Synopsis

Identifier: ZM2008/00090/00 **Study Number:** SRM105106

Title: A parallel-group, double-blind, randomized, placebo-controlled, active comparator, multicenter study to evaluate the efficacy, safety, tolerability and pharmacokinetics of two doses of GSK232802 administered orally as monotherapy for 12 weeks in healthy postmenopausal women with moderate to extremely severe vasomotor symptoms

Investigator(s): This was a multicenter study.

Study center(s): A total of 75 centers randomized subjects in the study: 2 in Spain, 3 each in Argentina, New Zealand and UK, 4 in Italy, 5 in Australia, 6 in Sweden, 12 in Germany, and 37 in the US.

Publication(s): None at the time of this report.

Study Period: 17-Jul-2007 to 23-Jul-2008

Phase of Development: IIa

Objectives: The primary objectives of this study were:

- To evaluate the safety and tolerability of two doses of GSK232802 administered once daily (QD) for 12 weeks in healthy postmenopausal women with moderate to extremely severe vasomotor symptoms (VMS)
- To evaluate the effect of two doses of GSK232802, administered over a 12-week treatment period, on change in frequency and severity of VMS from baseline compared with placebo
- To characterize the pharmacokinetics (PK) of GSK232802 (and its primary oxidative metabolite GSK1132184A) and evaluate the relationship between individual measures of exposure to GSK232802, as estimated by population PK methods, versus frequency and severity of VMS, safety, and pharmacodynamic (PD) endpoints, as appropriate

The secondary objectives of this study were:

- To evaluate the change from baseline in frequency and severity of VMS at Weeks 4 and 8 of the treatment period compared with placebo
- To compare the proportion of subjects who achieved a reduction in frequency and severity of VMS of at least 50%, at least 75%, and 100% from baseline to Week 12, after treatment with GSK232802 versus placebo
- To assess effects of GSK232802 on the following parameters over a 12-week treatment period in healthy postmenopausal women with moderate to extremely severe VMS:

- Questionnaires for menopause-related quality of life, sleep quality, fatigue, depressive symptoms, and work productivity
- Vulvar vaginal atrophy (VVA) symptoms
- PD markers: including serum hormone levels and serum bone biomarkers
- Body composition (to be evaluated at the selected study sites in subjects with a body mass index [BMI] $\geq 25 kg/m^2$)

The novel biomarker objectives of this study were to examine the molecular profiles of blood samples to identify factors that might influence biological and clinical responses to GSK232802 and/or factors associated with the development or progression of menopause-related or metabolic conditions.

Methodology: This was a multi-center, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, active comparator Phase II study to evaluate the safety, tolerability, efficacy, and PK of 2 doses of GSK232802 in the treatment of moderate to extremely severe VMS in healthy postmenopausal women.

The study consisted of a 5-week screening period that included a 2-week baseline evaluation of VMS, a 12-week double-blind treatment period, and a 4-week follow-up period, for total study duration of approximately 21 weeks. All subjects with a uterus were required to undergo ultrasonographic evaluations of endometrial thickness and endometrial biopsies at baseline and end-of-treatment, and to complete a 14-day oral regiment of medroxyprogesterone acetate (MPA) during the follow-up period. Biopsies were centrally processed and reported.

Randomization was stratified by country and by presence or absence of a uterus. Subjects eligible to enter the double-blind treatment period were randomized 1:1:1:1 ratio to one of four treatment groups:

- GSK232802 25mg
- GSK232802 75mg
- Low-dose estrogen (provided as over-encapsulated Premarin tablets in the US commercially available strength of 0.3 mg of conjugated equine estrogen [CEE])
- Placebo

Number of subjects:

Subject Disposition, n (%)	Placebo N=90	GSK232802 25 mg N=87	GSK232802 75 mg N=89	Premarin 0.3 mg N=90	Total N=356
Status					
Completed	81 (90%)	72 (83%)	73 (82%)	79 (88%)	305 (86%)
Withdrew from study	9 (10%)	15 (17%)	16 (18%)	11 (12%)	51 (14%)
Reason for Withdrawal					
Adverse event	2 (2%)	6 (7%)	7 (8%)	4 (4%)	19 (5%)
Consent withdrawn	4 (4%)	3 (3%)	5 (6%)	5 (6%)	17 (5%)
Lack of efficacy	3 (3%)	2 (2%)	1 (1%)	0	6 (2%)
Lost to follow-up	0	3 (3%)	1 (1%)	0	4 (1%)
Protocol deviation	0	1 (1%)	2 (2%)	0	3 (<1%)
Other	0	0	0	2 (2%)	2 (<1%)

