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:	90927 (301886)	NCT00185224
Study Phase:	II	
Official Study Title:	A single-center, open-label, controlled, randomized study to investigate the impact of a sequential oral contraceptive containing estradiol valerate (EV) and dienogest (DNG) (SH T00658ID) as compared to a sequential oral contraceptive containing ethinylestradiol (EE) and levonorgestrel (LNG) (SH D00264A) on plasma lipids, hemostatic variables, and carbohydrate metabolism in 60 healthy female subjects aged 18-50 years over 7 treatment cycles including the pharmacokinetics of estrone (E1), estradiol (E2), and DNG	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	EV/DNG (Qlaira, BAY86-5027, SH T00658K)	
Name of Active Ingredient:	Estradiol valerate (EV) + Dienogest (DNG)	
Dose and Mode of Administration:	Test Group: SH T006581D Sequential regimen Days 1-2: 3.0 mg EV Days 3-7: 2.0 mg EV + 2.0 mg DNG Days 8-24: 2.0 mg EV + 3.0 mg DNG Days 25-26: 1.0 mg EV Days 27-28: Placebo Daily oral intake of 1 tablet SH T00658ID for 28 days per cycle, no pill-free interval.	
Reference Therapy/Placebo		
Reference Therapy:	Ethinyl estradiol (EE) + Levonorgestrel (LNG) (Triquilar, SH D00264A)	
Dose and Mode of Administration:	Reference Group: SH D00264A Sequential regimen Days 1 – 6: 0.03 mg EE + 0.05 mg LNG Days 7 – 11: 0.04 mg EE + 0.075 mg LNG Days 12 – 21: 0.03 mg EE + 0.125 mg LNG Days 22 – 28 Placebo Daily oral intake of 1 tablet SH D00264A for 28 days per cycle, no pill-free interval.	
Duration of Treatment:	Seven cycles of 28 days each (no tablet-free intervals)	
Studied period:	Date of first subjects' first visit:	07 MAR 2005
	Date of last subjects' last visit:	24 MAR 2006
Premature Study Suspension / Termination:	No	

Substantial Study Protocol Amendments:	Amendment no. 1 (dated 22 JUN 2005) incorporated the following changes: • Evaluation of the effect of long-term treatment with SH T00658ID on the pharmacokinetics of estrone (E1), estradiol (E2), and DNG. Pharmacokinetic samples were taken during Cycle 4 and Cycle 7 at the corresponding study visits. • The reference range of Antithrombin III was changed from 86 - 122% to 75-125% while that of fibrinogen, from 1.50 - 4.50 g/L to 1.80-3.50 g/L • Since only limited information was available about the pharmacokinetics of EV and DNG in fertile women following the long-term use of SH T00658ID, it was decided to investigate the pharmacokinetic parameters in a subgroup of volunteers. Amendment no. 2 (dated 14 MAR 2007) was introduced after the end of the study. It was aimed at the assessment of additional hormone parameters: total and free testosterone and dehydroepiandrosterone (DHEA).
Study Centre(s):	The study was conducted at a single center in Germany.
Methodology:	This was a randomized, open-label, active treatment-controlled study. Subjects started continuous tablet intake on the first day of menstrual bleeding after Visit 2. A negative pregnancy test was a prerequisite for the start of treatment. A washout period of 2 months for sex hormones prior to start of treatment (6 months in case of long-acting progestins) was also required. Blood sampling for measurement of target variables (plasma lipids, hemostatic variables, carbohydrate metabolism [oral glucose tolerance test {OGTT}], thyroid parameters, sex hormone-binding globulin (SHBG), and cortisol-binding globulin (CBG) as well as free and total testosterone and dehydroepiandrosterone sulfate [DHEA-S]) were done at baseline and at visit 4 a. In addition, blood sampling for pharmacokinetic measurements (E1, E2, and DNG) were done at visit 3 and visit 4 b.
Indication/ Main Inclusion Criteria:	Indication: Oral contraception. Main Inclusion Criteria: Healthy female subjects aged 18 to 50 years requiring contraception (smokers: aged ≤30 years and maximal 10 cigarettes daily).
Study Objectives:	<u>Overall:</u> To investigate the impact of a sequential oral contraceptive containing EV and DNG (SH T00658ID) as compared to a sequential oral contraceptive containing EE and LNG (SH D00264A) on plasma lipids, hemostatic variables, carbohydrate metabolism, thyroid parameters, SHBG, CBG, and 3 additionally planned parameters (Amendment 2, 14 Mar 2007): free and total testosterone, and dehydroepiandrosterone sulfate. In a subgroup on SH T00658ID, pharmacokinetics of E1, E2, and DNG were evaluated. Tolerability and safety were assessed in terms of baseline findings, adverse events (AEs), safety laboratory tests, vital signs (blood pressure and heart rate), body weight, general physical and gynecological examination (including transvaginal ultrasonography [TVU], breast palpation, and cervical smear), bleeding patterns/cycle control, and pregnancy test/pregnancy.

