

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-090

CLINICAL PHARMACOLOGY and
BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

Submission Date: May 7, 1999
Div. Goal Date: February 22, 2000 (10-month due date: 3/07/2000)
NDA: 21090 (BB submissions: 5/12/99, 7/1/99, 10/28/99, 12/15/99, 12/27/99, 1/6/2000, 2/7/2000)
Related NDAs and INDs: N20713 (Mircette®), _____, N20071 (Desogen®) I32483, _____, _____
Drug: CTR77 (Cyclessa®), triphasic oral contraceptive; combination of desogestrel (DSG) and ethinyl estradiol (EE)
Sponsor: Organon INC.
Indication: Oral contraceptive
Type of Submission, Code: Original NDA 3S
Reviewer: Soraya Madani, Ph.D.

1 Synopsis

NDA 21-090 for CTR 77 (Cyclessa) was submitted to FDA by Organon, Inc. on May 7, 1999. The proposed indication for CTR77 is oral contraception. CTR 77 tablets provide 28-day oral contraception in triphasic regimen consisting of 7 light yellow tablets of 100 µg desogestrel (DSG)/ 25µg ethinyl estradiol (EE) (Days 1-7), 7 orange tablets of 125 µg DSG/ 25 µg EE (Days 8-14), 7 red tablets of 150 µg DSG/ 25 µg EE (Days 15-21) and 7 green placebo tablets (Days 22-28).

Desogestrel (DSG) and ethinyl estradiol (EE) are the main two drug components of CTR 77. They are currently approved in combination for use in oral contraception and are marketed in the US under the trade names Desogen®, Mircette™, Ortho-Cept 21® and Ortho-Cept 28®. These products are different in their dosing regimen.

For the indication of oral contraception, in addition to NDA 21090, _____ CTR 99 also contains DSG and EE; the differences are highlighted in the following table. The section of Clinical Pharmacology and Biopharmaceutics of these two NDAs are reviewed simultaneously by this reviewer. Although there are overlapping issues for these two NDAs, separate reviews are written for each.

CTR-77		
Days	DSG Dose (mg)	EE Dose (mg)
1-7	0.100	0.025
8-14	0.125	0.025
15-21	0.150	0.025
22-28	Placebo	Placebo

To support the approval of CTR77 sponsor has submitted two Phase III clinical studies (92001 and 92002). In addition, 3 relative bioavailability studies in healthy volunteers are included in the NDA. Those are:

92005 Relative BA study at lowest dose.....
 92006 Relative BA study at highest dose.....
 92004 Steady-State study with the proposed dosing regimen.....

There are differences between the to-be-marketed and clinical trials formulations, and the sponsor is requesting a bioequivalence (BE) waiver. In addition, the sponsor is requesting a waiver for the relative bioavailability (BA) study for the middle strength (125 µg DSG/ 25 µg EE) tablet. The requests for BA and BE waivers are addressed by comparison of the in vitro dissolution profiles. Based on the submitted data, this office grants both BA and BE waiver for CTR 77.

Desogestrel the progestin component of CTR 77 is extensively metabolized to its active metabolite, 3-keto-desogestrel (or etonogestrel, ENG), during first-pass, leading to undetectable DSG plasma concentrations. Therefore, with respect to pharmacokinetics, throughout the NDA, the sponsor makes reference to ENG and not DSG.

The sponsor has not performed studies that address drug-drug interaction, food-drug interaction or special population, i.e., hepatically and renally impaired individuals. Some of these issues are dealt with in the label (see Recommendation section).

Question Based Review (QBR) approach was taken in the review of this NDA and the review section is provided on p. 1-21. Study synopses, package insert (label) and the Figures are provided as attachments. Please note that the Study synopsis section is provided electronically by the sponsor and therefore, the conclusion remarks in that section are those of the sponsor. The review, however, reflects this reviewer's conclusions based on the sponsor's submitted results.

2 Recommendation

NDA 21090 submitted on May 7, 1999, has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II). This office finds NDA 21090 acceptable and based on the review of the submitted in vitro dissolution comparison data, OCPB/DPE2 has decided to grant the sponsors' request of the BA and BE waivers (see Biowaiver section).

