

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-252, Original 1

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY ADDENDUM

NDA: 022252	Submission Dates: 7/2/2009, 10/15/2009, 12/21/2009, 4/27/2010, 5/4/2010, and 5/5/2010
Brand Name	Natazia [®]
Generic Name	Estradiol Valerate (EV) / Dienogest (DNG)
Reviewer	Chongwoo Yu, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Bayer Healthcare Pharmaceuticals
Relevant IND	IND 064809 and (b) (4)
Submission Type	505(b)(1) Original
Formulation, Strength, Regimen	Oral immediate release (IR) film-coated tablets; Once daily 4-phasic (plus placebo phase), 28 day, sequential regimen: Cycle Days 1-2: 3 mg EV Cycle Days 3-7: 2 mg EV/2 mg DNG Cycle Days 8-24: 2 mg EV/3 mg DNG Cycle Days 25-26: 1 mg EV Cycle Days 27-28: placebo
Indication	Prevention of pregnancy

The purpose of this addendum is to address the Clinical Pharmacology related labeling changes that the Sponsor has made according to the Division's recommendations (refer to original Clinical Pharmacology review of NDA 022252, DARRTS, 4/2/2010). Important changes include:

- **Highlights:** Insertion of "Women taking strong CYP 3A4 inducers (for example, carbamazepine, phenytoin, rifampicin, and St. John's wort) should not choose Natazia as their oral contraceptive due to the possibility of decreased contraceptive efficacy" under the WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS sections.
- **Full Prescribing Information:**
 - Insertion of "Women who take medications that are strong CYP 3A4 inducers (for example, carbamazepine, phenytoin, rifampicin, and St. John's wort) should not choose Natazia as their oral contraceptive while using these inducers and for at least 28 days after discontinuation of these

inducers due to the possibility of decreased contraceptive efficacy” in Sections 5.13, 7.1, 12.3, and 17.1.

- Drug Interaction study results are added in Sections 7.1 and 12.3
- Several places in Section 12 (CLINICAL PHARMACOLOGY) including the *Pharmacokinetics* subsection were revised accordingly to reflect the study findings.
- **FDA-Approved Patient Labeling:**
 - Insertion of “You should not choose Natazia as your birth control pill if you take carbamazepine, phenytoin, rifampicin or St. John's wort, because these medicines may make Natazia ineffective. Some other medicines and herbal products may make birth control pills less effective, including: Barbiturates, Bosentan, Felbamate, Griseofulvin, Oxcarbazepine, and Topiramate. Consider using another birth control method when you take medicines that may make birth control pills less effective” in the Section of *What Else Should I Know about Taking Natazia?*

The final agreed upon label between the Sponsor and the Division was submitted by the Sponsor on 5/5/2010 (Supporting document number: 33). There are no outstanding Clinical Pharmacology issues.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds NDA 022252 acceptable from a Clinical Pharmacology perspective.

1.2 Phase IV Commitments

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22252	ORIG-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	Natazia

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/s/

CHONGWOO YU
05/06/2010

MYONG JIN KIM
05/06/2010

CLINICAL PHARMACOLOGY REVIEW

NDA:	22-252
Type/Category:	505(b)(1)/Original
Brand Name:	(b) (4) (Pending)
Generic Name:	Estradiol Valerate (EV) / Dienogest (DNG)
Relevant INDs:	IND 64,809 and (b) (4)
Indication:	Primary - Prevention of pregnancy Secondary - Treatment of heavy and/or prolonged menstrual bleeding
Dosage Form:	Immediate release (IR) film-coated tablets
Route of Administration:	Oral
Dosing Regimen and Strength:	Once daily 4-phasic (plus placebo phase), 28 day, sequential regimen Cycle Days 1-2: 3 mg EV Cycle Days 3-7: 2 mg EV/2 mg DNG Cycle Days 8-24: 2 mg EV/3 mg DNG Cycle Days 25-26: 1 mg EV Cycle Days 27-28: placebo
Sponsor:	Bayer Healthcare Pharmaceuticals
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Reproductive and Urologic Products (DRUP)
Submission Date:	July 2, 2009, October 15, 2009, and December 21, 2009
Reviewer:	Chongwoo Yu, Ph.D.
Team Leader:	Myong-Jin Kim, Pharm.D.

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1 EXECUTIVE SUMMARY

The Sponsor submitted a 505(b)(1) application for (b) (4)™. The proposed primary indication is the prevention of pregnancy, and the secondary indication is the treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who choose to use an oral contraceptive (OC) as their method of contraception.

(b) (4)™ is a blister pack of 28 immediate release (IR) film-coated tablets containing two active substances, estradiol valerate (EV) and dienogest (DNG), in combination or EV alone. DNG, the progestin component of (b) (4)™, is considered to be a new molecular entity (NME) in the U.S. (b) (4)™ is proposed to be given orally once daily (i.e., at the same time of the day), in a 28-day sequential regimen, consisting of 4 phases with active tablets and one placebo phase. (b) (4)

(b) (4) A 28-day sequential regimen was considered to improve performance in both ovarian inhibition and in cycle control

The Sponsor submitted 32 Biopharmaceutical and Clinical Pharmacology studies including dose linearity, absolute bioavailability (BA), single and multiple-dose pharmacokinetics (PK), metabolism, food effect, and drug-drug interaction (DDI) studies together with 5 pivotal Phase 3 clinical studies to support the approval of (b) (4)™. The 5 pivotal Phase 3 clinical studies are Studies A39818/A35179 assessing the efficacy and safety of (b) (4)™ for the prevention of pregnancy (i.e., pivotal Pearl Index [PI] studies), Study A35644 (i.e., pivotal bleeding patterns and cycle control study) and Studies A29849/A42568 (i.e., dysfunctional uterine bleeding [DUB] study).

Out of the 32 biopharmaceutical and Clinical Pharmacology studies submitted, 22 studies containing relevant information acquired during the (b) (4) product development were reviewed. (b) (4)

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed NDA 22-252 submitted on July 2, 2009, October 15, 2009, and December 21, 2009. The overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language.

1.2 POSTMARKETING REQUIREMENTS / COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Formulation:

(b) (4) tablets were developed as IR film-coated containing two active substances, EV and DNG, in combination or EV alone. During the development of (b) (4), 4 additional formulations were investigated in clinical trials (b) (4)

(b) (4) These are not part of the to-be-marketed (TBM) dosing regimen. The final TBM formulation was used in all pivotal, Phase 3 clinical studies and supporting clinical pharmacology studies.

Absorption, Distribution, Metabolism, and Excretion (ADME)

EV

After an oral administration of EV, cleavage to 17 β estradiol (E2) and valeric acid takes place during absorption by the intestinal mucosa or in the course of the first liver passage. Approximately 38% of E2 is bound to sex hormone binding globulin (SHBG), 60% to albumin, and 2-3% circulates in free form in serum. The apparent volume of distribution is approximately 1.2 l/kg following intravenous (IV) administration. After an oral administration, only approximately 3% of the dose remains bioavailable as metabolically unchanged E2. E2 is then extensively metabolized to estrone (E1) (15%), estrone sulfate (E1S) (65%), and other compounds. CYP 3A family is known to play the most important role in E2 human metabolism. Together with the pre-systemic metabolism in the liver, about 95% of the orally administered dose becomes metabolized before entering the systemic circulation. E2 and its metabolites including E1, glucuronide and sulfate conjugates are mainly excreted in urine. The terminal half-life of E2 is approximately 14 hr.

DNG

The absolute BA of DNG is approximately 91%. PK dose linearity of DNG is observed following single dose oral administration of tablets over a dose range of 1-8 mg in Caucasian premenopausal women. The steady-state is reached after 4-5 days of daily dosing. The mean accumulation ratio for AUC_(0-24h) is determined to be 1.24. Approximately 10% of circulating DNG is present in the free form, with approximately 90% being bound non-specifically to albumin. DNG does not bind to SHBG and cortisol binding globulin (CBG). The volume of distribution at steady state is 46 liters after IV administration of 85 μ g ³H-DNG. DNG is extensively metabolized by the known pathways of steroid metabolism (i.e., hydroxylation and conjugation), with the formation of mostly inactive metabolites. CYP 3A4 was identified as the predominant enzyme catalyzing the metabolism of DNG. DNG is mainly excreted renally in the form of polar and hydrophilic metabolites. Unchanged DNG is the dominating fraction in plasma. The terminal half-life of DNG is approximately 11 hr.

Single Dose PK Parameters

Table 1: Comparison of Arithmetic Mean (SD) Serum PK Parameters following A Single Dose of 2 mg EV/3 mg DNG in Postmenopausal Caucasian Women under Fasted Condition (Study A29972, N=17)

	DNG	E2	E1
C _{max} (pg/ml) ^a	91.7 (15.3)	31.9 (8.7)	263 (88.5)
T _{max} (hr) ^b	1 (0.5-1.5)	6 (0.5-16.0)	6 (3.0-8.0)
AUC(0-24) (pg·hr/ml) ^c	794 (158)	570 (150)	3933 (1335)
AUC(0-48) (pg·hr/ml) ^c	964 (223)	892 (267)	5693 (2053)
AUC(0-∞) (pg·hr/ml) ^c	1024 (268)	944 (243) ^d	6494 (2190) ^e
t _{1/2} (hr)	11.3 (2.48)	13.8 (3.50)	17.2 (1.55)

^a ng/ml for DNG; ^b Median (range) for T_{max}; ^c ng·hr/ml for DNG; ^d N=2; ^e N=4

Steady-state PK Parameters

Table 2: Comparison of Arithmetic Mean (SD) Serum PK Parameters at Steady-state (on Day 24) following repeated doses of 2 mg EV/3 mg DNG on Days 8-24 of the 4-phasic, 28-day sequential regimen in Premenopausal Caucasian Women under Fasted Condition (Study A25711, N=15)

	DNG	E2	E1
C _{max} (pg/ml) ^a	85.2 (19.7)	70.5 (25.9)	483 (198)
T _{max} (hr) ^b	1.5 (1.0-2.0)	3 (1.5-12)	4 (3-12)
AUC(0-24) (pg·hr/ml) ^c	828 (187)	1323 (480)	7562 (3403)
t _{1/2} (hr)	12.3 (1.4)	NA	NA

^a ng/ml for DNG; ^b Median (range) for T_{max}; ^c ng·hr/ml for DNG

Drug-Drug Interactions

Effects of Other Drugs on Combined Hormonal Contraceptives

CYP 3A4 Induction: In Study A24058 investigating the effect of CYP 3A4 inducer rifampicin on EV/DNG PK, co-administration of 600 mg rifampicin daily with 2 mg EV/3 mg DNG tablets resulted in a 52 % decrease in the mean C_{max} and a 83% in the AUC(0-24) for DNG. Co-administration of rifampicin resulted in a 25% decrease in C_{max} and a 44% decrease in AUC(0-24) for E2. In order to ensure contraceptive reliability and sufficient cycle control, (b) (4) should not be co-administered with strong CYP 3A4 inducers such as

rifampicin, phenytoin, St. John's Wort, avasimibe, and carbamazepine. For women on chronic treatment with CYP 3A4 inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

CYP 3A4 Inhibition: In Study A30020 investigating the effect of CYP 3A4 inhibitors on EV/DNG PK, co-administration of 400 mg ketoconazole daily with 2 mg EV/3 mg DNG tablets resulted in a 94% increase in the mean C_{max} and a 186% increase in the AUC(0-24) for DNG. Co-administration of ketoconazole resulted in a 65% increase in C_{max} and a 57% increase in AUC(0-24) for E2. Co-administration of 1500 mg erythromycin daily with EV/DNG tablets resulted in a 33% increase in the mean C_{max} and a 62% increase in the AUC(0-24) for DNG. Co-administration of erythromycin resulted in a 51% increase in C_{max} and a 33% increase in AUC(0-24) for E2.

Effects of Combined Hormonal Contraceptives on other Drugs

An *in vitro* study with human liver microsomes showed that DNG did not inhibit CYP 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4. Although with 100 μ M DNG the metabolism of tolbutamide (CYP 2C9) and S-mephenytoin (CYP 2C19) was reduced to values of 69% and 63%, respectively, of the reference samples, DNG at lower concentrations closer to the clinical dose (i.e., < 20 μ M) did not show any inhibition (Study B463).

In a single-center, open-label, randomized, parallel design study in healthy young women aged 21-32 yr to evaluate the influence of oral contraceptives, Valette[®] (0.03 mg EE/2 mg DNG) or Minisiston[®] (0.03 mg EE/0.125 mg levonorgestrel [LNG]), on PK of CYP 3A4 substrate, nifedipine. Co-administration of 0.03 mg EE/2 mg DNG did not have any effect on 10 mg nifedipine PK (Study B463).

Bioequivalence (BE) was demonstrated between 2 mg DNG vs. 2 mg EV/2 mg DNG with mean ratio (%) of DNG AUC and C_{max} being 103.7% (90% CI: 97.0-111.0%) and 106.9% (90% CI: 100.3-114.0%), respectively. Combined administration of 2 mg DNG together with 2 mg EV had no effect on 2 mg DNG PK. Also, BE was demonstrated between 4 mg EV/4 mg DNG vs. 4 mg EV with mean ratio (%) of E2 AUC being 106.99% (90% CI: 95.70-119.62%). Combined administration of 4 mg EV together with 4 mg DNG had no effect on EV 4 mg PK (Study A07769).

Food Effect

The effect of food (i.e., high fat, high calorie meal) intake on the PK of EV and DNG was investigated in Study A29143 using the 2 mg EV/3 mg DNG combination tablet, as a representative tablet of (b) (4) containing the highest amount of DNG. In this food effect study conducted in healthy Caucasian postmenopausal women, the C_{max} of DNG was decreased by 28% under fed conditions and the C_{max} of E2 was increased by 23% (i.e., failure to meet the 90% CI under fed condition for both DNG and EV) while AUC values for both DNG and E2 remained within the BE acceptance range. However, this should not affect the food intake instructions since the results of the Phase 3 efficacy and safety studies support the administration of (b) (4) regardless of food intake. Therefore, no special recommendation concerning food intake is considered to be necessary.

Specific Populations

Renal / hepatic impairment patients: The Sponsor did not conduct studies in renal and/or hepatic impaired patients for use of EV/DNG in premenopausal women. Furthermore, severe liver diseases are already considered as contraindication for combined oral contraceptives (COC). Considering that DNG and E2 are both extensively metabolized and mainly excreted renally as inactive metabolites and that the target population is premenopausal women, usage of (b) (4) in patients with renal and/or hepatic impairment would be relatively small and therefore, is less of a concern. However, the product labeling should clearly state that studies in patients with renal and hepatic impairments were not conducted.

Pediatric Study waiver request: No studies were performed in post-pubertal adolescents < 17 yr. The Sponsor requested a waiver from the requirement to submit data adequate to assess the safety and efficacy of EV and DNG in post-pubertal adolescents < 17 yr. The Sponsor has 15 yrs of postmarketing experience with EV and DNG in the European Union (EU). In addition, the Sponsor plans to conduct a postmarketing surveillance study

in 50,000 women in US and EU assessing the risk of venous thromboembolism (VTE) of EV/DNG tablets compared with other COCs in a non-selected target population (i.e., age group not-specified). Considering the target population and the reasons above, the Sponsor's request is acceptable from the Clinical Pharmacology standpoint. The Agency's pediatric review committee (PeRC) granted the Sponsor's waiver request on March 3, 2010.

Thorough QT Study

A thorough QT study (Study A35653) was conducted to evaluate the potential of a fixed combination of 2 mg EV/3 mg DNG (highest combination dose strength) at steady-state to delay cardiac repolarization in healthy postmenopausal women, to monitor safety and to evaluate the PK of DNG, E2, and E1. This study also included a supra-therapeutic DNG dose (10 mg DNG, 5 x 2 mg tablets) arm. This study showed that DNG at a dose of 3 mg in combination with 2 mg EV and at a dose of 10 mg did not lead to QT/QTc prolongation. The DNG exposure achieved with the 10 mg oral dose showed 3.4-fold increase in AUC(0-24) and 3.5-fold increase in C_{max} compared to those following oral doses of the 2 mg EV/3 mg DNG combination tablet and demonstrated no effect on QT interval.

Bioanalytical Methods

Validated analytical methods were used in clinical studies. All of the PK studies performed during the development of (b) (4)TM tablets have used a radioimmunoassay (RIA) method for the measurement of DNG in human serum or plasma. For the quantitation of E2, E1, and E1S, validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods were used. Acceptance criteria and assay performance for each analyte were in compliance with the *Bioanalytical Method Validation Guidance* and therefore found to be acceptable.

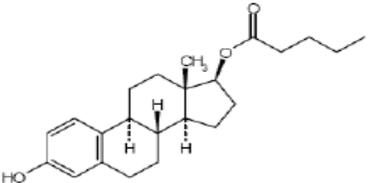
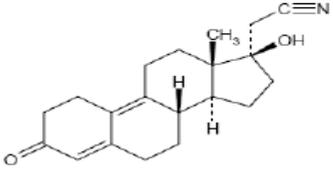
2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the active substances, DNG and EV?

Both active substances belong to the pharmacological class of steroid hormones, EV as a representative of an estrogen and DNG of a progestogen.

Table 1: Active Substances of (b) (4)

		
INN	Estradiol valerate	Dienogest
IUPAC / WHO	Estra-1,3,5(10)-triene-3,17β-diol-17-valerate (WHO)	17α-Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile (IUPAC)
Company codes	ZK 00005104, EV	ZK 00037659, DNG
Molecular formula	C ₂₃ H ₃₂ O ₃	C ₂₀ H ₂₅ N O ₂
Molecular weight	356.50	311.43
Appearance	White to almost white crystalline powder or colourless crystals	White to off-white crystalline powder

DNG, the progestin component of (b) (4) tablets, is a 19-norprogestin with progesterone receptor selectivity, leading to specific progestational action and to effective transformation of the endometrium. DNG is currently marketed in combination with EE as COC and in combination with EV as hormonal therapy (HT) in several European countries. DNG is considered to be an NME in the US.

EV is a prodrug of the natural human 17β-estradiol. The estrogenic component used in (b) (4) is different from the estrogens usually used in COC which are the synthetic estrogens, EE or its prodrug mestranol, both containing an ethinyl group on the 17α-position. After intake, EV is rapidly hydrolyzed pre-systemically into E2, which is the major natural estrogen in humans, and valeric acid. Currently, EV is approved only as an injectable product (Delestrogen®) in the US (NDA 09-402, approved on July 15, 1954 for treatment of moderate to severe vasomotor symptoms or vulvar and vaginal atrophy symptoms associated with the menopause).

2.1.2 What is the regulatory history of this product?

Prior to the submission of this NDA, the initial IND for this EV/DNG COC was filed under IND 64,809 on November 17, 2004 for the indication of prevention of pregnancy. Subsequently, IND (b) (4) was submitted on (b) (4) for the treatment of DUB in women desiring oral contraception.

2.1.3 What clinical data is submitted to support the approval of (b) (4)™?

The Sponsor submitted 32 Biopharmaceutical and Clinical Pharmacology studies including dose linearity, absolute BA, single and multiple-dose PK, metabolism, food effect, and DDI studies together with 5 pivotal Phase 3 clinical studies to support the approval of (b) (4). Sponsor submitted 5 safety and efficacy Phase 3 clinical studies (i.e., Studies A39818 and A35179 [pivotal PI studies]; A35644 [pivotal bleeding patterns and cycle control study]; A29849 and A42568 [DUB study]). The efficacy of (b) (4) in women with a body mass index (BMI) of > 30 kg/m² was not evaluated.

2.1.4 What is unique about (b) (4) and are there any other EV/DNG combination products marketed in other countries?

(b) (4) will provide the first COC containing EV instead of EE in the US. The (b) (4) tablets are currently approved for marketing under the trade name Qlaira® in 26 EU Member Countries (initial approval on November 3, 2008) and Australia with the same dosing regimen for the indication of prevention of pregnancy. Another DNG-containing COC (with EE) was approved on February 14, 1995 in Germany under the trade name Valette®. This product is currently marketed in 20 countries. In all countries except in Australia, it is marketed as 21 tablets containing 0.03 mg EE and 2 mg DNG (7 days of the 28-days regimen are tablet-free); in Australia it is marketed as 21 active tablets plus 7 placebo tablets. EV and/or DNG are also marketed for indications other than the prevention of pregnancy (e.g., Climodien®: 2 mg EV/2 mg DNG, 28 tablets, treatment of certain menopausal symptoms such as night sweats, hot flushes, vaginal dryness, and burning or itching) outside of US.

2.2 General Clinical Pharmacology and Biopharmaceutics

2.2.1 What Clinical Pharmacology and Biopharmaceutics related information have been submitted to support this NDA?

The original submission contained the following:

- Draft labeling in PLR format
- Information on the composition of drug products used in the clinical studies
- Full clinical study report of the 32 Biopharmaceutical and Clinical Pharmacology studies
- Bioanalytical study reports and method validation reports
- Request of waiver for pediatric studies
- The original submission contained the following:

2.2.2 What is the mechanism of action?

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

2.2.3 What are the dosing regimen and instructions?

(b) (4)™ should be taken orally, once daily, at the same time everyday with the following 4-phasic (plus placebo phase), 28-day, sequential regimen:

- Cycle Days 1-2: EV 3 mg
- Cycle Days 3-7: EV 2 mg + DNG 2 mg
- Cycle Days 8-24: EV 2 mg and DNG 3 mg
- Cycle Days 25-26: EV 1 mg
- Cycle Days 27-28: placebo

The 4-phasic sequential regimen is aimed at ensuring sufficient estrogen concentrations in the first half of the cycle, the period during which endometrial proliferation is promoted under the influence of estrogens, as estrogen levels are low at the beginning of the follicular phase.

2.2.4 Is the proposed dosing regimen and strength acceptable?

Nearly all marketed COCs contain EE as estrogen component, with daily dosages ranging between 0.02 and 0.05 mg. The success of EE is based on metabolic stability and a favorable PK profile leading to good cycle control. During the development of COCs over the last decades, EE has been reduced step-wise from initially >

0.050 mg to 0.015 mg without impairing contraceptive efficacy. This reduction is in line with the knowledge that lower EE doses lead to lower impact on metabolism parameters and enzyme synthesis in the liver. However, the reduction of the EE dose has also led to less favorable bleeding control in susceptible cases. Efforts have been made to replace EE by either natural estrogens such as E2 or their prodrugs such as EV to offer an alternative in COCs, as the endogenous estrogens are known to have a low liver estrogenicity (i.e., lower impact on enzyme synthesis in the liver) (Lindberg *et al.*, 1989; Wiegratz *et al.*, 2004). However, use of the monophasic attempts failed due to insufficient bleeding control (Csemiczky *et al.*, 1996). As DNG showed no anti-estrogenic activity (Oettel *et al.*, 1995), Sponsor selected DNG as the progestin component of this product hoping to reduce the bleeding irregularities (Hoffmann *et al.*, 1998). As monophasic EV/progestin or E2/progestin regimens provided sufficient ovulation suppression, but did not provide sufficient bleeding control, the Sponsor took the approach to modify the dosing regimen.

In the clinical development of this product, several different dosing regimens and strengths were explored. The proposed 4-phasic sequential regimen is aimed at ensuring sufficient estrogen concentrations in the first half of the cycle, the period during which endometrial proliferation is promoted under the influence of estrogens, as estrogen levels are low at the beginning of the follicular phase.

In Study B690, it was demonstrated that 2 mg EV can effectively inhibit ovulation and provide sufficient cycle control. In Studies AZ94, A00984, and A14191, a DNG dose of 2-3 mg/day was sufficient to inhibit ovulation and provide contraceptive reliability. For example, in a multi-center, open-labeled, uncontrolled study (Study AZ94) to investigate the efficacy and safety of a 4-phasic oral contraceptive SH T658I containing EV and DNG over 20 cycles in 1,600 healthy female volunteers, an unadjusted PI of 5.3 was obtained when DNG dose was decreased using the following regimen:

- Cycle Days 1-3: EV 3 mg
- Cycle Days 4-7: EV 2 mg + DNG 1 mg
- Cycle Days 8-23: EV 2 mg and DNG 2 mg
- Cycle Days 24-25: EV 1 mg
- Cycle Days 26-28: placebo

Table 2: Pearl Index obtained in the full-analysis set (FAS) population (Study AZ94)

Patient set / subset	No. of cycles	No. of cycles with back-up contraception	No. of pregnancies after start of study medication	Pearl Index	No. of pregnancies due to subject failure	Pearl Index
				Unadjusted		Adjusted
Total	12,125	342	48	5.3	9	4.3
≤ 29 years of age	5,563	192	23	5.6	5	4.4
> 29 years	6,562	150	25	5.1	4	4.3

Study AZ94 showed that DNG doses of 1-2 mg is not sufficient to maintain efficacy and when insufficient DNG dose is given efficacy can be significantly affected.

In Study A25364, the TBM dosing regimen was found to provide effective ovulation inhibition and was selected for further clinical development. See Section A.1.13 for details of the study information.

Due to the fact that the dose was decided based on the clinical efficacy end point (i.e., PI), these studies exploring different dosing regimens and strengths were not reviewed in detail by this reviewer. However, per clinical reviewer, Dr. Gerald Willett, the outcomes of the Phase 3 clinical studies with the proposed 4-phasic EV/DNG dosing regimen supports the safety and efficacy for the contraception indication. Therefore, the proposed dosing regimen and strength is found to be acceptable. (b) (4)

2.2.5 Does this drug prolong the QT or QTc interval?

A thorough QT study (Study A35653) was conducted to evaluate the potential of a fixed combination of 2 mg EV/3 mg DNG (i.e., highest combination dose strength) at steady-state to delay cardiac repolarization in healthy postmenopausal women, to monitor safety, and to evaluate the PK of DNG, E2, and E1. This study also included a supra-therapeutic DNG dose (i.e., 10 mg DNG, 5 x 2 mg DNG tablets) arm. This study showed that DNG at a dose of 3 mg in combination with 2 mg EV and at a dose of 10 mg did not lead to QT/QTc prolongation. As shown in Table 2, the DNG exposure achieved with the 10 mg oral dose showed 3.4-fold increase in AUC(0-24) and 3.5-fold increase in C_{max} compared to the therapeutic dose and demonstrated no effect on QT interval. Please refer to the QT-Interdisciplinary Review Team's (QT-IRT) thorough QT study review in DARRTS dated March 15, 2010 for details of the thorough QT study.

Table 3: Arithmetic Mean (SD) PK Parameters of DNG, E2, and E1 obtained in Healthy Postmenopausal Women after Repeated Daily Oral Administration of 10 mg DNG or 2 mg EV/3 mg DNG as a Fixed Combination (Study A35653)

Analyte	Parameter	2 mg EV / 3 mg DNG (Day 4; N=50)	10 mg DNG (Day 4; N=48)
DNG	C_{max} (ng/ml)	108 (18.6)	380 (67.7)
	T_{max} (hr)	1.57 (1.03-4.08)	1.55 (0.54-3.08)
	AUC(0-24) (ng·hr/ml)	1081 (230)	3680 (662)
E2	C_{max} (pg/ml)	70.3 (22.7)	-
	T_{max} (hr)	4.08 (0.56-12.08)	-
	AUC(0-24) (pg·hr/ml)	1284 (517)	-
E1	C_{max} (pg/ml)	456 (142)	-
	T_{max} (hr)	6.08 (3.08-6.29)	-
	AUC(0-24) (pg·hr/ml)	7948 (2964)	-

Median (range) for T_{max}

2.2.6 What are the PK parameters of DNG, E2, and E1 following single and multiple doses and highlights of their PK profiles?

Single Dose PK Parameters

Table 4: Comparison of Arithmetic Mean (SD) Serum PK Parameters following A Single Dose of 2 mg EV/3 mg DNG Combination Tablet in Postmenopausal Caucasian Women under Fasted Condition (Study A29972, N=17)

	DNG	E2	E1
C_{max} (pg/ml) ^a	91.7 (15.3)	31.9 (8.7)	263 (88.5)
T_{max} (hr) ^b	1 (0.5-1.5)	6 (0.5-16.0)	6 (3.0-8.0)
AUC(0-48) (pg·hr/ml) ^c	964 (223)	892 (267)	5693 (2053)
AUC(0-∞) (pg·hr/ml) ^c	1024 (268)	944 (243) ^d	6494 (2190) ^c
$t_{1/2}$ (hr)	11.3 (2.48)	13.8 (3.50)	17.2 (1.55)

^a ng/ml for DNG; ^b Median (range) for T_{max} ; ^c ng·hr/ml for DNG; ^d N=2; ^e N=4

Figure 1: Linear and Semi-logarithmic Mean Concentrations (\pm SD) of DNG after Single Oral Administration of Two Different Tablet Strengths (SH T00658GA, 2 mg EV/2 mg DNG and SH T00658 M, 2 mg EV/3 mg DNG, respectively) Compared to a Suspension SH P00658MA Containing 2 mg EV/3 mg DNG in Postmenopausal Women (Study A29972, N=17)

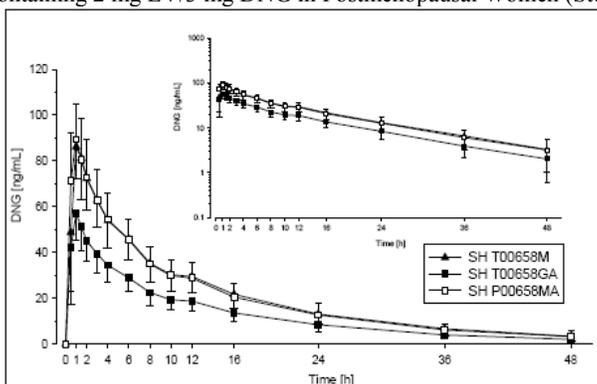


Table 5: Arithmetic Mean (SD) PK Parameters of DNG Following Oral Administration of Two Different Tablet Strengths (SH T00658GA, 2 mg EV/2 mg DNG and SH T00658 M, 2 mg EV/3 mg DNG, respectively) Compared to a Suspension SH P00658MA 2 mg EV/3 mg DNG in Postmenopausal Women (N=17)

Parameter	SH T00658GA	SH T00658M	SH P00658MA
C _{max} (ng/ml)	59.5 (10.2)	91.7 (15.3)	92.8 (17.4)
T _{max} (hr)	1 (0.5-1.5)	1 (0.5-1.5)	1 (0.5-1.5)
AUC(0-tlast) (ng·hr/ml)	613 (142)	964 (223)	956 (224)
AUC (ng·hr/ml)	648 (166)	1024 (268)	1014 (268)
t _{1/2} (hr)	11.0 (2.02)	11.3 (2.48)	11.2 (2.66)

SH T00658GA: Coated tablet containing 2 mg EV/2 mg DNG

SH T00658M: Coated tablet containing 2 mg EV/3 mg DNG

SH P00658MA: Suspension for oral use containing 2 mg EV/3 mg DNG

AUC: Area under the serum concentration-time curve from time of administration (t=0) extrapolated to infinity

Median (range) for T_{max}

Following a single dose administration of SH T00658M tablet (i.e., 2 mg EV/3 mg DNG TBM combination tablet) and SH P00658MA suspension (i.e., 2 mg EV/3 mg DNG), mean concentration time profiles and calculated PK parameters of DNG were comparable. As expected, due to the dose differences of DNG contained in the SH T00658GA tablet (i.e., 2 mg EV/2 mg DNG TBM combination tablet), comparison of the AUC and C_{max} values of this formulation showed approximately 1/3 lower values compared to the formulations containing 3 mg DNG. This finding is in line with the conclusion that DNG demonstrates dose linear PK in the range of 1-8 mg (Study B306).

Figure 2: Linear and Semi-logarithmic Mean Concentrations (± SD) of E2 After a Single Oral Administration of Tablets with Different DNG Strengths (SH T00658GA, 2 mg EV/ 2 mg DNG and SH T00658 M, 2 mg EV/3 mg DNG, respectively) Compared to a Suspension SH P00658MA 2 mg EV/3 mg DNG in Postmenopausal Women (Study A29972, N=17)

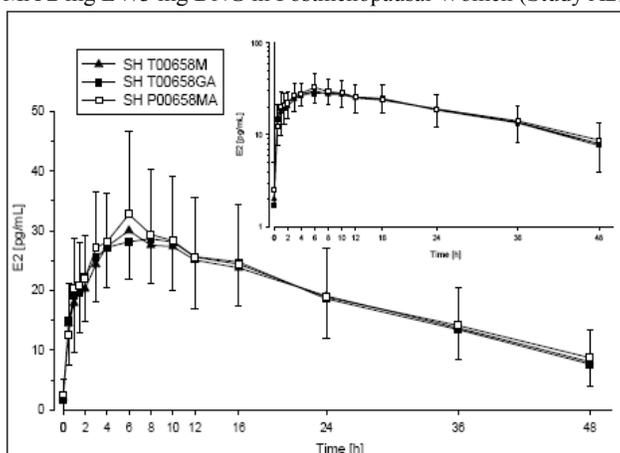


Table 6: Arithmetic Mean (SD) PK Parameters of E2 After a Single Oral Administration of Tablets with Different DNG Strengths (SH T00658GA, 2 mg EV/2 mg DNG and SH T00658 M, 2 mg EV/3 mg DNG, respectively) Compared to a Suspension SH P00658MA Containing 2 mg EV/3 mg DNG in Postmenopausal Women (N=17)

Parameter	SH T00658GA	SH T00658M	SH P00658MA
C _{max} (pg/ml)	32.4 (7.98)	31.9 (8.7)	36.0 (14.2)
T _{max} (hr)	6 (1.0-12.0)	6 (0.5-16.0)	6 (2.0-12.0)
AUC(0-tlast) (pg·hr/ml)	891 (249)	892 (267)	921 (334)
AUC (pg·hr/ml)	991 (169) ^a	944 (243) ^b	1134 (224) ^c
t _{1/2} (hr)	15.4 (2.05) ^a	13.8 (3.50) ^b	15.1 (0.785) ^c

SH T00658GA: Coated tablet containing 2 mg EV/2 mg DNG

SH T00658M: Coated tablet containing 2 mg EV/3 mg DNG

SH P00658MA: Suspension for oral use containing 2 mg EV/3 mg DNG

AUC: Area under the serum concentration-time curve from time of administration (t=0) extrapolated to infinity

Median (range) for T_{max}

^a N=6; ^b N=2; ^c N=3

The AUC and C_{max} values of E2 after oral administration of the 3 different formulations with same E2 strengths were comparable although the suspension formulation, SH P00658MA, appears to have higher values.

Figure 3: Linear and Semi-logarithmic Mean Concentrations (\pm SD) of E1 After a Single Oral Administration of Tablets with Different DNG Strengths Formulations (SH T00658GA, 2 mg EV/2 mg DNG and SH T00658 M, 2 mg EV/3 mg DNG, respectively) Compared to a Suspension SH P00658MA, 2 mg EV/3 mg DNG in Postmenopausal Women (Study A29972, N=17)

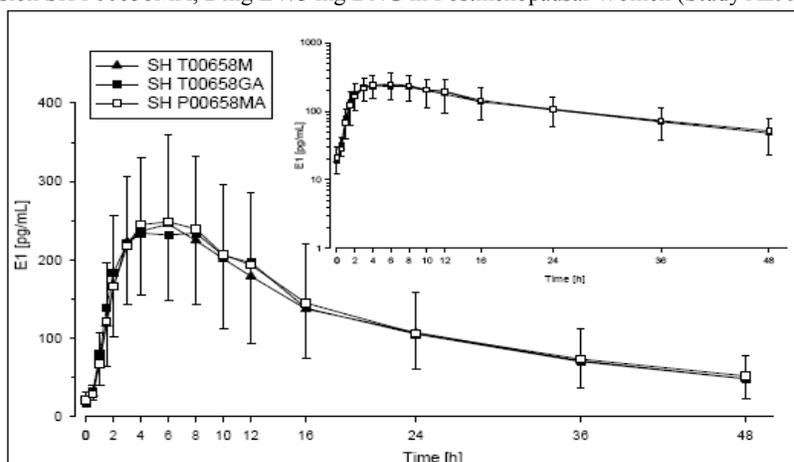


Table 7: Arithmetic Mean (SD) PK Parameters of E1 After a Single Oral Administration of Tablets with Different DNG Strengths (SH T00658GA, 2 mg EV/2 mg DNG and SH T00658 M, 2 mg EV/3 mg DNG, respectively) Compared to a Suspension SH P00658MA, 2 mg EV/3 mg DNG in Postmenopausal Women (N=17)

Parameter	SH T00658GA	SH T00658M	SH P00658MA
C_{max} (pg/ml)	262 (97)	263 (88.5)	270 (108)
T_{max} (hr)	4 (2.0-12.0)	6 (3.0-8.0)	6 (3.0-8.0)
AUC(0-tlast) (pg·hr/ml)	5742 (2258)	5693 (2053)	5873 (2584)
AUC (pg·hr/ml)	6982 (3139) ^a	6494 (2190) ^b	7160 (3139) ^a
$t_{1/2}$ (hr)	16.3 (1.47) ^a	17.2 (1.55) ^b	16.3 (1.07) ^a

SH T00658GA: Coated tablet containing 2 mg EV/2 mg DNG

SH T00658M: Coated tablet containing 2 mg EV/3 mg DNG

SH P00658MA: Suspension for oral use containing 2 mg EV/3 mg DNG

AUC: Area under the serum concentration-time curve from time of administration (t=0) extrapolated to infinity

Median (range) for T_{max}

^a N=6; ^b N=4

The AUC and C_{max} values of E1 after oral administration of the 3 different formulations were comparable although the suspension formulation, SH P00658MA, appears to have higher values.

Steady-state PK Parameters

Table 8: Arithmetic Mean (SD) Serum PK Parameters at Steady-state (on Day 24) Following Repeated Doses of 2 mg EV/3 mg DNG Combination Tablets on Days 8-24 of the 28-day 4-phasic Sequential Regimen in Premenopausal Caucasian Women Under Fasted Condition (Study A25711, N=15)

	DNG	E2	E1
C_{max} (pg/ml) ^a	85.2 (19.7)	70.5 (25.9)	483 (198)
T_{max} (hr) ^b	1.5 (1.0-2.0)	3 (1.5-12)	4 (3-12)
AUC(0-24) (pg·hr/ml) ^c	828 (187)	1323 (480)	7562 (3403)
$t_{1/2}$ (hr)	12.3 (1.4)	NA	NA

^a ng/ml for DNG; ^b Median (range) for T_{max} ; ^c ng·hr/ml for DNG

Steady-state PK of DNG

Figure 4: Mean (\pm SD) Concentration-Time Curve of DNG (ng/ml) Following Daily Oral Dose of (b) (4)TM in 15 Healthy Female Subjects (Study A25711)

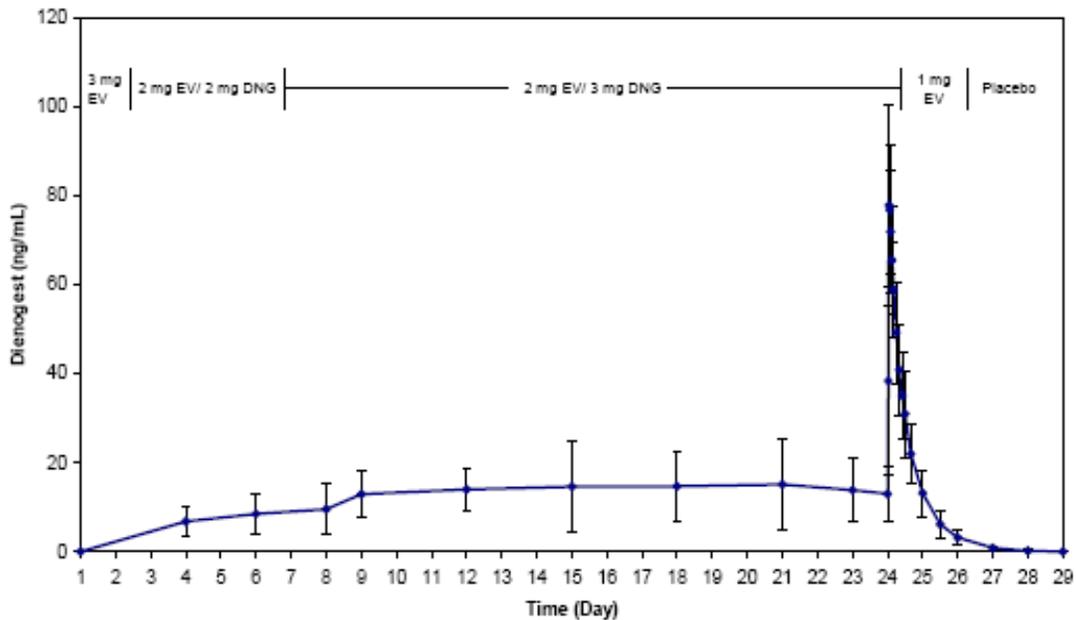
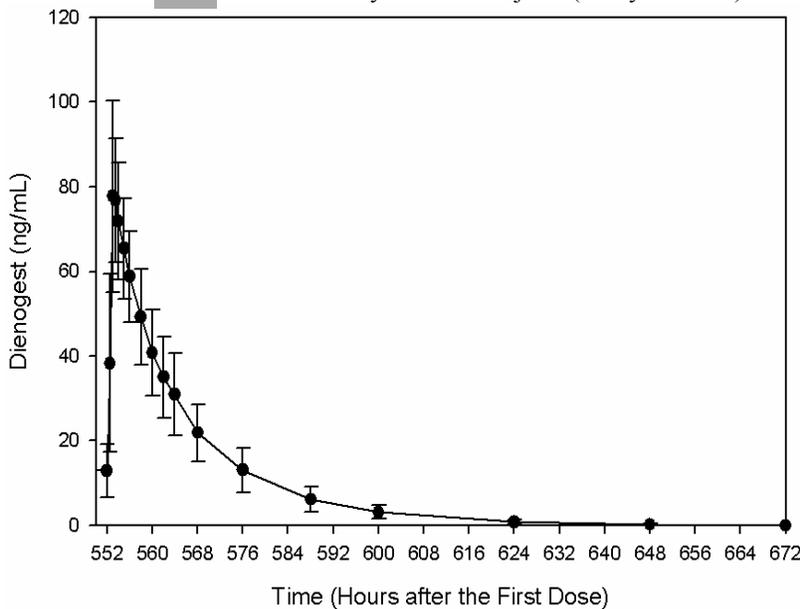


Figure 5: Mean (\pm SD) Concentration-Time Curve of DNG (ng/ml) on Day 24 Following Daily Oral Dose of (b) (4)TM in 15 Healthy Female Subjects (Study A25711)



It was noted that there is a graphical error on the DNG concentrations of Days 1-2 in Figure 4 (i.e., there was no DNG given on Days 1-2). Steady-state of DNG was reached within 4-5 days of dosing at each dose sequence. 2 mg DNG dose was started on Day 3 and the steady state was reached by pre-dose on Day 8 (5 days later). 3 mg DNG dose was started on Day 8 and steady-state was reached by Day 12 (4 days later). 3 mg DNG steady-state was reached earlier since 3 mg DNG dose sequence was started at the steady-state of 2 mg DNG sequence. This was in line with the observations in Study B276 where DNG steady-state concentrations were reached in about 4 days following the first dose of 2 mg DNG. The co-administration of 2 mg EV (on Days 3-24) did not alter the time to reach DNG steady-state. DNG steady-state PK following administration of 2 mg EV/3 mg DNG in different studies are summarized below.

Table 9: Comparison of Arithmetic Mean (SD) DNG Steady-state PK Parameters Following Administration of 2 mg EV/3 mg DNG Combination Tablets under Fasted Condition in Caucasian Women

	Study A25711	Study A30020
Population	Premenopausal (N=15)	Postmenopausal (N=12)
Regimen (Day)	Steady-state (Day 24)	Steady-state (Day 7)
C _{max} (ng/ml)	85.2 (19.7)	88.4 (13.3)
T _{max} (hr)	1.5 (1.0-2.0)	1.0 (0.5-2.0)
AUC(0-24) (ng·hr/ml)	828 (187)	827 (222)
t _{1/2} (hr)	12.3 (1.4)	NA

Median (range) for T_{max}

In Study A25711, SH T00658M (2 mg EV/3 mg DNG) was administered during the Period of Day 8-24 of the 28-day regimen

In Study A30020, SH T00658M (2 mg EV/3 mg DNG) was administered daily for 7 days (Day 1-7)

In a cross-study comparison, the DNG PK parameters were similar in premenopausal and postmenopausal women.

Steady-state PK of E2

Figure 6: Mean (± SD) Concentration-Time Curve of E2 (pg/ml) Following Daily Oral Dose of (b) (4)TM in 15 Healthy Female Subjects (Study A25711)

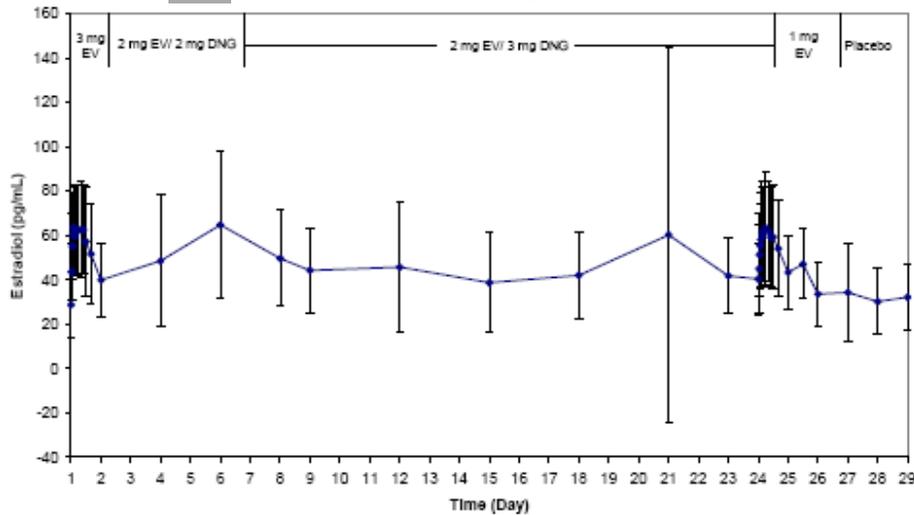
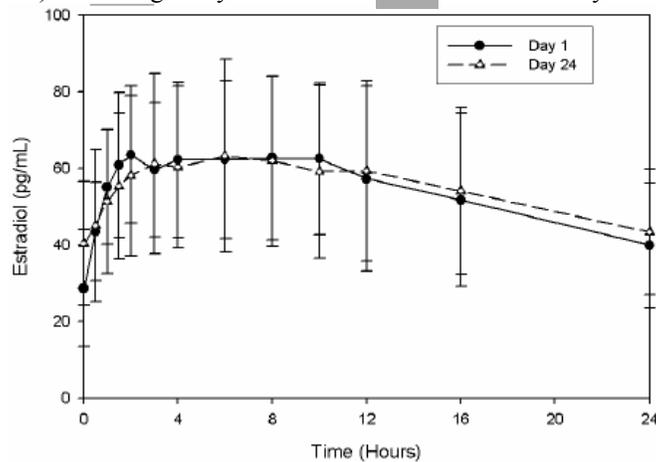


Figure 7: Mean (± SD) Concentration-Time Curve of E2 (pg/ml) on Days 1 (Single dose of 3 mg EV) and 24 (Steady-state following 2 mg EV/3 mg DNG) Following Daily Oral Dose of (b) (4)TM in 15 Healthy Female Subjects (Study A25711)



E2 steady-state PK following administration of 2 mg EV/3 mg DNG in different studies are summarized below.

Table 10: Comparison of Arithmetic Mean (SD) E2 Steady-state PK Parameters Following Administration of SH T00658M (2 mg EV/3 mg DNG) Under Fasted Conditions in Caucasian Women

	Study A25711	Study A30020
Population	Premenopausal (N=15)	Postmenopausal (N=12)
Regimen (Day)	Steady-state (Day 24)	Steady-state (Day 7)
C _{max} (ng/ml)	70.5 (25.9)	74.4 (31.5)
T _{max} (hr)	3 (1.5-12)	6 (2-16)
AUC(0-24) (ng·hr/ml)	1323 (480)	1328 (614)

Median (range) for T_{max}

In Study A25711, SH T00658M (2 mg EV/3 mg DNG) was administered during the Period of Day 8-24 of the 28-day regimen

In Study A30020, SH T00658M (2 mg EV/3 mg DNG) was administered daily for 7 days (Day 1-7)

A cross-study comparison showed that comparable E2 PK parameters were obtained between premenopausal and postmenopausal women at steady-state following daily dose of the same formulation under fasted condition.

Steady-state PK of E1

Figure 8: Mean (± SD) Concentration-Time Curve of E1 (pg/ml) Following Daily Oral Dose of (b) (4)TM in 15 Healthy Female Subjects (Study A25711)

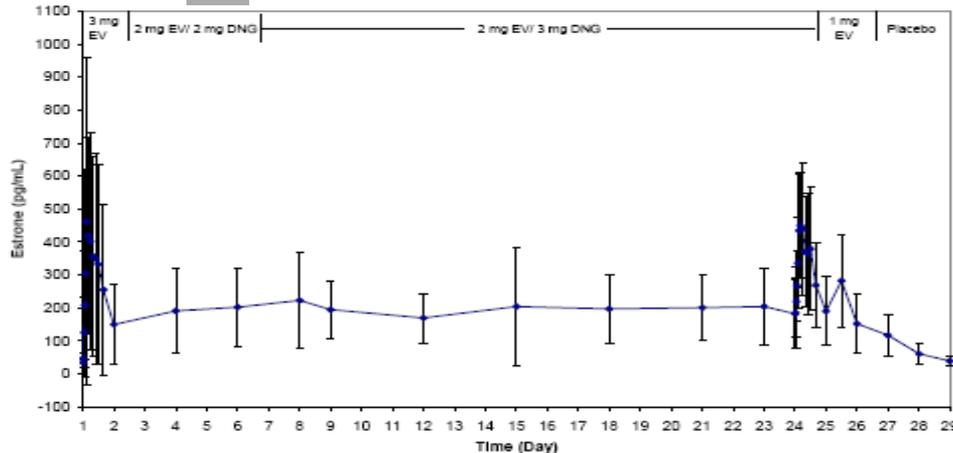


Figure 9: Mean (± SD) Concentration-Time Curve of E1 (pg/ml) on Days 1 and 24 Following Daily Oral Dose of (b) (4)TM in 15 Healthy Female Subjects (Study A25711)

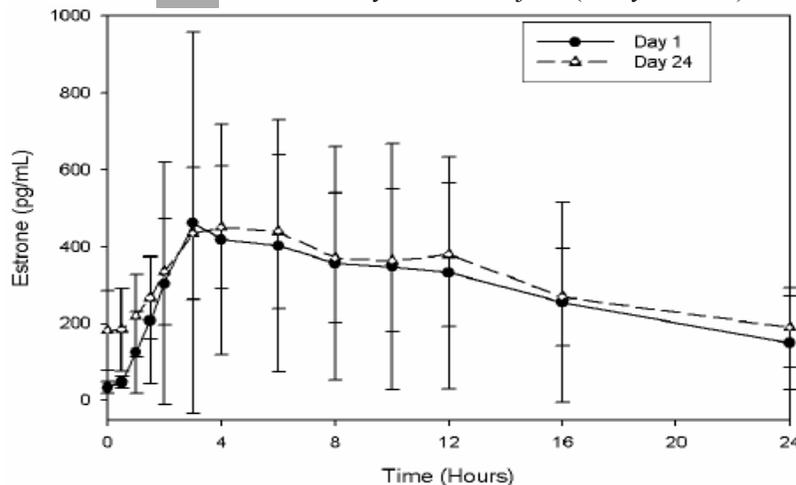


Table 11: Arithmetic Mean (SD) Serum E1 Steady-state PK Parameters (N=15)

	Day 24
AUC(0-24) (pg·hr/ml)	7562 (3403)
C _{max} (pg/ml)	483 (198)
T _{max} (hr) ^a	4 (3-12)

^a Median (range) for T_{max}

2.2.7 Was the PK dose linearity established for DNG?

As shown in Figure 10 and 11, the PK dose linearity of DNG AUC and C_{max} was observed following a single oral dose over the range of 1-8 mg in Caucasian premenopausal women (Study B306) as well as over the dose range of 0.5-2 mg in Japanese premenopausal women (Study A00681).

Figure 10: Relationship Between DNG Dose and Mean AUC(0-∞) Following Single Dosing in Premenopausal Women (Studies B306 [in Caucasian] and A00681 [in Japanese])

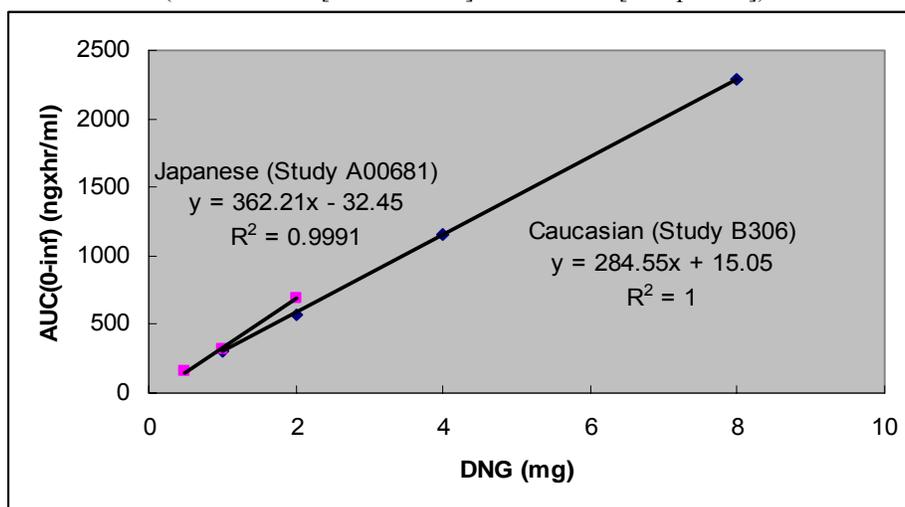
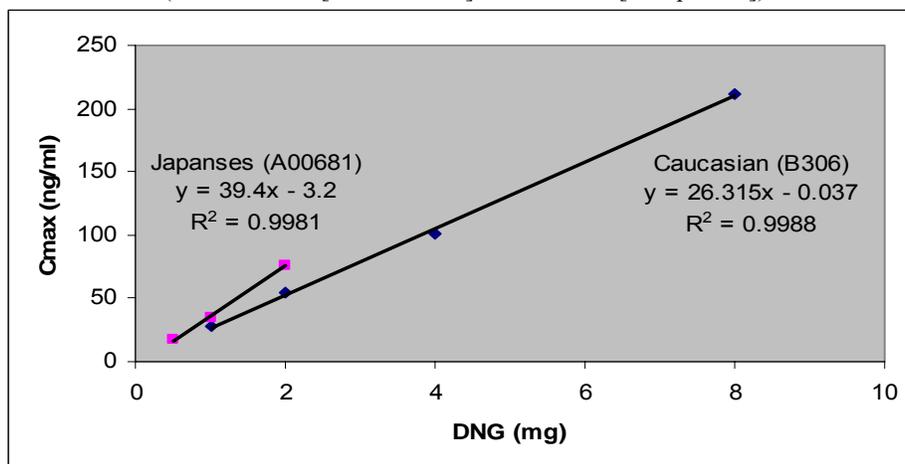


Figure 11: Relationship Between DNG Dose and Mean C_{max} Following Single Dosing in Premenopausal Women (Studies B306 [in Caucasian] and A00681 [in Japanese])



2.2.8 What are the characteristics of drug absorption?

EV

After oral administration, cleavage to E2 and valeric acid takes place during absorption by the intestinal mucosa or in the course of the first liver passage (Duesterberg and Nishino, 1982). This gives rise to E2 and its metabolites E1, E1S, and other compounds.