Evaluation Criteria:	Efficacy (Primary): • Lipid profile: Intraindividual relative changes (in percent) between Treatment Cycle 7 (Visit 4) and Baseline (Visit 2) in: ▪ High-density lipoprotein (HDL)-cholesterol ▪ Low-density lipoprotein (LDL)-cholesterol (calculated according to Friedewald). Efficacy (Secondary): • Lipid profile: Intraindividual (absolute and relative) changes between Treatment Cycle 7 (Visit 4) and Baseline (Visit 2) in: ▪ HDL-cholesterol (absolute change) ▪ LDL-cholesterol (absolute change) ▪ Total cholesterol ▪ Triglycerides ▪ HDL2-cholesterol ▪ Very low density lipoprotein (VLDL)-cholesterol (calculated) ▪ Lipoprotein (a) (Lp[a]) • Hemostatic parameters: ▪ Parameters of thrombin and fibrin turnover (activation markers): ➢ Prothrombin fragment 1+2; ➢ D-dimer ▪ (Pro)coagulatory variables: ➢ Fibrinogen ➢ Factor VII activity (VIIc) ➢ Factor VIII activity (VIIIc) ▪ Anticoagulatory variables: ➢ Antithrombin III (activity) ➢ Protein C (activity) ➢ Protein S (activity) ➢ Activated protein C (APC) resistance (based on the activated partial thromboplastin time [aPTT]) ➢ Activated protein C (APC) sensitivity ▪ Antifibrinolytic variable: ➢ Plasminogen activator inhibitor-1 (PAI-1) (antigen and activity) • Carbohydrate metabolism: ▪ OGTT: ➢ Plasma glucose ➢ Insulin ➢ C-peptide • Thyroid parameters: ▪ Thyroid-stimulating hormone (TSH) ▪ Thyroxine-binding globulin (TBG) ▪ Triiodothyronine (T3) and free triiodothyronine (fT3) ▪ Thyroxine (T4) and free thyroxine (fT4)

	• Other parameters: ▪ SHBG ▪ CBG ▪ Free testosterone ▪ Total testosterone ▪ DHEA-S Safety: • Baseline findings, AEs (AEs observed, mentioned upon general questioning, or spontaneously reported), and concomitant medication • Safety laboratory tests • Vital signs (blood pressure and heart rate) and body weight • General physical and gynecological examination (including TVU, breast examination by palpation, and cervical smear) • Bleeding patterns/cycle control • Pregnancy test/pregnancy during the study.
	Pharmacokinetics: Pharmacokinetics of SH T00658ID (pharmacokinetic parameters $AUC_{(0-24)}$, C_{max}, and t_{max} of E1, E2, and DNG).
Statistical Methods:	Efficacy (Primary): The primary target variables were evaluated by descriptive statistical methods for the two treatment groups. Intraindividual (absolute and relative) changes between Treatment Cycle 7 (Visit 4) and Baseline (Visit 2) were calculated. In addition, 95% two-sided normal confidence intervals were calculated. For the HDL- and LDL cholesterol values, boxplots for the intra-individual relative changes (in percent) of the value at Treatment Cycle 7 to Baseline (for each treatment group) were illustrated. Efficacy (Secondary): Descriptive statistics were used. Safety: Descriptive statistics were used.
	Pharmacokinetics: Descriptive statistics were used.
Number of Subjects:	Planned: 60 subjects (40 valid cases) Analyzed: 58 subjects (51 valid cases: Test group N=25 and reference group N=26) Pharmacokinetic analysis in 24 cases.

Study Results

Results Summary — Subject Disposition and Baseline

A total of 83 subjects were screened according to the selection criteria for inclusion in the study. Of them, 23 (27.7%) were considered ineligible: 2 (2.4%) of the screened subjects withdrew their consents during the screening phase, 18 (21.7%) failed to meet all inclusion and exclusion criteria, and 3 (3.6%) were not included due to other reasons (1x Non-

compliance; 1x Irregular menstrual bleedings; 1x Insufficient veins for blood sampling).

The randomization procedure to assign the subjects to treatment with either SH T00658ID (Test group) or SH D00264A (Reference group) was performed over 60 subjects; however, 2 of them (2 subjects assigned to the Reference group) did not take any study medication and dropped out before start of study treatment for the following reasons: Low fibrinogen value at Baseline and Serious baseline finding "Missed abortion". As a result, 58 subjects received at least 1 unit of the study drug dependent on their assignment to one of the 2 treatment groups: 30 subjects in the Test group and 28 in the Reference group. Of the 58 subjects who received study treatment, 50 completed the treatment period as planned; 8 subjects (13.8%) prematurely discontinued the intake of study medication. Of them, 5 dropouts (16.7%) belonged to the Test group versus 3 (10.7%) to the Reference group.

Table 1 summarizes the demographic characteristics of the different population sets.

Table 1: Basic demographic characteristics

Parameter	SH T00658ID **Test** group		SH D00264A **Reference** group		Total	
	FAS N=30	PPS N=25	**FAS** N=28	PPS N=25	**FAS** N=58	PPS N=50
Age [years]	28.1 ± 6.1	27.6 ± 6.0	31.1 ± 7.7	32.2 ± 7.3	29.6 ± 7.0	29.9 ± 7.0
Height [cm]	169.28 ± 5.32	169.3 ± 5.1	167.68 ± 8.18	167.2 ± 8.6	168.51 ± 6.84	168.3 ± 7.0
Body weight [kg]	66.50 ± 9.26	66.85 ± 8.93	62.33 ± 8.19	62.46 ± 8.09	64.49 ± 8.93	64.66 ± 8.72
Body mass index [BMI; kg/m^2]	23.16 ± 2.71	23.31 ± 2.75	22.13 ± 2.13	22.28 ± 1.98	22.66 ± 2.48	22.80 ± 2.43

Results Summary — Efficacy

The primary efficacy variables were the individual (i.e., intraindividual) relative changes of HDL-cholesterol and LDL-cholesterol from Baseline to Cycle 7 under one of the 2 study treatments, namely a sequential oral contraceptive containing EV and DNG (SH T00658ID/Test) in comparison to a sequential oral contraceptive containing EE and LNG (SH D00264A/Reference) (Test group: N=25 and Reference group N=26). The 95% confidence interval (CI) was used as inferential statistic for indicating the precision of the estimates of population characteristics.

