Repros Therapeutics

Development of small molecule drugs for major unmet medical needs that treat male and female reproductive disorders.

Repros Disclaimer

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In this presentation, we rely on and refer to information and statistics regarding the pharmaceutical industry. We obtained this information and these statistics from third-party sources, which we have supplemented where necessary with information from publicly available sources and our own internal estimates. Industry publications and surveys generally state that they have obtained information from sources believed to be reliable, but do not guarantee the accuracy and completeness of such information. While we believe that each of these studies and publications is reliable, we have not independently verified such data, and we make no any representation as to the accuracy of such information. Similarly, we believe our internal research is reliable, but it has not been verified by any independent sources.

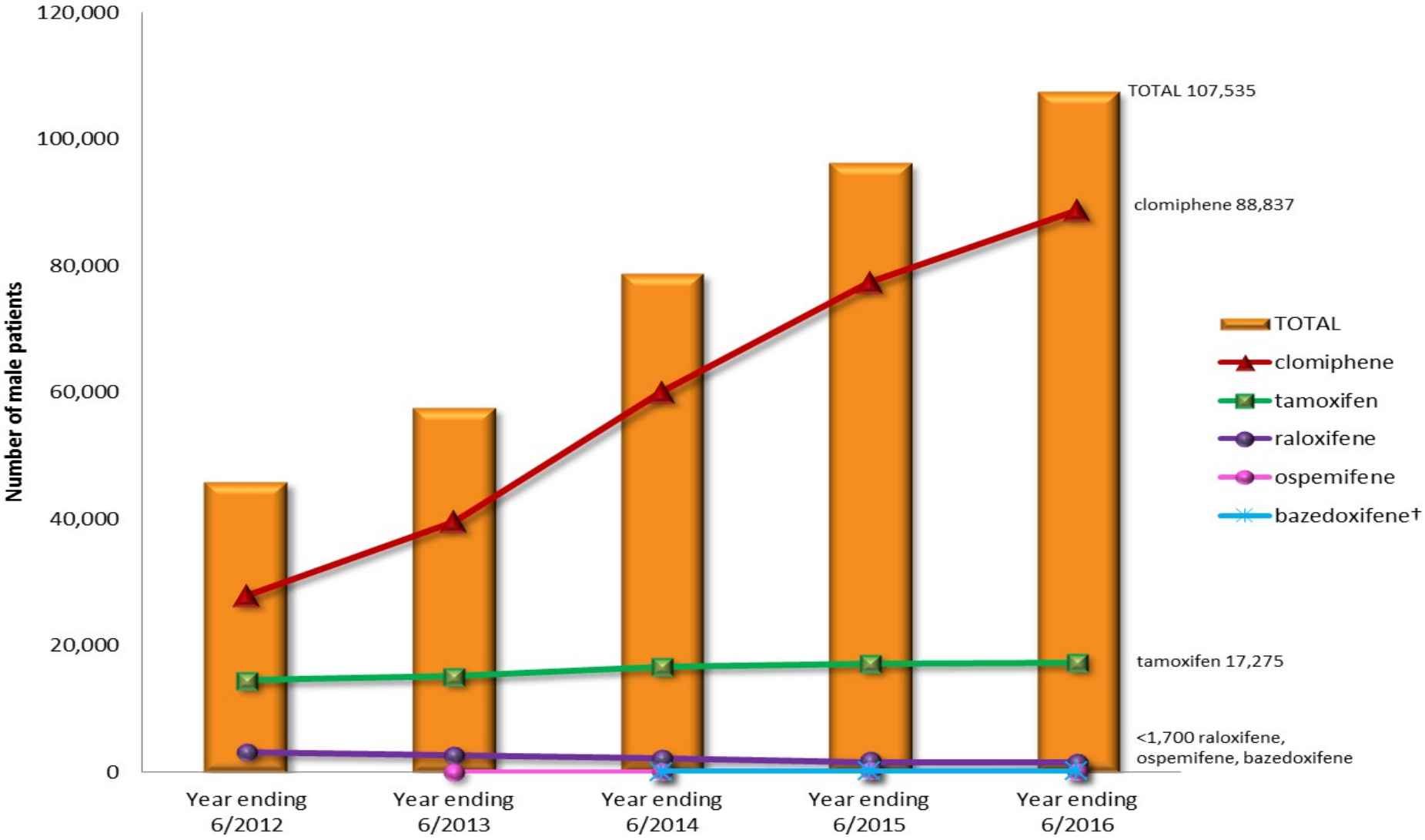
Encyzix (enclomiphene)

Rational treatment for secondary hypogonadism

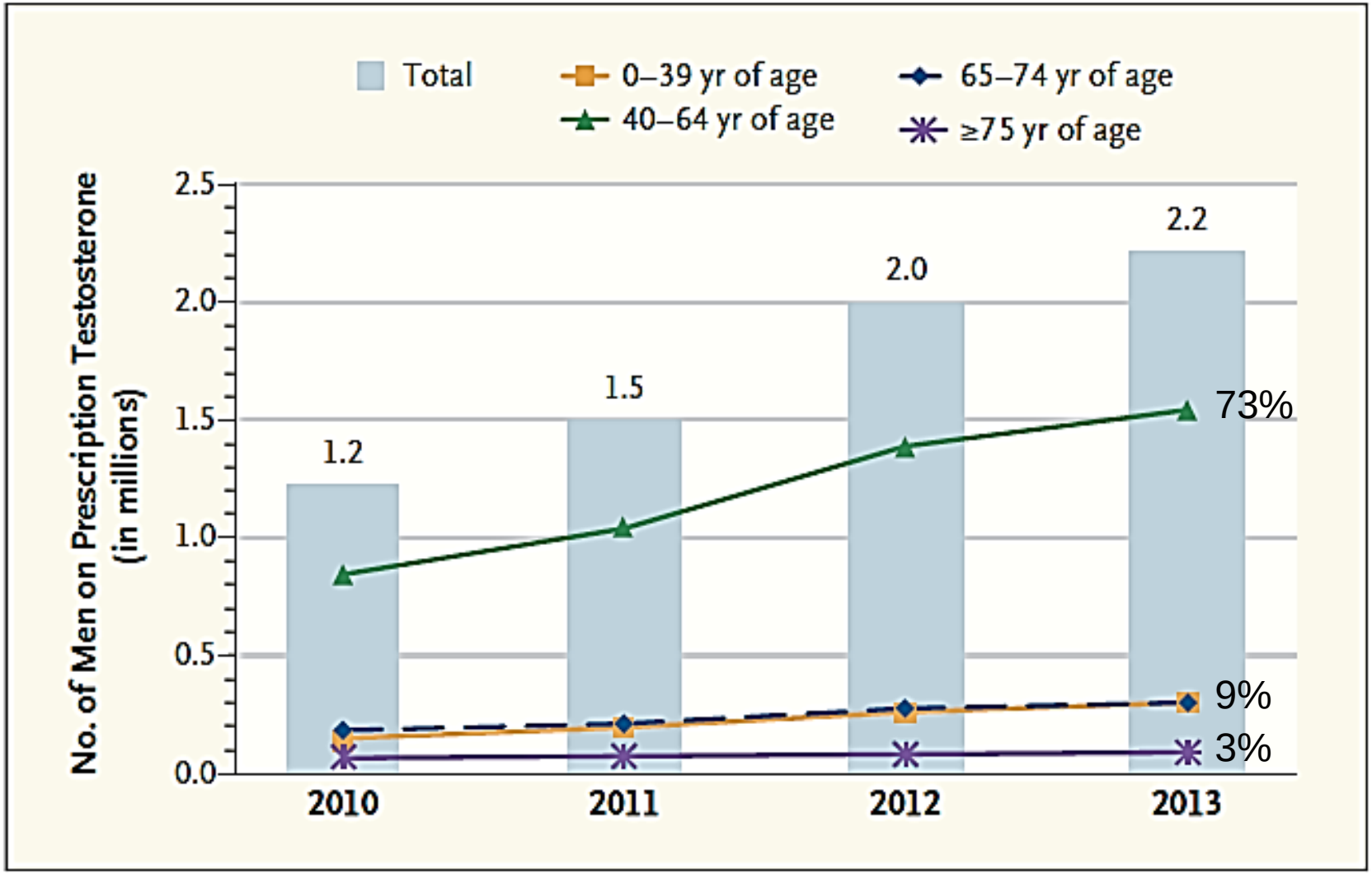
Enclomiphene Development Status

- Central EU filing ongoing for treatment of secondary hypogonadism
  - Anticipated marketing authorization Q4-’17
- Repros to present as sponsor at 12/6/16 FDA Adcom
  - “Agenda: The committee will 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.”
  - No T replacement to be discussed due to negative effects on testicular function
- US Phase 2 “Proof of Concept” to evaluate clinical benefit

Nationally Estimated Number of Male Patients Who Received Dispensed Prescriptions for Selected Estrogen Receptor Agonists/Antagonists* from U.S. Outpatient Retail Pharmacies from July 2011 through June 2016, Annually



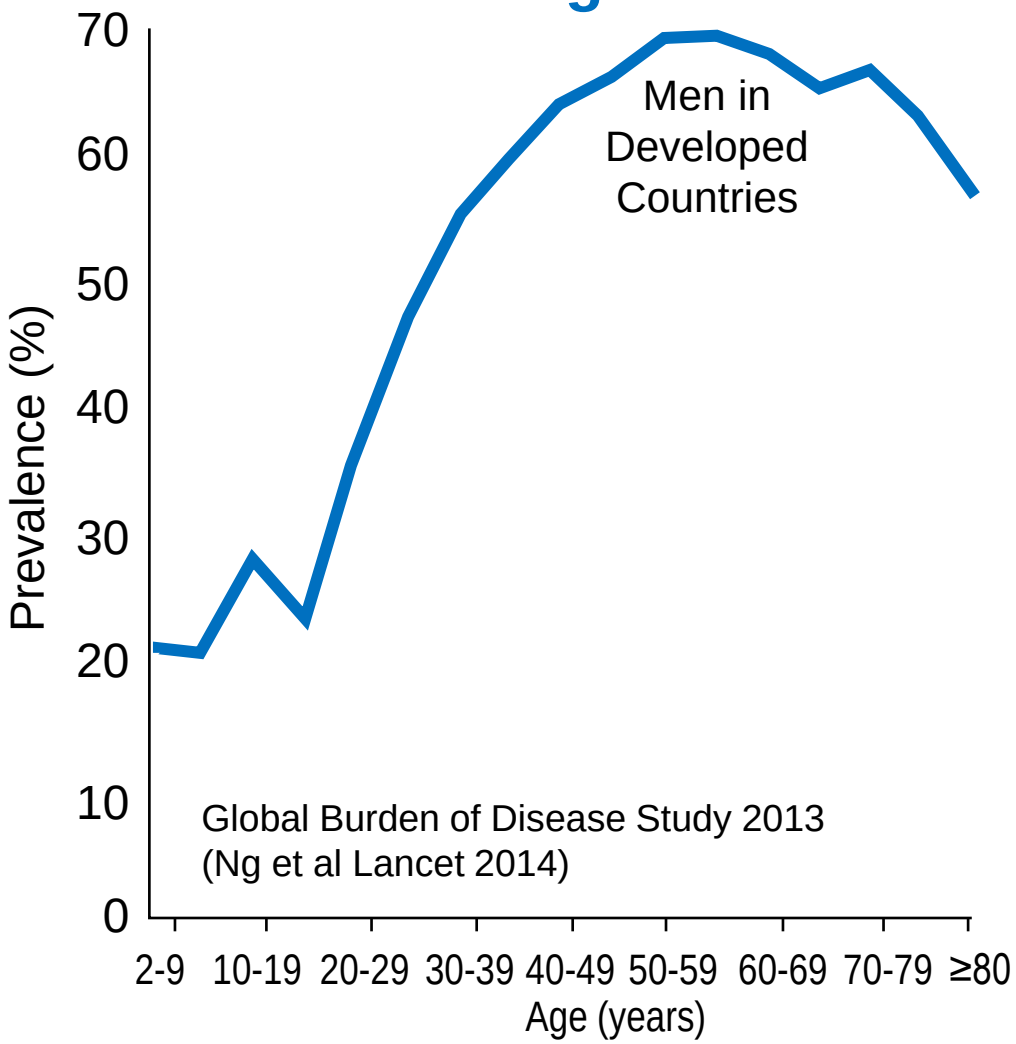
Prescription Claims for Testosterone Products