DNG

The absolute BA of DNG was investigated in healthy young men following the oral administration of a film-coated tablet containing 2 mg DNG (SH T00660AA) and the IV administration of a solution containing 2 mg DNG. The absolute BA of DNG was approximately 91% (Study B501). PK dose linearity of DNG was established following a single dose oral administration of tablets over a dose range of 1-8 mg in Caucasian premenopausal women (Study B306) and over a dose range of 0.5-2 mg in Japanese premenopausal women (Study A00681). Steady-state is reached after 4-5 days of dosing at each dose sequence (Study A25711 and Study B276). The mean accumulation ratio for AUC_(0-24h) was determined to be 1.24 (Study B276).

2.2.9 What are the characteristics of drug distribution?

EV

Approximately 38% of E2 is bound to SHBG, 60% to albumin and 2-3% circulates as free form in serum and the apparent volume of distribution is approximately 1.2 l/kg following IV administration (Kuhnz *et al.*, 1999).

DNG

Protein binding of DNG *in vitro* in fresh plasma was approximately 93.5-94.5% (Study A00560). DNG does not bind to the specific transport proteins SHBG and CBG (Study B427). It was noted that the mean SHBG concentrations and CBG in serum increased during daily treatment with (b) (4)TM tablets in healthy fertile women (Study A25711). This might be due to estrogen that is known to increase binding globulin levels. Approximately 10% of circulating DNG is present in the free form, with approximately 90% being bound non-specifically to albumin (Klinger *et al.*, 2001). The volume of distribution at steady state of DNG is 46 liters following IV administration of 85 µg ³H-DNG (Study B476).

Table 12: Relative Binding Affinities (RBA) of DNG in Comparison to Other Progestins for Binding to Human SHBG and CBG (Study B427)

Competitor steroid	Human pregnancy serum SHBG	SHBG purified	Human pregnancy serum, SHBG removed by chromatography	Human pregnancy serum, CBG
RBA values (%)				
Progesterone	< 0.1	< 0.1	< 0.1	53
Gestodene	65	70	< 0.1	< 0.1
3-keto-desogestrel	4	8	< 0.1	< 0.1
Levonorgestrel	45	50	< 0.1	< 0.1
DNG	< 0.1	< 0.1	< 0.1	< 0.1
DHT	100	100	< 0.1	0.6
Cortisol	NM	NM	NM	100

NM: Not measured

Table 13: Arithmetic Mean (SD) Serum Concentrations of SHBG, CBG, and Cortisol Following Daily Oral Dose of (b) (4)TM (Study A25711, N=15)

Analyte	Day 1	Day 8	Day 15	Day 21	Day 29
SHBG (nmol/l)	57.9 (24.8)	68.0 (34.0)	81.4 (32.6)	85.5 (30.1)	81.5 (31.0)
CBG (µg/l)	45.5 (25.2)	53.1 (19.0)	54.3 (14.2)	57.4 (14.7)	49.2 (12.2)
Cortisol (nmol/l)	339.4 (162.5)	455.2 (163.7)	425.4 (141.4)	461.4 (144.7)	437.8 (154.6)

2.2.10 What are the characteristics of drug metabolism?

EV

After oral administration, approximately 3% of the dose is directly bioavailable as E2 (Dusterberg *et al.*, 1985; Kuhnz *et al.*, 1993). E2 is then extensively metabolized to E1 (15%), E1S (65%), estradiol sulfate, and other

compounds. Together with the pre-systemic metabolism in the liver, approximately 95% of the orally administered dose becomes metabolized before entering the systemic circulation (Kuhnz *et al.*, 1999). E1 is a major circulating E2 metabolite with estrogenic activity, of which approximately 5% can be converted back to E2. E1S is the principal circulating E2 metabolite which itself is pharmacologically inactive but about 1.4% can be converted back to E2 and about 21% can be converted to E1 (Kuhnz *et al.* 1999). Besides E1 and E1S, several hydroxylated metabolites of E2 and E1 exist. Hydroxylation at position C-2, catalyzed by enzymes of the CYP 3A and, to a lesser extent, the CYP 1A families, plays the most important role in humans (Kuhnz *et al.* 1999).

DNG

DNG is extensively metabolized by the known pathways of steroid metabolism (i.e., hydroxylation and conjugation), with the formation of mostly inactive metabolites. CYP 3A4 was identified as a predominant enzyme catalyzing the metabolism of DNG (Study B482). Polar and hydrophilic metabolites are mainly eliminated renally. Because of the rapid elimination of the metabolites, unchanged DNG is the dominating fraction in plasma (Study B478).

2.2.11 What are the characteristics of drug excretion?

EV

E2, E1, and estriol are mainly excreted in urine with glucuronide and sulfate conjugates, with approximately 54% of the dose recovered in urine and 6% in feces within 24 hr (Dusterberg *et al.*, 1982). The terminal half-life of E2 is approximately 14 hr (Study A29972).

DNG

The total clearance following the IV administration of ³H-DNG was calculated to be 5.4 l/h (Study B478). DNG is excreted in the form of metabolites which are excreted at a urinary to fecal ratio of approximately 3:1 after oral administration of 0.1 mg/kg body wt. Following oral administration, 42% of the dose is eliminated within the first 24 hr and 63% within 6 days by renal excretion. A combined 86% of the dose is excreted by urine and feces after 6 days (Study B478). The terminal half-life of DNG is approximately 11 hr (Study A29972).

2.3 Intrinsic Factors

2.3.1 Is there any age effect observed in the PK of DNG, E2, or E1?

The target populations of (b) (4)TM are premenopausal women; however, the Sponsor conducted some studies including a food effect study and DDI studies in postmenopausal women. Therefore, any potential age effects on the PK of DNG, E2, and E1 was assessed by this reviewer. There were no specific studies conducted to assess the age effect. However, a cross-study comparison was done to compare the PK parameters of DNG, E2, and E1 PK characterized following oral administration of 2 mg EV/3 mg DNG in two different age groups (i.e., premenopausal vs. postmenopausal women). The PK parameters obtained in these studies are summarized in Table 14 below.

Table 14: Comparison of Arithmetic Mean (SD) DNG PK Parameters Following Administration of 2 mg EV/3 mg DNG Combination Tablets Under Fasted Conditions in Caucasian Women

	Study A25711	Study A30020
Population	Premenopausal (N=15)	Postmenopausal (N=12)
Regimen (Day)	Steady-state (Day 24)	Steady-state (Day 7)
C _{max} (ng/ml)	85.2 (19.7)	88.4 (13.3)
T _{max} (hr)	1.5 (1.0-2.0)	1.0 (0.5-2.0)
AUC(0-24) (ng·hr/ml)	828 (187)	827 (222)
t _{1/2} (hr)	12.3 (1.4)	NA

Median (range) for T_{max}

In Study A25711, SH T00658M (2 mg EV/3 mg DNG) was administered during the Period of Day 8-24 of the 28-day regimen
In Study A30020, SH T00658M (2 mg EV/3 mg DNG) was administered daily for 7 days (Day 1-7)

Table 15: Comparison of Arithmetic Mean (SD) E2 PK Parameters Following Administration of 2 mg EV/3 mg DNG Combination Tablets Under Fasted Condition in Caucasian Women

	Study A25711	Study A30020
Population	Premenopausal (N=15)	Postmenopausal (N=12)
Regimen (Day)	Steady-state (Day 24)	Steady-state (Day 7)
C _{max} (ng/ml)	70.5 (25.9)	74.4 (31.5)
T _{max} (hr)	3 (1.5-12)	6 (2-16)
AUC(0-24) (ng·hr/ml)	1323 (480)	1328 (614)

Median (range) for T_{max}

In Study A25711, SH T00658M (2 mg EV/3 mg DNG) was administered during the Period of Day 8-24 of the 28-day regimen

In Study A30020, SH T00658M (2 mg EV/3 mg DNG) was administered daily for 7 days (Day 1-7)

Table 16: Comparison of Arithmetic Mean (SD) E1 PK Parameters Following Administration of 2 mg EV/3 mg DNG Combination Tablets Under Fasted Condition in Caucasian Women

	Study A25711	Study A30020
Population	Premenopausal (N=15)	Postmenopausal (N=12)
Regimen (Day)	Steady-state (Day 24)	Steady-state (Day 7)
C _{max} (ng/ml)	483 (198)	474 (198)
T _{max} (hr)	4 (3-12)	5 (2-6)
AUC(0-24) (ng·hr/ml)	7562 (3403)	7314 (3112)

Median (range) for T_{max}

In Study A25711, SH T00658M (2 mg EV/3 mg DNG) was administered during the Period of Day 8-24 of the 28-day regimen

In Study A30020, SH T00658M (2 mg EV/3 mg DNG) was administered daily for 7 days (Day 1-7)

Although premenopausal women (Study A25711) had a higher mean E2 baseline concentration of 28.71 pg/ml (SD=15.22; range: 4.79-62 pg/ml) compared to postmenopausal women (Study A30020) having 2.10 pg/ml (SD=2.35; range: 0-5.8 pg/ml), PK parameters of DNG, E2, and E1 at steady-state following administration of 2 mg EV/3 mg DNG combination tablets in premenopausal women (Study A25711) were comparable to those observed in postmenopausal women with the same dose (Study A30020). This suggests that the EV/DNG regimen suppresses endogenous production of E2 in normal cycling women.

2.3.2 Is there any race effect observed in the exposure of EV/DNG?

In the clinical development of (b) (4)TM, the PK difference across race was not assessed. However, there were 2 studies assessing the PK dose linearity of DNG in different ethnic groups: Study B306, assessing a range of 1-8 mg in Caucasian premenopausal women and Study A00681, assessing a range of 0.5-2 mg in Japanese premenopausal women. The PK parameters are compared in Table 17 below.

Table 17: Comparison of Arithmetic Mean (SD or range) DNG PK Parameters Following Single Dose of DNG of Under Fasted Condition

Population	Study B306 (N=6)		Study A00681	
	Caucasian Premenopausal (N=6 per arm)		Japanese Premenopausal (N=6 per arm)	
Dose (mg)	1	2	1	2
C _{max} (ng/ml)	27.54 (5.20)	53.88 (8.97)	34.7 (3.1)	76.1 (14.6)
T _{max} (hr)	1.77 (0.5-4.0)	1.61 (0.75-2.0)	1.8 (0.6)	1.2 (0.4)
AUC(0-∞) (ng·hr/ml)	305.72 (65.18)	576.94 (146.03)	320.4 (56.7)	695.1 (114.2)

Both studies were conducted using units of 1 mg tablets. However, no information on components of the formulation was provided.

In a cross-study comparison, Japanese premenopausal women (Study A00681) showed higher AUC and C_{max} for DNG compared to Caucasian premenopausal women (Study B306).

Per clinical reviewer, Dr. Gerald Willett, there were 4 non-Caucasian women amongst the 15 "during treatment" pregnancies in the 2 pivotal Phase 3 contraceptive studies (i.e., Studies A35179 [in Europe] and A39818 [in US and Canada]).

- Subject 4505 = Hispanic = Subject failure to take medication properly

- Subject 4164 = Hispanic = Applicant could not categorize as either method or subject failure
- Subject 501028 = Hispanic = Subject failure to take medication properly
- Subject 505008 = Black = Subject failure to take medication properly

Therefore, none of the non-Caucasians pregnancies was deemed a definite method failure. 2 (0.15%) out of the 1377 subjects enrolled in Study A35179 were non-Caucasians while there were 119 (24.3%) out of 490 enrolled in Study A39818 were non-Caucasians.

Although Japanese premenopausal women showed higher C_{max} and AUC values compared to Caucasian premenopausal women following a single dose of the same DNG strength, considering the limitations of a cross-study comparison and the fact that there were no ethnic signals observed in the pivotal Phase 3 studies, it was concluded that there is a lack of evidence to believe the existence of race effect in the exposure of (b) (4)TM (EV/DNG).

2.3.3 What is the Sponsor's justification of the pediatric waiver request and is it acceptable?

No studies were performed in post-pubertal adolescents < 17 yr. The Sponsor requested a waiver from the requirement to submit data adequate to assess the safety and efficacy of EV and DNG in all relevant subpopulation such as post-pubertal adolescents < 17 yr. The Sponsor has 15 yrs of postmarketing experience with EV and DNG in the European Union (EU) (i.e., Qlaira[®], Climodien[®], and Valette[®]). In addition, the Sponsor plans to conduct a postmarketing surveillance study in 50,000 women in US and EU assessing the risk of VTE of EV/DNG tablets compared with other COCs in a non-selected target population (i.e., age group not-specified). Considering the target population and the reasons above, the Sponsor's request is acceptable from the Clinical Pharmacology standpoint. The Agency's pediatric review committee (PeRC) granted the Sponsor's waiver request on March 3, 2010.

2.3.4 Did the Sponsor conduct PK studies in population with renal or hepatic impairment?

No. The Sponsor did not conduct studies in renal and/or hepatic impaired patients for use of EV/DNG in premenopausal women. Severe liver diseases are already considered as contraindication for COCs.

The draft *Renal Impairment Guidance* (revised on September 16, 2009) states that "a PK study should be conducted in patients with impaired renal function when the drug is both likely to be used in these patients and when renal impairment is likely to mechanistically alter the PK of the drug and/or its active metabolites. This would most obviously be the case if the drug or a principal *active* metabolite is *substantially renally eliminated* (i.e., defined as the fraction of dose excreted unchanged in the urine is at least 30%), but it can also be the case if a drug is primarily metabolized or secreted in bile, as *renal impairment can inhibit some pathways of hepatic and gut drug metabolism and transport*. Therefore, a PK study in renal impairment should be conducted for most drugs intended for chronic use."

Considering that DNG and E2 are both extensively metabolized and mainly excreted renally as inactive metabolites and that the target population is premenopausal women, usage of (b) (4)TM in patients with renal and/or hepatic impairment would be relatively small and therefore, is less of a concern. However, the product labeling should clearly state that studies in patients with renal and hepatic impairments were not conducted.

2.4 Extrinsic Factors

2.4.1 What DDI investigations were conducted and what were the results?

The Sponsor conducted 5 clinical DDI studies in premenopausal or postmenopausal women. Healthy premenopausal women are the target population for (b) (4)TM. However, the endogenous estrogen production in younger women could have resulted in highly variable estrogen concentrations in serum, which could have interfered with the PK analysis of E2. Based on this rationale, the Sponsor conducted some DDI studies in

postmenopausal women who have a low endogenous estrogen production. This approach is acceptable given that the PK parameters of DNG, E2, and E1 at steady state following 2 mg EV/3 mg DNG in premenopausal women (Study A25711) were comparable to those observed in postmenopausal women with the same dose (Study A30020). Please Section 2.2.6 of the QBR above.

Effects of Other Drugs on Combined Hormonal Contraceptives

Effects of rifampicin (CYP3A4 induction) on EV/DNG PK

DNG is a substrate of CYP 3A4. The effect of the CYP 3A4 inducer rifampicin on EV/DNG PK was studied in healthy postmenopausal women (Study A24058). The study was conducted as a one-arm, open-label, non-randomized, single center study in one group of 16 healthy postmenopausal women. The steady-state PK of SH T00658M (2 mg EV/3 mg DNG combination tablet) were investigated prior to and after 5 days of treatment with 600 mg rifampicin daily (Days 12-16). All volunteers received a treatment regimen of SH T00658M, dosed once daily over 17 days, and of rifampicin, which was administered once daily in an oral dose of 600 mg on Days 12-16. 24-hr PK profiles of SH T00658M on Days 11 and 17 were compared.

Table 18: Statistical Comparison of Primary Target Variables Between Day 11 (without rifampicin) and Day 17 (rifampicin steady state) Following Co-administration of 600 mg Rifampicin Daily with 2 mg EV/3mg DNG Combination Tablets (Study A24058, N=16)

Treatment	Compound	PK Parameter	Geometric Mean Ratio (%)	90% CI (%)
SH T00658M + 600 mg rifampicin vs. SH T00658M alone	DNG	C _{max}	48	15.6-18.7
		AUC(0-24)	17	44.8-51.6
	E2	C _{max}	75	66.9-84.4
		AUC(0-24)	56	53.1-59.8
	E1	C _{max}	62	55.8-68.6
		AUC(0-24)	52	47.3-56.0
	E1S	C _{max}	41	36.3-46.3
		AUC(0-24)	28	25.1-32.1

As shown in Table 18, co-administration of 600 mg rifampicin daily with 2 mg EV/3 mg DNG combination tablets led to significant decreases in steady state C_{max} and AUC of DNG and E2, E1, and E1S which could potentially affect the contraceptive efficiency of the EV/DNG combination. In the dose-finding study (Study B690), it was demonstrated that 2 mg EV is necessary for effective ovulation inhibition and sufficient cycle control. For this particular 4-phasic regimen in combination with EV, a DNG dose of 2-3 mg/day was found to be necessary to sufficiently inhibit ovulation and provide contraceptive reliability (Studies A00984, A14191, and AZ94). For example, an 83% decrease shown in DNG AUC when (b) (4)TM is co-administered with rifampicin would reduce the AUC to the level expected when a DNG dose of approximately 0.5 mg is given and an 44% decrease shown in E2 AUC when (b) (4)TM is co-administered with rifampicin would reduce the AUC to the level expected when a EV dose of approximately 1.1 mg is given.

In a multi-center, open labeled, uncontrolled study (Study AZ94) to investigate the efficacy and safety of a 4-phasic oral contraceptive SH T 658 I containing EV and DNG over 20 cycles in 1,600 healthy female volunteers, an unacceptable unadjusted Pearl Index of 5.3 was obtained when DNG dose was decreased using the following regimen

- Cycle Days 1-3:EV 3 mg
- Cycle Days 4-7: EV 2 mg + DNG 1 mg
- Cycle Days 8-23: EV 2 mg and DNG 2 mg
- Cycle Days 24-25: EV 1 mg
- Cycle Days 26-28: placebo

Table 19: Pearl Index obtained in the full-analysis set (FAS) population (Study AZ94)

Patient set / subset	No. of cycles	No. of cycles with back-up contraception	No. of pregnancies after start of study medication	Pearl Index	No. of pregnancies due to subject failure	Pearl Index
				Unadjusted		Adjusted
Total	12,125	342	48	5.3	9	4.3
≤ 29 years of age	5,563	192	23	5.6	5	4.4
> 29 years	6,562	150	25	5.1	4	4.3

Study AZ94 clearly shows that when insufficient DNG dose is given efficacy can be significantly affected. Therefore, in order to ensure contraceptive reliability and sufficient cycle control, (b) (4)TM should not be co-administered with strong CYP 3A4 inducers such as rifampicin, phenytoin, St. John's Wort, avasimibe, and carbamazepine (as listed in Table 20 according to the *Guidance for Industry: Drug Interaction* [revised on March 11, 2010]). Although the extent of induction is unknown, moderate and weak CYP 3A4 inducers may also decrease the efficacy of (b) (4)TM. For women on chronic treatment with CYP 3A4 inducing active substances, another reliable, non-hormonal, method of contraception is recommended. This information should be reflected in the *Drug Interactions* section of the *Highlights* of the labeling.

Table 20: Classification of Inducers of CYP Enzymes

CYP Enzymes	Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
CYP1A2		Montelukast, phenytoin, smokers versus non-smokers ⁽²⁾	Moricizine, omeprazole, phenobarbital, tanshinone IIA, terbutaline
CYP2B6		Efavirenz, rifampin	Nevirapine
CYP2C8		Rifampin	
CYP2C9		Carbamazepine, rifampin	Aprepitant, bosentan, Phenobarbital, St. John's Wort ⁽³⁾
CYP2C19		Rifampin	Artemisinin
CYP3A	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's Wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea, pioglitazone, prednisone, rufinamide
CYP2D6	None known	None known	None known

From *Guidance for Industry: Drug Interaction* (revised March 11, 2010)

Effects of Ketoconazole and Erythromycin (CYP3A4 inhibition) on EV/DNG PK

Study A30020 investigated the effect of CYP 3A4 inhibitors (400 mg ketoconazole daily or 1500 mg erythromycin daily) on EV/DNG PK. This was an open-label, two parallel-groups, one-sequence, one-way crossover study in two groups of 12 healthy Caucasian postmenopausal women. One tablet of SH T00658M (2 mg EV/3 mg DNG) was orally administered once a day for 14 days for both treatment groups. Volunteers from Group 1 received an oral dose of 400 mg ketoconazole (i.e., 2 tablets Nizoral[®] containing 200 mg ketoconazole) once daily for 7 days (Days 8-14). Volunteers from Group 2 received an oral dose of 500 mg erythromycin (i.e., 1 tablet of Erythrocin[®]) three times a day for 7 days (Days 8-14). 24-hr PK profiles of SH T00658M on Days 7 and 14 were compared.

Table 21: Statistical Comparison of the Primary Target Variables Performed Using Day 7 (without ketoconazole or erythromycin) and Day 14 (with ketoconazole or erythromycin) Following Co-administration of 2 mg EV/3 mg DNG Tablets with 400 mg/day Ketoconazole or 1500 mg/day Erythromycin (Study A30020, N=12 per Group)

Treatment	Compound	PK Parameter	Geometric Mean Ratio (%)	90% CI (%)
SH T00658M + 400 mg ketoconazole (Day 14) vs. SH T00658M alone (Day 7)	DNG	C _{max}	194	184-205
		AUC(0-24)	286	263-311
	E2	C _{max}	165	149-182
		AUC(0-24)	157	145-171
SH T00658M + 1500 mg erythromycin (Day 14) vs. SH T00658M alone (Day 7)	DNG	C _{max}	133	123-144
		AUC(0-24)	162	146-180
	E2	C _{max}	151	136-168
		AUC(0-24)	133	118-150

In conclusion, the presence of a significant DDI between EV/DNG tablets and CYP 3A4 inhibitors, ketoconazole and erythromycin was demonstrated. Co-administration of EV/DNG tablets with ketoconazole or erythromycin resulted increases in steady state C_{max} and AUC(0-24) for both E2 and DNG. The lower impact of ketoconazole on E2 compared to it on DNG is likely due to multiple competing pathways involved in the metabolism of E2. Co-administration of moderate CYP 3A4 inhibitor, erythromycin, showed less impact on C_{max} and AUC(0-24) of both DNG and E2 compared to ketoconazole.

A thorough QT study (Study A35653) was conducted to evaluate the potential of a fixed combination of 2 mg EV/3 mg DNG (highest combination dose strength) at steady-state to delay cardiac repolarization in healthy postmenopausal women, to monitor safety and to evaluate the PK of DNG, E2, and E1. This study also included a supra-therapeutic DNG dose (10 mg DNG, 5 x 2 mg tablets) arm. This study showed that DNG at a dose of 3 mg in combination with 2 mg EV and at a dose of 10 mg did not lead to QT/QTc prolongation. The DNG exposure achieved with the 10 mg oral dose (3.4-fold increase in AUC(0-24) and 3.5-fold increase in C_{max} compared to those with 2 mg EV/3 mg DNG) was as high as can be expected when EV/DNG tablets are administered with 400 mg ketoconazole (i.e., CYP 3A4 strong inhibitor) daily (2.9-fold increase in AUC(0-24) and 1.9-fold increase in C_{max}) and demonstrated no effect on QT interval. Considering the outcome of the thorough QT study and the absence of correlations between DNG exposure and AEs observed, no dosage adjustment appears to be necessary. The clinical DDI study results should be reflected in the labeling.

For EV, daily co-administration with 400 mg ketoconazole resulted in approximately 57% and 65% increase in AUC(0-24) and C_{max}. Per clinical reviewer, Dr. Gerald Willett, nausea would be the main drug related AE to expect resulting from increase in E2 levels. The other common AE mentioned by the Sponsor was withdrawal bleeding. Examination of the individual exposure data of E2, E1, and DNG, revealed no correlation between the magnitude of AUC change of E2, E1, or DNG and the occurrence of these AEs.

Considering that the safety profiles from the Phase 3 clinical studies are similar to other COCs (per clinical reviewer, Dr. Gerald Willett) and the absence of correlations between E2 exposure and AEs observed, no dosage adjustment appears to be necessary. However, the clinical DDI study results should be reflected in the labeling.

Effects of Combined Hormonal Contraceptives on other Drugs

An *in vitro* study with human liver microsomes showed that DNG did not inhibit CYP 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4. Although with 100 µM DNG the metabolism of tolbutamide (CYP 2C9) and S-mephenytoin (CYP 2C19) was reduced to values of 69% and 63%, respectively, of the reference samples, DNG at lower concentrations closer to the clinical dose (i.e., < 20 µM) did not show any inhibition (Study B482).

In a single-center, open-label, randomized, parallel design study in healthy young women aged 21-32 yr to evaluate the influence of the oral contraceptives, Valette[®] (0.03 mg EE/2 mg DNG) and Minisiston[®] (0.03 mg EE/0.125 mg LNG) on PK of CYP 3A4 substrate, nifedipine. As shown in Table 22, co-administration of 0.03 mg EE/2 mg DNG did not have any effect on 10 mg nifedipine PK (Study B463).

Table 22: Statistic Comparison of PK Parameters (Nifedipine alone vs. EE/DNG + Nifedipine) (Study B463; N=12)

Analyte	Parameter	Mean Ratio (%)
Nifedipine	C _{max}	97.9
	AUC(0-∞)	97.6
	CL _{tot}	101.8

BE was demonstrated between 2 mg DNG vs. 2 mg EV/2 mg DNG with mean ratio (%) of DNG AUC and C_{max} being 103.7% (90% CI: 97.0-111.0%) and 106.9% (90% CI: 100.3-114.0%), respectively. Combined administration of 2 mg DNG together with 2 mg EV had no effect on 2 mg DNG PK (Study AR34). Also, BE was demonstrated between 4 mg EV/4 mg DNG vs. 4 mg EV with mean ratio (%) of E2 AUC being 106.99% (90% CI: 95.70-119.62%). Combined administration of 4 mg EV together with 4 mg DNG had no effect on 4 mg EV PK (Study A07769).

2.5 General Biopharmaceutics

2.5.1 What is the quantitative composition of the drug products used in the clinical trials of this application?

(b) (4)TM tablets were developed as IR film-coated tablets. All pivotal Phase 3 and supporting PK clinical studies were conducted using the TBM formulation. The composition of the TBM film-coated tablets is summarized in the Table 23 below:

Table 23: Composition of the TBM Film-coated (b) (4)TM Tablets

(b) (4)	SH T00658EA	SH T00658GA	SH T00658M	SH T00658HA	SH T00658P					
Estradiol valerate, (b) (4)	3.000 mg	2.000 mg	2.000 mg	1.000 mg	-					
Dienogest, (b) (4)	-	2.000 mg	3.000 mg	-	-					
Lactose monohydrate	(b) (4)									
Maize starch										
Maize starch, pregelatinized										
Povidone 25										
Magnesium stearate										
Hypromellose, (b) (4)										
Macrogol 6000										
Titanium dioxide										
Ferric oxide pigment yellow										
Ferric oxide pigment red										
Talc										
Total weight						83.000 mg	83.000 mg	83.00000 mg	83.0000 mg	82.0000 mg

2.5.2 What is the effect of concomitant food intake on the PK of EV and DNG?

The effect of concomitant food intake on the PK of EV and DNG was investigated in Study A29143 using the tablet containing 2 mg EV/ 3 mg DNG, as a representative tablet of (b) (4)TM.

A food effect study was conducted in healthy Caucasian postmenopausal women. The study was a single center, open-label, randomized, single-dose, crossover study with 2 treatment-periods, 2 treatments, 2 sequences. The treatments were receiving 1 tablet of SH T00658M (2 mg EV/3 mg DNG), either under fasted or fed conditions. For the fed treatment period, the study drug was administered immediately after a high fat, high calorie

breakfast. The washout period between the treatments was at least 2 weeks in order to ensure that all of the drug from the preceding treatment period was cleared from the body before administration of the subsequent treatment (half-life of E2 approximately 14 hr, half-life of DNG approximately 11 hr following single-dose administration; Study A25711)

In this food effect study, the C_{max} of DNG was decreased by 28% under fed conditions and the C_{max} of E2 was increased by 23% while AUC values for both DNG and E2 remained within the BE acceptance range (Tables 24 and 25).

Table 24: Statistical Analysis of Food Effect on PK of DNG (Study A29143, N=35 [N=33 for AUC])

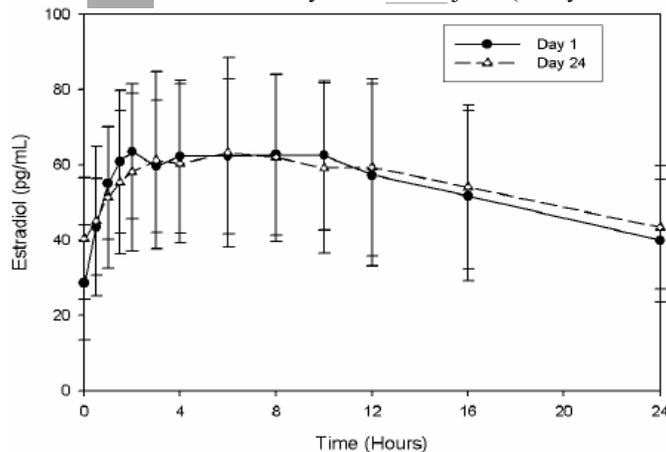
Parameters	Comparison	Geometric Mean Ratio (%)	90% CI (%)
C_{max}	Fed vs. Fasted	72.0	67.6-76.8
AUC(0-48)	Fed vs. Fasted	102	99.3-105
AUC(0-∞)	Fed vs. Fasted	103	99.5-106

Table 25: Statistical Analysis of Food Effect on PK of E2 (Study A29143, N=33)

Parameters	Comparison	Geometric Mean Ratio (%)	90% CI (%)
C_{max}	Fed vs. Fasted	123	110-137
AUC(0-48)	Fed vs. Fasted	117	111-123

As shown in Figure 12 below, comparable 24 hr E2 PK profiles were observed on Day 1 (following administration of 3 mg EV alone) and Day 24 (following daily dose of 2 mg EV/3 mg DNG on Days 8-24 of the 28-day sequential regimen) (Study A25711). Therefore, the outcome of this study also supports the EV only phase as well.

Figure 12: Mean (\pm SD) Concentration-Time Curve of E2 (pg/ml) on Days 1 and 24 Following Daily Oral Dose of (b) (4)TM in 15 Healthy Female Subjects (Study A25711)



The Sponsor proposes the following language on the labeling: (b) (4) Given the fact that the absence of food effect is not established due to the change of C_{max} of both DNG and E2 (i.e., failure to meet the 90% CI under fed condition) the data should be reflected in the labeling. However, it appears that this should not affect the food intake instructions since the results of the Phase 3 efficacy and safety studies support the administration of (b) (4)TM regardless of food intake. Therefore, no special recommendation concerning food intake is considered to be necessary.

2.6 Analytical Section

2.6.1 Did the Sponsor use validated bioanalytical methods to generate the study data?

Validated analytical methods were used in clinical studies. All of the PK studies performed during the development of (b) (4)TM tablets have used a radioimmunoassay (RIA) method for the measurement of DNG in human serum or plasma. For the quantitation of E2, E1, and E1S, validated LC-MS/MS methods were used.

Dynamic ranges varied between the methods used in each individual study. Bioanalytical method validation reports were submitted for all studies that were reviewed except for Study B478 (i.e., conducted as a pre-Good Clinical Practice (GCP)/Good Laboratory Practice (GLP) study). Acceptance criteria and assay performance for each analyte were in compliance with the *Bioanalytical Method Validation Guidance* and the bioanalytical methods were found to be acceptable. Bioanalytical methods are summarized in Table 22.

Table 22: Summary of Bioanalytical Methods

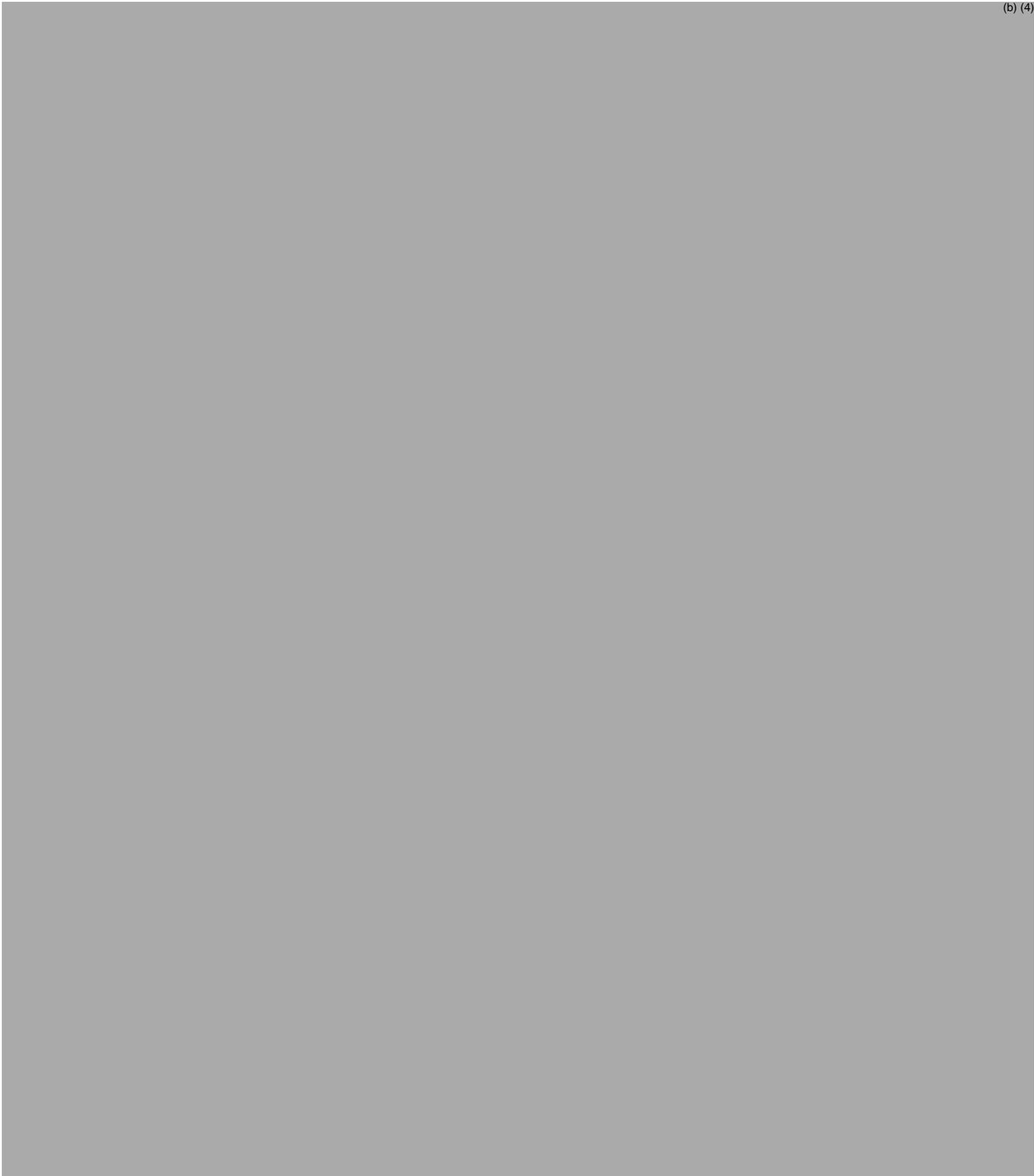
Study Number	Study Title	Biological Matrix	Analyte	Method	LLOQ
A29972	Relative BA EV/DNG tablets vs. suspension	Serum	E1	LC-MS/MS	5 pg/ml
		Serum	E2	LC-MS/MS	2.5 pg/ml
		Serum	DNG	RIA	0.3 ng/ml
A29143	Food Effect study with 2 mg EV/3 mg DNG tablets	Serum	E1	LC-MS/MS	5 pg/ml
		Serum	E2	LC-MS/MS	2.5 pg/ml
		Serum	DNG	RIA	0.3 ng/ml
B501	Absolute BA of DNG	Serum	DNG	RIA	1 ng/ml
A25711	Multiple dose PK study with EV/DNG tablets	Serum	E1	LC-MS/MS	5 pg/ml
		Serum	E1S	LC-MS/MS	50 pg/ml
		Serum	E2	LC-MS/MS	2.5 pg/ml
		Serum	DNG	RIA	0.3 ng/ml
B478	PK of ³ H-labelled DNG after oral and IV administration of 0.1mg/kg	Plasma	DNG	HPLC	NA ^a
B306	Investigation of DNG PK Dose Linearity	Plasma	DNG	RIA	2.77 ng/ml
B276	PK of DNG 2 mg after single and multiple dosing	Serum	DNG	RIA	0.5 ng/ml
A00681	Tolerability and PK of a single oral dose of DNG in healthy adult Japanese females	Plasma	DNG	HPLC	1 ng/ml
		Urine	DNG	HPLC	10 ng/ml
AR34	Effect of EV on DNG PK	Plasma	DNG	RIA	0.3 ng/ml
A07769	Effect of DNG on EV PK	Serum	E1	GC-MS	10 pg/ml
		Serum	E1S	GC-MS	50 pg/ml
		Serum	E2	GC-MS	5 pg/ml
		Serum	DNG	RIA	0.3 ng/ml
A24058	DDI study with CYP 3A4 Inducer – rifampicin	Serum	E1	LC-MS/MS	5 pg/ml
		Serum	E1S	LC-MS/MS	50 pg/ml
		Serum	E2	LC-MS/MS	2.5 pg/ml
		Serum	DNG	RIA	0.3 ng/ml
		Plasma	Rifampicin	HPLC	100 ng/ml
		Urine	6β-OH-cortisol	LC-MS/MS	5 ng/ml
A30020	DDI study with CYP 3A4 Inhibitors – ketoconazole and erythromycin	Serum	E1	LC-MS/MS	5 pg/ml
		Serum	E1S	LC-MS/MS	50 pg/ml
		Serum	E2	LC-MS/MS	2.5 pg/ml
		Serum	DNG	RIA	0.3 ng/ml
		Plasma	Erythromycin	LC-MS/MS	20 ng/ml
		Plasma	Ketoconazole	LC-MS/MS	20 ng/ml
A33022	PK over multiple treatment cycles	Serum	E1	LC-MS/MS	5 pg/ml
		Serum	E2	LC-MS/MS	2.5 pg/ml
		Serum	DNG	RIA	0.3 ng/ml
A25364	Inhibition of ovulation – EV/DNG tablets vs. DNG-increased regimen	Serum	DNG	RIA	0.3 ng/ml

^a Study B478 was conducted as a pre-GCP/GLP study. There was no formal bioanalytical method validation reports submitted.

LABELING

The following Clinical Pharmacology related parts of the Sponsor's proposed label were submitted together with this NDA.

(b) (4)



Reviewer's Comments

- *Several places in the Clinical Pharmacology Section including the PK subsection will have to be revised accordingly to reflect our findings and analyses.*
- *DDI study results needs to be reflected.*
- *The Sponsor proposes the following language on the label:* (b) (4)
However, given the fact that the absence of food effect is not established due to the change of C_{max} of both DNG and E2 (i.e., failure to meet the 90% CI under fed condition) the data should be reflected in the labeling.
- *COC class labeling language will be implemented as appropriate.*

Appendix

A.1. Individual Study Review

A.1.1. Study A29143

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

Protocol No: A29143
Phase: 1
Principal Investigator: B. Rohde, M.D.
Clinical Study Center: Clinical Pharmacology, Schering AG, Berlin, Germany
Clinical Study Dates: March 16, 2006 - May 31, 2006
Analytical Study Facility: (b) (4) and Schering Oy, Finland (DNG)
Analytical Study Dates: June 29, 2006 - August 22, 2006 (E2 and E1) and October 2006 - December 2006 (DNG)

OBJECTIVE

The objective of this study was to evaluate the effect of food on the BA of E2 and DNG given as a tablet containing 2 mg EV/3 mg DNG (SH T00658M).

STUDY ENDPOINTS

The primary endpoints were:

- AUC from time of administration (time zero) extrapolated until infinity
- AUC from time of administration ($t=0$) to time of last quantifiable serum concentration (t_{last}) (AUC(0- t_{last}))
- C_{max} of E2 and DNG

Secondary endpoints were:

- T_{max} , terminal $t_{1/2}$, terminal disposition rate (λ_z) of E2 and DNG
- AUC and AUC(0- t_{last}), C_{max} , T_{max} , λ_z , and $t_{1/2}$ of estrone (E1)
- AEs and clinical laboratory tests at screening and follow-up.

STUDY DESIGN, TREATMENT, AND SUBJECTS

The study was a single center, open-label, randomized, single-dose, crossover study with 2 treatment-periods, 2 treatments, 2 sequences. The treatments were:

- T1 = Test 1: 1 tablet of SH T00658M, under fasted conditions
- T2 = Test 2: 1 tablet of SH T00658M, under fed conditions.

Table A-1-1: Study Treatments Sequences

Sequence	Period 1	Period 2
1	Test 1	Test 2
2	Test 2	Test 1

The study drug was administered as a single oral dose. Each volunteer received the treatment under both conditions. The study drug was administered on an empty stomach for Test 1 (following a 10-hr fasted period)

in the morning between 7:00 and 9:00 hr. The tablet was taken with 250 ml noncarbonated water at ambient temperature. Drinking of water was allowed except for 1 hr before and after drug administration. Following the administration of Test 1 (i.e., under fasted conditions), the volunteers had to fast for 4 hr after study drug administration. For Test 2 (under fed condition), the study drug was administered immediately after a high fat, high calorie breakfast according to the Agency's *Guideline for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies* (2002) in the morning between 7:00 and 9:00 hr. The breakfast had to be finished within approximately 25 min. The volunteers had to maintain an upright posture (sitting, standing, and walking) for at least 4 hr after dosing. For follow-up, volunteers had to come to the study center in a fasted state for blood sampling.

The washout phase between the treatments was at least 2 weeks in order to ensure that all of the drug from the preceding treatment period was cleared from the body before administration of the subsequent treatment (Study A25711 shows that terminal half-life of E2 was approximately 13.8 hr and terminal half-life of DNG was approximately 11.3 hr following single-dose administration).

As EV is rapidly metabolized to E2, levels of E2 measured in premenopausal women could not be differentiated from the endogenous hormone. Subsequently, healthy postmenopausal volunteers with low endogenous E2 levels (≤ 20 pg/ml) were included in this study. 38 out of 70 screened volunteers were included in the study and 35 of which completed the study and were treated with SH T00658M both with and without food. 3 volunteers discontinued the study prematurely due to AEs and therefore only participated in one treatment sequence. 38 Caucasian female volunteers with an average age of 60.9 yr (range: 51-72 yr) were included in the full analysis set used for the evaluation of safety. Their mean height and weight were 163 cm (range: 155-174 cm) and 68.1 kg (range: 52.0-82.5 kg), respectively. The mean body mass index was 25.6 kg/m² (range: 20.1-29.9 kg/m²). The evaluation of PK included 35 volunteers for DNG and 33 volunteers for E2 and E1. 2 volunteers were excluded from the E1 and E2 evaluation due to high E2 baseline values of 91.5 and 108 pg/ml obtained under fasted condition.

The study inclusion criteria included the following:

- Healthy female, postmenopausal volunteer (Age: 45-75 yr)
- Postmenopausal state, revealed by:
 - medical history, if applicable (natural menopause at least 2 yr prior to first study drug administration; or surgical menopause by bilateral ovariectomy at least 3 months prior to first study drug administration), and
 - hormone analyses in serum (estradiol ≤ 20 pg/ml and follicle stimulating hormone (FSH) ≥ 30 IU/l)
- Body mass index (BMI): > 20 and < 30 kg/m²

FORMULATION

The formulation (SH T00658M) with the highest dosed combination of both EV and DNG (containing 2 mg EV/3 mg DNG) in this 4-phasic treatment regimen was chosen for this study to evaluate the effect of food on the BA of both E2 and DNG. The study drug was administered twice as single doses only.

Table A-1-2: Identity of Investigational Product(s)

Generic name	Estradiol valerate	Dienogest
ZK number	5104	37659
SH number	SH T00658M	
Dosage form	tablet	
Strength per unit	2 mg	3 mg
Manufacturer	Schering AG	

PHARMACOKINETIC EVALUATION

Blood sampling

Blood samples for PK measurements (identical in both periods) were taken at the following time points: 0.5 hr pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hr post-dose.

Concomitant Therapy

If a volunteer used concomitant medication, this was documented by type (brand name, if applicable), indication, regimen (total daily dose and route), and duration on the appropriate case report form (CRF). The investigator then decided whether the volunteer had to be excluded

Other Restrictions

- Blood / Plasma donation: Not permitted during the 4 weeks before first drug administration until the last follow-up examination
- Smoking: Not permitted
- Caffeine: Not permitted for 12 hr prior to drug administration and for 24 hr post drug administration
- Alcohol: Not permitted starting 48 hr before drug administration up to 48 hr post drug administration per period
- Grapefruit / Grapefruit juice: Not permitted starting 7 days before drug administration up to 72 hr post drug administration
- Physical activity: Usual activities permitted. Volunteers had to maintain an upright position (sitting, standing, walking) for at least 4 hr after study drug administration in each period

Bioanalytical method

Determination of E2 and E1 Concentrations

E2 and E1 measurements were conducted at (b) (4) E2 and E1 were extracted from human serum by liquid-liquid extraction, with estrone-2,4,16,16-d₄ and 17β-estradiol-16,16,17-d₃ as internal standards (IS). Extracts were analyzed by LC-MS/MS using an electrospray ionization (ESI) interface and multiple reaction monitoring (MRM) detection for the determination of E2 and E1 concentrations. The lower limit of quantitation (LLOQ) for the determination of E2 and E1 in serum samples was established to be 2.50 pg/ml and 5.00 pg/ml, respectively, and the upper limit of quantitation (ULOQ) was set to 250 pg/ml and 500 pg/ml for the assay using a 500 μl aliquot of human serum.

Frozen-state stability of E2 and E1 in stripped human serum was established for 567 days at -20 °C. Frozen-state stability of E2 and E1 in unstripped human serum was established for 552 days at -20 °C. Freeze-thaw (F-T) stability and room temperature stability was established up to 3 F-T cycles and for 25 hr prior to extraction and analysis, respectively.

Quality controls (QC) were prepared and analyzed with each batch of samples against separately prepared calibration standards to assess the day-to-day performance of the assay. Precision and accuracy were evaluated by replicate analyses of human serum QC pools prepared at five concentrations spanning the calibration range.

Determination of DNG Concentrations

Bioanalytical measurements for DNG were done at Schering Oy, Finland. The method used for the quantitative determination of DNG in human serum is a competitive RIA based on the detection of ³H-labeled DNG tracer bound to anti-DNG polyclonal antibody. The samples were extracted with diethylether before RIA analysis. The LLOQ and ULOQ for the determination of DNG in the matrix samples were established to be 0.3 ng/ml and 5.00 ng/ml, respectively.

The long-term temperature stability analyte was proven to be stable in human serum stored at -20 °C and -70 °C for 42 months. QCs at concentrations of 0.600, 1.50, and 4.00 ng/ml were prepared and analyzed with each batch of samples against separately prepared calibration standards to assess the day-to-day performance of the assay.

Acceptance criteria and assay performance for each analyte were in compliance with the *Bioanalytical Method Validation Guidance*.

Safety Assessments

To assure the good health of the volunteers, screening physical and gynecological examinations, electrocardiogram (ECG) and clinical laboratory testing including biochemistry, hematology, virology, and urinalysis were performed. Clinical laboratory testing was repeated at the end of the study. Blood sampling for PK evaluation was done before and up to 48 hr after study drug administration. During the treatment periods, the volunteers were monitored for AEs and concomitant medication.

DATA ANALYSIS

Pharmacokinetic Analysis

Non-compartmental PK analysis was performed on the serum concentrations of E2, E1, and DNG. All serum concentration values below the LLOQ were set to zero. C_{max} and T_{max} were directly read off the concentration-time profiles. The AUC and AUC(0-tlast) were calculated according to the trapezoidal rule. The terminal disposition rate constant (λ_z) was calculated by means of regression analysis of the perceivable linear part of the curve in a semi-logarithmic plot (λ_z : slope of the regression line).

The corresponding terminal half-life ($t_{1/2}$) was calculated by:

$$t_{1/2} = \ln 2 / \lambda_z$$

The AUC was calculated by extrapolation according to:

$$AUC = AUC(0-t_{last}) + C_{t_{last}} / \lambda_z$$

with $C_{t_{last}}$ as the concentration at the last data point (t_{last}).

Individual half-life values were not accepted if the time range covered by the perceivable linear part of the curve was less than 2 half-lives. In all cases, at least 3 data points were used for the half-life calculation. Individual AUC values were not accepted if the extrapolated area was greater than 20% of the calculated AUC value.

Safety Evaluations and Adverse Events

AEs observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the volunteer were documented. AEs still present at the end of the observation phase were followed as long as possible.

PHARMACOKINETIC RESULTS

PK of DNG

Mean PK parameters of DNG after daily oral administration of SH T00658M (2 mg EV/3 mg DNG), under fasted and fed conditions, respectively, in postmenopausal women are summarized in Table A-1-3.

Table A-1-3: Geometric Mean (%CV) PK Parameters of DNG After a Single Oral Dose Administration of 2 mg EV/3 mg DNG Combination Tablet Under Fasted and Fed Conditions, respectively, in Postmenopausal Women

For C_{max} , $t_{1/2}$ and AUCs the geometric mean with the geometric coefficient of variation (in parentheses) are given. For t_{max} , the median and the range (in parentheses) are provided.

analyte	parameter	unit	fasting	fed
DNG (N=35)	C_{max}	ng/mL	86.8 (18.7%)	62.6 (20.3%)
	t_{max}	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)
	$t_{1/2}$	h	10.6 (15.2%) (N=34)	10.5 (14.3%) (N=32)

Legend:

C_{max} = Maximum serum concentration

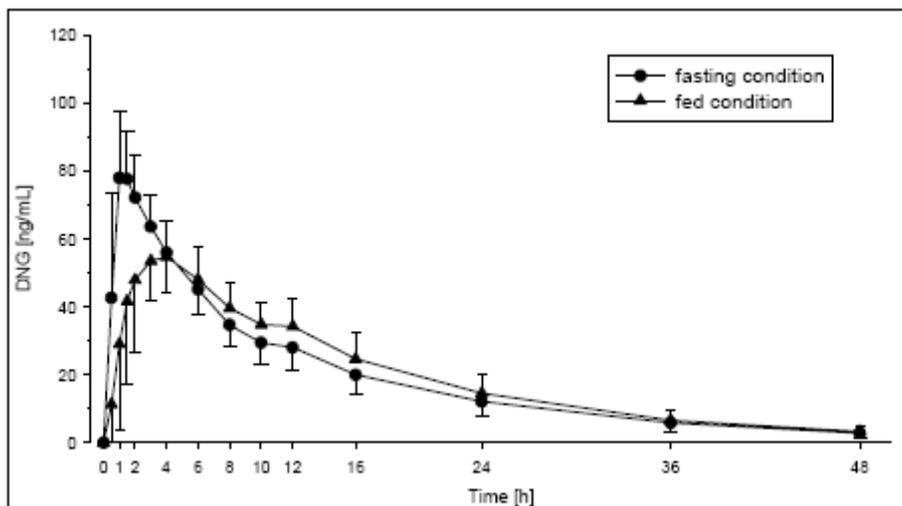
t_{max} = Time to reach maximum concentration

AUC(0-tlast) = Area under the concentration-time curve from 0 h data point up to the last data point above the LLOQ

AUC = Area under the concentration-time curve

$t_{1/2}$ = terminal half-life

Figure A-1-1: Mean (\pm SD) Serum Concentration-Time Curves of DNG Following a Single Oral Dose of 2 mg EV/3 mg DNG Combination Tablet under Fasted and Fed Conditions in Healthy Postmenopausal Women (N=35)



Reviewer’s comment: The arithmetic mean $t_{1/2}$, C_{max} , and $AUC(0-\infty)$ values obtained under fasted conditions in this study (10.7 hr, 88.3 ng/ml, and 962 ng·hr/ml, respectively) was comparable to those obtained in Study A29972 under fasted conditions (11.3 hr, 91.7 ng/ml, and 1024 ng·hr/ml, respectively) using the same formulation (SH T00658M).

PK of E2

Mean PK parameters of E2 after daily oral administration of SH T00658M (2 mg EV/3 mg DNG), under fasted and fed conditions, respectively, in postmenopausal women are summarized in Table A-1-4. Only a limited number of subjects (n=8 for fasted and n=6 for fed) has appropriately determined $t_{1/2}$ and AUC values. AUC and $t_{1/2}$ could not be calculated for all subjects due to insufficient data collection to cover more than 2 half-lives.

Table A-1-4: Geometric (%CV) Mean PK Parameters of E2 After a Single Oral Dose Administration of 2 mg EV/3 mg DNG Combination Tablet under Fasted and Fed Conditions, respectively, in Postmenopausal Women

For C_{max} and AUCs the geometric mean with the geometric coefficient of variation (in parentheses) are given, for t_{max} the median and the range (in parentheses) are provided.

analyte	parameter	unit	fasting	fed
E2 (N=33)	C_{max}	pg/mL	32.9 (29.8%)	40.6 (42.1%)
	t_{max}	h	6 (1-16)	3 (1-24)
	AUC(0-tlast)	h·pg/mL	838 (50.6%)	980 (42.9%)
	AUC	h·pg/mL	721 (45.9%) (N=8)	904 (49.1%) (N=6)
	$t_{1/2}$	h	14.6 (16.9%) (N=8)	16.8 (12.9%) (N=6)

Legend:

C_{max} = Maximum serum concentration

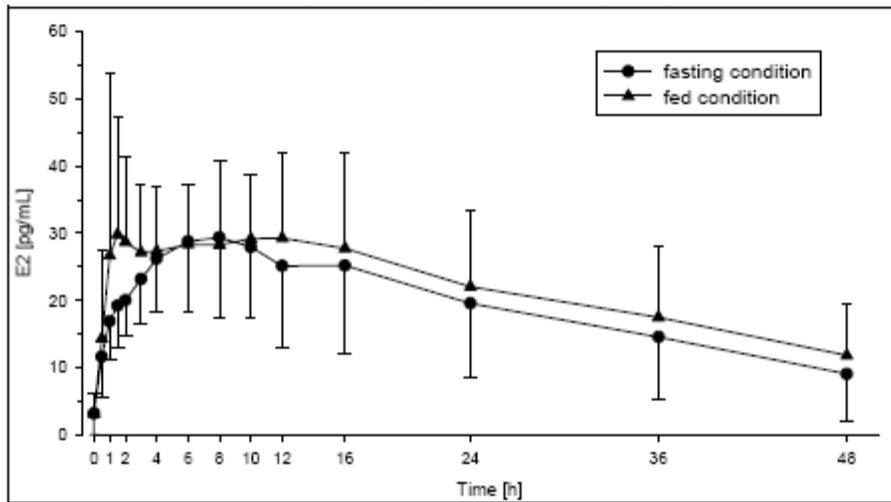
t_{max} = Time to reach maximum concentration

AUC(0-tlast) = Area under the concentration-time curve from 0h data point up to the last data point above the LLOQ

AUC = Area under the concentration-time curve

$t_{1/2}$ = terminal half-life

Figure A-1-2: Mean (\pm SD) Serum Concentration-Time Curves of E2 Following a Single Oral Dose of 2 mg EV/3 mg DNG Combination Tablet Under Fasted and Fed Conditions in Healthy Postmenopausal Women (N=33)



Reviewer's comment: The arithmetic mean $t_{1/2}$ and AUC(0-tlast) values obtained under fasted conditions in this study (14.8 hr and 934 pg·hr/ml) was comparable to those obtained in Study A29972 under fasted conditions (13.8 hr and 892 pg·hr/ml) using the same formulation (SH T00658M) although a 1 hr difference in $t_{1/2}$ was noted. The AUC value reported appears to be unreliable given that it has a smaller value compared to the AUC(0-tlast). This appears to be due to the insufficient data collection for AUC.