The individual relative change of HDL-cholesterol in the full analysis set (FAS) was 7.9% (95% CI [-1.1; 16.9]) for the treatment with SH T00658ID (Test) and -2.3% (95% CI [-8.1; 3.5]) for the treatment with SH D00264A (Reference). This resulted in a treatment difference of 10.2% (95% CI [-0.2; 20.5]).

The individual relative change of LDL-cholesterol in the FAS was -6.5% (95% CI [-13.1; 0.1]) for the treatment with SH T00658ID (Test) and -3.0% (95% CI [-10.0; 4.0]) for the treatment with SH D00264A (Reference). This resulted in a treatment difference of -3.5% (95% CI [-12.9; 5.9]).

In summary, the differences between the Baseline and Cycle 7 values of serum HDL-cholesterol and LDL-cholesterol in both treatment groups were not statistically significant at the 0.05 level. Mean HDL-cholesterol level slightly increased in the Test group in contrast to minimal decrease in the Reference group during Cycle 7 ($p = 0.0545$). Mean LDL-cholesterol levels slightly decreased in both treatment groups during Cycle 7 as compared to Baseline; the decrease was marginally more pronounced in the Test group ($p = 0.4577$).

The effect of the 2 study drugs on all other plasma lipids assessed (total cholesterol, triglycerides, HDL2-cholesterol, VLDL-cholesterol, and lipoprotein(a)) was not clinically relevant. The differences between mean Baseline and Cycle 7 values were marginal considering the high variability of data (as represented by high standard deviations); however, a weak trend towards increase was seen for triglycerides and VLDL-cholesterol (the latter more pronounced in the Reference group), whereas the mean levels of HDL2-cholesterol and lipoprotein(a) remained unchanged. The comparison of the individual plasma lipid levels between the 2 treatment groups also resulted in only minimal differences.

Table 2 summarizes the lipid profile at Cycle 7 in Test and Reference groups.

Table 2: Lipid profile: Overview of levels and individual relative changes at Cycle 7 (Week 28) – FAS

Parameter [Normal range and unit]	Levels at Cycle 7 (mean ± SD, [median])		Individual relative change at Cycle 7 [mean ± SD %]	
	SH T00658ID Test group	SH D00264A Reference group	SH T00658ID Test group	SH D00264A Reference group
HDL-cholesterol [0.91 – 2.33 mmol/L]	1.617 ± 0.241 [1.550]	1.493 ± 0.234 [1.435]	7.873 ± 21.797	-2.282 ± 14.413
LDL-cholesterol [0 – 4.4 mmol/L]	2.375 ± 0.479 [2.250]	2.771 ± 0.770 [2.720]	-6.487 ± 15.938	-2.989 ± 17.362
Total cholesterol [4.14 – 6.73 mmol/L]	4.401 ± 0.616 [4.560]	4.765 ± 0.870 [4.820]	0.511 ± 11.410	0.226 ± 11.359
Triglycerides [0.8 – 1.94 mmol/L]	0.899 ± 0.326 [0.870]	1.105 ± 0.439 [0.910]	27.327 ± 48.228	48.760 ± 42.511
HDL2-cholesterol [0.28 – 0.65 mmol/L]	0.259 ± 0.092 [0.230]	0.238 ± 0.098 [0.230]	6.418 ± 36.618	-0.116 ± 46.635
VLDL-cholesterol [0 – 0.88 mmol/L]	0.406 ± 0.147 [0.390]	0.501 ± 0.200 [0.410]	27.349 ± 48.965	48.486 ± 43.386
Lipoprotein(a) [0 – 0.3 g/L]	0.198 ± 0.178 [0.100]	0.203 ± 0.209 [0.100]	0.785 ± 21.080	-4.230 ± 22.202

The analysis of the effects of the 2 study treatments on hemostatic parameters revealed the following:

- Mean levels of the parameters of thrombin and fibrin turnover (prothrombin fragment 1+2 and D-dimer) remained in both treatment groups in the lower half of the normal range. A stronger increase was seen in both parameters in the Reference group. The proportion of subjects with low values of prothrombin fragment 1+2 at the end of treatment remained higher in the Test group whereas it decreased in the Reference group in favor of values within the normal range.
- The mean values of the (pro)coagulatory parameters (fibrinogen, factor VII activity, and factor VIII activity) were within the normal range and just marginally affected by the 2 study treatments. The changes in the levels of fibrinogen and factor VII activity in the Reference group were more pronounced as compared to those in the Test group. Only few abnormal values were seen. Slightly more elevated values of factor VII activity were seen at the end of treatment in both treatment groups with a slight prevalence of those in the Reference group.
- Anticoagulatory parameters (antithrombin III activity, protein C activity, protein S activity, and activated protein C resistance) displayed generally comparable results with slightly more pronounced changes in the Reference group as compared to the Test group. Only few abnormal values occurred in both treatment groups. In accordance with the study protocol, the Rosing test for assessment of APC sensitivity was not performed, since there were not

any clinically relevant changes in other hemostatic parameters requiring further analysis.

- Antifibrinolytic parameters (plasminogen activator inhibitor-1 (PAI-1) antigen and PAI-1 activity) were characterized by low levels in both treatment groups at Baseline as well as at the end of study treatment. Mean levels of PAI-1 antigen were below the lower limit of the normal range in both treatment groups at Baseline and even further decreased at the end of treatment. The decrease of both PAI-1 antigen and PAI-1 activity was more marked in the Reference group. A high number of abnormally low PAI-1 antigen values were seen in both treatment groups at the 2 examination time-points. Mean PAI-1 activity was close to the lower limit of the normal range and no abnormal values were detected.