However, the OCPB/DPEII has the following recommendations for the sponsor:

- **In Vitro Dissolution Specification:**

Based on the review of in vitro dissolution profiles provided in the Biopharm. section (reviewed by this reviewer) as well as Stability data provided in the CMC section (reviewed by Dr. Al-Hakim, Chemistry reviewer), it is decided that the current dissolution specifications are too wide. To assure the quality control and consistency between batches, this office recommends the sponsor to tighten the in vitro specifications to:

Sponsor proposal	FDA recommendation
Not less than $Q=$ — (Q) of the labeled amount dissolved in 30 minutes	Not less than $Q=$ — (Q) of the labeled amount dissolved in 15 minutes

In a T-Con with the sponsor on March 2, 2000, it was mutually agreed that release specification will be changed to $Q=$ — in 15 minutes (FDA recommendation). However, the stability specifications will remain as $Q=$ — in 30 minutes until more data is submitted (see the

attached report). Since the stability issue is a Chemistry review issue, for more details see Dr. Al-Hakim's review, the Chemistry reviewer.

- **Label:**

Further clarification is recommended in the label. The recommended label modifications are in two sections of the label, **CLINICAL PHARMACOLOGY** and **PRECAUTION sections**. For details, please see the label attachment.

The suggested recommendations in the label were communicated to the sponsor on Feb 18, 2000.

- **Drug-Drug interaction:**

(see label).

 / S / 3/3/2000

Soraya Madani, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by Ameeta Parekh, Ph.D., Team Leader
FT signed by Ameeta Parekh, Ph.D., Team Leader

 / S / 3/3/00

cc:

NDA 21-090

HFD-870 (M. Chen, S. Huang, A. Parekh, S. Madani)

HFD-580 (J. Mercier, D. Davis, B. Gierhart, S. Allen)

CDR (Barbara Murphy for Drug)

**APPEARS THIS WAY
ON ORIGINAL**

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3 List of Abbreviations

ANOVA	Analysis of Variance
AUC _{0-∞}	Area Under the Concentration Versus Time Curve - 0 hr to Infinity
AUC ₀₋₂₄	Area Under the Concentration Versus Time Curve - 0 to 24 hours
AUC _{0-tfix}	Area Under the Concentration Versus Time from zero to the last common measurable data point
C	Centigrade, Celsius
C _{av}	Average Serum Drug Concentration
CHD	Coronary Heart Disease
C.I.	Confidence Interval
CL	Apparent Clearance
C _{max}	Maximum Serum Drug Concentration
C _{ss,min}	Minimum Steady State Serum Concentration
CTR 77	The Triphasic OC Under Study
C.V.	Coefficient of Variation
d	Day
DF	Degree of Fluctuation (%)
DSG	Desogestrel (Org 2969)
EE	Ethinyl Estradiol (Org 224)
ENG	Etonogestrel (3-keto-desogestrel) - Active metabolite of DSG (Org3236)
F	Relative Bioavailability
FDA	Food and Drug Administration
F _{tr}	Truncated Relative Bioavailability
f ₂	Similarity Factor
GC	Gas Chromatography
GCP	Good Clinical Practice
HPLC	High Performance Liquid Chromatography
hr	Hour
i.v.	Intravenous
kg	Kilogram
L	Liter
LOQ	Limit of Quantitation
L.S. Mean	Least Squares Mean
M	Males
Max	Maximum
mcg	Microgram
MD	Multiple Dose
mg	Milligram
min	Minutes
mL	Milliliter
N	Sample Size
n.a.	Not Applicable
n-AUC ₀₋₂₄	AUC Normalized to 1 mcg Administered
n.c.	Not Calculated
n-C _{av}	Average Serum Drug Concentration Normalized to 1 mcg Administered
n-C _{max}	The C _{max} Normalized to 1 mcg Administered
n-C _{ss,min}	Minimum Steady State Serum Drug Concentration Normalized to 1 mcg Administered

N.D.	Not Done
NDA	New Drug Application
NF	National Formulary
ng	Nanogram
OC	Oral Contraceptive
Org 224	Ethinyl Estradiol (EE)
Org 2969	Desogestrel (DSG)
Org 3236	3-keto-desogestrel (etonogestrel, ENG)
Pg	Page
p value	Probability
RIA	Radioimmunoassay
rpm	Revolutions Per Minute
SAS	Statistical Analysis System
SD	Standard Deviation, Single Dose
SE	Standard Error
SHBG	Sex Hormone-Binding Globulin
SUPAC IR form	Scale-Up and Post-Approval Changes Immediate Release Solid Oral Dosage
t_{max}	Time at Which maximum Serum Drug Concentration Occurs
$t_{1/2}$	Elimination Half-Life
μg	Microgram, mcg
USAN	United States Adopted Name
USP	United States Pharmacopoeia

