadism



6.2.3 Assessment of Overall Clinical Benefit

In men who present with oligozoospermia (impaired spermatogenesis) and hypogonadotropic hypogonadism as a cause for their male factor infertility, the meaningful overall clinical benefit of treatment with non-testosterone products like MSS-722 that raise intra-testicular testosterone will be a statistically and clinically meaningfully increase in the proportion of men who have normal sperm concentrations (>15 million/mL) on the drug versus the placebo groups, with acceptable safety.

6.3 Estrogen Antagonists

As a reminder, the FDA has asked the Advisory Committee to:

> *…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.*

There are two areas for consideration, both of which are addressed below:

- Clinical trial design, which includes:
  - Subject selection
  - Timing of testosterone measurements
  - Assessment of spermatogenesis
- Demonstration of clinical benefit
  - Testosterone assessment
  - Spermatogenesis
  - Potential for patient reported outcomes

6.3.1 Clinical Trial Design

A diagnosis of secondary hypogonadism should be confirmed in the population of subjects treated. A LH of 9.4 mIU/mL and a morning testosterone of <300 ng/dL should be the upper bounds for subjects to be tested. The suggested lower testosterone limit of 300 ng/mL is consistent with the Endocrine Society finding that symptoms of hypogonadism are more likely below this level [Bhasin, 2010]. Morning testosterone assessment (between 8 and 10 am) is highly recommended given the diurnal nature of male testosterone synthesis [Brambilla, 2009]. This is particularly important for the overweight secondary hypogonadal male who still has functional but under stimulated testes due to the negative estrogen feedback effect.

Though secondary hypogonadism can present as a panoply of symptoms, subjects should present with at least one symptom other than being overweight, to be sure that the population will be representative of those men seeking treatment.

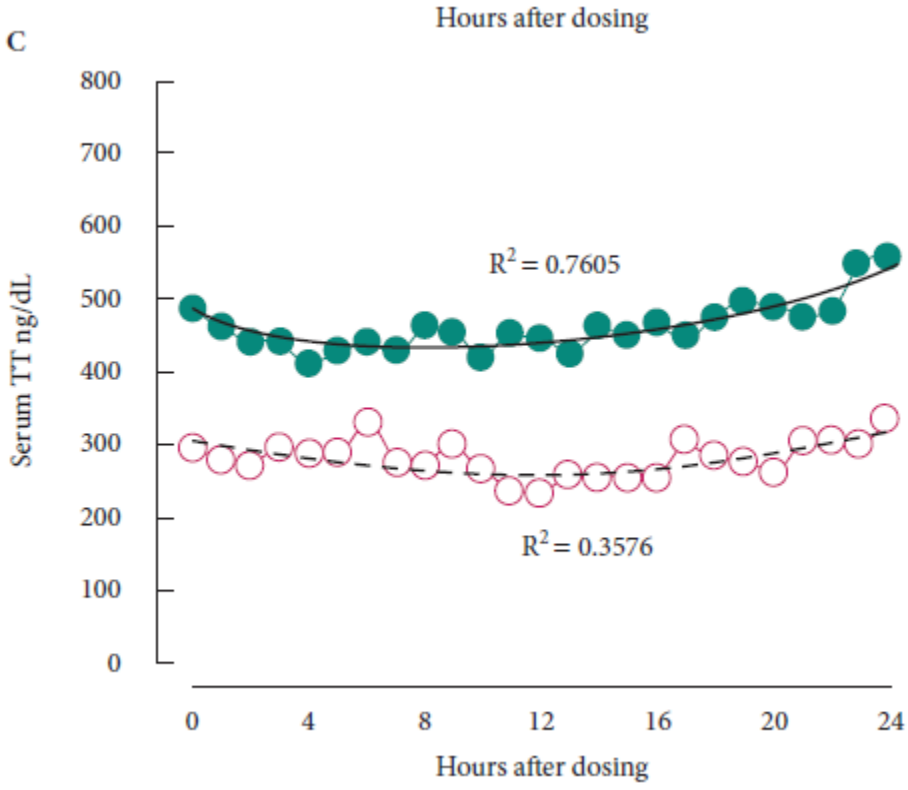
Subjects treated in studies to show preservation of spermatogenesis should have their baseline sperm concentration evaluated. Abstinence should occur for at least 2 days before sampling and two assessments should be made on separate days, at least two days apart. Eligible men should exhibit a mean sperm concentration of >15 million/mL. These assessments should be performed in a central facility in order to avoid operator bias. The lower limit for "normal" sperm concentration of 15 M/mL (95% CI 12-16) is proposed based on WHO 2010 reference values [Cooper, 2010]. This value is the lower limit of the 5th centile for men who were known to have fathered a child within the last 12 months. When the general population of men was considered, the lower 5th centile was found to be 9 M/mL (95% CI 6-11). Thus, the suggested cut point of 15 M/mL sets a fairly high bar for defining fertility potential when considering the general population. A cut-point of 15M/mL for sperm concentration is clinically meaningful as it means that a patient would be likely to father a child within a year.

