Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare Pharmaceuticals Inc.	
Study Number:	91508	NCT00522873
Study Phase:	III	
Official Study Title:	A double-blind, randomized, multi-center study to investigate the endometrial safety of a continuous, combined, oral estrogen/progestin preparation (0.5 mg 17b-estradiol [E2] / 0.25 mg drospirenone [DRSP]) and to compare the bleeding pattern of subjects treated with 0.5 mg E2 / 0.25 mg DRSP with the bleeding pattern of subjects treated with 1.0 mg E2 / 0.5 mg norethisterone acetate (NETA) when used for hormone therapy (HT) for 1 year in post-menopausal women	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	DRSP/E2 (0.25 mg/0.5 mg)	
Name of Active Ingredient:	Drospirenone (DRSP)/17 beta-estradiol (E2)	
Dose and Mode of Administration:	1 encapsulated tablet DRSP/E2 (0.25 mg/0.5 mg) daily, oral	
Reference Therapy/Placebo		
Reference Therapy:	Norethisterone acetate (NETA)/E2 (0.5 mg/1.0 mg)	
Dose and Mode of Administration:	1 encapsulated tablet NETA/E2 (0.5 mg/1.0 mg) daily, oral	
Duration of Treatment:	Up to 1 year (13 cycles)	
Studied period:	Date of first subjects' first visit:	21 Aug 2007
	Date of last subjects' last visit:	17 Aug 2009

Study Center(s):	48 investigational sites treated subjects in 7 countries: 5 centers in Argentina, 12 centers in Austria, 3 centers in Denmark, 8 centers in Italy, 3 centers in Mexico, 4 centers in Russia, 13 centers in USA)
Methodology:	This was a multi-center, double-blind, randomized study to investigate the endometrial safety of a continuous, combined, oral estrogen/progestin preparation (0.25 mg DRSP/0.5 mg E2) and to compare the bleeding pattern of subjects treated with 0.25 mg DRSP/0.5 mg E2 with the bleeding pattern of subjects treated with 0.5 mg NETA/1.0 mg E2 when used for HT for 1 year in post-menopausal women.
Indication/ Main Inclusion Criteria:	Postmenopausal symptoms / Non-hysterectomized, postmenopausal women requiring hormone therapy in the opinion of the investigator. An endometrial biopsy at screening was to show no evidence of endometrial hyperplasia or cancer
Study Objectives:	Overall: To investigate the endometrial safety of a continuous, combined, oral progestin/estrogen preparation (0.25 mg DRSP / 0.5 mg E2) and to compare the bleeding pattern of subjects treated with 0.25 mg DRSP / 0.5 mg E2 with the bleeding pattern of subjects treated with 0.5 mg NETA / 1.0 mg E2 when used for HT for 1 year in post-menopausal women
Evaluation Criteria:	Efficacy (Primary): The proportion of subjects in the DRSP/E2 group with an assessment of endometrial hyperplasia or worse during or after 13 cycles of treatment Efficacy (Secondary): The incidence rate of amenorrhea during months 1-3 and 10-12 Safety: Adverse events (AEs), clinical laboratory evaluations, gynecological examination incl. Pap smear, vital signs, cumulative amenorrhea and no-bleeding rate.
Statistical Methods:	Efficacy (Primary): The proportion of subjects with an assessment of endometrial hyperplasia or worse during or after 13 cycles of treatment was to be reported for the DRSP/E2 group together with an exact two-sided 95% Clopper-Pearson confidence interval.