PK of E1

Mean PK parameters of E1 after daily oral administration of SH T00658M (2 mg EV/3 mg DNG), under fasted and fed conditions, respectively, in postmenopausal women are summarized in Table A-1-5. Only a limited number of subjects (n=8) has appropriately determined $t_{1/2}$ and AUC values. AUC and $t_{1/2}$ could not be calculated due to insufficient data collection to cover more than 2 half-lives.

Table A-1-5: Geometric (%CV) Mean PK Parameters of E1 After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablet Under Fasted 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
E1 (N=33)	Cmax	pg/mL	239 (33.1%)	237 (33.5%)
	tmax	h	6 (3-12)	6 (2-24)
	AUC(0-tlast)	h·pg/mL	4934 (51.7%)	5446 (49.5%)
	AUC	h·pg/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

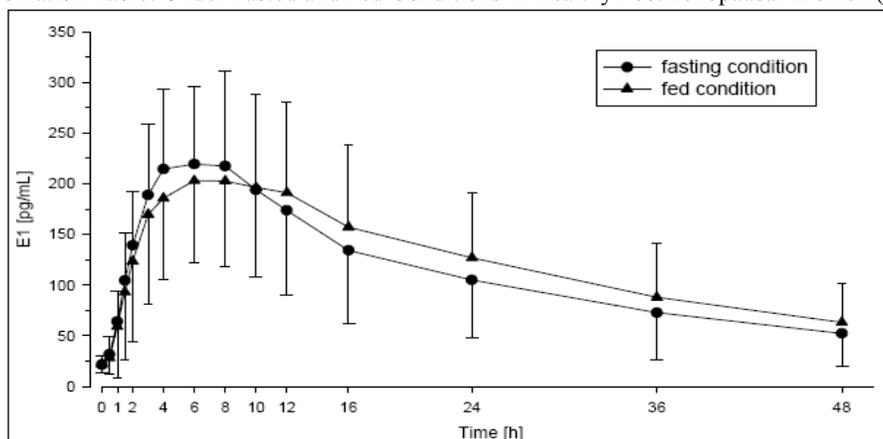
AUC(0-tlast) = Area under the concentration-time curve from 0h data point up to the last data point above the LLOQ

AUC = Area under the concentration-time curve

t1/2 = terminal half-life

After administration on a fed stomach, mean E1 concentrations reached a mean concentration of approximately 200 pg/ml after about 6 hr, then remaining more or less constant up to 8 hr and afterwards decreased gradually up to 48 hr post-dose. After administration on an empty stomach, a similar pattern was seen, but the maximum concentration was reached faster and was higher: mean E1 concentrations reached 210 pg/ml after approximately 3 hr, then remaining more or less constant up to 8 hr and afterwards decreasing up to 48 hr post-dose.

Figure A-1-3: Mean (\pm SD) Serum Concentration-Time Curves of E1 Following a Single Oral Dose of 2 gm EV/3 mg DNG Combination Tablet Under Fasted and Fed Conditions in Healthy Postmenopausal Women (N=33)



Reviewer’s comment: The arithmetic $t_{1/2}$ and $AUC(0-t_{last})$ values obtained under fasted conditions in this study (16.4 hr and 6121 pg-hr/ml) was comparable to that obtained in Study A29972 under fasted conditions (17.2 hr and 6494 pg-hr/ml) using the same formulation (SH T00658M).

STATSTICAL ANALYSIS

Statistical Analysis of DNG PK Parameters

Analysis of variance (ANOVA) was performed to assess the food effect on the BA of DNG following a single oral dose of SH T00658M tablets. Table A-1-6 summarizes the geometric mean ratios and the 90% CI of primary PK variables for DNG when compared fed to fasted conditions.

Table A-1-6: Statistical analysis of food effect on DNG PK (N=35 [N=33 for AUC])

Parameters	Comparison	Geometric Mean Ratio (%)	90% CI (%)
C_{max}	Fed vs. Fasted	72.0	67.6-76.8
$AUC(0-t_{last})$	Fed vs. Fasted	102	99.3-105
$AUC(0-\infty)$	Fed vs. Fasted	103	99.5-106

The results indicated that the AUC of DNG was not affected by the high fat food as both $AUC(0-t_{last})$ and AUC are BE between fed and fasted conditions. However, food was found to affect the C_{max} of DNG. The mean C_{max} of DNG was decreased by 28% under the fed conditions and the median T_{max} was delayed from 1 hr (under fasted) to 4 hr (under fed).

Statistical Analysis of E2 PK Parameters

ANOVA was performed to assess the food effect on the BA of E2 following a single oral dose of SH T00658M. Table A-1-7 summarizes the geometric mean ratios and the 90% CI of primary PK variables for E2 when compared fed to fasted conditions. Analysis was not performed on AUC of E2 because only a limited number of subjects (n=8) has appropriately determined $t_{1/2}$ and AUC values. AUC and $t_{1/2}$ could not be calculated for all subjects due to insufficient data collection to cover more than 2 half-lives. The arithmetic mean $AUC(0-t_{last})$ values obtained under fasted conditions in this study (934 pg-hr/ml) was comparable to those obtained in Study A29972 under fasted conditions (892 pg-hr/ml) using the same formulation (SH T00658M).

Table A-1-7: Statistical analysis of food effect on E2 PK (N=33)

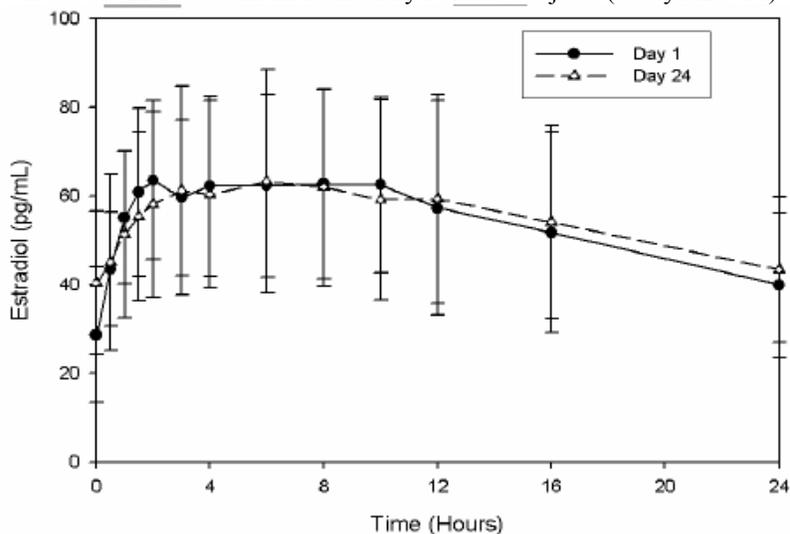
Parameters	Comparison	Geometric Mean Ratio (%)	90% CI (%)
C_{max}	Fed vs. Fasted	123	110-137
$AUC(0-t_{last})$	Fed vs. Fasted	117	111-123

The results indicated that the AUC of E2 was not affected by the high fat food as AUC(0-tlast) is BE between fed and fasted conditions. However, C_{max} of E2 was increased by 23% and failed to meet the 90% CI under fed condition.

Reviewer's comment: *In this case, food effect comparison based on AUC(0-tlast) appears to be more reliable given that the reported mean AUC value is smaller than mean AUC(0-tlast). This appears to be due to the insufficient data collection for AUC.*

As shown in Figure A-1-4 below, comparable 24 hr E2 PK profiles were observed on Day 1 (following administration of 3 mg EV alone) and Day 24 (following daily dose of 2 mg EV/3 mg DNG on Days 8-24 of the 28-day regimen) (Study A25711). Therefore, the outcome of this study also supports the EV only administration phase as well.

Figure A-1-4: Mean (\pm SD) Concentration-Time Curve of E2 (pg/ml) on Days 1 and 24 Following Daily Oral Dose of SH T00658ID in 15 Healthy Female Subjects (Study A25711)



The Sponsor proposes the following language on the labeling:

(b) (4)

Given the fact that the absence of food effect is not established due to the change of C_{max} of both DNG and E2 (i.e., failure to meet the 90% CI under fed condition), the study data should be reflected in the labeling. However, it appears that this should not affect the food intake instructions since the results of the Phase 3 efficacy and safety studies support the administration of Isbeia™ regardless of food intake. Therefore, no special recommendation concerning food intake is considered to be necessary.

SAFETY RESULTS

No deaths or serious AEs were reported during this study. 3 volunteers had AEs that led to withdrawal from the study: nasopharyngitis (volunteer 33), nausea / vomiting (volunteer 4), and vomiting (volunteer 11). The most frequently occurring AEs were nausea (6 events in 5 volunteers, 13.2%), vomiting (4 events in 4 volunteers, 10.5%) as well as fatigue, headache, and seasonal allergy (3 events in 3 volunteers, 7.9% each symptom) and dizziness (1 event in 1 volunteer, 2.6%).

CONCLUSION

This food-effect study in healthy postmenopausal women demonstrated that the C_{max} of DNG was decreased by 28% and the C_{max} of E2 was increased by 23% and failed to meet the 90% CI under fed condition, while AUC values for both DNG and E2 were BE. The median T_{max} for DNG was delayed from 1 hr (under fasted) to 4 hr (under fed). The absence of food effect is not established due to the change of C_{max} of both DNG and E2 and

failure to meet the 90% CI under fed condition. However, this should not affect the food intake instructions since the results of the Phase 3 efficacy and safety studies support the administration of (b) (4)TM regardless of food intake.

A.1.2. Study B501

Study of the Absolute Bioavailability of Dienogest (DNG) in Male Subjects

Protocol No: B501
Phase: 1
Principal Investigator: Annemarie Hoffmann, M.D.
Clinical Study Center: [REDACTED] (b) (4)
Clinical Study Dates: October 26, 1993 - December 17, 1993
Analytical Study Facility: [REDACTED] (b) (4)

OBJECTIVE

The primary objective of the study was to evaluate the absolute BA of DNG.

STUDY ENDPOINTS

The primary endpoints of the study were $AUC_{0-\infty}$, AUC_{0-48} , C_{max} , T_{max} , and $t_{1/2}$.

STUDY DESIGN, TREATMENT, AND SUBJECTS

The study was a randomized, single dose, single center, open label, 2-way crossover study. A total of 22 healthy, Caucasian male subjects met the inclusion criteria and were included in the study. 20 subjects, aged 22-33 yrs, completed the study.

After 10 hr fasting, each of the subjects was treated with a single dose of 2.0 mg of DNG once in the form of film-coated tablets and another time as an IV infusion. Blood samples were collected for 48 hr after each administration. 14 blood samples collected after the oral administration and 17 blood samples were collected following IV administration. The subjects were hospitalized for 12 hr following administration. The interval between treatments was 1-2 weeks.

A subject was eligible for inclusion in this study only if all of the following criteria apply:

- Male between 18-50 yr of age
- Clinical examination without any pathological findings of clinical relevance to the trial
- Fasting for the last 10 hr before administration
- No alcohol allowed for 24 hr before administration

A subject was not eligible for inclusion in this study if any of the following criteria applied:

- Indication in the subject's clinical history and/or clinical examination of the presence of a serious organic or psychic disease
- Indication in the subject's clinical history of chronic consumption of drugs; tobacco (more than 10 cigarettes a day) or alcohol (more than 20 g of alcohol a day)
- Indication in the subject's clinical history of drug intolerance, allergies or idiosyncrasies
- Consumption of drugs within the last 30 days before the beginning of the trial

FORMULATION

Test product:

- Active substance: DNG
- Dose: 2.0 mg of DNG
- Formulation: film-coated tablet
- Batch designation: 30901
- Producer: [REDACTED] (b) (4)

Reference product:

- Active substance: DNG
- Dose: 2.0 mg of DNG
- Formulation: Each 52.5 ml of injection solution contains
 - 2.5 ml of concentrate:
 - DNG 2.00 mg
 - Ethanol 96 % 0.06 mg
 - Water for injection ad 2.50 ml
 - 50 ml of 0.9% isotonic saline solution.
- Batch designation: K/930893
- Producer [REDACTED] (b) (4)

PHARMACOKINETIC EVALUATION

Blood sampling

The blood samples for serum determination were collected immediately before the administration of the test substance and exactly at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 30, and 48 hr after administration. Additional samples were collected at times 0, 10, and 20 min after the end of IV administration each with an appropriately labelled sampling system (Monovette, Vacutainer).

Concomitant Therapy

There were no reports of concomitant therapy use.

Bioanalytical method

The determination of DNG concentration in the serum samples by RIA is preceded by an extraction step. The extract is evaporated *in vacuo* and resolved in a small amount of ethanol and then in buffer. Aliquots are pipetted for the measurement of recovery and for the RIA, the competitive binding reaction with [³H]-DNG tracer to the antiserum. After incubation overnight at 4°C the unbound tracer is separated by adsorption to charcoal-dextran. The bound tracer is counted for [³H] activity in a liquid-scintillation counter (LSC). The concentration of DNG is determined according to a standard curve and the recovery of extraction. The LLOQ of DNG was established to be 1 ng/ml. Coefficients of variation (CV) were in the range of 2.9-12.7 % (intra-assay) and 3.4-11.2 % (inter-assay) that are in a common range for RIA. All acceptance criteria and performance were in compliance with the *Bioanalytical Method Validation Guidance*.

Safety Assessments

The following variables were checked before administration of the test product: blood pressure lying and standing; pulse rate; and axillary body temperature

Subjects were allowed to receive the test medication if the blood pressure values were between 95 and 160 mm Hg systolic and 50 and 95 mm Hg diastolic.

DATA ANALYSIS

Pharmacokinetic Analysis

The analysis of statistical data was performed using SAS for Windows 3.1, version S.08 (Statistical Analyse System, SAS-Institute, NC, U.S.A.). All calculations of the PK characteristics values are based on the measured raw data and set time. Values less than LLOQ were replaced by 0.

PHARMACOKINETIC RESULTS

In all cases the residual areas AUC_{0-48} were more than 80% of the total area under the curve, $AUC_{0-\infty}$. The medians of the residual area were 6.57% and 6.21% for formulations A and B, respectively. The median half-lives were 8.37 hr and 3.20 hr for A and B, respectively. There was no significant deviation from normal distribution of the ANOVA residuals of logarithmic transformed AUC_{0-48} , $AUC_{0-\infty}$, and C_{max} . Thus a parametric

approach was used for the calculation of the 90 % CI. None of the variables showed a significant period or sequence effect.

The geometric mean of AUC_{0-48} test formulation is 419.84 ng·h/ml, that of the reference formulation 464.91 ng·h/ml. The AUC_{0-48} ratio and 90% CI are 90.31% and 86.23-94.57%, respectively. The geometric mean of $AUC_{0-\infty}$ of the test formulation is 443.13 ng·h/ml, that of the reference formulation 494.90 ng·h/ml. The $AUC_{0-\infty}$ ratio of the test vs. reference formulation and the 90% CI are 90.92% and 86.59-94.69%, respectively. The absolute BA of DNG based on $AUC_{0-\infty}$ is 90.92 %. The 90% CI is 86.59-94.69%.

Table A-2-1: Summary of DNG PK Parameters Following a Single Dose (Mean values are arithmetic means)

Parameter	DNG Formulation	
	A	B
AUC_{0-48}	Mean value	427.91
	Standard deviation	85.31
DNG ng/ml·h	Variation coefficient	19.94
	Central value	430.10
$AUC_{0-\infty}$	Mean value	455.74
	Standard deviation	84.88
DNG ng/ml·h	Variation coefficient	18.63
	Central value	461.87
c_{max}	Mean value	39.95
	Standard deviation	7.47
DNG ng/ml	Variation coefficient	18.71
	Central value	39.48
t_{max} (h)	Mean value	1.625
	Standard deviation	0.930
	Variation coefficient	57.24
	Central value	1.5
$t_{1/2}$ (h)	Mean value	8.48
	Standard deviation	1.22
	Variation coefficient	14.43
	Central value	8.37

Formulation A Dienogest (film-coated tablet)

Formulation B Dienogest (injection solution)

AUC_{0-48} = Area under the curve from t = 0 to t = 48

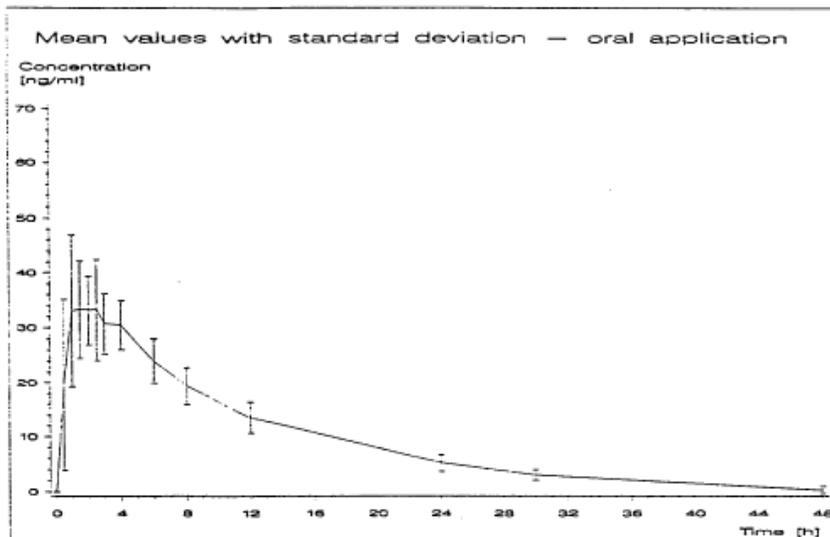
$AUC_{0-\infty}$ = Area under the extrapolated curve

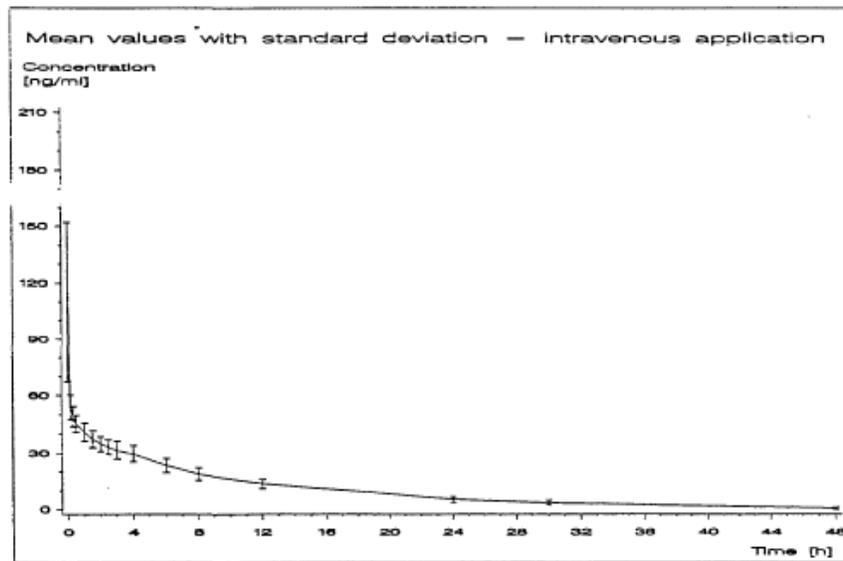
c_{max} = Concentration maximum

t_{max} = Time of maximum

$t_{1/2}$ = Half-life

Figure A-2-1: DNG Time-Concentration Profiles with using Arithmetic Mean Values and Standard Deviations Following a Single Dose





SAFETY RESULTS

No AEs were found in any case.

CONCLUSION

The absolute BA of DNG is 90.92%. The terminal half-life period of DNG is 8.37 hr (test preparation tablet) and 8.20 hr (reference preparation solution), respectively, on an average.

A.1.3. Study A00681

Tolerability and Pharmacokinetics of a Single Oral Dose of DNG (MJR-35) in Healthy Adult Females

Protocol No: A00681
Phase: 1
Principal Investigator: Prof. H. Mizoguchi
Clinical Study Center: (b) (4)
Clinical Study Dates: January 2004 - March 2004
Analytical Study Facility: (b) (4)

OBJECTIVE

The primary objective was to investigate the tolerability and PK of a single oral dose of DNG (MJR-35) in healthy adult females.

STUDY DESIGN, TREATMENT, AND SUBJECTS

The study was divided into three stages for each dose level from the low dose to the high dose and proceeded to the next stage as tolerability was confirmed. Confirmation of tolerability at each stage and progression to the next stage were determined by agreement between the chief investigator and investigators.

The study drug was taken with 100 ml of water at 8 a.m. following overnight fasting from 8 pm the day before (fasted for 12 hr). One dose was given at each dose level (single dose). The dose levels and the number of subjects treated are summarized below:

- | | |
|--|----------------------------|
| • 0.5 mg: 0.25 mg x 2 (n=6) | Placebo: placebo x 2 (n=2) |
| • 1.0 mg: 1.0 mg x 1 + placebo x 1 (n=6) | Placebo: placebo x 2 (n=2) |
| • 2.0 mg: 1.0 mg x 2 (n=6) | Placebo: placebo x 2 (n=2) |

Inclusion criteria:

- Healthy adult females (age: 21-45 yr)
- Persons judged to have passed the following tests for subject selection: interview (subjective symptoms, objective signs); physical findings (height, weight, temperature, blood pressure, heart rate, respiratory rate, and ECG); general haematology (RBC, Hb, Ht, WBC, and platelets); blood coagulation tests (Prothrombin time, APTT, AT III, fibrinogen, and plasminogen); blood biochemistry (GOT, GPT, ALP, LDH, γ -GTP, total bilirubin, BUN, creatinine, uric acid, Na, K, Cl, Ca, total cholesterol, HDL, triglycerides, total protein, albumin, A/G, and cortisol); Urinalysis (pH, specific gravity, sugar, protein, and urobilinogen)

Exclusion criteria:

- Pregnant or possibly pregnant women
- Breastfeeding women
- Women still bleeding during menstruation
- Those on regular medication
- Smokers
- Habitual consumers of alcohol
- Diabetics
- Persons with heart disease, liver disease, renal disease or blood
- Persons with a history of hypersensitivity to drugs in general

Study subjects were admitted the day before the study drug was to be administered. They were discharged after they had been interviewed and given a blood sample at 8 a.m. on Day 4.

Concomitant Therapy, Food, and Drinks

Study subjects were instructed to watch their health from a week before the start of the study and were forbidden to take any other drugs. During admission, they were forbidden to take any food other than that prepared by the centre and drinking and vigorous exercise were also forbidden during the study period, as were the taking of caffeine-containing drinks and smoking.

Safety and Clinical Laboratory Measurements

Table A-3-1: Safety and Clinical Laboratory Measurements

Item		Details
Interview		Subjective symptoms, objective signs
Physical findings		Weight, temperature, blood pressure, heart rate, respiratory rate, ECG
Laboratory tests	General haematology	RBC, Hb, Ht, WBC, Platelets
	Coagulation fibrinolysis	Prothrombin time, APTT, AT III, fibrinogen, plasminogen
	Blood biochemistry	GOT, GPT, AL-P, LDH, γ -GTP, total bilirubin, BUN, creatinine, uric acid, Na, K, Cl, Ca, total cholesterol, HDL, triglycerides, total protein, albumin, A/G, cortisol
	Urinalysis	pH, specific gravity, sugar, protein, urobilinogen
Menstrual cycle		Check starting date of menstruation after dose of study drug

Pharmacokinetic Measurements

Measurement of plasma concentration: Blood samples were taken just before the study drug dose and at 0.5, 1, 2, 3, 4, 6, 12, 24, 48, and 72 hr after the dose.

Measurement of urine concentration: Urine (cumulative urine) was collected in each of the periods from the first micturition on the morning of the day of the dose of the study drug until just before the dose, and at 0-6 hr, 6-12 hr, 12-24 hr, 24-48 hr, and 48-72 hr after the dose

Bioanalytical Method

DNG in Human Plasma

A bioanalytical method for DNG in human plasma based on high performance liquid chromatography (HPLC) using ethinyl estradiol (EE) as the IS was developed in order to characterize the PK of DNG in plasma. 1 ml of plasma was applied to a solid phase extraction (SPE) column, it was washed with phosphate buffer, water, 20% acetonitrile, and 70% methanol then further extracted with 90% methanol. The eluate was concentrated and analyzed by HPLC using a reversed phase column.

In the specificity tests, no impurity peaks corresponding to the elution times for DNG and the IS were noted on the HPLC chromatograms obtained by this bioanalytical method, and accuracy relative to the theoretical values (% of difference) of 0.38% and precision (CV) of 4.83% were found for the mean assay values for six specimens of plasma spiked with 1 mg/ml. The calibration curve exhibited good linearity over the dynamic range of 1-50 ng/ml. For intra-assay variation, % of difference was 1.64-4.55% of the theoretical value and CV was 1.53-7.25%. For inter-assay variation, % of difference was 0.49-2.43% of the theoretical value and CV was 2.71-11.18%.

DNG in Human Urine

Method for the determination of DNG and its metabolites M1, M2 and M3 in human urine based on HPLC using EE as the IS substance were established in order to permit investigations of drug PK during clinical studies on DNG. Methods for measuring the glucuronide conjugate of DNG and glucuronide conjugate of M1

were also devised. DNG and metabolite M5 were assayed simultaneously, as were metabolites M1, M2, and M3.

In both procedures, 1 ml of urine was applied to a SPE column, it was washed with PBS, distilled water, 20% acetonitrile, then, for DNG and M5 determination, with 70% methanol and for M1, M2, and M3 determination, with 20% methanol, whereupon they were extracted with 90% methanol. The eluates obtained were further extracted with ethyl acetate. The extracts were concentrated and analyzed by HPLC using a reversed phase column.

In the specificity tests, no impurity peaks affecting the assays were noted near the elution times for DNG, M1, M2, M3, and M5 on the HPLC chromatograms obtained by this bioanalytical method, and taking the mean assay values for urine spiked with each metabolite to give a concentration of 10 ng/ml, accuracy (% of difference) was -18.14-2.86% relative to the theoretical values and precision (CV) was 1.94-4.81%. The calibration curve exhibited good linearity over the dynamic range of 10-500 ng/ml, the intra-assay accuracy relative to the theoretical values and precision were respectively -14.33-8.57% and 0.63-6.45%. Accuracy relative to the theoretical values and precision in the inter-assay tests were respectively -13.80-6.92% and 2.06-16.04%. When urine spiked with a high concentration of DNG and each of its metabolites was diluted to within the assay concentration range and determined, accuracy relative to the theoretical values was -9.97-0.93%. Regarding the conjugates, no impurity peaks affecting the assay of DNG and M1 were noted on the HPLC chromatograms when blank human urine specimens were treated.

All acceptance criteria and performances of the bioanalytical methods were in compliance with the *Bioanalytical Method Validation Guidance*.

DATA ANALYSIS

Pharmacokinetic Parameters

The PK parameters (C_{max} , T_{max} , $t_{1/2}$, AUC, etc.) were calculated from the course of the plasma concentrations of the study drug. The excretion rates were calculated from the intact compound and metabolites in the urine.

Safety Measurement

Physical signs, general haematology, blood biochemistry, urinalysis: variations in the laboratory values from the time of the dose onwards relative to the baseline values were investigated for any abnormality and any abnormal values. The tolerability of DNG (MJR-35) was also investigated based on the results.

RESULTS

Plasma Pharmacokinetics

The course of the plasma concentration of the intact compound is illustrated in Figure A-3-1 and the PK parameters in Table A-3-2.

Figure A-3-1: Plasma Concentrations of Unchanged DNG following a Single Dose Administration

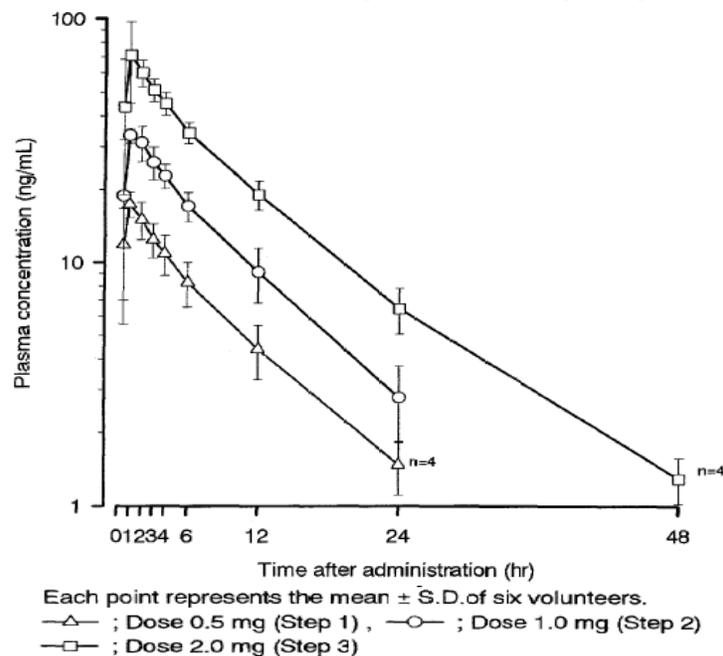


Table A-3-2: PK Parameters of Unchanged DNG in Human Plasma following a Single Dose Administration

Step No.	Dose (mg)	C _{max} (ng/mL)	T _{max} (hr)	T _{1/2α} (hr)	T _{1/2β} (hr)	AUC _{0-12hr} (ng·hr/mL)	AUC _{0-∞} (ng·hr/mL)	MRT (hr)	Cl _{tot} /F* (L/hr/body)	V _{dβ} /F* (L/body)
1	0.5	17.5 \pm 2.2	0.9 \pm 0.2	0.749 \pm 0.201	7.06 \pm 1.00	109.0 \pm 19.5	154.9 \pm 34.2	9.252 \pm 1.233	3.386 \pm 0.876	33.79 \pm 5.88
2	1	34.7 \pm 3.1	1.3 \pm 0.6	0.772 \pm 0.364	6.65 \pm 1.49	221.1 \pm 27.6	320.4 \pm 56.7	9.391 \pm 1.586	3.191 \pm 0.479	30.04 \pm 4.80
3	2	76.1 \pm 14.6	1.2 \pm 0.4	0.580 \pm 0.209	7.66 \pm 1.22	448.3 \pm 83.4	695.1 \pm 114.2	10.702 \pm 0.829	2.949 \pm 0.534	31.91 \pm 2.50

Each value represents the mean \pm S.D. of six volunteers.

The half-lives and β were estimated by a two-compartment model with first order absorption.

*; V_{dβ}/F = dose/(β ·AUC_{0-∞}), Cl_{tot}/F = dose/AUC_{0-∞}.

F; the extent of bioavailability, β ; the kinetic constant of the elimination phase.

The T_{max} was 0.9-1.3 hr. The C_{max} and AUC₀₋₁₂ showed dose-dependently higher values. The half-life in plasma (t_{1/2}) was 6.65-7.66 hr. The linearity of the PK of DNG had been retained over the dose range of 0.5-2.0 mg.

Reviewer’s comment: Japanese women showed higher AUC and C_{max} values compared to Caucasian women (18-40 yr). Cross-study comparison with Study B306 reveals that Japanese women had 4.8% and 20.5% higher mean AUC values than Caucasian women at doses of 1 and 2 mg DNG, respectively. Also, Japanese women had 26.2% and 41.9% higher mean AUC values than Caucasian women at doses of 1 and 2 mg DNG, respectively.

Table A-3-3: Comparison of Arithmetic Mean (SD or range) DNG PK Parameters Following Single Dose of DNG of Under Fasted Condition

Population	Study B306 (N=6)		Study A00681	
	Caucasian Premenopausal (N=6 per arm)		Japanese Premenopausal (N=6 per arm)	
Dose (mg)	1	2	1	2
C _{max} (ng/ml)	27.54 (5.20)	53.88 (8.97)	34.7 (3.1)	76.1 (14.6)
T _{max} (hr)	1.77 (0.5-4.0)	1.61 (0.75-2.0)	1.8 (0.6)	1.2 (0.4)
AUC(0-∞) (ng·hr/ml)	305.72 (65.18)	576.94 (146.03)	320.4 (56.7)	695.1 (114.2)

Both studies were conducted using units of 1 mg tablets. However, no information on components of the formulation was provided.

Per clinical reviewer, Dr. Gerald Willett, there were 4 non-Caucasians women amongst the 15 "during treatment" pregnancies in the 2 pivotal Phase 3 contraceptive studies (Studies A35179 and A39818)

- Subject 4505 = Hispanic = Subject failure to take medication properly
- Subject 4164 = Hispanic = Applicant could not categorize as either method or subject failure
- Subject 501028 = Hispanic = Subject failure to take medication properly
- Subject 505008 = Black = Subject failure to take medication properly

Therefore, none of the non-Caucasians pregnancies was deemed a definite method failure. It appears that there was no signal of race effect observed.

Although Japanese premenopausal women showed higher C_{max} and AUC values compared to Caucasian premenopausal women following a single dose of the same DNG strength, considering the limitations of a cross-study comparison and the fact that there were no ethnic signals observed in the pivotal Phase 3 studies, it was concluded that there is still a lack of evidence to believe the existence of race effect in the exposure of (b) (4)™ (EV/DNG).

Urinary Pharmacokinetics

Excretion ratios for the intact compound and metabolites in the urine were calculated from the urine concentrations and are shown in Table A-3-4.

Table A-3-4: Urinary Excretion of DNG (MJR-35) Intact Compound and Metabolites following a Single Dose Stage 1 (0.5 mg)

Collection period (hr)	Urinary excretion (% of dose)				Total
	MJR-35 Free + Conjugate	M1 Free	M2 Free	M3 Free	
Before	N. D.	N. D.	N. D.	N. D.	N. D.
0 – 6	3.7 ± 1.1	3.9 ± 0.9	1.0 ± 0.2	N. D.	8.7 ± 2.0
6 – 12	2.7 ± 0.6	3.7 ± 0.8	0.9 ± 0.1 (n=4)	N. D.	7.0 ± 1.4
12 – 24	2.2 ± 1.2 (n=5)	2.6 ± 0.9	N. D.	N. D.	4.5 ± 1.9
24 – 48	2.8 (n=2)	2.2 ± 0.8 (n=4)	N. D.	N. D.	3.6 ± 1.5 (n=4)
48 – 72	N. D.	N. D.	N. D.	N. D.	N. D.
0 – 72	9.2 ± 3.2	11.7 ± 2.8	1.6 ± 0.6	N. D.	22.5 ± 5.3

Each data represents the mean ± S. D. of six volunteers.
 N. D. : Not detected (below assay limit)
 (n=4), (n=5) : Each data represents the mean ± S. D. of four or five volunteers because the data of the other volunteers are below the assay limits.
 (n=2): Each data represents the mean of two volunteers because the data of the other volunteers are below the assay limits.

Stage 2 (1.0 mg)

Collection period (hr)	Urinary excretion (% of dose)				Total
	MJR-35 Free + Conjugate	M1 Free	M2 Free	M3 Free	
Before	N. D.	N. D.	N. D.	N. D.	N. D.
0 – 6	4.7 ± 0.6	4.8 ± 1.8	1.3 ± 0.5	0.2 ± 0.1 (n=3)	10.9 ± 2.7
6 – 12	2.7 ± 0.6	3.5 ± 1.0	0.7 ± 0.2	N. D.	6.9 ± 1.6
12 – 24	2.1 ± 0.8	3.3 ± 1.2	0.8 ± 0.3 (n=5)	0.2 (n=1)	6.1 ± 1.5
24 – 48	2.6 ± 1.7 (n=5)	2.1 ± 0.7 (n=5)	N. D.	N. D.	4.6 ± 2.3 (n=5)
48 – 72	1.0 (n=1)	N. D.	N. D.	N. D.	1.0 (n=1)
0 – 72	11.8 ± 1.6	13.3 ± 3.9	2.7 ± 1.0	0.3 ± 0.1 (n=3)	28.0 ± 5.3

Each data represents the mean ± S. D. of six volunteers.
 N. D. : Not detected (below assay limit)
 (n=3), (n=5) : Each data represents the mean ± S. D. of three or five volunteers because the data of the other volunteers are below the assay limits.
 (n=1): Each data represents the mean of one volunteer because the data of the other volunteers are below the assay limits.

Stage 3 (2.0 mg)

Collection period (hr)	Urinary excretion (% of dose)							Total
	MJR-35		M1		M2	M3	M5	
	Free	Free + Conjugate	Free	Conjugate	Free	Free	Free	
Before	N. D.	N. D.	N. D.	N. D.	N. D.	N. D.	N. D.	N. D.
0 – 6	N. D.	2.1 ± 1.1	2.8 ± 1.6	0.3 ± 0.2 (n=3)	0.8 ± 0.4	0.1 (n=2)	N. D.	5.9 ± 3.0
6 – 12	N. D.	2.6 ± 0.9	4.1 ± 1.2	0.4 ± 0.4 (n=4)	1.0 ± 0.2	0.4 (n=1)	N. D.	7.9 ± 2.0
12 – 24	N. D.	1.8 ± 0.9	3.1 ± 1.1	0.4 ± 0.3 (n=3)	0.7 ± 0.2	N. D.	N. D.	5.8 ± 1.9
24 – 48	N. D.	1.0 ± 0.4	1.9 ± 0.5	N. D.	0.6 (n=1)	N. D.	N. D.	3.1 ± 0.9
48 – 72	N. D.	0.4 (n=1)	0.4 (n=2)	N. D.	N. D.	N. D.	N. D.	0.6 (n=2)
0 – 72	N. D.	7.6 ± 1.6	12.0 ± 2.3	1.0 ± 0.8 (n=4)	2.6 ± 0.4	0.3 (n=2)	N. D.	23.0 ± 2.6

Each data represents the mean ± S. D. of six volunteers.
 N. D. : Not detected (below assay limit)
 (n=3), (n=4) : Each data represents the mean ± S. D. of three or four volunteers because the data of the other volunteers are below the assay limits.
 (n=2): Each data represents the mean of two volunteers because the data of the other volunteers are below the assay limits.
 (n=1): Each data represents the mean of one volunteer because the data of the other volunteers are below the assay limits.

The total urinary excretion of DNG and its metabolites up to 72 hr following a dose of 0.5, 1.0, and 2.0 mg was 22.5, 28.0, and 23.0%, respectively. As most of this had been excreted within 48 hr of the dose, it was suggested that DNG has mostly disappeared from the body within 48 hr after the dose.

Safety, Menstrual Cycle, Laboratory Test Results

No abnormal variations had been observed in any of the subjects. All the subjects menstruated after administration of the study drug and it was confirmed that none had become pregnant during the trials.

CONCLUSIONS

The PK of orally-administered DNG showed dose-linearity over a dose range of 0.5-2 mg in Japanese women and that the drug has virtually disappeared from the body within 48 hr following the dose.

A.1.4. Study B306

Open Randomized (Latin square design) Trial to Determine Linearity of Dienogest Pharmacokinetics in 12 Healthy Female Volunteers, Treated with 1, 2, 4, and 8 mg of Dienogest, Administered Successively as a Single Dose after Wash-out Corresponding to Duration of the Menstrual Cycle (Dienogest Tablets Containing 1 mg)

Protocol No: B306
Phase: 1
Principal Investigator: Prof. G. Strauch
Clinical Study Center: (b) (4)
Clinical Study Dates: April 20, 1993 – January 19, 1994
Analytical Study Facility: (b) (4)

OBJECTIVE

The objective of the study was:

- To investigate the dose linearity of DNG PK
- To determine and compare the principal plasma PK parameters of DNG after oral administration, at different doses.

STUDY DESIGN

The study was an open-label, single center, randomized, single dose study. 12 Caucasian healthy female volunteers (age of 20-34 yr, mean age 26.7 yr [SD=4.6 yr], mean height 166.9 cm [SD=6.9 cm], and mean weight 60.3 kg [SD=8.5 kg]) under non-hormonal contraception received each of the 4 studied doses, interspaced by a cycle, and administered in random order.

The tablets were administered with 150 ml of water, in standing position. Dosage was as follows: 1, 2, 4, or 8 mg (as a function of the trial period), as a single dose, in the morning after at least 8 hr fasting. The test drug was DNG formulated as 1 mg tablets.

Each administration of the drug took place between Day 1 and Day 7 of the cycle, and duration of the wash-out period was a function of cycle duration:

- The subjects presented at the Clinical Pharmacology Unit of (b) (4) in the morning, after fasting for at least 8 hr.
- A clinical examination, consisting of blood pressure and heart rate recordings, was performed.
- Blood samples (5 ml) were taken at the following times: Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 34, and 48 hr post-dose (i.e., 16 samples).

In the 3 subjects who initially received 8 mg (in keeping with the randomization), urine specimens were collected according to a specific objective, different from that of the overall trial (fundamental metabolism studies). Urine specimens were collected at intervals of 0-4 hr, 4-12 hr, and 12-24 hr.

The subjects were requested to collect urine over the last 12 hr preceding dosage, in a jar supplied for this purpose. During the 24-hr monitoring on-site at the Unit, meals were served 4 hr then 11 hr after administration of the drug. After 24 hr, the subjects could leave the Unit, their clinical status having first been verified.

The inclusion criteria were as follows:

- Healthy female volunteers of Caucasian race (age of 18-40 yr),
- With weight ranging between ideal weight and ideal weight $\pm 10\%$ indicated in the table of weights with the protocol.
- Having had regular menstrual cycles, ranging from 25-32 days, during the 3 months preceding the trial,

- Using efficacious non-hormonal contraception (loop, diaphragm and/or spermicide, condom), regularly for at least one month, throughout the duration of the trial and during the following month.
- Non-smoker, or moderate smoker (≤ 5 cigarettes/day),

The following subjects were excluded from the trial:

- Having presented or presenting cardiovascular, renal, hepatic, gastrointestinal, endocrine, neuropsychological or allergic disorders incompatible with conduct of the trial,
- Pregnant subjects,
- Subjects taking hormonal contraception or using a hormonal intrauterine device,
- Subjects taking other long-term medication, or medication within the 15 days preceding the trial,

Concomitant Therapy

Except in emergency cases, no medication other than the test drug was absorbed throughout duration of the trial.

Pharmacokinetics and Statistical Analysis

For each subject, the following parameters had to be calculated after each administration of DNG:

- C_{max} , T_{max} , $t_{1/2}$, AUC_{0-48} , $AUC_{0-\infty}$, apparent plasma clearance (CL), and apparent distribution volume (V_d).

For C_{max} and $AUC_{0-\infty}$:

- Linear regression expressing C_{max} logarithms and AUC as a function of the logarithm of the administered dose for each of the 12 subjects, and comparison of obtained slopes to unit 1, characterizing linearity by t-tests for paired series.
- Analysis of variance taking into account subject, order of administration, dose, and period factors, performed on the parameter logarithms with calculation of the CIs for the mean ratio, taking the 1 mg dose as reference dose.

For T_{max} : comparison of T_{max} by the Friedman test.

For elimination half-lives: analysis of variance taking into account subject, order of administration, dose, and period factors

Data input, determination of PK parameters, and statistical analysis were performed on the VAX (DEC) of the (b) (4) with SAS software (SAS Institute), version 6.07, for data entry, description, and statistical tests, and PHARM-NCA (SIMED) for determination of PK parameters.

Bioanalytical Methods

DNG was measured by a RIA method. The DNG (present in the plasma sample) is allowed to compete with tritium-labeled DNG for a specific antiserum. At the end of the antigen-antibody incubation, the bound and free forms of the antigen are separated by adsorption of the free form on dextran charcoal. After centrifugation, the radioactivity of an aliquot of the supernatant (bound fraction) was determined by LSC.

Each day of the study, 4 QCs are subjected to exactly the same treatment as the samples for analysis. The values from these checks allowed the validation of the results of the concentration measurements performed on each day of the study. All acceptance criteria and performance were in compliance with the *Bioanalytical Method Validation Guidance*.

Safety and Clinical Laboratory Measurements

An end-of-trial clinical examination was performed 48 hr after the last administration of the test drug consisting of a standard clinical examination with measurement of blood pressure; a 12-lead ECG; and a laboratory examination identical to the inclusion examination.

RESULTS

Pharmacokinetics

The arithmetic mean values, standard deviation, minimum and maximum for the PK parameters of the 12 subjects were as follows:

Table A-4-1: PK Parameters following Administration of DNG 1 mg

Parameters	Mean	Standard deviation	Minimum	Maximum
C _{MAX} (ng/ml)	27.54	5.20	19.21	37.84
T _{MAX} (h)	1.77	0.99	0.50	4.00
Half-life (h)	7.93	2.13	5.70	12.67
AUC 0-48 (ng.h/ml)	277.53	60.58	193.91	396.35
Extrapolated AUC (ng.h/ml)	305.72	65.18	213.40	429.60
Clearance/F (l/h)	3.41	0.74	2.33	4.69
Distribution volume/F (l)	37.40	4.95	28.37	43.58

Table A-4-2: PK Parameters following Administration of DNG 2 mg (1 mg x 2 tablets)

Parameters	Mean	Standard deviation	Minimum	Maximum
C _{MAX} (ng/ml)	53.88	8.97	40.97	71.17
T _{MAX} (h)	1.61	0.42	0.75	2.00
Half-life (h)	7.52	2.19	3.47	11.65
AUC 0-48 (ng.h/ml)	551.21	139.56	267.33	785.76
Extrapolated AUC (ng.h/ml)	576.94	146.03	283.90	810.60
Clearance/F (l/h)	3.74	1.24	2.47	7.04
Distribution volume/F (l)	37.65	5.94	30.84	47.21

Table A-4-3: PK Parameters following Administration of DNG 4 mg (1 mg x 4 tablets)

Parameters	Mean	Standard deviation	Minimum	Maximum
C _{MAX} (ng/ml)	101.08	10.82	81.28	119.03
T _{MAX} (h)	1.79	0.72	0.50	3.00
Half-life (h)	8.32	2.22	3.95	12.90
AUC 0-48 (ng.h/ml)	1119.76	222.46	646.69	1399.05
Extrapolated AUC (ng.h/ml)	1153.32	237.93	661.80	1451.00
Clearance/F (l/h)	3.64	0.93	2.76	6.04
Distribution volume/F (l)	41.55	7.12	34.47	59.23

Table A-4-4: PK Parameters following Administration of DNG 8 mg (1 mg x 8 tablets)

Parameters	Mean	Standard deviation	Minimum	Maximum
C _{MAX} (ng/ml)	212.07	43.92	161.24	330.35
T _{MAX} (h)	1.51	0.82	0.50	3.00
Half-life (h)	8.91	1.94	5.97	12.86
AUC 0-48 (ng.h/ml)	2229.58	419.76	1524.27	2999.27
Extrapolated AUC (ng.h/ml)	2292.41	447.66	1532.10	3115.30
Clearance/F (l/h)	3.61	0.72	2.57	5.22
Distribution volume/F (l)	45.43	9.35	36.65	68.24

Comparison of the principal PK parameters after administration of 1, 2, 4, or 8 mg yielded the following results:

AUC_{0-∞}

- Linear regression of the type $\log(\text{AUC}) = A' + B' \times \log(\text{number of mg})$ performed for each of the 12 subjects showed proportionality between the number of mg administered and the resultant AUC.
- The obtained B' coefficients did not significantly differ from 1 (t-test for paired series: $p = 0.27$).
- The obtained mean B' coefficient is equal to 0.98 ± 0.08 , with a confidence interval equal (0.91-1.02).

C_{max}

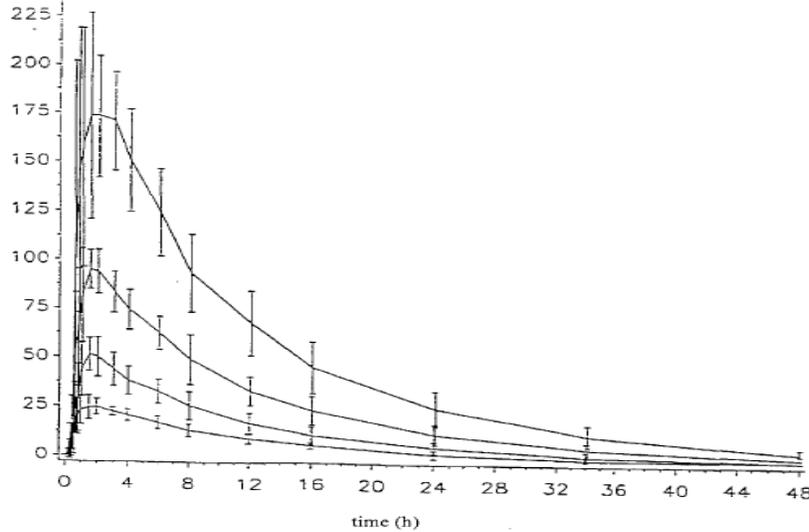
- Linear regressions of the type $\log(C_{\text{max}}) = A + B \times \log(\text{number of mg})$ also showed proportionality between the number of mg administered and the value of the resultant C_{max}.

- The obtained B coefficients do not significantly differ from 1 (t- test for paired series $p = 0.37$).
- The obtained mean B coefficient is equal to 0.98 ± 0.09 , with a confidence interval equal to $(0.91-1.03)$.

T_{max}

- No significant different was found between the values obtained with the different doses: $p = 0.83$.

Figure A-4-1: Mean \pm SD DNG Concentration (ng/ml)–Time Curve following Administration of 1, 2, 4, and 8 mg Tablets



Reviewer’s comment: As shown in Figure 10 and 11, the PK dose linearity of DNG AUC and C_{max} was established following single oral dose over the range of 1-8 mg in Caucasian premenopausal women (Study B306) as well as over a dose range of 0.5-2 mg in Japanese premenopausal women (Study A00681).

Figure 10: Relationship Between DNG Dose and Mean AUC(0- ∞) Following Single Dosing in Premenopausal Women (Studies B306 [in Caucasian] and A00681 [in Japanese])

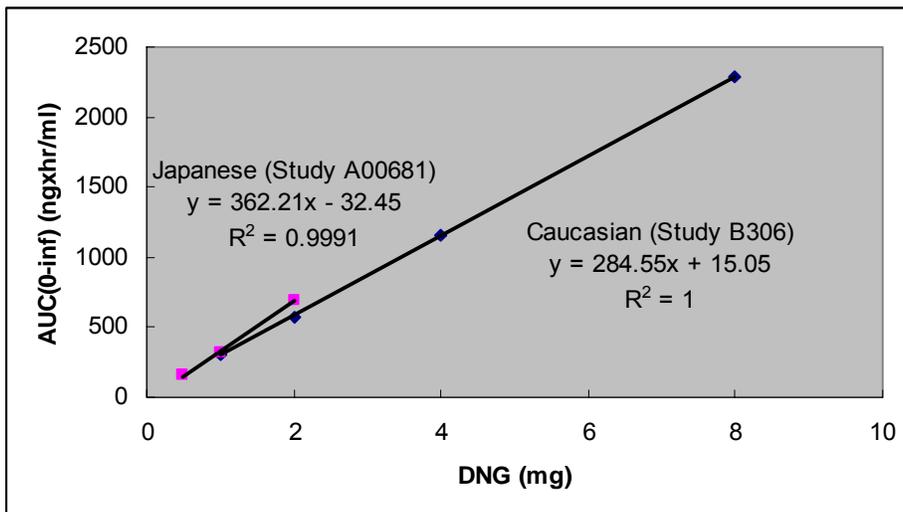
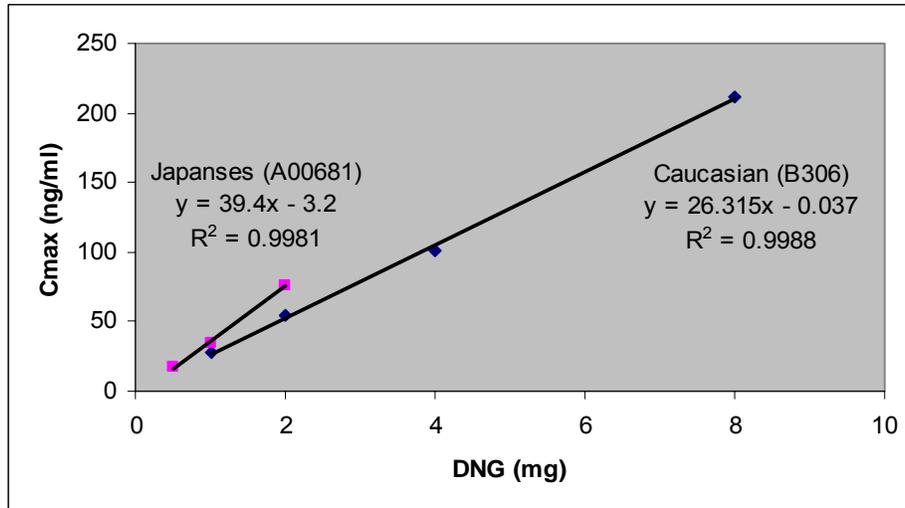


Figure 11: Relationship between DNG Dose and Mean C_{max} Following Single Dosing in Premenopausal Women (Studies B306 [in Caucasian] and A00681 [in Japanese])



Safety Results

The AEs occurred during the study included the following: nausea and anorexia, vomiting, headache, abdominal flatulence, pelvic pain, spotting, delayed menstruation, and leucorrhea.

CONCLUSIONS

12 healthy females received 4 single doses of DNG 1, 2, 4, and 8 mg in a randomized order, during 4 consecutive menstrual cycles. In each respective cycle, 48 hr PK analyses were performed to determine DNG linearity at these doses. The results obtained for the PK parameters showed that the DNG PK was linear over the dose range of 1-8 mg.

A.1.5. Study B276

Open-label Study to Investigate the Single Dose and the Repeated Dose (for 14 days) Pharmacokinetics of the Final Tablet Formulation of 2 mg Dienogest (DNG) in 16 Healthy Young Women

Protocol No: B276
Phase: 1
Principal Investigator: Eric Sicard, M.D.
Clinical Study Center: Clinical Pharmacology, Schering AG, Berlin, Germany
Clinical Study Dates: May 17, 1999 - August 19, 1999
Analytical Study Facility: (b) (4)
Analytical Study Dates: August 1999 - November 1999

OBJECTIVE

Evaluation of the single dose and repeated dose (for 14 days) PK of the final tablet formulation containing 2 mg DNG.

STUDY DESIGN, TREATMENTS, AND SUBJECTS

This study combined the evaluation of single dose PK with the evaluation of repeated dose PK. To reduce intrinsic (hormonal) influences, the study drug was administered cycle-dependently, and both treatments were started in the first half of the same menstrual cycle. For this purpose, the study had 2 treatments both within the same menstrual cycle. No control or reference group was needed. The duration of the wash-out period had been set to 5 days based on the known serum elimination half-life of 5-10 hr for DNG. A treatment period of 14 days was chosen for the repeated dose PK of DNG to ensure steady state conditions.

16 female Caucasian volunteers participated in this study. Their mean age was 33.68 yr (range: 24-38 yr). They weighed on the average 62.75 kg (range: 55-72 kg). Their mean height was determined to be 168.56 cm ranging between 159.0-176.0 cm. The corresponding calculated mean body mass index (BMI) was 22.13 kg/m² (range: 18.7-26.0 kg/m²).

Volunteers received 1 tablet containing 2 mg DNG orally as a single dose treatment. After a wash-out period of 5 days volunteers received 1 tablet orally containing 2 mg DNG daily over a period of 14 days as repeated dose treatment. The investigational product (ZK number: 37659) was provided by Schering AG, Berlin, Germany.

