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 AG	
Study Number:	91544 (310781)	NCT00537836 EudraCT Number: 2007-001791-36
Study Phase:	IIa	
Official Study Title:	A double-blind, randomized, placebo and active controlled, multicenter study to investigate efficacy and safety after oral administration of 2 and 3 mg ZK 283197, 1 mg 17ß-estradiol and placebo once daily for 8 weeks in postmenopausal women with hot flushes	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	BAY86-5310 (ZK 283197)	
Name of Active Ingredient:	ZK 283197	
Dose and Mode of Administration:	2 mg and 3 mg ZK 283197, oral administration, once daily over 8 week	
Reference Therapy/Placebo		
Reference Therapy:	17beta estradiol, matching placebo	
Dose and Mode of Administration:	1 mg 17beta estradiol, oral administration, once daily over 8 weeks or matching placebo, oral administration, once daily over 8 weeks	
Duration of Treatment:	56 days	
Studied period:	Date of first subjects' first visit:	22 Oct 2007
	Date of last subjects' last visit:	22 Dec 2008
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 dated 16 Jan 2008 introduced the following substantial change: a) Addition of exclusion criterion: Patients, who by their own admission, are suffering severely from climacteric symptoms and desire treatment or continuation of treatment with hormone therapy amendment no 2 dated 18 Jul 2008 introduced the following substantial change: b) The number of volunteers was increased from 112 to a maximum of 118.	
Study Centre(s):	Germany: 2 centers, UK: 1 center, The Netherlands: 1 center	
Methodology:	Double-blind, randomized, placebo- and active-controlled, multicenter study with at least 112 (up to 118) postmenopausal women with hot flushes randomly assigned to one of the following four different treatment groups (oral treatment once daily over 8 weeks): • 3 mg ZK 283197 (N = 36) • Placebo (N = 36)	

	• 2 mg ZK 283197 (N = 20) • 1 mg 17beta-estradiol (N = 20)
Indication/ Main Inclusion Criteria:	Post-menopausal women 45–65 years of age with at least 35 moderate to severe hot flushes on seven consecutive days during the two-week run-in phase, intact uterus, and transvaginal sonography revealing an endometrial thickness of <5 mm(double layer) were included. Women with significant gynecological abnormalities or history of major gynecological disease, those undergoing treatment with hormones or other relevant medication, those with relevant deviations from normal laboratory or vital-signs values or other clinically relevant findings, and smokers were excluded
Study Objectives:	Overall: The objective of this study was to investigate the influence of an 8-week multiple-dose treatment, with two oral doses of ZK 283197 in comparison with E2 and placebo by determining the following: Primary: Primary objective: Efficacy of ZK 283197 in the reduction of moderate to severe hot flushes Secondary: Secondary objectives: Safety and tolerability; pharmacodynamics including vaginal cytology, endometrial thickness, endometrial histology (biopsy); pharmacokinetics; exposure–response relationship
Evaluation Criteria:	Efficacy (Primary): Change in frequency of moderate to severe hot flushes per week between baseline (2-week run-in phase) and Week 8 of the treatment phase. Efficacy (Secondary): Change from baseline to all treatment weeks in frequency and severity of moderate to severe hot flushes; change from baseline to all treatment weeks in severity and frequency of all hot flushes; evaluation of an exposure–response relationship. Safety: Standard safety laboratory parameters in blood/urine, vital signs (blood pressure/heart rate), electrocardiogram (ECG), adverse events, body weight, endometrial thickness, endometrial histology, vaginal cytology, maturation value, karyopycnotic index, bone resorption markers in blood, marker of hepatic estrogenicity in blood, bleeding pattern
	Pharmacokinetics: Trough levels at every visit, kinetic profile at steady state (between Weeks 4 and 8); area under the curve from administration to 24 hours after administration (AUC_{0-24h}), maximum concentration (C_{max}) and time to reach maximum concentration (t_{max}), minimum concentration (C_{min}) and average concentration(C_{ave})

Statistical Methods:	Efficacy (Primary): The primary target variable was the relative change in frequency of moderate to severe hot flushes per week between baseline (2-week run-in phase) and Week 8 of the treatment phase. The primary analysis was for superiority of ZK 283197 (3 mg) compared with placebo in the primary efficacy variable, by using the Wilcoxon rank sum test (alpha = 0.025, one-sided). Estimation and confidence interval of difference between ZK 283197 (3 mg) and E2 with respect to the primary efficacy variable was carried out by using the Hodges-Lehmann estimator. Efficacy (Secondary): Secondary: Exploratory analysis of exposure-response relationship using two dosages of ZK 283197 and placebo by means of regression techniques. Descriptive statistics for the secondary efficacy variables. Safety: Descriptive statistics, AE terms are summarized by Medical Dictionary for Regulatory Activities (MedDRA) system Pharmacokinetics - if applicable: Descriptive statistics
Number of Subjects:	Planned: 3 mg ZK 283197 (N = 36), Placebo (N = 36), 2 mg ZK 283197 (N = 20), 1 mg 17beta-estradiol (N = 20) Analyzed: 3 mg ZK 283197 (N = 37), Placebo (N = 38), 2 mg ZK 283197 (N = 20), 1 mg 17beta-estradiol (N = 21) (full analysis set)