Diagnosis and main criteria for inclusion: To be eligible for this study, subjects were required to meet all inclusion and exclusion criteria. Subjects were to be healthy postmenopausal females aged 40 to 65 years of age. For naturally menopausal subjects, biochemical confirmation of menopausal status was required prior to randomization (follicle stimulating hormone [FSH] >40 mIU/mL [SI: >40 IU/L] and estradiol <35 pg/mL [SI: <128 pmol/L]). For surgically menopausal subjects, documented evidence of bilateral oophorectomy was sufficient to establish menopausal status. Eligible subjects must have had a minimum average frequency of 7 daily moderate to extremely severe hot flashes or episodes of night sweats recorded via a daily electronic diary for 2 weeks during the screening period. Subjects were required to have a bi-layer endometrial thickness <5 mm as determined by transvaginal ultrasound (TVUS) or for subjects with a non-informative TVUS, a single endometrial layer thickness for each anterior and posterior wall of <3 mm determined by saline infusion sonohysterography (SIS). Subjects must have not been on hormone therapy or other putative treatments for VMS prior to study entry for the protocol-specified time windows.

Treatment administration: GSK232802 was provided as red film-coated tablets containing 25mg of GSK232802A, the primary oxidative metabolite of GSK232802 (batch number 061128408); Premarin was provided as an over-encapsulation of the USA commercially available strength of 0.3mg CEE (batch number 071134489); placebo was provided to visually match the GSK3232802 tablets and the over-encapsulated Premarin (batch numbers 061127199 and 061127578, respectively). All treatments were administered orally QD for a period of 12 weeks. Subjects were instructed to take 1 tablet or capsule from each of 4 bottles at approximately the same time each morning, to bring their study medication with them to the clinic (Visits 6, 7, and 8) and arrive in a fasted state. Study medication was re-supplied at 4-week intervals.

After completion of the 12-week treatment period, subjects with a uterus received a 14-day cycle of MPA 10mg QD to induce withdrawal bleeding. All subjects were required to return to clinic for the Follow-Up Visit (Visit 9). Commercially available MPA was supplied by the study sites as 10mg or 5mg tablets.

Criteria for evaluation: The safety evaluations included:

- Incidence and severity of adverse events (AEs), serious adverse events (SAEs)
- Change from baseline in vital signs, physical examination, clinical chemistry, hematology, thyroid-stimulating hormone (TSH), free thyroxine (T4), fasting lipid profile, and thrombotic and inflammatory markers
- Absolute change in bi-layer endometrial thickness measured by TVUS or SIS, endometrial biopsy pathology, and the occurrence of withdrawal bleeding
- Gynecological assessments and breast assessments

Primary efficacy variables were mean change in frequency of VMS from baseline to Week 12 and mean change in severity of VMS from baseline to Week 12. Secondary efficacy variables included mean change in frequency and severity of VMS from baseline to Weeks 4 and 8, change in Menopause Quality of Life score, change in Medical Outcomes Study Sleep score, changes in VVA symptom score, change in Brief Fatigue Inventory score, change in the Centers for Epidemiologic Studies in Depression score, change in Work Productivity and Activity Impairment score, change in vaginal pH and percentage of superficial cells, change in serum hormone levels, and absolute change in body weight, BMI, waist and hip circumference. Additional body composition assessments were to be evaluated (neck and thigh circumference; total, visceral, and subcutaneous body fat assessed by EchoMRI, dual-energy X-ray absorptiometry, and computed tomography scan) at selected study sites in the subjects with BMIs $\geq 25 kg/m^2$.

PK and PD data were also collected and analyzed. ,

Statistical methods: The primary comparisons of interest were the comparisons between each dose group of GSK232802 and the placebo group. With 60 subjects per treatment group, there was 80% power to detect differences between GSK232802 dose groups and placebo for the mean change in average daily frequency of VMS from baseline to Week 12, with a standard deviation of 4.5 using a two-sided test with a type I error rate of 5%. The difference of 2.3 events corresponds to a 20% difference between a GSK232802 dose group and placebo group, assuming a baseline average daily frequency of 11.5 events.