Study Drug Administration

- For *PK profiles* on Day 1/Period 1 and on Day 14/Period 2: The volunteers were instructed to fast after 21:00 hr the previous evening (drinking of water was allowed) in order to ensure a fasting period of at least 10 hr before intake. In the morning, the tablets were to be taken between 7:00 and 9:00 hr with 200 ml non-carbonated water at room temperature.
- For *trough levels*: The tablets were to be taken on an empty stomach with a glass of water. Intake took place immediately after blood sampling preferably at the same time as on Day 1/Period 2.
- For *intake at home*: The volunteers were instructed to take the tablets on an empty stomach with a glass of water preferably at the same time as on Day 1/Period 2.

Inclusion criteria

Volunteers had to fulfill all the following criteria before being included in the treatment:

- Nonsmoking healthy female (age: 18-40 yr)
- BMI: ≥ 18 kg/m² and ≤ 26 kg/m²
- Following delivery, abortion or lactation, volunteers should have had at least two normal cycles of 24-35 days
- Willingness to use non hormonal methods of contraception during the study or to accept abstinence

Exclusion criteria

Volunteers with the following conditions which might have had an impact on PK parameters were excluded:

Medical history:

- Significant history of pulmonary, cardiovascular, hepatic, gastrointestinal, biliary, renal, hematological, endocrine, neurological, or psychiatric disease
- During pregnancy

Medication/drug use and special behavioral patterns:

- Within 8 weeks before study drug administration, use of systemic or topical medications or substances which opposed the study objectives or which might have influenced them, e.g., an investigational compound, any other drug known to induce (rifampicin, dexamethasone, phenobarbital, anticonvulsants) or inhibit (macrolides, ketoconazole, erythromycin, cimetidine, verapamil) liver enzymes, ampicillin, amoxicillin, or any broad spectrum antibiotic
- Use of sex hormones within 2 months (oral, transdermal, transvaginal) or 2/6 months (long acting injectable [once per month/once per three months] or implanted preparations) before first study drug administration
- Regular intake of medication

Concomitant Therapy

If a volunteer used concomitant therapy, this was to be documented by type (generic name, if applicable), amount, indication, and duration on the appropriate CRF.

Bioanalytical Methods

The quantitative determination of DNG in serum was performed using a RIA. Briefly, DNG was extracted from serum with diethylether. The extract was dried under nitrogen and the remainder was redissolved in a buffer solution. This solution was incubated overnight in the cold with specific antiserum and tracer (³H-DNG). Following incubation, the antibody-bound drug was separated from unbound drug by use of dextran-coated charcoal and the fraction containing the antibody-drug complex was subjected to radiometric analysis. The concentration of DNG in serum samples was calculated by means of the PK LIMS software 3.7 (Schering AG) using a calibration curve as a reference. Individual assays were monitored for precision and accuracy using QC samples which were analyzed under the same conditions as the samples of unknown DNG concentration. The LLOQ was set to 0.5 ng/ml using a sample volume of 100 µl. Values below the LLOQ were set to zero. All acceptance criteria and performance were in compliance with the *Bioanalytical Method Validation Guidance*.

Safety and Clinical Laboratory Measurements

An additional drug screen and a pregnancy test in urine were carried out at the study site before the first drug administration of the repeated dose treatment (Day 1/Period 2). The calculated mean values for all volunteers for all laboratory parameters were within the normal range at recruitment. The urine drug screens were negative for all volunteers.

PHARMACOKINETICS RESULTS

The mean DNG serum concentration versus time curve assessed after administration of the Day 14 dose in study Period 2 is shown in Figures A-5-1 (linear scale) and A-5-2 (semi-logarithmic scale) together with the mean concentration versus time curves observed after single dosing.

In all samples taken before the first administration of DNG in study Period 2, i.e., after a 5-day washout period, the DNG serum concentration was below the LLOQ. After the last administration of the study medication on Day 14 in this study period, DNG serum concentrations were quantifiable for at least 36 hr in all subjects. In 11 out of 16 subjects, minor amounts of DNG were still quantifiable in the last sample taken in this study period, i.e., 60 hr after administration.

The mean DNG serum concentration versus time curves showed similar profiles for the two administration modes. After repeated administration, however, the mean DNG serum concentrations were generally slightly higher than after single administration.

Figure A-5-1: Mean DNG Serum Concentrations After Single and Repeated (Day 14) Oral Administration of 2 mg DNG Daily to 16 Healthy, Young Women (Arithmetic Means and Standard Deviations; Linear Scale)

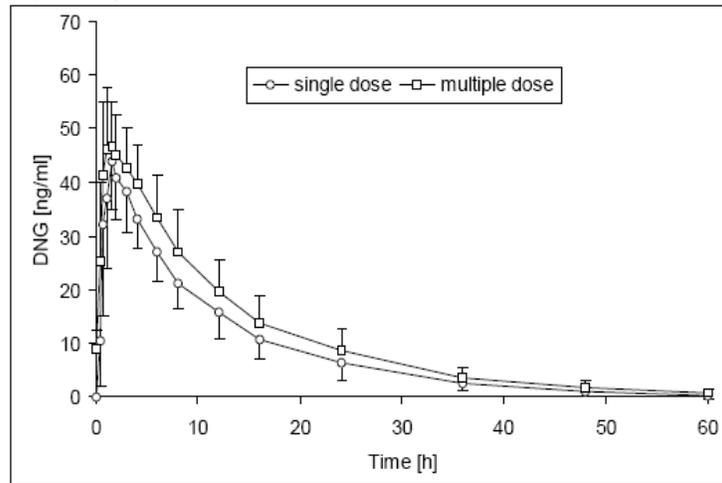


Figure A-5-2: Mean DNG Serum Concentrations After Single and Repeated (Day 14) Oral Administration of 2 mg DNG Daily to 16 Healthy, Young Women (Arithmetic Means and Standard Deviations; Semi-logarithmic Scale)

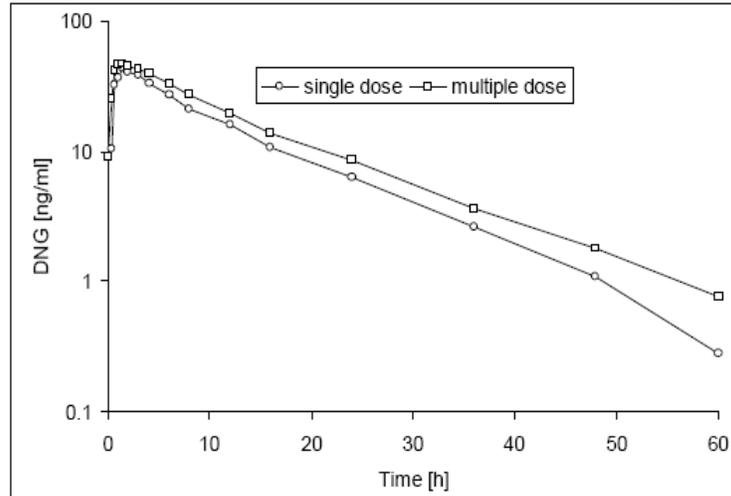


Table A-5-1: Arithmetic Mean (SD) PK Parameters Following Oral Administration of 2 mg DNG

PK Parameter	Single Dose	Steady State
C_{max} (ng/ml)	47.6 (8.74)	52.2 (8.32)
T_{max} (hr) ^a	1.50 (0.67-3.00)	1.25 (0.67-6.00)
$t_{1/2}$ (hr)	9.38 (1.94)	10.2 (1.76)
AUC(0-24) (ng·hr/ml)	441 (92.4)	547 (129)
AUC(0-tlast) (ng·hr/ml)	519 (137)	666 (195)
AUC(0-∞) (ng·hr/ml)	535 (138.4)	682 (205)
CL/f (ml/min)	66.3 (17.4)	64.1 (14.6)

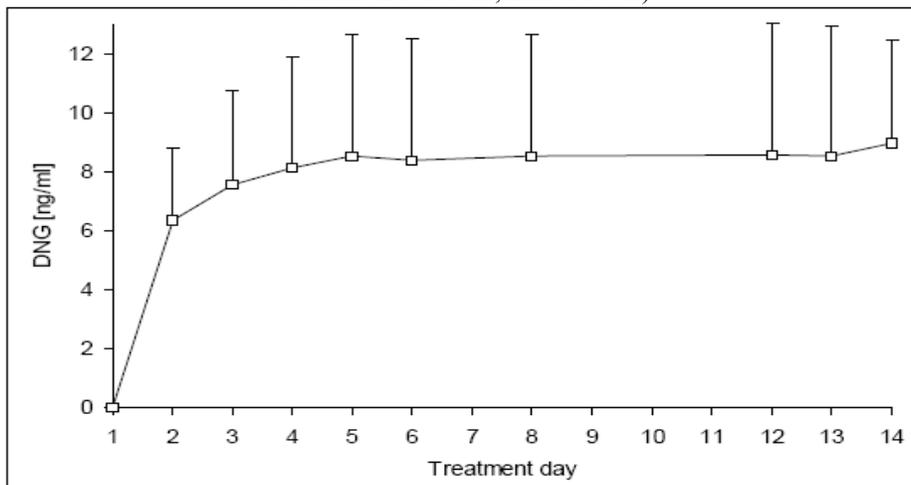
^a Median (range)

- Mean (SD) accumulation ratio for AUC(0-24) = $AUC(0-24)_{SS} / AUC(0-24)_{SD} = 1.24$ (0.13)
- Mean (SD) mass balance factor = $AUC(0-24)_{SS} / AUC(0-\infty)_{SD} = 1.03$ (0.10)

Figure A-5-3 shows the mean DNG serum concentrations measured at the ends of the 24 hr dosing intervals prior to new dosing (trough concentrations). On multiple dosing, arithmetic mean DNG trough concentrations

increased from 6.36 ng/ml at the end of the first dosing interval until a plateau of approximately 8.50 ng/ml was reached on Day 5, i.e., after the 4th dose. A further minor increase in mean DNG trough concentrations to 8.98 ng/ml was observed at the end of the treatment period, before administration of the last dose on Day 14. 24 hr after administration of the last dose on Day 14 (i.e., multiple dose profiling day), however, the mean DNG serum concentration was down to 8.57 ng/ml again, thus indicating that steady-state conditions were reached during the 14 day treatment period.

Figure A-5-3: Mean DNG Serum Concentrations Before New Dosing (Trough Concentrations) on Repeated Oral Administration of 2 mg DNG Daily to 16 Healthy, Young Women (Arithmetic Means and Standard Deviations; Linear Scale)



Safety Results

A total of 49 AEs were reported for the single (12 AEs) and repeated dose treatments (37 AEs). The most frequently reported AEs of the related category were intermenstrual bleeding and headache. In 6 cases, AEs were reported as being severe headache, intermenstrual bleeding, or breast enlargement. No serious AEs (SAE) were reported.

CONCLUSIONS

Inspection of mean trough DNG serum concentrations during multiple dosing showed that a plateau was reached on Day 5 after about four 24 hr dosing intervals. Thus, the PK parameters determined after the Day 14 administration represent steady-state characteristics.

Comparison of DNG PK after single administration and at steady-state revealed a slight accumulation during the two weeks treatment period. The AUC(0-24) at steady-state was on average 1.24 times higher than the corresponding AUC(0-24) after single administration. The mass balance factor which was determined to be 1.03 on average, thus showing the AUC within a dosage interval at steady-state is equal to the total AUC after single dose. Terminal half-life of DNG following single and multiple dose is approximately 10 hr. Furthermore, the terminal half-life and the oral clearance remained unchanged when PK after single administration and at steady-state were compared.

In conclusion, the present study showed that DNG concentrations in serum increase during the initial treatment phase after daily administration of 2 mg DNG and reach steady-state concentrations in about 4 days following the first dose (i.e., on Day 5). Steady-state DNG PK is predictable from those obtained after single administration.

A.1.6. Study A25711

An Open-label, Non-randomized, Multiple-dose Study to Investigate the Pharmacokinetics of a 28-day Four-phasic Oral Contraceptive Containing Estradiol Valerate and Dienogest (SH T00658ID) in 18 Healthy Female Subjects

Protocol No: A25711
Phase: 1
Principal Investigator: Dennis N. Morrison, DO
Clinical Study Center: (b) (4)
Clinical Study Dates: January 5, 2005 - June 28, 2005
Analytical Study Facility: (b) (4) (E2, E1, and E1S) and Schering Oy, Finland (DNG)
Analytical Study Dates: April 26, 2005 - June 8, 2005 (E2, E1, and E1S) and March 2005 - July 2005 (DNG)

OBJECTIVE

The objective of this study was to evaluate the PK of E2 and DNG after multiple oral doses in healthy women.

STUDY ENDPOINTS

The primary endpoints were PK parameters including AUC(0-24), C_{max}, and T_{max} were determined for DNG, E2, E1, and E1S. The half-life of DNG was also estimated.

STUDY DESIGN, TREATMENT, AND SUBJECTS

This was an open-label, non-randomized, 1 period, 1 treatment, multiple-dose PK study of EV/DNG (SH T00658ID: 4-phasic TBM regimen) tablets in healthy premenopausal female subjects. In addition, the potential effect of the SH T00658ID regimen on serum concentrations of SHBG, cortisol, and CBG were evaluated weekly during the treatment period.

All 18 subjects in this study were healthy premenopausal females, ranging in age 18-46 yr (mean age: 26.6 yr). Most subjects (94%) were Caucasian. The mean BMI of the Safety Analysis Set was 24.2 kg/m². The mean body weight and height of the safety analysis set was 68.6 kg and 168.5 cm, respectively. 16 (89%) subjects completed the study and 15 subjects (83%) were included in the PK analysis set.

Inclusion Criteria:

- Nonsmoking healthy female subject ranging in age from 18-50 yr old
- BMI within range: $18 \leq \text{BMI} \leq 26 \text{ kg/m}^2$
- Regular menstrual cycles
- FSH within normal range for fertile women
- Negative pregnancy test
- At least 3 normal menstrual cycles following delivery, abortion, or lactation
- Willingness to use non-hormonal methods for contraception during the washout period and during the cycle with the multiple dose treatment (e.g., non-medicated intrauterine devices, condoms, diaphragms, spermicidal vaginal suppositories, or abstinence)

Exclusion Criteria:

Medical history - A history of relevant diseases, especially:

- Incompletely healed or pre-existing diseases for which it can be assumed that the absorption, distribution, metabolism, elimination, and effect of the study drugs will not be normal
- Known metabolic disorders (e.g., hyperlipidemia, diabetes mellitus)

Medication, drug use, and special behavior patterns:

- Regular intake of medication (other than OCs)
- Use of OCs (OC users may be included after at least 2 washout cycles, i.e., at least an 8-week OC-free interval before first study drug administration)
- Use of depot preparations (injectables or implants or medicated intrauterine devices) containing sex hormones during the last 6 months before first study drug administration

The start of treatment for each subject was dependent on her menstrual cycle, i.e., the first dose was administered on the 2nd day of the individual's menstrual cycle. Dosing with EV/DNG tablets was for 28 days.

On PK days (Day 1 and Day 24), subjects were allowed to eat and drink as usual until 21:00 hr on the day before study drug administration. Thereafter, subjects could only drink water (fasting period of ≥ 10 hr before study drug administration) except for 1 hr before and after dosing. The treatment was administered in the morning between 07:00 and 09:00 hr before breakfast. A light breakfast was provided at the site 2 hr after dosing.

FORMULATION

The investigational drug employed in the study is described below:

Table A-6-1: Pharmaceutical Information on Investigational Product - Blister Package SH T00658ID

Pharmaceutical Information	SH T00658ID - Blister Package				
Generic name	EV	EV/DNG	EV/DNG	EV	Placebo
ZK number	5104	5104/37659	5104/37659	5104	N/A
SH Number	SH T00658EA	SH T00658GA	SH T00658M	SH T00658HA	SH T00658P
Amount of drug substance per unit	3 mg EV	2 mg EV, 2 mg DNG	2 mg EV, 3 mg DNG	1 mg EV	N/A
Type of formulation ^a	Dark yellow, round, coated	Medium red, round, coated	Light yellow, round, coated	Dark red, round, coated	White, coated
Route of administration	Oral	Oral	Oral	Oral	Oral
Dosing day	1-2	3-7	8-24	25-26	27-28
Batch number	CL-3188				
Vehicle composition	Lactose, maize starch, stearate, titanium (IV) oxide, ferric oxide	(b) (4)	(b) (4)	(b) (4) magnesium stearate, (b) (4) talc,	(b) (4)
Type of packaging and units per package	Blister card with 26 active tablets and 2 placebo tablets per card				
Expiry date	August 2007 ^b				
Manufacturer	Schering AG, Berlin, Germany				

EV = estradiol valerate, DNG = dienogest.

^a Non-white tablet coloring achieved with yellow or red pigment.

^b Expiry date was not included on the label as stability studies were ongoing during the conduct of the study.

PHARMACOKINETIC EVALUATION

Blood sampling

Blood samples were collected as below for determination of DNG, E2, E1, and E1S serum concentrations:

- Day 1: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hr post-dose
- Day 24: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 36 hr post-dose
- Additional pre-dose blood samples were also collected on Treatment Days 4, 6, 8, 9, 12, 15, 18, 21, 23, 26, 27, 28, and 29 (24 hr after last dose) to measure trough serum concentrations

SHBG, serum cortisol, and cortisol binding globulin (CBG) were monitored before treatment and on Treatment Days 8, 15, 21, and 29.

Concomitant Therapy

Any medications prescribed for the subject during her participation was recorded on the appropriate CRF page.

Other restrictions

- Alcoholic beverages were not permitted within 48 hr before dosing and throughout the study
- Food or beverages containing grapefruit were not permitted within 48 hr before dosing and throughout the study
- Drinking water was not allowed for 1 hr before and after dosing

Bioanalytical method



(b) (4)

Determination of E1S Concentrations



(b) (4)

Acceptance criteria and performance for each analyte were in compliance with the *Bioanalytical Method Validation Guidance*.

Safety Assessments

Clinical laboratory variables or evaluations (at baseline - Screening Visit 1 and Follow-up Visit 1): hematology, coagulation parameters, serum chemistry, urinalysis, and serum cortisol and CBG (monitored at pre-treatment and on Days 8, 15, 21, and 29). Follow-up laboratory examinations were performed within 4 weeks after the last dose of study medication with the following tests: ECG (12-lead), physical examination, vital signs (height, weight, blood pressure, and heart rate), and blood and urine tests.

DATA ANALYSIS

Pharmacokinetics

Summary statistics (number of observations, arithmetic mean, standard deviation, coefficient of variation, minimum, median, maximum, and geometric mean) were submitted for the PK parameters.

Safety Evaluations and Adverse Events

AEs were to be coded using an internationally recognized dictionary. Signs/symptoms before first study drug administration were recorded as baseline findings or serious baseline findings. AEs observed by the investigator or spontaneously reported by the volunteer were documented.

PHARMACOKINETIC RESULTS

PK of DNG

Mean serum concentration–time profile is presented in Figures A-6-1 and A-6-2. Mean PK parameters of DNG are summarized in Table A-6-2. DNG mean (SD) half-life was 12.3 (1.4) hr.

Figure A-6-1: Mean (\pm SD) Concentration-Time Curve of DNG (ng/ml) Following Daily Oral Dose of SH T00658ID in 15 Healthy Female Subjects

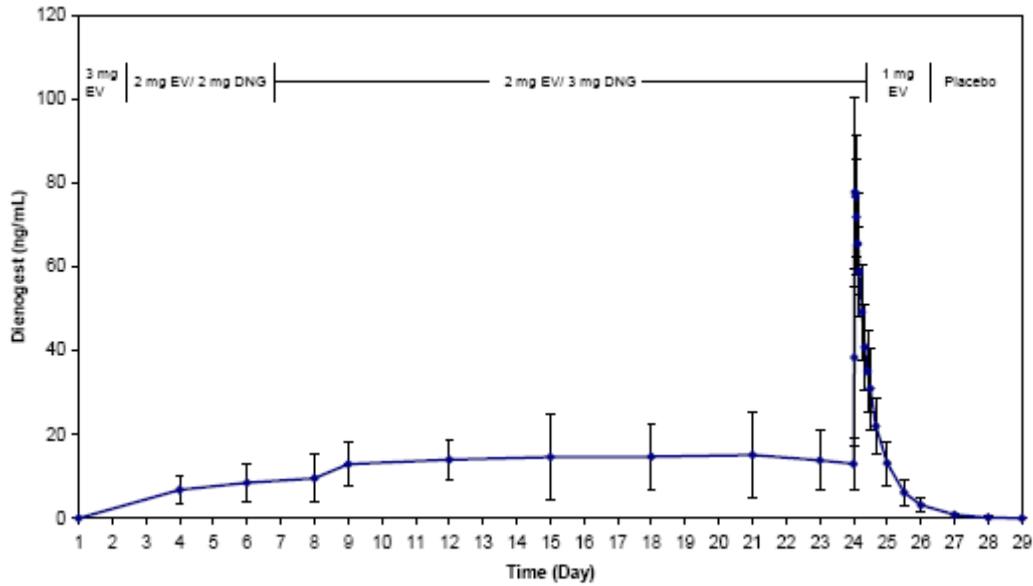
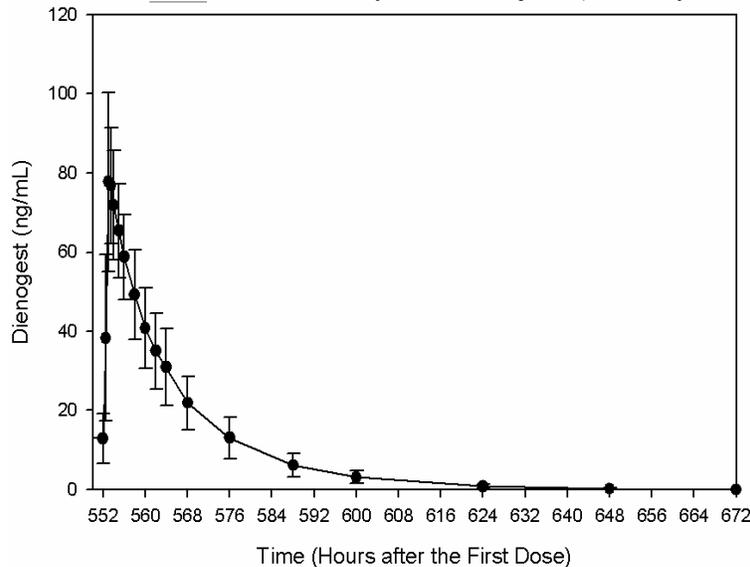


Figure A-6-2: Mean (\pm SD) Concentration-Time Curve of DNG (ng/ml) on Day 24 Following Daily Oral Dose of SH T00658ID in 15 Healthy Female Subjects (PK Analysis Set)



Reviewer's comment: Steady-state of DNG was reached within 4-5 days of dosing at each dose sequence. DNG 2 mg dose started on Day 3 and steady-state was reached by pre-dose on Day 8 (i.e., 5 days later). DNG 3 mg dose started on Day 8 and steady-state was reached by Day 12 (i.e., 4 days later). DNG 3 mg steady state was reached earlier since DNG 3 mg dose sequence started at the steady-state of DNG 2 mg sequence. This was in line with the observations in Study B276 where DNG steady-state concentrations were reached in about 4 days following the first dose of DNG 2 mg. The co-administration of E2 (3 mg on Days 1-2 and 2 mg on Days 3-24) did not alter the time to reach DNG steady-state.

DNG PK characterized following administration of 2 mg EV/3 mg DNG in different studies are summarized below

Table A-6-2: Comparison of Arithmetic Mean (SD) DNG PK Parameters following Administration of SH T00658M (2 mg EV/3 mg DNG) Under Fasted Conditions in Caucasian Women

	Study A25711	Study A30020	Study A29143	Study A29972
Population	Premenopausal (N=15)	Postmenopausal (N=12)	Postmenopausal (N=35)	Postmenopausal (N=17)
Regimen (Day)	Steady-state (Day 24)	Steady-state (Day 7)	Single dose (Day 1)	Single dose (Day 1)
C _{max} (ng/ml)	85.2 (19.7)	88.4 (13.3)	88.3 (16.6)	91.7 (15.3)
T _{max} (hr)	1.5 (1.0-2.0)	1.0 (0.5-2.0)	1.0 (0.5-3.0)	1.0 (0.5-1.5)
AUC(0-24) (ng·hr/ml)	828 (187)	827 (222)	768 (135)	794 (158)
t _{1/2} (hr)	12.3 (1.4)	NA	10.7 (1.63)	11.3 (2.48)

Median (range) for T_{max}

In Study A25711, SH T00658M (2 mg EV/3 mg DNG) was administered during the Period of Day 8-24 of the 28-day regimen

In Study A30020, SH T00658M (2 mg EV/3 mg DNG) was administered daily for 7 days (Day 1-7)

Although AUC(0-24) were higher and t_{1/2} were longer in Studies A25711 and A30020 than those obtained from the other 2 studies, considering that these were obtained at steady-state, the DNG PK parameters obtained from the 4 different studies under fasted condition were comparable. No significant differences in PK parameters were observed between premenopausal and postmenopausal women.

PK of E2

Mean serum concentration–time profile is presented in Figures A-6-3 and A-6-4. Mean PK parameters of E2 are summarized in Table A-6-3.

Figure A-6-3: Mean (± SD) Concentration-Time Curve of E2 (pg/ml) Following Daily Oral Dose of SH T00658ID in 15 Healthy Female Subjects

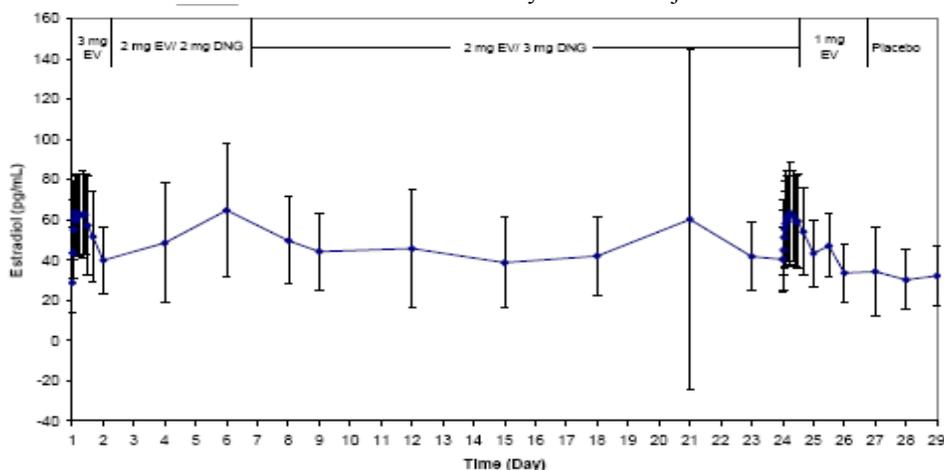
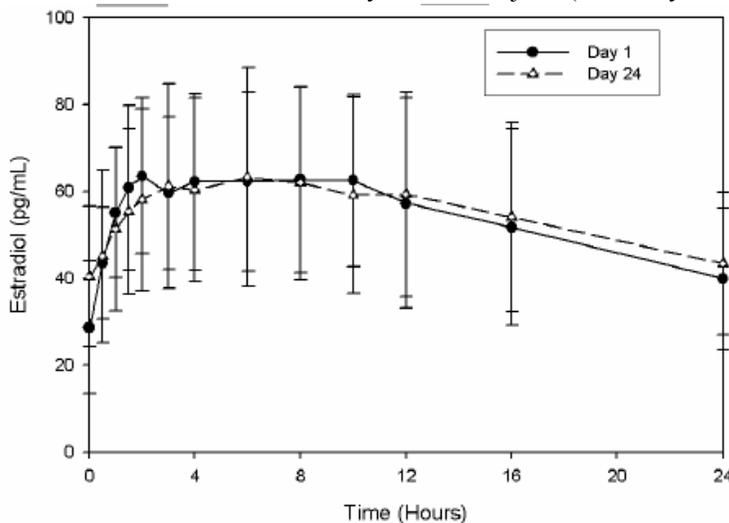


Figure A-6-4: Mean (± SD) Concentration-Time Curve of E2 (pg/ml) on Days 1 and 24 Following Daily Oral Dose of SH T00658ID in 15 Healthy Female Subjects (PK Analysis Set)



Reviewer’s comment: A mean (SD) C_{max} of 73.3 (22.6) pg/ml and AUC(0-24) of 1301 (445) pg·hr/ml was observed following a single oral dose of 3 mg EV tablet under fasted condition. Median T_{max} was 6 hr and ranged between 1.5-12 hr. Comparable 24 hr E2 PK profiles were observed on Days 1 and 24. E2 PK characterized following administration of 2 mg EV/3 mg DNG in different studies are summarized below.

Table A-6-3: Comparison of Arithmetic Mean (SD) E2 PK Parameters Following Administration of SH T00658M (2 mg EV/3 mg DNG) Under Fasted Conditions in Caucasian Women

	Study A25711	Study A30020	Study A29143	Study A29972
Population	Premenopausal (N=15)	Postmenopausal (N=12)	Postmenopausal (N=33)	Postmenopausal (N=17)
Regimen (Day)	Steady-state (Day 24)	Steady-state (Day 7)	Single dose (Day 1)	Single dose (Day 1)
C_{max} (ng/ml)	70.5 (25.9)	74.4 (31.5)	34.4 (11.0)	31.9 (8.7)
T_{max} (hr)	3 (1.5-12)	6 (2-16)	6 (1-16)	6 (0.5-16)
AUC(0-24) (ng·hr/ml)	1323 (480)	1328 (614)	584 (228)	570 (150)
$t_{1/2}$ (hr)	NA	NA	14.8 (2.54) ^a	13.8 (3.50) ^b

Median (range) for T_{max}

In Study A25711, SH T00658M (2 mg EV/3 mg DNG) was administered during the Period of Day 8-24 of the 28-day regimen

In Study A30020, SH T00658M (2 mg EV/3 mg DNG) was administered daily for 7 days (Day 1-7)

^a N=8; ^b N=2

Although premenopausal women (Study A25711) had a higher mean E2 baseline level of 28.71 pg/ml (SD=15.22; range: 4.79-62 pg/ml) compared to postmenopausal women (Study A30020) having 2.10 pg/ml (SD=2.35; range: 0-5.8 pg/ml), cross-study comparison reveals that comparable E2 PK parameters were obtained between premenopausal and postmenopausal women at steady-state following daily dose of the same formulation under fasted condition. Also, consistent E2 PK parameters were obtained in postmenopausal women following a single dose of the same formulation under fasted condition across different studies. It appears that the proposed EV/DNG regimen suppresses endogenous production of E2 in premenopausal women.

PK of E1

Mean serum concentration–time profile is presented in Figures A-6-5 and A-6-6. Mean PK parameters of E1 are summarized in Tables A-6-4 and A-6-5.

Figure A-6-5: Mean (\pm SD) Concentration-Time Curve of E1 (pg/ml) Following Daily Oral Dose of SH T00658ID in 15 Healthy Female Subjects

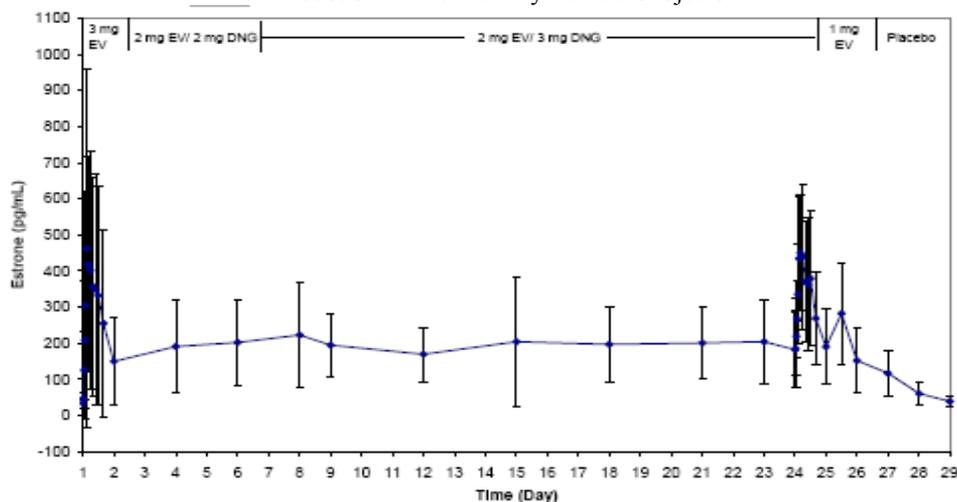
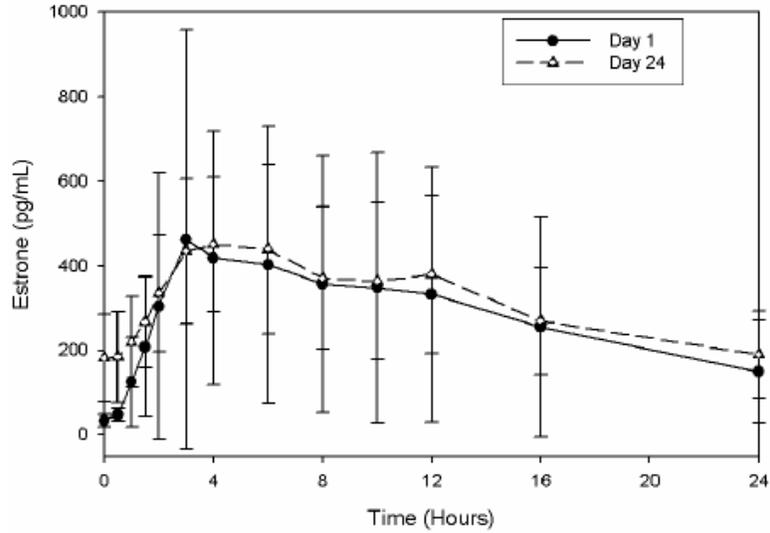


Figure A-6-6: Mean (\pm SD) Concentration-Time Curve of E1 (pg/ml) on Days 1 and 24 Following Daily Oral Dose of SH T00658ID in 15 Healthy Female Subjects (PK Analysis Set)



PK of E1S

Mean serum concentration-time profile is presented in Figures A-6-7 and A-6-8. Mean PK parameters of E1S are summarized in Tables A-6-4 and A-6-5.

Figure A-6-7: Mean (\pm SD) Concentration-Time Curve of E1S (pg/ml) Following Daily Oral Dose of SH T00658ID in 15 Healthy Female Subjects

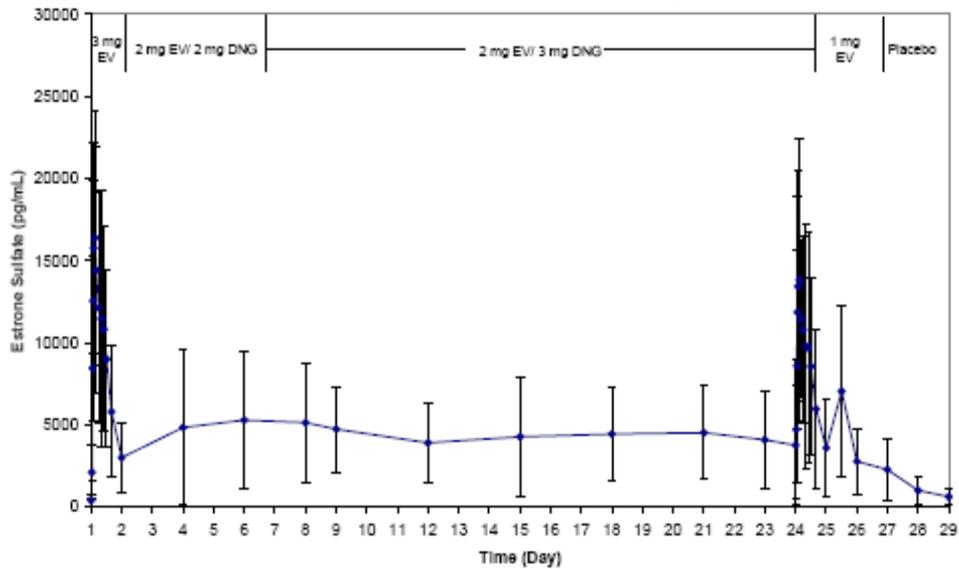


Figure A-6-8: Mean (\pm SD) Concentration-Time Curve of E1S (pg/ml) on Days 1 and 24 Following Daily Oral Dose of SH T00658ID in 15 Healthy Female Subjects (PK Analysis Set)

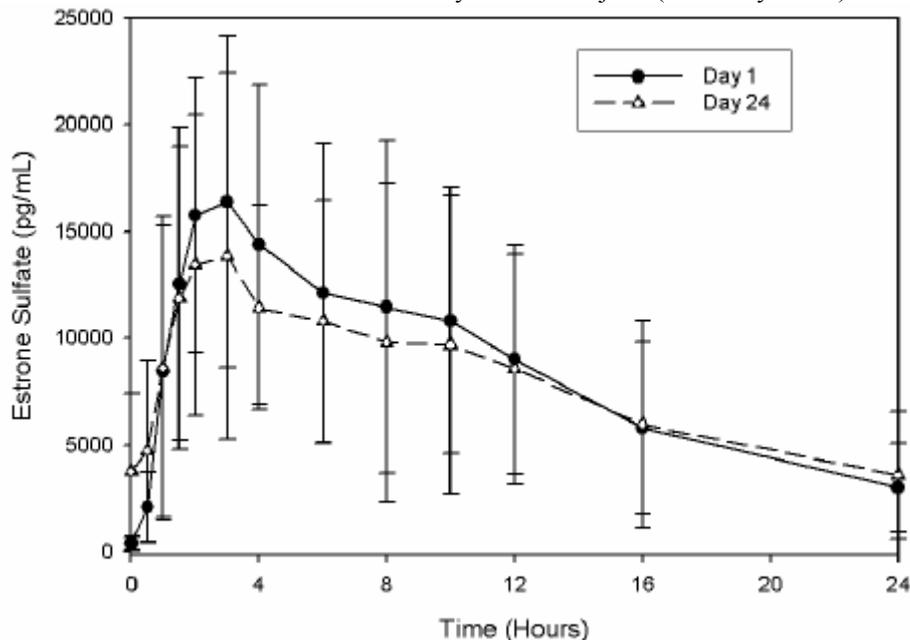


Table A-6-4: Arithmetic Mean (SD) Serum E1 and E1S PK Parameters – Day 1 (N=15)

	E1	E1S
AUC(0-24) (pg-hr/ml)	6800 (6020)	201839 (108152)
C _{max} (pg/ml)	500 (484)	18355 (8935)
T _{max} (hr) ^a	4 (3-12)	3 (1.5-10)

^a Median (range) for T_{max}

Table A-6-5: Arithmetic Mean (SD) Serum E1 and E1S PK Parameters – Day 24 (N=15)

	E1	E1S
AUC(0-24) (pg-hr/ml)	7562 (3403)	189457 (122755)
C _{max} (pg/ml)	483 (198)	15319 (8602)
T _{max} (hr) ^a	4 (3-12)	3 (1.5-12)

^a Median (range) for T_{max}

SHBG and CBG serum concentrations

Serum levels of SHBG, CBG, and cortisol were monitored throughout the study duration.

Table A-6-6: Arithmetic Mean (SD) Serum Concentrations of SHBG, CBG, and Cortisol following Daily Oral Dose of (b) (4) (N=15)

Analyte	Day 1	Day 8	Day 15	Day 21	Day 29
SHBG (nmol/l)	57.9 (24.8)	68.0 (34.0)	81.4 (32.6)	85.5 (30.1)	81.5 (31.0)
CBG (μ g/l)	45.5 (25.2)	53.1 (19.0)	54.3 (14.2)	57.4 (14.7)	49.2 (12.2)
Cortisol (nmol/l)	339.4 (162.5)	455.2 (163.7)	425.4 (141.4)	461.4 (144.7)	437.8 (154.6)

Reviewer's comment: It was noted that there were increases in mean serum concentrations of SHBG and CBG. This might be due to estrogen that is known to increase binding globulin levels.

SAFETY RESULTS

There were no deaths, no SAEs, and no subjects discontinued the study due to an AE. The most drug-related AEs were metrorrhagia and headache, reported by 4 (22%) and 3 (17%) subjects, respectively.

CONCLUSION

Steady state of DNG was reached within 4-5 days of dosing at each dose sequence. Cross-study comparison of DNG PK parameters across multiple studies under fasted condition, revealed that comparable PK parameters were obtained between premenopausal and postmenopausal women administered with the same EV/DNG combination tablet formulation.

Despite the different EV dose, comparable 24 hr E2 PK profiles were observed on Days 1 and 24. Cross-study comparison reveals that comparable E2 PK parameters were obtained between premenopausal and postmenopausal women at steady-state following daily dose of the same formulation under fasted condition and consistent E2 PK parameters were obtained in postmenopausal women following a single dose of the same formulation under fasted condition.

A.1.7. Study A33022

A Single-center, Open-label, Controlled, Randomized Study to Investigate the Impact of a Sequential Oral Contraceptive Containing Estradiol Valerate and Dienogest (SH T00658ID) as Compared to a Sequential Oral Contraceptive Containing Ethinyl Estradiol and Levonorgestrel (SH D00264A) on Plasma Lipids, Hemostatic Variables, and Carbohydrate Metabolism in 60 Healthy Female Volunteers Aged 18-50 Years Over 7 Treatment Cycles Including the Pharmacokinetics of E1, E2, and DNG [PK Sub-study Review]

Protocol No: A33022
Phase: 2
Principal Investigator: Dr. Renate Maibauer
Clinical Study Center: Bayer Schering Pharma AG, Berlin, Germany
Clinical Study Dates: March 7, 2005 - March 24, 2006
Analytical Study Facility: (b) (4) and Schering Oy, Finland (DNG)
Analytical Study Dates: February 27, 2006 - April 11, 2006 (E2 and E1) and February 2006 - March 2006

OBJECTIVE

The objective of this study was to investigate the impact of a sequential oral contraceptive containing EV and DNG (SH T00658ID; the 4-phasic TBM regimen) as compared to a sequential oral contraceptive containing EE and levonorgestrel (LNG) (SH D00264A) on plasma lipids, hemostatic variables, carbohydrate metabolism, thyroid parameters, SHBG, CBG, free and total testosterone, and dehydroepiandrosterone sulfate (DHEA-S).

In a subgroup on SH T00658ID, PK of E1, E2, and DNG were evaluated. Tolerability and safety were assessed in terms of baseline findings, AEs, safety laboratory tests, vital signs, body weight, general physical and gynecological examination, bleeding patterns / cycle control, and pregnancy. This review will focus on the PK component of the study and other components of the study will be reviewed by the clinical reviewer, Dr. Gerald Willett.

STUDY ENDPOINTS

PK parameters including AUC(0-24), C_{max}, and T_{max} were determined for DNG, E2, and E1.

STUDY DESIGN, TREATMENT, AND SUBJECTS

The study was conducted at one center as an open-label, active treatment-controlled, randomized trial in healthy female volunteers aged 18-50 yr inclusive (smokers at a maximum age of 30 yr and with a daily cigarette consumption not exceeding 10). After ascertaining the individual baseline safety status of 60 women seeking contraception, who gave their consent, the volunteers were randomly assigned to one of the 2 treatments:

- Test product: SH T00658ID
- Reference product: SH D00264A.

The reference product used in this study (SH D00264A) was marketed as Logynon ED (UK) and Trionetta 28 (Sweden) both using a 28 day regimen with placebo tablets to be taken during Days 22-28 of the cycle.

Volunteers were randomized to one of the two treatment groups of 30 to receive either the test product, SH T00658ID (EV/DNG) or the reference product, SH D00264A (EE/LNG). The treatment duration was 7 cycles of 28 days each (196 consecutive days). The study drugs were taken without pill-free intervals. PK samples were collected following an overnight fasting of at least 10 hr. No food was allowed in the morning of the tests. Volunteers received all meals at the study center: breakfast 2 hr after drug intake, lunch after 4 hr, and dinner after 8 hr. After the 6th sampling (12 hr post-dose), volunteers were allowed to go home and come back to the study center in time for the last measurement (24 hr post-dose). The next intake of study medication after this

24-hr period was immediately after the last blood sampling. Both the Test and the Reference products were administered exactly the same way. Volunteers started tablet intake on the first day of menstrual bleeding after Visit 2 (Baseline). A negative pregnancy test was prerequisite for the start of treatment. A washout period of 2 months for sex hormones (6 months in case of long-acting progestins) prior to start of treatment was required. One tablet per day was swallowed as a whole at the same daytime (± 2 hr) with some liquid. The PK of E1, E2, and DNG were assessed.

Inclusion Criteria:

- Healthy female volunteers requiring contraception
- Age between 18-50 yr (inclusive) at Visit 1, smokers not older than 30 yr and with a daily cigarette consumption not exceeding 10

Exclusion Criteria:

- Pregnancy, lactation
- Occurrence of less than 3 menstrual cycles before Visit 1 following delivery, abortion, or lactation
- Known liver, vascular, or metabolic diseases
- Prohibited concomitant medication: Additional sex steroids, hydantoin (e.g., phenytoin), barbiturates (e.g., primidone), carbamazepine, rifampicin, griseofulvin, phenylbutazone, the herbal remedy St. John’s Wort, continuous use of antibiotics (e.g., ampicillin, tetracycline) for > 10 days, any anticoagulatory drugs (e.g., heparin, coumarin)
- Sex hormones prior to start of treatment: Oral, transdermal, intrauterine, or intravaginal administration within 2 months prior to start of treatment; implants within 2 months prior to start of treatment; any long-acting progestins within 6 months prior to start of treatment
- Considerable overweight (BMI > 30 kg/m²) or underweight (BMI < 17.5 kg/m²)

FORMULATION

The test and reference drug employed in the study are described below.

Table A-7-1: Description of the Investigational (Test) Product SH T00658ID (EV/DNG)

SH T00658ID			
Dosage form	Film coated tablets		
Daily dose / Route of administration	One tablet / Oral		
Dosage per time unit	Cycle days	Dose	Color of the tablet
	1 - 2	3.0 mg EV	Dark yellow
	3 - 7	2.0 mg EV + 2.0 mg DNG	Medium red
	8 - 24	2.0 mg EV + 3.0 mg DNG	Light yellow
	25 - 26	1.0 mg EV	Dark red
	27 - 28	No active ingredient (placebo)	White
Duration of treatment	7 cycles of 28 days each (196 consecutive days)		
Maximum cumulative dose (7 cycles)	EV: 364 mg; DNG: 427 mg		

Table A-7-2: Description of the Reference (Reference) Product SH D00264A (EE/LNG)

SH D00264A			
Dosage form	Sugar coated tablets		
Daily dose / Route of administration	One tablet / Oral		
Dosage per time unit	Cycle days	Dose	Color of the tablet
	1 - 6	0.03 mg EE + 0.05 mg LNG	Light brown
	7 - 11	0.04 mg EE + 0.075 mg LNG	White
	12 - 21	0.03 mg EE + 0.125 mg LNG	Ochre
	22 - 28	No active ingredient (placebo)	White
Duration of treatment	7 cycles of 28 days each (196 consecutive days)		
Maximum cumulative dose (7 cycles)	EE: 4.76 mg; LNG: 13.475 mg		

PHARMACOKINETIC EVALUATION

Blood sampling

For the PK measurements, blood samples were obtained from the volunteers during Visit 3 and Visit 4b that occurred between Days 14 and 21 during Cycles 4 and 7, respectively, at the following time points: pre-dose, 1, 2, 4, 8, 12, and 24 hr post-dose. The pre-dose was drawn when the volunteer was in a fasted state, after an overnight fasting of at least 10 hr.

Bioanalytical method

Determination of E2 and E1 Concentrations

(b) (4)

(b) (4)

Determination of DNG Concentrations

(b) (4)

Acceptance criteria and performance for each analyte were in compliance with the *Bioanalytical Method Validation Guidance*.

SAFETY ASSESSMENTS

- Baseline findings, AEs, and concomitant medication
- Safety laboratory tests
- Vital signs (blood pressure and heart rate) and body weight
- General physical and gynecological examination (r)
- Bleeding patterns / cycle control
- Pregnancy test / pregnancy during the study

DATA ANALYSIS

Pharmacokinetics

Non-compartmental PK sample analysis was performed on the serum concentrations of E2, E1, and DNG using a commercially available software tool. All serum concentration values below the LLOQ were set to zero. C_{max} and T_{max} values were directly read off the concentration-time profiles. $AUC(0-24)$ was calculated according to the mixed log-linear trapezoidal rule.

PHARMACOKINETIC RESULTS

PK of DNG

Mean serum concentration–time profile is presented in Figure A-7-1. Mean PK parameters of DNG are summarized in Tables A-7-3.

Figure A-7-1: Mean (\pm SD) Concentration-Time Curves of DNG in Cycle 4 and Cycle 7 After Daily Oral Administration of SH T00658ID to 24 Healthy Female Volunteers

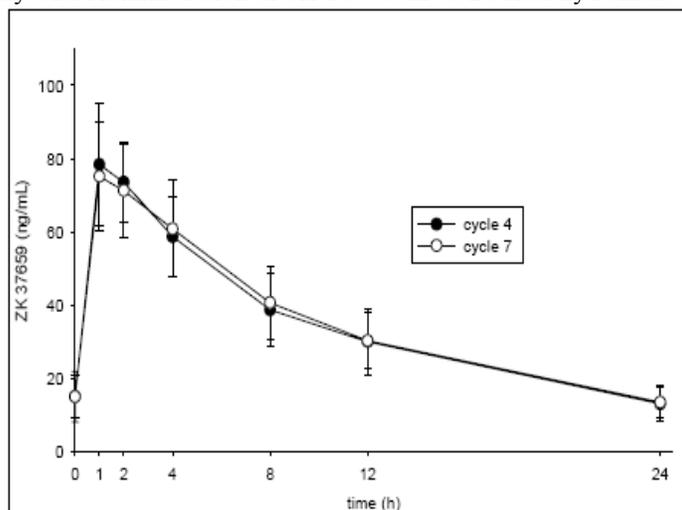


Table A-7-3: Arithmetic Mean (SD) PK Parameters of DNG Obtained at Steady State Under Fasted Condition During Cycles 4 and 7 After Daily Oral Administration of SH T00658ID in 24 Healthy Female Volunteers

Cycle	C_{max} (ng/ml)	T_{max} (hr) ^a	$AUC(0-24)$ (ng·hr/ml)
1 ^b	85.2 (19.7)	1.5 (1-2)	828 (187)
4	82.7 (14.7)	1 (1-2)	826 (179)
7	79.1 (12.6)	1 (1-2)	839 (180)

^a Median (range) for T_{max}

^b Data from Study A25711 (N=15)

Reviewer's comment: *The DNG PK profiles of Cycles 4 and 7 at steady-state were similar to each other. The arithmetic mean (SD) DNG PK parameters obtained at steady-state during Cycles 4 and 7 (between Days 14 and 21) were comparable to those obtained at steady-state during Cycle 1 (on Day 24) under fasted condition following daily oral administration of the TBM formulation/regimen.*

PK of E2

Mean serum concentration–time profile is presented in Figure A-7-2. Mean PK parameters of E2 are summarized in Table A-7-4.

Figure A-7-2: Mean (\pm SD) Concentration-Time Curves of E2 in Cycle 4 and Cycle 7 After Daily Oral Administration of SH T00658ID to 24 Healthy Female Volunteers

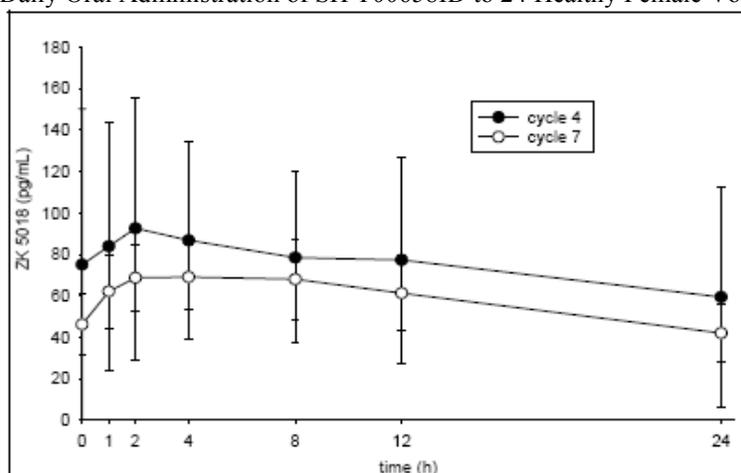


Table A-7-4: Arithmetic Mean (SD) PK Parameters of E2 obtained at Steady-state Under Fasted Conditions During Cycles 1, 4, and 7 After Daily Oral Administration of SH T00658ID in 24 Healthy Female Volunteers

Cycle	C_{max} (pg/ml)	T_{max} (hr) ^a	AUC(0-24) (pg·hr/ml)
1 ^c	70.5 (25.9)	3 (1.5-12)	1323 (480)
4	100 (69.2)	4 (0-12)	1799 (1193)
4 ^b	76.5 (26.2)	4 (1-12)	1364 (539)
7	74.0 (17.5)	4 (1-8)	1401 (370)

^a Median (range) for T_{max}

^b After excluding 4 subjects with high E2 baselines

^c Data from Study A25711 (N=15)

Reviewer's comment: Mean PK profiles of E2 appear to be higher at Cycle 4 than at Cycle 7. It was noted that 4 subjects (Volunteers 5, 48, 67, and 77) at Cycle 4 had higher baseline E2 levels (range: 151-299 pg/ml) than other subjects (range: 23.2-82.4 pg/ml).

Intra-subject comparison of E2 PK profiles (concentration-time curve) between Cycles 4 and 7 shows that the PK profiles are comparable with the exception of these 4 subjects. It was also noted that the Cycle 7 E2 PK profiles of these 4 subjects were comparable to those from Cycles 4 and 7 of other subjects.

The arithmetic mean of C_{max} at Cycle 4, if excluding the 4 subjects, would have been 76.5 pg/ml, which is close to the 74.0 pg/ml value at Cycle 7. The arithmetic mean of AUC(0-24) at Cycle 4, if excluding the 4 subjects, would have been and 1364 pg·hr/ml, which is also close to the respective value of 1401 pg·hr/ml at Cycle 7.

Considering these facts, it can be concluded that E2 PK parameters from Cycles 4 and 7 are comparable with those obtained at steady-state during Cycle 1 (on Day 24) from Study A25711 under fasted condition following daily oral administration of the same formulation/regimen with the exception of the 4 subjects that had higher baseline E2 levels in Cycle 4.

PK of E1

Mean serum concentration-time profile is presented in Figure A-7-3. Mean PK parameters of E1 are summarized in Table A-7-5.