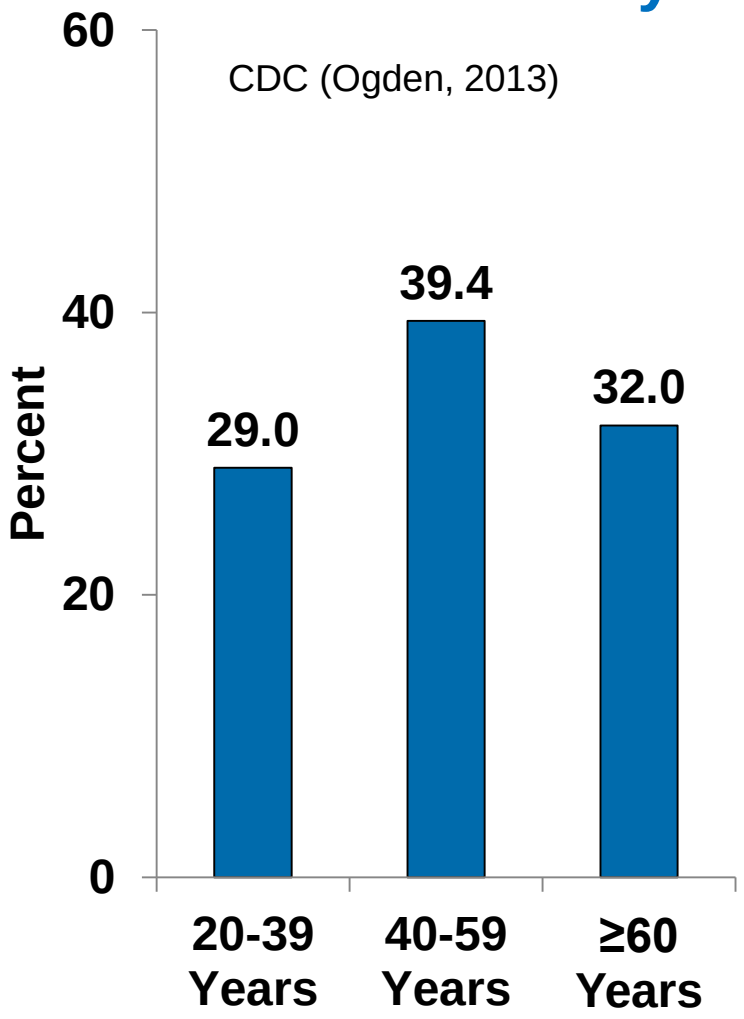
Nguyen et al N Eng J Med 2015

Prevalence of Overweight and Obesity

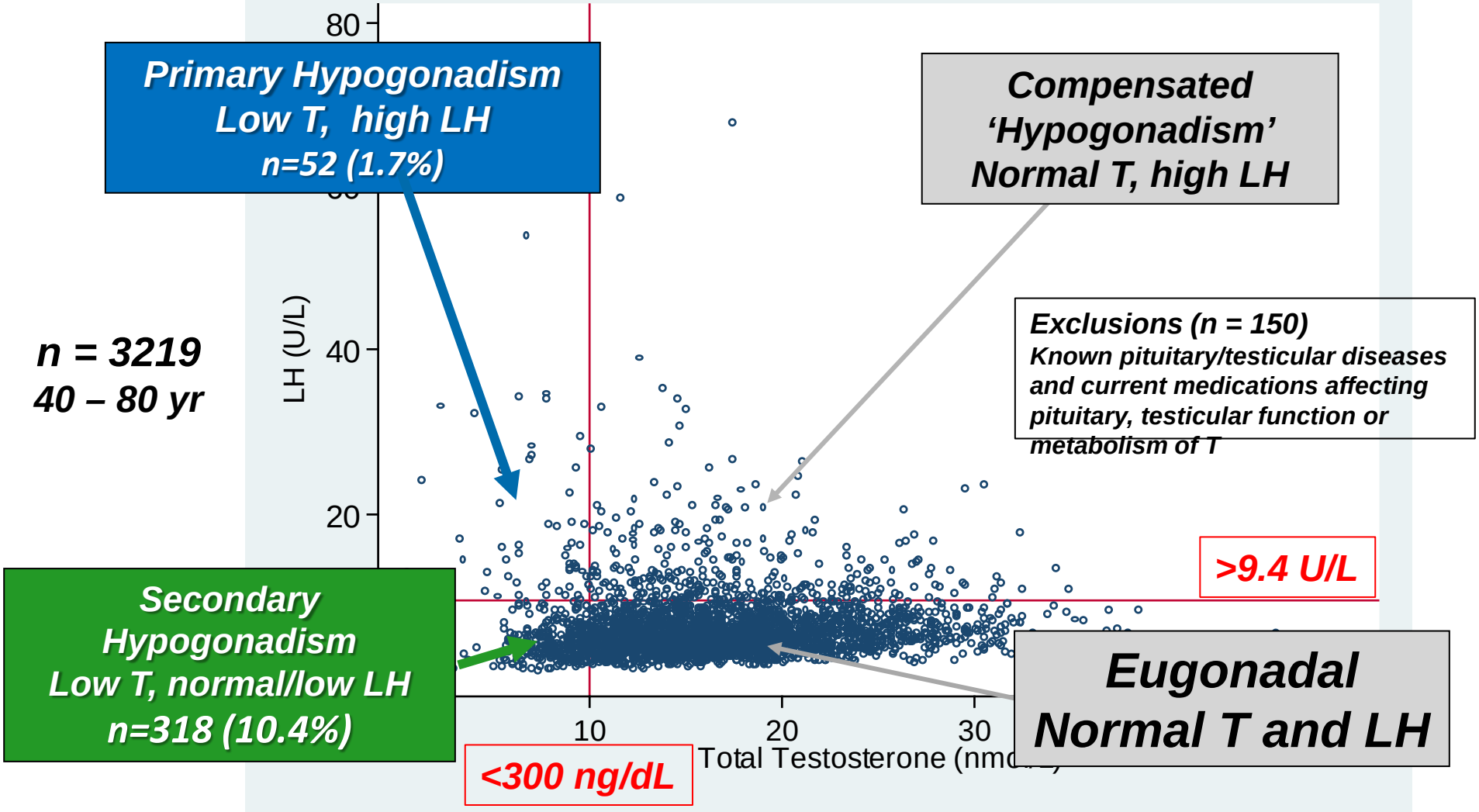
Overweight and Obese



Obese Only

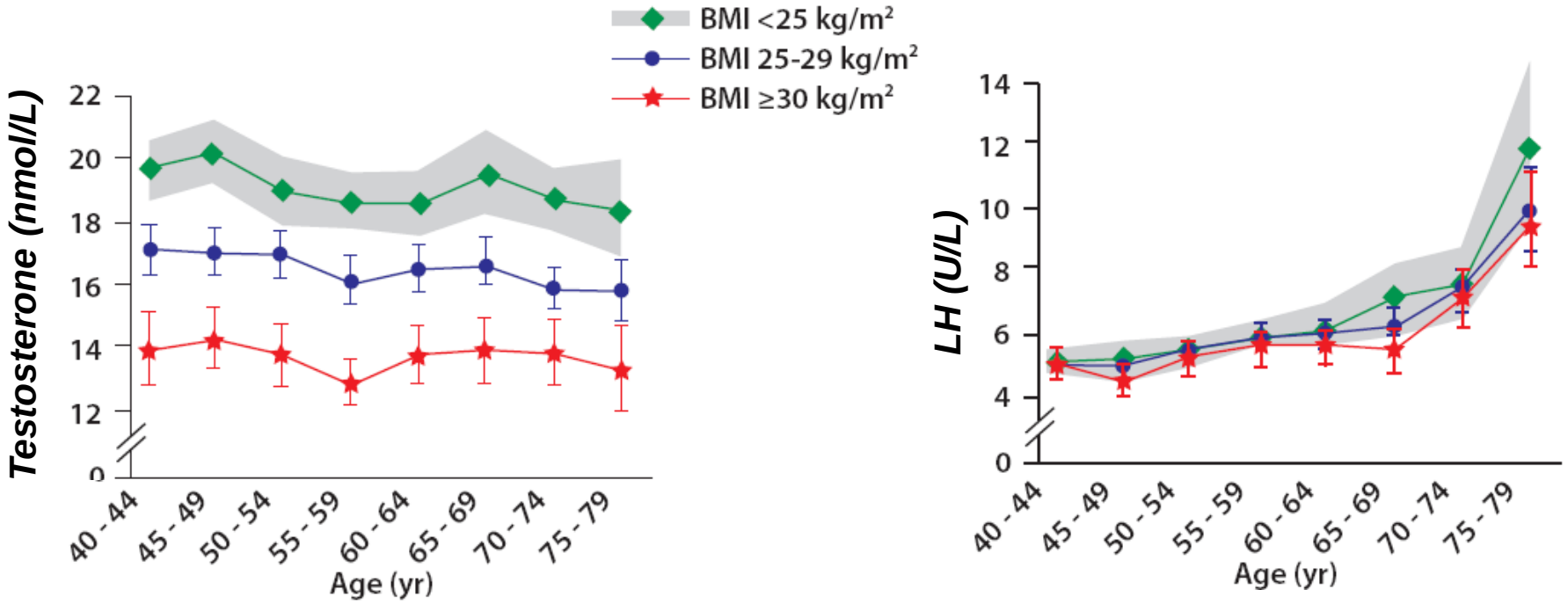


Categorizing Gonadal Status by Testosterone and LH



EMAS Tajar, JCEM 2010

BMI and Age: Different Effects on Hormones



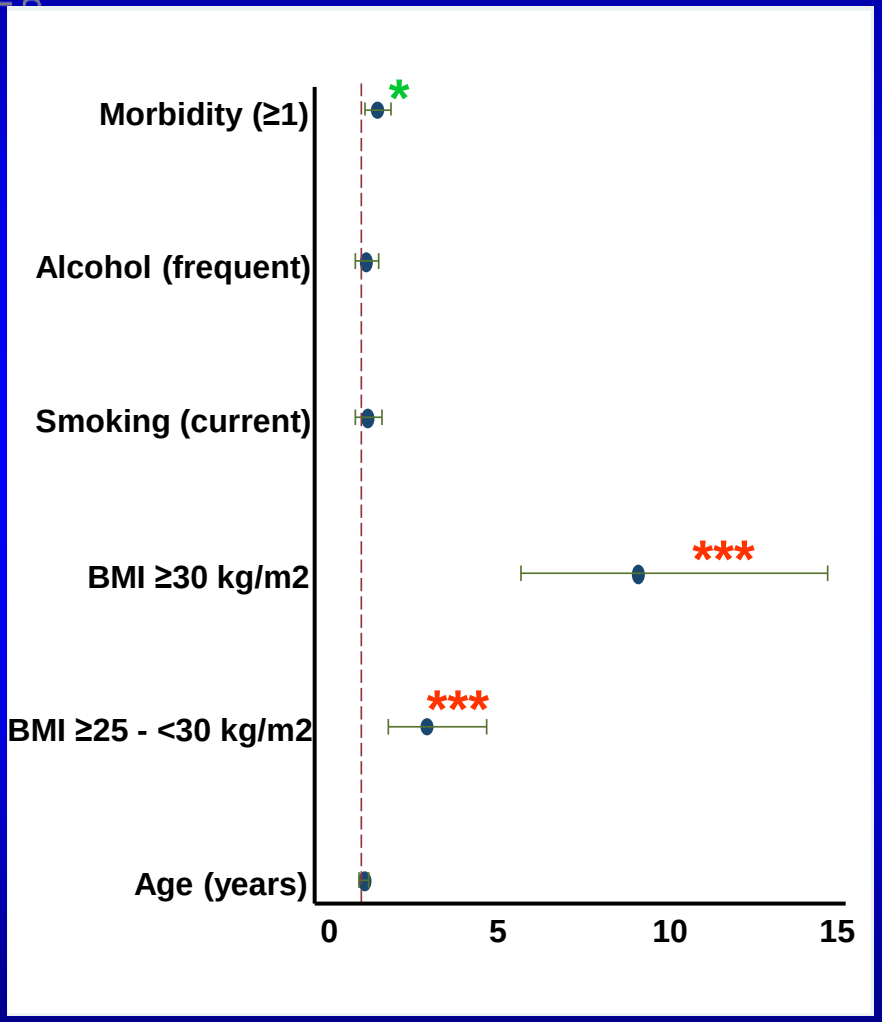
- ***With <u>obesity,</u> LH does not respond to fall in testosterone – functional hypothalamic / pituitary suppression***
- ***With <u>aging</u>, increasing LH compensates for failing testicular function so that any age-related decline of testosterone is minimized***