Table 3 summarizes the hemostatic parameters at Cycle 7 in Test and Reference groups.

Table 3: Hemostasis: Overview of levels and individual relative changes at Cycle 7 (Week 28) – FAS

Parameter [Normal range and unit]	Levels at Cycle 7 (mean ± SD, [median])		Individual relative change at Cycle 7 [mean ± SD %]	
	SH T00658ID Test group	SH D00264A Reference group	SH T00658ID Test group	SH D00264A Reference group
Activation markers (thrombin / fibrin turnover)				
Prothrombin fragment 1+2 [0.07 – 0.23 nmol/L]	0.070 ± 0.018 [0.060]	0.139 ± 0.177 [0.105]	0.630 ± 30.284	117.318 ± 358.000
D-dimer [0 – 500 ng/mL]	126.0 ±72.3 [108.0]	207.3 ± 165.6 [153.0]	2.100 ± 43.541	62.852 ± 99.455
(Pro)-coagulatory				
Fibrinogen [1.8 – 3.5 g/L]	2.506 ± 0.501 [2.370]	2.934 ± 0.786 [2.665]	7.938 ± 13.730	28.096 ± 29.773
Factor VII activity (VIIc) [70 – 120%]	100.7 ± 24.1 [99.0]	112.5 ± 23.7 [112.5]	13.546 ± 14.856	24.361 ± 20.872
Factor VIII activity (VIIIc) [70-150%]	94.1 ± 21.9 [86.0]	94.4 ± 21.4 [89.5]	6.906 ± 16.868	7.517 ± 13.361
Anti-coagulatory				
Anti-thrombin III activity [75 -125%]	91.5 ± 8.8 [92.0]	87.0 ± 7.7 [86.0]	0.834 ± 6.631	-2.974 ± 8.369
Protein C activity [70 – 150%]	115.0 ± 21.8 [113.0]	118.3 ± 22.2 [114.5]	8.329 ± 11.912	14.505 ± 16.997
Protein S activity [52 – 118%]	86.1 ± 9.7 [86.0]	77.2 ± 15.0 [77.5]	1.756 ± 7.549	-11.676 ± 10.016
APC resistance [2 – 5 Unit: 1]	2.823 ± 0.401 [2.830]	2.761 ± 0.374 [2.810]	-5.322 ± 9.849	-7.028 ± 5.581
Antifibrinolytic				
PAI-1 antigen [7 – 43 ng/mL]	3.5 ± 3.8 [2.0]	1.8 ± 2.5 [1.0]	10.561 ± 123.226	-36.200 ± 48.556
PAI-1 activity [0.0 – 5.0 ng/mL]	0.54 ± 0.20 [0.50]	0.50 ± 0.00 [0.50]	-3.725 ± 13.332	-5.143 ± 18.499

Parameters of carbohydrate metabolism (glucose and C-peptide) remained stable and within the normal range under the 2 study treatments (Table 4). Increase of insulin levels within the lower part of the normal range in both groups was more pronounced under the Reference drug. Only few abnormal values of small extent were detected by means of the OGTT. One subject was prematurely discontinued at the beginning of the study due to high Baseline glucose and insulin levels; the remaining abnormalities only slightly exceeded the normal range and were not considered clinically relevant.

Table 4: Carbohydrate metabolism: Overview of levels and individual relative changes at Cycle 7 on Week 28 – FAS

Parameter [Normal range and unit]	Levels at Cycle 7 (mean ± SD, [median])		Individual relative change at Cycle 7 [mean ± SD %]	
	SH T00658ID Test group	SH D00264A Reference group	SH T00658ID Test group	SH D00264A Reference group
Glucose [3.05 – 6.38 mmol/L]	5.080 ± 0.328 [5.050]	4.895 ± 0.285 [4.885]	0.679 ± 5.763	-1.017 ± 7.572
Insulin [2.6 – 24.9 mU/L]	6.38 ± 2.34 [6.10]	7.01 ± 3.18 [6.40]	33.843 ± 44.860	52.716 ± 74.510
C-peptide [1.1 – 4.4 ng/mL]	1.698 ± 0.365 [1.610]	1.806 ± 0.487 [1.750]	-4.259 ± 20.764	6.401 ± 27.059
AUC(0-120 min) Glucose [h*mmol/L][1]	11.886 ± 1.431 [12.060]	12.492 ± 2.139 [12.341]	5.029 ± 15.754	8.092 ± 20.683
AUC(0-120 min) Insulin [h*mU/L][2]	82.443 ± 26.141 [76.750]	96.793 ± 34.575 [91.025]	5.498 ± 34.538	29.221 ± 43.788
AUC(0-120 min) C-peptide [h*ng/mL][3]	11.690 ± 2.897 [11.620]	12.803 ± 2.823 [13.371]	-9.909 ± 20.138	1.705 ± 19.255

* The asterisk represents a multiplication sign in the AUC units.
[1]) Normal ranges for glucose after glucose challenge in OGTT:
- 30 min: 3.05 – 6.38 mmol/L
+ 60 min: 3.05 – 9.99 mmol/L
+120 min: 3.05 – 6.66 mmol/L)
[2]) and [3]) There were no corresponding normal ranges for these parameters after glucose challenge in OGTT.