Figure A-7-3: Mean (\pm SD) Concentration-Time Curves of E1 in Cycle 4 and Cycle 7 After Daily Oral Administration of SH T00658ID to 24 Healthy Female Volunteers

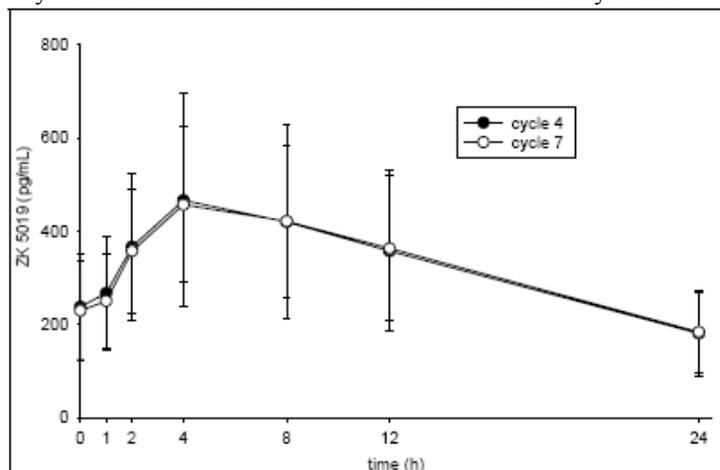


Table A-7-5: Arithmetic Mean (SD) PK Parameters of E1 Obtained During Cycles 4 and 7 After Daily Oral Administration of SH T00658ID in 24 Healthy Female Volunteers

Cycle	C _{max} (pg/ml)	T _{max} (hr) ^a	AUC(0-24) (pg·hr/ml)
1 ^b	483 (198)	4 (3-12)	7562 (3403)
4	487 (236)	4 (2-12)	7811 (3664)
7	468 (169)	4 (4-12)	7822 (3098)

^a Median (range) for T_{max}

^b Data from Study A25711 (N=15)

Reviewer's comment: *The E1 PK profiles of Cycles 4 and 7 at steady-state were similar to each other. The arithmetic mean (SD) E1 PK parameters obtained at steady-state during Cycles 4 and 7 (between Days 14 and 21) were comparable to those obtained at steady-state during Cycle 1 (on Day 24) under fasted condition following daily oral administration of the TBM formulation/regimen.*

SAFETY RESULTS

The most frequent drug-related AE in both treatment groups was Headache [in 14 volunteers (46.6%) of the Test group versus 8 (28.6%) of the Reference group].

CONCLUSION

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

A.1.8. Study A478

Metabolism of DNG (STS 557) in Women

Protocol No: A478
Phase: 1
Principal Investigator: Dr. G. Hobe
Clinical Study Center: [REDACTED] (b) (4)

Clinical Report Date: January 1983

OBJECTIVE

Aim of the present study using a dose of 0.1 mg/kg body wt. (range: 5.2-7.8 mg ³H-DNG) was to obtain more information on DNG (STS 557) biotransformation in human. Simultaneously, the study was utilized for obtaining additional PK data at a higher dose level. The investigation on DNG biotransformation and plasma protein binding of DNG was conducted.

STUDY DESIGN, TREATMENT, AND SUBJECTS

The studies were carried out in premenopausal female volunteers. They did not suffer from renal and hepatic diseases, respectively, and no other drugs were taken during the time of investigation.

Table A-8-1: Demographics of Study Participants

Volunteer	Age [y]	Body weight [kg]	Dose	
			[µg]	[µCi]
Eh	40	78	7798	100.42
Wa	31	52	5197	100.39
Sei	33	60	5998	100.43
Ba	41	60	5998	100.42
Wre	20	54	5397	100.37
Vo	33	72	7198	100.43

A dose of 0.1 mg/kg body wt. (range: 5.2-7.8 mg ³H-DNG) was administered. For oral administration, the substance was administered in gelatin capsules on 100 mg lactone/starch 3:1 at 7 a.m. For the IV administration, the dose was 100 µg.

PHARMACOKINETIC EVALUATION

Sampling

- Blood: Samples taken at 0.5, 1, 2, 3, 4, 6, 12, 24, 36, 48, 96, and 120 hr post-dose.
- Urine: Collected on Day 1 at 0-6, 6-12, and 12-24 hr and subsequently, in 24 hr portions up to Day 6.
- Feces: Collected in daily portions up to Day 6.

Bioanalytical method

Radioactivity Measurements

(b) (4)

Determination of DNG in Plasma

Reviewer's comment: *This was conducted as a pre-GCP/GLP study. No formal bioanalytical method validation reports were submitted.*

DATA ANALYSIS

Pharmacokinetic Analysis

Plasma total radioactivity was used for calculating the following PK parameters: K_1 , T_{max} , C_{max} , AUC, and CL_{tot} . K_1 was derived from the invasion term of the exponential function with fitted to the plasma total radioactivity. The area under the plasma level curve (AUC) was calculated according to the trapezoidal rule. Plasma clearance was obtained according to the relationship:

$$CL_{tot} = \text{Dose}/AUC_0$$

Elimination half life of DNG was determined by means of a regression analysis of the plasma concentrations determined by HPLC in the time range $> t_{max}$ to 48 hr post-dose.

Plasma Protein Binding

Equilibrium dialysis

The system consists of 1 ml pooled plasma ($n = 5$) diluted 1:4 with phosphate buffer pH 7.4 (inside the dialysis bag) and 5 ml phosphate buffer containing 100,000 dpm (corresponding to 233 pg) ^3H -STS 557 + 1, 10, and 100 ng non-labelled STS 557 (outside). After 15 hr agitation at room temperature, radioactivity is measured in the inside and outside media, and protein binding is calculated as follows:

% binding= 100 (1- {[dpm outside x volume inside]/[dpm inside x volume outside]}))

PHARMACOKINETIC RESULTS

Figure A-8-1: (a) Normal and (b) Semi-logarithmic Mean Plasma Concentration Curves of Total Radioactivity (TA), DNG (STS 557) and the Metabolite Fraction Following Oral Administration of 0.1 mg/kg b. wt. ³H-DNG in Female Volunteers (n = 6)

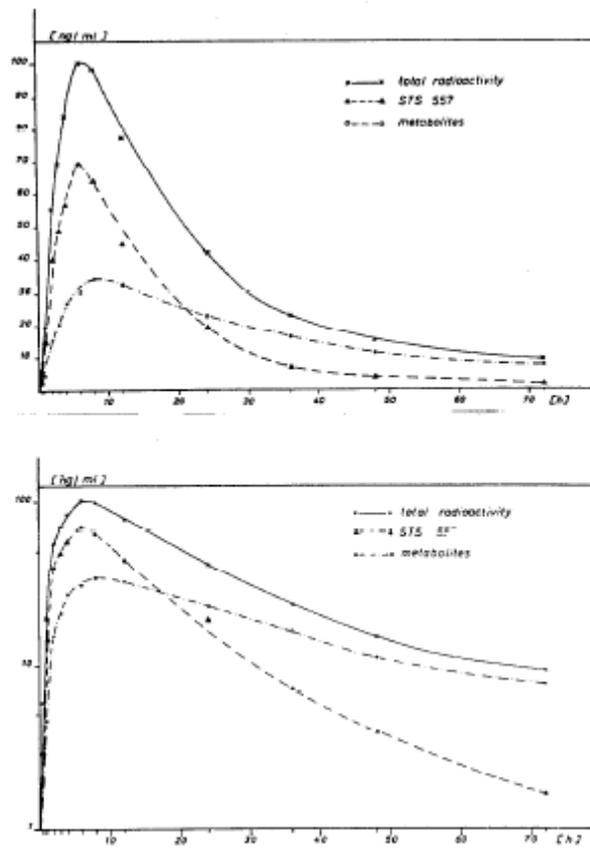


Table A-8-2: DNG PK Parameters Derived from the Plasma Level Course Following Oral Administration of 0.1 mg/kg body wt. ³H-DNG

Volunteer	C _{max}	C ₂₄ [ng/ml]	C ₄₈	k _{el} [h ⁻¹]	t _{1/2 el} [h]	τ + t _{abs.} [h]	AUC ₀₋₂₄ [ng/ml x h]	AUC _{0-∞}	Cl _{tot} [l/h]	AUC ₀₋₂₄ STS 557 AUC ₀₋₂₄ TA	AUC ₀₋₄₈ STS 557 AUC ₀₋₄₈ TA
Eh	59	20	4.5	0.057	12.2	16.8	875	1198	6.53	0.53	0.46
Wa	57	8	0.7	0.100	6.9	7.0	672	754	6.90	0.49	0.43
Sei	111	27	6.5	0.063	11.0	10.7	1639	2109	2.83	0.78	0.71
Bä	65	15	1.9	0.086	8.1	7.6	765	923	6.48	0.47	0.43
Vo	71	28	6.1	0.057	12.2	11.7	970	1414	5.09	0.62	0.60
Wre	88	18	2.6	0.086	8.1		1010	1229	4.39	0.66	0.57
m ± sD	75 ± 21	19 ± 8	3.7 ± 2.4	0.075 ± 0.018	9.7 ± 2.3	10.8 ± 3.9	988 ± 343	1271 ± 473	5.37 ± 1.57	0.59 ± 0.12	0.53 ± 0.11

T_{max} following oral and IV dose were approximately 5.2 hr and 1 hr, respectively. AUC(0-24) of DNG was found to be 988 ± 343 ng-hr/ml, and is thus 59 times the AUC(0-24) determined with the 100 µg IV dose (16.9 ng-hr/ml).

Reviewer's comment: *Considering the oral dose range of 5-7 mg, this suggests dose-proportional BA of DNG (With approximately 60-fold dose [6 mg (oral dose) ÷ 0.1 mg (IV dose)], 59-fold AUC(0-24) obtained).*

Table A-8-3: Urinary and Fecal Radioactivity Excretion (in % dose) Following Oral Administration of 0.1 mg/kg body wt. ³H-DNG

Volunteer	U ₂₄	U ₄₈	U ₁₄₄	F ₁₄₄	E _{tot}	U : F	k _{ren} [h ⁻¹]	t _{1/2 ren} [h]
Eh	35.9	50.5	61.4	32.0	93.4	1.9	0.0376	18.5
Wa	50.3	63.9	69.9	25.4	95.3	2.7	0.0506	13.7
Sei	47.6	64.8	71.7	19.6	91.3	3.7	0.0484	14.3
Bä	42.2	57.0	60.2	28.7	88.9	2.1	0.0545	12.7
Wre	32.0	48.3	52.3	9.6	61.9	5.4	0.0536	12.9
m ± sD	41.6 ± 7.7	56.9 ± 7.5	63.1 ± 7.9	23.1 ± 8.8	86.2 ± 13.8	3.2 ± 1.4	0.0489 ± 0.0068	14.4 ± 2.4

Symbols: U₂₄, U₄₈, U₁₄₄ = urinary excretion in 24, 48 and 144 h; F₁₄₄ = fecal excretion; E_{tot} = total excretion; k_{ren} = renal elimination constant

BIOTRANSFORMATION RESULTS

The metabolite pattern of DNG in urine indicates the predominance of strongly polar, obviously hydroxylated compounds, whereas hydrogenated metabolites play a minor role. The plasma patterns reveal that unchanged DNG is dominant. Because of the small quantity of DNG administered, no metabolites were isolated in this investigation.

PROTEIN BINDING RESULTS

Using the method of equilibrium dialysis, a relatively high portion of DNG was found to be in a free, non-protein-bound state in plasma.

CONCLUSION

0.1 mg/kg body wt. oral administration and IV administration of a total dose of 100 µg of ³H-DNG to female volunteers yielded the following PK data:

- Absorption of the 100 µg IV dose is rapid and complete. Plasma C_{max} was reached already about 1 hr post-dose while T_{max} following oral dose was approximately 5.2 hr.
- AUC(0-24) of DNG was found to be 988 ± 343 ng-hr/ml, and is thus 59 times the determined with the 100 µg IV dose (16.9 ng-hr/ml). Considering the oral dose range of 5-7 mg, this suggests dose-proportional BA of DNG. There is no significant "first-pass-effect" in oral administration.

- Elimination half life following IV administration of DNG isolated by means of TLC was found to be 6 hr on average while the mean elimination half-life following oral administration was 9.7 hr. The portion of DNG in plasma total radioactivity constitutes approximately 59% and 53 % in the first 24 and 48 hr post-dose, respectively.
- Within 5 days, 82.7 ± 6.7 % (oral) and 80.6 ± 8 % (IV) of the administered dose were excreted. Renal excretion dominated (71.9 ± 6.4 % [oral] and 67.9 ± 7.9 % [IV], respectively).
- The total clearance following the IV administration of ^3H -DNG was calculated to be 5.4 l/hr which was approximately the same as that following oral administration.

Because of the small quantity of DNG administered, no metabolites were isolated in this investigation.

A.1.9. Study A30020

Open-label, Two-group, One-sequence, One-way Crossover Study to Evaluate the Effect of Ketoconazole and Erythromycin on the Steady-state Pharmacokinetics of SH T00658M (2 mg Estradiol Valerate and 3 mg Dienogest) in Healthy Postmenopausal Women

Protocol No: A30020
Phase: 1
Principal Investigator: Dr. B. Rohde
Clinical Study Center: Clinical Pharmacology, Schering AG, Berlin, Germany
Clinical Study Dates: April 13, 2006 - July 10, 2006
Analytical Study Facility: (b) (4) (E2, E1, and E1S), Schering Oy, Finland (DNG), and SFBC Anapharm, Quebec, Canada (Ketoconazole and Erythromycin)
Analytical Study Dates: July 21, 2006 - September 15, 2006 (E2, E1, and E1S), August 2006 - October 2006 (DNG), August 7, 2006 - August 10, 2006 (Ketoconazole), and October 11, 2006 (Erythromycin)

OBJECTIVE

The objective of study was to evaluate the effect of CYP 3A4 inhibitors, ketoconazole and erythromycin, on the steady state PK of DNG and EV.

STUDY ENDPOINTS

Primary endpoints for E2 and DNG (on Days 7 and 14) were: AUC(0-24) and C_{max} .

Secondary endpoints were:

- AUC(0-24) and C_{max} of E1 and E1S
- T_{max} of E1, E1S, E2, and DNG

STUDY DESIGN, TREATMENT, AND SUBJECTS

This was an open-label, two parallel-groups, one-sequence, one-way crossover study in 2 groups of 12 healthy postmenopausal women.

SH T00658M was supplied as film coated tablets containing 3 mg DNG and 2 mg EV. One tablet of SH T00658M was administered orally once a day for 14 days for both treatment groups. The SH T00658M tablet was administered in the morning between 07:00 hr to 09:00 hr with 250 ml mineral water (non-carbonated, room temperature) following approximately 10 hr fasted.

Volunteers from Group 1 received an oral dose of 400 mg ketoconazole (i.e., 2 tablets Nizoral[®] containing 200 mg ketoconazole) once daily for 7 days (Day 8 to Day 14).

Volunteers from Group 2 received an oral dose of 500 mg erythromycin (i.e., 1 tablet of Erythrocin[®] 500 Neo Filmtabletten) 3 times a day for 7 days (Day 8 to Day 14). The morning dose of erythromycin was administered with SH T00658M between 07:00 to 09:00 hr, the second daily dose was administered between 14:00 to 16:00 hr, and the third daily dose was taken between 21:00 to 23:00 hr.

Table A-9-1: Treatment Schedule

Group	Number of volunteers	Days 1 - 7	Days 8 - 14
1	12	SH T00658M once daily	SH T00658M once daily ketoconazole 400 mg once daily
2	12	SH T00658M once daily	SH T00658M once daily Erythromycin 500 mg three times a day

In total, 57 female volunteers were screened. 24 female, healthy, post-menopausal Caucasian women aged 45-75 yr, non-smokers, with follicle stimulating hormone ≥ 30 IU/l and E2 ≤ 20 pg/ml at screening were enrolled, randomized, and treated according to the study protocol. There were no discontinuations.

Pre-dose blood samples for PK evaluation were collected on Days 1, 5, 6, 7, 8, 12, 13, and 14. On Days 7 and 14, blood samples were collected for 24 hr. During this time, standard safety measures were carried out (clinical laboratory tests, 12 lead ECG), and the volunteers were monitored for AEs and concomitant medication.

The present study evaluated the effect of CYP 3A4 inhibition by ketoconazole and erythromycin at steady-state PK of DNG and EV given in a fixed combination of 2 mg EV and 3 mg DNG. The SH T00658M (2 mg EV/3 mg DNG) formulation was chosen because it was the highest dose in the 4-phasic TBM regimen. Ketoconazole and erythromycin represent strong and moderate inhibitors of CYP3A4, respectively.

Healthy pre-menopausal women are the target population for SH T00658M. However, the endogenous estrogen production in younger women could have resulted in highly variable estrogen concentrations in serum, which would have interfered with the PK analysis of EV. The investigation was therefore done in postmenopausal women who have a low endogenous estrogen production. This approach is acceptable given that the PK parameters of DNG, E2, and E1 at steady state following 2 mg EV/3 mg DNG in premenopausal women (Study A25711) were comparable to those observed in postmenopausal women with the same dose (Study A30020).

Inclusion Criteria

Volunteers had fulfilled all of the following criteria before being included in the treatment phase:

- Healthy female, postmenopausal volunteer
- Postmenopausal state, revealed by:
 - medical history, if applicable (natural menopause at least 2 yr prior to first study drug administration; or surgical menopause by bilateral ovariectomy at least 3 months prior to first study drug administration), and
 - serum hormone analyses (estradiol ≤ 20 pg/ml, follicle stimulating hormone ≥ 30 IU/l)
- Age: 45-75 yr
- BMI: > 20 and < 30 kg/m²

FORMULATION

SH T00658M was supplied as film coated tablets containing the highest dosed combination of both EV and DNG (2 mg EV/3 mg DNG).

PHARMACOKINETIC EVALUATION

Blood sampling

Sampling times for determination of DNG, E2, E1, and E1S:

- Pre-dose on Days 1, 5, 6, 7, 8, 12, 13, and 14
- At 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hr post-dose on Days 7 and 14

Sampling times for determination of ketoconazole and erythromycin:

- Pre-dose on Days 8, 12, 13, and 14

Concomitant Therapy

If a volunteer used concomitant medication, this was documented by type (brand name, if applicable), indication, regimen (total daily dose and route), and duration on the appropriate CRF.

Other Restrictions

- Smoking: not permitted
- Alcohol: not permitted within 48 hr before the 1st study drug administration until 72 hr after the last drug administration
- Caffeine: not permitted within 24 hr before the 1st study drug administration until 72 hr after the last drug administration
- Grapefruit not permitted within 72 hr before the 1st study drug administration until 72 hr after the last drug administration

Bioanalytical method

Determination of E2, E1, and E1S Concentrations



(b) (4)

Acceptance criteria for method validation and assay performance for each analyte were in compliance with the *Bioanalytical Method Validation Guidance*.

Safety Assessments

To ensure the volunteers' safety after intake of either SH T00658M alone or SH T00658M plus ketoconazole or erythromycin the following parameters were studied during the treatment period:

- Standard laboratory examination of blood and urine prior to dosing on Days 1 and 12, respectively, and on Day 18
- AE and concomitant medication

DATA ANALYSIS

Pharmacokinetic Analysis

Non-compartmental PK analysis was performed on the serum concentrations of E2, E1, E1S, and DNG. All serum concentration values below the LLOQ were set to zero. C_{max} and T_{max} were directly read off the concentration-time profiles. The AUC(0-24) was calculated according to the mixed linear-log trapezoidal rule using a commercially available software tool (Kinetica™, version 4.3, Thermo Electron corporation, Waltham, MA, US) without recourse to model assumptions. Relevant deviations from planned sampling time and planned dose were taken into account.

Drug-Drug Interaction Analysis

To evaluate the effect of CYP 3A4 inhibitors, ketoconazole and erythromycin, on the steady-state PK of DNG and EV, the 90% CIs about the geometric mean ratio of the observed PK measures (i.e., AUC(0-24) and C_{max}) with ketoconazole and erythromycin and without the interacting drug were provided.

The estimation of the geometric mean ratio and its confidence limits were derived from the E2, DNG, E1, and E1S PK parameter estimations by antilogarithm transformation and 90% CIs of the differences of the logarithms of the target variables between treatment without and treatment with interacting drug. The 90% CIs were calculated based on the t-test for paired observations.

Statistic Methods

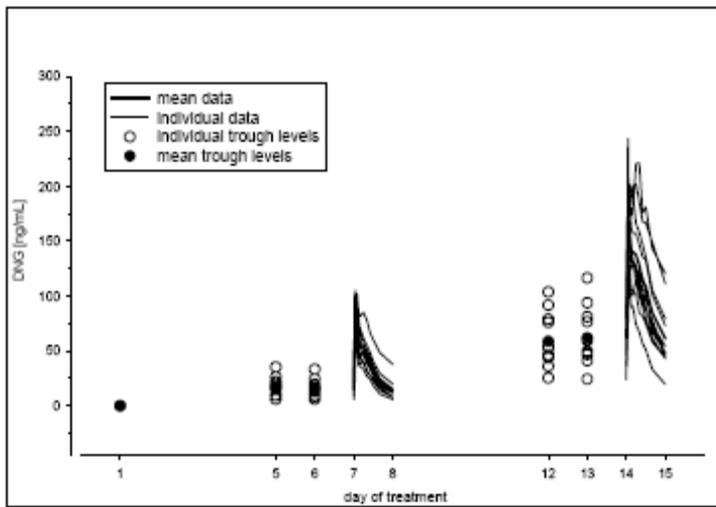
Descriptive statistics were performed for PK parameters. Antilog transformations were to render the corresponding two-sided 90% CIs on the original scale.

PHARMACOKINETIC RESULTS

Achievement of Steady state for DNG and E2

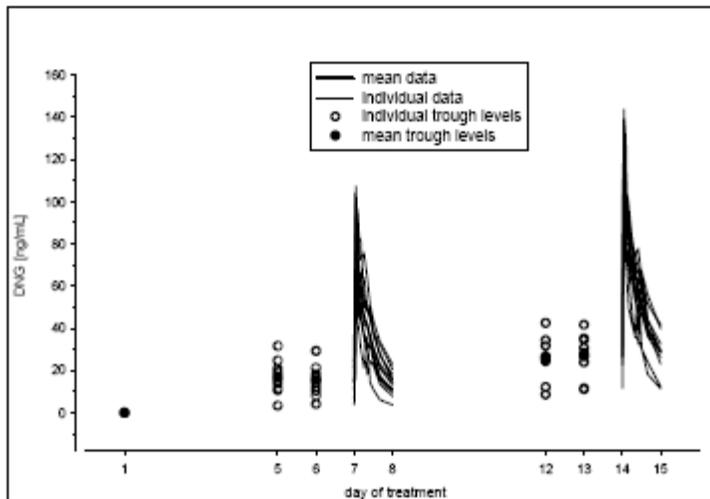
As shown in Figure A-9-1 through Figure A-9-4, steady-states of DNG and E2 were already reached after 5 days of dosing. Steady-states of E1 and E1S were also already reached after 5 days of dosing as well (data not shown).

Figure A-9-1: Superimposed Individual and Mean Concentration – Time Curves of DNG in Serum After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets (Day 1 to Day 14) and 400 mg ketoconazole (Day 8 to Day 14) in 12 Healthy Postmenopausal Women (Group 1).



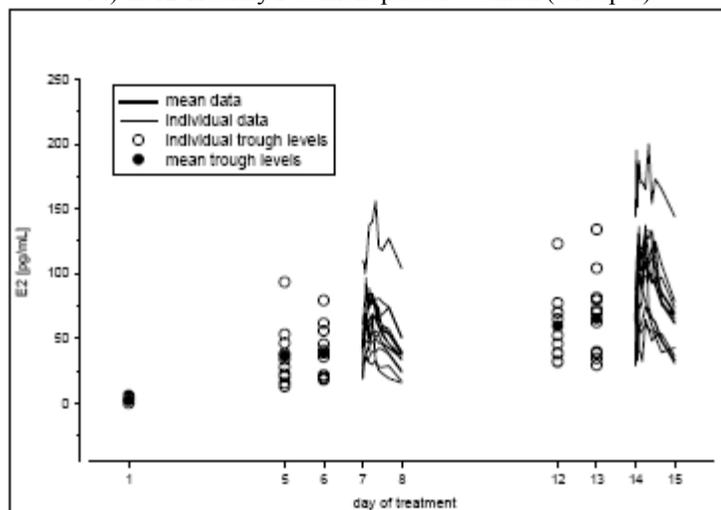
DNG concentrations already achieved steady-state by Day 7 of treatment as demonstrated by the comparable mean trough levels between Days 5, 6, and 7. Following co-administration with ketoconazole, steady-state of DNG was reached again by Day 14. Co-administration with ketoconazole increased mean DNG trough levels at steady-state from 14.1 ng/ml on Day 8 (without ketoconazole) to 61.1 ng/ml on Day 15 (with ketoconazole).

Figure A-9-2: Superimposed Individual and Mean Concentration–Time Curves of DNG in Serum After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets (Day 1 to Day 14) and 500 mg erythromycin (three times a day, Day 8 to Day 14) in 12 Healthy Postmenopausal Women (Group 2)



DNG concentrations already achieved steady-state by Day 7 of treatment as demonstrated by the comparable mean trough levels between Days 5, 6, and 7. Following co-administration with erythromycin, steady state of DNG was reached again by Day 14. Co-administration with erythromycin treatment, mean DNG trough levels increased from 13.5 ng/ml on Day 8 (without erythromycin) to 28.7 ng/ml on Day 15 (with erythromycin).

Figure A-9-3: Superimposed Individual and Mean Concentration–Time Curves of E2 in Serum After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets (Day 1 to Day 14) and 400 mg ketoconazole (Day 8 to Day 14) in 12 Healthy Postmenopausal Women (Group 1).

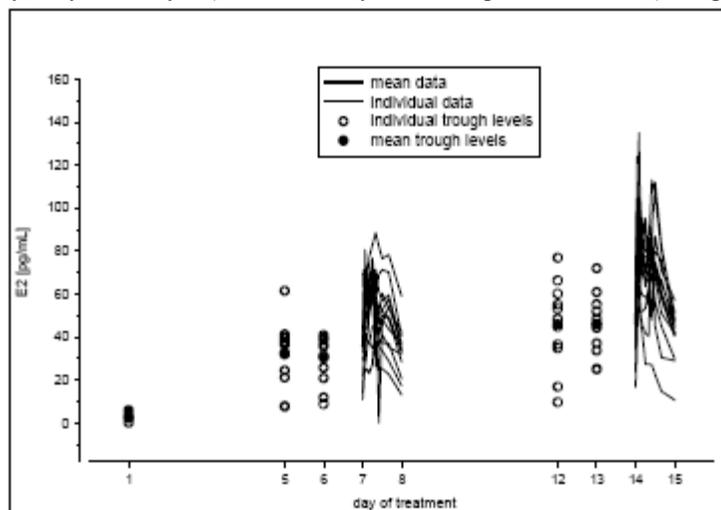


Comparable mean E2 trough concentrations were detected between Day 5 and 7 as well as between Day 12 and 14 (at an increased level). Following the ketoconazole treatment, mean E2 trough levels increased from 39.1 pg/ml on Day 8 (without ketoconazole) to 62.0 pg/ml on Day 15 (with ketoconazole).

In a similar manner, comparable mean E1 and E1S trough concentrations were detected between Day 5 and 7 and between Day 12 and 14 (at an increased level; data not shown). Following the ketoconazole treatment, mean E1 and E1S trough levels increased from 190 pg/ml on Day 8 (without ketoconazole) to 303 pg/ml on Day 15 (with ketoconazole), and from 4.07 ng/ml on Day 8 (without ketoconazole) to 6.34 ng/ml on Day 15 (with ketoconazole), respectively.

Ketoconazole’s steady-state was reached by Day 13 (6th day of the ketoconazole treatment period).

Figure A-9-4: Superimposed Individual and Mean Concentration–Time Curves of E2 in Serum After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets (Day 1 to Day 14) and 500 mg erythromycin (three times a day, Day 8 to Day 14) in 12 Healthy Postmenopausal Women (Group 2)



Comparable mean E2 trough concentrations were detected between Day 5 and 7 as well as between Day 12 and 14 (at an increased level). Following the erythromycin treatment, mean E2 trough levels increased from 33.2 pg/ml on Day 8 (without erythromycin) to 41.0 pg/ml on Day 15 (with erythromycin).

In a similar manner, comparable mean E1 and E1S trough concentrations were detected between Day 5 and 7 and between Day 12 and 14 (at an increased level for E1; data not shown). Following the erythromycin treatment, mean E1 trough levels increased from 162 pg/ml on Day 8 (without erythromycin) to 206 pg/ml on Day 15 (with erythromycin). There were almost no changes in mean E1S trough levels, 5.22 ng/ml on Day 8 (without erythromycin) versus 5.36 ng/ml on Day 15 (with erythromycin).

Erythromycin's steady-state was reached by Day 12 (5th day of the erythromycin treatment period).

Effect of Ketoconazole Co-administration on E2 PK

Figure A-9-5 shows the mean concentration time curves for E2, after administration of SH T00658M (2 mg EV/3 mg DNG) to the 12 volunteers, before and after co-administration of 400 mg ketoconazole. Mean PK parameters of E2 are summarized in Table A-9-2.

Figure A-9-5: Mean (\pm SD) Concentration-Time Curves of E2 on Day 7 and Day 14 After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets (Day 1 to Day 14) and 400 mg Ketoconazole (Day 8 to Day 14) in 12 Healthy Postmenopausal Women (Group 1)

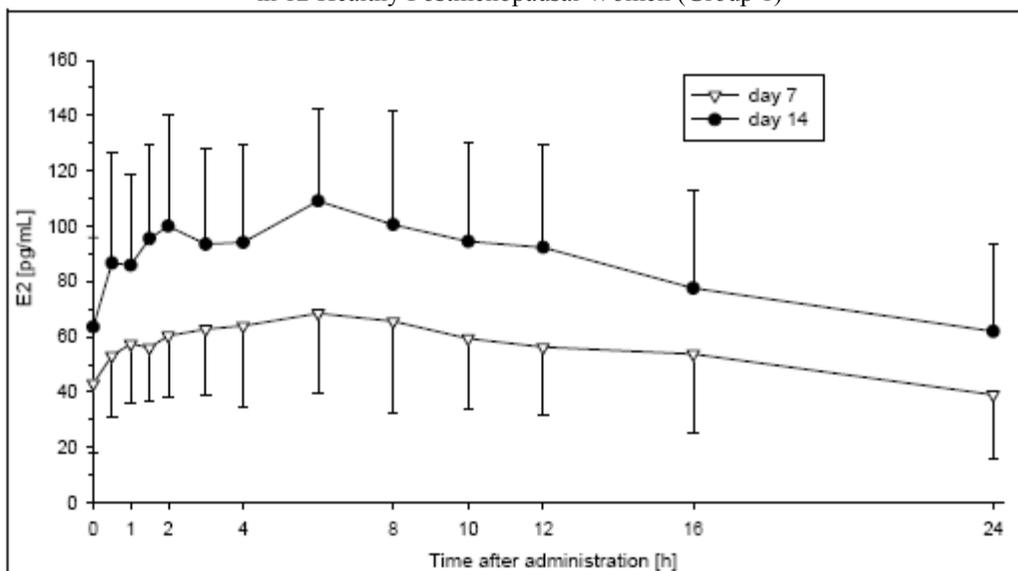


Table A-9-2: Mean PK parameters of E2 on Day 7 and Day 14 Following the Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and Ketoconazole (400 mg/day from Day 8 to Day 14) in 12 Healthy Postmenopausal Women

Treatment	C _{max} (pg/mL)	t _{max} (h)	AUC(0-24h) (h·pg/mL)
Day 7 (SH T00658M only)	69.1 (40.8%)	6.00 (2.0-16.0)	1222 (43.7%)
Day 14 (SHT00658M + 400 mg ketoconazole)	114 (32.0%)	6.00 (1.5-12.0)	1921 (39.1%)

C_{max} = Maximum concentration
t_{max} = Time to reach maximum concentration
AUC(0-24h) = Area under the concentration-time curve from 0h data point up to 24 h post administration
For t_{max}, the median and the range in parentheses are provided. The other parameters are given as geometric means followed by the geometric coefficients of variation (CV) in parentheses.

As a result of treatment with ketoconazole (400 mg/day for 7 days), the mean C_{max} and AUC(0-24) of E2 increased and the median T_{max} of E2 remained unchanged as shown in Table A-9-2.

Effect of Ketoconazole Co-administration on DNG PK

Figure A-9-6 shows the mean concentration time curves for DNG, after administration of SH T00658M (2 mg EV/3 mg DNG) to the 12 volunteers, before and after co-administration of 400 mg ketoconazole. Mean PK parameters of DNG are summarized in Table A-9-3.

Figure A-9-6: Mean (\pm SD) Concentration-Time Curves of DNG on Day 7 and Day 14 After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets (Day 1 to Day 14) and 400 mg Ketoconazole (Day 8 to Day 14) in 12 Healthy Postmenopausal Women (Group 1)

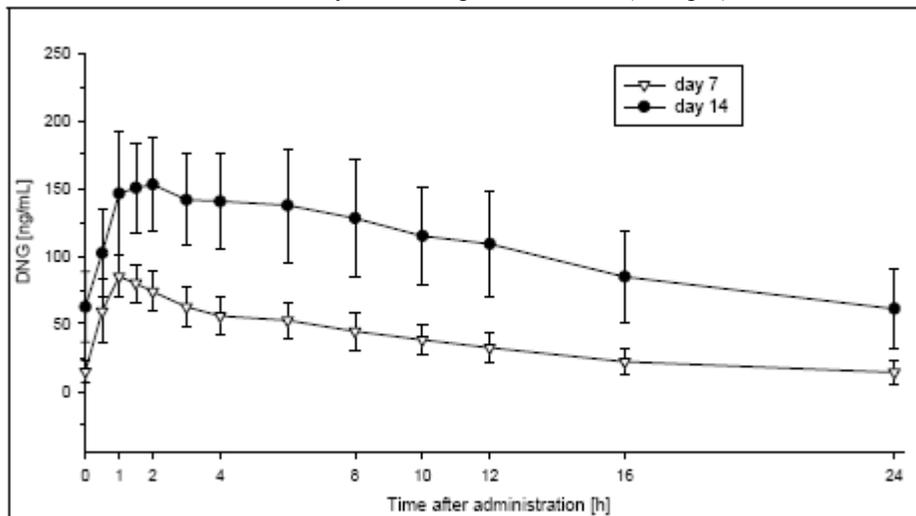


Table A-9-3: Mean PK Parameters of DNG on Day 7 and Day 14 Following the Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and Ketoconazole (400 mg/day from Day 8 to Day 14) in 12 Healthy Postmenopausal Women

Treatment	C_{max} (ng/mL)	t_{max} (h)	AUC(0-24h) (h·ng/mL)
Day 7 (SH T00658M only)	86.7 (18.0%)	1.00 (0.5-2.0)	838 (27.9%)
Day 14 (SHT00658M + 400 mg ketoconazole)	168 (24.7%)	1.75 (1.0-8.0)	2393 (33.5%)

C_{max} = Maximum concentration
 t_{max} = Time to reach maximum concentration
AUC(0-24h) = Area under the concentration-time curve from 0h data point up to 24 h post administration
For t_{max} , the median and the range in parentheses are provided. The other parameters are given as geometric means followed by the geometric coefficients of variation (CV) in parentheses.

As a result of treatment with ketoconazole (400 mg/day for 7 days), the mean C_{max} , AUC(0-24), and median T_{max} of DNG increased as shown in Table A-9-3.

Effect of Ketoconazole Co-administration on E1 PK

Figure A-9-7 shows the mean concentration time curves for E1, after administration of SH T00658M (2 mg EV/3 mg DNG) to the 12 volunteers, before and after co-administration of 400 mg ketoconazole. Mean PK parameters of E1 are summarized in Table A-9-4.

Figure A-9-7: Mean (\pm SD) Concentration-Time Curves of E1 on Day 7 and Day 14 After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets (Day 1 to Day 14) and 400 mg Ketoconazole (Day 8 to Day 14) in 12 Healthy Postmenopausal Women (Group 1)

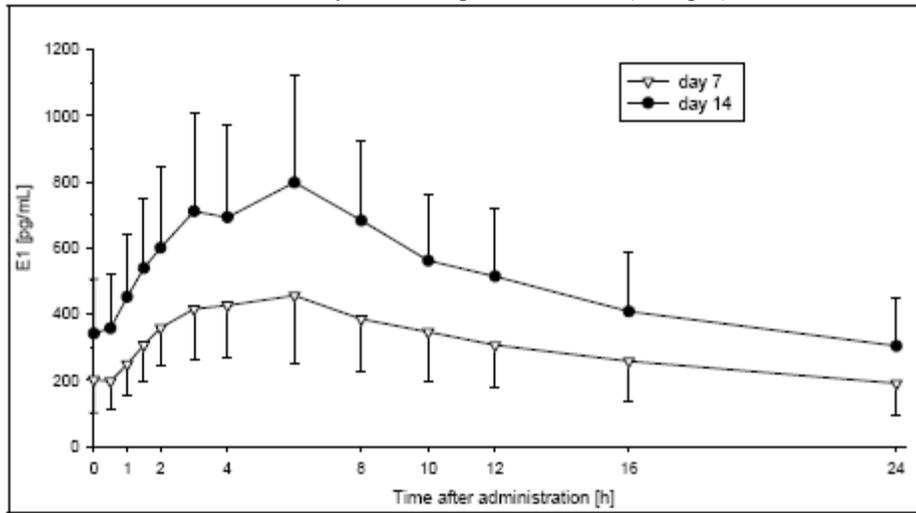


Table A-9-4: Mean PK Parameters of E1 on Day 7 and Day 14 Following the Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and Ketoconazole (400 mg/day from Day 8 to Day 14) in 12 Healthy Postmenopausal Women

Treatment	C _{max} (pg/mL)	t _{max} (h)	AUC(0-24h) (h·pg/mL)
Day 7 (SH T00658M only)	442 (39.9%)	5.00 (2.0-6.0)	6737 (44.8%)
Day 14 (SHT00658M + 400 mg ketoconazole)	808 (39.8%)	5.00 (1.5-6.0)	11395 (40.3%)
C _{max} = Maximum concentration t _{max} = Time to reach maximum concentration AUC(0-24h) = Area under the concentration-time curve from 0h data point up to 24 h post administration For t _{max} , the median and the range in parentheses are provided. The other parameters are given as geometric means followed by the geometric coefficients of variation (CV) in parentheses.			

As a result of treatment with ketoconazole (400 mg/day for 7 days), the mean C_{max} and AUC(0-24) increased and the median T_{max} remained unchanged as shown in Table A-9-4. As a prodrug of E2, EV is rapidly hydrolyzed to E2 in the intestinal tract following the oral administration.

Effect of Ketoconazole Co-administration on E1S PK

Figure A-9-8 shows the mean concentration time curves for E1S, after administration of SH T00658M (2 mg EV/3 mg DNG) to the 12 volunteers, before and after co-administration of 400 mg ketoconazole. Mean PK parameters of E1S are summarized in Table A-9-5.

Figure A-9-8: Mean (\pm SD) Concentration-Time Curves of E1S on Day 7 and Day 14 After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets (Day 1 to Day 14) and 400 mg Ketoconazole (Day 8 to Day 14) in 12 Healthy Postmenopausal Women (Group 1)

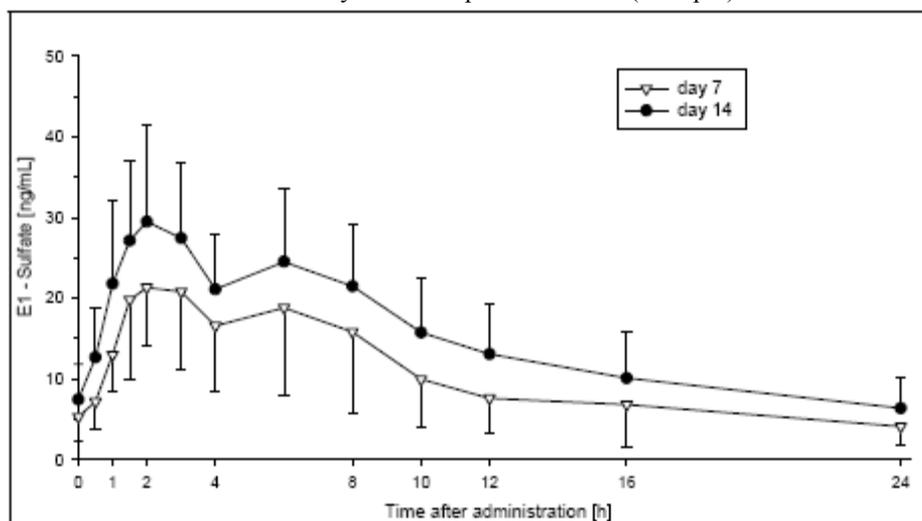


Table A-9-5: Mean PK Parameters of E1S on Day 7 and Day 14 Following the Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and Ketoconazole (400 mg/day from Day 8 to Day 14) in 12 Healthy Postmenopausal Women

Treatment	C _{max} (ng/mL)	t _{max} (h)	AUC(0-24h) (h·ng/mL)
Day 7 (SH T00658M only)	22.7 (35.4%)	2.00 (1.5-8.0)	223 (52.0%)
Day 14 (SHT00658M + 400 mg ketoconazole)	32.7 (32.1%)	2.00 (1.5-6.0)	334 (43.0%)

C_{max} = Maximum concentration
t_{max} = Time to reach maximum concentration
AUC(0-24h) = Area under the concentration-time curve from 0h data point up to 24 h post administration
For t_{max}, the median and the range in parentheses are provided. The other parameters are given as geometric means followed by the geometric coefficients of variation (CV) in parentheses.

As a result of treatment with ketoconazole (400 mg/day for 7 days), the mean C_{max} and AUC(0-24) increased and the median T_{max} remained unchanged as shown in Table A-9-5.

Effect of Erythromycin Co-administration on E2 PK

Figure A-9-9 shows the mean concentration time curves for E2, after administration of SH T00658M (2 mg EV/3 mg DNG) to the 12 volunteers, before and after co-administration of 1500 mg erythromycin 3 times a day for 7 days. Mean PK parameters of E2 are summarized in Table A-9-6.

Figure A-9-9: Mean (\pm SD) Concentration-Time Curves of E2 on Day 7 and Day 14 After Daily Oral Administration of 2 mg EV/3 mg DNG (Day 1 to Day 14) and 1500 mg Erythromycin (Day 8 to Day 14) in 12 Healthy Postmenopausal Women (Group 2)

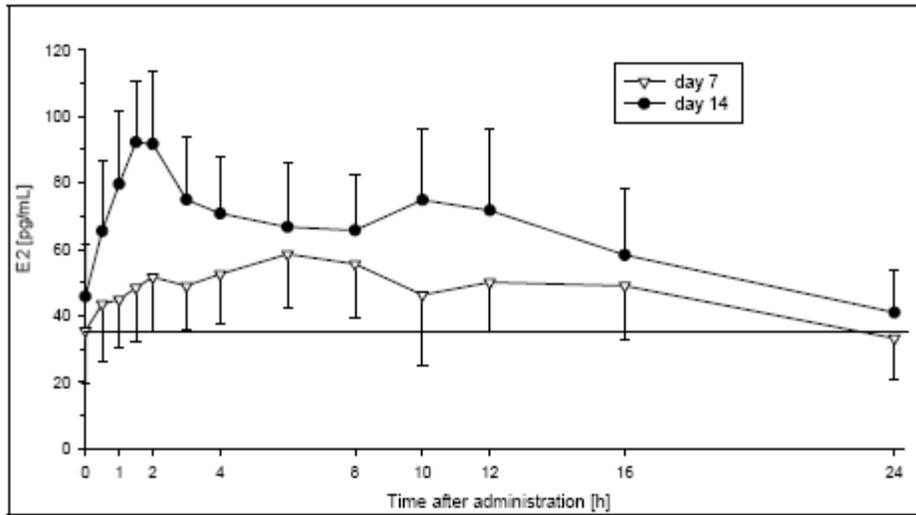


Table A-9-6: Mean PK parameters of E2 on Day 7 and Day 14 Following the Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and 500 mg erythromycin (three times a day, Day 8 to Day 14) in 12 Healthy Postmenopausal Women

Treatment	C _{max} (pg/mL)	t _{max} (h)	AUC(0-24h) (h·pg/mL)
Day 7 (SH T00658M only)	63.6 (23.2%)	6.00 (0.5-8.0)	1090 (31.8%)
Day 14 (SHT00658M + 1500 mg erythromycin)	96.1 (20.8%)	1.75 (1.5-10.0)	1451 (35.0%)

C_{max} = Maximum concentration
t_{max} = Time to reach maximum concentration
AUC(0-24h) = Area under the concentration-time curve from 0h data point up to 24 h post administration
For t_{max}, the median and the range in parentheses are provided. The other parameters are given as geometric means followed by the geometric coefficients of variation (CV) in parentheses.

As a result of treatment with erythromycin (500 mg three times a day, Day 8 to Day 14), the mean C_{max} and AUC(0-24) increased and the median T_{max} was occurred earlier as shown in Table A-9-6.

Effect of Erythromycin Co-administration on DNG PK

Figure A-9-10 shows the mean concentration time curves for DNG, after administration of SH T00658M (2 mg EV/3 mg DNG) to the 12 volunteers, before and after co-administration of 1500 mg erythromycin 3 times a day for 7 days. Mean PK parameters of DNG are summarized in Table A-9-7.

Figure A-9-10: Mean (\pm SD) Concentration-Time Curves of DNG on Day 7 and Day 14 After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets (Day 1 to Day 14) and 1500 mg Erythromycin (Day 8 to Day 14) in 12 Healthy Postmenopausal Women (Group 2)

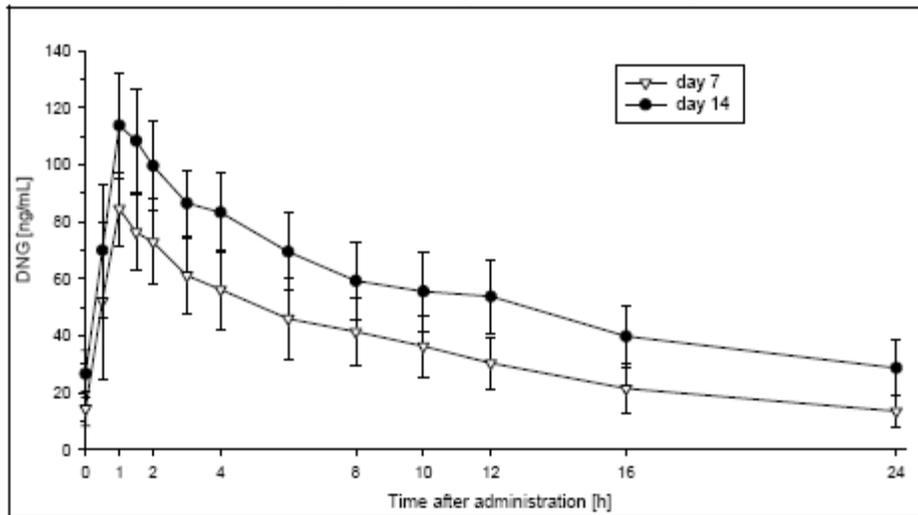


Table A-9-7: Mean PK Parameters of E1 on Day 7 and Day 14 Following the Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and 500 mg Erythromycin (three times a day, Day 8 to Day 14) in 12 Healthy Postmenopausal Women

Treatment	C _{max} (ng/mL)	t _{max} (h)	AUC(0-24h) (h·ng/mL)
Day 7 (SH T00658M only)	87.4 (15.8%)	1.00 (0.5-2.0)	797 (29.5%)
Day 14 (SHT00658M + 1500 mg erythromycin)	116 (15.5%)	1.00 (0.5-2.0)	1290 (22.2%)

C_{max} = Maximum concentration
t_{max} = 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
For t_{max}, the median and the range in parentheses are provided. The other parameters are given as geometric means followed by the geometric coefficients of variation (CV) in parentheses.

As a result of treatment with erythromycin (500 mg three times daily for 7 days), the mean C_{max} and AUC(0-24) increased and the median T_{max} remained unchanged as shown in Table A-9-7.

Effect of Erythromycin Co-administration on E1 PK

Figure A-9-11 shows the mean concentration time curves for E1, after administration of SH T00658M (2 mg EV/3 mg DNG) to the 12 volunteers, before and after co-administration of 1500 mg erythromycin 3 times a day for 7 days. Mean PK parameters of E1 are summarized in Table A-9-8.

Figure A-9-11: Mean (\pm SD) Concentration-Time Curves of E1 on Day 7 and Day 14 After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets (Day 1 to Day 14) and 1500 mg Erythromycin (Day 8 to Day 14) in 12 Healthy Postmenopausal Women (Group 2)

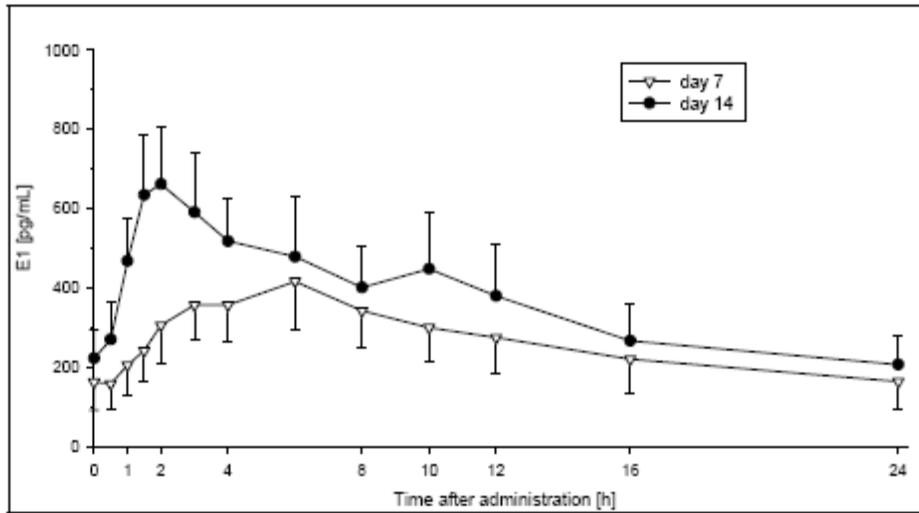


Table A-9-8: Mean PK Parameters of E1 on Day 7 and Day 14 Following the Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and 500 mg Erythromycin (three times a day, Day 8 to Day 14) in 12 Healthy Postmenopausal Women

Treatment	C _{max} (pg/mL)	t _{max} (h)	AUC(0-24h) (h·pg/mL)
Day 7 (SH T00658M only)	434 (22.3%)	6.00 (3.0-8.0)	6079 (30.8%)
Day 14 (SHT00658M + 1500 mg erythromycin)	672 (23.1%)	2.00 (1.5-6.0)	8429 (32.8%)
C _{max} = Maximum concentration t _{max} = Time to reach maximum concentration AUC(0-24h) = Area under the concentration-time curve from 0h data point up to 24 h post administration For t _{max} , the median and the range in parentheses are provided. The other parameters are given as geometric means followed by the geometric coefficients of variation (CV) in parentheses.			

As a result of treatment with erythromycin (500 mg three times a day, Day 8 to Day 14), the mean C_{max} and AUC(0-24) increased and the median T_{max} occurred earlier.

Effect of Erythromycin Co-administration on E1S PK

Figure A-9-12 shows the mean concentration time curves for E1S, after administration of SH T00658M (2 mg EV/3 mg DNG) to the 12 volunteers, before and after co-administration of 1500 mg erythromycin 3 times a day for 7 days. Mean PK parameters of E1S are summarized in Table A-9-9.

Figure A-9-12: Mean (\pm SD) Concentration-Time Curves of E1S on Day 7 and Day 14 After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets (Day 1 to Day 14) and 1500 mg Erythromycin (Day 8 to Day 14) in 12 Healthy Postmenopausal Women (Group 2)

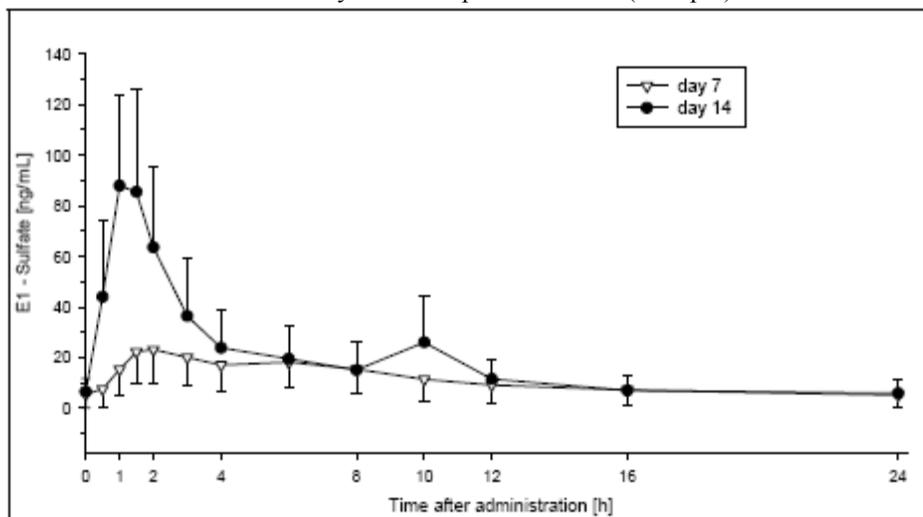


Table A-9-9: Mean PK Parameters of E1S on Day 7 and Day 14 Following the Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and 500 mg Erythromycin (three times a day, Day 8 to Day 14) in 12 Healthy Postmenopausal Women

Treatment	C _{max} (ng/mL)	t _{max} (h)	AUC(0-24h) (h·ng/mL)
Day 7 (SH T00658M only)	22.3 (53.7%)	2.00 (1.5-8.0)	221 (73.1%)
Day 14 (SHT00658M + 1500 mg erythromycin)	91.5 (44.4%)	1.00 (0.5-1.5)	389 (58.4%)

C_{max} = Maximum concentration
t_{max} = Time to reach maximum concentration
AUC(0-24h) = Area under the concentration-time curve from 0h data point up to 24 h post administration
For t_{max}, the median and the range in parentheses are provided. The other parameters are given as geometric means followed by the geometric coefficients of variation (CV) in parentheses.

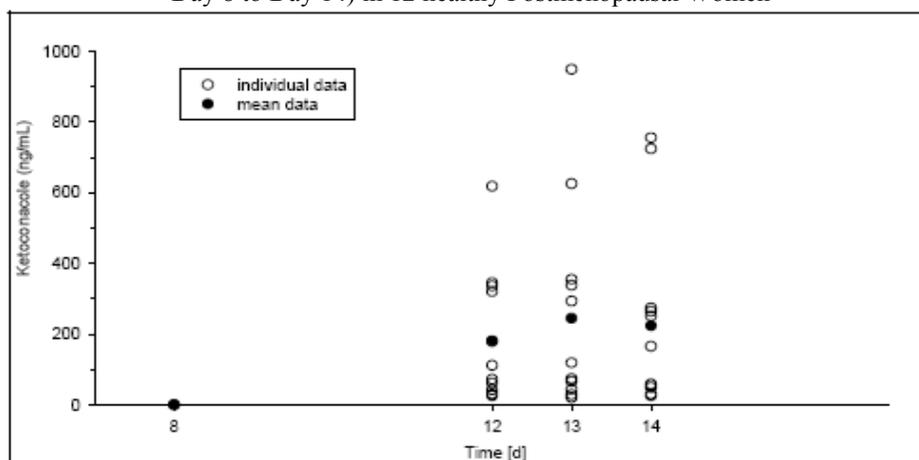
As a result of treatment with erythromycin (500 mg three times a day, Day 8 to Day 14), the mean C_{max} and AUC(0-24) increased and the median T_{max} occurred earlier.

E2 is then extensively metabolized to E1 (15%), E1S (65%), estradiol sulfate, and other compounds (Kuhnz *et al.*, 1999). CYP 3A4 is the major isozyme responsible for the hydroxylation of E2 at C-2, C-4 and C-16 and for the 16 α -hydroxylation of E1. The impact of CYP 3A4 inhibition on E1 and E2 is likely due to the decreased CYP 3A4-mediated metabolism and consequently decreased the clearance of E1 (69.1% and 38.7% increase in AUC(0-24) following co-administration of ketoconazole and erythromycin, respectively) and E2 (57.2% and 33.1% increase in AUC(0-24) following co-administration of ketoconazole and erythromycin, respectively). E1S levels were also affected and mean AUC(0-24) were increased following co-administration of both ketoconazole and erythromycin. Although it is known that E1S is not directly metabolized by CYP 3A4, the increased concentrations of E1S is likely caused by the higher E1 level.