In order to adequately assess effects on spermatogenesis, subjects should be treated for at least 12 weeks duration, to allow for a complete cycle of spermatogenesis, estimated to be 74 days [Amann, 2008].

6.3.2 Morning Testosterone or 24 hour Testosterone Assessment

The FDA has rightfully insisted on 24 hour testosterone assessment for hormone replacement therapies. The Sponsor believes this is appropriate for therapies that blunt the diurnal rhythm but not those that maintain this rhythm such as anti-estrogens. In early phase studies, 24 hour assessment is appropriate to confirm the diurnal effect. In those studies morning testosterone assessments should be shown to be highly correlated with T_{max} and 24 hour testosterone average. This was demonstrated in a Phase 2 study which included an enclomiphene 12.5 mg/day arm. Figure 11 below is taken from a published report of this study [Wiehle, 2013]. It shows that at initial dosing (open circles), and after 6 weeks of dosing (closed circles), T_{max} and 24 hour testosterone average can be reliably approximated by a single morning testosterone measurement. Morning testosterone was highly predictive of T_{max} and 24 hour average testosterone. These correlations were 0.9 with p-values < 0.0001.

Figure 11. 24-Hour Testosterone Assessments



Open circles=First day of treatment, closed circles=End of treatment, from Wiehle, 2013

Once it has been confirmed that the product produces a natural diurnal effect on testosterone, assessment of a single morning testosterone is adequate. Late stage development studies can

focus on the assessment of morning testosterone between 8 and 10 am to assess treatment effect and make decisions for dose escalation.

6.3.3 Semen Analysis

As long as LH and FSH remain unaffected or improved, spermatogenesis will not be negatively affected. For new agents, placebo controlled Phase 2 studies should be powered to show that active treatment exhibits non-inferiority compared to placebo when assessing the changes from baseline in sperm concentration and morphology.

Abstinence should occur for at least 2 days before sampling and two assessments should be made both at baseline and end of study on separate days, at least two days apart. The study duration should be at least 12 weeks of active treatment to allow for a complete spermatogenesis cycle. In order to avoid basement effects all men studied should exhibit a mean sperm concentration of >15 million/mL. These assessments should be performed in a central facility in order to avoid operator bias. Due to viability issues associated with shipping semen samples, sperm motility should be assessed in a subset of subjects in locally qualified facilities.

6.3.4 The Primary Endpoint

The primary efficacy measure of the study should be a co-primary endpoint comparing active drug to placebo. The goal of treatment is to raise morning testosterone into the normal range while preserving spermatogenesis.

- A composite endpoint incorporating both testosterone and spermatogenesis should be the first endpoint. Subjects will be deemed a success if they have a normal end of study testosterone (testosterone >300 ng/dL) and a normal sperm concentration (>15 million/mL). The incidence of successful treatment will be the endpoint comparing experimental treatment to placebo. It will be expected that the experimental treatment would be statistically superior in the percentage of subjects in the normal range.
- The incidence of end of study sperm concentration <15 million/mL in subjects treated with the experimental product should be found to be statistically non-inferior to the incidence exhibited in placebo-treated subjects. A 95% confidence interval on the difference in the incidence should not exceed 20%.