EMAS Wu, JCEM 2008

Secondary Hypogonadism at Baseline

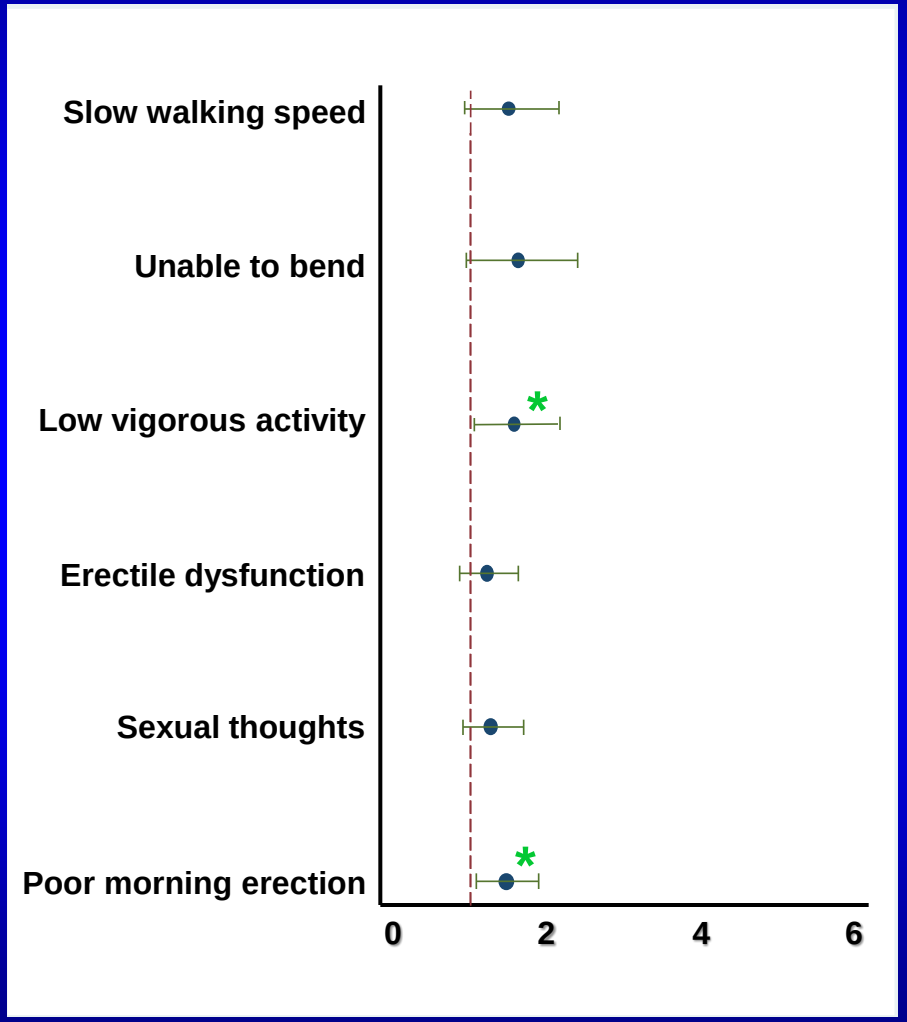
Risk factors

*p <0.05 **p<0.01 ***p<0.001



Adjusted Relative Risk Ratio

Symptoms



Adjusted Odds Ratio

Tajar et al. JCEM 2010

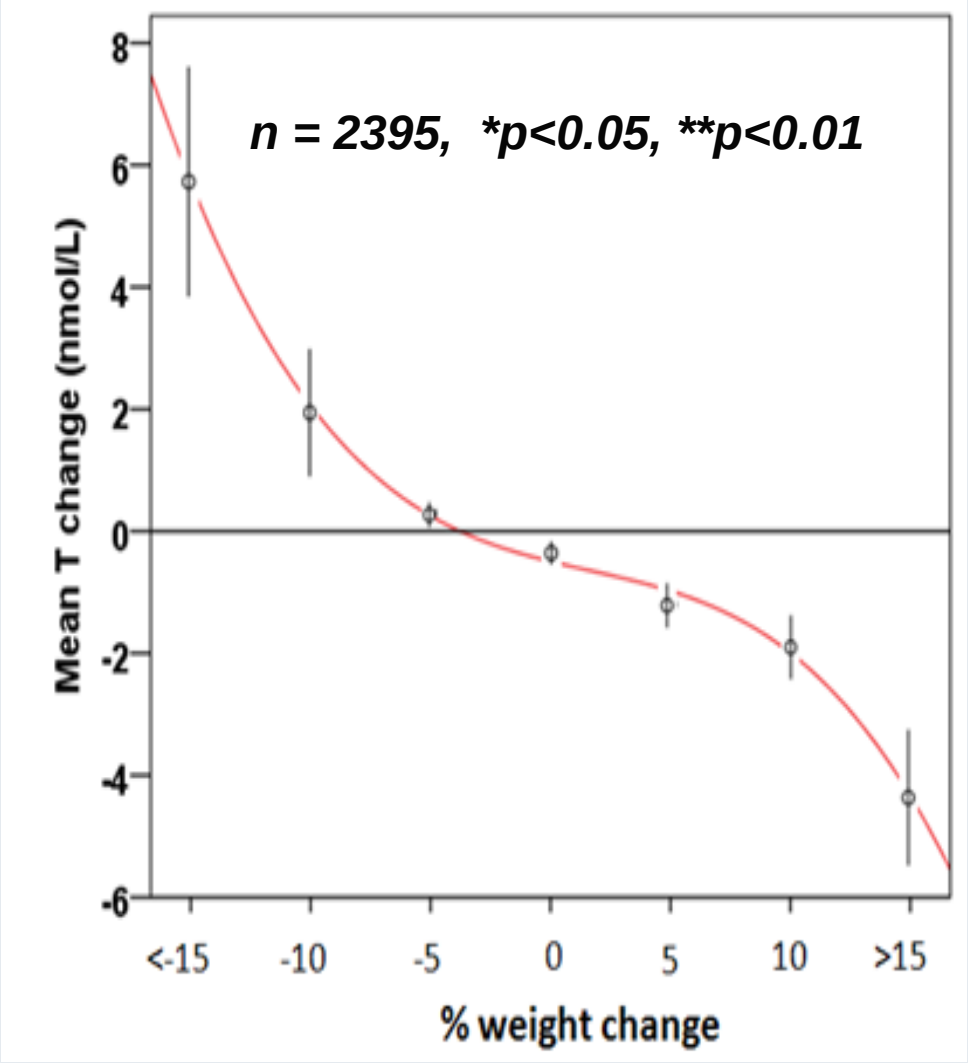
Obesity Related Hypogonadism is the Leading Cause of Secondary Hypogonadism

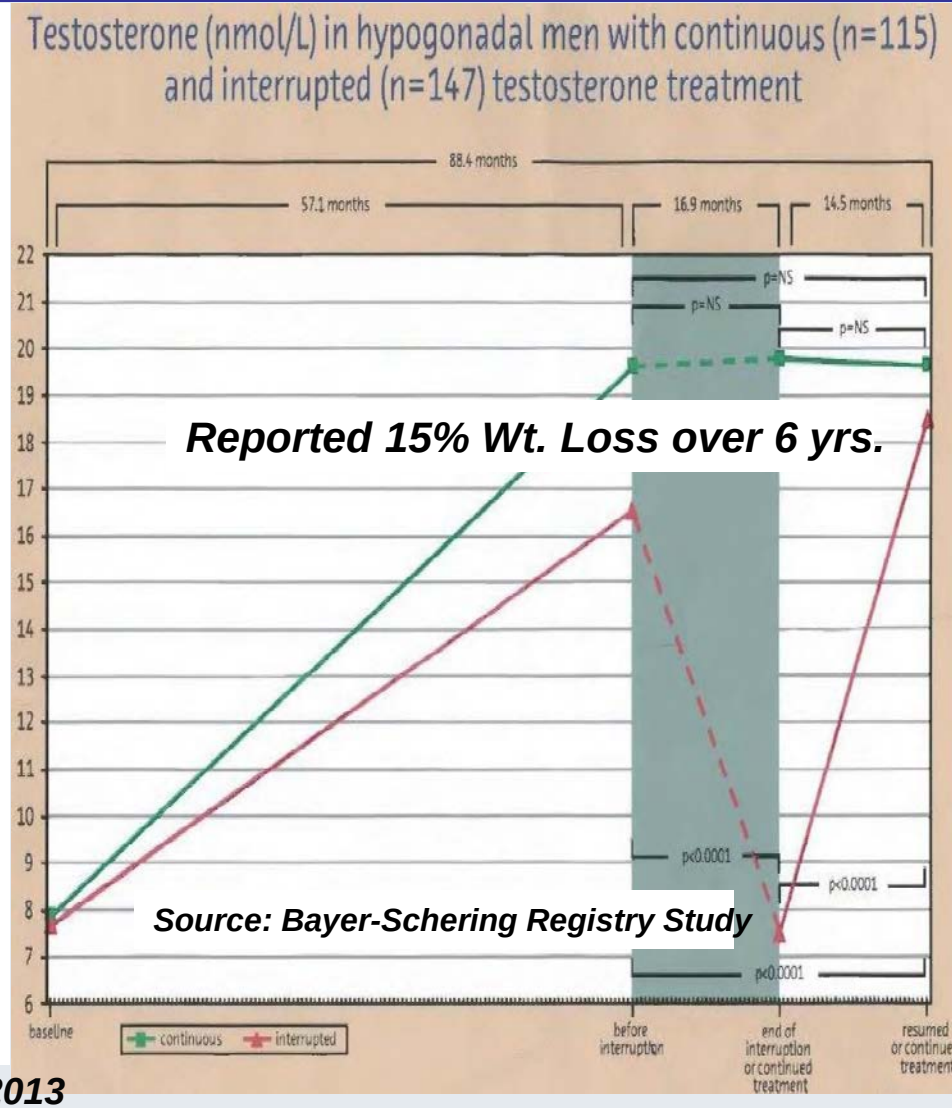
- Obesity has been shown to attenuate LH pulse amplitude but maintain pulse frequency (Vermeulen, JCEM,1993)
- EMAS (Tajar, JCEM, 2010) notes a decrease in the T:E ratio in secondary hypogonadal men compared to eugonadal

	T (nmol/L)	E_2 (pmol/L)	T:E molar ratio
Eugonadal	17.8	74.1	240.2
Secondary	8.7	57.2	152.1

- Anti-estrogens have been shown to increase both LH and T in secondary hypogonadal men

Obesity Related Hypogonadism is a Reversible Disorder Treatment with Exogenous T "May require lifelong therapy" (Bayer abstract quote)