Trough concentrations of ketoconazole and erythromycin

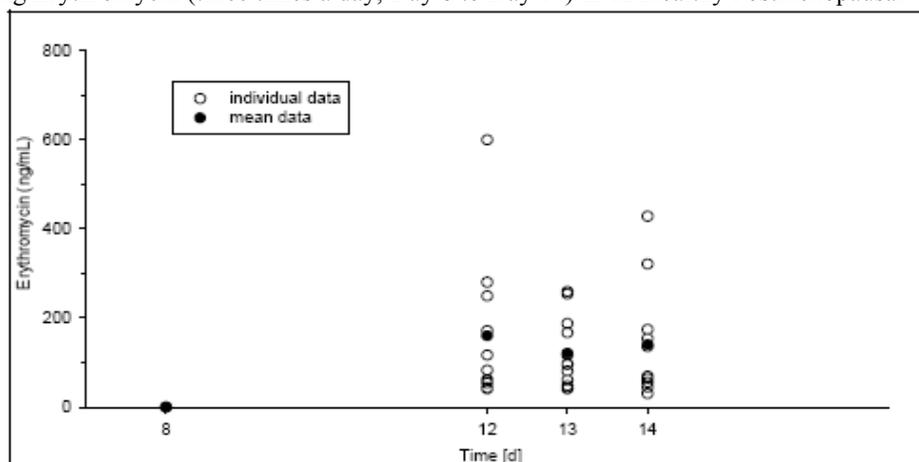
Plasma concentrations of ketoconazole were measured at pre-dose on Days 8, 12, 13, and 14. Figure A-9-13 illustrates the individual and mean plasma concentrations of ketoconazole in the individual volunteers.

Figure A-9-13: Individual and Mean Plasma Concentrations of Ketoconazole at Pre-dose on Days 8, 12, 13, and 14 Following a Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and Ketoconazole (400 mg/day from Day 8 to Day 14) in 12 healthy Postmenopausal Women



Plasma concentrations of erythromycin were measured at pre-dose on Days 8, 12, 13, and 14. Figure A-9-14 illustrates the individual and mean plasma concentrations of erythromycin in the individual volunteers.

Figure A-9-14: Individual and Mean Plasma Concentrations of Erythromycin at Pre-dose on Days 8, 12, 13 and 14 Following the Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and 500 mg Erythromycin (three times a day, Day 8 to Day 14) in 12 Healthy Postmenopausal Women



STATSTICAL ANALYSIS

The statistical comparison of the primary target variables was performed using Day 7 (without ketoconazole or erythromycin) and Day 14 (with ketoconazole or erythromycin). Table A-9-10 summarizes the geometric mean ratios and 90% CIs for the primary target variables for DNG and E2.

Table A-9-10: Statistical Comparison of the Primary Target Variables Performed Using Day 7 (without Ketoconazole or Erythromycin) and Day 14 (with Ketoconazole or Erythromycin) Following Co-administration of EV 2 mg/DNG 3 mg Tablets with 400 mg/day Ketoconazole or 1500 mg/day Erythromycin (N=12 per Group)

Treatment	Compound	PK Parameter	Geometric Mean Ratio (%)	90% CI (%)
SH T00658M + 400 mg ketoconazole (Day 14) vs. SH T00658M alone (Day 7)	DNG	C _{max}	194	184-205
		AUC(0-24)	286	263-311
	E2	C _{max}	165	149-182
		AUC(0-24)	157	145-171
SH T00658M + 1500 mg erythromycin (Day 14) vs. SH T00658M alone (Day 7)	DNG	C _{max}	133	123-144
		AUC(0-24)	162	146-180
	E2	C _{max}	151	136-168
		AUC(0-24)	133	118-150

Ketoconazole is a potent inhibitor of CYP 3A4 and DNG is extensively metabolized by CYP 3A4. The presence of a significant DDI between EV/DNG tablets and CYP 3A4 inhibitors, ketoconazole and erythromycin was demonstrated. The study showed that co-administration of ketoconazole with EV/DNG tablets resulted in a 94% increase in the mean C_{max} and a 186% increase in the AUC(0-24) for DNG. The magnitude of increases is less than the 5 to 10-fold increase normally observed with other drugs that are eliminated predominantly by CYP 3A4. Increase in E2 C_{max} (51.1%) and AUC(0-24) (33.1%) from the erythromycin arm is relatively lower compared to those (65.0% and 57.2%, respectively) from the ketoconazole arm. Considering the known smaller extent of erythromycin inhibition compared to that of ketoconazole, this would be expected.

Reviewer's comment: *A thorough QT study (Study A35653) was conducted to evaluate the potential of a fixed combination of 2 mg EV/3 mg DNG (i.e., highest combination dose strength) at steady-state to delay cardiac repolarization in healthy postmenopausal women, to monitor safety and to evaluate the PK of DNG, E2, and E1. This study included a supra-therapeutic DNG dose (10 mg DNG, 5 x 2 mg tablets) arm. This study showed that DNG at a dose of 3 mg in combination with 2 mg EV and at a dose of 10 mg did not lead to QT/QTc prolongation. The DNG exposure achieved with the 10 mg oral dose (3.4-fold increase in AUC(0-24) and 3.5-fold increase in C_{max} compared to those of 2 mg EV/3 mg DNG) was as high as can be expected when EV/DNG tablets are administered with 400 mg ketoconazole (i.e., CYP 3A4 strong inhibitor) daily (2.9-fold increase in AUC(0-24) and 1.9-fold increase in C_{max}) and demonstrated no effect on QT interval. Therefore, although a significant DDI between CYP 3A4 inhibitors were shown, no dosage adjustment should be necessary. However, the clinical DDI study data should be reflected in the labeling.*

For EV, daily co-administration with 400 mg ketoconazole resulted in approximately 57% and 65% increase in AUC(0-24) and C_{max}. Per clinical reviewer, Dr. Gerald Willett, nausea would be the drug related AE to watch out for increase in E2 levels. The other common AE mentioned by the Sponsor was withdrawal bleeding (7 events in 7 volunteers, 29.2%). Examination of the individual exposure data of E2, E1, and DNG, reveals no correlation between the magnitude of AUC change of E2, E1, or DNG and the occurrence of these AEs. Considering that the safety profiles from the Phase 3 clinical studies are similar to other COCs (per clinical reviewer, Dr. Gerald Willett) and the absence of correlations between E2 exposure and AEs observed, no dosage adjustment should be necessary. However, the clinical DDI study results should be reflected in the labeling.

Although there were several subjects with relatively low ketoconazole (N=6 with < 100 ng/ml) or erythromycin (N=6 with < 100 ng/ml) steady-state plasma concentrations, the extent of inhibition observed in these individuals were not affected and were found to be comparable to others. The results of comparison are summarized in the Tables A-9-11 through A-9-14 below:

Table A-9-11: Statistical Comparison of the Mean Ratio of DNG Primary Target Variables Between All Subjects and Low Ketoconazole Level (< 100 ng/ml) Subjects

	EV/DNG + Ketoconazole			
	C_{max} (Day 14/Day 7)	C_{max} (Day 14/Day 7)	AUC(0-24) (Day 14/Day 7)	AUC(0-24) (Day 14/Day 7)
Subjects	All subjects (N=12)	Low Ketoconazole (N=6)	All subjects (N=12)	Low Ketoconazole (N=6)
Mean	1.95	1.86	2.90	2.91
SD	0.22	0.24	0.53	0.55
Min	1.68	1.68	2.28	2.28
Max	2.31	2.31	3.66	3.65

Table A-9-12: Statistical Comparison of the Mean Ratio of DNG Primary Target Variables Between All Subjects and Low Erythromycin Level (< 100 ng/ml) Subjects

	EV/DNG + Erythromycin			
	C_{max} (Day 14/Day 7)	C_{max} (Day 14/Day 7)	AUC(0-24) (Day 14/Day 7)	AUC(0-24) (Day 14/Day 7)
Subjects	All subjects (N=12)	Low Erythromycin (N=6)	All subjects (N=12)	Low Erythromycin (N=6)
Mean	1.35	1.27	1.66	1.67
SD	0.22	0.22	0.38	0.31
Min	1.06	1.06	1.18	1.18
Max	1.73	1.59	2.47	2.07

Table A-9-13: Statistical Comparison of the Mean Ratio of E2 Primary Target Variables Between All Subjects and Low Ketoconazole Level (< 100 ng/ml) Subjects

	EV/DNG + Ketoconazole			
	C_{max} (Day 14/Day 7)	C_{max} (Day 14/Day 7)	AUC(0-24) (Day 14/Day 7)	AUC(0-24) (Day 14/Day 7)
Subjects	All subjects (N=12)	Low Ketoconazole (N=6)	All subjects (N=12)	Low Ketoconazole (N=6)
Mean	1.68	1.52	1.60	1.44
SD	0.42	0.09	0.30	0.15
Min	1.28	1.42	1.24	1.24
Max	2.80	1.66	2.24	1.63

Table A-9-14: Statistical Comparison of the Mean Ratio of E2 Primary Target Variables Between All Subjects and Low Erythromycin Level (< 100 ng/ml) Subjects

	EV/DNG + Erythromycin			
	C_{max} (Day 14/Day 7)	C_{max} (Day 14/Day 7)	AUC(0-24) (Day 14/Day 7)	AUC(0-24) (Day 14/Day 7)
Subjects	All subjects (N=12)	Low Erythromycin (N=6)	All subjects (N=12)	Low Erythromycin (N=6)
Mean	1.55	1.51	1.37	1.30
SD	0.37	0.33	0.33	0.38
Min	1.15	1.28	0.78 (1.05) ^a	0.78 (1.13) ^a
Max	2.41	2.07	1.78	1.77

^a Min value if excluding the current Min value (which seems to be an outlier)

In summary, this study demonstrated the presence of a significant DDI between EV/DNG combination tablets and CYP 3A4 inhibitors, ketoconazole and erythromycin. Co-administration of EV/DNG tablets with ketoconazole and erythromycin resulted in increases of C_{max} and AUC(0-24) values for both E2 and DNG.

SAFETY RESULTS

No deaths and no serious adverse events were reported during this study. In total, 21 AEs (17 with 2 mg EV/3 mg DNG + Ketoconazole, 4 with 2 mg EV/3 mg DNG + Erythromycin) were documented in 12 out of 24 (50.0%) volunteers. The common AEs were withdrawal bleeding (7 events in 7 volunteers, 29.2%) and myalgia reported as muscle pain in one or both legs (3 events in 3 volunteers, 12.5%).

CONCLUSION

The treatment with 2 mg EV/3 mg DNG combination tablets (SH T00658M) once daily for 14 days and the concomitant medication with 400 mg/day ketoconazole or 1500 mg/day erythromycin between Days 8 and 14 was demonstrated the presence of a significant DDI between 2 mg EV/3 mg DNG tablets and CYP 3A4 inhibitors, ketoconazole and erythromycin. Co-administration of 2 mg EV/3 mg DNG tablets with ketoconazole and erythromycin resulted in increases of C_{max} and AUC(0-24) values for both E2 and DNG. Although a

significant DDI between CYP 3A4 inhibitors were shown, no dosage adjustment should be necessary. However, the clinical DDI study data should be reflected in the labeling.

A.1.10. Study A24058

One-arm, Open-label, Non-randomized Study to Evaluate the Effect of Rifampicin 600 mg/day, Given Over 5 days p.o., on the Steady-state Pharmacokinetics of SH T00658M (2 mg Estradiol Valerate and 3 mg Dienogest) in Healthy Postmenopausal Volunteers

Protocol No: A24058
Phase: 1
Principal Investigator: Dr. T. Zimmermann
Clinical Study Center: Clinical Pharmacology, Schering AG, Berlin, Germany
Clinical Study Dates: March 1, 2005 - May 17, 2005
Analytical Study Facility: (b) (4) (E2, E1, and E1S), Schering Oy, Finland (DNG), and SFBC Anapharm, Quebec, Canada (Ketoconazole and Erythromycin)
Analytical Study Dates: May 2005 - October 2005

OBJECTIVE

The primary objective of the study was the evaluation of the influence of CYP induction by rifampicin on the steady-state PK of DNG and EV.

STUDY ENDPOINTS

Primary endpoints for E2 and DNG (on Days 11 and 17) were serum AUC(0-24) and C_{max} .

Secondary endpoints were:

- AUC(0-24) and C_{max} of E1 and E1S
- T_{max} of E1, E1S, E2, and DNG
- 6 β -hydroxycortisol urinary 24 hr excretion
- Rifampicin exposure

STUDY DESIGN, TREATMENT, AND SUBJECTS

The study was conducted as a one-arm, open-label, non-randomized, single center study in one group of 16 healthy female, postmenopausal volunteers. The steady-state PK of SH T00658M (containing 2 mg EV and 3 mg DNG) were investigated prior to and after 5 days of treatment with 600 mg rifampicin daily. All volunteers received a treatment regimen of 2 mg EV/3 mg DNG, dosed once daily over 17 days, and of rifampicin, which was administered once daily in an oral dose of 600 mg on Days 12-16. 24-hr PK profiles of 2 mg EV/3 mg DNG on Days 11 and 17 were compared.

The 2 mg EV/3 mg DNG tablet was taken in the morning, with 250 ml mineral water (non-carbonated, room temperature). For intake on Days 1 and 8-17, the volunteers were instructed to fast after 21:00 hr of the previous evening, to ensure a fasting period of at least 10 hr before administration of the 2 mg EV/3 mg DNG tablet. On study Days 2-7, volunteers were to take the tablet at home and document this in a specific diary (which was to be provided by Schering) immediately after drug intake. On Days 11 and 17, fasting was to continue until 2 hr after administration; drinking water was allowed, except from 1 hr before to 1 hr after study drug administration, which was to take place in the morning between 07:00 hr and 09:00 hr at the study site.

Rifampicin (Days 12-16) was administered 1 hr after a light breakfast (given 0.5 hr after administration of 2 mg EV/3 mg DNG) and 1.5 hr (± 10 min) after intake of the 2 mg EV/3 mg DNG tablet, together with 100 ml of mineral water (non-carbonated, room temperature).

Table A-10-1: Treatment Schedule

Sequence	Number of volunteers	Day 1 -11	Day 12 - 16	Day 17
1	16	SH T00658M alone	SH T00658M and rifampicin	SH T00658M alone

On study Days 11 and 17, 24-hr urinary excretion of 6 β -hydroxycortisol was determined, as an *in vivo* marker for CYP 3A induction. Standard safety measures were carried out (i.e., clinical laboratory tests, vital signs) and the volunteers were to be monitored for AEs and concomitant medication.

A total of 39 female subjects were screened. 16 Caucasian female, healthy, post-menopausal volunteers with an average age of 59.9 yr (range: 54-64 yr), nonsmokers, with follicle stimulating hormone \geq 40 IU/l and E2 \leq 20 pg/ml on screening were enrolled, randomized and treated according to the study protocol. Their mean height was 166 cm (range: 154-173 cm) and their mean weight 67.9 kg (range: 48.5-79.4 kg). Their mean BMI was 24.7 kg/m² (range: 20.5-28.5 kg/m²). There were no discontinuations.

The influence of CYP induction on the steady-state PK of DNG and EV given in a fixed combination of 2 mg EV/3 mg DNG was evaluated. DNG reaches the PK steady-state after approximately 4-5 days of dosing; EV does so within about 6 days of dosing (Study A25711). 2 mg EV/3 mg DNG was given over a period of 11 days prior to rifampicin induction; this period appears to be sufficient to reach and demonstrate steady-state of both DNG and EV. Rifampicin was administered from Day 12 to Day 16 in the recommended daily dose of 600 mg, together with continued dosing of 2 mg EV/3 mg DNG. Effect of CYP induction was evaluated by monitoring the change in the steady-state PK of DNG and of EV on Day 17, the day after the last rifampicin dose.

Healthy pre-menopausal women are the target population for 2 mg EV/3 mg DNG. However, the endogenous estrogen production in younger women could have resulted in highly variable estrogen concentrations in serum, which would have interfered with the PK analysis of EV. The investigation was therefore, done in postmenopausal women who have a low endogenous estrogen production. This approach is acceptable given that the PK parameters of DNG, E2, and E1 at steady state following 2 mg EV/3 mg DNG in premenopausal women (Study A25711) were comparable to those observed in postmenopausal women with the same dose (Study A30020).

Inclusion Criteria

Volunteers had fulfilled all of the following criteria before being included in the treatment phase:

- Nonsmoking healthy postmenopausal female volunteer
- Postmenopausal state: serum hormone analyses (estradiol \leq 20 pg/ml, follicle stimulating hormone \geq 30 IU/l)
- Age: 45-65 yr
- BMI: $>$ 20 and $<$ 30 kg/m²

FORMULATION

SH T00658M was to be supplied as film coated tablets containing 2 mg EV and 3 mg DNG (manufactured by Schering AG, Germany). Rifampicin was to be supplied as film coated tablets, containing 600 mg rifampicin (Eremfat[®]).

PHARMACOKINETIC EVALUATION

Blood sampling

Sampling times for determination of DNG, E2, E1, and E1S:

- Pre-dose on Days 1 and 8-17 (Day 12: 1st rifampicin day)
- At 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hr post-dose on Days 11 and 17

Sampling times for determination of rifampicin:

- Pre-dose on Day 12 (1st rifampicin day)
- 8 hr after rifampicin dose on Days 12-16 (Day 16: last rifampicin day)

Sampling times for determination of 6 β -OH-cortisol:

- 24 hr urine collection on Days 11 and 17: measurement of CYP induction in liver

Concomitant Therapy

If a volunteer used concomitant medication, this was documented by type (brand name, if applicable), indication, regimen (total daily dose and route), and duration on the appropriate CRF.

Other Restrictions

- Smoking: not permitted
- Alcohol: not permitted within 48 hr before the 1st study drug administration until Day 18
- Caffeine: not permitted within 24 hr before the 1st study drug administration until 2 hr after the last drug administration
- Grapefruit not permitted from 7 days before the 1st study drug administration until Day 18

Bioanalytical method

(b) (4)

Acceptance criteria for method validation and assay performance for each analyte were in compliance with the *Bioanalytical Method Validation Guidance*.

Safety Assessments

To ensure the volunteers' safety after intake of either 2 mg EV/3 mg DNG alone or 2 mg EV/3 mg DNG plus rifampicin the following parameters were studied during the treatment period:

- Standard laboratory examination of blood and urine prior to dosing on Days 1 and 12, respectively, and on Day 18
- AE and concomitant medication

DATA ANALYSIS

Pharmacokinetic Analysis

The PK parameters were calculated using a commercially available software tool (Kinetica™, version 4.2, InnaPhase Corporation) without recourse to model assumptions. All serum concentration values below the LLOQ were set to zero. C_{max} and T_{max} were directly read off the data. The AUC(0-24) was calculated according to the mixed linear-log trapezoidal rule. Rifampicin exposure was checked by single point plasma concentrations determined on Days 12-16 at 8 hr after dose. Urinary excretion of 6 β -hydroxycortisol is compared between Day 17 and 11.

Statistic Methods

Descriptive statistics were performed for PK parameters. Antilog transformations were to render the corresponding two-sided 90% CIs on the original scale. No interim analysis was carried out.

PHARMACOKINETIC RESULTS

Achievement of Steady-state

E2 steady state was reached on Day 10 of treatment with a mean trough concentration of approximately 41 pg/ml. DNG reached steady state on Day 8 of treatment as demonstrated by the almost constant mean trough concentrations of approximately 11 ng/ml between Day 8 to Day 11.

Table A-10-2: Arithmetic Mean (\pm SD) Trough Concentrations of E2 and DNG After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets to 16 healthy postmenopausal women

	E2 (pg/ml)	DNG (ng/ml)
Day 8	36.2 (11.0)	11.2 (6.10)
Day 9	39.5 (11.6)	11.0 (5.42)
Day 10	41.7 (14.6)	10.7 (5.32)
Day 11	41.3 (11.7)	11.0 (5.15)

PK of E2: Before and after co-administration of rifampicin

Figure A-10-1 shows the mean concentration time curves for E2, after administration of 2 mg EV/3 mg to the 16 volunteers, before and after co-administration of 600 mg rifampicin daily. Mean PK parameters of E2 are summarized in Table A-10-3.

Figure A-10-1: Mean (\pm SD) Concentration-Time Curves of E2 on Day 11 and Day 17 After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets to 16 Healthy Postmenopausal Women.

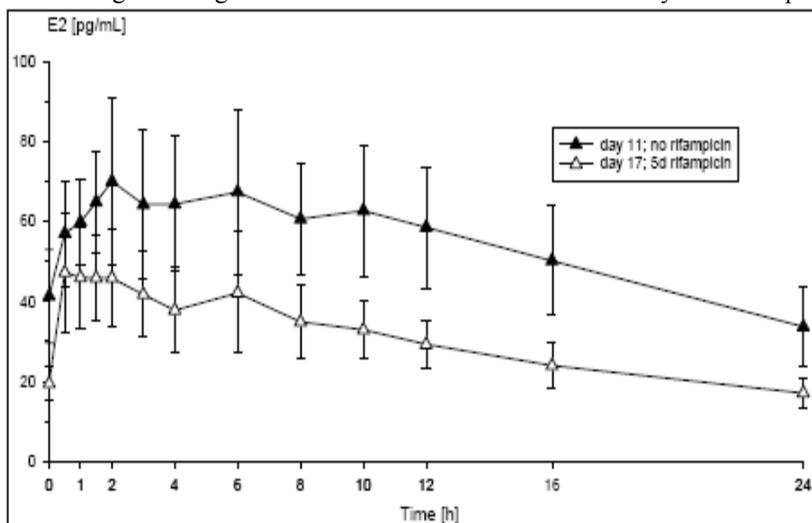


Table A-10-3: Mean PK Parameters of E2 on Day 11 and Day 17 Following the Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and Rifampicin (600 mg/day from Day 12 to Day 16) in 16 Healthy Postmenopausal Women

Treatment	C _{max} (pg/mL)	t _{max} (h)	AUC(0-24h) (h·pg/mL)
Day 11 (SH T00658M only)	75.0 (28.6%)	2.04 (0.5-15.9)	1261 (22.9%)
Day 17 (SHT00658M + 600 mg rifampicin)	56.4 (22.2%)	1.51 (0.49-10.0)	710 (19.9%)

C_{max} = Maximum serum concentration
t_{max} = Time to reach maximum concentration
AUC(0-24h) = Area under the concentration-time curve from 0h data point up to 24 h post administration

For t_{max}, the median and the range in parentheses are provided. The other parameters are given as geometric means followed by the geometric coefficients of variation (CV) in parentheses.

As a result of treatment with rifampicin (600 mg/day for 5 days), the mean C_{max}, AUC(0-24), and the median T_{max} of E2 decreased as shown in Table A-10-3. During rifampicin treatment, mean E2 trough concentration continuously decreased from 33.6 pg/ml (Day 12) to 19.5 pg/ml (Day 17).

PK of DNG: Before and after co-administration of rifampicin

Figure A-10-2 shows the mean concentration time curves for DNG, after administration of 2 mg EV/3 mg DNG combination tablets to the 16 volunteers, before and after co-administration of 600 mg rifampicin daily. Mean PK parameters of DNG are summarized in Table A-10-4.

Figure A-10-2: Mean (\pm SD) Concentration-Time Curves of DNG on Day 11 and Day 17 After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and Rifampicin (600 mg/day from Day 12 to Day 16) to 16 Healthy Postmenopausal Women

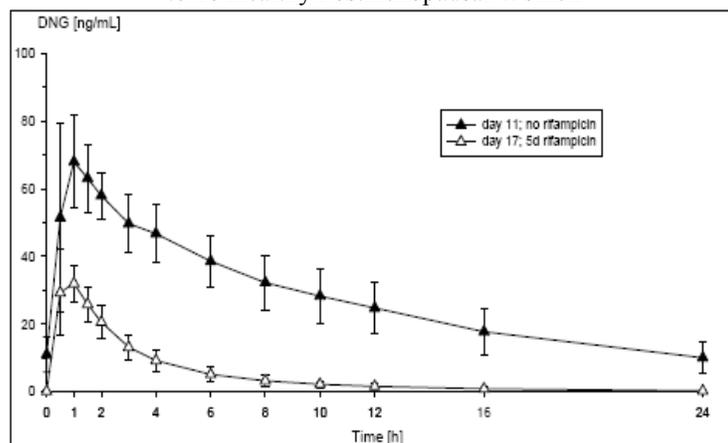


Table A-10-4: Mean PK Parameters of DNG on Day 11 and Day 17 Following the Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and Rifampicin (600 mg/day from Day 12 to Day 16) in 16 Healthy Postmenopausal Women

Treatment	C _{max} (ng/mL)	t _{max} (h)	AUC(0-24h) (h·ng/mL)
Day 11 (SH T00658M only)	72.3 (14.8%)	1 (0.5-3)	651 (25.2%)
Day 17 (SHT00658M + 600 mg rifampicin)	34.8 (20.3%)	0.51 (0.49-1.02)	111 (27.2%)

C_{max} = Maximum serum concentration
t_{max} = Time to reach maximum concentration
AUC(0-24h) = Area under the concentration-time curve from 0h data point up to 24 h post administration

For t_{max}, the median and the range in parentheses are provided. The other parameters are given as geometric means followed by the geometric coefficients of variation (CV) in parentheses.

As a result of treatment with rifampicin (600 mg/day for 5 days), the mean C_{max}, AUC(0-24), and median T_{max} of DNG decreased as shown in Table A-10-4. During rifampicin treatment, mean DNG trough levels continuously decreased from 10.0 ng/ml (Day 12) to 0.153 ng/ml (Day 17).

PK of E1: Before and after co-administration of rifampicin

Figure A-10-3 shows the mean concentration time curves for E1, after administration of 2 mg EV/3 mg DNG combination tablets to the 16 volunteers, before and after co-administration of 600 mg rifampicin daily. Mean PK parameters of E1 are summarized in Table A-10-5.

Figure A-10-3: Mean (\pm SD) Concentration-Time Curves of E1 on Day 11 and Day 17 After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets to 16 Healthy Postmenopausal Women.

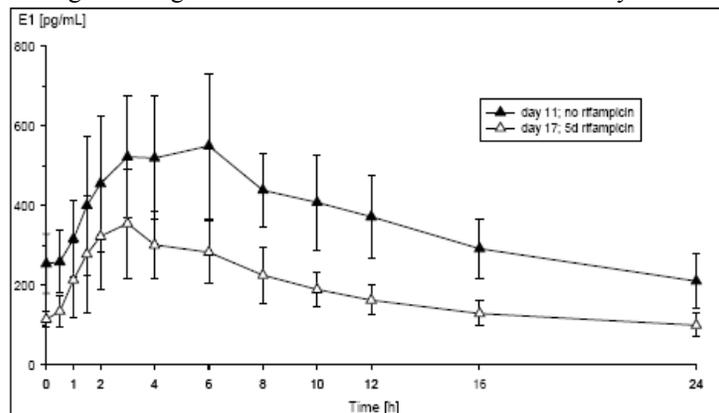


Table A-10-5: Mean PK Parameters of E1 on Day 11 and Day 17 Following the Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and Rifampicin (600 mg/day from Day 12 to Day 16) in 16 healthy Postmenopausal Women

Treatment	C _{max} (pg/mL)	t _{max} (h)	AUC(0-24h) (h·pg/mL)
Day 11	562 (29.9%)	4 (2.01-6.12)	8339 (26.8%)
Day 17	347 (32.8%)	3.01 (2-6.03)	4294 (24.0%)

C_{max} = Maximum serum concentration
t_{max} = Time to reach maximum concentration
AUC(0-24h) = Area under the concentration-time curve from 0h data point up to 24 h post administration
For t_{max}, the median and the range in parentheses are provided. The other parameters are given as geometric means followed by the geometric coefficients of variation (CV) in parentheses.

As a result of treatment with rifampicin (600 mg/day for 5 days), the mean C_{max}, AUC(0-24), and the median T_{max} of E1 decreased as shown in Table A-10-5. During rifampicin treatment, mean E1 trough concentration continuously decreased from 210 pg/ml (Day 12) to 115 pg/ml (Day 17).

PK of E1S: Before and after co-administration of rifampicin

Figure A-10-4 shows the mean concentration time curves for E1S, after administration of 2 mg EV/3 mg DNG combination tablets to the 16 volunteers, before and after co-administration of 600 mg rifampicin daily. Mean PK parameters of E1S are summarized in Table A-10-6.

Figure A-10-4: Mean (\pm SD) Concentration-Time Curves of E1S on Day 11 and Day 17 After Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets to 16 Healthy Postmenopausal Women.

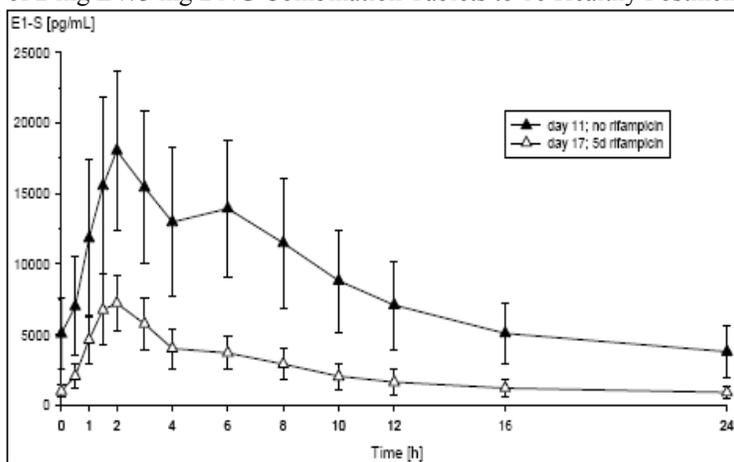


Table A-10-6: Mean PK Parameters of E1S on Day 11 and Day 17 Following the Daily Oral Administration of 2 mg EV/3 mg DNG Combination Tablets and Rifampicin (600 mg/day from Day 12 to Day 16) in 16 Healthy Postmenopausal Women

Treatment	C _{max} (pg/mL)	T _{max} (h)	AUC(0-24h) (h·pg/mL)
Day 11 (SH T00658M only)	18300 (32.4%)	2.02 (1.5-8.01)	189381 (37.8%)
Day 17 (SHT00658M + 600 mg rifampicin)	7504 (30.3%)	2 (1.49-3.02)	53726 (34.0%)
C _{max} = Maximum serum concentration t _{max} = Time to reach maximum concentration AUC(0-24h) = Area under the concentration-time curve from 0h data point up to 24 h post administration For t _{max} , the median and the range in parentheses are provided. The other parameters are given as geometric means followed by the geometric coefficients of variation (CV) in parentheses.			

As a result of treatment with rifampicin (600 mg/day for 5 days), the mean C_{max}, AUC(0-24), and the median T_{max} of E1S decreased as shown in Table A-10-6. During rifampicin treatment, mean E1S trough concentration continuously decreased from 3794 pg/ml (Day 12) to 1000 pg/ml (Day 17).

Statistical Analyses on the Effect of Rifampicin on DNG, E2, E1, and E1S PK

The effect of CYP 3A4 inducer, rifampicin, on the steady-state PK of DNG, E2, E1, and E1S was evaluated by statistical comparison of PK parameters between Day 11 and Day 17. Table A-10-7 summarizes the geometric mean ratios and 90% CI for the primary target variables for DNG and E2, when comparing Day 17 to Day 11.

Table A-10-7: Statistical Comparison of Primary Target Variables Between Day 11 (without rifampicin) and Day 17 (rifampicin steady-state) Following Co-administration of 600 mg Rifampicin Daily with EV 2 mg/DNG 3 mg Tablets (N=16)

Treatment	Compound	PK Parameter	Geometric Mean Ratio (%)	90% CI (%)
SH T00658M + 600 mg rifampicin vs. SH T00658M alone	DNG	C _{max}	48	15.6-18.7
		AUC(0-24)	17	44.8-51.6
	E2	C _{max}	75	66.9-84.4
		AUC(0-24)	56	53.1-59.8
	E1	C _{max}	62	55.8-68.6
		AUC(0-24)	52	47.3-56.0
	E1S	C _{max}	41	36.3-46.3
		AUC(0-24)	28	25.1-32.1

DNG: The geometric mean of AUC(0-24) (90% CI) of Day 17 was 17% (15.6-18.7%) of it on Day 11. The geometric mean of C_{max} (90% CI) of Day 17 was 48% (44.8-51.6%) of it on Day 11. Both 90% CI fell below the lower boundary of 80-125%, indicating that co-administration of rifampicin significantly decreased the C_{max} and AUC(0-24) for DNG.

E2: The geometric mean of AUC(0-24) (90% CI) of Day 17 was 56% (53.1-59.8%) of it on Day 11. The geometric mean of C_{max} (90% CI) of Day 17 was 75% (66.9-84.4%) of it on Day 11. Both 90% CI fell below the lower boundary of 80-125%, indicating that co-administration of rifampicin significantly decreased the C_{max} and AUC(0-24) for E2.

E1: The geometric mean of AUC(0-24) (90% CI) of Day 17 was 52% (47.3-56.0%) of it on Day 11. The geometric mean of C_{max} (90% CI) of Day 17 was 62% (55.8-68.6%) of it on Day 11. Both 90% CI fell below the lower boundary of 80-125%, indicating that co-administration of rifampicin significantly decreased the C_{max} and AUC(0-24) for E1.

E1S: The geometric mean of AUC(0-24) (90% CI) of Day 17 was 28% (25.1-32.1%) of it on Day 11. The geometric mean of C_{max} (90% CI) of Day 17 was 41% (36.3-46.3%) of it on Day 11. Both 90% CI fell below

the lower boundary of 80-125%, indicating that co-administration of rifampicin significantly decreased the C_{max} and AUC(0-24) for E1S.

Reviewer’s comment: *As a prodrug of E2, EV is rapidly hydrolyzed to E2 in the intestinal tract following the oral administration. E2 is then extensively metabolized to E1 (15%), E1S (65%), estradiol sulfate, and other compounds (Kuhnz et al., 1999). CYP 3A4 is the major isozyme responsible for the hydroxylation of E2 at C-2, C-4 and C-16 and for the 16 α -hydroxylation of E1. The impact of CYP 3A4 induction on E1 and E2 is likely due to the increased CYP 3A4-mediated metabolism and consequently increased the clearance of E1 and E2. E1S levels were also affected and mean AUC(0-24) was reduced by 72% following the rifampicin treatment. Although it is known that E1S is not directly metabolized by CYP 3A4, the decreased concentrations of E1S is likely caused by the lower E1 level.*

As shown in Table A-10-7, co-administration of 600 mg rifampicin daily with EV 2 mg/DNG 3 mg tablets led to significant decreases in steady state C_{max} and AUC of DNG, E2, E1, and E1S which could potentially affect the contraceptive efficiency of the E2/DNG combination. In the dose-finding study (Study B690), it was demonstrated that 2 mg EV is necessary for effective ovulation inhibition and sufficient cycle control. For this particular 4-phasic regimen in combination with EV, a DNG dose of 2-3 mg/day was found to be necessary to sufficiently inhibit ovulation and provide contraceptive reliability (Studies A00984, A14191, and AZ94). For example, an 83% decrease shown in DNG AUC when (b) (4)™ is co-administered with rifampicin would reduce the AUC to the level expected when a DNG dose of approximately 0.5 mg is given and an 44% decrease shown in E2 AUC when (b) (4)™ is co-administered with rifampicin would reduce the AUC to the level expected when a EV dose of approximately 1.1 mg is given.

In a multi-center, open labeled, uncontrolled study (Study AZ94) to investigate the efficacy and safety of a 4-phasic oral contraceptive SH T 658 I containing EV and DNG over 20 cycles in 1,600 healthy female volunteers, an unacceptable unadjusted Pearl Index of 5.3 was obtained when DNG dose was decreased using the following regimen

- Cycle Days 1-3: EV 3 mg
- Cycle Days 4-7: EV 2 mg + DNG 1 mg
- Cycle Days 8-23: EV 2 mg and DNG 2 mg
- Cycle Days 24-25: EV 1 mg
- Cycle Days 26-28: placebo

Table A-10-8: Pearl Index obtained in the full-analysis set (FAS) population (Study AZ94)

Patient set / subset	No. of cycles	No. of cycles with back-up contraception	No. of pregnancies after start of study medication	Pearl Index	No. of pregnancies due to subject failure	Pearl Index
				Unadjusted		Adjusted
Total	12,125	342	48	5.3	9	4.3
≤ 29 years of age	5,563	192	23	5.6	5	4.4
> 29 years	6,562	150	25	5.1	4	4.3

Study AZ94 clearly shows that when insufficient DNG dose is given efficacy can be significantly affected. Therefore, in order to ensure contraceptive reliability and sufficient cycle control, (b) (4)™ should not be co-administered with strong CYP 3A4 inducers such as rifampicin, phenytoin, St. John’s Wort, avasimibe, and carbamazepine (as listed in Table A-10-9 according to the Guidance for Industry: Drug Interaction [revised on March 11, 2010]). For women on chronic treatment with CYP 3A4 inducing active substances, another reliable, non-hormonal, method of contraception is recommended. This information should be reflected in the Drug Interactions section of the Highlights of the labeling.

Table A-10-9: Classification of inducers of CYP enzymes

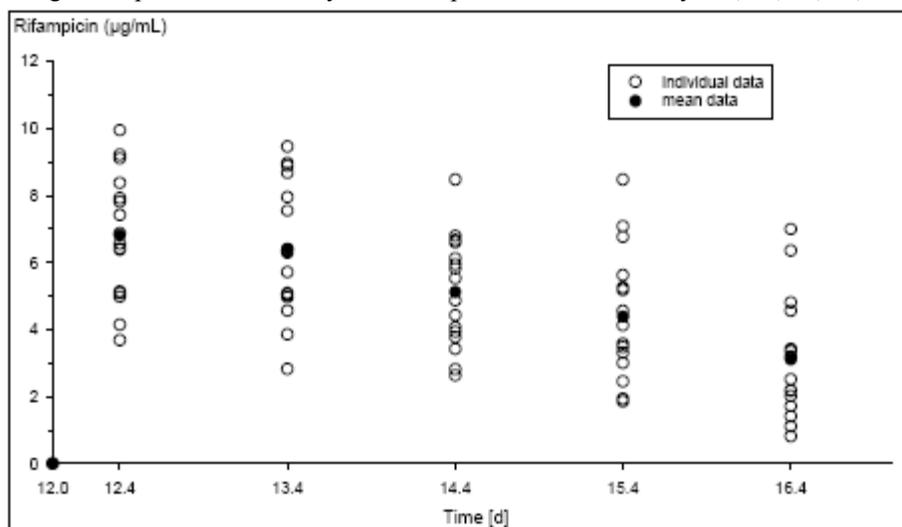
CYP Enzymes	Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
CYP1A2		Montelukast, phenytoin, smokers versus non-smokers ⁽²⁾	Moricizine, omeprazole, phenobarbital, tanshinone IIA, terbutaline
CYP2B6		Efavirenz, rifampin	Nevirapine
CYP2C8		Rifampin	
CYP2C9		Carbamazepine, rifampin	Aprepitant, bosentan, Phenobarbital, St. John's Wort ⁽³⁾
CYP2C19		Rifampin	Artemisinin
CYP3A	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's Wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea, pioglitazone, prednisone, rufinamide
CYP2D6	None known	None known	None known

From *Guidance for Industry: Drug Interaction* (March 11, 2010 draft)

PK of Rifampicin

Plasma concentrations of rifampicin were measured at pre-dose on Day 12, and at 8 hr after rifampicin intake on Days 12, 13, 14, 15, and 16. Figure A-10-5 illustrates the individual and mean plasma concentrations of rifampicin in the individual volunteers.

Figure A-10-5: Plasma Concentrations of Rifampicin at Pre-dose on Day 12 and at 8 hr After Daily Oral Administration of 600 mg Rifampicin to 16 Healthy Postmenopausal Women on Days 12, 13, 14, 15, and 16



12.0: Pre-dose on Day 12

12.4, 13.4, 14.4, 15.4, and 16.4: at 8 hr post-dose on Days 12, 13, 14, 15, and 16, respectively.

The mean plasma rifampicin concentration, initially zero at pre-dose, rose to a mean value of 6.81 µg/ml (CV 27.4%) at 8 hr post-dose on the first day of administration, slowly decreasing to 6.40 µg/ml (CV 31.2%, second day), 5.11 µg/ml (CV 32.0%, third day), 4.38 µg/ml (CV 43.3%, fourth day) and 3.11 µg/ml (CV 57.6%, fifth day).

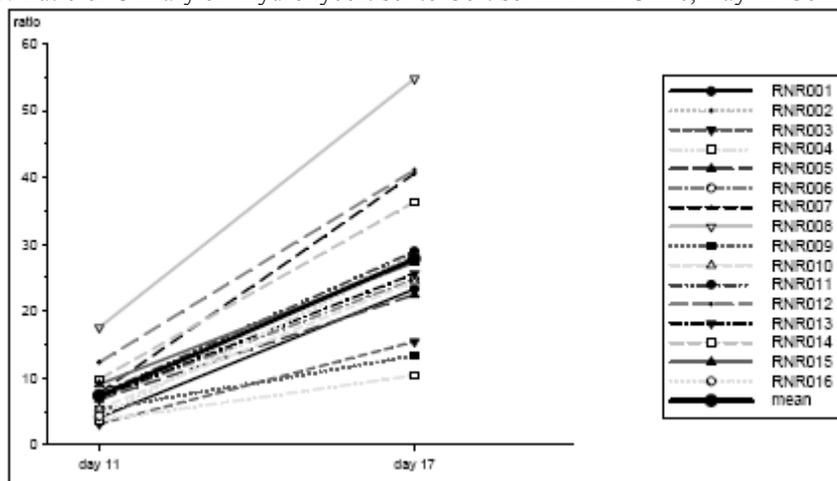
Although rifampicin concentration measurements were only performed once a day at 8 hr post-dose during the rifampicin treatment period, it still reveals the clear trend of rifampicin concentration decreasing in all individual subjects during the rifampicin treatment period. This might possibly be linked to the known ability of rifampicin to induce its own metabolism (Acocella, 1979).

Considering that the T_{max} was approximately 2 hr following a single oral dose of 600 mg rifampicin in healthy adults and the average half-life is approximately 2-3 hr with repeated administration of 600 mg rifampicin in healthy adults, the single point assessment at 8 hr approach in this study is acceptable since main objective of this assessment was to ensure the BA of rifampicin post-dose during the rifampicin treatment period. Also, it was reported that sampling schedule up to 8 hr was sufficient to compare the absorption process of rifampicin and ensure both the rate and extent rifampicin absorption, without affecting the precision in evaluating BE (Agrawal *et al.*, 2005).

Ratio of urinary 6 β -hydroxycortisol to cortisol

Figure A-10-6 illustrates the individual and mean values of the 24 hr-urinary 6 β -hydroxycortisol to cortisol ratio, before and after 5 days of treatment with 600 mg/day oral rifampicin (i.e., Day 12 compared to Day 16). The ratio increased in all 16 volunteers, with a geometric mean of 6.65 (3.13-17.6) on Days 11-12 and 25.7 (range 10.4-54.8) on Days 17-18. There was also an increase in the 24 hr urinary excretion of 6 β -hydroxycortisol, from 208 μ g (CV 26.8%) on Days 11-12, to 1065 μ g (CV 25.8%) on Days 17-18. The increase in the ratio of 6 β -hydroxycortisol to cortisol in all volunteers confirmed that the CYP 3A4 activity was induced in all cases.

Figure A-10-6: Ratio of Urinary 6 β -Hydroxycortisol to Cortisol in 24 hr-Urine, Day 11 Compared to Day 17



SAFETY RESULTS

A total of 36 AEs were reported in 15 volunteers. The most frequent AEs were headache and fatigue. There were no serious, severe, or significant AEs. There were no deaths.

CONCLUSION

Co-administration of rifampicin with 2 mg EV/3 mg DNG combination tablets led to a significant decrease in both C_{max} and AUC(0-24) of DNG and E2 at steady-state indicating a drug interaction between rifampicin and EV/DNG. Considering the potential of affecting the contraceptive efficiency of the EV/DNG combination due to the decreases in steady state C_{max} and AUC of DNG, E2, E1, and E1S, (b) (4)TM should not be co-administered with strong CYP 3A4 inducers such as rifampicin, phenytoin, St. John's Wort, avasimibe, and carbamazepine. This information should be reflected in the *Drug Interactions* section of the *Highlights* of the labeling.

A.1.11. Study A29972

Open-label, Randomized, Single dose, Three way Crossover, Two Parallel Group Study to Evaluate the Relative Bioavailability of the Estradiol Valerate and/or Dienogest Tablet Formulations Contained in SH T00658ID versus Suspensions, Containing the Same Drugs After Oral Administration in Healthy Postmenopausal Women

Protocol No: A29972
Phase: 1
Principal Investigator: Dr. B. Rohde
Clinical Study Center: Clinical Pharmacology, Schering AG, Berlin, Germany
Clinical Study Dates: June 1, 2006 - August 31, 2006
Analytical Study Facility: (b) (4) (E2 and E1), Schering Oy, Finland (DNG)
Analytical Study Dates: August 2006 - January 2007

OBJECTIVE

To evaluate the relative BA of:

- EV and DNG from SH T00658M (TBM formulation) and SH T00658GA (TBM formulation) with suspension SH P00658MA
- EV from SH T00658EA (TBM formulation) and SH T00658HA (TBM formulation) with suspension SH P00658EA

STUDY ENDPOINTS

Primary endpoints for E2 and DNG (in Group 1 only) were AUC(0-tlast) and C_{max} .

Secondary endpoints for E2, E1, and DNG (in Group 1 only) were:

- T_{max} and terminal half-life ($t_{1/2}$)
- Terminal disposition rate constant (i.e., the slope of the least square regression of the natural logarithm of the terminal drug concentration value on the time), λ_z
- AUC, AUC(0-tlast), and C_{max} of E1

STUDY DESIGN, TREATMENT, AND SUBJECTS

The study was a single-center, open-label, randomized, single-dose, three-way crossover-study with 2 parallel groups, 3 periods, 3 treatments, and 6 sequences. The treatments were:

Group 1

- Treatment A: 1 coated tablet of SH T00658GA, containing 2 mg EV/2 mg DNG
- Treatment B: 1 coated tablet of SH T00658M, containing 2 mg EV/3 mg DNG
- Treatment C: suspension for oral use SH P00658MA, containing 2 mg EV/3 mg DNG

Group 2

- Treatment D: 1 coated tablet of SH T00658EA, containing 3 mg EV
- Treatment E: 3 coated tablets of SH T00658HA, containing 1 mg EV
- Treatment F: suspension for oral use SH P00658EA, containing 3 mg EV

36 healthy postmenopausal women were randomly assigned to one of the following treatment sequences (see Tables A-11-1 and A-11-2). The washout phase between the treatments had to be at least 14 days.

Table A-11-1: Treatment Sequence for Group 1

Sequence	Treatment period 1	Treatment period 2	Treatment period 3
1	Treatment C	Treatment A	Treatment B
2	Treatment C	Treatment B	Treatment A
3	Treatment A	Treatment C	Treatment B
4	Treatment A	Treatment B	Treatment C
5	Treatment B	Treatment C	Treatment A
6	Treatment B	Treatment A	Treatment C

Table A-11-2: Treatment Sequence for Group 2

Sequence	Treatment period 1	Treatment period 2	Treatment period 3
1	Treatment F	Treatment D	Treatment E
2	Treatment F	Treatment E	Treatment D
3	Treatment D	Treatment F	Treatment E
4	Treatment D	Treatment E	Treatment F
5	Treatment E	Treatment F	Treatment D
6	Treatment E	Treatment D	Treatment F

The study drugs were administered on an empty stomach (following 10-hr fasting) in the morning between 7:00 and 9:00 hr. Drinking of water was allowed except for 1 hr before and after drug administration. The volunteers had to fast 4 hr after drug administration. The tablets were taken with 150 ml noncarbonated water at ambient temperature. The suspension for oral use was prepared for use according to the manufacturer's instructions and the total amount of water intake was 150 ml.

64 female volunteers were screened, and 36 volunteers were included at 1 center. Of these, 35 volunteers completed the study, and 1 volunteer discontinued participation in the study prematurely. In Group 1, 18 Caucasian female volunteers with an average age of 60.7 yr (range: 55-69 yr) were included. Their mean height and weight were 164 cm (range: 156-173 cm) and 67.4 kg (range: 49.5-85.6 kg), respectively. The mean BMI was 25.0 kg/m² (range: 20.3-29.7 kg/m²). In Group 2, 18 Caucasian female volunteers with an average age of 58.4 yr (range: 52-69 yr) were included. Their mean height and weight were 163 cm (range: 150-173 cm) and 70.8 kg (range: 59.3-89.2 kg), respectively.

Inclusion Criteria

Volunteers had to fulfill all of the following criteria before being included in the treatment period:

- Healthy female volunteer
- Age: 45-75 yr
- BMI: ≥ 20 and ≤ 30 kg/m²
- Postmenopausal status: serum levels of FSH ≥ 30 IU/l and of E2 ≤ 20 pg/ml.

To assure the good health of the volunteers, screening physical and gynecological examinations, ECG, and clinical laboratory testing including biochemistry, hematology, virology, and urinalysis were performed. Clinical laboratory testing was repeated at the end of the study. The volunteers were monitored for AEs and concomitant medication.

PHARMACOKINETIC EVALUATION

Blood sampling

Blood sampling for PK evaluation was done before and up to 48 hr after study drug administration at the

following time points:

- Group 1 (for DNG, E2, and E1): pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hr post-dose
- Group 2 (for E2 and E1): pre-dose and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hr post-dose

Concomitant Therapy

If a volunteer used concomitant medication, this was documented by type (brand name, if applicable), indication, regimen (total daily dose and route), and duration on the appropriate CRF.

Other Restrictions

- Smoking: not permitted
- Alcohol: not permitted from 48 hr before study drug administration until 48 hr post-administration per period
- Caffeine: not permitted from 12 hr before study drug administration until 24 hr after the post-administration per period
- Grapefruit not permitted from 7 days before the Period 1 up to the last blood sample in treatment period 3 (48 hr after the last study drug administration)

Bioanalytical method

(b) (4)

Acceptance criteria for method validation and assay performance of all analytes were in compliance with the *Bioanalytical Method Validation Guidance*.

Safety Assessments

To ensure the volunteers' safety after intake of either 2 mg EV/3 mg DNG combination tablet alone or 2 mg EV/3 mg DNG combination tablet plus rifampicin the following parameters were studied during the treatment period:

- Standard laboratory examination of blood and urine prior to dosing on Days 1 and 12, respectively, and on Day 18
- AE and concomitant medication

DATA ANALYSIS

Pharmacokinetic Analysis

Non-compartmental PK analysis was performed on the serum concentrations of E2, E1, and DNG. All serum concentration values below the LLOQ were set to zero. C_{max} and t_{max} were directly read from the concentration-time profiles. The AUC and AUC(0-tlast) were calculated according to the mixed linear-log trapezoidal rule using a commercially available software tool (EPS-Kinetica, version 2.6.1, Thermo Electron corporation, Waltham, MA, US) without recourse to model assumptions. Relevant deviations from planned sampling time and planned dose were taken into account. The terminal disposition rate constant (λ_z) was calculated by means of regression analysis of the perceivable linear part of the curve in a semi-logarithmic plot (λ_z : slope of the regression line). The corresponding terminal half-life ($t_{1/2}$) was calculated by:

$$t_{1/2} = \ln 2 / \lambda_z$$

The AUC was calculated by extrapolation according to:

$$AUC = AUC(0-t_{last}) + C_{t_{last}} / \lambda_z$$

with $C_{t_{last}}$ as the concentration at the last data point (t_{last}).

Statistic Methods

Descriptive statistics and analysis of variance were performed for the primary PK parameters. Estimation of BA including 90% CIs were performed.

PHARMACOKINETIC RESULTS

PK of DNG (Group 1)

Figure A-11-1 shows the linear and semi-logarithmic mean concentration time curves for DNG, after a single oral administration of two different tablet formulations (SH T00658GA, containing 2 mg EV and 2 mg DNG and SH T00658 M, containing 2 mg EV and 3 mg DNG, respectively) compared to a suspension SH P00658MA containing 2 mg EV and 3 mg DNG. Mean PK parameters of DNG are summarized in Table A-11-3.

Figure A-11-1: Linear and Semi-logarithmic Mean Concentrations (\pm SD) of DNG After Single Oral Administration of Two Different Tablet Formulations (SH T00658GA, containing 2 mg EV + 2 mg DNG and SH T00658 M, containing 2 mg EV + 3 mg DNG, respectively) Compared to a Suspension SH P00658MA Containing 2 mg EV + 3 mg DNG in Postmenopausal Women (N=17)

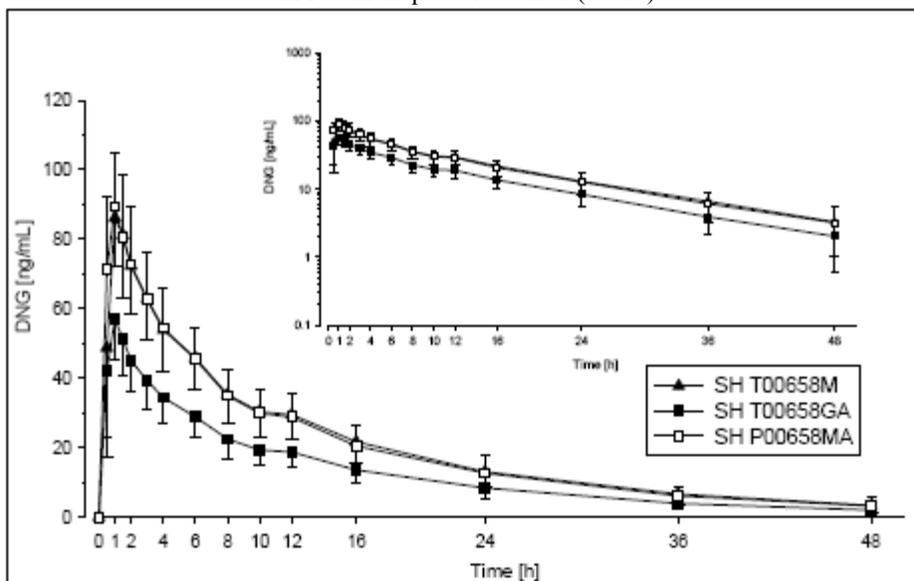


Table A-11-3: Arithmetic Mean (SD) PK Parameters of DNG Following Oral Administration of Two Different Tablet Formulations (SH T00658GA, containing 2 mg EV + 2 mg DNG and SH T00658 M, containing 2 mg EV + 3 mg DNG, respectively) Compared to a Suspension SH P00658MA containing 2 mg EV + 3 mg DNG in Postmenopausal Women (N=17)

Parameter	SH T00658GA	SH T00658M	SH P00658MA
C_{max} (ng/ml)	59.5 (10.2)	91.7 (15.3)	92.8 (17.4)
T_{max} (hr)	1 (0.5-1.5)	1 (0.5-1.5)	1 (0.5-1.5)
AUC(0-tlast) (ng·hr/ml)	613 (142)	964 (223)	956 (224)
AUC (ng·hr/ml)	648 (166)	1024 (268)	1014 (268)
$t_{1/2}$ (hr)	11.0 (2.02)	11.3 (2.48)	11.2 (2.66)

SH T00658GA: Coated tablet containing 2 mg EV/2 mg DNG

SH T00658M: Coated tablet containing 2 mg EV/3 mg DNG

SH P00658MA: Suspension for oral use containing 2 mg EV/3 mg DNG

AUC: Area under the serum concentration-time curve from time of administration (t=0) extrapolated to infinity

Median (range) for T_{max}

Reviewer's comment: Following single doses of the tablet SH T00658M (2 mg EV and 3 mg DNG) and a suspension SH P00658MA (2 mg EV and 3 mg DNG), mean concentration time profiles and calculated PK parameters of DNG were comparable.