For justification of the cut-point for sperm concentration of 15M/mL see Section 6.3.1.

6.3.5 Patient Reported Outcomes

Although traditionally not considered as “hard evidence”, and seldom reflected in approved labeling, patient reported outcomes (PROs) are gaining in popularity. Since many of the signs and symptoms of secondary hypogonadism, such as decreased energy, poor concentration, and depressed mood are perceived by the patient, it is tempting to construct a PRO based on such complaints, and expect a therapy to ameliorate these symptoms. In reality, the process is much more complicated. Development of a PRO is a long, rigorous process, followed by another long period of use in clinical trials.

Patients may report any combination of such symptoms, in varying degrees of severity. There are many literature reports of studies either finding or not finding changes is signs and symptoms in response to treatment with testosterone. This is partly due to the fact that many studies did not distinguish between primary and secondary hypogonadism, did not control for underlying conditions, and may have included subjects of various ages. More importantly is the fact that all of these symptoms are non-specific. For example, depressed mood in a patient with hypogonadism may be related to his work environment or a poor relationship with his spouse, which may also be influenced by his low testosterone concentration. In order for a PRO to be successful, it must be clearly linked to the disorder (specificity), and be able to detect a clinically meaningful treatment effect (sensitivity). To date, no such PRO exists for treatment of secondary hypogonadism, yet men are being treated with testosterone. Currently available PROs focus on specific signs and symptoms rather than the varied signs and symptoms with which patients with secondary hypogonadism present.

The Sponsor is of the opinion that for men seeking treatment for secondary hypogonadism who wish to preserve their reproductive potential, demonstration of normalization of testosterone levels while maintaining sperm concentration is appropriate evidence of clinical benefit. However, if additional claims for individual symptoms are sought, development and implementation of a PRO specific to that symptom(s) may be of value.

7. REFERENCES

Allag IS, Alexander NJ. Clomiphene therapy for male infertility.Urology.1979 Nov;14(5):500-3.PMID: 388805

Amann RP. The cycle of the seminiferous epithelium in humans: a need to revisit? J Androl. 2008 Sep-Oct;29(5):469-87.Epub 2008 May 22. PMID:18497337. DOI: 10.2164/jandrol.107.004655

Androgel 1.62% Prescribing Information. http://www.rxabbvie.com/pdf/androgel1_62_PI.pdf. Accessed 10/21/16.

Araujo AB, O'Donnell AB, Brambilla DJ, Simpson WB, Longcope C, Matsumoto AM, McKinlay JB. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. J Clin Endocrinol Metab. 2004;89(12):5920-5926. PMID: 15579739. DOI: http://dx.doi.org/10.1210/jc.2003-031719.

Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, Williams RE, Clark RV and McKinlay JB. Prevalence of Symptomatic Androgen Deficiency in Men. J Clin Endocrinol Metab. 2007 Nov; 92 (11): 4241-4247. PMID: 17698901. DOI: http://dx.doi.org/10.1210/jc.2007-1245.

Barron JL, Noakes TD, Levy W, Smith C, Millar RP. Hypothalamic dysfunction in overtrained athletes. J Clin Endocrinol Metab 1985; 60(4): 803–806. PMID: 2982908. DOI: 10.1210/jcem-60-4-803

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab.2006;91(6):1995–2010. PMID: 20525905. DOI: http://dx.doi.org/10.1210/jc.2005-2847

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline.J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59. PMID:20525905. DOI:10.1210/jc.2009-2354

Bouloux PG, Nieschlag E, Burger HG, et al. Induction of spermatogenesis by recombinant follicle stimulating hormone (Puregon) in hypogonadotrophic azoospermic men who fail to respond to human chorionic gonadotrophin alone.J Androl 2003;24(4):604-11.PMID:12826700

Brambilla DJ, Matsumoto AM, Araujo AB, McKinlay JB. The effect of diurnal variation on clinical measurement of serum testosterone and other sexhormone levels in men.J Clin Endocrinol Metab. 2009 Mar;94(3):907-13. Epub 2008 Dec 16. PMID:19088162. PMCID:PMC2681273. DOI: 10.1210/jc.2008-1902