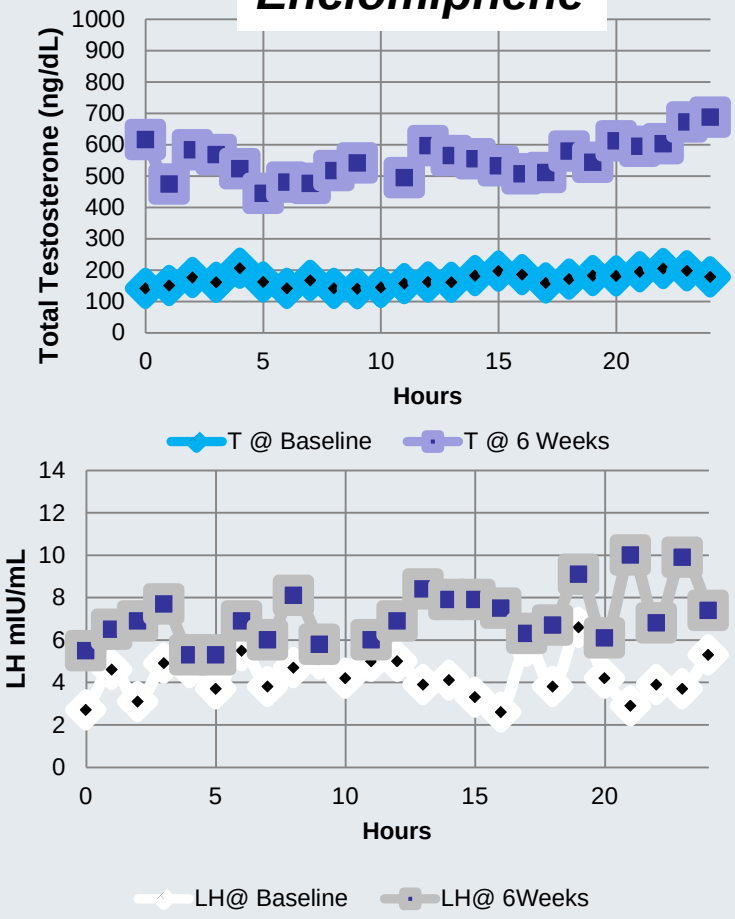
Camacho et al. European Journal of Endocrinology 2013

Relavent Experience Gleaned during the Development of Enclomiphene for the Treatment of Secondary Hypogonadism in Overweight or Obese Men

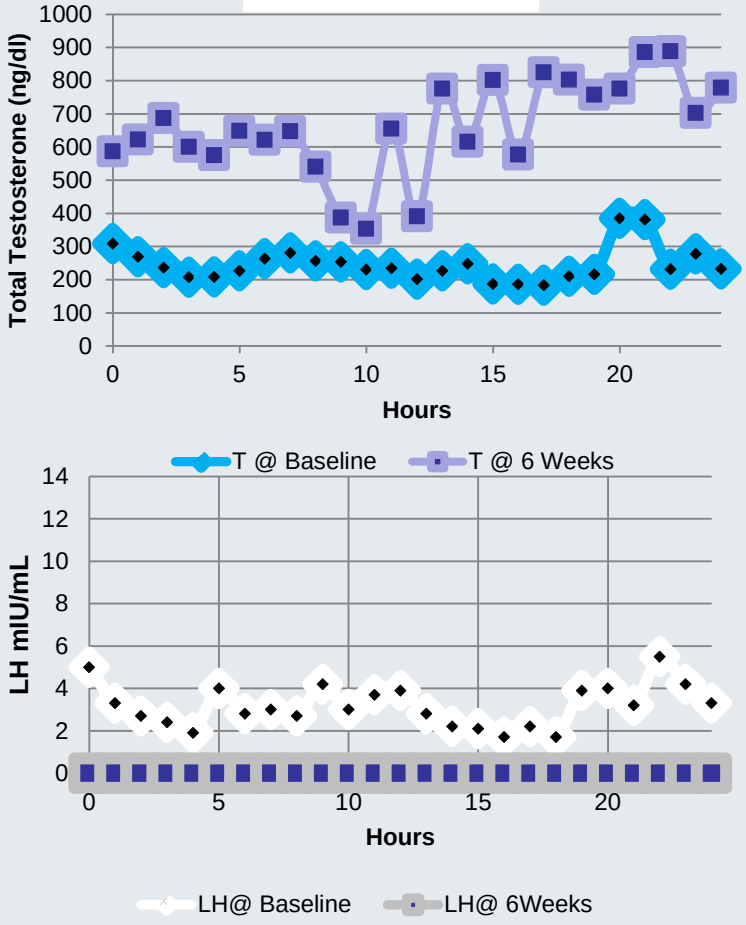
- ***All studies enrolled secondary hypogonadal men***
  - ***Morning T <300 ng/dL***
  - ***LH < 9.4 mIU/mL***
  - ***BMI > 25***
  - ***Age < 60 years***
- ***Screening failures:*** *Lessons learned from studies assessing testosterone and spermatogenesis effects of enclomiphene*
  - ***Sperm concentration (studies 301, 302, 304 & 305)***
    - ***10.6% (186/1,761 screened) did not meet sperm concentration of > 15 Million/mL***
  - ***Morning Testosterone (Pivotal studies 304 & 305)***
    - ***24% (156/642 screened) did not meet morning T < 300 ng/mL***
    - ***Average age of T screen failures: 46.4 (9.2) years***
    - ***Average T of T screen failures: 372 (79.7) ng/dL***

The Anti-estrogen Enclomiphene and Topical Testosterone Exhibit Different Effects on LH in the Overweight/Obese Hypogonadal Male

Enclomiphene



AndroGel®

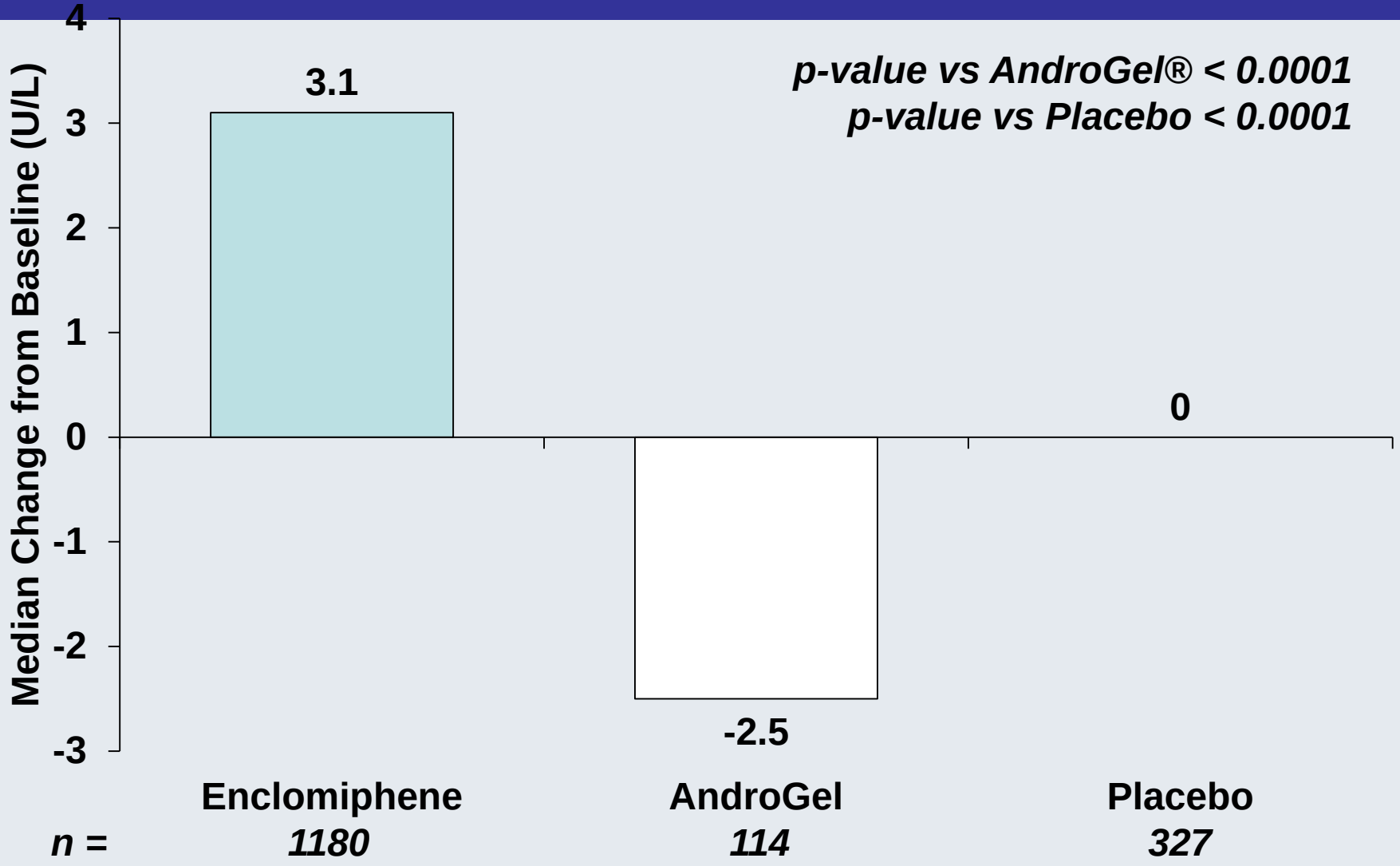


- ***Enclomiphene blocks estradiol, raising LH and maintains pulsatile behavior***
- ***T further suppresses the axis***