Among the thyroid parameters investigated at Baseline and Cycle 7 (TSH, TBG, T3 and fT3, T4 and fT4), a noticeable increase occurred only in the levels of TBG with a prevalence of the changes in the Reference group and the levels of total thyroxine (Table 5). A higher frequency of abnormally increased values was seen only in TBG, and this mainly in the Reference group (12.0% in the Test group versus 38.5% in the Reference group).

Table 5: Thyroid parameters: Overview of levels and individual relative changes at Cycle 7 (Week 28) – FAS

Parameter [Normal range and unit]	Levels at Cycle 7 (mean ± SD, [median])		Individual relative change at Cycle 7 [mean ± SD %]	
	SH T00658ID Test group	SH D00264A Reference group	SH T00658ID Test group	SH D00264A Reference group
TSH [0.27 – 4.2 mU/L]	2.508 ± 1.257 [2.520]	2.686 ± 1.422 [2.190]	3.175 ± 37.013	24.466 ± 61.820
TBG [186 – 597 nmol/L]	495.7 ± 86.9 [513.0]	555.8 ± 84.9 [517.0]	29.997 ± 16.148	49.370 ± 13.606
T3 [1.21 – 3.03 nmol/L]	2.148 ± 0.346 [2.120]	2.175 ± 0.302 [2.155]	19.267 ± 12.564	24.550 ± 21.526
fT3 [3.9 – 6.7 pmol/L]	4.97 ± 0.64 [4.70]	4.57 ± 0.59 [4.50]	5.204 ± 9.381	-0.950 ± 13.860
T4 [66 – 181 nmol/L]	120.0 ± 16.1 [118.0]	119.2 ± 16.3 [120.0]	27.852 ± 10.912	25.239 ± 15.558
fT4 [12.9 – 23.1 pmol/L]	15.98 ± 1.22 [15.90]	14.48 ± 1.58 [14.55]	6.415 ± 8.056	-5.728 ± 8.905

The levels of SHBG increased slightly within the normal range in the test group as compared to baseline and markedly in the reference group exceeding the normal range (Table 6). The changes were paralleled by an increase of the frequency of slightly to moderately increased SHBG values measured in individual subjects (52.0% of the subjects in the Test group versus 84.6% in the Reference group). Mean levels of CBG remained in both treatment groups within the normal range toward the end of treatment. A slight increase in the Test group and

more marked increase in the Reference group were observed. In addition, there was a shift of all abnormally low CBG values measured at Baseline (26.7% of the subjects in the Test group versus 28.6% in the Reference group) to normal values at the end of study treatment (Cycle 7).

Table 6: Sex hormone-binding globulin (SHBG) and Cortisol-binding globulin (CBG): Overview of levels and individual relative changes at Cycle 7 (Week 28) – FAS

Parameter [Normal range and unit]	Levels at Cycle 7 (mean ± SD, [median])		Individual relative change at Cycle 7 [mean ± SD %]	
	SH T00658ID Test group	SH D00264A Reference group	SH T00658ID Test group	SH D00264A Reference group
SHBG [26.1 – 110 nmol/L]	108.16 ± 31.71 [111.60]	151.12 ± 42.98 [150.70]	62.740 ± 50.506	111.554 ± 48.043
CBG [0.75 – 2.91 µmol/L]	1.045 ± 0.165 [1.060]	2.094 ± 0.457 [2.150]	27.806 ± 20.401	146.285 ± 48.928

The mean serum levels of free and total testosterone and DHEA-S decreased toward the end of the study in both treatment groups as compared to Baseline (Table 7). Note that these additional parameters were assayed in the serum samples of less subjects than the other parameters, namely, Test group: N = 19 instead of 25 and Reference group: N = 22 instead of 26. It is characteristic that the decline was markedly more pronounced in the Reference group. The most noticeable decrease occurred in the levels of free testosterone (mean individual relative change was approximately -42 ± 20% in the Test group versus approximately -70 ± 12% in the Reference group) followed by total testosterone (mean individual relative change was approximately -17 ± 22% in the Test group versus approximately -44 ± 19% in the Reference group) and DHEA-S (mean individual relative change was approximately -3 ± 17% in the Test group versus approximately -18 ± 26% in the Reference group).

Table 7: Free and total testosterone and DHEA-S: Overview of levels and individual relative changes at Cycle 7 (Week 28) – FAS

Parameter [Normal range and unit]	Levels at Cycle 7 (mean ± SD, [median])		Individual relative change at Cycle 7 [mean ± SD %]	
	SH T00658ID Test group	SH D00264A Reference group	SH T00658ID Test group	SH D00264A Reference group
Free testosterone [0.003 – 0.037 nmol/L]	0.0121 ± 0.0116 [0.0080]	0.0060 ± 0.0055 [0.0040]	-41.989 ± 19.599	-70.146 ± 12.367
Total testosterone [0.22 – 2.9 nmol/L]	1.315 ± 0.669 [1.390]	0.953 ± 0.662 [0.800]	-17.042 ± 22.015	-43.558 ± 18.652
DHEA-S [35 - 430 µg/dL]	171.1 ± 84.7 [146.0]	149.1 ± 104.4 [122.0]	-3.147 ± 17.457	-17.606 ± 26.267

Results Summary — Safety

A comparable number of subjects in both treatment groups experienced AEs during the study, namely, 24 subjects with AEs of 30 (80.0%) versus 25 of 28 (89.3%) in the Reference group. The number of AEs in the 2 treatment groups was also similar (88 AEs in the Test group versus 86 AEs in the Reference group) and this was paralleled by similar proportions of the AEs assessed as probably and possibly drug-related (44 AEs in the Test group versus 44 AEs in the Reference group).