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4 Background

- **What chemical and therapeutic class CTR 77 belongs to? Are there other drugs on the market from this class?**
(Volume 3 and PDR)

Oral contraceptives (OC), one of the most common methods of birth control, often consist of two steroid components, estrogenic and progestogenic. Since their introduction to the market during the 1960s, changes have been made with respect to both components of OCs. Following the dose-dependent observations of venous thromboembolic events associated with estrogen component, the dose of ethinyl estradiol (EE), the most common estrogen used in OCs, has been reduced to 30-40 µg/day compared to 150 µg/day. Similarly, epidemiological reports later showed association of progestins with change in metabolism of certain lipid profiles related to increased risk of developing coronary heart disease (CHD). Initial efforts were made to reduce the progestin dose by the introduction of more potent progestins, e.g., levonorgestrel. However, even with the higher progestational activity and lower dose, the relative androgenicity of these progestins was shown to be associated with potentially negative changes in lipid metabolism parameters. Subsequently, a triphasic regimen was introduced which allowed a decrease in the overall dose by utilizing a varying dose of progestin during the consecutive phases of the cycle in an attempt to minimize the negative metabolic impact. In addition, newer progestins, like desogestrel (DSG), with lower androgenic activities were introduced to the market.

CTR 77 is consisted of desogestrel and ethinyl estradiol. Desogestrel, a prodrug, during the first-pass is almost completely metabolized to its metabolite, etonogestrel (ENG), the active progestin moiety. This leads to undetectable DSG concentration in the plasma and therefore, ENG is used for pharmacokinetic assessments instead of the parent drug, DSG.

Ethinyl estradiol is the most commonly used estrogen component of OCs. It is considered a medium extraction drug with large inter-individual variation of plasma concentrations.

Currently the following DSG and EE combination OCs are approved in the US market. **Mircette®** by Organon, Inc. (21 days of 150 µg DGS/20µg EE, 2 days of placebo and 5 days of 10 µg EE), **Desogen®** by Organon (21 days of 150 µg DGS/30µg EE and 7 days of placebo), **Ortho-Cept 21®** (21 days of 150 µg DGS/30µg EE), and **Ortho-Cept 28®** (21 days of 150 µg DGS/30µg EE and 7 days of placebo).

To further reduce the total dose of progestin per cycle, Organon, Inc. and the _____ combined the selective progestin DSG with a triphasic regimen. This triphasic preparation is known as CTR 77, and consists of the following dosing schedule and regimen:

CTR 77 Dosing Regimen		
Days	DSG Dose (mg)	EE Dose (mg)
1-7	0.100	0.025
8-14	0.125	0.025
15-21	0.150	0.025
22-28	Placebo	

5 Formulation

- **What formulation is being used in the pivotal clinical trial? Is it the same as the to-be-marketed? If not, is a bioequivalence study performed to compare the clinical formulation with the to-be-marketed formulation?**

(V.16, P. 52-76)

CTR77 is an immediate release oral capsule formulation. The three lots of drug product (R5729, R5730 and R5731) used in the clinical and bioavailability/pharmacokinetic studies (092-001, 092-002, 092-004, 092-005 and 092-006) were r _____

The commercial batches, however, are manufactured by another manufacturer, N.V. Organon. Table 1 compares the components and compositions of the three strengths of DSG/EE tablets used for the clinical formulations (_____) with the proposed marketed formulation (Organon).

Table 1 . Composition Statement of CTR 77 Clinical and Commercial Formulations

Manufacturer:	Organon Lot #	Organon Lot #	Organon Lot #
Lot Number:			
Ingredients (Color)	0.100/0.025 (15/1) yellow	0.125/0.025 (orange)	0.150/0.025 (red)
Core Composition (mg/tab.)			
Desogestrel	0.100	0.125	0.150
Ethinyl Estradiol, USP	0.025	0.025	0.025
Vitamin E _____, USP			
Stearic Acid, NF			
Pregelatinized Starch NF			
Lactose, Monohydrate (_____) (qs to 65)			

a = Removed during processing.

NP = Not present

Gary area is commercial formulation

The method of manufacture of a _____ Organon batch is based on the production process of _____ with the following differences:

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.