Bridges N, Trofimenko V, Fields S, Carrell D, Aston K, Hotaling J. Male factor infertility and clomiphene citrate: A Meta-Analysis- The effect of clomiphene citrate on oligospermia. 2015 Jul; 2:199-205. DOI: https://dx.doi.org/10.1016/j.urpr.2014.10.007

Camacho EM, Huhtaniemi IT, O'Neill TW, Finn JD, Pye SR, Lee DM, Tajar A, Bartfai G, Boonen S, Casanueva FF, Forti G, Giwercman A, Han TS, Kula K, Keevil B, Lean ME, Pendleton N, Punab M, Vanderschueren D, Wu FC; EMAS Group. Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. Eur. J Endoclinol. 2013;168(3): 445-455. PMID: 23425925. DOI:10.1530/EJE-12-0890

Chehab M, Madala A, Trussell JC. On-label and off-label drugs used in the treatment of male infertility. 2015 Mar; 103(3): 595-604. DOI: http://dx.doi.org/10.1016/j.fertnstert.2014.12.122

Chua ME, Escusa KG, Luna S, Tapia LC, Dofitas B, Morales M. Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male infertility: a meta-analysis. Andrology. 2013 Sep;1(5):749-757. PMID:23970453. DOI:10.1111/j.2047-2927.2013.00107.x

Chudnovsky A, Niederberger CS. Gonadotropin therapy for infertile men with hypogonadotropic hypogonadism. J Androl. 2007 Sep-Oct;28(5):644-646. Epub 2007 May 23. PubMed PMID: 17522414. DOI:10.2164/jandrol.107.003400.

Cole LA. New discoveries on the biology and detection of human chorionic gonadotropin. Reprod Biol Endocrinol. 2009 Jan 26;7:8. doi: 10.1186/1477-7827-7-8. PMID:19171054. PMCID:PMC2649930. DOI:10.1186/1477-7827-7-8

Cooper TG, Noonan E, Eckardstein SV, Auger J, Baker HW, Behre HM, Haugen TB, Kruger T, Wang C, Mbizvo MT, Vogelsong KM. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010 May-Jun;16(3):231-245. PMID:19934213. DOI: 10.1093/humupd/dmp048

Coviello AD, Matsumoto AM, Bremner WJ, Herbst KL, Amory JK, Anawalt BD, Sutton PR, Wright WW, Brown TR, Yan X, Zirkin BR, Jarow JP. Low-Dose Human Chorionic Gonadotropin MaintainsIntratesticular Testosterone in Normal Men with Testosterone-Induced Gonadotropin Suppression. Journal of Clinical Endocrinology and Metabolism. 2005;90(5):2595-2602. DOI: http://dx.doi.org/10.1210/jc.2004-0802

Crosnoe LE, Grober E, Ohl D, Kim ED. Exogenous testosterone: a preventable cause of male infertility. Transl Androl Urol. 2013 Jun;2(2):106-113. PMCID: PMC4708215 DOI:10.3978/j.issn.2223-4683.2013.06.01

Damani, M, Shaban, S. Medical Treatment of Male Infertility. In The Global Library of Women's Medicine. (ISSN: 1756-2228) 2008; DOI: 10.3843/GLOWM.10334.

de Kretser DM. The effects of systemic disease on the function of the testis. Clin Endocrinol Metab. 1979 Nov;8(3):487-498. PubMed PMID: 389487.

Ding EL, Song Y, Malik VS, Liu S. Sex differences of endoge- nous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2006;295(11):1288-1299. PMID: 16537739. DOI: 10.1001/jama.295.11.1288. http://www.natural-progesterone-advisory-network.com/citations/TEstosDiabFemaleMale%20Ding_2006.pdf

Garevik N, Strahm E, Garle M, Lundmark J, Stahle L, Ekstrom L, Rane A. Long term perturbation of endocrine parameters and cholesterol metabolism after discontinued abuse of anabolic androgenic steroids. J Steroid Biochem Mol Biol. 2011; 127(3-5): 295-300. PMID 21884791. DOI: 10.1016/j.jsbmb.2011.08.005

