Tibolone histology of the endometrium and breast endpoints study: design of the trial and endometrial histology at baseline in postmenopausal women

David F. Archer, M.D.,[a] *Susan Hendrix, D.O.,*[b] *Alex Ferenczy, M.D.,*[c] *Juan Felix, M.D.,*[d] *J. Chris Gallagher, M.D.,*[e] *Janice Rymer, M.D., Ph.D.,*[f] *Sven O. Skouby, M.D.,*[g] *Wil den Hollander, Ph.D.,*[h] *Victoria Stathopoulos, Ph.D.,*[i] *and Frans A. Helmond, Ph.D.,*[i] *for the THEBES Study Group*

[a] Department of Obstetrics and Gynecology, Contraceptive Research and Development Program Clinical Research Center, Eastern Virginia Medical School, Norfolk, Virginia; [b] Wayne State University/Hutzel Women's Hospital, Detroit, Michigan; [c] McGill University and Sir Mortimer B. Davis-Jewish General Hospital, Montreal, Quebec, Canada; [d] Department of Pathology, Keck School of Medicine, University of Southern California, Los Angeles, California; [e] Bone Metabolism Section, Creighton University Medical Center, Omaha, Nebraska; [f] King's College School of Medicine at Guy's and St. Thomas' Hospitals, Division of Obstetrics and Gynaecology, London, United Kingdom; [g] Department of Obstetrics and Gynecology, Frederiksberg Hospital, Copenhagen, Denmark; [h] NV Organon, Oss, the Netherlands; and [i] Organon International, Roseland, New Jersey

Objective: To address the endometrial safety of tibolone.
Design: The Tibolone Histology of the Endometrium and Breast Endpoints Study (THEBES) is a randomized, double-blind, parallel-group trial of tibolone compared with continuous combined conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA).
Setting: Multi-country, multi-center ambulatory care setting.
Patient(s): A total of 5,185 subjects were screened, and biopsies were obtained from 4,446 women.
Intervention(s): Participants were randomized in a 1:1:2 ratio, to tibolone (1.25 or 2.5 mg/d) or CEE-MPA.
Main Outcome Measure(s): The one-sided 95% confidence intervals for the incidence of hyperplasia or cancer were evaluated for tibolone compared with CEE-MPA.
Result(s): Endometrial biopsy results at baseline: atrophic (87.29%), inactive (0.25%), proliferative (6.12%), secretory (2.86%), menstrual type (0.40%), and hyperplasia (0.18%). Only subjects with atrophic or inactive endometrium were eligible for this study, and 3% of the women at screening either had no tissue (0.18%) or had an amount of tissue that was insufficient for diagnosis (2.72%). Three thousand two hundred forty postmenopausal women with a mean (±SD) age of 54.4 ± 4.4 years and a mean time since menopause of 4.5 ± 3.6 years were randomized.
Conclusion(s): The Tibolone Histology of the Endometrium and Breast Endpoints Study is a prospective, randomized clinical trial, designed to provide evidence of the endometrial safety of tibolone compared with estrogen and progestogen. Screening endometrial histology shows a low prevalence of endometrial hyperplasia (0.18%) and no carcinoma. (Fertil Steril® 2007;88:866–78. ©2007 by American Society for Reproductive Medicine.)

Key Words: Tibolone, hormone therapy, endometrial safety, endometrial histology, endometrial hyperplasia, endometrial cancer, breast tenderness, vaginal bleeding, estrogen, progestin

Received May 26, 2006; revised and accepted December 27, 2006.
The THEBES Study Group participants are listed in the Appendix.
The THEBES study was supported by NV Organon (Oss, the Netherlands; protocol 32972). NV Organon funded the study, contributed to its design, oversaw quality control at the clinical centers including periodic site visits, and validated the data collected by the centers. The sponsor did not have access to the blinding code, and played no role in collecting or adjudicating disease outcomes. The first draft of the manuscript has been prepared by an independent medical writing group. D.F.A., S.H., A.F., J.C.G., J.R., and S.O.S. are consultants and have received lecture fees and grant support from Organon. J.F. has a contractual relationship with Organon for this study. W.d.H., V.S., and F.A.H. are employees of Organon.
Reprint requests: David F. Archer, M.D., Eastern Virginia Medical School, CONRAD Clinical Research Center, 601 Colley Avenue, Norfolk, Virginia 23507 (FAX: 757-446-8988; E-mail: archerdf@evms.edu).

Estrogen therapy (ET) is well known to relieve vasomotor symptoms and prevent osteoporosis in postmenopausal women. Unopposed Es promote endometrial proliferation and are associated with an increased risk of endometrial hyperplasia and carcinoma in women with an intact uterus (1–5). The addition of a progestogen, either sequentially or continuously (estrogen plus progestin [EPT]), offsets this risk (1, 3–6) but may cause adverse effects such as vaginal bleeding or spotting (1, 7), changes in mood (7–9), and an increased risk of breast cancer (10–14).