The sponsor considers these changes minor and addressed the issue by comparing the in vitro dissolution profiles of tablets manufactured at _____ with those by N.V. Organon (see In Vitro Dissolution Section).

6 Pharmacokinetics and Clinical Pharmacology

6.1 Mass balance, ADME, $F_{absolute}$ or $F_{relative}$

(Vol 3, Literature, IND 43-289 NIM-036, Vol. 17, 20, 23, 25 (191), 27, 30(167))

Absolute bioavailability of EE, DGS and ENG are not studied in this NDA and the sponsor makes no reference to the published literature or previous NDAs with that regard. The mass balance study was performed as a Phase 4 commitment for NDA 20-713 (Mircette®). For in vitro metabolism studies, sponsor makes reference to the reported studies in the literature as well as an unpublished manuscript. Dr. Wakelkamp has reviewed the information provided by the sponsor for both mass balance and in vitro metabolism. The following is this reviewer's review in light of Dr. Wakelkamp's review.

- *How are different pharmacologically active components of CTR77 (EE and ENG) eliminated and what are their disposition characteristics (distribution, metabolism and excretion)?*
- *Are there any active metabolites? How are they eliminated?*

Mass balance: Following a single oral dose of 150 µg of ¹⁴C-desogestrel plus 30 µg EE (as one capsule), urinary excretion accounted for 64% and fecal excretion accounted for 38% of total radioactivity (of DSG) after 18 days. The total radioactivity had a $t_{1/2}$ of 146 hours. In another single oral dose study total radioactivity of 150 µg of desogestrel plus 30 µg of ¹⁴C-EE (as one capsule) was measured. After 13 days, 55% of total radioactivity was recovered in the urine and 41% in the feces. The $t_{1/2}$ of the total radioactivity was estimated to be 34 hours.

Both of these studies have only measured the total radioactivity with no specific information on the routes of elimination of the parent drugs (EE and DSG) and/or the active metabolite (ENG). In addition the submitted report does not provide any information with respect to the extent of first pass metabolism and absorption of EE or DGS. This is because the plasma concentrations and excretion information from the total radioactivity is confounded by the kinetics of multiple metabolites. If the plasma concentration of the parent drug as well as the metabolites had each been measured, it could have provided us with valuable information on the extent of drug absorption. Moreover, proper mass balance study should be designed and analyzed to provide information on the route of elimination of the active moieties, being EE and ENG. The analysis of data as they stand provides limited information on absorption, metabolism and elimination of DSG : EE combination capsules. This makes any judgment of the effect of hepatic or renal impairment on the pharmacokinetics of CTR 77 very difficult.

In vitro metabolism: For in vitro metabolism of DSG the sponsor refers to two literature articles by Gentile et al. (1998)¹ and a manuscript². Both of the studies are performed in human liver microsomes. The results of these studies suggest that DSG is metabolized to 3 α -hydroxy-DSG and 3 β -hydroxy-DSG. Both these parallel pathways are mediated mainly via CYP2C9 with some contribution from CYP2C19. Both of these metabolites undergo very rapid sequential

¹ The role of CYP2C in the in vitro bioactivation of the contraceptive steroid desogestrel. J Pharmacol Exp Ther 1998 ; 287 : 975-982

² CYP3A4 is responsible for the metabolism of etonogestrel in vitro. Gentile et al. manuscript

oxidation to form the active metabolite, ENG (3-keto-DSG). 3-keto-DSG (etonogestrel, ENG) undergoes further metabolism mainly via CYP3A4.

Since desogestrol is metabolized to its active metabolite 3-keto-desogestrel (ENG), mostly via CYP2C9 (CYP2C19 a minor contributor) and given that both these enzymes are polymorphically expressed³; there is concerns with respect to CTR77 failing in women who are poor metabolizers of CYP2C enzymes (for CYP2C19: ~ 30% in Asian and 1% in Caucasians; for CYP2C9: ~ 1% in Asian and 6-9% in Caucasians). This issue was discussed with the Medical Officer Dr. Davis. His review of clinical trials indicates about 1% failures for CTR 77. However, since the individual subjects were not genotyped or phenotyped for CYP2C9, it is difficult to conclude if polymorphism was the underlying mechanism for the failures. One belief could be that the doses of DSG for CTR77 are high enough to overcome the low concentrations associated with polymorphism. This assumption is consistent with higher failure rates observed for CTR05, an OC combination with lower DSG dose (_____)

Similar situation can be faced when CTR77 is co-administered with inhibitors or other substrates of CYP2C9 (or maybe CYP2C19), this possibility is overlooked by the sponsor. However, the issue of drug interaction can be addressed by proper in vitro drug interaction studies (followed by in vivo drug interaction studies if appropriate) and/or by referencing literature data followed by appropriate warnings in the label.