Glass AR, Swerdloff RS, Brady GA, Dahms WT, Atkinson RL. Low serum testosterone and sex-hormone-binding-globulin in massively obese men. J. Clin Endocrinol Metab. 1977 Dec;45(6):1211-9. PMID:338622. DOI:10.1210/jcem-45-6-1211

Guay AT, Bansal S, Heatley GJ. Effect of raising endogenous testosterone levels in impotent men with secondary hypogonadism: double blind placebo-controlled trial with clomiphene citrate. J. Clin Endocrinol Metab.1995 Dec;80(12):3546-3552. PMID: 8530597. DOI:10.1210/jcem.80.12.8530597

Guay A, Seftel AD, Traish A. Hypogonadism in men with erectile dysfunction may be related to a host of chronic illnesses. Int J Impot Res. 2010 Jan-Feb; 22(1):9-19. PMID: 19798059. DOI:10.1038/ijir.2009.46

Hamilton JA, Cissen M, Brandes M, Smeenk JM, de Bruin JP, Kremer JA, Nelen WL, Hamilton CJ. Total motile sperm count: a better indicator for the severity of male factor infertility than the WHO sperm classification system. Hum Reprod. 2015 May;30(5):1110-1121. PMID:25788568. DOI:10.1093/humrep/dev058

Handelsman D, Goebel C, Idan A, Jimenez M, Trout G, Kazlauskas R. Effects of recombinant human LH and hCG on serum and urine LH and androgens in men. Clinical Endocrinology. 2009 Sep; 71(3): 417-428. PMID:19170708. DOI:10.1111/j.1365-2265.2008.03516.x

Huhtaniemi I. A short evolutionary history of FSH-stimulated spermatogenesis. Hormones (Athens). 2015 Oct-Dec;14(4):468-478. PMID:26732152. DOI:10.14310/horm.2002.1632

Kacker R, Traish AM, Morgentaler A. Estrogens in men: clinical implications for sexual function and the treatment of testosterone deficiency. J Sex Med. 2012 Jun;9(6):1681-1696. PMID: 22512993. DOI:10.1111/j.1743-6109.2012.02726.x

Kaminetsky J, Werner M, Fontenot G, Wiehle RD. Oral enclomiphene citrate stimulates the endogenous production of testosterone and sperm counts in men with low testosterone: comparison with testosterone gel. J Sex Med. 2013 Jun;10(6):1628-35. doi: 10.1111/jsm.12116. Epub 2013 Mar 26. PMID:23530575. DOI:10.1111/jsm.12116

Kim ED, Crosnoe L, Bar-Chama N, Khera M and Lipshultz LI. The Treatment of Hypogonadism in Men of Reproductive Age. Fertil and Steril. 2013; 99(3): 718-724. PMID:23219010. DOI:10.1016/j.fertnstert.2012.10.052

Kim ED, McCullough A, Kaminetsky J. Oral enclomiphene citrate raises testosterone and preserves sperm counts in obese hypogonadal men, unlike topical testosterone: restoration instead of replacement. BJU Int. 2016 Apr;117(4):677-685. PMID:26496621. DOI:10.1111/bju.13337

Ko EY, Siddiqi K, Brannigan RE, Sabanegh ES Jr. Empirical medical therapy for idiopathic male infertility: a survey of the American Urological Association. J Urol. 2012 Mar;187(3):973-978. PMID:22264467.DOI:10.1016/j.juro.2011.10.137

Liu PY, Wishart SM, Handelsman DJ. A double-blind, placebo-controlled, randomized clinical trial of recombinant human chorionic gonadotropin on muscle strength and physical function and activity in older men with partial age-related androgen deficiency. J Clin Endocrinol Metab. 2002 Jul;87(7):3125-35. PMID:12107212. DOI:10.1210/jcem.87.7.8630

Luboshitzky R, Aviv A, Hefetz A, Herer P, Shen-Orr Z, Lavie L, Lavie P. Decreased pituitary-gonadal secretion in men with obstructive sleep apnea. J Clin Endocrinol Metab. 2002;87(7):3394-3398. PMID: 12107256. DOI: 10.1210/jcem.87.7.8663.

