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:	90908 (304341)	
Study Phase:	I	
Official Study Title:	Open-label, single-dose, randomized, two-way crossover study to evaluate the effect of food on the bioavailability of estradiol and dienogest following a single oral administration of SH T00658M (2 mg estradiol valerate and 3 mg dienogest) in healthy postmenopausal women	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	Estradiol valerate, Dienogest (SH T00658M) film-coated tablet	
Name of Active Ingredient:	Estradiol valerate (EV), Dienogest (DNG)	
Dose and Mode of Administration:	Tablets containing 2 mg EV + 3 mg DNG administered orally.	
Reference Therapy/Placebo		
Reference Therapy:	Not applicable	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	Single doses of SH T00658M under fasting and fed conditions (separated by a washout phase of at least 2 weeks).	
Studied period:	Date of first subjects' first visit:	16 MAR 2006
	Date of last subjects' last visit:	31 MAY 2006
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	None	
Study Centre(s):	The study was conducted at a single center in Germany.	
Methodology:	The study comprised of 5 periods: Screening, pre-dose, treatment period 1, treatment period 2, and follow-up. The study drug was administered under fasting conditions for 10 h, after which the subjects fasted for a further 4 h. Under fed condition, the study drug was administered immediately after a standard breakfast according to the Food and Drug Administration (FDA) guideline. The (treatment) periods 1 and 2 started with baseline measurements (after randomization), and ended with the last measurement related to each treatment and the end of washout (14 days). The follow-up period contained the post-treatment examinations including control measurements. Blood sampling for pharmacokinetic (PK) evaluation (Estrone [E1], Estradiol [E2], and DNG) was done before and up to 48 hours after study drug administration. During the treatment periods, the subjects were monitored for adverse events (AEs) and concomitant medication.	

Indication/ Main Inclusion Criteria:	Indication: Oral contraception Main Inclusion Criteria: • Healthy postmenopausal females of age 45 to 75 years. • estradiol ≤20 pg/ml and follicle stimulating hormone (FSH) ≥30 IU/l at screening.
Study Objectives:	Overall: To evaluate the effect of food on the bioavailability of estradiol (E2) and DNG.
Evaluation Criteria:	Efficacy (Primary): Not applicable Efficacy (Secondary): Not applicable Safety: AEs and laboratory parameters were evaluated at screening and follow-up.
	Pharmacokinetics: • Primary target variables: Area under the serum concentration-time curve from time of administration (time zero) extrapolated until infinity (AUC), area under concentration-time curve from time of administration (t = 0) to time of last quantifiable serum concentration (t_{last}) (AUC(0-t_{last})) and maximum serum concentration (C_{max}) of estradiol (E2) and DNG. • Secondary target variables: Time to reach maximum serum concentration (t_{max}), terminal half-life ($t_{1/2}$), terminal disposition rate lambda z of E2, DNG; and AUC and AUC(0-t_{last}), C_{max}, t_{max}, lambda z and $t_{1/2}$ of estrone (E1).
Statistical Methods:	Efficacy (Primary): Not applicable Efficacy (Secondary): Not applicable Safety: Baseline findings and AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA; version 9). A frequency analysis by System Organ Class according to MedDRA was performed. Assessments of laboratory values and laboratory results (including urine) were analyzed by descriptive statistics and frequency analyses as appropriate.

	Pharmacokinetics: Analysis of variance, estimation of relative bioavailability for treatment with and without food for AUC, AUC(0-t_{last}) and C_{max} using a 90% confidence interval for the ratios to test the hypothesis $u_{fed}/u_{not\ fed} \notin$ (80%, 125%), descriptive statistics.
Number of Subjects:	Planned: 36 Analyzed: 38 included, 35 completed, 3 dropouts.