None of the AEs was rated as serious AE and none of the AEs had a fatal outcome.

Study drug withdrawals due to AE occurred rarely: the study drug was withdrawn in 2 subjects of the Test group (6.7%) due to severe Headache and moderate Abdominal pain in 1

subject and mild Paresthesia in another subject compared to 1 subject of the Reference group (3.6%) in whom Reference drug was withdrawn due to moderate Acne and moderate Weight increase (approximately 6.0 kg). All mentioned AEs were considered as causally related to the study drug. In the majority of subjects with AEs, "Dose not changed" was recorded as most relevant study drug action, namely, for 80 AEs in 23 subjects (76.7%) of the Test group and for 74 AEs in 25 subjects (89.3%) of the Reference group.

Overall, the proportions of AEs assessed as related and non-related to the study drugs were very similar in the 2 treatment groups: 44 AEs in 20 subjects (66.7%) of the Test group were considered as related versus 44 AEs in 21 subjects (75.0%) of the Reference group; 44 AEs in 20 subjects (66.7%) of the Test group were considered as non-related versus 42 AEs in 20 subjects (71.4%) of the Reference group. Note, that none of the AEs was considered as definitely drug-related.

A comparative look at the affected SOCs revealed the following distribution of drug-related AEs (by frequency):

- Nervous system disorders in 15 subjects (50.0%) of the Test group [Headache in 14 subjects, Dizziness in 2 subjects, and Migraine and Paresthesia in 1 subject each] versus 8 (28.6%) of the Reference group [Headache in 8 subjects and Migraine in 1 subject].
- Gastrointestinal disorders in 6 subjects (20.0%) of the Test group [Gastrointestinal disorder and Nausea in 2 subjects each, Abdominal pain in 1 subject, Abdominal pain lower in 1 subject, Vomiting in 1 subject] versus 7 (25.0%) of the Reference group [Nausea in 4 subjects, Abdominal pain lower in 2 subjects, and Abdominal discomfort and Diarrhea in 1 subject each].
- Reproductive system and breast disorders in 5 subjects (16.7%) of the Test group [Breast pain and Dysmenorrhea in 2 subjects each and Vaginal discharge in 1 subject] versus 2 (7.1%) of the Reference group [Breast swelling and Ovarian cyst in 1 subject each].
- Psychiatric disorders in 4 subjects (13.3%) of the Test group [Mood swings in 3 subjects and Libido decreased in 1 subject] versus 2 (7.1%) of the Reference group [Depressed mood, Libido decreased, Mood swings, and Nervousness in 1 subject each].
- Investigations in 2 subjects (6.7%) of the Test group [Weight decreased and Weight increased in 1 subject each] versus 7 (25.0%) of the Reference group [Weight increased in 6 subjects and Blood pressure diastolic increased in 1 subject].
- Skin and subcutaneous tissue disorders in 2 subjects (6.7%) of the Test group [Acne in 1 subject] versus 6 (21.4%) of the Reference group [Acne in 4 subjects and Hypertrichosis, Rash pruritic, and Skin disorder in 1 subject each].
- Infections and infestations in 1 subject (3.3%) of the Test group versus 2 (7.1%) of the Reference group.
- Metabolism and nutrition disorders in 1 subject (3.3%) of the Test group [Increased appetite in 1 subject]
- Vascular disorders in 1 subject (3.6%) of the Reference group [Hot flush in 1 subject].

In this open-label study, the following events were considered as adverse drug reactions (ADRs):

- In the Test group: Headache (in 14 subjects), Mood swings (in 3 subjects), Gastrointestinal disorder, Nausea, Dizziness, Breast pain, Dysmenorrhea, and Acne (each occurred in 2 subjects), Abdominal pain, Abdominal pain lower, Vomiting, Vaginal candidiasis, Weight decreased, Weight increased, Increased appetite, Migraine, Paresthesia, Libido decreased, and Vaginal discharge (each occurred in 1 subject).

- In the Reference group: Headache (in 8 subjects), Weight increased (in 6 subjects), Nausea and Acne (each occurred in 4 subjects), Abdominal pain lower (in 2 subjects), Abdominal discomfort, Diarrhea, Rash pustular, Vaginal infection, Blood pressure diastolic increased, Migraine, Depressive mood, Libido decreased, Mood swings, Nervousness, Breast swelling, Ovarian cyst, Hypertrichosis, Rash pruritic, Skin disorder, and Hot flush (each occurred in 1 subject).

The most frequent drug-related AE in both treatment groups was Headache [in 14 subjects (46.6%) of the Test group versus 8 (28.6%) of the Reference group]. Further notable differences between the treatment groups were seen in the occurrence of the following drug-related AEs: Weight increased [in 1 subject (3.3%) of the Test group versus 6 subjects (21.4%) of the Reference group], Nausea and Acne [each in 2 subjects (6.6%) of the Test group versus 4 subjects (14.3%) of the Reference group], and Mood swings (in 3 subjects [10.0%] of the Test group versus 1 subject [3.6%] of the Reference group).

The number of AEs of severe, moderate, and mild intensity in particular and of subjects who experienced them was very similar in the 2 treatment groups: 12 AEs in 8 subjects of the Test group (26.7%) were of severe intensity versus 9 AEs in 7 subjects of the Reference group (25.0%); 42 AEs in 18 subjects of the Test group (60.0%) were of moderate intensity versus 40 AEs in 16 subjects of the Reference group (57.1%); and 34 AEs in 19 subjects of the Test group (63.3%) and 36 AEs in 19 subjects of the Reference group (67.9%) were of mild intensity. The following AEs were assessed as severe:

- In the Test group: Abdominal pain lower, Gastrointestinal disorder, Nausea, Vomiting, Fatigue, Nasopharyngitis, Back pain, Cervicobrachial syndrome, Headache, Acne.
- In the Reference group: Cystitis, Nasopharyngitis, Rhinitis, Upper respiratory tract infection, Contusion, Headache, Migraine.