Maseroli E, Corona G, Rastrelli G, Lotti F, Cipriani S, Forti G, Mannucci E, Maggi M. Prevalence of endocrine and metabolic disorders in subjects with erectile dysfunction: a comparative study. J Sex Med. 2015; 12(4): 956-965. PMID: 25689116. DOI: 10.1111/jsm.12832. Epub 2015 Feb 16.

Mendelson JH, Inturrisi CE, Renault P, Senay EC. Effects of acetylmethadol on plasma testosterone. Clin Pharmacol Ther. 1976; 19 (3):371-374. PMID: 1261171

Mosher WD, Pratt WF. Fecundity and infertility in the United States: incidence and trends. Fertil Steril. 1991 Aug;56(2):192-193. PMID: 2070846.

Mousavi SA, Kouchari MR, Samdani-Fard SH, Gilvaee ZN, Arabi M. Relationship between Serum Levels of Testosterone and the Severity of Chronic Obstructive Pulmonary Disease.Tanaffos. 2012;11(3):32-35. PMID: 25191426. PMCID: PMC4153207.

Murray KS, James A, McGeady JB, Reed ML, Kuang WW, Nangia AK. The effect of the new 2010 World Health Organization criteria for semen analyses on male infertility. Fertil Steril. 2012 Dec;98(6):1428-1431. PMID:22921910. DOI:10.1016/j.fertnstert.2012.07.1130

Patel DP, Brant WO, Myers JB, Presson AP, Johnstone EB, Dorais JA, Aston KI, Carrell DT, Hotaling JM. The safety and efficacy of clomiphene citrate in hypoandrogenic and subfertile men. Int J Impot Res. 2015 Nov-Dec;27(6):221-224. Epub 2015 Aug 20. PMID:26289907. DOI:10.1038/ijir.2015.21

Pitteloud N[a], Hardin M, Dwyer AA, Valassi E, Yialamas M, Elhadi D, Hayes FJ. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. J Clin Endocrinol Metab. 2005; 90(5): 2636-2641. PMID: 15713702. DOI: 10.1210/jc.2004-2190

Pitteloud N[b], Mootha VK, Dwyer AA, Hardin M, Lee H, Eriksson KF, Tripathy D, Yialamas M, Groop L, Elahi D, Hayes FJ. Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. Diabetes Care. 2005 Jul;28(7):1636-42. PMID: 15983313. DOI: http://dx.doi.org/10.2337/diacare.28.7.1636

Pitteloud N, Dwyer AA, DeCruz S, Lee H, Boepple PA, Crowley WF Jr, Hayes FJ. Inhibition of luteinizing hormone secretion by testosterone in men requires aromatization for its pituitary but not its hypothalamic effects: evidence from the tandem study of normal and gonadotropin-releasing hormone-deficient men. J. Clin Endocrinol Metab. 2008 Mar;93(3):784-91. Epub 2007 Dec 11. PMID:18073301.PMCID:PMC2266963.DOI:10.1210/jc.2007-2156

Pope HG Jr, Wood RI, Rogol A, Nyberg F, Bowers L, Bhasin S. Adverse health consequences of performance-enhancing drugs: an Endocrine Society scientific statement. Endocr Rev. 2014 Jun; 35(3):341-375. Epub 2013 Dec 17.PMID: 24423981. DOI: 10.1210/er.2013-1058

Practice Committee of the American Society for Reproductive Medicine. Definition of "infertility". Fertil Steril. 2004 Sep;82 Suppl 1:S206. PMID:15363731.DOI:10.1016/j.fertnstert.2004.05.055

Practice Committee of American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: a committee opinion. Fertil Steril. 2012 Aug;98(2):294-301. PMID:22698639. DOI: 10.1016/j.fertnstert.2012.05.033

Rahnema CD, Lipshultz LI, Crosnoe LE, Kovac JR, Kim ED. Anabolic steroid-induced hypogonadism:diagnosis and treatment. Fertil Steril. 2014 May;101(5):1271-1279. PMID: 24636400. DOI: 10.1016/j.fertnstert.2014.02.002