For EE, the sponsor does not provide any metabolism information in the NDA. A brief survey of literature by this reviewer indicates that despite extensive use of this drug, metabolism of EE is not well characterized. Earlier in vivo human studies in the literature indicated that EE is mainly conjugated, mostly via sulfation and some glucuronidation. More recent in vitro studies in human liver microsomes suggest that EE undergo oxidation via P450 enzymes. The main enzyme is identified to be CYP3A4. The label addresses the issue of interaction with OC generally. Most of the drugs that may have clinically significant interaction with the EE component of CTR77 are listed in the proposed label.

Plasma protein binding: EE is mostly bound to albumin and to a lesser extent to SHBG. In contrast, ENG is extensively bound to SHBG.

Sex hormone-binding globulin (SHBG) is one of the carrier proteins that binds steroid hormones. As with several other carrier proteins, the rate of hepatic synthesis is increased by endogenous and synthetic estrogens. It is also known that synthetic progestins suppress the estrogen-induced increase in SHBG concentrations to varying degrees depending on the relative androgenicity of the particular progestin and the dose used. The sponsor has measured the degree of SHBG change for each study, under single dose and multiple-dose conditions (see 6.2 and 6.3 sections).

6.2 Single Dose

- **What are the concentration-time profile characteristics of EE and ENG after a SD and MD administration of oral CTR 77?**
- **Do C_{max} and AUC of EE and ENG increase proportionally with dose?**
- **Is there a relationship between dose (concentration) and effect or side effects?**

³ Genetic polymorphism of the CYP2C subfamily. Chiba K. Nippon Yakurigaku Zasshi 1998, 112(1) : 15-21

(vol. 23 and 27)

Bioavailability: The absolute bioavailability has not been studied for CTR77. However, the sponsor has performed three relative bioavailability studies. Study 092-005 examined the bioavailability of two 0.100 mg DSG/0.025 mg EE combination tablets compared with a combination oral solution, and Study 092-006 examined the bioavailability of the two 0.150 mg DSG/0.025 mg EE combination tablets compared with a combination oral solution. The sponsor indicates that based on the results of these studies and the comparative dissolution data submitted in this NDA, the FDA has agreed to consider a waiver of an in vivo bioavailability study for the intermediate dose (0.125 mg DSG/0.025 mg EE). The results of the in vitro dissolution comparison are reviewed in section 7 (and 7.1). Studies 092-005 and 092-006 examine the single dose relative bioavailability of the lowest and highest strength of the combination tablets included in CTR 77 (0.100 mg DSG/0.025 mg EE in 092-005 and 0.150 mg DSG/0.025 mg EE in 092-006). Two tablets or two aliquots of solution, for a total dose of 0.200 mg DSG + 0.050 mg EE (in study 092-005) and 0.300 mg DSG + 0.050 mg EE (in study 092-006), were administered. This was done in order to obtain adequate blood levels for measurement of both components for at least three half-lives (if only single tablet or single solution aliquot is administered, the sponsor expects inability to detect EE and ENG). Since DSG is rapidly converted to its active metabolite ENG (etonogestrel), relative bioavailability was assessed by measuring ENG serum concentrations rather than DSG concentrations. These two SD (single Dose) studies were open-labeled, randomized, cross-over and were performed in two consecutive menstrual cycles. The solution or tablets were given on days 2 to 7 of the cycle. Blood samples were collected up to 72 hours. Table 2 summarizes the PK results from these two studies. The sponsor did not measure renal clearance of ENG, DSG or EE.

Table 2. Mean PK parameter values for EE and ENG after single dose (92005 and -006) administration of (DGS/EE) tablets and solution.