Wiehle 2013

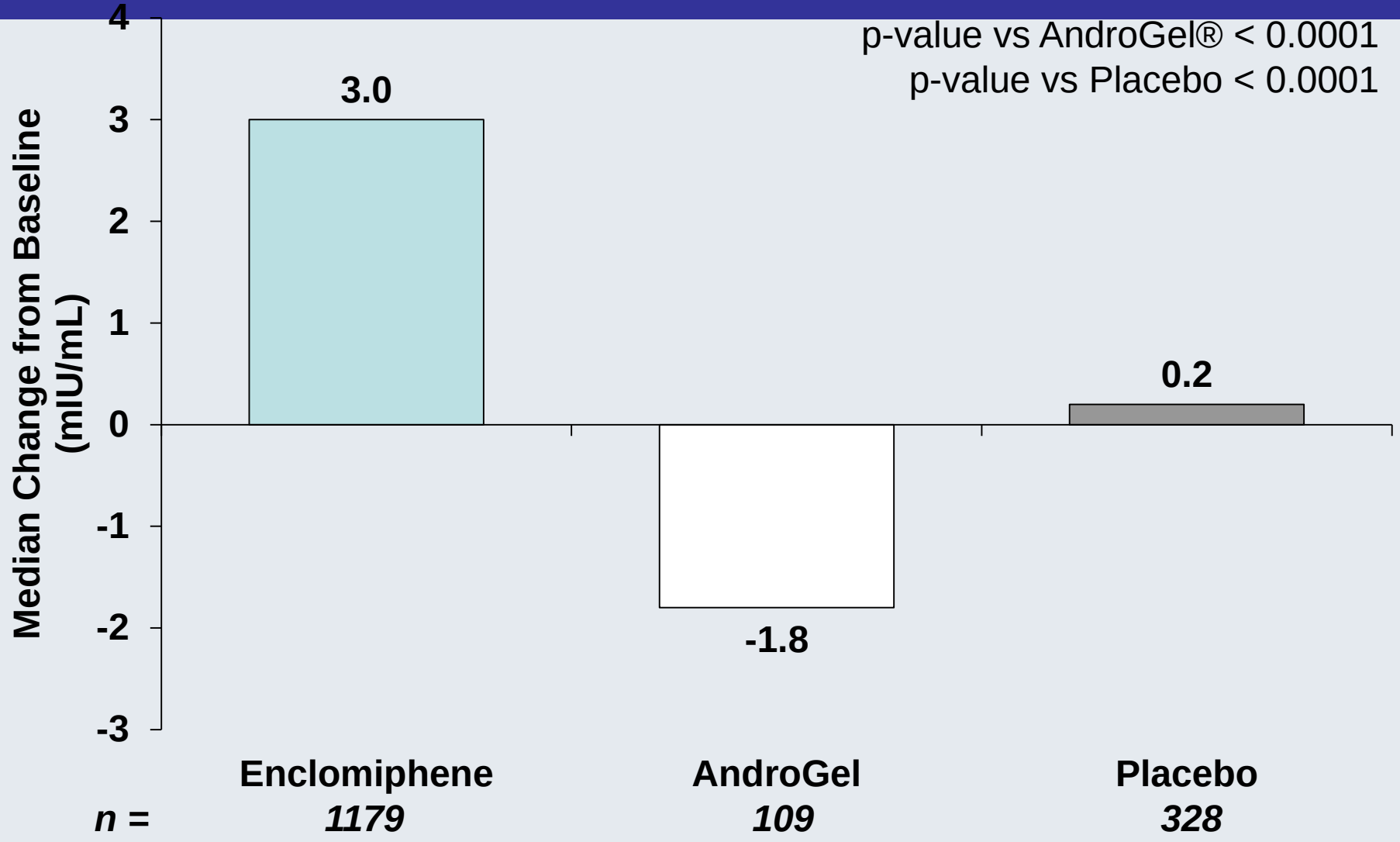
Change from Baseline in FSH

Phase 2/3 Pool

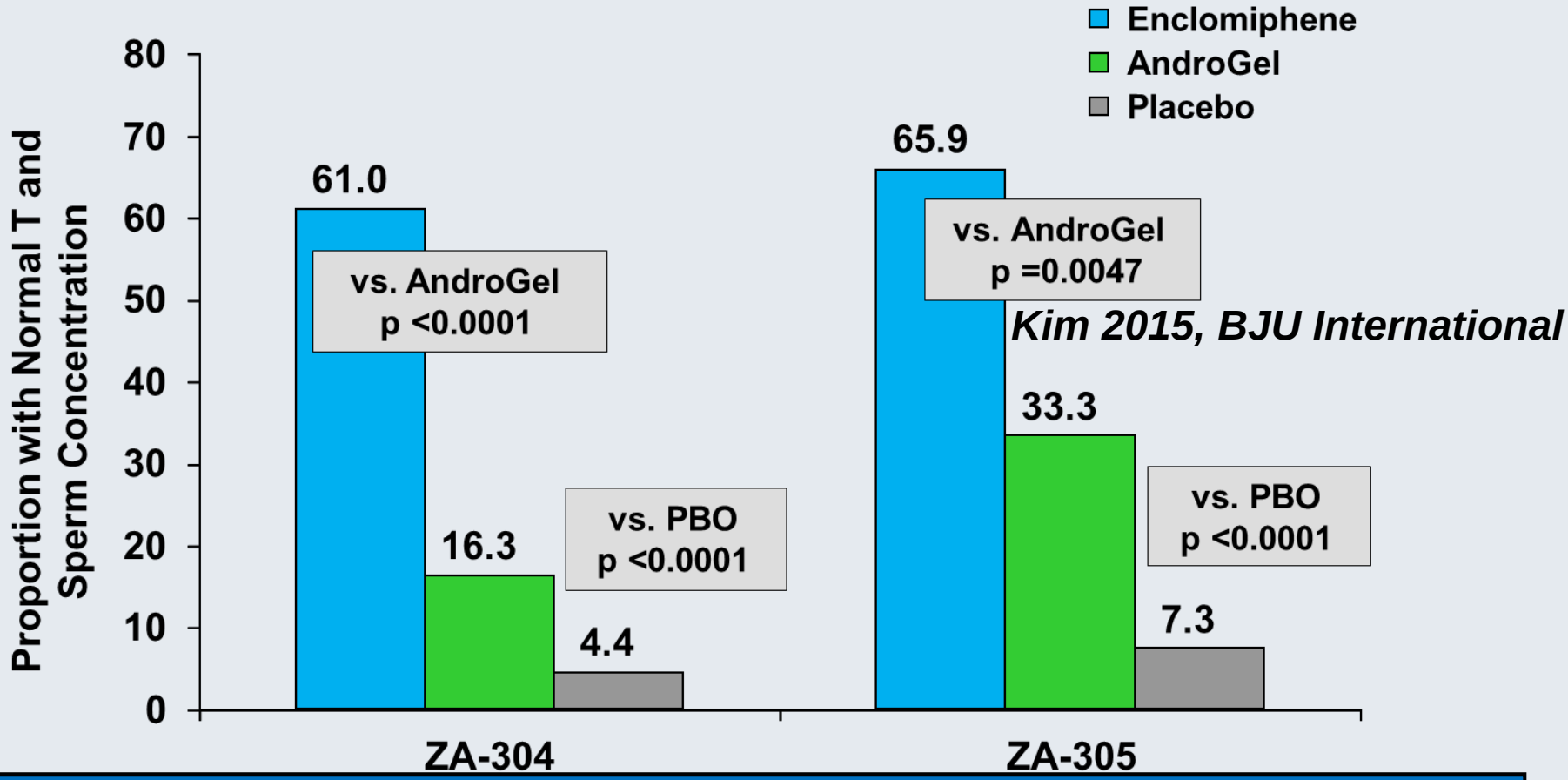


Change from Baseline in LH

Phase 2/3 Pool

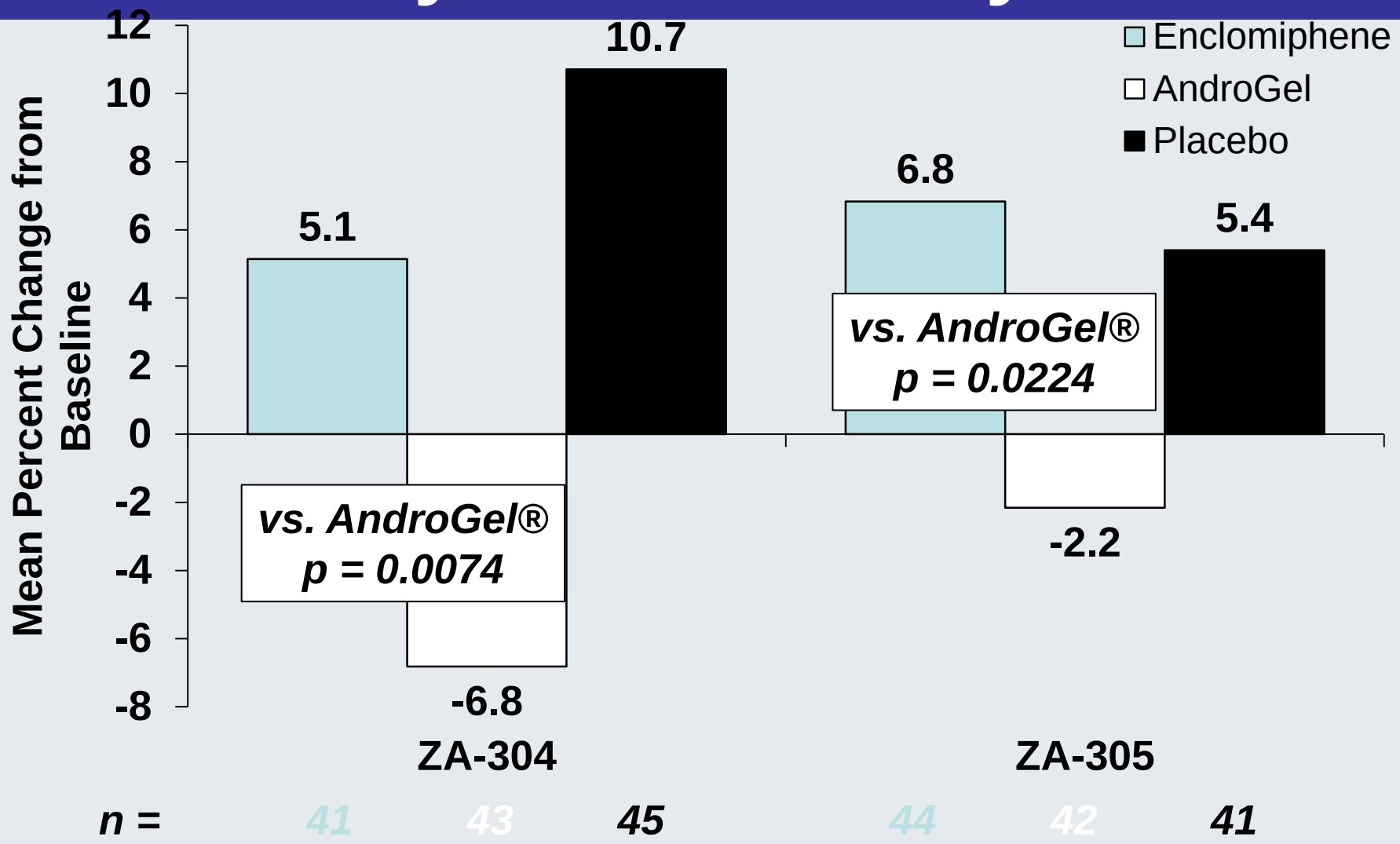


The Effects of Topical T Treatment



Enclomiphene restores normal testosterone levels and maintains sperm concentrations

Percent Change in Testicular Volume by Orchidometry



Phase 2 Proof of Concept "Diet & Exercise" Study in Obese Hypogonadal Men - Baseline Findings

Screen 98 to enroll 50 15 Month Study

- Enrollment (n=50 in 5 weeks @ 5 sites)
- Demographics (stdev)
  - Age: 43.3 (9.2)
  - BMI: 36.8 (3.2)
  - Waist: 46.9" (4.1)
  - % Body Fat: 38.1 (5.2)
- Hormonal Status
  - Testosterone: 221.9 (52.7) ng/dL
  - Estradiol: 48.1 (14.8) pg/mL
  - T:E Ratio: 4.95 (1.7) *normal 20-25*

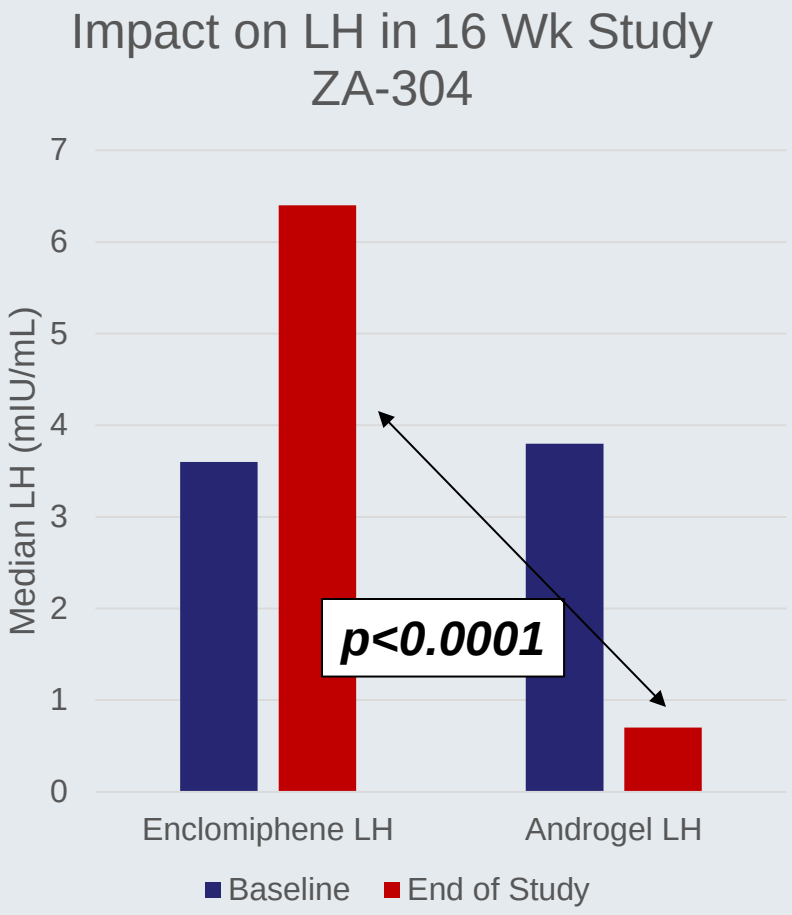
- Top 4 Reported Baseline Symptoms (% of Enrollees)
  - Fatigue/Lack of Energy: 96%
  - Depression, Irritability Lack of Focus: 74%
  - Poor Libido: 60%
  - Muscle Weakness: 48%