Ramasamy R, Armstrong JM, Lipshultz LI. Preserving fertility in the hypogonadal patient: an update. Asian J Androl.2015 Mar-Apr;17(2):197-200. PMID:25337850. PMCID: PMC4378070. DOI:10.4103/1008-682X.142772

Rambhatla A, Mills JN, Raifer J. The Role of Estrogen Modulators in Male Hypogonadism and Infertility. J. Rev Urol 2016;18(2):66-72. PMID: 27601965. PMCID: PMC5010627

Rasmussen JJ, Selmer C, Østergren PB, Pedersen KB, Schou M, Gustafsson F, Faber J, Juul A, Kistorp C. Former Abusers of Anabolic Androgenic Steroids Exhibit Decreased Testosterone Levels and Hypogonadal Symptoms Years after Cessation: A Case-Control Study. PLoS One. 2016 Aug 17;11(8):e0161208. PMID: 27532478. PMCID:PMC4988681.DOI: 10.1371/journal.pone.0161208

Rochira V, Zirilli L, Orlando G, Santi D, Brigante G, Diazzi C, Carli F, Carani C, Guraladi G. Premature decline of serum total testosterone in HIV-infected men in the HAART-era. PLoS One. 2011;6(12): e28512. PMID: 22174826. PMCID:PMC3235128. doi: http://dx.doi.org/10.1371/journal.pone.0028512

Rose RM, Bourne PG, Poe RO, Mougey EH, Collins DR, Mason JW. Androgen responses to stress. II. Excretion of testosterone, epitestosterone, androsterone and etiocholanolone during basic combat training and under threat of attack. Psychosom Med. 1969 Sep-Oct; 31(5): 418–436. PMID: 5350299.

Roth MY, Page ST, Lin K, Anawalt BD, Matsumoto AM, Snyder CN, Marck BT, Bremner WJ, Amory JK. Dose-dependent increase in intratesticular testosterone by very low-dose human chorionic gonadotropin in normal men with experimental gonadotropin deficiency. J Clin Endocrinol Metab 2010;95(8):3806–3813. PMID:20484472. PMCID:PMC2913032. DOI:10.1210/jc.2010-0360

Roth LW, Ryan AR, Meacham RB. Clomiphene citrate in the management of male infertility. Semin Reprod Med. 2013 Jul;31(4):245-50. doi: 10.1055/s-0033-1345271. Epub 2013 Jun 17. PMID: 23775379. DOI:10.1055/s-0033-1345271

Sabanegh ES Jr, Agarwal A. Male Infertility. 2011. Current Clinical Urology. XII. Section VI: 616-647.

Scott HM, Mason JI, Sharpe RM. Steroidogenesis in the fetal testis and its susceptibility to disruption by exogenous compounds. Endocr Rev. 2009 Dec;30(7):883-925. PMID:19887492. DOI:10.1210/er.2009-0016

Sorokin I, Welliver C, Feustel P, Parker A,Thompson J, Fontenot G, Wiehle R, McCullough A. PD07-08: Changes in testicular volume and function after testosterone replacement vs. restoration: analysis of a randomized, double blind, placebo-controlled trial of enclomiphene citrate vs. Androgel™ 1.62% in men with secondary hypogonadism. 2016; 195(4):225-226. DOI: http://dx.doi.org/10.1016/j.juro.2016.02.2811

Tajar A, Forti G, O'Neill TW, Lee DM, Silman AJ, Finn JD, Bartfai G, Boonen S, Casanueva FF, Giwercman A, Han TS, Kula K, Labrie F, Lean MEJ, Pendelton N, Punab M, Vanderschuren D, Huhtaniemi IT, Wu FCW, EMAS Group. Characteristics of secondary, primary and compensated hypogonadism in aging men: evidence from the European male aging

study. J Clin Endocrinol Metab.2010; 95: 1810-1818. PMID: 20173018. DOI: http://dx.doi.org/10.1210/jc.2009-1796

Ventimiglia E, Capogrosso P, Boeri L, Ippolito S, Scano R, Moschini M, Gandaglia G, Papaleo E, Montorsi F, Salonia A. Validation of the American Society for Reproductive Medicine guidelines/recommendations in white European men presenting for couple's infertility. Fertil Steril. 2016 Oct;106(5):1076-1082. PMID:27473348. DOI:10.1016/j.fertnstert.2016.06.044