Study Results

Results Summary — Subject Disposition and Baseline

Out of 70 screened subjects, 38 were enrolled in the study. Thirty-five of these completed the study and were treated with SH T00658M both with and without food. Three subjects discontinued the study prematurely due to AEs and therefore only participated in one treatment sequence. Thirty-eight Caucasian female subjects with an average age of 60.9 years (range: 51 to 72) were included in the full analysis set used for the evaluation of safety. The mean body mass index was 25.6 kg/m^2 (range: 20.1 to 29.9). The evaluation of pharmacokinetics included 35 subjects for DNG and 33 subjects for E2 and E1. Two subjects were excluded from the E1/E2 evaluation due to high E2 baseline values.

Results Summary — Efficacy

Not applicable

Results Summary — Safety

No deaths or serious adverse events were reported during this study.

Three subjects had AEs that led to withdrawal from the study: subject 33 –nasopharyngitis, subject 4 – nausea/vomiting and subject 11 – vomiting.

In total, 36 AEs (8 with SH T00658M/fasting, 21 with SH T00658M/fed, 7 during follow-up) were documented in 20 out of 38 (52.6%) subjects.

The AE intensity was mild for 27 AEs, moderate for 8 AEs and severe for 1 AE. The AE with a severe intensity was headache with SH T00658M/fed (subject 31).

The most frequently occurring AEs were nausea (6 events in 5 subjects, 13.2%), vomiting (4 events in 4 subjects, 10.5%) as well as fatigue, headache and seasonal allergy (3 events in 3 subjects, 7.9% each symptom).

The related AEs (all assessed as possibly related) were nausea (6 events in 5 subjects, 13.2%), vomiting (4 events in 4 subjects, 10.5%), fatigue (3 events in 3 subjects, 7.9%), headache (3 events in 3 subjects, 7.9%) and dizziness (1 event in 1 subject, 2.6%).

The investigated clinical, biochemical, hematological and clotting parameters as well as urinalysis revealed clinically relevant changes in the differential white blood cell count for 2 subjects, in the serum ferritin level for 1 subject, in the serum chloride level for 2 subjects, and in the urinalysis (presence of erythrocytes) in 1 subject when comparing the screening and follow-up values. These findings were assessed as being not related to the treatment administered. All other laboratory parameters were without clinically relevant findings.

Results Summary — Pharmacokinetics

Table 1 summarizes the mean pharmacokinetic parameters of DNG, E2, and E1 after a single dose oral administration of SH T00658M (3 mg DNG and 2 mg EV), under fasting and fed conditions, respectively, in postmenopausal women.

Table 1: Mean pharmacokinetic parameters of dienogest (DNG), estradiol (E2), and estrone (E1) after a single dose oral administration of SH T00658M (3 mg DNG and 2 mg estradiol valerate), under fasting and fed conditions, respectively, in postmenopausal women

For Cmax and AUCs the geometric mean with the geometric coefficient of variation (in parentheses) are given, for tmax the median and the range (in parentheses) are provided.

analyte	parameter	unit	fasting	fed
DNG (N=35)	Cmax	ng/mL	86.8 (18.7%)	62.6 (20.3%)
	tmax	h	1 (0.5-3)	4 (1-12)
	AUC(0-tlast)	hxng/mL	901 (21.3%)	919 (19.2%)
	AUC	hxng/mL	937 (23.2%) (N=34)	963 (21.6% (N=32)
	t1/2	h	10.6 (15.2%) (N=34)	10.5 (14.3%) (N=32)
E2 (N=33)	Cmax	pg/mL	32.9 (29.8%)	40.6 (42.1%)
	tmax	h	6 (1-16)	3 (1-24)
	AUC(0-tlast)	hxpg/mL	838 (50.6%)	980 (42.9%)
	AUC	hxpg/mL	721 (45.9%) (N=8)	904 (49.1%) (N=6)
	t1/2	h	14.6 (16.9%) (N=8)	16.8 (12.9%) (N=6)
E1 (N=33)	Cmax	pg/mL	239 (33.1%)	237 (33.5%)
	tmax	h	6 (3-12)	6 (2-24)
	AUC(0-tlast)	hxpg/mL	4934 (51.7%)	5446 (49.5%)
	AUC	hxpg/mL	5573 (51.7%) (N=8)	6079 (44.1 %) (N=8)
	t1/2	h	16.3 (8.29%) (N=8)	16.5 (15.1%) (N=8)