Single dose studies

Study Number	Route	No. Anal.	Dose (mg)	C _{max} (pg/mL)	t _{max} (hr)	t _{1/2} (hr)	AUC ₀₋₂₄ (pg/mL*hr)	AUC _{0-inf} (pg/mL*hr)	Apparent CL (L/hr)	
092-005	oral	22	0.200 DSG (two 100 µg)	Tablet	2429.55	1.17	34.29	12875.99	17701.63	n.a.
				Solution	2095.91	1.34	34.62*	12686.88	18774.37*	n.a.
			0.050 EE (two 25 µg)	Tablet	144.95	1.26	14.90	1052.60	1498.34	n.a.
				Solution	165.67	1.12	14.45	1169.85	1614.88	n.a.
092-006	oral	22	0.300 DSG (two 150 µg)	Tablet	3161.82	1.37	33.76	17553.00	27817.69	n.a.
				Solution	3072.27	1.28	32.81	17442.29	27383.90	n.a.
			0.050 EE (two 25 µg)	Tablet	137.02	1.29	16.37	966.34	1310.64	n.a.
				Solution	149.13	1.19	17.12	973.84	1331.13	n.a.

a N=19

n.a. Not applicable

n.c. Not calculated

b N varies from 17-21 depending on parameter

In general, the mean relative bioavailability was greater than 95% for both studies. As shown in Table 2, for most PK parameters, the difference between tablet and solution was not statistically

significant at both high and low dose strengths. The exceptions are C_{max} and AUC_{0-inf} of EE, and only C_{max} of ENG, at the lower dose strength.

Comparing lower and higher strength tablets, for EE, the mean half-life was slightly longer (9%) at higher than lower strength (16.3 hrs vs., 14.9 hrs). Whereas, for ENG, this parameter is unchanged.

Since it is not easy to discern the amount of ENG formed (the dose) from DSG dose, the sponsor has not reported the values of the apparent clearance (in this case oral clearance) for ENG. The mean C_{max} and AUC_{0-inf} of ENG increased proportionally with increase in DSG dose. The same parameters slightly decreased for EE (5 and 14 % respectively).

It is this reviewer's opinion that unless _____ formulation versus the tablet formulation, the relative SD (Single Dose) bioavailability studies such as the ones that the sponsor has conducted, are not the most informative studies. An absolute F study or a more informative mass-balance study would have provided more valuable information with respect to the extent of absorption and first-pass metabolism as well as distributional characteristics of EE and DSG. However, sponsors often engage in these types of studies because according to 21 CFR 320.26 a SD in vivo bioavailability study should be designed to compare the drug product (in this case CTR 77 tablets) with a reference material (in this case CTR 77 solutions) in a crossover comparison in healthy volunteers.

SHBG concentrations were also measured in these two single dose studies. The measurements took place pre-dose and at the end of the study (after 3 days). At both higher and lower dose strengths, the change in the SHBG concentrations were considered clinically insignificant. The mean serum SHBG level (\pm SEM) decreased less than 5% in study 92005 (from 49.46 (\pm 4.51) nmol/L to 48.83 (\pm 3.67) nmol/L for tablets and from 44.79 (\pm 8.75) nmol/L to 42.56 (\pm 9.01) nmol/L for solution). This decrease was around 10% for the higher strength dose in study 92006 (mean serum SHBG level (\pm SEM) decreased from 73.10 (\pm 12.06) nmol/L to 66.94 (\pm 9.81) nmol/L for tablets and decreased from 51.21 (\pm 6.30) nmol/L to 45.80 (\pm 5.77) nmol/L for solution). The decreased in the SHBG concentration can mostly lead to an increase in the unbound concentration of ENG. Since ENG is not a narrow therapeutic index drug, less than 10% change in SHBG concentration is not expected to result in clinically significant increase in unbound ENG plasma concentration.

In summary, first-order kinetics was obeyed with respect to ENG concentrations for DSG dose range studied. In addition, after a single dose administration of CTR 77, the SHBG concentrations did not change significantly. This is to be expected since the SHBG changes are long term effects and can be better assessed after a multiple dose study under steady-state conditions rather than single dose study (see section 6.3).