	Efficacy (Secondary): In both treatment groups the incidence rate of amenorrhea during months 1-3 and 10-12 was to be estimated together with exact two-sided 95% Clopper-Pearson confidence intervals. Safety: Descriptive statistics
Number of Subjects:	Planned: 600 (DRSP/E2: 450, NETA/E2: 150) Analyzed: 662 (DRSP/E2: 490, NETA/E2: 172)

Study Results

Results Summary — Subject Disposition and Baseline

The women admitted to the study were non-hysterectomized, postmenopausal, ≥ 40 and ≤ 65 years of age, with symptoms requiring HT in the opinion of the investigator. A total of 944 women were screened for inclusion in the study, leading to a total of 662 women from 7 countries who were randomized. Only one woman who was randomized was not treated, leading to a total of 489 women treated with 0.25 mg DRSP/0.5 mg E2 and 172 women treated with 0.5 mg NETA/1.0 mg E2, who provided study data for analysis (full analysis set [FAS] = 661 subjects).
A total of 474/661 women in the FAS were Caucasian, 46 were Hispanic, 29 were Black, 6 were Asian, and 106 were of other race (all "South American"). The mean age of the subjects was approx. 53 years (53.5 [SD 4.9]; range 40-65 years). The demographics and baseline characteristics of the 661 women in the FAS were similar in the 2 treatment groups.

The study was composed of 3 phases; screening, baseline and a 13-cycle treatment phase. During screening all women received placebo run-in treatment.

Results Summary — Efficacy

None of the 309 subjects in the DRSP/E2 group (Primary analysis set [PAS]) had an overall biopsy result of 'hyperplasia or worse' during or after 13 cycles, which led to a point estimate of 0 for the probability of developing a hyperplasia or worse during 13 cycles of treatment and a 95% confidence interval (Clopper/Pearson) of (0.0%, 1.2%). 'Hyperplasia or worse' (a carcinoma) was diagnosed by one reader in one subject but this was not confirmed by the other readers. The diagnosis was followed up clinically and cancer and hyperplasia were excluded. None of the 305 subjects in the mPPS in the DRSP/E2 group had a biopsy result classified as abnormal ("hyperplasia or worse") leading to a point estimate of 0 with a 95% confidence interval of (0.0%, 1.2%).
As requested by the FDA, a sensitivity analysis was performed, where cases described as "insufficient tissue and (TVUS ≥ 5mm)" were classified as hyperplasia. Only one such case occurred in the DRSP/E2 group, leading to one event in the 310 subjects under consideration. This resulted in a point estimate of 0.32% and a 95% confidence interval of (0.0%, 1.8%). For all three analyses the requirements of both the FDA and the EMEA were satisfied, i.e., the point estimate was below 1% and the upper limit of the two-sided 95% confidence interval was below 2% (and consequently the upper limit of the one-sided 95% confidence interval was below 4%).

Note: none of the subjects in the NETA/E2 arm had a biopsy with an overall assessment classified as either 'hyperplasia or worse' or as 'tissue insufficient for diagnosis and TVUS ≥ 5 mm'.

With respect to the secondary variable, the incidence rate of amenorrhea during months 1-3 and 10-12, the amenorrhea rate in months 1 to 3 was considerably higher in the DRSP/E2 group than in the NETA/E2 group (68.7% vs. 59.3% in the per protocol set [PPS], 69.0% vs. 56.0% in the FAS). In months 10-12 the amenorrhea rate in both treatment groups was high (approx. 80%, in both analysis sets).

Results Summary — Safety

A total of 386 subjects (58.4%) in the FAS reported at least 1 AE. The reporting of AEs was comparable in the two treatment groups. Subjects reported AEs most frequently in the following SOCs: reproductive system and breast disorders: 127 subjects (19.2%), infections and infestations: 124 subjects (18.8%), gastrointestinal disorders: 76 subjects (11.5%). In each of the remaining SOCs, fewer than 10% of subjects overall reported AEs. The SOC musculoskeletal and connective tissue disorders was the only one in which a substantial difference in occurrences was seen between the two groups (DRSP/E2: 10.8%, NETA/E2: 5.2%). In the DRSP/E2 group, the most frequently reported AEs by preferred term were: headache (32 subjects; 6.5%), and breast pain and influenza (each in 21 subjects: 4.3%). In the NETA/E2 group, the most frequently reported AEs by preferred term were: breast pain (10 subjects; 5.8%), postmenopausal hemorrhage (9 subjects; 5.2%), and cervical dysplasia and headache (each in 7 subjects; 4.1%).