Legend:
Cmax = Maximum serum concentration
tmax = Time to reach maximum concentration
AUC(0-tlast) = Area under concentration-time curve from time of administration (t = 0) to time of last quantifiable serum concentration (tlast)
AUC = Area under the serum concentration-time curve from time of administration (time zero) extrapolated until infinity
t1/2 = terminal half-life

Analysis of variance (ANOVA) was performed to assess the food effect on the bioavailability of SH T00658M. Table 2 summarizes the statistics of PK variables for DNG and E2 in fed and fasted states.

Table 2: Geometric mean ratios and 90% confidence intervals (CI) of primary pharmacokinetic variables for DNG and E2 between fed and fasted states

Analyte	Parameters	Comparison	Geometric mean ratio (%)	90% CI (%)
DNG	Cmax	Fed vs. Fasted	72.0	67.6 – 76.8
	AUC(0-tlast)	Fed vs. Fasted	102	99.2 - 105
	AUC	Fed vs. Fasted	103	99.5 - 106
E2	Cmax	Fed vs. Fasted	123	110 - 137
	AUC(0-tlast)	Fed vs. Fasted	117	111 - 123

The results indicate that the systemic exposure of DNG and E2 was not affected by food. But the C_{max} of DNG was decreased by 28% while C_{max} of E2 was slightly increased by 23% under the fed conditions.

Conclusion(s)
In this study, single dose oral administration of SH T00658M both with and without food was tolerated by all but two subjects (discontinuation of study participation due to nausea and/or vomiting) examined in this study. The results of this study do not raise any safety concerns for the combined oral medication of DNG and EV. The current food-effect study in healthy postmenopausal women demonstrated that under fed conditions the C_{max} of DNG was decreased by 28% and the C_{max} of E2 was increased by 23%, while AUC values for both DNG and E2 remained unchanged. The slight changes in C_{max} of DNG and E2 are not considered to be clinically relevant, and therefore, SH T00658M can be taken without regard to meals.

Publication(s):	None		
Date Created or Date Last Updated:	03 MAY 2012	Date of Clinical Study Report:	09 MAY 2007

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Vital GmbH
Postal Address	D-51368 Leverkusen, Germany
Sponsor in Germany	
Legal Entity Name	Bayer HealthCare AG
Postal Address	D-51368 Leverkusen, Germany

List of Investigational Sites

No	Facility Name	Street	ZIP Code	City	Country
1	Bayer Pharma AG	Global Drug Discovery Clinical Pharmacology Sellerstr. 31	13353	Berlin	GERMANY

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Natazia
Brand/Trade Name(s) ex-US	Qlaira, Klaira
Generic Name	Estradiol valerate, Dienogest
Main Product Company Code	BAY86-5027
Other Company Code(s)	SH T 00658 ID
Chemical Description	Estra–1,3,5(10)–triene–3,17β–diol–17–valerate (WHO) 19-Norpregna-4,9-diene-21-nitrile, 17-hydroxy-3-oxo-17α-Cyanomethyl-17β-hydroxy-estra-4,9-dien-3-one (CAS)
Other Product Aliases	Estradiol 17–valerate Estradiol 17β–valerate Estra–1,3,5(10)–triene–3,17–diol (17β), 17–pentanoate 1,3,5(10)–Estratriene–3,17β–diol–17–valerate ZK 5104 17α-Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile (IUPAC) 17β-Hydroxy-3-oxo-19-nor-17α-pregna-4,9-diene-21-nitrile (17α)-17-Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile ZK00037659 FS-10101-N

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