Study Results

Results Summary — Subject Disposition and Baseline

A total of 261 volunteers were screened, of whom 116 were randomized and treated. Four volunteers (two each in the placebo and the ZK 283197 3 mg groups) discontinued their participation prematurely. Of the 38, 21, 20 and 37 volunteers treated in the placebo, E2, ZK 283197 2 mg and 3 mg group (respectively) and analyzed in the Full Analysis Set (FAS), 32, 20, 16 and 30 were eligible for analysis in the Per-Protocol Set (PPS) for efficacy and pharmacodynamics. There were seven major protocol violations. There were no conspicuous findings in the volunteers' recorded medical histories, clinical examination or baseline values. In the full analysis set, the volunteers were aged 54.9 ± 4.55 years (mean ± standard deviation) and had a body mass index of 24.4 ± 2.8 kg/m2, and all were Caucasian.

Results Summary — Efficacy

The effect of treatment with ZK 283197 3 mg and 2 mg respectively was a mean (median) reduction in weekly hot flushes, between baseline and after 8 weeks of treatment, by 41% (47%) and 44% (44%) compared with 34% (31%) after treatment with placebo and 85% (96%) after treatment with E2. On the basis of a one-sided Wilcoxon rank sum test at a significance level of alpha = 0.025, the differences between the treatment groups ZK 283197 3 mg and ZK 283197 2 mg and placebo did not reach the level of statistical significance (one-sided p = 0.2061 and p = 0.1898 respectively). On the basis of the Hodges–Lehmann estimator, there was a significant difference between the relative change after treatment with ZK 283197 3 mg compared with E2 and also for treatment with placebo compared with E2, both in favor of the E2 group.

The mean daily severity of moderate to severe hot flushes was approximately 2.2–2.4 in all treatment groups at baseline (scale from 0 = none to 3 = worst severity). In Week 8 the mean daily severity in the E2 group had decreased to 0.9, while that in the placebo group was 2.1 and those in the ZK 283197 groups were ~1.7 (ZK 283197 3 mg) and ~2.1 (ZK 283197 2 mg). For median values the contrast between the treatment groups was greater, with the severity in the E2 group being ~0.4 while that in all other treatment groups remained above 2.0 (median at baseline for all groups: ca. 2.1–2.5).

The mean daily severity of all hot flushes in all treatment groups at baseline was above 2.1 (in the E2 group above 2.0). In the early weeks of treatment a clear decrease was seen in the E2 group relative to the other treatment groups. By Week 8 the mean daily severity was clearly lowest in the E2 group and had also decreased somewhat in the ZK 283197 3 mg group.

No apparent relationship between AUC(0–24h), dose, Cmax or Cave of ZK 283197 and the relative change in hot flushes was observed. The numbers of volunteers with at least a given percentage (50%, 75%, 90%) reduction in frequency of moderate to severe hot flushes were compared between the treatment groups. In each case the E2 group showed the greatest treatment effect. E2 was considerably more efficacious than ZK 283197.

Results Summary — Safety

There were no serious adverse events in this study. Overall, the highest number of adverse events was observed in the placebo group (157 events recorded for 38 volunteers), followed by the ZK 283197 3 mg group (136 events in 37 volunteers). For the two other groups, 91 events (21 volunteers, E2 group) and 67 events (20 volunteers, ZK 283197 2 mg group) were recorded. More volunteers in the E2 group reported adverse events associated with the reproductive system (71% of volunteers vis-à-vis 21–35% in the other treatment groups). These events were principally endometrial hypertrophy and vaginal discharge. The most common adverse events were headache (30–60% of volunteers), followed by endometrial hypertrophy (2–43% of volunteers), nasopharyngitis (4–30%) and nausea (5–16%). Most of the adverse events were rated as mild, approximately 30% as moderate and 3% as severe. Two volunteers withdrew from the study because of adverse events: alopecia (placebo group) and elevated alanine aminotransferase (ZK 283197 3 mg group). Laboratory values and laboratory-related adverse events were generally inconspicuous; there was a trend towards higher hepatic values (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase) in the ZK 283197 3 mg group only. The other safety variables (vital signs, ECG, body weight) and the gynecological examination did not reveal any effect giving rise to concern about the safety of the treatment with E2 or with ZK 283197. The number of volunteers with endometrial stimulation (i.e., endometrium thickness > 5 mm or histological description not categorized as atrophic/inactive in week 8) was clearly higher in the E2 treatment group (~50%) as compared with all other treatment groups (2–10% of volunteers). The mean numbers of days with spotting or bleeding during the 56-day reference period were 1.2 ± 2.0, 0.2 ± 0.6, 0.6 ± 1.2 and 0.9 ± 1.5 for the four groups placebo, E2, ZK 283197 2 mg and ZK 283197 3 mg respectively, thus being clearly the least in the E2 group. When the 56-day reference period for recording these results was split into two equal intervals (28 days), then spotting and – as far as it occurred – bleeding were more frequent in the first than in the second 28-day interval. The number of volunteers with any bleeding/spotting during the first 28 days of treatment was between 20 and 45%, being the highest in the placebo group.