A sample size of 60 subjects per treatment group would provide over 98% power to detect differences between GSK232802 dose groups and placebo for the mean change in severity from baseline to Week 12 of 0.75 units, with a standard deviation of 1.0 using a two-sided test with a type I error rate of 5%. Statistical testing for the mean change in severity from baseline was designed to proceed only if the frequency endpoint was significant; otherwise any testing for mean change in severity was considered exploratory.

The intent-to-treat (ITT) Population, which was defined as all randomized subjects, was used for the efficacy analysis. The Safety Population was defined as all randomized subjects who received at least 1 dose of study medication and was used for the safety analysis. The Uterine Safety Population was defined as all randomized subjects who had

a uterus and received at least 1 dose of study medication. The Uterine Safety Population was used for assessing uterine safety.

Duration of exposure to study medication was calculated.

For the purposes of this report, AEs and SAEs were summarized by incidence, investigator's assessment of relationship to study medication, severity, and whether the events led to permanent discontinuation of study medication.

Analyses of the changes from baseline in VMS frequency and in VMS severity included parametric analysis of covariance, including terms for investigative site cluster, uterine status, the baseline efficacy measure, and treatment group. The primary analysis for both VMS frequency and VMS severity were based on the last observation carried forward (LOCF) data, with supportive analysis provided using the observed cases data. Point estimates, nominal 95% confidence intervals, and associated p-values were provided for the adjusted mean difference between each GSK232802 dose group and the placebo group; comparisons between the low-dose estrogen group and the GSK232802 groups were for descriptive purposes only and did not include statistical testing.

Summary:

Study Population:

Three hundred and fifty-six healthy postmenopausal subjects with moderate to extremely severe vasomotor symptoms were randomized to treatment and constituted the ITT Population (90 to placebo, 87 to GSK232802 25mg, 89 to GSK232802 75mg, and 90 to Premarin 0.3mg). Two hundred and ten subjects with an intact uterus received at least one dose of study medication and comprised the Uterine Safety Population. Overall, 305 subjects (86%) completed the study and 51 subjects (14%) were withdrawn from the study. The most common reasons for withdrawal were adverse events (19 subjects, 5%) and consent withdrawn (17 subjects, 5%).

Safety:

Extent of Exposure

The mean duration of exposure to study medication was similar across treatment groups (ranging from 77 to 83 days).

On-treatment Adverse Events

A total of 202 subjects (57%) reported at least one on-treatment AE. Most AEs were reported with a mild or moderate intensity, and the most common ones were non-specific though these were not distributed evenly among the treatment groups. The overall incidence of AEs in the GSK232802 75mg group (51%) was lower than other treatment groups (57% to 60%).

Most frequently reported AEs in each treatment group were as follows:

Headache (16%), nasopharyngitis (9%), nausea and upper respiratory tract infection (6% each) in the placebo group;

Headache (9%), nausea, and diarrhea (7% each) in the GSK232802 25mg group;

Headache (8%), nasopharyngitis, and nausea (6% each) in the GSK232802 75mg group;

Nausea (7%), nasopharyngitis (6%), influenza, muscle spasms, pain in extremity (4% each), and headache (3%) in the Premarin 3mg group.

Ninety subjects experienced an AE that was considered to be related to study medication (20 subjects [22%] in the placebo group, 23 subjects [26%] in the GSK232802 25mg group, 18 subjects [20%] in the GSK232802 75mg group, and 29 subjects [32%] in the Premarin 0.3mg group). AEs considered by the investigator to be possibly related to GSK232802 and reported in 2 or more subjects were: headache (7 subjects, 8%), nausea (5 subjects, 6%), breast tenderness and migraine (3 subjects each, 3%), and breast pain and muscle spasms (2 subjects each, 2%) for the 25mg group; nausea (5 subjects, 6%), insomnia (3 subjects, 3%), and diarrhea and dry mouth (2 subjects each, 2%) for the 75mg group.

Drug-related AEs of vaginal hemorrhage were observed in both GSK232802 groups and the Premarin group (1 subject in each group). Vaginal discharges were observed in both GSK232802 groups (1 subject in each group) and vaginal disorder occurred in 1 subject in the GSK232802 75mg group.