As expected, due to the dose differences of DNG contained in the SH T00658GA tablet (containing 2 mg DNG), comparison of the AUC and C_{max} values of this formulation showed approximately 1/3 lower values compared to the formulations containing 3 mg DNG. This finding is in line with the conclusion that DNG demonstrates dose linear PK in the range of 1-8 mg (Study B306).

PK of E2 (Group 1)

Figure A-11-2 shows the linear and semi-logarithmic mean concentration time curves for E2, after a single oral administration of two different tablet formulations (SH T00658GA, containing 2 mg EV + 2 mg DNG and SH T00658 M, containing 2 mg EV + 3 mg DNG, respectively) compared to a suspension SH P00658MA containing 2 mg EV + 3 mg DNG. Mean PK parameters of E2 are summarized in Table A-11-4.

Figure A-11-2: Linear and Semi-logarithmic Mean Concentrations (\pm SD) of E2 After a Single Oral Administration of Two Different Tablet Formulations (SH T00658GA, containing 2 mg EV + 2 mg DNG and SH T00658 M, containing 2 mg EV + 3 mg DNG, respectively) Compared to a Suspension SH P00658MA containing 2 mg EV + 3 mg DNG in Postmenopausal Women (N=17)

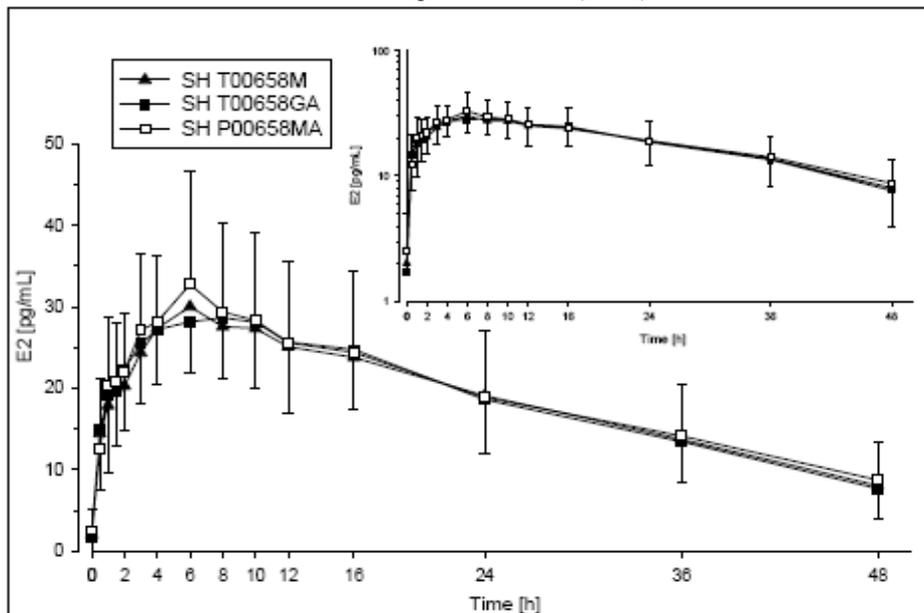


Table A-11-4: Arithmetic Mean (SD) PK Parameters of E2 After a Single Oral Administration of Two Different Tablet Formulations (SH T00658GA, containing 2 mg EV + 2 mg DNG and SH T00658 M, containing 2 mg EV + 3 mg DNG, respectively) Compared to a Suspension SH P00658MA containing 2 mg EV + 3 mg DNG in Postmenopausal Women (N=17)

Parameter	SH T00658GA	SH T00658M	SH P00658MA
C_{max} (pg/ml)	32.4 (7.98)	31.9 (8.7)	36.0 (14.2)
T_{max} (hr)	6 (1.0-12.0)	6 (0.5-16.0)	6 (2.0-12.0)
AUC(0-tlast) (pg·hr/ml)	891 (249)	892 (267)	921 (334)
AUC (pg·hr/ml)	991 (169)	944 (243)	1134 (224)
$t_{1/2}$ (hr)	15.4 (2.05)	13.8 (3.50)	15.1 (0.785)

SH T00658GA: Coated tablet containing 2 mg EV/2 mg DNG

SH T00658M: Coated tablet containing 2 mg EV/3 mg DNG

SH P00658MA: Suspension for oral use containing 2 mg EV/3 mg DNG

AUC: Area under the serum concentration-time curve from time of administration (t=0) extrapolated to infinity

Median (range) for T_{max}

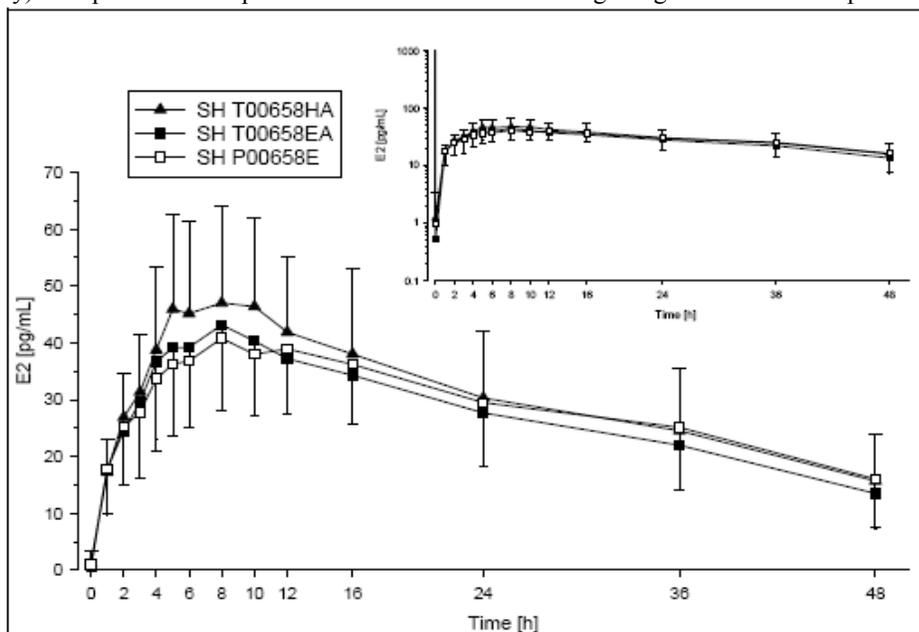
The AUC and $t_{1/2}$ of E2 could only be calculated for 6 volunteers with SH T00658 GA, for 2 volunteers with SH T00658M and for 3 volunteers with SH P00658MA. The remaining volunteers had insufficient data points collected during the terminal elimination phase of the concentration time profile and therefore reliable estimates for AUC and $t_{1/2}$ could not be calculated.

Reviewer's comment: *The AUC and C_{max} values of E2 after oral administration of the 3 different formulations were comparable although the suspension formulation, SH P00658MA, had slightly higher values. The AUC(0-tlast) values appear to be more reliable for comparison between the 3 different formulations due to the lack of data for AUC as mentioned above.*

PK of E2 (Group 2)

Figure A-11-3 shows the linear and semi-logarithmic mean concentration time curves of E2, after a single oral administration of two different tablet formulations (SH T00658EA, containing 3 mg EV and SH T00658 HA, 3 tablets each containing 1 mg EV, respectively) compared to a suspension SH P00658EA containing 3 mg EV. Mean PK parameters of E2 are summarized in Table A-11-5.

Figure A-11-3: Linear and Semi-logarithmic Mean Concentrations (\pm SD) of E2 After a Single Oral Administration of Two Different Tablet Formulations (SH T00658EA, containing 3 mg EV and SH T00658 HA, 3 tablets each containing 1 mg EV, respectively) Compared to a Suspension SH P00658EA containing 3 mg EV in Postmenopausal Women (N=18)



SH P00658E = SH P00658EA

Table A-11-5: Arithmetic Mean (SD) PK Parameters of E2 After a Single Oral Administration of Two Different Tablet Formulations (SH T00658EA, containing 3 mg EV, and SH T00658HA, 3 tablets each containing 1 mg EV, respectively) Compared to a Suspension SH P00658EA containing 3 mg EV in Postmenopausal Women (N=18)

Parameter	SH T00658EA ^a	SH T00658HA	SH P00658EA
C _{max} (pg/ml)	45.9 (11.8)	50.6 (17.4)	43.7 (11.8)
T _{max} (hr)	8 (4.0-16.0)	8 (4.0-16.0)	8 (1.0-36.0)
AUC(0-tlast) (pg·hr/ml)	1303 (284)	1396 (541)	1341 (425)
AUC (pg·hr/ml)	1174 (416)	1215 (448)	NA
t _{1/2} (hr)	13.0 (1.61)	13.6 (1.12)	NA

SH T00658EA: Coated tablet containing 3 mg EV

SH T00658HA: Coated tablet containing 1 mg EV (Treatment E: 3 x 1 mg EV)

SH P00658EA: Suspension for oral use containing 3 mg EV

AUC: Area under the serum concentration-time curve from time of administration (t=0) extrapolated to infinity

Median (range) for T_{max}

^a Per protocol, 1 volunteer excluded from statistics, due to the high E2 baseline value (N=17)

The AUC and t_{1/2} of E2 could only be calculated for 2 volunteers with SH T00658EA and with SH T00658HA, respectively. The remaining volunteers had insufficient data points collected during the terminal elimination phase of the concentration time profile and therefore reliable estimates for AUC and t_{1/2} could not be calculated.

Reviewer's comment: *It was noted that SH T00658HA (3 tablets each containing 1 mg EV) had higher E2 AUC, C_{max} and mean concentration values between 5 and 12 hr post-administration compared to the other tablet formulation, SH T00658EA (3 mg EV). The AUC(0-tlast) values appear to be more reliable for comparison between the 3 different formulations due to the lack of data for AUC as mentioned above.*

PK of E1 (Group 1)

Figure A-11-4 shows the linear and semi-logarithmic mean concentration time curves for E1, after single oral administration of two different tablet formulations (SH T00658GA, containing 2 mg EV and 2 mg DNG and SH T00658 M, containing 2 mg EV and 3 mg DNG, respectively) compared to a suspension SH P00658MA containing 2 mg EV and 3 mg DNG. Mean PK parameters of E1 are summarized in Table A-11-6.

Figure A-11-4: Linear and Semi-logarithmic Mean Concentrations (± SD) of E1 After a Single Oral Administration of Two Different Tablet Formulations (SH T00658GA, containing 2 mg EV + 2 mg DNG and SH T00658 M, containing 2 mg EV + 3 mg DNG, respectively) Compared to a Suspension SH P00658MA Containing 2 mg EV + 3 mg DNG in Postmenopausal Women (N=17)

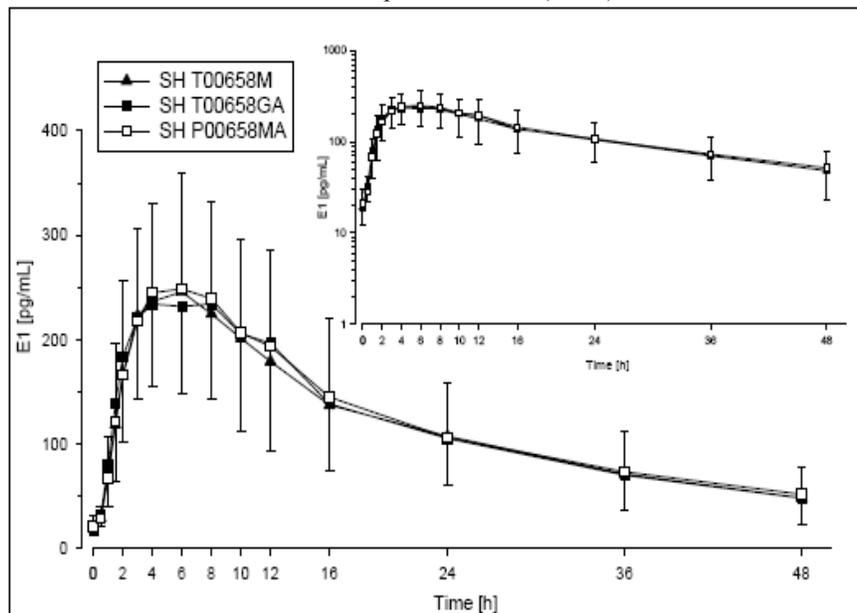


Table A-11-6: Arithmetic Mean (SD) PK Parameters of E1 After a Single Oral Administration of Two Different Tablet Formulations (SH T00658GA, containing 2 mg EV + 2 mg DNG and SH T00658 M, containing 2 mg EV + 3 mg DNG, respectively) Compared to a Suspension SH P00658MA containing 2 mg EV + 3 mg DNG in Postmenopausal Women (N=17)

Parameter	SH T00658GA	SH T00658M	SH P00658MA
C_{max} (pg/ml)	262 (97)	263 (88.5)	270 (108)
T_{max} (hr)	4 (2.0-12.0)	6 (3.0-8.0)	6 (3.0-8.0)
AUC(0-tlast) (pg·hr/ml)	5742 (2258)	5693 (2053)	5873 (2584)
AUC (pg·hr/ml)	6982 (3139)	6494 (2190)	7160 (3139)
$t_{1/2}$ (hr)	16.3 (1.47)	17.2 (1.55)	16.3 (1.07)

SH T00658GA: Coated tablet containing 2 mg EV/2 mg DNG

SH T00658M: Coated tablet containing 2 mg EV/3 mg DNG

SH P00658MA: Suspension for oral use containing 2 mg EV/3 mg DNG

AUC: Area under the serum concentration-time curve from time of administration (t=0) extrapolated to infinity

Median (range) for T_{max}

The AUC and $t_{1/2}$ of E1 could only be calculated for 6 volunteers with SH T00658 GA, for 4 volunteers with SH T00658M, and for 6 volunteers with SH P00658MA. The remaining volunteers had insufficient data points collected during the terminal elimination phase of the concentration time profile and therefore reliable estimates for AUC and $t_{1/2}$ could not be calculated.

Reviewer's comment: *The AUC and C_{max} values of E1 after oral administration of the 3 different formulations were comparable although the suspension formulation, SH P00658MA, appears to have higher values. The AUC(0-tlast) values appear to be more reliable for comparison between the 3 different formulations due to the lack of data for AUC as mentioned above.*

PK of E1 (Group 2)

Figure A-11-5 shows the linear and semi-logarithmic mean concentration time curves of E1, after a single oral administration of two different tablet formulations (SH T00658EA, containing 3 mg EV and SH T00658 HA, 3 tablets each containing 1 mg EV, respectively) compared to a suspension SH P00658EA containing 3 mg EV. Mean PK parameters of E1 are summarized in Table A-11-7.

Figure A-11-5: Linear and Semi-logarithmic Mean Concentrations (\pm SD) of E1 After Daily Oral Administration of Two Different Tablet Formulations (SH T00658EA, containing 3 mg EV and SH T00658 HA, 3 tablets each containing 1 mg EV, respectively) Compared to a Suspension SH P00658EA containing 3 mg EV in Postmenopausal Women (N=18)

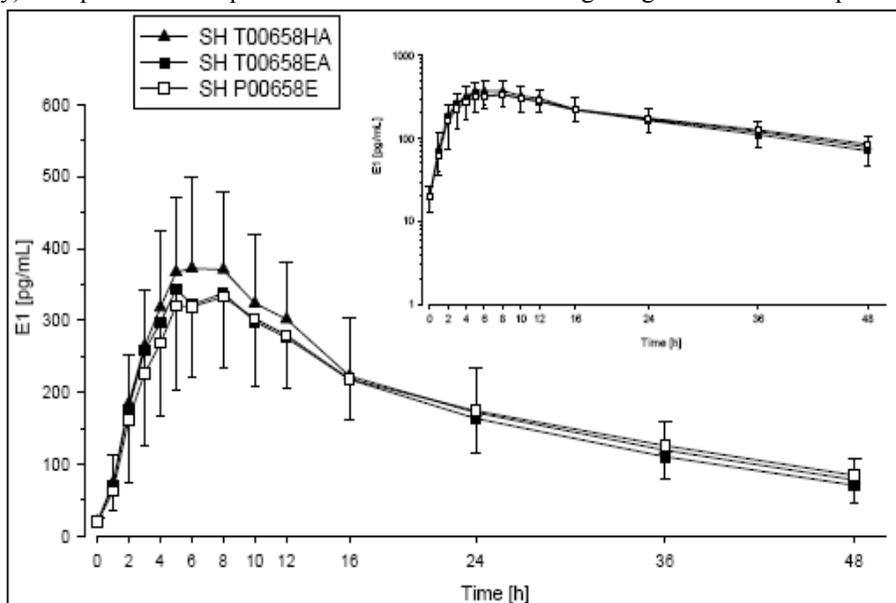


Table A-11-7: Arithmetic Mean (SD) PK Parameters of E1 After Daily Oral Administration of Two Different Tablet Formulations (SH T00658EA, containing 3 mg EV and SH T00658 HA, 3 tablets each containing 1 mg EV, respectively) Compared to a Suspension SH P00658EA containing 3 mg EV in Postmenopausal Women (N=18)

Parameter	SH T00658EA ^a	SH T00658HA	SH P00658EA
C _{max} (pg/ml)	361 (126)	386 (129)	346 (117)
T _{max} (hr)	8 (4.0-8.0)	6 (4.0-12.0)	8 (4.0-10.0)
AUC(0-tlast) (pg·hr/ml)	8094 (2011)	8594 (3049)	8322 (2590)
AUC (pg·hr/ml)	9376 (2101)	9138 (2283)	9410 (2060)
t _{1/2} (hr)	17.1 (1.52)	16.9 (2.06)	17.2 (1.46)

SH T00658EA: Coated tablet containing 3 mg EV

SH T00658HA: Coated tablet containing 1 mg EV (Treatment E: 3 x 1 mg EV)

SH P00658EA: Suspension for oral use containing 3 mg EV

AUC: Area under the serum concentration-time curve from time of administration (t=0) extrapolated to infinity

Median (range) for T_{max}

^a Per protocol, 1 volunteer excluded from statistics, due to the high E2 baseline value (N=17)

The AUC and t_{1/2} of E1 could be calculated for 9 volunteers with SH T00658 EA, for 7 volunteers with SH T00658HA and for 7 volunteers with SH P00658EA. The remaining volunteers had insufficient data points collected during the terminal elimination phase of the concentration time profile and therefore reliable estimates for AUC and t_{1/2} could not be calculated.

Reviewer's comment: *It was noted that SH T00658HA (3 tablets each containing 1 mg EV) had higher E1 AUC, C_{max} and mean concentration values between 5 and 12 hr post-administration compared to the other tablet formulation, SH T00658EA (3 mg EV). The AUC(0-tlast) values appear to be more reliable for comparison between the 3 different formulations due to the lack of data for AUC as mentioned above.*

The CIs for assessment in BA are summarized in Table A-11-8 below.

Table A-11-8: Confidence Intervals for Assessment of Bioavailability of DNG, E2, and E1

Pharmacokinetic Parameter	Test	Mean ratio	Lower confidence limit	Upper confidence limit
DNG in group 1				
AUC	SH P00658 MA vs. SH T00658 GA	63.9003	61.6785	66.2022
AUC	SH P00658 MA vs. SH T00658 M	100.84	97.3339	104.47
C _{max}	SH P00658 MA vs. SH T00658 GA	64.4101	60.4858	68.5892
C _{max}	SH P00658 MA vs. SH T00658 M	99.3857	93.3303	105.83
E2 in group 1				
AUC (0-tlast)	SH P00658 MA vs. SH T00658 GA	97.8532	91.5732	104.56
AUC (0-tlast)	SH P00658 MA vs. SH T00658 M	98.5847	92.2577	105.35
C _{max}	SH P00658 MA vs. SH T00658 GA	93.3807	85.8992	101.51
C _{max}	SH P00658 MA vs. SH T00658 M	91.9917	84.6215	100.00
E2 in group 2				
AUC (0-tlast)	SH P00658 EA vs. SH T00658 EA	96.7272	88.0999	106.20
AUC (0-tlast)	SH P00658 EA vs. SH T00658 HA	103.62	94.3746	113.76
C _{max}	SH P00658 EA vs. SH T00658 EA	104.46	94.5491	115.40
C _{max}	SH P00658 EA vs. SH T00658 HA	114.46	103.60	126.45

SAFETY RESULTS

No deaths and no SAEs were reported during this study. In total, 35 AEs were documented in 20 (56.9%) out of 36 volunteers. The most frequently occurring AE was headache (16 events in 13 volunteers, 36.1%).

CONCLUSION

Following single doses of the tablet SH T00658M (2 mg EV/3 mg DNG) and a suspension SH P00658MA (2 mg EV + 3 mg DNG), mean concentration time profiles and calculated PK parameters of DNG were comparable. SH T00658GA tablet (containing 2 mg DNG), AUC, and C_{max} values showed approximately 1/3 lower values compared to the formulations containing 3 mg DNG.

For E2 and E1 after oral administration of the suspension formulation, SH P00658MA, appears to have slightly higher AUC and C_{max} values compared to tablet formulations, SH T00658GA (2 mg EV + 2 mg DNG) and SH T00658M (2 mg EV + 3 mg DNG). It was noted that SH T00658HA (3 tablets each containing 1 mg EV) had higher AUC, C_{max} , and mean concentration values of E2 and E1 between 5 and 12 hr post-administration compared to the other tablet formulation, SH T00658EA (3 mg EV).

A.1.12. Study B482

Metabolism of Dienogest (ZK 37659) in Human Liver Microsomes *in vitro*

Protocol No:	B482
Phase:	Pre-clinical
Principal Investigator:	Dr. T. Zimmermann
Study Center:	Metabolism and Bioanalysis; Pharmacokinetics, Bayer Schering Pharma AG, Berlin, Germany
Study Dates:	November 1998 – April 1999

DESCRIPTION OF STUDY

A commercially available pool of human liver microsomes was applied for this *in vitro* study (IIAM, PA, USA). The metabolism of ³H-labelled dienogest was investigated time and concentration-dependent in this microsomal preparation. An incubation time of 60 min was used to estimate V_{max} and $K_{M(app)}$ values.

The influence of isoenzyme specific inhibitors was studied concerning the metabolism of dienogest. Each inhibitor was used at three concentrations. After an incubation time of 120 min the reaction was terminated by protein precipitation and extraction of the samples. The analyses were carried out by HPLC and on-line radioactivity detection. The formation of metabolites was quantified and correlated with the isoenzyme specific inhibitors. In addition, the metabolism of dienogest was studied with preparations of the suggested isoenzymes, heterologously expressed. The concentration-dependent effect of dienogest on the biotransformation of model substrates was investigated in human liver microsomes. Isoenzyme specific substrates were used at a constant concentration whereas the concentration of dienogest was varied between 2 μ M and 100 μ M.

SUMMARY OF RESULTS

Dienogest was metabolized in human liver microsomes by NADPH-dependent reactions. One main and up to four smaller metabolite zones were detected by HPLC radiochromatography analysis. The influence of various chemicals, which are widely used as inhibitory probes for selected individual cytochrome P450 enzymes, was studied concerning the biodegradation of dienogest in human liver microsomes (HLM). The applications of the inhibitors troleandomycin (TAO) and diethyldithiocarbamate (DDC) resulted in a strong reduction of the biotransformation. In single enzyme preparations (CYP2A6, CYP2C19, CYP2E1, CYP3A4, heterologously expressed) CYP3A4 was verified as important for the biodegradation of dienogest. In contrast, CYP2A6, CYP2C19 and CYP2E1 did not produce detectable amounts of metabolites. Dienogest did neither inhibit dextromethorphan O-demethylation (mediated by CYP2D6), chlorzoxazone 6-hydroxylation (mediated by CYP2E1) nor testosterone 6 β -hydroxylation (mediated by CYP3A4) in HLM. Using high concentration of dienogest (100 μ M) the metabolism of tolbutamide, catalyzed by CYP2C9, as well as the metabolism of S-mephenytoin, catalyzed by CYP2C19, was reduced by about one third. The dealkylation of 7-methoxy-resorufin (catalyzed by CYP1A2) was not influenced by dienogest.

CONCLUSIONS

- The metabolism of dienogest in human liver microsomes was described by Michaelis-Menten kinetics with $K_{M(\text{app})} = 283 \mu\text{M}$ and $V_{\text{max}} = 143 \text{ nmol/mg/h}$.
- CYP3A4 was identified as predominant isoenzyme catalyzing the metabolism of dienogest.
- CYP1A2, CYP2C9, CYP2A6, CYP2C19 and CYP2E1 are not involved in the main biodegradation pathways of dienogest in vitro.
- Dienogest (2 μM to 100 μM) does not inhibit the metabolism of model substrates for CYP1A2, CYP2D6, CYP2E1, CYP3A4 in vitro.
- The metabolism of model substrates for CYP2C9 and CYP2C19 were reduced by about one third in human liver microsomes, using an unphysiologically high concentration of 100 μM dienogest.
- The results indicate that at clinically relevant concentrations dienogest does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.

Reviewer's comment: *This study was conducted to identify the metabolic pathways of DNG and drug interaction potentials in vitro and was not reviewed in detail. Although DNG did not show CYP 3A4 inhibition in vitro, the Sponsor conducted clinical DDI studies based on the fact that CYP 3A4 was identified as the major metabolic pathway. Although with 100 μM DNG the metabolism of tolbutamide (CYP 2C9) and S-mephenytoin (CYP 2C19) was reduced to values of 69% and 63%, respectively, of the reference samples, DNG at lower concentrations (i.e., < 20 μM) did not show any inhibition. According to the Sponsor's experience with Kimodien (2 mg EV/2 mg DNG, marketed in the EU), C_{max} following a daily dose at steady-state was determined to be 0.21 μM . Therefore, this would not be a concern at lower concentrations that would be closer to the clinical dose.*

A.1.13. Investigation of Dosing regimen for EV/DNG

Summary of EV/DNG Dosing Regimen Investigation

Study No: Studies A00984, B690, A24194, AZ94, A14191, and A25364
Phase: Phases 2 and 3

SUMMARY

As DNG showed no anti-estrogenic activity (Oettel *et al.*, 1995), Sponsor selected DNG as the progestin component of this product hoping to reduce the bleeding irregularities (Hoffmann *et al.*, 1998). As mono-phasic EV/progestin or E2/progestin regimens provided sufficient ovulation suppression, but did not provide sufficient bleeding control, the Sponsor took the approach to modify the dosing regimen. In the clinical development of this product, several different dosing regimens and strengths were explored.

First approach regimen (used in Studies A00984, B690, A24194, and AZ94):

This regimen, the first approach extensively tested in the clinical development program, failed in the evaluation of the PI due to an unacceptable number of pregnancies. In a multi-center, open labeled, uncontrolled study (Study AZ94) to investigate the efficacy and safety of a 4-phasic oral contraceptive SH T 658 I containing EV and DNG over 20 cycles in 1,600 healthy female volunteers, an unacceptable unadjusted PI of 5.3 was obtained when DNG dose was decreased using the following regimen:

- Cycle Days 1-3: EV 3 mg
- Cycle Days 4-7: EV 2 mg + DNG 1 mg
- Cycle Days 8-23: EV 2 mg and DNG 2 mg
- Cycle Days 24-25: EV 1 mg
- Cycle Days 26-28: placebo

Table A-13-1: Pearl Index obtained in the full-analysis set (FAS) population (Study AZ94)

Patient set / subset	No. of cycles	No. of cycles with back-up contraception	No. of pregnancies after start of study medication	Pearl Index	No. of pregnancies due to subject failure	Pearl Index
				Unadjusted		Adjusted
Total	12,125	342	48	5.3	9	4.3
≤ 29 years of age	5,563	192	23	5.6	5	4.4
> 29 years	6,562	150	25	5.1	4	4.3

Study AZ94 clearly shows that when insufficient DNG dose is given efficacy can be significantly affected. As a consequence, the regimen was modified by replacing 1 tablet containing 3 mg EV and 1 placebo tablet by 2 combination tablets, resulting in the ‘modified regimen’.

Modified regimen (used in Study A14191)

In this regimen, 1 tablet containing 3 mg EV was replaced by 1 tablet containing 2 mg EV/1 mg DNG on Day 3 and 1 placebo tablet was replaced by 1 tablet containing 2 mg EV/2 mg DNG in order to extend the combination phase. This regimen did show acceptable tolerability and safety, but the percentage of women who ovulated per cycle was not acceptable by the Sponsor. As a consequence, the regimen was modified a second time by increasing the DNG dose, which led to 2 dose-increased regimens with different DNG dosages (‘EV/DNG’ and ‘DNG-increased regimen’).

EV/DNG and DNG-increased regimen (study A25364)

Both of these dose-increased regimens (‘EV/DNG’ and ‘DNG-increased regimen’) provided effective ovulation inhibition. In the ‘DNG-increased regimen’, the DNG dosage is increased by 2 mg DNG, to 3 mg on Days 3 to 7, and thereafter to 4 mg on Days 8 to 24 of the cycle. This regimen was tested in comparison to the ‘EV/DNG

regimen'. Due to the effective ovulation inhibition from the 'EV/DNG regimen' with lower dosages of DNG, this regimen was pursued for further clinical development.

The study designs and dosing regimens are summarized in Table A-13-2 below.

Table A-13-2: Overview of Clinical Phase 2/3 studies investigating different dosing regimens of EV/DNG

Study (protocol no.)	Main study objective	Study design	Treatment regimen	Main inclusion criteria	Duration of treatment (cycles)	Number of treated women
Phase						
A00984 (97088) phase 2 (phase 3 according to the study protocol)	Ovulation inhibition	Single-center, open, uncontrolled, 1-arm	'First approach regimen' days 1 to 3: 3 mg EV days 4 to 7: 2 mg EV + 1 mg DNG days 8 to 23: 2 mg EV + 2 mg DNG days 24 to 25: 1 mg EV days 26 to 28: placebo	Healthy women between 19 and 35 years of age (max. 30 if smokers; limit: 10 cigarettes/day), regular ovulatory cycles	3	22
B690 (97179) phase 2	Cycle control	Multicenter, double-blind, randomized, controlled	'First approach regimen' with 2 different EV doses: Treatment A days 1 to 3: 3 mg EV days 4 to 7: 2 mg EV + 1 mg DNG days 8 to 23: 2 mg EV + 2 mg DNG days 24 to 25: 1 mg EV days 26 to 28: placebo Treatment B days 1 to 3: 2 mg EV days 4 to 7: 1 mg EV + 1 mg DNG days 8 to 23: 1 mg EV + 2 mg DNG days 24 to 25: 0.5 mg EV days 26 to 28: placebo	Healthy women between 18 and 40 years of age without contraindications for use of combined estrogen/progestin OCs	6	221 (treatment A: 111 women; treatment B: 110 women)
Study (protocol no.)	Main study objective	Study design	Treatment regimen	Main inclusion criteria	Duration of treatment (cycles)	Number of treated women
Phase						
A24194 (JPH01695) phase 2/3	Contra-ceptive efficacy and cycle control	Multicenter, open, randomized, controlled	'First approach regimen' with 2 different progestins (DNG and desogestrel [DSG]) Treatment A days 1 to 3: 3 mg EV days 4 to 7: 2 mg EV + 1 mg DNG days 8 to 23: 2 mg EV + 2 mg DNG days 24 to 25: 1 mg EV days 26 to 28: placebo Treatment B days 1 to 3: 3 mg EV days 4 to 7: 2 mg EV + 0.1 mg DSG days 8 to 23: 2 mg EV + 0.15 mg DSG days 24 to 25: 1 mg EV days 26 to 28: placebo	Healthy women 18 to 40 years of age with normal ovulatory cycles fulfilling the criteria for OC use	6	199 (treatment A: 100 women; treatment B: 99 women)
AZ94 (98102) phase 3	Pearl Index	Multicenter, open, uncontrolled	'First approach regimen' days 1 to 3: 3 mg EV days 4 to 7: 2 mg EV + 1 mg DNG days 8 to 23: 2 mg EV + 2 mg DNG days 24 to 25: 1 mg EV days 26 to 28: placebo	Healthy women between 18 (Austria: 19) and 50 years (inclusive) of age, smokers up to the age of 29 (inclusive), requiring contraception	planned: 20; actual maximum duration: 14 cycles	1779
Study (protocol no.)	Main study objective	Study design	Treatment regimen	Main inclusion criteria	Duration of treatment (cycles)	Number of treated women
Phase						
A14191 (305444) phase 2	Ovulation inhibition	Multicenter, open-label	'First approach regimen' days 1 to 3: 3 mg EV days 4 to 7: 2 mg EV + 1 mg DNG days 8 to 23: 2 mg EV + 2 mg DNG days 24 to 25: 1 mg EV days 26 to 28: placebo 'Modified regimen' days 1 to 2: 3 mg EV days 3 to 7: 2 mg EV + 1 mg DNG days 8 to 24: 2 mg EV + 2 mg DNG days 25 to 26: 1 mg EV days 27 to 28: placebo	Healthy women 18 to 35 years of age inclusive requesting contraception, smokers up to 30 years, with follicular diameter ≥ 15 mm at visit 6 or an observed ovulation	2 cycles; third treatment cycle only for women with a non-persisting follicle-like structure (FLS) > 13 mm in cycle 2	192 (96 women each group)
A25364 (307300) phase 2	Ovulation inhibition	Multicenter, open-label, randomized, comparative study	'EV/DNG tablets' [1] 'DNG-increased regimen' days 1 to 2: 3 mg EV days 3 to 7: 2 mg EV + 3 mg DNG days 8 to 24: 2 mg EV + 4 mg DNG days 25 to 26: 1 mg EV days 27 to 28: placebo	Healthy women requesting contraception, 18 to 35 years of age inclusive, smokers up to 30 years (inclusive), with follicle diameter ≥ 15 mm at visit 6 or an observed ovulation	3	203 (EV/DNG: 100 women; 'DNG-increased regimen': 103 women)

[1] In study A25364, the dose of 2 mg EV and 3 mg DNG (i.e. third phase of the regimen) was administered by 2 tablets: 1 film-coated tablet containing 2 mg EV and 1 mg DNG and 1 tablet containing 2 mg DNG

Reviewer's Comment:

Sponsor's effort in early development of dosing regimen is described in Hoffmann et al., 1998. The proposed 4-phasic sequential regimen is aimed at ensuring sufficient estrogen concentrations in the first half of the cycle, the period during which endometrial proliferation is promoted under the influence of estrogens, as estrogen levels are low at the beginning of the follicular phase. The start out of a 3 mg EV only treatment for 2 days is in line with this goal.

In Study B690, it was demonstrated that 2 mg EV are necessary for effective ovulation inhibition and sufficient cycle control. In Studies, AZ94, A00984, and A14191, it was found that a DNG dose of 2-3 mg/day was found to be necessary to sufficiently inhibit ovulation and provide contraceptive reliability. In Study A25364, the TBM dosing regimen was found to provide effective ovulation inhibition as the lowest effective dose of DNG and was selected for further clinical development.

Due to the fact that the dose was decided based on the clinical efficacy end point, ovulation inhibition, these studies exploring different dosing regimens and strengths were not reviewed in detail by this reviewer. However, per clinical reviewer, Dr. Gerald Willett, the outcomes of the Phase 3 clinical studies with the proposed 4-phasic EV/DNG dosing regimen supports the safety and efficacy for the contraception indication. Therefore, the proposed dosing regimen and strength is found to be acceptable.

A.1.14. Study A07769

Open-label, Randomized, Two-way Crossover Study to Assess the Effect of Dienogest on Estradiol Valerate Pharmacokinetics After Single Oral Administration of Two Different Microcrystalline Suspensions Containing 4 mg Estradiol Valerate or 4 mg Estradiol Valerate + 4 mg Dienogest in 24 Healthy Postmenopausal Volunteers

Protocol No: A07769
Phase: 1
Principal Investigator: Dr. B. Schütt
Clinical Study Center: Clinical Pharmacology, Schering AG, Berlin, Germany
Clinical Study Dates: June 2002 - October 2002
Analytical Study Facility: (b) (4) Schering Oy, Finland (DNG)
Analytical Study Dates: August 2006 - January 2007

STUDY SYNOPSIS

Name of finished product:	--		
Name of active ingredient:	estradiol valerate (E2val), dienogest (DNG)		
Title of study:	Open-label, randomized, two-way crossover study to assess the effect of dienogest on estradiol valerate pharmacokinetics after single oral administration of two different microcrystalline suspensions containing 4 mg estradiol valerate or 4 mg estradiol valerate + 4 mg dienogest in 24 healthy postmenopausal volunteers		
Investigator(s):	Dr. B. Schütt (Study Manager), Dr. R. Maibauer, Dr. S. Penz		
Study center(s):	One (Clinical Pharmacology Schering, 13342 Berlin)		
Publication (reference):	N/A		
Study period (years)	date of first enrollment:	Jun 2002	Clinical phase: I
	date of last completion:	Oct 2002	
Objectives:	To compare the pharmacokinetics of estradiol after administration of only E2val and E2val + DNG		
Methodology:	Collection of blood samples from 48 h before until up to 72 hours after application; Blood sampling times: -48 h, -24 h, -12 h, -0.5 h, 20 min, 40 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 16 h, 24 h, 36 h, 48 h, 72 h Determination of serum levels of estradiol, estrone, estrone sulfate using validated gas chromatography/mass spectrometry methods and of DNG using a validated radioimmunoassay		
Total number of subjects (planned and analyzed):	Planned: 24, Analyzed: 24		
Diagnosis and main criteria for inclusion:	Healthy postmenopausal woman aged 50-75 years, follicle stimulating hormone ≥ 40 IU/l, estradiol ≤ 10 pg/ml		
Test product:	Microcrystalline suspension containing estradiol and DNG (SH P00661B)		
dose:	4 mg E2val and 4 mg DNG		
mode of administration:	Oral		
batch number:	040502		
Duration of treatment:	single administration		
Reference therapy:	Microcrystalline suspension containing E2val (SH P00661A)		
dose:	4 mg E2val		
mode of administration:	Oral		
batch number:	050602		
Duration of treatment:	single administration		
Criteria for evaluation:			
Efficacy:	N/A		
Safety:	adverse events, laboratory parameters (screening and follow-up)		
Pharmacokinetics:	Primary variable: area under the drug concentration versus time curve from administration to the last measurement time point at which the concentration was above the lower limit of quantification (AUC(0-tlast)) of estradiol Secondary variables: variables for estradiol, estrone, estrone sulfate and DNG		
Pharmacodynamics:	N/A		
Statistical methods:	descriptive statistics, analysis of variance for the primary variable, 90%-confidence interval of the difference of the logarithms of AUC (0-tlast) between treatment test and treatment reference		

Summary/conclusions:**Efficacy results:**

N/A

Safety results:

In total, 45 adverse events were observed in 19 out of 24 volunteers (79.2%): 21 AEs in 16 volunteers with SH P00661A (4 mg E2val, reference) and 24 AEs in 14 volunteers with SH P00661B (4 mg E2val + 4mg DNG, test).

There were no deaths and no serious adverse events.

All AEs had a mild or moderate intensity. None of the volunteers experienced symptoms with a severe intensity.

The HARTS codes of the adverse events headache (N=17: 6 times with SH P00661A and 11 times with SH P00661B), injection site hemorrhage (N=7: 3 times with SH P00661A and 4 times with SH P00661B) and injection site pain (N=3: 2 times with SH P00661A and once with SH P00661B) were reported more than twice. Of these, only the symptom headache was assessed as being related (possibly, probably or definitely) to the treatment administered.

The laboratory parameters evaluated before and after the treatment period included serum chemistry (measuring hepatic and renal functions; electrolytes; proteins, ferritin), hematology, hemostasis and urinalysis. Clinically relevant laboratory changes / abnormalities were found in 6 volunteers. None of these findings were of a serious or severe nature. Follow-up values showed improvement, either approaching or reaching the reference range by the end of the follow-up phase.

Pharmacokinetic/pharmacodynamic results:

Pharmacodynamics: N/A

The pharmacokinetic parameters of estradiol and estrone were determined after single oral administration of two different microcrystalline suspensions containing 4 mg E2val or 4 mg E2val + 4 mg DNG in healthy postmenopausal women. For DNG the pharmacokinetic parameters were determined after single oral administration of a microcrystalline suspension containing 4 mg E2val + 4 mg DNG.

Pharmacokinetic/pharmacodynamic results (cont'd):

The results are summarized in the following table. Values are given as geometric means followed by the geometric coefficients of variation (CV) in parentheses. An exception is made for t_{max} , where the median and the range in parentheses are provided.

Mean pharmacokinetic parameters of estradiol, estrone and DNG after single oral administration of two different microcrystalline suspensions containing 4 mg E2val (reference) or 4 mg E2val + 4 mg DNG (test) in healthy postmenopausal women. (n = 24 per group).

Analyte	Treatment	C_{max} [pg/mL]	t_{max} [h]	AUC(0- t_{last}) [pgxh/mL]	AUC [pgxh/mL]	$t_{1/2}$ [h]
Estradiol	test	56.6 (32.7%)	6 (1-24)	1644 (53.5%)	--	--
	reference	60.2 (49.4%)	7 (0.67-16)	1537 (67.4%)	--	--
Estrone	test	450 (33.8%)	6 (3-12)	10192 (52.1%)	--	--
	reference	404 (47.7%)	6 (3-12)	9149 (60.5%)	--	--

Analyte	Treatment	C_{max} [ng/mL]	t_{max} [h]	AUC(0- t_{last}) [ngxh/mL]	AUC [ngxh/mL]	$t_{1/2}$ [h]
DNG	test	94.6 (16.5%)	1 (0.67-2)	1090 (20.1%)	1109 (21.0%)	10.9 (25.5%)

C_{max} = maximum concentration

t_{max} = time to reach C_{max}

AUC(0- t_{last}) = area under the concentration-time curve up to the last data point

$t_{1/2}$ = terminal half-life

AUC = area under the concentration-time curve up to infinity

Comparable pharmacokinetic parameters for both estradiol and estrone were obtained with the two treatments. The mean ratio of the area under the estradiol (E2) concentration time curve from administration to the last concentration measurement (AUC(0- t_{last})) for the test (4 mg E2val + 4 mg DNG) versus the reference (4 mg E2val) treatment was 106.99% with 90% confidence interval of 95.70% to 119.62%.

For estrone sulfate, the AUC(0-72h) was determined in pooled serum samples. The mean AUC(0-72h) of estrone sulfate was slightly higher in the test treatment (309548 pg/mLxh) compared to the reference treatment (270288 pg/mLxh).

Conclusions:

Single dose administrations of a microcrystalline suspension containing 4 mg E2val and 4 mg DNG (SH P00661B, test) and a microcrystalline suspension containing 4 mg E2val (SH P00661A, reference) were well tolerated by the postmenopausal female volunteers examined in this study.

Equivalence between the test and the reference treatment was concluded (90% CI = (95.70%, 119.62%)). Thus, co-administration of DNG was demonstrated to have no clinically relevant impact on the pharmacokinetics of estradiol valerate.

Reviewer's comment: *Combined administration of EV 4 mg together with DNG 4 mg has no effect on EV 4 mg PK (Study A07769). The Division has agreed that no additional DDI studies are required to investigate the potential drug interactions between DNG and EV. Reference is made to the minutes of the pre-IND meeting held on March 17, 2004.*

A.1.15. Study AR34

Bioequivalence of Dienogest (DNG) as a Single Substance vs. Dienogest in Combination with Estradiol Valerate (EV) After Single Administration in Healthy, Postmenopausal Women

Protocol No: AR34
Phase: 1
Principal Investigator: Dr. R. Maibauer
Clinical Study Center: Clinical Pharmacology, Schering AG, Berlin, Germany
Clinical Study Dates: June 1997 – July 1997
Analytical Study Facility: (b) (4)

STUDY SYNOPSIS

Name of finished product:	--
Name of active ingredients:	dienogest (DNG), estradiol valerate (EV)
Title of study:	Bioequivalence of DNG as a single substance vs. DNG in combination with EV after single administration in healthy, postmenopausal women
Investigator(s):	Dr. R. Maibauer, B. Schütt
Study center(s):	1 center in Germany
Publication (reference):	none
Studied period (years):	date of first enrollment: Jun. 97 date of last completion: Jul. 97
Clinical phase:	I
Objectives:	Bioequivalence of DNG given as a single substance in comparison to DNG given as a fixed combination with EV
Methodology:	open-label, randomized (order of treatments), intraindividual comparison, double crossover with 2 single administrations at an interval of 1 week
Total number of subjects (planned and analyzed):	planned: 16, analyzed: 16
Diagnosis and main criteria for inclusion:	Healthy postmenopausal women, age 45 - 75 years, FSH > 50 U/l
Test product:	DNG
dose:	2 mg per tablet
mode of administration:	oral
batch number:	660497
Duration of treatment:	Single administration
Reference therapy:	DNG + EV
dose:	2 mg DNG + 2 mg EV per coated tablet
mode of administration:	oral
batch number:	61001
Criteria for evaluation:	
Efficacy:	not applicable
Safety:	Documentation of adverse events, standard laboratory parameters (only prestudy and poststudy examinations)
Pharmacokinetics (if appropriate):	Primary variables: AUC, C _{max} of DNG Secondary variables: t _{max} , t _{1/2} , AUC (0-t _{last}) of DNG
Pharmacodynamics (if appropriate):	not applicable
Statistical methods:	Descriptive statistics, variance analysis

Efficacy Results: not applicable

Safety Results:

In total, 27 adverse events (AEs) were reported for 12 out of 16 volunteers. Of these, 12 events were assessed as being related to the study drug and 15 events as not related to the study drug. Headache was the most common AE in the related category. Of these, volunteer 10 experienced one severe headache in period 1 (DNG given as single substance) which was assessed as possibly associated with the test product. There were no serious or significant adverse events reported.

Regarding laboratory parameters, the observed deviations from the normal range in the poststudy examination and from the prestudy values for each volunteer were considered by the clinical trial director to be of no clinical relevance.

Pharmacodynamic Results: not applicable

Pharmacokinetic Results:

The pharmacokinetic results for DNG are summarized below:

Parameter	Unit	Test	Reference
C_{max} Geo-Mean	[ng/ml]	45.16	42.23
AUC(0-t_{last}) Geo-Mean	[h*ng/ml]	481.83	458.07
AUC Geo-Mean	[h*ng/ml]	522.80	503.92
t_{max} Arith.-Mean	[h]	1.39	1.38
t_{1/2} Arith.- Mean	[h]	9.88	10.40

The 90% confidence intervals calculated for the two target parameters AUC (area under the curve) and C_{max} (maximum substance concentration) were within the acceptance limits for bioequivalence. Therefore, bioequivalence was established for the comparison of 2 mg DNG administered alone as a tablet to the fixed reference formulation of 2 mg DNG + 2 mg EV as a coated tablet.

Conclusions:

The test and reference preparations were both well tolerated. No serious or unexpected AEs were reported.

Bioequivalence was demonstrated for 2 mg DNG when given as a single substance (tablet) compared to the fixed formulation 2 mg DNG + 2 mg EV (coated tablet). Therefore, the 2 mg DNG monopreparation may be administered as a progestogen additive separately in combination with the administration of estrogen hormone replacement therapy (HRT).

TT 11: 90% confidence intervals for assessment of bioequivalence

Pharmacokinetic parameter	Analyte	Treatments	Mean ratio %	Lower confidence limit %	Upper confidence limit %	Lower equivalence limit %	Upper equivalence limit %	Bio-equivalence criterion
AUC	DNG	test vs. reference	103.7	97.0	111.0	80	125	fulfilled
C _{max}	DNG	test vs. reference	106.9	100.3	114.0	70	143	fulfilled

Reviewer's comment: Combined administration of DNG 2 mg together with EV 2 mg has no effect on DNG 2 mg PK. The Division has agreed that no additional DDI studies are required to investigate the potential drug interactions between DNG and EV. Reference is made to the minutes of the pre-IND meeting held on March 17, 2004.

A.1.16. Studies B475 and B476

PK and Biotransformation of ³H-labelled DNG after Oral and I.V. Administration of about 0.1 mg DNG

Protocol No: B475 and B476
Phase: 1
Clinical Study Center: (b) (4)
Clinical Study Dates: 1979

SUMMARY

These studies were performed to investigate the PK of ³H-labeled DNG. The study was performed as a single-center, open-label study in 5 healthy women aged 30-38 yr. In the first period, the women received a gelatin capsule containing 101.3 µg ³H-labeled DNG. After 10 weeks washout, approximately 80 µg ³H-labeled DNG in (ethanol/propylenglycol/sorbitol solution) was injected IV. Blood samples were collected up to 72 h after administration. Urine was collected in the periods from 0-6 hr, 6-12 hr, 12-24 hr, and thereafter in 24 hr periods up to Day 5 after administration. Feces were sampled in 24 hr intervals.

In study B475, total radioactivity in plasma, whole blood, urine, and feces as well as radioactivity of the freely extractable fraction (toluene extractable) in plasma was determined by means of LSC. The freely extractable fraction was supposed to contain the parent compound and lipophilic metabolites. In study B476, DNG was measured by LSC after thin layer chromatography. Mean PK parameters are summarized below.

Table A-16-1: Summary of Single Dose Pharmacokinetic Studies with ³H-DNG

Study/ Protocol (Country)	# Subjects Entered/ Completed (M/F)	HV/P ¹ (Age: Mean: Range)	Treatments	Analyte	Urinary excretion (% of dose)	Fecal excretion (% of dose)	Mean Pharmacokinetic Parameters of DNG ²				
							C _{max} ng/ml	T _{max} h	AUC(0-24h) ng-h/ml	AUC(0-∞) ng-h/ml	T _{1/2} h
B475/ B476 (Germany)	5F/5F	HV (34.8: 30-38)	³ H-DNG 101.3 µg (Gelatin capsule)	DNG			1.8	1	16.7		5.9
				DNG					15.7		6.3
			³ H-DNG 101.3 µg (Gelatin capsule)	Total radioactivity	71.9 ± 6.4 ³	10.9 ± 1.1		27.6 ± 5.1 ⁴	37.4 ± 7.4 ⁴	11.7 ± 1.8	
				Total radioactivity	67.9 ± 7.9 ³	12.7 ± 1.5		28.7 ± 4.4 ⁴	37.8 ± 4.5 ⁴	12.6 ± 2.5	

¹ HV=Healthy Volunteers, P=Patients

² given as mean ± standard deviation

³ within 5 days

⁴ Unit: h · (% of the dose / l)

The total radioactivity in whole blood and plasma showed a parallel time-course with the whole blood concentrations lower than the plasma concentrations. The maximum plasma concentration of total and freely extractable radioactivity occurred within 2 hr after oral administration. The AUC of the freely extractable fraction amounted to approximately 65% of the AUC of the total radioactivity. The plasma elimination half-life of total radioactivity was 11.7 hr after oral and 12.6 hr after IV administration, those of the freely extractable fraction were 8.4 hr and 9 hr, respectively. The difference between the total radioactivity and the free fraction was attributed to the hydrophilic metabolite fraction. The elimination of this fraction was considerably slower with a terminal elimination half-life of about 19 hr after both oral and IV administration.

54% of the applied dose was already renally excreted within the first 24 hr after oral administration. Renal excretion within 5 days amounted to 71.9% of the applied dose. After IV administration 50.8% were renally

excreted within the first 24 hr and 67.9% within 5 days. The total excretion via feces amounted to 10.9% of the applied dose within 5 days after oral administration and to 12.7% after IV administration. The total amount of radioactivity excreted in urine and feces up to the 5th day amounted to 82.7% of the applied dose after oral administration and to 80.6% after IV administration, respectively (Study B475).

The volume of distribution at steady state is 46 liters after IV administration of 84.5 μg ^3H -labeled DNG (Study B476).

Reviewer's comment: *The major route of excretion was via the kidney.*

A.1.17. Study B427

Dienogest (STS 557): Characterization of Binding to Different Receptor Proteins and CBG and SHBG

Protocol No: B427
Phase: Preclinical
Clinical Study Center: (b) (4)
Clinical Study Dates: 1992

SUMMARY

Estrogen and progesterone receptor binding of DNG and other steroid hormones was determined using human uterine cytosol. The binding to androgen receptors was determined in cytosol of castrated rats, that to glucocorticoid receptors in livers of adrenalectomized female rats and that to mineralocorticoid receptors in kidneys of adrenalectomized female rats. The competitor steroids were tested in concentration ranges from 10^{10} - 10^{-5} mol/l, the ligand concentration was 8 nmol/l. The incubation was overnight at 4°C. The resulting binding affinities of DNG and other progestogens are presented in Table A-17-1.

Table A-17-1: Relative Binding Affinities of Dienogest in Comparison to Other Progestins for Binding to Human Uterine Progesterone and Estradiol Receptors, Rat Glucocorticoid Receptor, Rat Kidney Mineralocorticoid Receptor and Rat Prostate Androgen Receptor

Competitor Steroid	Progesterone receptor *[R5020]	Glucocorticoid receptor *[dexamethasone]	Mineralocorticoid receptor *[aldosterone]	Androgen receptor *[R1881]	Estrogen receptor *[estradiol]
RBA values [%]					
Progesterone	30	10	100	< 0.01	< 0.1
R5020	100	17	53	< 0.1	< 0.1
Gestodene	76	28	290	72	< 0.1
3-Ketodesogestrel	180	9.6	< 0.01	29	< 0.1
Levonorgestrel	250	0.95	79	53	< 0.1
Dienogest	3.6	0.96	< 0.01	0.84	< 0.1

* Ligand = 100 % affinity by definition

The progesterone receptor binding of DNG was 10 times less than that of progesterone and 3.6% of the synthetic progestogen R5020. The R5020-receptor-complex dissociated very slowly ($t_{1/2} = 388$ min), whereas progesterone and DNG dissociated in a much shorter time (progesterone: $t_{1/2} = 74$ min, DNG: $t_{1/2} = 32$ min). In a Scatchard plot analysis, the dissociation constant of R5020 was 5.32×10^{-9} mol/l and that of DNG as ligand 1.12×10^{-8} mol/l, which is approximately one order of magnitude less than that measured with R5020. DNG was practically not bound to the mineralocorticoid and to the estrogen receptor. There was a slight binding to the androgen and the glucocorticoid receptor. Relative binding affinities of DNG towards SHBG and cortisol binding globulin (CBG) were determined using diluted stripped human pregnancy serum or purified human SHBG; ^3H -cortisol and ^3H -DHT were used as ligands in a final concentration of 8 nmol/l. The incubation period was 2 hr at 4°C. The relative binding affinities of DNG and other progestogens are presented in Table A-17-2.

Table A-17-2: Relative Binding Affinities of DNG in Comparison to Other Progestins for Binding to Human SHBG and CBG.

Competitor steroid	Human pregnancy serum SHBG	SHBG purified	Human pregnancy serum, SHBG removed by chromatography	Human pregnancy serum, CBG
RBA values (%)				
Progesterone	< 0.1	< 0.1	< 0.1	53
Gestodene	65	70	< 0.1	< 0.1
3-keto-desogestrel	4	8	< 0.1	< 0.1
Levonorgestrel	45	50	< 0.1	< 0.1
DNG	< 0.1	< 0.1	< 0.1	< 0.1
DHT	100	100	< 0.1	0.6
Cortisol	NM	NM	NM	100

NM: Not measured

In contrast to other progestogens, DNG did not bind to SHBG and CBG.