A total of 28 women (4.2% of the total study population) reported AEs that were rated by the investigator as severe in intensity (DRSP/E2: 23 [4.7%], NETA/E2: 5 [2.9%]), but no events of severe intensity occurred in more than 2 subjects each. Those that occurred in 2 subjects were headache, hot flush, postmenopausal hemorrhage, and vulvovaginal dryness. All other severe AEs occurred in 1 subject only. For 172 women (26.0%) the maximum intensity of AEs was mild and for 181 women (27.4%) the maximum intensity was moderate. The distribution of women with mild, moderate and severe AEs was approximately equal in the two treatment groups.

A total of 134 women (20.3%) experienced at least 1 AE assessed to be related to study drug by the investigator (DRSP/E2: 90 subjects, 18.4%; NETA/E2: 44 subjects, 25.6%). The AEs breast pain, postmenopausal hemorrhage, headache, breast tenderness and endometrial hypertrophy were those that were most frequently considered to be study drug related in both treatment groups, with a slightly higher frequency in the NETA/E2 group. All other events occurred in < 2.0% of subjects in either treatment group.

No deaths were reported. There were no confirmed cases of endometrial hyperplasia. A total of 22 subjects (3.3%), 16 (3.3%) in the DRSP/E2 group and 6 (3.5%) in the NETA/E2 group, experienced at least one SAE. Of these, one subject in the DRSP/E2 group (acute pancreatitis) and one subject in the NETA/E2 group (retinal vascular thrombosis) experienced SAEs that were considered by the investigator to be related to study drug. The sponsor also assessed the events as related to study drug. Another SAE, a transient ischemic attack in one subject in the DRSP/E2 group, was rated as related by the sponsor, but as not related by the investigator.

A total of 67 subjects (10.1% of the FAS) prematurely discontinued study drug due to AEs. These were 41 subjects (8.4%) in the DRSP/E2 group and 26 subjects (15.1%) in the NETA/E2 group. In the DRSP/E2 group the most frequently reported AEs leading to discontinuation by preferred term were postmenopausal hemorrhage (5 subjects), headache (4 subjects), and abdominal pain and weight increased (3 subjects each). All other AEs occurred in 1 or 2 subjects only. In the NETA/E2 group the most frequently reported AEs leading to discontinuation by preferred term were postmenopausal hemorrhage (6 subjects),

and headache and breast tenderness (3 subjects each). All other AEs occurred in 1 or 2 subjects only. In 41 subjects (6.2%) events leading to discontinuation of study drug were considered to be related to DRSP/E2 (24 subjects, 4.9%) or NETA/E2 (17 subjects, 9.9%).

Thromboembolic and cardiovascular events, and events in the MedDRA SOCs 'reproductive system and breast disorders' and 'neoplasms' were particularly scrutinized. The treatment groups were affected in equal measure, no trends were seen, and the numbers of women affected gave no cause for concern.

The majority of women had normal laboratory values at Screening (88.0%) and at end of study (95.8%). Note: the definition of abnormalities was stricter at Screening. Abnormalities were distributed evenly between the treatment groups. No abnormal laboratory test results were classified as SAEs. There were no relevant differences between the treatment groups or trends over time in the incidence of treatment-emergent abnormalities in any laboratory parameter.

No Pap smear findings gave cause for concern. No relevant differences in vital signs were noted between the treatment groups or over time.