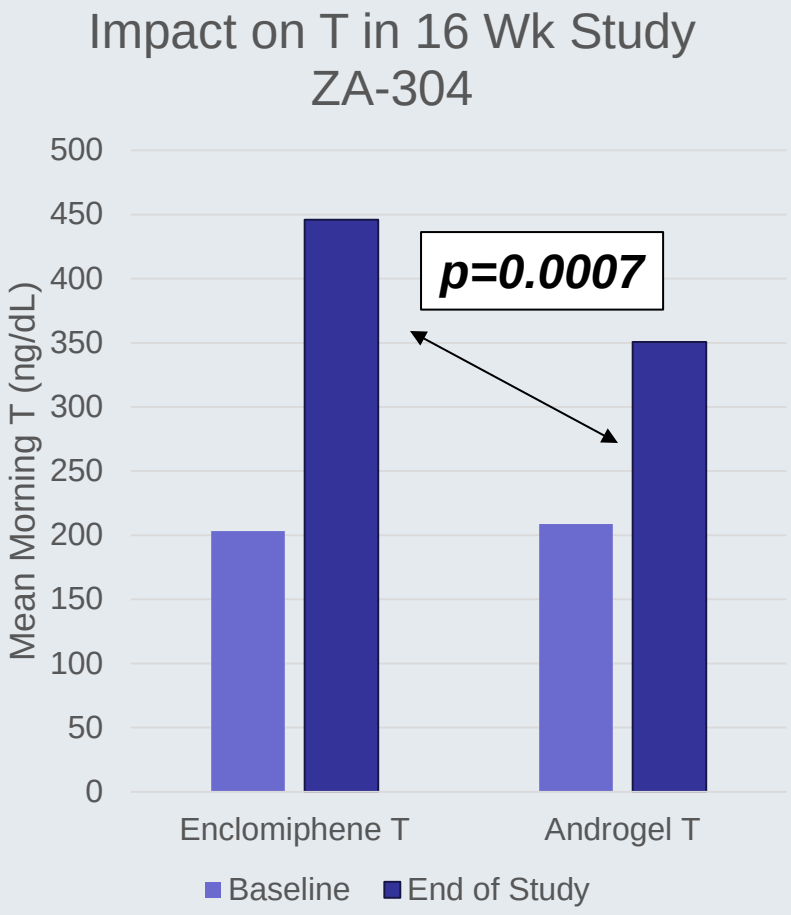
Seeks to show:

- ***The disorder is reversible with weight loss***
- ***Raising endogenous T provides benefit while attempting to diet and exercise***

How Enclomiphene Works

Enclomiphene *blocks estrogen at the level of the H-P axis increasing LH levels which in turn increases endogenous production of T*

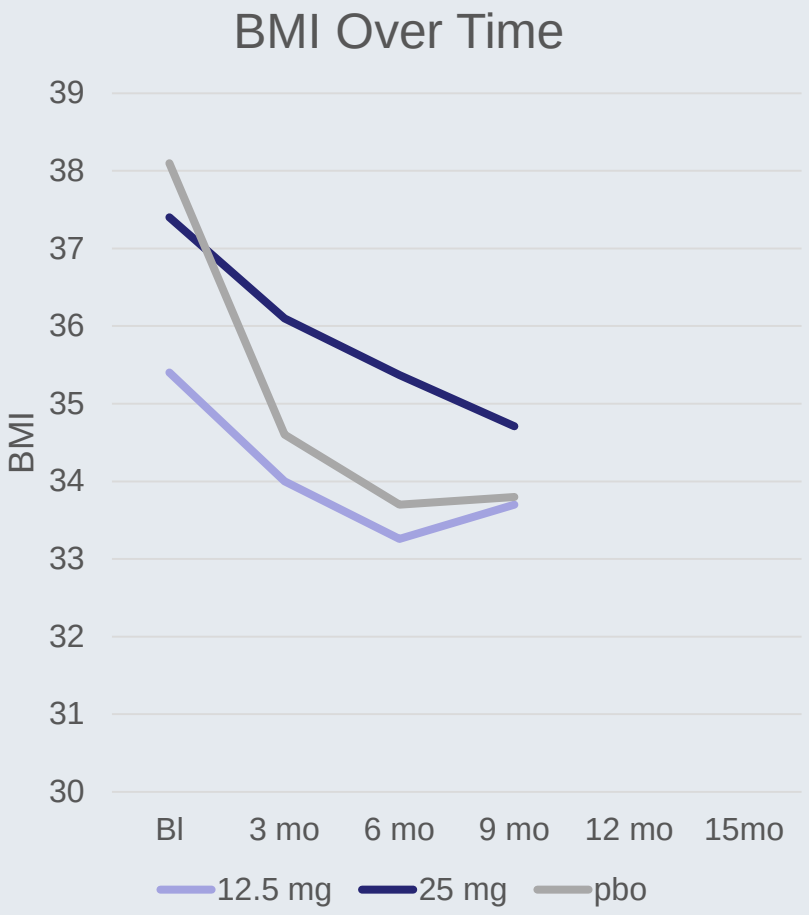


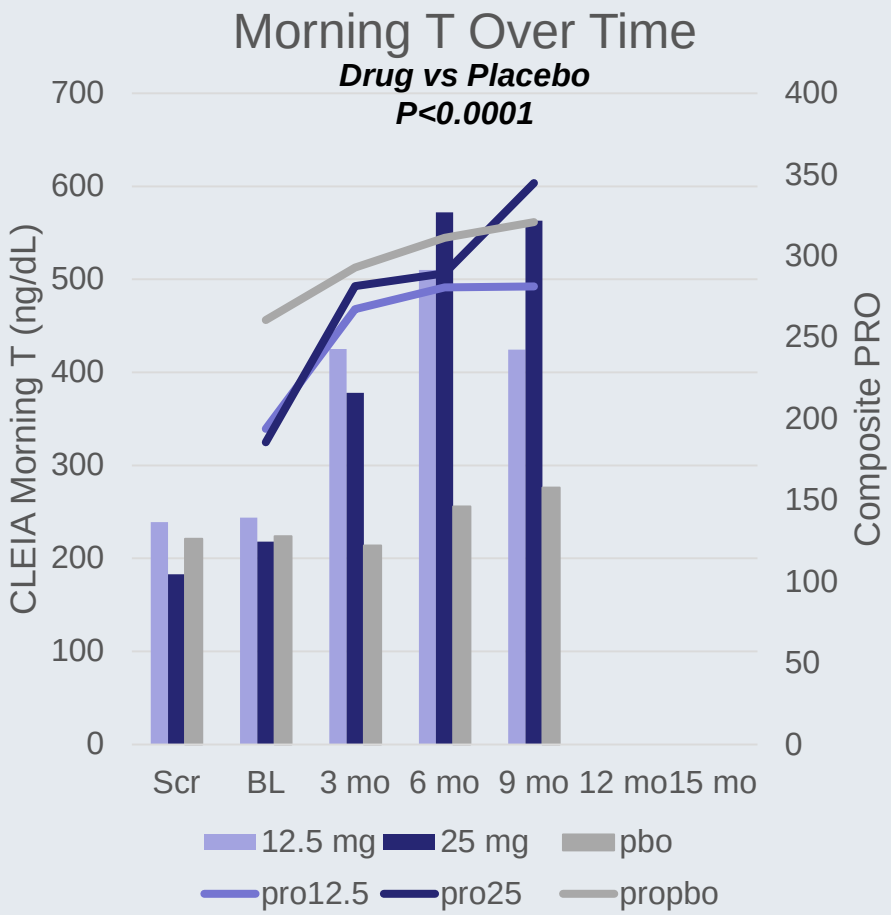


Induction of infertility and shrinking testicles in AndroGel® arm

Interim 9 Month Data

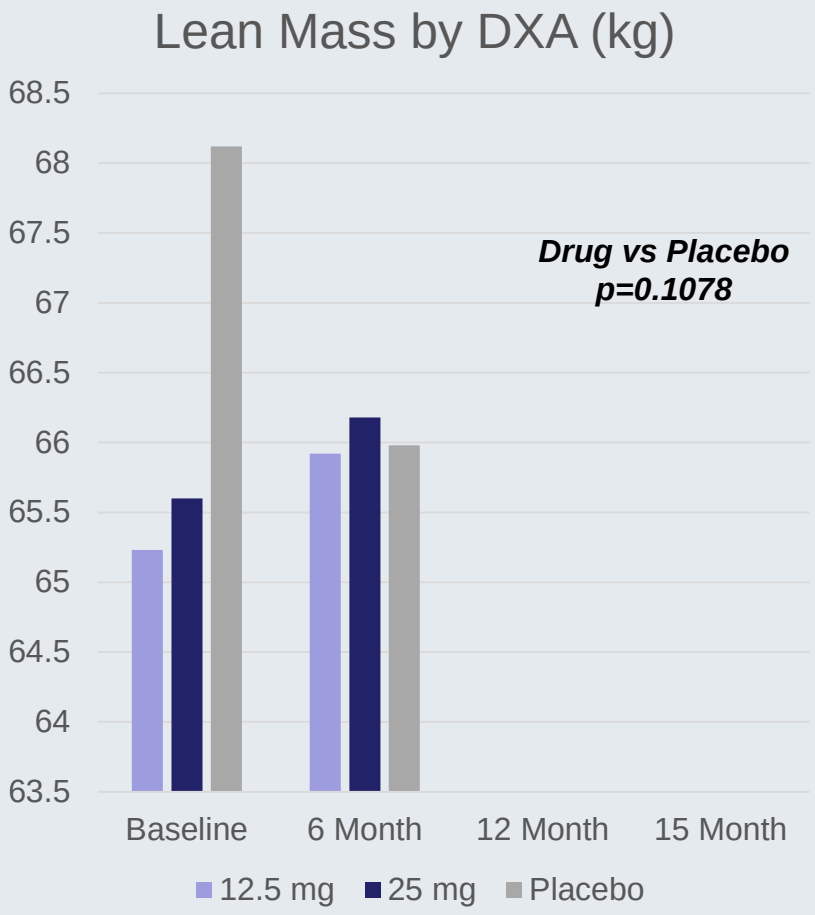
ZA-205

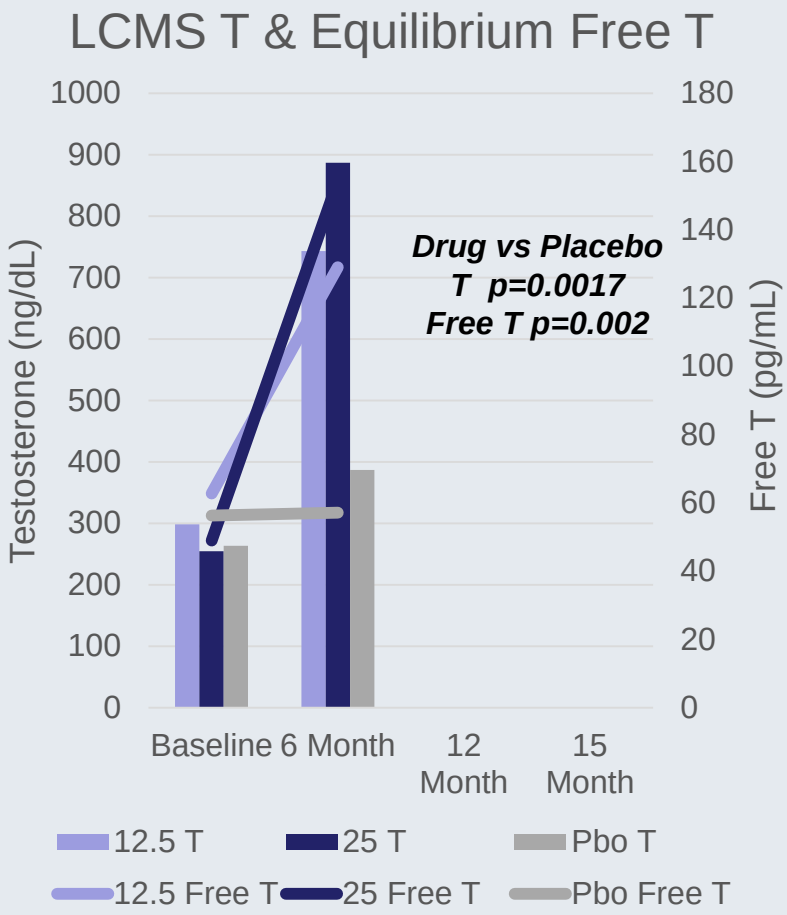




Commercial diet ends at 6 months.
Personal trainer ends at 12 months.