Concerning the outcome of AEs, 86 AEs in 24 subjects of the Test group (80.0%) and 84 AEs in 25 subjects (89.3%) of the Reference group were completely recovered/resolved. One AE (Joint injury) in a subject of the Test group and 1 AE (Contusion) in a subject of the Reference group was recovering/resolving; both AEs were non-related to the study treatment. One AE (Erythema) in a subject of the Test group remained recovered/resolved with residual effects; the AE was considered unlikely related to the study drug. During the study, only 1 subject of the Reference group did not recover from 1 AE considered unlikely drug-related (Blood fibrinogen increased).

Mean levels of all safety laboratory parameters (hematological, blood chemistry, liver enzymes and carbohydrate metabolism, and, coagulation parameters) assessed in the present study remained well within the normal range and generally stable. Only minor differences between the 2 treatment groups were seen. A noticeable difference was found concerning alanine aminotransferase (ALAT) values which decreased in the Test group at the end of treatment (Mean values ± SD: from 19.3 ± 12.6 to 13.9 ± 3.6 U/L) while remaining stable in the Reference group. This change was mainly attributable to the values obtained in 5 subjects with initially slightly and moderately increased ALAT values that all normalized at the end of study treatment.

Occasional laboratory abnormalities of small extent were seen in individual subjects of both treatment groups. Shift analyses between Screening and Final examination were unremarkable with balanced changes from normal to abnormal and from abnormal to normal values; the only exception was seen in ALAT values (as mentioned above). Only 1 clinically noteworthy abnormality was detected in 1 subject of the Reference group (the hemoglobin HbA_{1C} value at the Final examination was within the Alert range). The subject was withdrawn from study treatment due to high plasma glucose values following glucose challenge during the OGTT.

The mean systolic and diastolic blood pressure levels were comparable between the 2 treatment groups displaying relative lowering at the interim visits as compared to the Screening and Final visit; note, that in both treatment groups the values at the Final examination were similar to those obtained at Screening. The 2 treatment groups were also comparable regarding the frequency of increased blood pressure findings. Slightly elevated values of blood pressure (>140 and / or >90 mmHg) occasionally occurred in 2 subjects of the Test group (at 1 visit each) and systematically (throughout all visits) in 1 more subject. In this subject, the increased systolic blood pressure value at Screening was documented as baseline finding. Slightly increased blood pressure values were seen only occasionally in 4 subjects of the Reference group (at 1 visit each). Mean heart rate values were comparable between the 2 treatment groups at Screening. They remained stable in the Reference group throughout the study visits in contrast to slightly lower values in the Test group especially at the interim visits. The mean body weight and BMI during the study remained stable in both treatment groups.

Any abnormal findings of the physical and gynecological examinations (including breast palpation and transvaginal ultrasonography) were documented either as baseline findings or as AEs and thus included in the respective analyses. Cervical smear assessment at Screening provided normal findings in 100% of the subjects. At the Final visit, normal results were obtained in all subjects who completed the study treatment.

Bleeding patterns were analyzed on the basis of 2 reference periods of 90 days each covering 180 of all 196 days of study treatment (7 cycles x 28 days). The 2 study treatments were comparable with regard to the number of bleeding/spotting days and episodes as well as to the length of bleeding/spotting episodes. A slight prevalence of the number of bleeding/spotting days was seen during the 2nd reference period in subjects of the Reference group (median values were 12.5 days in the Test group versus 16.0 days in the Reference group). Conversely, the analysis of spotting-only days, episodes, and their duration revealed higher mean and median values in the Test group. The median number of spotting-only days reported during the 2nd reference period was 6.0 days in the Test group versus 2.0 days in the Reference group. During the 2nd reference period, spotting-only episodes were recorded in 14 subjects of the Test group versus 4 in the Reference group. Since the mean numbers of days with bleeding/spotting and numbers and length of bleeding/spotting episodes were similar in the 2 treatment groups, the higher proportion of spotting-only days in the Test group accounted for a lower blood loss.

Cycle control analysis based on the individual cycles of 28 days each revealed some differences between the 2 study drugs. The frequency of subjects with withdrawal bleeding ranged from 92.3% (Cycle 2) to 60.0% (Cycle 7) in the Test group versus 100% (Cycle 3) to 92.3% (Cycle 7) in the Reference group. The proportion of subjects in the Test group who experienced withdrawal bleeding was smaller in comparison to that in the Reference group. The mean length of withdrawal bleedings ranged from 5.7 ± 3.6 days (Cycle 2) to 3.4 ± 1.5 days (Cycle 7) in the Test group versus 5.2 ± 1.2 days (Cycle 5) to 4.5 ± 1.3 days (Cycle 7) in the Reference group. The frequency of subjects with heavy withdrawal bleedings was higher in the Reference group during Cycles 1 to 3 (1, 0, and 1 subjects of the Test group versus 4, 2, and 2 subjects of the Reference group); the remaining cycles were comparable concerning frequency of heavy withdrawal bleedings reported. The frequency of subjects with intracyclic bleeding episodes ranged from 30.8% to 8.0% in the Test group versus values from 14.8% to 0 in the Reference group. The higher frequency of subjects with intracyclic bleeding in the Test group, especially during Cycles 1 to 3, corresponded with the prevalence of spotting-only episodes in the Test group, as revealed by the reference period-based analysis of bleeding-patterns.