Results Summary — Pharmacokinetics

Except for t_{max}, the mean pharmacokinetic results of ZK 283197, estradiol and estrone are displayed as the geometric mean and geometric coefficient of variation (CV, in parentheses) in the following tables. For t_{max} the median is provided.

Pharmacokinetic parameters of ZK 283197 in serum after oral administration of 3 mg and 2 mg ZK 283197,respectively

Parameter	unit	2 mg (N=19)	3 mg (N=35)

		Geo. mean (%CV)	Range	Geo. mean (%CV)	Range
C_{max}	ng/L	37.8 (125)	10.5 - 360	55.1 (97.2)	18.2 - 570
t_{max}	h	0.333	0.28 – 8.00	0.333	0.30 – 4.95
C_{min}	ng/L	8.62 (94.4)	3.10 – 53.9	12.8 (72.9)	4.20 – 46.2
C_{ave}	ng/L	12.5 (98.6)	4.33 – 82.7	18.9 (64.3)	7.59 – 59.6
$AUC_{(0-24)}$	h•ng/L	301 (98.6)	104 - 1986	454 (64.3)	182 - 1430

Pharmacokinetic parameters of estradiol and estrone in serum after oral administration of 1 mg estradiol (N=21)

Parameter	unit	Estradiol		Estrone	
		Geo. mean (%CV)	Range	Geo. mean (%CV)	Range
C_{max}	ng/L	54.0 (38.6)	26.6 - 129	333 (31.5)	198 - 689
t_{max}	h	2.08	0.25 – 12.0	3.0	2.0 – 8.0
C_{min}	ng/L	23.4 (43.4)	10.3 – 66.2	116 (34.7)	57.5 - 234
C_{ave}	ng/L	37.5 (34.1)	18.4 – 73.7	215 (33.0)	107 - 452
$AUC_{(0-24)}$	h•ng/L	900 (34.1)	442 - 1768	5163 (33.0)	2576 - 11000

C_{max} = maximum drug serum concentration, t_{max} = time to reach C_{max}, C_{min} = minimum drug serum concentration, C_{ave} = average steady state drug serum concentration, $AUC_{(0-24)}$ = area under the drug concentration vs. time curve from time 0 up to 24h post administration, N = number of volunteers

Results Summary — Other

ZK 283197 had little or no effect upon the pharmacodynamic variables. In contrast, E2 was associated with an increase in maturation value and karyopycnotic index (vaginal cytology). A clear decrease in the bone resorption marker as well as an increase in hepatic estrogenicity marker (clear increase in sex-hormone-binding globulin, small increase in corticosteroid-binding globulin) was observed after treatment with E2, while there were no apparent changes in the other treatment groups.

Conclusion(s)

ZK 283197 was not efficacious in the reduction of hot flushes as compared to placebo. There was no statistically significant or clinically meaningful difference between the ZK 283197 groups and the placebo group. The treatment with E2 1 mg/day for eight weeks clearly reduced the number of hot flushes.

None of the treatments raised any major safety concerns, although certain gynecologically relevant adverse events were more frequent in the E2 group, notably endometrial hypertrophy and vaginal discharge. There was a trend towards higher hepatic values in the ZK 283197 3 mg group only. Endometrial stimulation was observed more often after treatment with estradiol.

Average steady-state concentrations of ZK 283197 were in the range of 4.33 to 82.7 ng/L, thus including the target exposure range > 20 ng/L. There was no trend towards an increase of efficacy with increasing exposure.

The treatment with E2 had detectable effects on vaginal cytology as well as bone resorption and hepatic estrogenicity markers, while that with ZK 283197 did not.

Publication(s):	No		
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