Interim 6 Month Data
Lean Mass, LCMS T & Free T

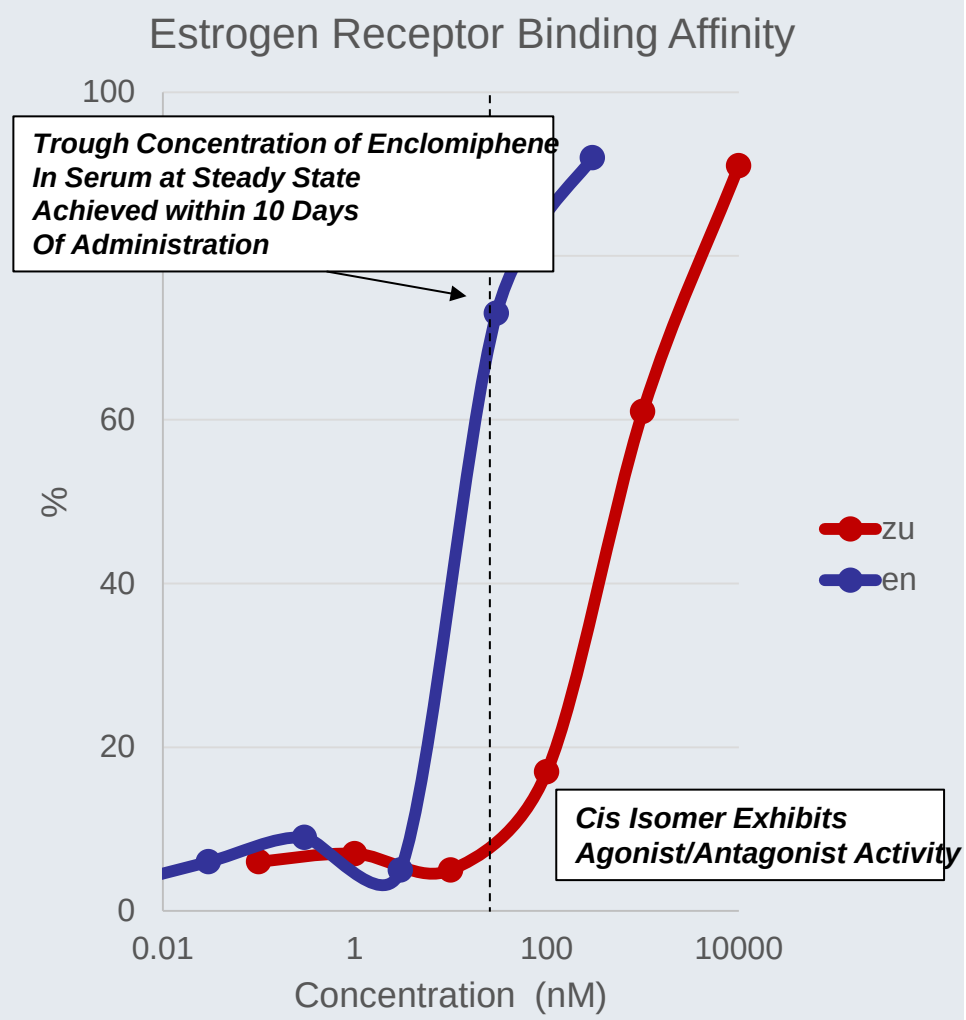




Enclomiphene arms gaining lean mass
Placebo arm losing lean mass

Why Not Just Use Clomid?

Enclomiphene (Patented)
Trans Isomer (Pure Estrogen Antagonist) of Clomiphene
Commercial Clomid (60% Trans, 40% Cis)



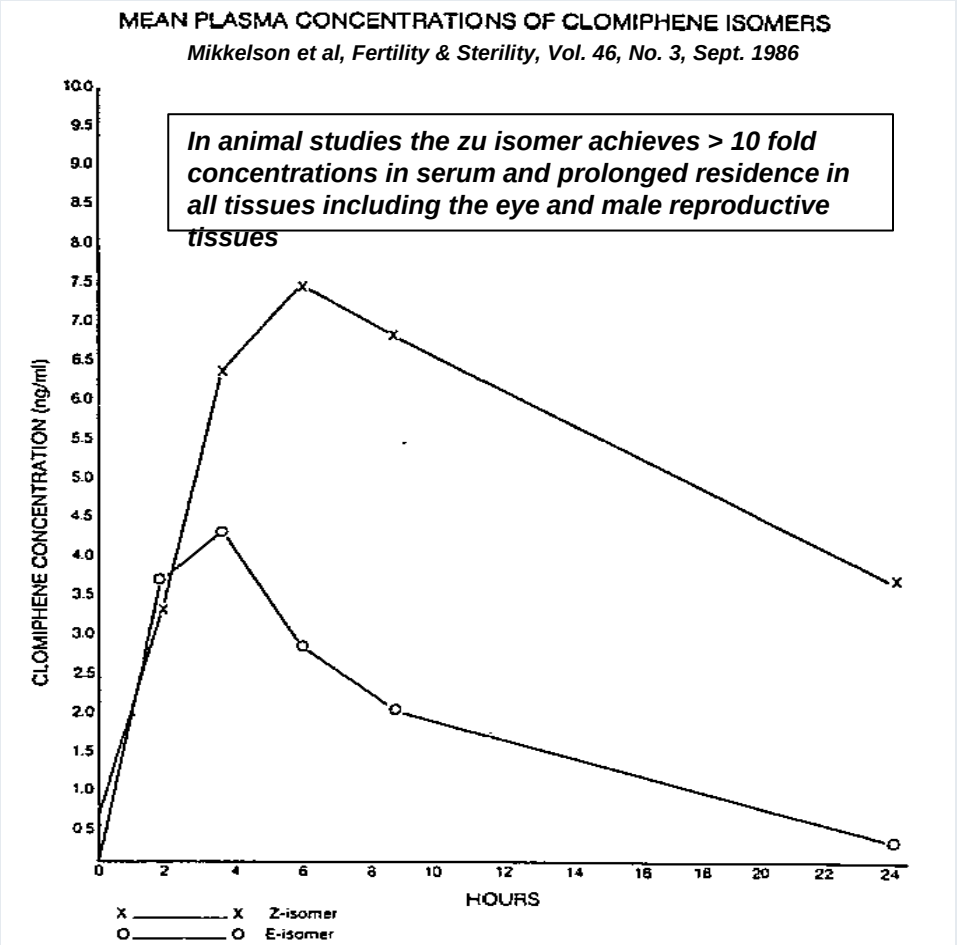
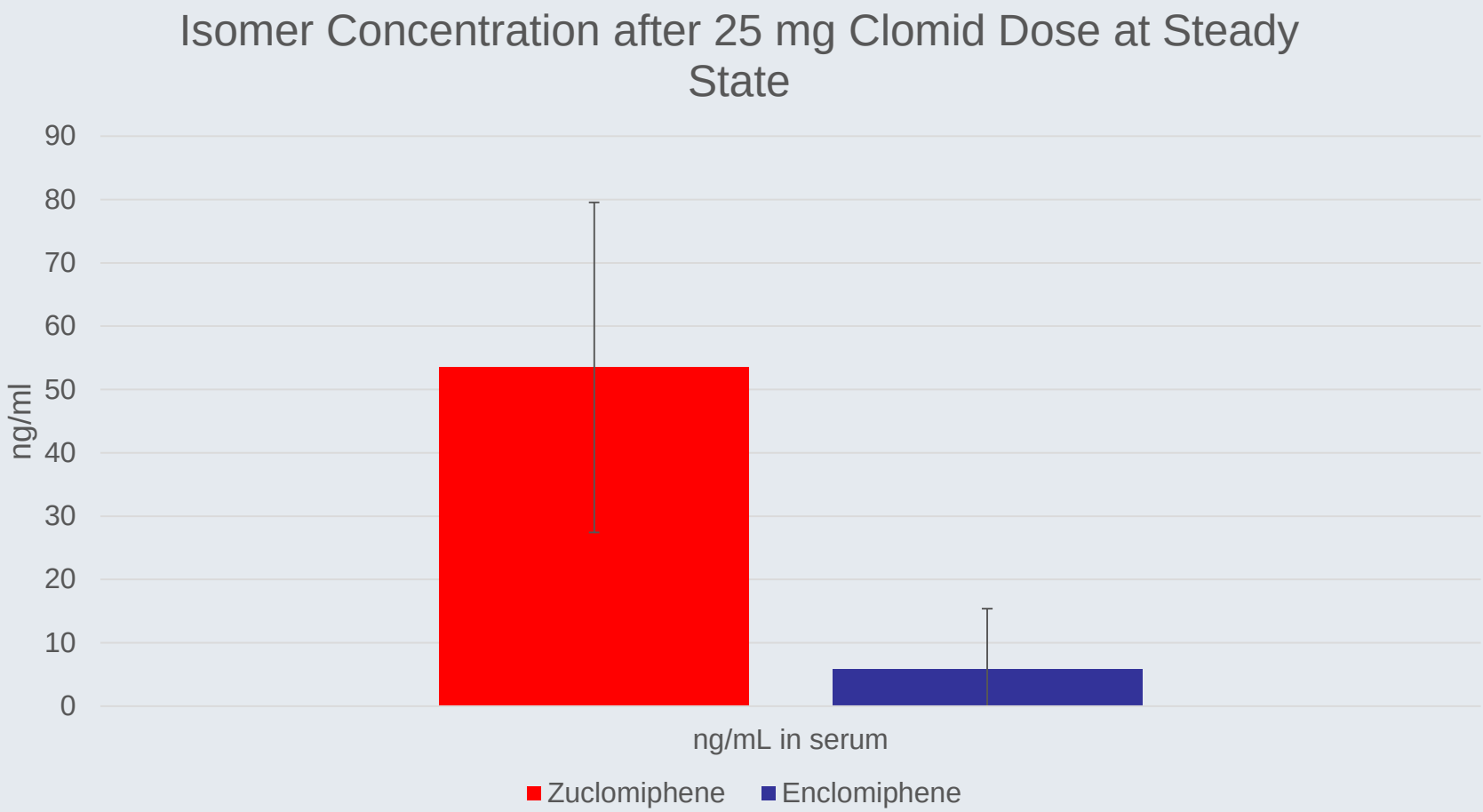