There were no positive results of pregnancy testing during the period of study treatment and no pregnancies occured. A pregnancy occurred only in a subject before start of study

treatment leading to exclusion from the study (subject belonged to the listing-only set, LOS).

Concomitant medication starting after the first administration of the study drugs was used by a generally comparable number of subjects in the 2 treatment groups with a slight prevalence of those in the Reference group. In particular, 19 subjects (63.3%) of the Test group versus 21 (75.0%) of the Reference group took concomitant medication. The most commonly administered types of medication were Salicylic acid and derivatives, Anilides, and Propionic acid derivatives; these were recorded in a comparable number of subjects of the 2 treatment groups.

Results Summary — Pharmacokinetics

Mean pharmacokinetic parameters of dienogest , estradiol , and estrone obtained in Cycle 4 and Cycle 7 after daily oral administration of SH T00685ID in 24 healthy female subjects are summarized in Table 8. These pharmacokinetic parameters correspond to the oral dose of 3 mg DNG and 2 mg EV as blood samples were collected during Day 14 to Day 21 of Cycles 4 and 7.

Table 8: Descriptive statistics of pharmacokinetic parameters of dienogest, estradiol, and estrone obtained in Cycle 4 and Cycle 7, after daily oral administrations of SH T00658ID in 24 healthy female subjects

Analyte	Parameter	Unit	Cycle 4	Cycle 7
Dienogest	Cmax [geometric mean (CV)]	ng/mL	81.4 (18.5%)	78.0 (17.0%)
	tmax [median (range)]	h	1 (1 - 2)	1 (1 - 2)
	AUC(0-24h) [geometric mean (CV)]	h*ng/mL^3	807 (22.6%)	820 (22.5%)
Estradiol	Cmax [geometric mean (CV)]	pg/mL	85.1 (59.6%)	72.0 (24.6%)
	tmax [median (range)]	h	4 (0 - 12)	4 (1 - 8)
	AUC(0-24h) [geometric mean (CV)]	h*pg/mL	1527 (60.2%)	1353 (27.9%)
Estrone	Cmax [geometric mean (CV)]	pg/mL	432 (55.6%)	439 (38.0%)
	tmax [median (range)]	h	4 (2 - 12)	4 (4 - 12)
	AUC(0-24h) [geometric mean (CV)]	h*pg /mL	6865 (60.6%)	7215 (44.3%)%)

LEGEND:
Cmax = Maximum serum concentration
tmax = Time to reach maximum concentration
AUC(0-24h) = Area under the concentration-time curve from 0 h data point up to 24 h post administration
* The asterisk represents a multiplication sign in the AUC units.

Conclusion(s)

In this study, the metabolic investigations showed no clinically relevant differences between the Test and the Reference drug and no marked changes between baseline and post-treatment levels of numerous metabolic parameters.

Under the Test treatment, the mean individual relative increase in the levels of the protective lipoprotein HDL-cholesterol and the decrease in the levels of the risk factor LDL-cholesterol from Baseline to the end of treatment during Cycle 7 were not statistically significant (at the 0.05 level). There were also no statistically significant differences between the effects of the two study drugs, even though a mean individual relative decrease was seen in HDL-cholesterol under the Reference treatment in contrast to the trend under the Test drug.

The mean levels of other serum lipids, hemostatic, thyroid, and carbohydrate metabolism parameters remained generally stable and comparable under both study treatments after 7 cycles. Nonetheless, slightly more pronounced changes became manifest in individual parameters under the Reference treatment. Comparing the absolute and relative changes in hemostatic parameters under both treatments, a stronger expression of the changes was seen in most parameters under the Reference drug. The same was true for the serum levels of SHBG and CBG. The mean serum levels of free and total testosterone and DHEA-S decreased under both study treatments remaining within the normal ranges. For all parameters, the observed changes were more pronounced in the Reference group.

Abnormal mean levels were found in both treatment groups in HDL2-cholesterol (decreased), PAI-1 antigen (decreased) at both Baseline and Cycle 7, and only in the Reference group in SHBG (increased) at the end of treatment (during Cycle 7). A trend toward increase (without exceeding the normal range) was seen in both treatment groups for thyroxine-binding globulin, total triiodothyronine, and total thyroxine; elevated levels of thyroxine-binding globulin and total triiodothyronine were more manifested in the Reference group.

Pharmacokinetics of DNG, E1, and E2 were comparable between Cycle 4 and Cycle 7 following the daily administration of SH T00658ID and therefore were cycle-independent.

Through the treatment cycles, the frequency of subjects experiencing withdrawal bleeding was lower and the length of withdrawal bleeding decreased under the Test treatment. Intracyclic bleeding, mainly spotting and light bleeding, was more frequent in the Test group in all cycles besides Cycle 7.

The safety profiles and the tolerability of both study treatments were similar. No safety issues unexpected for oral contraceptives occured during the study and no clinical concerns arose from the safety analyses.

Publication(s):	Junge W, Mellinger U, Parke S, Serrani M. Metabolic and haemostatic effects of estradiol valerate/dienogest, a novel oral contraceptive: a randomized, open-label, single-centre study. Clin Drug Investig. 2011;31(8):573-84.		
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Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Vital GmbH
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Sponsor in Germany	
Legal Entity Name	Bayer HealthCare AG
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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, Qlair, Qlairista
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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