Vermeulen A, Kaufman JM, Deslypere JP, Thomas G. Attenuated luteinizing hormone (LH) pulse amplitude but normal LH pulse frequency, and its relation to plasma androgens in hypogonadism of obese men. J. Clin endocrinol Metab. 1993 May;76(5):1140-6. PMID:8496304. DOI:10.1210/jcem.76.5.8496304

Vescovi PP, Pezzarossa A, Ceresini G, Rastelli G, Valenti G, Gerra G. Effects of dopamine receptor stimulation on opiate-induced modifications of pituitary-gonadal function. Hormone Res. 1985;2(3):155–159. PMID 3997064.

Vignera S, Condorelli R, Cimino L, Russo G, Morgia G, Calogero A Late-onset hypogonadism: the advantages of treatment with human chorionic gonadotropin rather than testosterone. Aging Male. 2016; 19(1): 34-39. PMID:26488941. DOI:10.3109/13685538.2015.1092021

Vogel AV, Peake GT, Rada RT. Pituitary-testicular axis dysfunction in burned men. J Clin Endocrinol Metab. 1985; 60(4): 658–665. PMID: 4038713. DOI: 10.1210/jcem-60-4-658

Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain-Misconceptions and Mitigation Strategies. N Engl J Med 2016; 374 (13):1253-1263. PMID: 270289015. DOI: 10.1056/NEJMra1507771

Whitten SJ, Nangia AK, Kolettis PN. Select patients with hypogonadotrophic hypogonadism may respond to treatment with clomiphene citrate. Fertil steril. 2006 Dec; 86(6):1664-1668. Epub 2006 Sep 27. PMID:17007848. DOI:10.1016/j.fertnstert.2006.05.042

WHO Task Force On Methods for the regulation of male fertility. Contraceptive efficacy of testosterone-induced azoospermia in normal men. The Lancet. 20 October 1990:336(8721):955-959.

WHO Task Force On Methods for the regulation of male fertility. Contraceptive efficacy of testosterone-induced azoospermia in normal men. Fertil Steril. 1996 Apr;65(4):821-9. PMID:8654646

Wiehle R, Cunningham GC, Pitteloud,N, Wike J, Hsu K, Fontenot GK, Rosner M, Dwyer A, Podolski J. Testosterone restoration using enclomiphene citrate in men with secondary hypogonadism: a pharmacodynamic and pharmacokinetic study.BJU Int. 2013 Dec; 112(8): 1188–1200. PMCID: PMC4155868.DOI: 10.1111/bju.12363

Wiehle RD, Fontenot GK, Wike J, Hsu K, Nydell J, Lipshultz L; ZA-203 Clinical Study Group. Enclomiphene citrate stimulates testosterone production while preventing oligospermia: a randomized phase II clinical trial comparing topical testosterone. Fertil Steril. 2014 Sep;102(3):720-7. doi: 10.1016/j.fertnstert.2014.06.004. Epub 2014 Jul 17. PMID:25044085. DOI:10.1016/j.fertnstert.2014.06.004

Woolf PD, Hamill RW, McDonald JV, Lee LA, Kelly M. Transient hypogonadotropic hypogonadism after head trauma: effects on steroid precursors and correlation with sympathetic nervous system activity. Clin Endocrinol (Oxf). 1986; 25 (3): 265–274. PMID: 3098464.

Yeap BB, Grossmann M, McLachlan RI, Handelsman DJ, Wittert GA, Conway AJ, Stuckey BG, Lording DW, Allan CA, Zajac JD, Burger HG. Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy. Med J Aust. 2016 Aug 15;205(4):173-178. PMID: 27510348. DOI:10.5694/mja16.00393

Young J, Rey R, Schaison G, Chanson P. Hypogonadotropic hypogonadism as a model of post-natal testicular anti-Müllerian hormone secretion in humans. Mol Cell Endocrinol. 2003 Dec 15;211(1-2):51-4. PMID: 14656476.