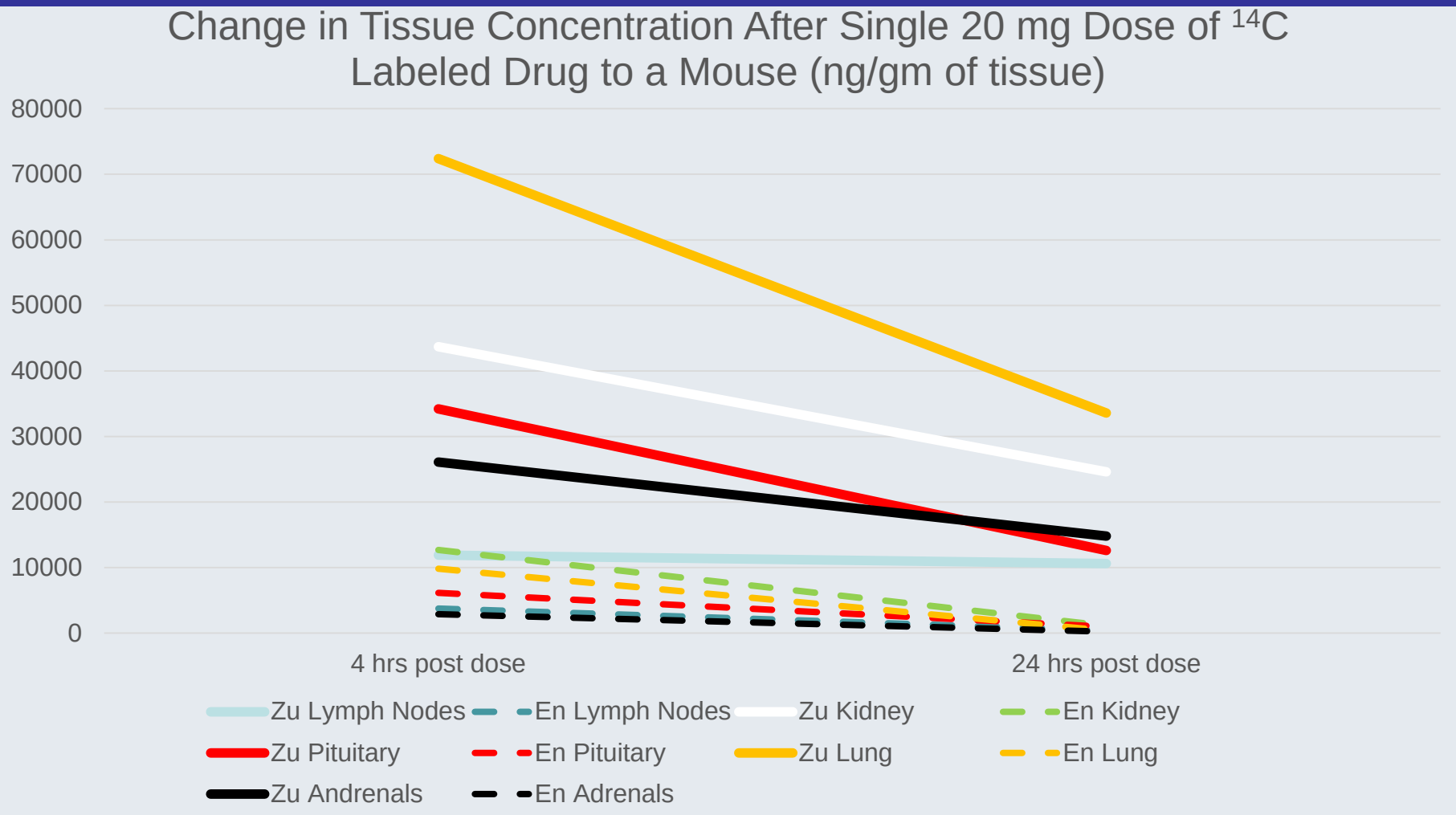
Figure 2
Mean plasma concentrations of zuclomiphene (×——×) and enclomiphene (○——○) after oral administration of one 50-mg tablet of CC (n = 23).

25 mg Daily Clomiphene Administration Isomer Concentrations (n=15 subjects)

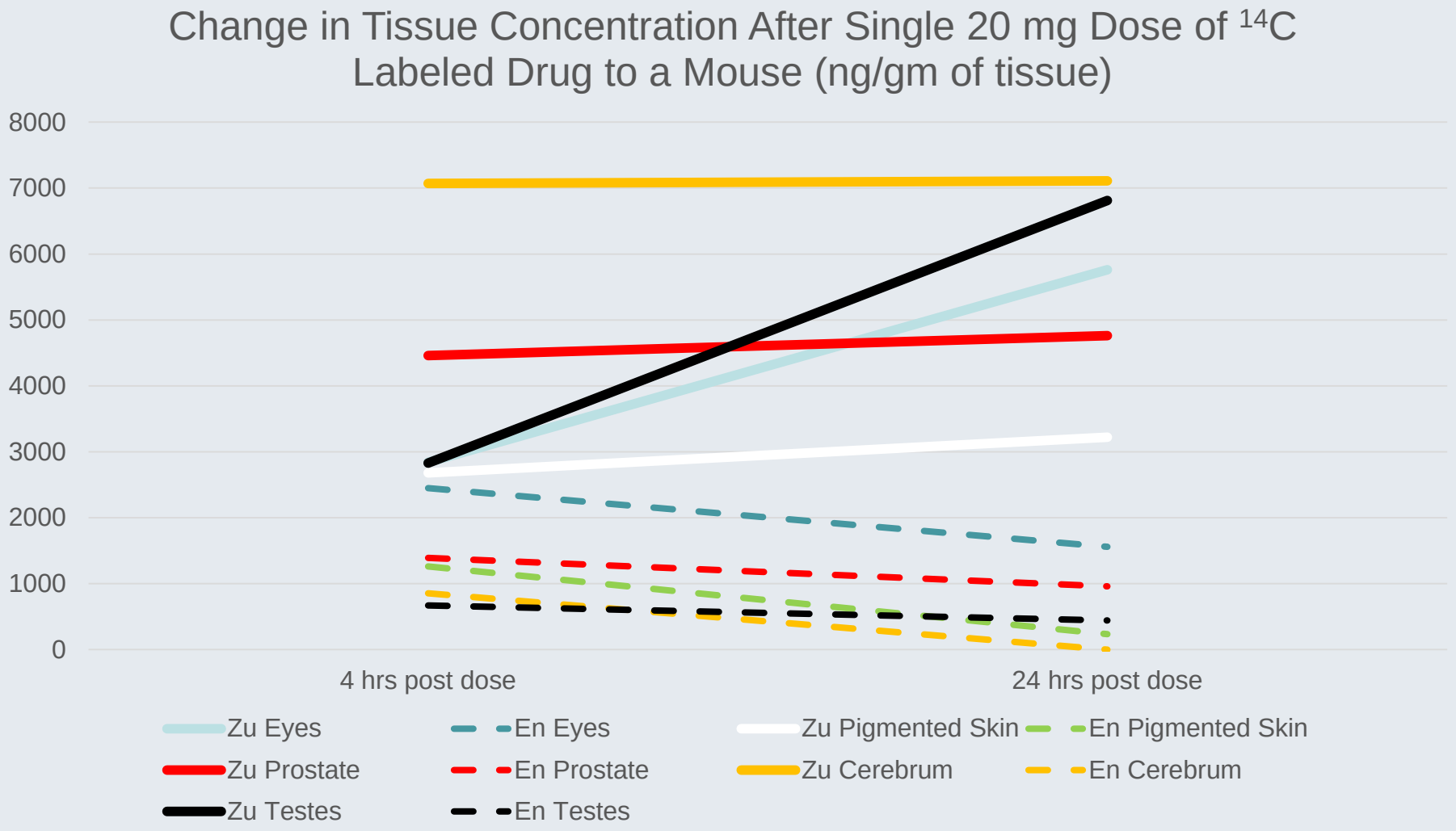


Clomid approximately 60-70% enclomiphene

Enclomiphene and Zuclomiphene Clear and Accumulate Differently in Different Tissues

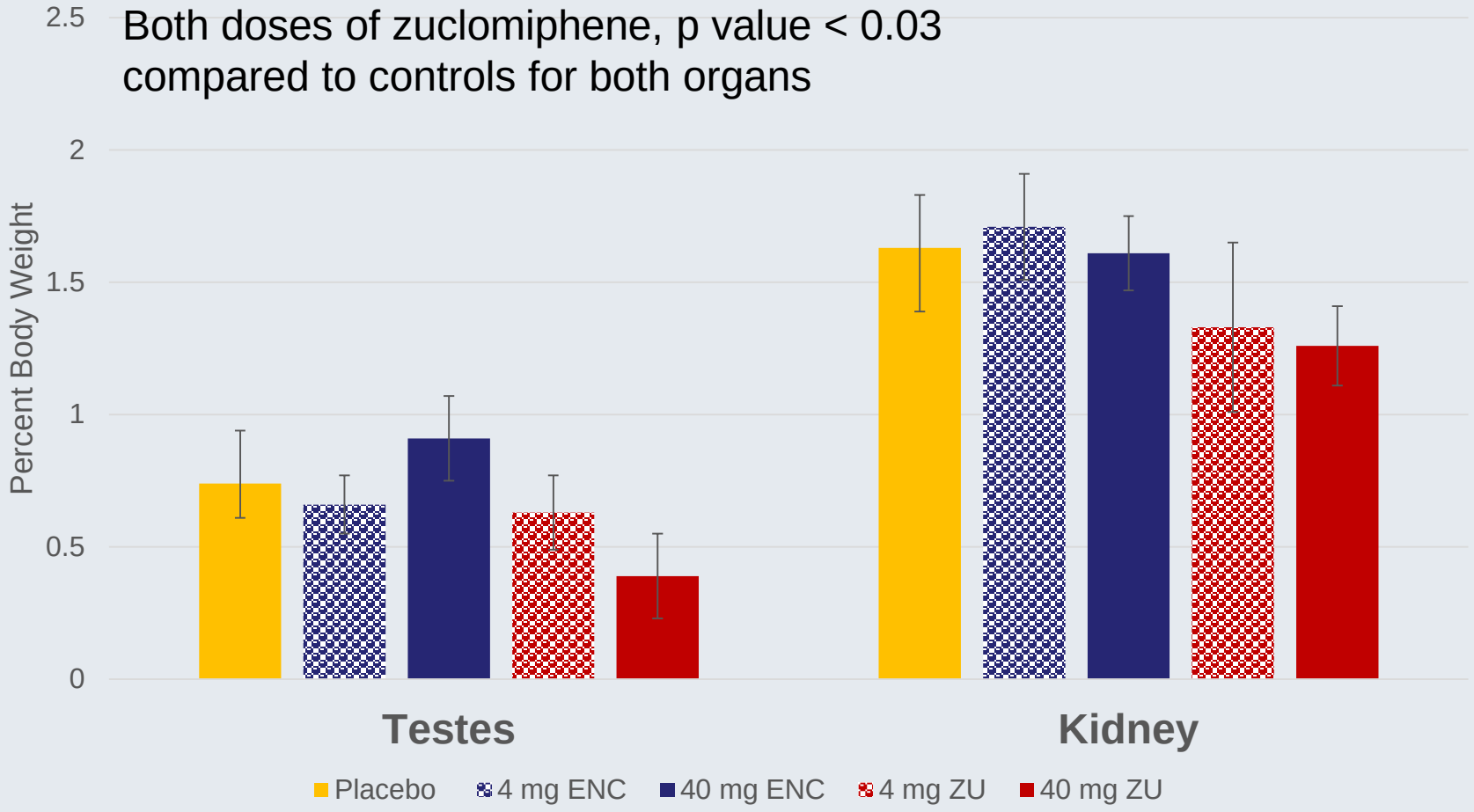


Enclomiphene and Zuclomiphene Clear and Accumulate Differently in Different Tissues



Impact of 90 Day Administration of 4 & 40 mg/kg of Either Enclomiphene or Zuclomiphene to Male Mice (n=15/group)

Both Doses of Zu Isomer Negatively Affect Organ Size Compared to Control



BJUI. 2015 Jul 27, Fontenot et al

Enclomiphene Exhibits Unique Profile with Numerous Advantages vs Approved Hormone Replacement

- The Enclomiphene Advantages
  - Oral
  - Not controlled substance, cannot be abused
  - No supernormal levels of T achieved
  - No transference risk
  - Restores normal function (no loss of testicular function)
  - Testosterone replacement shrinks the testes
  - Does not develop dependency
  - Avoids withdrawal symptoms
  - With lifestyle change can reverse disorder and result in no need for therapy

Repros Late Stage Assets

Repros seeking regional or global development/commercialization partners

Financial Summary

- **Cash and equivalents** (unaudited Dec. 31, 2016)**:** $8.7 M
- **Cash used in 2016** (unaudited)**:** $12.7 M
- **Cash runway:** into Q3 2017
- **Current shares outstanding:** 25.8 M shares

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