Deaths and Non-Fatal SAEs

No deaths due to SAEs were reported during the course of study.

Six subjects reported at least one post-randomization SAE. None of these SAEs were considered by the investigator to be related to study medication. With the exception of breast cancer, none of these events led to withdrawal.

AEs Leading to Withdrawal

A total of 19 subjects (5%) were withdrawn from the study due to an AE or SAE. The highest incidence of withdrawals was observed in the GSK232802 75mg group (7 subjects) followed by the GSK232802 25mg group (6 subjects), the Premarin group (4 subjects), and the placebo group (2 subjects). Most of these events, with moderate or severe intensity, were considered by the investigator to be related to study medication.

Breast Disorders

Breast disorders were reported in 11 subjects (3%) and included terms of breast cancer, breast enlargement, breast mass, breast pain, breast tenderness fibrocystic breast disease, and abnormal mammogram. The highest incidence of breast disorders was observed in the GSK232802 25mg treatment group (7 subjects, 8%) followed by 2 subjects (2%) in the placebo group, and 1 subject (1%) in each of the GSK232802 75mg and the Premarin

groups. Most of the events were reported as drug-related events with a mild or moderate intensity. Most of these events were either resolved or in the process of resolving at the time of reporting.

One subject in the GSK232802 25mg group was diagnosed with breast cancer 21 days after the start of GSK 232802 treatment. The event was considered by the investigator to be unrelated to study medication. At screening, the subject's mammogram was reported as benign and physical exam was unremarkable. The subject had a medical history of fibrocystic breast disease. There was a family history of breast cancer in her maternal grandmother and aunts.

Venous Thrombotic Disorders

One subject in the GSK232802 75mg group experienced a moderate AE of deep vein thrombosis 86 days after the start of GSK232802 treatment (2 days after the last dose of treatment). The event occurred 7 days later after the subject fell of ramp at home and injured her right ankle. The event was resolving at the time of reporting and was judged by the investigator to be unrelated to study medication.

Ovarian disorders

Ovarian disorders included terms of dermoid cyst of ovary and ovarian enlargement that occurred in 1 subject each during the study. Both subjects were in the GSK232802 75mg treatment group and neither of these 2 subjects was withdrawn from the study. The event of ovarian enlargement resolved and was judged by the investigator to be related to GSK232802. The event of dermoid cyst of ovary was not resolved at the time of reporting and was considered by the investigator to be unrelated to GSK232802.
Vaginal Disorders

Vaginal disorders included terms of vaginal discharge, vaginal hemorrhage, genital hemorrhage (vaginal spotting as verbatim term), vulva cyst, and vulvovaginal pruritus. The highest incidences of vaginal disorders were observed in the Premarin 0.3mg group (7 subjects, 8%) followed by the GSK232802 75mg group (4 subjects, 5%). All events were mild or moderate in intensity and were either resolved or were in the process of resolving at the time of reporting. Most of the events were considered by the investigator to be related to study medication. Two events, vaginal discharge in the GSK232802 25mg group and vaginal hemorrhage in the GSK232802 75mg group, led to withdrawals.

Lipid Disorders

Lipid disorders included terms of increased triglycerides, hyperlipidemia, and hypercholesterolemia. A total of 11 subjects experienced a post-randomization AE of lipid disorders and the incidence was similar across the treatment groups. Nearly half of these AEs (5/11) were considered by the investigator to be related to study medication; the majority of these events was moderate or severe in intensity and not resolved at the time of reporting. One subject in the GSK232802 25mg group experienced a severe AE of hyperlipidemia and the event led to withdrawal.

Uterine Safety

A total of 210 subjects received at least one dose of study medication (GSK232802 or Premarin or placebo) and had an intact uterus. Uterine safety results are presented for these subjects.

The changes in mean TVUS bi-layer endometrial thickness at end of treatment from baseline were minimal for the placebo and GSK232802 25mg groups (-0.07mm and 0.13mm, respectively). The Premarin group had a greater change in mean TVUS bi-layer endometrial thickness at end of treatment from baseline compared with the other 3 treatment groups (1.12mm vs. ≤0.79mm). A few subjects in the GSK232802 75mg (4, 9%) and the Premarin groups (8, 18%) had a >3mm change in mean TVUS bi-layer endometrial thickness at end of treatment from baseline.