The bleeding profiles of the women in the two treatment groups were similar. Between 90-day reference periods 1 and 4 the number of women with any bleeding/spotting steadily decreased, from 31.0% to 20.3% in the DRSP/E2 group and from 44.0% to 17.5% in the NETA/E2 group. The NETA/E2 group had the highest proportion of subjects who experienced bleeding/spotting in all reference periods except the fourth. In general, bleeding patterns by 90-day reference periods and by 28-day cycle showed the same trends. The analysis of spotting-only days by 28-day cycle showed more spotting in the NETA/E2 group in the early cycles (mean > 1.0 days), but then a greater reduction over the course of the study to reach a similar mean to the DRSP/E2 group by Cycle 13 (DRSP/E2: 0.4 days, SD 1.8; NETA/E2: 0.5 days, SD 2.5). The mean results for 90-day reference periods are summarized in the table below. Bleeding/spotting and spotting only episodes were defined as days of bleeding/spotting or spotting only that were preceded and followed by at least 2 bleed-free days.

	Bleeding/ spotting days	Bleeding days	Spotting only days	Bleeding/ spotting episodes	Spotting only episodes
Bleeding patterns by 90-day reference periods					
DRSP/E2					
Ref. period 1	3.4 (SD 8.1)	1.4 (SD 4.9)	1.9 (SD 5.3)	0.7 (SD 1.4)	0.4 (SD 1.0)
Ref. period 2	3.2 (SD 8.0)	1.3 (SD 4.4)	1.9 (SD 5.2)	0.6 (SD 1.4)	0.4 (SD 1.0)
Ref. period 3	2.6 (SD 8.2)	1.0 (SD 4.5)	1.6 (SD 5.5)	0.5 (SD 1.3)	0.3 (SD 0.8)
Ref. period 4	2.1 (SD 6.1)	0.5 (SD 2.4)	1.5 (SD 5.3)	0.5 (SD 1.2)	0.3 (SD 1.0)
NETA/E2					
Ref. period 1	6.7 (SD 11.4)	2.9 (SD 6.9)	3.9 (SD 6.7)	1.1 (SD 1.6)	0.6 (SD 1.1)
Ref. period 2	4.4 (SD 9.2)	1.7 (SD 4.9)	2.8 (SD 6.3)	0.9 (SD 1.8)	0.5 (SD 1.4)
Ref. period 3	2.4 (SD 7.5)	1.1 (SD 4.5)	1.3 (SD 4.1)	0.5 (SD 1.3)	0.3 (SD 0.9)
Ref. period 4	2.4 (SD 7.5)	1.1 (SD 3.8)	1.3 (SD 4.6)	0.4 (SD 1.0)	0.2 (SD 0.6)

n = mean number of days or episodes

The decrease in bleeding over the course of the study resulted in amenorrhea (no spotting and no bleeding) for a large proportion of women. From Cycle 1 to Cycle 7 the amenorrhea rate in the FAS was higher in the DRSP/E2 group (81.2%-86.0%; NETA/E2 70.0-83.9%), but from Cycle 8 to Cycle 13 the rate in the two treatment groups was similar (approx. 88.0%). The cumulative amenorrhea rate for subjects in the FAS with complete data for 13 cycles was similar in the two treatment groups. The rate steadily increased over the course of the study

and at the end of Cycle 13 was 90.3% in the DRSP/E2 group and 86.7% in the NETA/E2 group. The no-bleeding rate (no bleeding, with or without spotting) showed the same trends as the amenorrhea rate in both treatment groups.

Conclusion(s)

The continuous, combined, oral estrogen/progestin preparation (0.25 mg DRSP/0.5 mg E2) was seen to be safe for the endometrium when given over one year to women with postmenopausal symptoms requiring treatment. The women treated were equally as satisfied with the improvement of their menopausal symptoms as those treated with 0.5 mg NETA/1.0 mg E2, even though the latter had double the dose of E2. The cumulative amenorrhea and no-bleeding rates were better than those in the 0.5 mg NETA/1.0 mg E2 group, and the benefit/risk profile was favorable.

Publication(s):	Not applicable
Date Created or Date Last Updated:	30 Aug 2010