Tibolone (NV Organon, Oss, the Netherlands) has specific effects on different tissues as a result of its tissue-selective metabolism, enzyme regulation, and/or receptor binding

0015-0282/07/$32.00
doi:10.1016/j.fertnstert.2006.12.052

and activation. It is therefore referred to as a selective tissue estrogenic activity regulator (STEAR) (15). Conversion of tibolone to 3α-OH and 3β-OH tibolone metabolites results in E-like effects on bone, vagina, mood, and climacteric symptoms. Tibolone itself and the third metabolite, the Δ^4 isomer, have progestogen-like (and androgen-like) properties and prevent the E-induced stimulation of the endometrium.

In vitro studies using endometrial cell lines have shown that tibolone is selectively converted to the progestogenic Δ^4 metabolite (which cannot be reduced by 5α-reductase) (16–18). Tibolone, through regulation of the sulfotransferase–sulfatase system, reduces endometrial (and breast) E-like activity by converting the active estrogenic metabolites into sulfated metabolites (19). A lack of endometrial stimulation by tibolone was observed in a comparison with conjugated equine estrogens (CEE), with or without medroxyprogesterone acetate (MPA), in ovariectomized female cynomolgus monkeys (20).

Clinical trials investigating the changes in endometrial histology during tibolone treatment have found mainly a high level of atrophic endometrium with no increased incidence of proliferation, hyperplasia, and/or cancer (21–23). No significant differences in ultrasound measures of endometrial thickness between tibolone-treated women and controls have been observed in studies conducted over periods of $\leq$10 years (23, 24). When compared with EPT, tibolone had a similar (continuous combined EPT) or less marked (sequential EPT) effect on endometrial thickness (25, 26).

Two observational trials from the United Kingdom (27, 28) have suggested an increased risk of endometrial cancer for tibolone users when compared with sequential EPT and nonusers, respectively. These findings may reflect preferential prescribing behavior in the United Kingdom (29), further stressing the need for a prospective randomized controlled trial. To resolve the discrepancy in endometrial histological results between the biological data and the earlier clinical trials (and the recently published observational United Kingdom data), a prospective randomized controlled clinical trial was designed to investigate the endometrial safety of tibolone.

The Tibolone Histology of the Endometrium and Breast Endpoints Study (THEBES) was designed to confirm and to extend the knowledge about the endometrial safety of tibolone. Two doses of tibolone, 1.25 and 2.5 mg/d, were used. The 2.5-mg dose of tibolone is the one recommended for the treatment of moderate to severe vasomotor symptoms, whereas the lower dose has also proven to be effective in the prevention of postmenopausal bone loss (30, 31). Conjugated equine estrogen–MPA was chosen as the comparator because it is the most frequently prescribed EPT in the United States, and its endometrial safety has been confirmed in a number of large pivotal studies (32–35). The design and rationale of the THEBES trial, together with the baseline characteristics of the subjects are described in this report.

MATERIALS AND METHODS

General

The THEBES is a multicountry, multisite, prospective, randomized, active-controlled, double-blind, parallel-group trial of oral tibolone (1.25 or 2.5 mg/d) and continuous combined oral CEE-MPA (0.625 mg + 2.5 mg/d) in postmenopausal women. A summary of the protocol has been posted online (http://www.organon-trials.com). A total of 5,185 women were screened, and 3,240 were randomized into the clinical trial. Participants were recruited from 77 US centers, 70 European centers (Belgium, 6 centers; Czech Republic, 9 centers; Denmark, 4 centers; Finland, 5 centers; France, 3 centers; Germany, 1 center; Hungary, 11 centers; Italy, 1 center; the Netherlands, 6 centers; Norway, 5 centers; Poland, 2 centers; the Slovak Republic, 7 centers; Spain, 2 centers; Sweden, 6 centers; and the United Kingdom, 2 centers), and 4 centers in Chile. Endometrial biopsies were obtained at baseline and repeated after 1 and 2 years of treatment.

The primary objective of this 2-year trial was to determine the endometrial safety of tibolone by evaluating the one-sided 95% confidence intervals for the incidence of abnormal endometrium (hyperplasia or cancer) and for hyperplasia and cancer separately, for each of the two tibolone treatment groups (and for the tibolone treatment groups combined) after 1 and 2 years of treatment with tibolone. The continuous combined preparation of 0.625 mg of CEE and 2.5 mg of MPA has been used as an active comparator in this trial.

Secondary aims were to compare the effects of both treatments on incidence rate of abnormal endometrial histology, double-layer endometrial thickness as measured by transvaginal ultrasound (TVUS), vaginal bleeding patterns, the incidence of breast pain or tenderness and vaginal dryness, body weight, mammographic density (in a subgroup), and health-related quality of life and sexual functioning.

Approval for the conduct of the THEBES was obtained from the independent ethics committee or the institutional review board at each participating center. Written informed consent was obtained from all study participants before any trial assessment.

Eligibility and Exclusion Criteria

The inclusion and exclusion criteria are summarized in Table 1. The study was designed so that the subjects reflected a large proportion of women who might potentially benefit from tibolone or EPT. The exclusion criteria therefore were largely limited to medical contraindications for the use of tibolone or EPT and a high risk of failing to complete the study or of developing serious side effects.

Recruitment

Potential participants were recruited from the investigators' practices, referrals from clinical staff, existing ongoing population-based cohorts, and advertisements in local print and broadcast media. A total of 5,185 women were screened, of