An endometrial biopsy was performed at baseline and at the end of treatment for subjects with a uterus. The majority of subjects had a normal endometrial biopsy result for the post menopausal population at baseline as well as at end of treatment for all treatment groups. Three subjects (7%) in the Premarin group and 1 subject (2%) in the GSK232802 25mg group revealed some endometrial a proliferation with no evidence of atypia. One subject in the Premarin group had an endometrial polyp at end of treatment..

Almost all subjects from each treatment group (≥91%) in the Uterine Safety Population received MPA 10mg for 14 days after completion of the 12 weeks treatment to induce shedding of the endometrial lining. At least 71% of subjects in the placebo group and in both GSK232802 groups self-reported neither spotting nor bleeding while taking MPA. More than half of the subjects in the Premarin group reported either spotting or bleeding or both while taking MPA and spotting/bleeding for ≥5 days was reported in 15 subjects (32%).

Clinical laboratory Values

Hematology abnormalities within the range of potential clinical concern occurred primarily in white blood cell counts. Many of these abnormalities were present at baseline and there was no increase in the incidence over time in the study. While low values for hemoglobin and platelet were observed for few subjects in each treatment group during the study, there were no trends identified. None of the hematology values of potential clinical concern were reported as AEs.

There were no trends in mean clinical chemistry parameters over time in the study. Increased alanine aminotransferase (ALT) values of potential clinical concern were reported as an AE for 3 subjects (1 in the placebo and 2 in the Premarin 0.3mg groups). None of these subjects were withdrawn due to these specific laboratory abnormalities. With the exception of 1 subject in the Premarin group, none of these laboratory abnormalities were considered to be related to study medication by the investigator.

An AE of abnormal thyroid function test was reported in 1 subject in the Premarin group. Her TSH was above the upper threshold of potential clinical concern at screening and was further elevated at baseline and during the first 4 weeks of treatment. Her TSH

decreased at the subsequent laboratory visit but was still above the upper threshold of potential clinical concern. Her TSH returned to the screening level at the follow-up visit. This subject had low T4 levels at baseline and at on-treatment visits but her T4 level retuned to within normal reference range at the follow-up visit. The event was judged by the investigator to be unrelated to study medication.

Vital Signs

No clinically relevant trend on vital signs was observed.

Efficacy

Change in VMS Frequency from Baseline to Week 12

A general linear model (adjusted for treatment, baseline, country, and uterine strata) was used to analyze the mean changes in frequency of VMS for the GSK232802 groups and the Premarin 0.3mg group compared with the placebo group. There were no reductions in adjusted mean VMS frequency from baseline to Week 12 for either of the GSK232802 groups when compared with the placebo group. A statistically significant reduction in mean VMS frequency (adjusted mean difference) from baseline to Week 12 was observed in the Premarin 0.3mg group when compared with the placebo group.

Mean changes in VMS frequency for the GSK232802 treatment groups were also compared with the Premarin 0.3mg group as descriptive analyses. The Premarin 0.3mg group showed greater reductions in VMS frequency at Week 12 than either dose of GSK232802.

Change in VMS Severity from Baseline to Week 12

There were no reductions in adjusted mean VMS severity from baseline to Week 12 for either GSK232802 groups when compared with the placebo group. A statistically significant reduction from baseline to Week 12 in mean VMS severity (adjusted mean difference) was observed in the Premarin 0.3mg group when compared with the placebo group.

Mean changes in VMS severity for the GSK232802 treatment groups were also compared with the Premarin 0.3mg group as descriptive analyses. There were no reductions in adjusted mean VMS for either GSK232802 groups when compared with the Premarin group.

Conclusions:

GSK232802 administered orally at daily doses of 25mg and 75mg for 12 weeks for the treatment of VMS in healthy postmenopausal women was generally well-tolerated. There were no safety signals of clinical concern identified.

Although GSK232802 displayed dose-related effects consistent with estrogen receptor mediated pharmacology, neither dose provided evidence of significant benefit for VMS frequency or severity in comparison to placebo. The 0.3mg dose of Premarin demonstrated reductions in both VMS frequency and severity consistent with published literature and substantiated the appropriateness of the target population and study design. Based upon these findings, further investigation of GSK232802 for treatment of postmenopausal VMS is not indicated.

Date of Report: April 2009