Reaction to the recent publication by Rosemary Basson entitled 'Testosterone therapy for reduced libido in women'

Stephen M. Simes and Michael C. Snabes

Ther Adv Endocrinol Metab

(2011) 2(2) 95–96

DOI: 10.1177/
2042018811404034

© The Author(s), 2011.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Dear Editor,

We write in reaction to the recent publication by Rosemary Basson entitled 'Testosterone therapy for reduced libido in women' [Basson, 2010]. We compliment the author on her review of the subject and we are grateful for the citation of our publication 'Approved hormonal treatments for HSDD: an unmet medical need' [Snabes and Simes, 2009].

Dr Basson states that the 'Long-term risks of testosterone supplementation are basically unknown.' We trust this correspondence will provide information that may not have been available to the author at the time of her writing.

Off-label use of testosterone for the treatment of women with hypoactive sexual desire disorder (HSDD) continues to be widespread in the US. We reported [Snabes *et al.* 2011b] that recent survey data on testosterone prescribing by US physicians in 2009 suggest that more than four million prescriptions were written off-label for women. The products commonly used are estrogen/androgen oral medications, compounded testosterone, and brand testosterone approved for use in men.

Most healthcare practitioners are well aware that there is no pharmaceutical product approved by the US Food and Drug Administration (FDA) for treatment of women with HSDD. A full 12 years after the approval of Viagra, and subsequently other PDE-5 inhibitors for men, we believe there is a strong national sentiment that women should have an FDA-approved therapeutic option to treat their most common sexual health issue. BioSante Pharmaceuticals, Inc. has taken on the challenge of obtaining approval for a medication to treat women with HSDD, and has

worked in a collaborative effort with the Division of Reproductive and Urologic Products (DRUP) at FDA to develop a robust clinical program. We are well into phase III clinical development of LibiGel® (testosterone gel) to treat postmenopausal women who have low sexual desire causing personal distress. The daily LibiGel dose provides 300 µg/day, increasing serum testosterone into the normal range of a premenopausal woman.

To obtain FDA approval of a product for a new indication a sponsor conducts two successful, adequate and well-controlled phase III clinical trials which demonstrate efficacy and safety. In the case of LibiGel treatment of HSDD in women, the ongoing efficacy trials have two primary efficacy endpoints and one key secondary endpoint. The primary endpoints include demonstration of an increase in the number of satisfying sexual events and an increase in sexual desire statistically and clinically significantly greater than placebo. The secondary endpoint is to show a decrease in distress associated with the low sexual desire. These requirements have not changed significantly since 2000 when the FDA published its guidance on the development of products for the treatment of female sexual dysfunction [CDER, 2000].

There is an additional key requirement in the development of testosterone to treat HSDD: the pre-approval demonstration of cardiovascular and breast cancer safety, in a long-term safety study. The stated objective of the FDA [Shames *et al.* 2007] is to eliminate a certain level of risk pre-approval with the study continuing post-approval. The challenge that the FDA has acknowledged is the difficulty involved in demonstrating preapproval safety in the intended population: a relatively young, healthy

Correspondence to:

Stephen M. Simes
BioSante
Pharmaceuticals, 111
Barclay Boulevard,
Lincolnshire, IL 60069,
USA
[ssimes@
biosantepharm.com](mailto:ssimes@biosantepharm.com)

**Michael C. Snabes, MD,
PhD**
BioSante
Pharmaceuticals, 111
Barclay Boulevard,
Lincolnshire, IL 60069,
USA

population at low cardiovascular risk [Borer *et al.* 2007]. With detailed FDA agreement, we developed and have ongoing the required long-term LibiGel safety study. Indeed, this study is entering its fourth year of randomized, placebo-controlled conduct. To date, we have enrolled more than 2800 menopausal women who all have increased cardiovascular risk, e.g. hypertension, diabetes, smoking, and hypercholesterolemia among other risk factors. As of February 2011, more than 2800 women-years of exposure have been gathered, yielding an average per subject exposure of 12 months each. In fact, the FDA requirement for the submission of a new drug application (NDA) is a minimum average exposure to study drug of 12 months.

To date, we have reported 14 cardiovascular events that have been adjudicated by the study's independent, blinded cardiovascular events committee [Snabes *et al.* 2011a]. The cardiovascular event rate of approximately 0.50% is lower than expected in enrolled study subjects with cardiovascular risk who now average greater than 60 years of age. To date, there have been eight breast cancers reported, a breast cancer rate of about 0.29%. As a reference, the breast cancer rate in women 50–60 years of age on placebo in the estrogen only arm of the Women's Health Initiative was 0.28% [Anderson *et al.* 2004]. We anticipate completion of enrollment in the safety study in the first half of 2011, and all enrolled women will be followed for 5 years in total.

Professor Basson and our reading colleagues should be interested to know that we are conducting a novel, and we believe definitive, study to ascertain the safety and potential risks of testosterone in postmenopausal women. The ongoing LibiGel safety study remains blinded to all except the study's independent Data Monitoring Committee (DMC). The DMC has performed four reviews of all unblinded safety data and after each review stated that the study should continue without changes to the FDA-agreed protocol, the best result one could anticipate from an ongoing safety study. We believe the results to date, even though the study is blinded, support the basic safety of testosterone in postmenopausal women. The primary analysis and determination of the long-term cardiovascular and breast safety of testosterone will be known once the blind is broken and the data analyzed, which should occur in the next 12 months.

The time has come for women to have an FDA-approved choice for their most common sexual health issue. Our efforts to date provide a pathway to approval for LibiGel to treat postmenopausal women with HSDD, potentially the first therapeutic approved for this indication.

Funding

This article received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Stephen M. Simes and Michael C. Snabes are employed by BioSante Pharmaceuticals, Inc.

References

- Anderson, G.L., Limacher, M., Assaf, A.R., Bassford, T., Beresford, S.A., Black, H. *et al.* (2004) Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 291: 1701–1712.
- Basson, R. (2010) Review: Testosterone therapy for reduced libido in women. *Therapeut Adv Endocrinol Metab* 1: 155–164.
- Borer, J.S., Pouleur, H., Abadie, E., Follath, F., Wittes, J., Pfeffer, M.A. *et al.* (2007) Cardiovascular safety of drugs not intended for cardiovascular use: need for a new conceptual basis for assessment and approval. *Eur Heart J* 28: 1904–1909.
- CDER (2000) 2000 Draft Guidance for Industry: Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment, Center for Drug Evaluation and Research (CDER), US Department of Health and Human Services, Food and Drug Administration.
- Shames, D., Monroe, S.E., Davis, D. and Soule, L. (2007) Regulatory perspective on clinical trials and end points for female sexual dysfunction, in particular, hypoactive sexual desire disorder: formulating recommendations in an environment of evolving clinical science. *Int J Impot Res* 19: 30–36.
- Snabes, M.C., Berry, S., Zborowski, J. and White, W. (2011a) Low cardiovascular event rate in postmenopausal women with increased cardiovascular risk: two year blinded summary from the ongoing LibiGel (testosterone gel) safety study. *Program of the Annual Meeting of the International Society for the Study of Women's Sexual Health*, Abstract 17A.
- Snabes, M.C., Milling, W.M. and Simes, S.M. (2011b) Without FDA-approved testosterone to treat women with hypoactive sexual desire disorder providers rely on off-label prescribing. *Program of the Annual Meeting of the International Society for the Study of Women's Sexual Health*, Abstract 18A.
- Snabes, M.C. and Simes, S.M. (2009) Approved hormonal treatments for HSDD: an unmet medical need. *J Sex Med* 6: 1846–1849.