A.1.18. Study A00560

Kinetic Experiments with M 18575. Absorption, Distribution, and Excretion in Rats and Dogs

Protocol No: A00560
Phase: Preclinical
Clinical Study Center: (b) (4)
Clinical Study Dates: July 7, 1993 – March 28, 1994

SUMMARY

¹⁴C-DNG with a specific activity of 6.15MBq/mg was used for the experiments, radiochemical purity was >97%. Fresh blood plasma (anticoagulant: heparin sodium) was used for the experiments. For the separation of protein bound DNG from unbound DNG the method of centrifugal ultra-filtration (1000 x g, 4°C, 20 min) was used. DNG concentrations in plasma were 100, 250 and 1000 ng/ml. Blood plasma protein binding ratio of ¹⁴C-DNG was 89.6-89.8% in female rats, 87.0-92.8% in female dogs, 90.7-92.0% in female monkeys and 93.5-94.5% in healthy adult women.

For the determination of the blood cell to plasma distribution ratio, ¹⁴C-DNG was added to blood; the final DNG concentration was 500 ng/ml. Fresh blood from female rats, female dogs, female monkeys, and healthy adult women was incubated for 5, 15, and 30 min at 37°C, hematocrit value was measured, and radioactivity in blood and blood plasma was estimated. The blood cell to plasma distribution ratio was calculated from the radioactivity concentration obtained in blood and blood plasma and hematocrit value. The blood plasma reversibility ratio *in vitro* was 7.3-10.4% for rats, 17.8-19.7% for dogs, 14.5-16.2% for monkeys and 13.3-15.5% for humans.

A.1.19. Study B463

The Influence of Certostat 30 (Valette) and Minisiston on the Elimination of Nifedipine as well as the Influence of the Progestin Dienogest and Levonorgestrel (LNG) Contained in the Two Products on the Accumulation of Ethinyl Estrdiol

Protocol No: B463
Phase: Phase 3/4
Clinical Study Center: (b) (4)
Clinical Study Dates: March 1993 - August 1993

SUMMARY

Purpose: The primary aim of the study was to examine the influence of the oral contraceptives Valette (0.03 mg EE + 2 mg DNG) and Minisiston (0.03 mg EE + 0.125 mg LNG) on the CYP 3A4 activity by means of the model substance nifedipine.

Design: The study was performed as a single-center, open-label, randomized, parallel-design study in healthy young women aged 21-32 yr. 25 volunteers were included (12 received DNG+EE and 13 LNG+EE) and 23 completed the study. There were 2 drop outs, one due to pregnancy and one due to an AE (bleeding).

Each of the volunteers received a single dose of 10 mg nifedipine on Day 21 of the control cycle and on treatment Day 21 of the treatment cycle. Serum samples for the determination of nifedipine and its major metabolite dehydronifedipine were taken up to 23.5 hr after nifedipine intake. In the treatment cycle, the oral contraceptives were taken over 21 days beginning on Day 4 of the menstrual cycle. The serum concentrations of EE, DNG, and LNG were determined on Days 1 and 21 of the treatment cycle. Furthermore, the trough levels of EE, DNG, and LNG were determined in the mornings of Days 7 and 14. Concentrations of nifedipine and its metabolite dehydronifedipine were determined by means of a validated gas chromatography with electron capture detector (GC-ECD). DNG, EE, and LNG were determined by means of validated RIAs, for the determination of EE in the presence of LNG a HPLC separation was performed before the RIA.

Target variables were:

- AUC (0-23.5 h) for nifedipine and dehydronifedipine
- AUC (0-24 h) for DNG, LNG, and EE,
- C_{max} , C_{min} , CL, MRT, t_{max} , and $t_{1/2}$.

Results: The clinical and laboratory tolerability during the study was acceptable. No SAEs were reported, no clinically significant laboratory anomaly was observed. The most frequent AEs were headache, breast tenderness and nausea.

AUC(0-∞), C_{max} , and CL_{tot} of nifedipine remained unchanged with co-administration of EE/DNG.

Table A-19-1: Statistic Comparison of PK Parameters (Nifedipine alone vs. EE/DNG + Nifedipine)

Analyte	Parameter	Mean Ratio (%)
Nifedipine	C_{max}	97.9
	AUC(0-∞)	97.6
	CL_{tot}	101.8

Reviewer's comment: This study with DNG in combination with EE was performed for the development of an oral contraceptive containing 2 mg DNG and 0.03 mg EE. The study was performed in 1993 according to EC-GCP and therefore, is not complete to today's expectation level of a clinical study in the US and 90% CIs were not reported. Co-administration of EE/DNG did not result in changes of AUC(0-∞), C_{max} , and CL_{tot} of nifedipine. Therefore, it can be concluded that Co-administration of 0.03 mg EE/2 mg DNG has no effect on 10 mg nifedipine PK

A.2. Clinical Pharmacology Filing Memo

<i>Office of Clinical Pharmacology</i>				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA Number	22-252		Brand Name	Qlaira
OCP Division	DCP3		Generic Name	Estradiol Valerate / Dienogest
Medical Division	DRUP		Drug Class	Combination oral contraceptive (COC)
OCP Reviewer	Chongwoo Yu, Ph.D		Indication(s)	Primary: prevention of pregnancy Secondary: treatment of heavy and/or prolonged menstrual bleeding
OCP Team Leader	Myong Jin Kim, Pharm. D.		Dosage Form	Immediate release (IR) film-coated tablets
Secondary Reviewer	Myong Jin Kim, Pharm. D.		Dosing Regimen	Once daily 4-phasic (plus placebo phase), 28 day, sequential regimen
Date of Submission	July 2, 2009		Route of Administration	Oral
Estimated Due Date of OCP Review	March 2, 2010		Sponsor	Bayer Healthcare Pharmaceuticals
PDUFA Due Date	May 2, 2010		Priority Classification	Standard
Division Due Date	April 11, 2010			
<u>Clin. Pharm. and Biopharm. Information</u>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	4		B473, A12603, A37060, A37059
I. Clinical Pharmacology				
Mass balance:	X	3		B475, B476, B478
Isozyme characterization:	X	1		A00680
Blood/plasma ratio:	X	1		A00560
Plasma protein binding:	X	1		A00560
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:	X	4		A25711, B276, B471, B472,
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		B306
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		A24058, A30020
In-vivo effects of primary drug:	X	3		AR34, A07769, B463
In-vitro:	X	2		B482, A05426
Subpopulation studies -				

ethnicity:	X	1		A00681
gender:				
pediatrics:	NA			Pediatric waiver request
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:	X	5		B468, A03128, B470, A02263, B709
Phase 2:	X	3		A00984, A14191, A25364
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		A33022
Phase 3 clinical trial:				
Population Analyses -				
PK:				
PD:				
II. Biopharmaceutics				
Absolute bioavailability:	X	1		B501
Relative bioavailability -				
solution as reference:	X	2		A29972, AV69
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		A29143, BO08
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Immunogenicity profile				
Thorough QT study	X	1		A35653
Literature References	X	14		
Total Number of Studies		52		
Other comments				
	Comments			
QBR questions (key issues to be considered)	<ol style="list-style-type: none"> 1. Dosing regimen 2. Drug-drug interaction potential 3. Food effect 4. Specific population 5. Thorough QT 6. Acceptability of the pediatric waiver request 7. Sufficient bioanalytical assay validation information? 8. Acceptability of the in vitro dissolution comparison between formulations 			
Other comments or information not included above	<ol style="list-style-type: none"> 1. Given that the time course of estradiol in plasma after oral administration is influenced by a large pool of circulating estrone sulfate and the back conversion of estrone sulfate to estrone and estradiol, the Division requests the Sponsor to add the mean PK parameters of estrone sulfate to Table 1 in Section 12.3 of the Sponsor's proposed label. 			

* An Optional Inter-Division Clinical Pharmacology Briefing was held on Thursday, March 11, 2010. The attendees are as follows: C Yu, HY Ahn, D Bashaw, MJ Kim, H Kim, D Tran, L Lee, S Cho, L Soule, G Willett, J Lazor, G Burckart, L Zhang, S Choe, Y Xu, L Zhou, JE Lee, D Jappar, L Jain, A Agrawal

Filing Memo

Clinical Pharmacology Review

NDA: 22-252
Compound: Qlaira™ (Estradiol Valerate [EV] / Dienogest [DNG])
Sponsor: Bayer Healthcare Pharmaceuticals

Date: 8/14/2009
Reviewer: Chongwoo Yu, Ph.D.

Introduction:

This New Drug Application (NDA) for EV and DNG was submitted for the primary indication of prevention of pregnancy, and for the secondary indication of treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who choose to use an oral contraceptive (OC) as their method of contraception. The initial IND for this EV/DNG combined oral contraceptive (COC) was filed under IND 64,809 on November 17, 2004 for the indication of prevention of pregnancy. Subsequently, IND (b) (4) was submitted on (b) (4) for the treatment of dysfunctional uterine bleeding (DUB) in women desiring oral contraception.

The investigational product contains the two active substances, EV and DNG in combination or EV alone in a sequential application regimen, consisting of 4 phases with active tablets and one placebo phase. A blister pack of EV/DNG (28 film-coated tablets) contains in the following order:

- Cycle Days 1-2: EV 3 mg (dark yellow tablets)
- Cycle Days 3-7: EV 2 mg + DNG 2 mg (medium red tablets)
- Cycle Days 8-24: EV 2 mg and DNG 3 mg (light yellow tablets)
- Cycle Days 25-26: EV 1 mg (dark red tablets)
- Cycle Days 27-28: placebo (white tablets)

One film-coated tablet is to be taken daily for 28 consecutive days.

The investigational product Qlaira™ contains EV as estrogen component instead of ethinyl estradiol (EE). After intake, EV is rapidly hydrolyzed presystemically into 17β-estradiol, which is the major natural estrogen in humans, and valeric acid. Currently, EV is approved only as an injectable product (Delestrogen®) in the US (NDA 09-402, approved on July 15, 1954). The progestogenic component of Qlaira™, the 19-norprogesterin DNG, is currently marketed in combination with EE as combined oral contraceptive (COC; such as Valette®) and in combination with EV as hormonal therapy (HT) such as Climodien® 2/2 in several European and non-European countries. DNG is considered to be a new molecular entity (NME) in the US.

Qlaira™ will provide the first COC containing EV instead of EE in the US. The Qlaira™ tablets are currently approved for marketing in 26 European Union Member Countries (initial approval on November 3, 2008) and Australia for the indication prevention of pregnancy. Introduction into the market under the trade name Qlaira® occurred in May 2009 in some of these countries. Another DNG-containing COC (with EE) was initially approved on February 14, 1995 in Germany under the trade name Valette®. This product has subsequently been approved in 36 countries and is marketed in 20 countries. In all countries except Australia, it is marketed as 21 tablets containing EE 0.03 mg and DNG 2 mg (7 of 28 days are tablet-free); in Australia it is marketed as 21 active tablets plus 7 placebo tablets. EV and/or DNG are also marketed for indications other than the prevention of pregnancy (e.g., Climodien®: EV 2 mg / DNG 2 mg, 28 tablets) outside of US.

The clinical development program of combined EV and DNG for OC has led to a regimen consisting of 4 active phases, each phase containing different doses of EV, either alone or in combination with different doses of DNG. This sequence is followed by 2 days with placebo tablets. The 4-phasic sequential regimen is aimed at ensuring sufficient estrogen levels in the first half of the cycle, the period during which endometrial proliferation is promoted under the influence of estrogens. In an extensive dose-finding process, it was decided by the Sponsor that a step-up combination of 5 days with EV 2 mg / DNG 2 mg followed by 17 days with EV 2 mg / DNG 3 mg is the lowest possible combination able to provide sufficient ovulation inhibition. The Sponsor believes that Qlaira™ provides endometrial stability and subsequently better cycle control compared to monophasic approaches can be obtained.

Sponsor's submission of proof of the clinical efficacy of Qlaira™ is based on the low number of pregnancies in 3 large clinical Phase 3 studies, i.e., Studies A39818 in North America and A35179 in Europe (pivotal Pearl Index studies) and A35644 (pivotal with regard to bleeding patterns and cycle control). Two pivotal Phase 3, double-blinded, placebo-controlled clinical studies (Studies A29849 in US and Canada and A42568 in Europe and Australia) were conducted to demonstrate the efficacy and safety for treating symptoms of DUB. The following Table gives an overview of the studies as part of the clinical pharmacology and biopharmaceutics development program of Qlaira™.

Study No. / Location	Short title	Volunteers included/ completed	Main objective
Bioavailability (BA) study reports			
A29972 / 5.3.1.1 A29972	Relative bioavailability EV/DNG tablets vs. suspension	36/35 p.m.	relative BA
A29143 / 5.3.1.1 A29143	Food effect study with 2 mg EV / 3 mg DNG tablets	38/35 p.m.	PK (effect of food)
B008 / 5.3.1.1 B008	Food effect study with DNG tablets	24/22 y.m.	PK (effect of food)
B501 / 5.3.1.1 B501	Absolute bioavailability of DNG	22/20 y.m.	PK (absol. BA)
AV69 / 5.3.1.1 AV69	Relative bioavailability of Climodien 2/2 and Climodien 2/3	19/18 p.m.	PK (relative BA)
Healthy volunteer pharmacokinetics (PK) and initial tolerability study reports			
A25711 / 5.3.3.1 A25711	Multiple dose PK study with EV/DNG tablets	18/16 y.f.	PK (multiple dosing)
B475 / 5.3.3.1 B475 B476* / 5.3.3.1 B476	PK of ³ H-labelled DNG after oral and i.v. administration of about 0.1 mg DNG	5/5 y.f.	PK (blood, plasma, urine, faeces)
B478* / 5.3.3.1 B478	PK of ³ H-labelled DNG after oral administration of 0.1 mg/kg	6/6 y.f.	PK (plasma, urine, feces, metabolite profile)
B306 / 5.3.3.1 B306	Investigation on dose linearity of DNG PK	14/12 y.f.	PK (dose linearity)
B467* / 5.3.3.1 B467	Tolerability after single doses of 0.5 and 2 mg DNG	19/19 y.f.	Tolerability single dose
B276 / 5.3.3.1 B276	PK of DNG 2 mg after single and multiple dosing	16/16 y.f.	PK (single and multiple dosing)
B471 / 5.3.3.1 B471	PK of Climodien 2/3 (2 mg EV + 3 mg DNG) after single and multiple dosing	16/15 p.m.	PK (single and multiple dosing)
B472 / 5.3.3.1 B472	PK of Climodien 2/2 (2 mg EV + 2 mg DNG) after single and multiple dosing	16/15 p.m.	PK (single and multiple dosing)

*pre-Good Clinical Practice (GCP) study, #not all volunteers in these studies received DNG (in study A00681 (5.3.3.3 A00681), 18 volunteers received DNG and 6 placebo; in study B463 (5.3.3.4 B463), 12 volunteers received DNG and 13 LNG; in study B468 (5.3.4.1 B468) (transformation dose), 32 volunteers received DNG and 12 LNG y. = young, f. = female, m. = male, p.m. = postmenopausal

Study No. / Location	Short title	Volunteers included/ completed	Main objective
Patient PK and initial tolerability study reports			
B469* / 5.3.3.2 B469	Tolerability of DNG in 24 endometrial cancer patients	24/24 f (mean age: 60)	Tolerability (21 days of treatment)
A04431 / 5.3.3.2 A04431	Effectiveness and tolerability of 20 mg DNG per day over 24 weeks in the treatment of endometriosis	20/21 y.f.	Tolerability multiple dose
Intrinsic factor PK study reports			
A00681 / 5.3.3.3 A00681	Tolerability and PK of a single oral dose of DNG in healthy adult Japanese females	24/24 y.f.# (Japanese)	Tolerability, PK (plasma, urine)
Extrinsic factor PK study reports			
AR34 / 5.3.3.4 AR34	Effect of EV on DNG PK	16/16 p.m.	PK (interaction)
A07769 / 5.3.3.4 A07769	Effect of DNG on EV PK	24/24 p.m.	PK (interaction)
A24058 / 5.3.3.4 A24058	Drug-drug interaction (DDI) study with CYP 3A4 inducer – rifampicin	16/16 p.m.	steady state PK (single and multiple dosing, interaction)
A30020 / 5.3.3.4 A30020	DDI study with CYP 3A4 inhibitors – ketoconazole and erythromycin	24/24 p.m.	steady state PK (single and multiple dosing, interaction)
B463 / 5.3.3.4 B463	Influence of 0.03 mg EE + 2 mg DNG and 0.03 mg EE + 0.125 mg levonorgestrel (LNG) on nifedipine PK	25/23 y.f.#	PK (single and multiple dosing, interaction)
Healthy volunteer pharmacodynamics and pharmacokinetics / pharmacodynamics study reports			
B468* / 5.3.4.1 B468	Determination of antagonistic activity and transformation dose of DNG	21/21 y.f. and 44/44 p.m.#	PD (antigonadotropic effect, endometrial effect)
A03128 / 5.3.4.1 A03128	Determination of the transformation dose of DNG	40/39 p.m.	PD (endometrial effect)
B470 / 5.3.4.1 B470	Determination of the ovulation inhibition dose of DNG	22/21 y.f.	PD (ovulation inhibition)
A02263 / 5.3.4.1 A02263	Pulsation pattern of gonadotropin secretion under DNG and DNG + EE	15/15 y.f.	PD (antigonadotropic effect)

*pre-Good Clinical Practice (GCP) study, #not all volunteers in these studies received DNG (in study A00681 (5.3.3.3 A00681), 18 volunteers received DNG and 6 placebo; in study B463 (5.3.3.4 B463), 12 volunteers received DNG and 13 LNG; in study B468 (5.3.4.1 B468) (transformation dose), 32 volunteers received DNG and 12 LNG y. = young, f. = female, m. = male, p.m. = postmenopausal

Study No. / Location	Short title	Volunteers included/ completed	Main objective
Healthy volunteer pharmacodynamics and pharmacokinetics / pharmacodynamics study reports (cont'd)			
A00984 / 5.3.4.1 A00984	Inhibition of ovulation I - first approach regimen	22/21 y.f.	PD (ovulation inhibition)
A14191 / 5.3.4.1 A14191	Inhibition of ovulation II - first approach vs. modified regimen	192/176 y.f.	PD (ovulation inhibition)
A25364 / 5.3.4.1 A25364	Inhibition of ovulation III -EV/DNG tablets vs. DNG-increased regimen	203/185 y.f.	PD (ovulation inhibition)
A33022 / 5.3.4.1 A33022	Plasma lipids, hemostatic variables and carbohydrate metabolism (see section 2.7.4) PK over multiple treatment cycles (described here)	58/50 y.f. 24 analyzed for PK	PK of E1, E2 and DNG Effects on hormones, lipids, hemostasis (see section 2.7.4)
A38220 / 5.3.4.1 A38220	Hemostatic variables (see section 2.7.4)	29 / 26	Effects on hemostasis (see section 2.7.4)
B709 / 5.3.4.1 B709	Estrogenic effects of estradiol sulfamate in comparison to EE, EV and placebo	49/47 p.m.	PD (estrogenic activity of different estrogens)
A35653 / 5.3.4.1 A35653	Thorough QT study	53/40 p.m.	Effects on cardiac repolarization

y. = young, f. = female, m. = male, p.m. = postmenopausal

Drug Product Formulation:

Qlaira™ tablets were developed as immediate release (IR) film-coated tablets. During the clinical development program of Qlaira™, only slight modifications of the formulation were implemented, with the final formulation used in all pivotal, Phase 3 efficacy trials and supporting pharmacokinetic (PK) studies. In the Phase 2 ovulation inhibition study (Study A25364), while all other tablets of the sequential application regimen were identical with the to-be-marketed (TBM) formulation, two tablets (1 tablet containing EV 2 mg / DNG 1 mg [SHT00658FA] and 1 tablet containing DNG 2 mg only [SHT006600AA]) were co-administered to achieve the EV 2 mg / DNG 3 mg dose level of the EV/DNG regimen, which in the final EV/DNG formulation (TBM formulation: SHT00658M) is one tablet. Per Sponsor, similarity of *in vitro* dissolution was demonstrated for the tablet containing EV 2 mg / DNG 1 mg, the tablet containing DNG 2 mg and the final formulation containing EV 2 mg / DNG 3 mg. The Sponsor concludes that the *in vitro* dissolution data showed complete and comparable dissolution of all the formulations used. The composition of the TBM film-coated tablets is summarized in the Table below:

		SH T00658EA	SH T00658GA	SH T00658M	SH T00658HA	SH T00658P
(b) (4)	Estradiol valerate, (b) (4)	3.000 mg	2.000 mg	2.000 mg	1.000 mg	-
	Dienogest, (b) (4)	-	2.000 mg	3.000 mg	-	-
	Lactose monohydrate	(b) (4)				
	Maize starch					
	Maize starch, pregelatinized					
	Povidone 25					
(b) (4)	Magnesium stearate					
	Hypromellose, (b) (4)					
	Macrogol 6000					
	Titanium dioxide					
	Ferric oxide pigment yellow					
	Ferric oxide pigment red					
	Talc					
Total weight		83.000 mg	83.000 mg	83.00000 mg	83.0000 mg	82.0000 mg

Absorption

- EV: After oral administration, EV is completely absorbed. Cleavage to 17β estradiol and valeric acid takes place during absorption by the intestinal mucosa or in the course of the first liver passage. This gives rise to estradiol (E2) and its metabolites, estrone (E1) and estrone sulfate (E1S). Per Sponsor, Maximum serum E2 concentrations of 70.6 pg/mL are reached between 1.5 and 12 hours after single ingestion of a tablet containing EV 3 mg on Day 1 (Study A25711). In young women, the measured E2 plasma levels are a composite of the endogenous E2 and the E2 generated from Qlaira™. Per

Sponsor, during the treatment phase of EV 2 mg and DNG 3 mg, maximum and average serum E2 concentrations at steady state are 66.0 pg/mL, and 51.6 pg/mL, respectively. Per Sponsor, stable minimum E2 concentrations were maintained throughout the 28-day cycle and ranged from 28.7 pg/mL to 64.7 pg/mL (Study A25711).

- DNG: Orally administered DNG is rapidly and almost completely absorbed. Per Sponsor, maximum serum concentrations of 90.5 ng/mL are reached at about 1 hour after single oral administration of a Qlaira™ tablet containing EV 2 mg / DNG 3 mg (Study A29972) and bioavailability is about 91% (Study B501). The PK of DNG are dose-proportional within the dose range of 1-8 mg (Study B306). For DNG, steady state is reached after 3 days of the same dosage of DNG 3 mg in combination with 2 EV 2 mg. Trough, maximum and average DNG serum concentrations at steady state are 11.8 ng/mL, 82.9 ng/mL, and 33.7 ng/mL, respectively (Study A25711). The mean accumulation ratio for $AUC_{(0-24h)}$ was determined to be 1.24 (Study B276).

Distribution

- EV: In serum, 38% of E2 is bound to SHBG, 60% to albumin and 2-3% circulates in free form. E2 can slightly induce the serum concentrations of SHBG in a dose dependent manner. Per Sponsor, on Day 21 of the treatment cycle, SHBG was approximately 148% of the baseline, and decreased to about 141% of the baseline by the end of placebo phase, Day 28 (Study A25711). An apparent volume of distribution of approximately 1.2 L/kg was determined after IV administration.
- DNG: A relatively high fraction (10%) of circulating DNG is present in the free form, with approximately 90% being bound non-specifically to albumin. Per Sponsor, DNG does not bind to the specific transport proteins SHBG and CBG (Study B427). The Sponsor believes that any influence on physiological transport processes for endogenous steroids is consequently unlikely. The volume of distribution at steady state ($V_{d,ss}$) of DNG is 46 l after the intravenous administration of 85 µg 3H-dienogest.

Metabolism

- EV: After oral administration, approximately 3% of the dose is directly bioavailable as E2. E2 undergoes an extensive first-pass effect and a considerable part of the dose administered is already metabolized in the gastrointestinal mucosa. Together with the pre-systemic metabolism in the liver, about 95 % of the orally administered dose becomes metabolized before entering the systemic circulation. The main metabolites are E1 and E1S.
- DNG: Per Sponsor, DNG is nearly completely metabolized by the known pathways of steroid metabolism (hydroxylation, conjugation) (Studies B478 and B455), with the formation of endocrinologically mostly inactive metabolites. The metabolites are excreted very quickly so that in plasma unchanged DNG is the dominating fraction (Study B478). The total clearance following the intravenous administration of 3H-dienogest was calculated as 5.4 L/h (Study B478).

Excretion

- EV: The plasma half-life of circulating E2 is about 90 min. After oral administration, however, the situation differs. Because of the large circulating pool of ES, as well as enterohepatic recirculation, the terminal half-life of E2 after oral administration represents a composite parameter which is dependent on all of these processes and is in the range of about 13-20 hours. E2 and its metabolites are mainly excreted in urine, with about 10% being excreted in the feces.
- DNG: Per Sponsor, the plasma half-life of DNG is approximately 11 hours (Study A25711). DNG is excreted in the form of metabolites which are excreted at a urinary to fecal ratio of about 3:1 after oral administration of 0.1 mg/kg. Following oral administration, 42% of the dose is eliminated within the first 24 hours and 63% within 6 days by renal excretion. A combined 86% of the dose is excreted by urine and feces after 6 days (Study B478).

Drug-Drug Interactions:

Effects of Other Drugs on Combined Hormonal Contraceptives

DNG is a substrate of cytochrome P450 (CYP) 3A4. Interactions can occur with drugs that induce CYP enzymes which can result in increased clearance of sex hormones. The effect of the CYP 3A4 inducer rifampicin was studied in healthy postmenopausal women. Per Sponsor, coadministration of 600 mg rifampicin daily with EV 2 mg / DNG 3 mg tablets led to significant decreases in steady state concentrations and systemic exposures to DNG and E2 (Study A24058). CYP3A4 inhibitors may increase plasma levels of DNG. In a study investigating the effect of CYP 3A4 inhibitors (400 mg ketoconazole daily or 1500 mg erythromycin daily), the Sponsor concludes that steady state $AUC_{(0-24h)}$ DNG and E2 plasma levels were increased (Study A30020).

Effects of Combined Hormonal Contraceptives on other Drugs

The Sponsor has submitted information/data in support of their following conclusions: *In vitro* studies with human CYP enzymes did not indicate an inhibitory potential of DNG at clinically relevant concentrations (Study B482). Combined administration of DNG 2 mg together with EV 2 mg has no effect on DNG 2 mg PK (Study AR34). The same holds true for EV, whereby combined administration of EV 4 mg together with DNG 4 mg has no effect on EV 4 mg PK (Study A07769). The Division has agreed that no additional drug-drug interaction (DDI) studies are required to investigate the potential drug interactions between DNG and EV. Reference is made to the minutes of the pre-IND meeting held on March 17, 2004.

Specific Population and Waivers:

- Renal / hepatic impairment patients: The Sponsor has provided acceptable justification for not conducting studies in renal and/or hepatic impaired patients for use of EV/DNG in premenopausal women. If and when approved, appropriate language for renal and/or hepatic impairment will be included in the product label at the time of approval. Reference is made to the letter that the Division sent to the Sponsor on June 15, 2005. The Sponsor believes that no special risk for these patients is to

be expected, because EV is transformed into the natural 17 β -estradiol, which is also produced endogenously in the target population and because DNG is metabolized before excretion and its metabolites are pharmacologically inactive. Furthermore, DNG was shown to be safe in clinical use up to doses of 20 mg/day over 6 months per Sponsor (Study A04431).

- Liver impaired patients: No studies were performed in patients with impaired liver function because severe liver diseases are already considered as contraindication for COCs.
- Pediatric Study waiver request: No studies were performed in children because Qlaira™ is not indicated before menarche. The Sponsor requests a full waiver from the requirement to submit data adequate to assess the safety and efficacy of EV and DNG in all relevant pediatric subpopulations.

Food Effect:

Per Sponsor, PK of DNG when given as a tablet containing DNG 2 mg was not affected by concomitant intake of a high-fat meal (Study BO08). The effect of concomitant food intake on the PK of EV and DNG was investigated in Study A29143 using the tablet containing EV 2 mg / DNG 3 mg, as a representative tablet of Qlaira™. The Division has agreed to this approach of using one dose (EV 2 mg / DNG 3 mg) to be sufficient for investigation of food-effect as this tablet contains the highest amount of DNG in any of the tablets included in Qlaira™. Reference is made to the minutes of the pre-IND meeting held on March 17, 2004. In this food effect study in healthy postmenopausal women, the C_{max} of DNG was decreased by 28% under fed conditions and the C_{max} of E2 was increased by 23% while AUC values for both DNG and E2 remained unchanged. The Sponsor concludes that Qlaira™ tablets can be taken without regard to meals during all phases of the Qlaira™ regimen. The Sponsor believes that this is further supported by the fact that all of the clinical trials with the Qlaira™ tablets were performed without any restrictions concerning food intake and that the clinical efficacy and safety of the drug was demonstrated in these clinical studies. Therefore, no special recommendation concerning food intake is considered to be necessary by Sponsor regarding the patient information. The Sponsor proposes the following language on the label: (b) (4)

(b) (4)

Thorough QT Study

In study A35653, the potential effect of Qlaira™ to delay cardiac repolarization was investigated in healthy postmenopausal women. Placebo tablets, a fixed combination of EV 2 mg / DNG 3 mg and a supraphysiologic dose of DNG 10 mg (5 x 2 mg tablets, SHT00660AA) were given once-a-day over a period of 4 days. For the active treatments with DNG, no QT/QTc prolongation was observed. As expected, the positive control moxifloxacin showed a clear QTcF prolongation from time points 30 minutes up to 24 hours post-treatment.

Bioanalytical Method validation:

Validated analytical methods were used in the *in vivo* studies. A radioimmunoassay (RIA) was used for the quantitation of DNG in serum or plasma. This RIA was cross-validated using liquid chromatography - mass spectrometry (LC-MS). All of the PK studies performed during the development of Qlaira™ tablets have used the RIA method for the measurement of DNG in human serum. For the quantitation of E2, E1, and E1S, a validated liquid chromatography – tandem mass spectrometry (LC-MS/MS) method was used. Bioanalytical method validation reports are submitted for review.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 22-252 is fileable.

Comments for the Sponsor:

- Given that the time course of estradiol in plasma after oral administration is influenced by a large pool of circulating estrone sulfate and the back conversion of estrone sulfate to estrone and estradiol, the Division requests the Sponsor to add the mean PK parameters of estrone sulfate to Table 1 in Section 12.3 of the Sponsor's proposed label.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22252

ORIG-1

BAYER
HEALTHCARE
PHARMACEUTICA
LS INC

Qlaira

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHONGWOO YU
03/30/2010

MYONG JIN KIM
04/02/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Pediatric waiver submitted
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Pediatric waiver submitted
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

- *None*

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- *Given that the time course of estradiol in plasma after oral administration is influenced by a large pool of circulating estrone sulfate and the back conversion of estrone sulfate to estrone and estradiol, the Division requests the Sponsor to add the mean PK parameters of estrone sulfate to Table 1 in Section 12.3 of the Sponsor's proposed label.*

Chongwoo Yu

8/14/2009

Reviewing Clinical Pharmacologist

Date

Myong Jin Kim

8/14/2009

Team Leader/Supervisor

Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memo

Clinical Pharmacology Review

NDA: 22-252
Compound: Qlaira™ (Estradiol Valerate [EV] / Dienogest [DNG])
Sponsor: Bayer Healthcare Pharmaceuticals

Date: 8/14/2009
Reviewer: Chongwoo Yu, Ph.D.

Introduction:

This New Drug Application (NDA) for EV and DNG was submitted for the primary indication of prevention of pregnancy, and for the secondary indication of treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who choose to use an oral contraceptive (OC) as their method of contraception. The initial IND for this EV/DNG combined oral contraceptive (COC) was filed under IND 64,809 on November 17, 2004 for the indication of prevention of pregnancy. Subsequently, IND (b) (4) was submitted on (b) (4) for the treatment of dysfunctional uterine bleeding (DUB) in women desiring oral contraception.

The investigational product contains the two active substances, EV and DNG in combination or EV alone in a sequential application regimen, consisting of 4 phases with active tablets and one placebo phase. A blister pack of EV/DNG (28 film-coated tablets) contains in the following order:

- Cycle Days 1-2: EV 3 mg (dark yellow tablets)
- Cycle Days 3-7: EV 2 mg + DNG 2 mg (medium red tablets)
- Cycle Days 8-24: EV 2 mg and DNG 3 mg (light yellow tablets)
- Cycle Days 25-26: EV 1 mg (dark red tablets)
- Cycle Days 27-28: placebo (white tablets)

One film-coated tablet is to be taken daily for 28 consecutive days.

The investigational product Qlaira™ contains EV as estrogen component instead of ethinyl estradiol (EE). After intake, EV is rapidly hydrolyzed presystemically into 17β-estradiol, which is the major natural estrogen in humans, and valeric acid. Currently, EV is approved only as an injectable product (Delestrogen®) in the US (NDA 09-402, approved on July 15, 1954). The progestogenic component of Qlaira™, the 19-norprogesterone DNG, is currently marketed in combination with EE as combined oral contraceptive (COC; such as Valette®) and in combination with EV as hormonal therapy (HT) such as Climodien® 2/2 in several European and non-European countries. DNG is considered to be a new molecular entity (NME) in the US.

Qlaira™ will provide the first COC containing EV instead of EE in the US. The Qlaira™ tablets are currently approved for marketing in 26 European Union Member Countries (initial approval on November 3, 2008) and Australia for the indication prevention of pregnancy. Introduction into the market under the trade name Qlaira® occurred in May 2009 in some of these countries. Another DNG-containing COC (with EE) was initially approved on February 14, 1995 in Germany under the trade name Valette®. This product has subsequently been approved in 36 countries and is marketed in 20 countries. In all countries except Australia, it is marketed as 21 tablets containing EE 0.03 mg and DNG 2 mg (7 of 28 days are tablet-free); in Australia it is marketed as 21 active tablets plus 7 placebo tablets. EV and/or DNG are also marketed for indications other than the prevention of pregnancy (e.g., Climodien®: EV 2 mg / DNG 2 mg, 28 tablets) outside of US.

The clinical development program of combined EV and DNG for OC has led to a regimen consisting of 4 active phases, each phase containing different doses of EV, either alone or in combination with different doses of DNG. This sequence is followed by 2 days with placebo tablets. The 4-phasic sequential regimen is aimed at ensuring sufficient estrogen levels in the first half of the cycle, the period during which endometrial proliferation is promoted under the influence of estrogens. In an extensive dose-finding process, it was decided by the Sponsor that a step-up combination of 5 days with EV 2 mg / DNG 2 mg followed by 17 days with EV 2 mg / DNG 3 mg is the lowest possible combination able to provide sufficient ovulation inhibition. The Sponsor believes that Qlaira™ provides endometrial stability and subsequently better cycle control compared to monophasic approaches can be obtained.

Sponsor's submission of proof of the clinical efficacy of Qlaira™ is based on the low number of pregnancies in 3 large clinical Phase 3 studies, i.e., Studies A39818 in North America and A35179 in Europe (pivotal Pearl Index studies) and A35644 (pivotal with regard to bleeding patterns and cycle control). Two pivotal Phase 3, double-blinded, placebo-controlled clinical studies (Studies A29849 in US and Canada and A42568 in Europe and Australia) were conducted to demonstrate the efficacy and safety for treating symptoms of DUB. The following Table gives an overview of the studies as part of the clinical pharmacology and biopharmaceutics development program of Qlaira™.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Study No. / Location	Short title	Volunteers included/ completed	Main objective
Bioavailability (BA) study reports			
A29972 / 5.3.1.1 A29972	Relative bioavailability EV/DNG tablets vs. suspension	36/35 p.m.	relative BA
A29143 / 5.3.1.1 A29143	Food effect study with 2 mg EV / 3 mg DNG tablets	38/35 p.m.	PK (effect of food)
BO08 / 5.3.1.1 BO08	Food effect study with DNG tablets	24/22 y.m.	PK (effect of food)
B501 / 5.3.1.1 B501	Absolute bioavailability of DNG	22/20 y.m.	PK (absol. BA)
AV69 / 5.3.1.1 AV69	Relative bioavailability of Climodien 2/2 and Climodien 2/3	19/18 p.m.	PK (relative BA)
Healthy volunteer pharmacokinetics (PK) and initial tolerability study reports			
A25711 / 5.3.3.1 A25711	Multiple dose PK study with EV/DNG tablets	18/16 y.f.	PK (multiple dosing)
B475 / 5.3.3.1 B475 B476* / 5.3.3.1 B476	PK of ³ H-labelled DNG after oral and i.v. administration of about 0.1 mg DNG	5/5 y.f.	PK (blood, plasma, urine, feces)
B478* / 5.3.3.1 B478	PK of ³ H-labelled DNG after oral administration of 0.1 mg/kg	6/6 y.f.	PK (plasma, urine, feces, metabolite profile)
B306 / 5.3.3.1 B306	Investigation on dose linearity of DNG PK	14/12 y.f.	PK (dose linearity)
B467* / 5.3.3.1 B467	Tolerability after single doses of 0.5 and 2 mg DNG	19/19 y.f.	Tolerability single dose
B276 / 5.3.3.1 B276	PK of DNG 2 mg after single and multiple dosing	16/16 y.f.	PK (single and multiple dosing)
B471 / 5.3.3.1 B471	PK of Climodien 2/3 (2 mg EV + 3 mg DNG) after single and multiple dosing	16/15 p.m.	PK (single and multiple dosing)
B472 / 5.3.3.1 B472	PK of Climodien 2/2 (2 mg EV + 2 mg DNG) after single and multiple dosing	16/15 p.m.	PK (single and multiple dosing)
*pre-Good Clinical Practice (GCP) study, #not all volunteers in these studies received DNG (in study A00681 (5.3.3.3 A00681), 18 volunteers received DNG and 6 placebo; in study B463 (5.3.3.4 B463), 12 volunteers received DNG and 13 LNG; in study B468 (5.3.4.1 B468) (transformation dose), 32 volunteers received DNG and 12 LNG y. = young, f. = female, m. = male, p.m. = postmenopausal			
Study No. / Location	Short title	Volunteers included/ completed	Main objective
Patient PK and initial tolerability study reports			
B469* / 5.3.3.2 B469	Tolerability of DNG in 24 endometrial cancer patients	24/24 f (mean age: 60)	Tolerability (21 days of treatment)
A04431 / 5.3.3.2 A04431	Effectiveness and tolerability of 20 mg DNG per day over 24 weeks in the treatment of endometriosis	20/21 y.f.	Tolerability multiple dose
Intrinsic factor PK study reports			
A00681 / 5.3.3.3 A00681	Tolerability and PK of a single oral dose of DNG in healthy adult Japanese females	24/24 y.f.# (Japanese)	Tolerability, PK (plasma, urine)
Extrinsic factor PK study reports			
AR34 / 5.3.3.4 AR34	Effect of EV on DNG PK	16/16 p.m.	PK (interaction)
A07769 / 5.3.3.4 A07769	Effect of DNG on EV PK	24/24 p.m.	PK (interaction)
A24058 / 5.3.3.4 A24058	Drug-drug interaction (DDI) study with CYP 3A4 inducer – rifampicin	16/16 p.m.	steady state PK (single and multiple dosing, interaction)
A30020 / 5.3.3.4 A30020	DDI study with CYP 3A4 inhibitors – ketoconazole and erythromycin	24/24 p.m.	steady state PK (single and multiple dosing, interaction)
B463 / 5.3.3.4 B463	Influence of 0.03 mg EE + 2 mg DNG and 0.03 mg EE + 0.125 mg levonorgestrel (LNG) on nifedipine PK	25/23 y.f.#	PK (single and multiple dosing, interaction)
Healthy volunteer pharmacodynamics and pharmacokinetics / pharmacodynamics study reports			
B468* / 5.3.4.1 B468	Determination of antigonadotropic activity and transformation dose of DNG	21/21 y.f. and 44/44 p.m.#	PD (antigonadotropic effect, endometrial effect)
A03128 / 5.3.4.1 A03128	Determination of the transformation dose of DNG	40/39 p.m.	PD (endometrial effect)
B470 / 5.3.4.1 B470	Determination of the ovulation inhibition dose of DNG	22/21 y.f.	PD (ovulation inhibition)
A02263 / 5.3.4.1 A02263	Pulsation pattern of gonadotropin secretion under DNG and DNG + EE	15/15 y.f.	PD (antigonadotropic effect)
*pre-Good Clinical Practice (GCP) study, #not all volunteers in these studies received DNG (in study A00681 (5.3.3.3 A00681), 18 volunteers received DNG and 6 placebo; in study B463 (5.3.3.4 B463), 12 volunteers received DNG and 13 LNG; in study B468 (5.3.4.1 B468) (transformation dose), 32 volunteers received DNG and 12 LNG y. = young, f. = female, m. = male, p.m. = postmenopausal			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Study No. / Location	Short title	Volunteers included/ completed	Main objective
Healthy volunteer pharmacodynamics and pharmacokinetics / pharmacodynamics study reports (cont'd)			
A00984 / 5.3.4.1 A00984	Inhibition of ovulation I - first approach regimen	22/21 y.f.	PD (ovulation inhibition)
A14191 / 5.3.4.1 A14191	Inhibition of ovulation II - first approach vs. modified regimen	192/176 y.f.	PD (ovulation inhibition)
A25364 / 5.3.4.1 A25364	Inhibition of ovulation III -EV/DNG tablets vs. DNG-increased regimen	203/185 y.f.	PD (ovulation inhibition)
A33022 / 5.3.4.1 A33022	Plasma lipids, hemostatic variables and carbohydrate metabolism (see section 2.7.4) PK over multiple treatment cycles (described here)	58/50 y.f. 24 analyzed for PK	PK of E1, E2 and DNG Effects on hormones, lipids, hemostasis (see section 2.7.4)
A38220 / 5.3.4.1 A38220	Hemostatic variables (see section 2.7.4)	29 / 26	Effects on hemostasis (see section 2.7.4)
B709 / 5.3.4.1 B709	Estrogenic effects of estradiol sulfamate in comparison to EE, EV and placebo	49/47 p.m.	PD (estrogenic activity of different estrogens)
A35653 / 5.3.4.1 A35653	Thorough QT study	53/40 p.m.	Effects on cardiac repolarization

y. = young, f. = female, m. = male, p.m. = postmenopausal

Drug Product Formulation:

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The Sponsor concludes that the *in vitro* dissolution data showed complete and comparable dissolution of all the formulations used. The composition of the TBM film-coated tablets is summarized in the Table below:

		SH T00658EA	SH T00658GA	SH T00658M	SH T00658HA	SH T00658P
(b) (4)	Estradiol valerate, (b) (4)	3.000 mg	2.000 mg	2.000 mg	1.000 mg	-
	Dienogest (b) (4)	-	2.000 mg	3.000 mg	-	-
	Lactose monohydrate	(b) (4)				
	Maize starch					
	Maize starch, pregelatinized					
	Povidone 25					
	Magnesium stearate					
(b) (4)	Hypromellose (b) (4)					
	Macrogol 6000					
	Titanium dioxide					
	Ferric oxide pigment yellow					
	Ferric oxide pigment red					
	Talc					
Total weight		83.000 mg	83.000 mg	83.00000 mg	83.0000 mg	82.0000 mg

Absorption

- EV: After oral administration, EV is completely absorbed. Cleavage to 17β estradiol and valeric acid takes place during absorption by the intestinal mucosa or in the course of the first liver passage. This gives rise to estradiol (E2) and its metabolites, estrone (E1) and estrone sulfate (E1S). Per Sponsor, Maximum serum E2 concentrations of 70.6 pg/mL are reached between 1.5 and 12 hours after single ingestion of a tablet containing EV 3 mg on Day 1 (Study A25711). In young women, the measured E2 plasma levels are a composite of the endogenous E2 and the E2 generated from Qlaira™. Per

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Sponsor, during the treatment phase of EV 2 mg and DNG 3 mg, maximum and average serum E2 concentrations at steady state are 66.0 pg/mL, and 51.6 pg/mL, respectively. Per Sponsor, stable minimum E2 concentrations were maintained throughout the 28-day cycle and ranged from 28.7 pg/mL to 64.7 pg/mL (Study A25711).

- DNG: Orally administered DNG is rapidly and almost completely absorbed. Per Sponsor, maximum serum concentrations of 90.5 ng/mL are reached at about 1 hour after single oral administration of a QlairaTM tablet containing EV 2 mg / DNG 3 mg (Study A29972) and bioavailability is about 91% (Study B501). The PK of DNG are dose-proportional within the dose range of 1-8 mg (Study B306). For DNG, steady state is reached after 3 days of the same dosage of DNG 3 mg in combination with 2 EV 2 mg. Trough, maximum and average DNG serum concentrations at steady state are 11.8 ng/mL, 82.9 ng/mL, and 33.7 ng/mL, respectively (Study A25711). The mean accumulation ratio for AUC_(0-24h) was determined to be 1.24 (Study B276).

Distribution

- EV: In serum, 38% of E2 is bound to SHBG, 60% to albumin and 2-3% circulates in free form. E2 can slightly induce the serum concentrations of SHBG in a dose dependent manner. Per Sponsor, on Day 21 of the treatment cycle, SHBG was approximately 148% of the baseline, and decreased to about 141% of the baseline by the end of placebo phase, Day 28 (Study A25711). An apparent volume of distribution of approximately 1.2 L/kg was determined after IV administration.
- DNG: A relatively high fraction (10%) of circulating DNG is present in the free form, with approximately 90% being bound non-specifically to albumin. Per Sponsor, DNG does not bind to the specific transport proteins SHBG and CBG (Study B427). The Sponsor believes that any influence on physiological transport processes for endogenous steroids is consequently unlikely. The volume of distribution at steady state ($V_{d,ss}$) of DNG is 46 l after the intravenous administration of 85 µg 3H-dienogest.

Metabolism

- EV: After oral administration, approximately 3% of the dose is directly bioavailable as E2. E2 undergoes an extensive first-pass effect and a considerable part of the dose administered is already metabolized in the gastrointestinal mucosa. Together with the pre-systemic metabolism in the liver, about 95 % of the orally administered dose becomes metabolized before entering the systemic circulation. The main metabolites are E1 and E1S.
- DNG: Per Sponsor, DNG is nearly completely metabolized by the known pathways of steroid metabolism (hydroxylation, conjugation) (Studies B478 and B455), with the formation of endocrinologically mostly inactive metabolites. The metabolites are excreted very quickly so that in plasma unchanged DNG is the dominating fraction (Study B478). The total clearance following the intravenous administration of 3H-dienogest was calculated as 5.4 L/h (Study B478).

Excretion

- EV: The plasma half-life of circulating E2 is about 90 min. After oral administration, however, the situation differs. Because of the large circulating pool of ES, as well as enterohepatic recirculation, the terminal half-life of E2 after oral administration represents a composite parameter which is dependent on all of these processes and is in the range of about 13-20 hours. E2 and its metabolites are mainly excreted in urine, with about 10% being excreted in the feces.
- DNG: Per Sponsor, the plasma half-life of DNG is approximately 11 hours (Study A25711). DNG is excreted in the form of metabolites which are excreted at a urinary to fecal ratio of about 3:1 after oral administration of 0.1 mg/kg. Following oral administration, 42% of the dose is eliminated within the first 24 hours and 63% within 6 days by renal excretion. A combined 86% of the dose is excreted by urine and feces after 6 days (Study B478).

Drug-Drug Interactions:

Effects of Other Drugs on Combined Hormonal Contraceptives

DNG is a substrate of cytochrome P450 (CYP) 3A4. Interactions can occur with drugs that induce CYP enzymes which can result in increased clearance of sex hormones. The effect of the CYP 3A4 inducer rifampicin was studied in healthy postmenopausal women. Per Sponsor, coadministration of 600 mg rifampicin daily with EV 2 mg / DNG 3 mg tablets led to significant decreases in steady state concentrations and systemic exposures to DNG and E2 (Study A24058). CYP3A4 inhibitors may increase plasma levels of DNG. In a study investigating the effect of CYP 3A4 inhibitors (400 mg ketoconazole daily or 1500 mg erythromycin daily), the Sponsor concludes that steady state AUC_(0-24h) DNG and E2 plasma levels were increased (Study A30020).

Effects of Combined Hormonal Contraceptives on other Drugs

The Sponsor has submitted information/data in support of their following conclusions: *In vitro* studies with human CYP enzymes did not indicate an inhibitory potential of DNG at clinically relevant concentrations (Study B482). Combined administration of DNG 2 mg together with EV 2 mg has no effect on DNG 2 mg PK (Study AR34). The same holds true for EV, whereby combined administration of EV 4 mg together with DNG 4 mg has no effect on EV 4 mg PK (Study A07769). The Division has agreed that no additional drug-drug interaction (DDI) studies are required to investigate the potential drug interactions between DNG and EV. Reference is made to the minutes of the pre-IND meeting held on March 17, 2004.

Specific Population and Waivers:

- Renal / hepatic impairment patients: The Sponsor has provided acceptable justification for not conducting studies in renal and/or hepatic impaired patients for use of EV/DNG in premenopausal women. If and when approved, appropriate language for renal and/or hepatic impairment will be included in the product label at the time of approval. Reference is made to the letter that the Division sent to the Sponsor on June 15, 2005. The Sponsor believes that no special risk for these patients is to

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be expected, because EV is transformed into the natural 17 β -estradiol, which is also produced endogenously in the target population and because DNG is metabolized before excretion and its metabolites are pharmacologically inactive. Furthermore, DNG was shown to be safe in clinical use up to doses of 20 mg/day over 6 months per Sponsor (Study A04431).

- Liver impaired patients: No studies were performed in patients with impaired liver function because severe liver diseases are already considered as contraindication for COCs.
- Pediatric Study waiver request: No studies were performed in children because Qlaira™ is not indicated before menarche. The Sponsor requests a full waiver from the requirement to submit data adequate to assess the safety and efficacy of EV and DNG in all relevant pediatric subpopulations.

Food Effect:

Per Sponsor, PK of DNG when given as a tablet containing DNG 2 mg was not affected by concomitant intake of a high-fat meal (Study BO08). The effect of concomitant food intake on the PK of EV and DNG was investigated in Study A29143 using the tablet containing EV 2 mg / DNG 3 mg, as a representative tablet of Qlaira™. The Division has agreed to this approach of using one dose (EV 2 mg / DNG 3 mg) to be sufficient for investigation of food-effect as this tablet contains the highest amount of DNG in any of the tablets included in Qlaira™. Reference is made to the minutes of the pre-IND meeting held on March 17, 2004. In this food effect study in healthy postmenopausal women, the C_{max} of DNG was decreased by 28% under fed conditions and the C_{max} of E2 was increased by 23% while AUC values for both DNG and E2 remained unchanged. The Sponsor concludes that Qlaira™ tablets can be taken without regard to meals during all phases of the Qlaira™ regimen. The Sponsor believes that this is further supported by the fact that all of the clinical trials with the Qlaira™ tablets were performed without any restrictions concerning food intake and that the clinical efficacy and safety of the drug was demonstrated in these clinical studies. Therefore, no special recommendation concerning food intake is considered to be necessary by Sponsor regarding the patient information. The Sponsor proposes the following language on the label: (b) (4)

Thorough QT Study

In study A35653, the potential effect of Qlaira™ to delay cardiac repolarization was investigated in healthy postmenopausal women. Placebo tablets, a fixed combination of EV 2 mg / DNG 3 mg and a supraphysiologic dose of DNG 10 mg (5 x 2 mg tablets, SHT00660AA) were given once-a-day over a period of 4 days. For the active treatments with DNG, no QT/QTc prolongation was observed. As expected, the positive control moxifloxacin showed a clear QTcF prolongation from time points 30 minutes up to 24 hours post-treatment.

Bioanalytical Method validation:

Validated analytical methods were used in the *in vivo* studies. A radioimmunoassay (RIA) was used for the quantitation of DNG in serum or plasma. This RIA was cross-validated using liquid chromatography - mass spectrometry (LC-MS). All of the PK studies performed during the development of Qlaira™ tablets have used the RIA method for the measurement of DNG in human serum. For the quantitation of E2, E1, and E1S, a validated liquid chromatography – tandem mass spectrometry (LC-MS/MS) method was used. Bioanalytical method validation reports are submitted for review.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 22-252 is fileable.

Comments for the Sponsor:

- Given that the time course of estradiol in plasma after oral administration is influenced by a large pool of circulating estrone sulfate and the back conversion of estrone sulfate to estrone and estradiol, the Division requests the Sponsor to add the mean PK parameters of estrone sulfate to Table 1 in Section 12.3 of the Sponsor's proposed label.

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<i>Office of Clinical Pharmacology</i> <i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA Number	22-252	Brand Name	Qlaira	
OCP Division	DCP3	Generic Name	Estradiol Valerate / Dienogest	
Medical Division	DRUP	Drug Class	Combination oral contraceptive (COC)	
OCP Reviewer	Chongwoo Yu, Ph.D	Indication(s)	Primary: prevention of pregnancy Secondary: treatment of heavy and/or prolonged menstrual bleeding	
OCP Team Leader	Myong Jin Kim, Pharm. D.	Dosage Form	Immediate release (IR) film-coated tablets	
Secondary Reviewer	Myong Jin Kim, Pharm. D.	Dosing Regimen	Once daily 4-phasic (plus placebo phase), 28 day, sequential regimen	
Date of Submission	July 2, 2009	Route of Administration	Oral	
Estimated Due Date of OCP Review	March 2, 2010	Sponsor	Bayer Healthcare Pharmaceuticals	
PDUFA Due Date	May 2, 2010	Priority Classification	Standard	
Division Due Date	April 11, 2010			
<u>Clin. Pharm. and Biopharm. Information</u>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	4		B473, A12603, A37060, A37059
I. Clinical Pharmacology				
Mass balance:	X	3		B475, B476, B478
Isozyme characterization:	X	1		A00680
Blood/plasma ratio:	X	1		A00560
Plasma protein binding:	X	1		A00560
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	X	4		A25711, B276, B471, B472,
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		B306
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		A24058, A30020
In-vivo effects of primary drug:	X	3		AR34, A07769, B463
In-vitro:	X	2		B482, A05426
Subpopulation studies -				

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ethnicity:	X	1		A00681
gender:				
pediatrics:	NA			Pediatric waiver request
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:	X	5		B468, A03128, B470, A02263, B709
Phase 2:	X	3		A00984, A14191, A25364
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		A33022
Phase 3 clinical trial:				
Population Analyses -				
PK:				
PD:				
II. Biopharmaceutics				
Absolute bioavailability:	X	1		B501
Relative bioavailability -				
solution as reference:	X	2		A29972, AV69
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		A29143, BO08
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Immunogenicity profile				
Thorough QT study	X	1		A35653
Literature References	X	14		
Total Number of Studies		52		
Other comments				
	Comments			
QBR questions (key issues to be considered)	<ol style="list-style-type: none"> 1. Dosing regimen 2. Drug-drug interaction potential 3. Food effect 4. Specific population 5. Thorough QT 6. Acceptability of the pediatric waiver request 7. Sufficient bioanalytical assay validation information? 8. Acceptability of the in vitro dissolution comparison between formulations 			
Other comments or information not included above	<ol style="list-style-type: none"> 1. Given that the time course of estradiol in plasma after oral administration is influenced by a large pool of circulating estrone sulfate and the back conversion of estrone sulfate to estrone and estradiol, the Division requests the Sponsor to add the mean PK parameters of estrone sulfate to Table 1 in Section 12.3 of the Sponsor's proposed label. 			

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/s/

CHONGWOO YU
09/11/2009

MYONG JIN KIM
09/11/2009