6.3 Multiple Dose

- ***Does the active drug entities (EE and ENG) accumulate upon multiple dosing?***
- ***Is there an interaction between EE and DSG?***
- ***How is the SHBG profile changed after CTR77 is administered?***

(Vol 17)

Study 092004 was an open-label, single center, PK study of triphasic Combination OC, CTR77. Plasma concentrations of EE and ENG (the active metabolite of DSG) were measured during dosing phases 1-3 in twenty-one (n = 21) healthy 18-50 years old women. The study was conducted for 3 consecutive menstrual cycles. However, the blood samples were only obtained

during Cycle 3. The first objective of this study was to investigate whether during Cycle 3, for both EE and ENG, steady-state (SS) was reached within each dosing phase (1, 2, and 3). Achievement of steady-state per phase was determined via statistical analyses of pre-dose serum concentrations (trough concentrations). Blood samples were taken at 0 hour (pre-dose) for Day 1, 5, 6, 7, 12, 13, 14, 19, 20 and 21 of Cycle 3. On Day 7 (last day of phase 1) and 14 (last day of phase 2) multiple samples were taken up to 24 hours post-dosing and on Day 21 (last day of phase 3) multiple samples were taken up to 72 hours. Free testosterone and SHBG were measured on Days 1, 7, 14 and 21 at 0 hour (pre-dose). Since testosterone concentrations are associated with acne, sometimes sponsors monitor its plasma levels in subjects using OCs. However, no claims can be made based on testosterone measurements unless a separate clinical efficacy study is performed for treatment of acne indication. Table 3 tabulates the mean and standard of deviation (SD) of PK parameters for EE and ENG at steady-state.

Table 3.

Parameter		Etonogestrel (ENG)			Ethinyl Estradiol (EE)		
		100/25 (Phase 1)	125/25 (Phase 2)	150/25 (Phase 3)	100/25 (Phase 1)	125/25 (Phase 2)	150/25 (Phase 3)
t_{max} (hr)	Mean	1.62	1.14	1.52	1.45	1.18	1.19
	SD	0.72	0.33	0.75	0.82	1.20	0.68
C_{max} (pg/mL)	Mean	2163.33	3241.50	3855.71	85.42	91.27	90.09
	SD	856.40	1296.53	1273.07	51.66	52.17	48.22
$C_{ss,min}$ (pg/mL)	Mean	525.83	815.17	1111.83	15.35	17.79	17.54
	SD	222.23	356.55	543.28	8.35	10.71	9.18
C_{av} (pg/mL)	Mean	816.70	1220.60	1603.70	27.54	30.22	29.44
	SD	313.95	442.79	650.03	12.02	16.12	13.70
DF (%), Fluctuation degree	Mean	212.38	211.98	191.86	252.83	246.71	248.10
	SD	84.45	85.43	104.66	89.76	69.05	91.13
$t_{1/2}$ (hr)	Mean	n.a.	n.a.	37.09	n.a.	n.a.	28.23
	SD	n.a.	n.a.	14.77	n.a.	n.a.	10.47
Apparent CL (L/hr)	Mean	6.11 (~0.1 L/min)	5.08 (~0.08 L/min)	4.64 (~0.08 L/min)	43.49 (~0.72 L/min)	41.74 (~0.7 L/min)	42.51 (~0.7 L/min)
	SD	2.26	1.89	1.63	15.00	15.45	18.70
n- C_{max} (pg/mL/ μ g)	Mean	21.63	25.93	25.70	3.42	3.65	3.60
	SD	8.56	10.37	8.49	2.07	2.09	1.93
n- AUC_{0-24} (pg.hr/mL/ μ g)	Mean	196.01	234.36	256.59	26.44	29.01	28.26
	SD	75.35	85.01	104.00	11.54	15.48	13.16

n.a. - not applicable

During dosing Phase 1 and dosing Phase 3 it was found that steady-state for ENG (active metabolite of DSG) was reached after 4 days of treatment; however, it took 5 days of treatment to achieve steady-state in dosing Phase 2. Achievement of steady-state for EE was reached after 4 days of treatment in all dosing phases. Table 4. summarizes the accumulation factor for ENG and EE, calculated by this reviewer. Using, mean ratio of C_{av} , C_{min} , C_{max} , and AUC_{0-24} of Day 21 to Day 7 at steady-state.

Table 4. Mean Ratios of Day 21/Day 7 during Cycle 3 under steady-State conditions

Parameter	EE	ENG
-----------	----	-----

C_{min}	1.14	2.11
C_{max}	1.05	1.78
C_{av}	1.06	1.96
n-AUC ₀₋₂₄	1.06	1.30
n- C_{max}	-	1.18
n- C_{min}	-	1.41
n- C_{av}	-	1.31

n- represents normalized for the dose

For ENG, the mean t_{1/2} values were similar in SD compared to MD study (34-37 hours). However, for EE the mean t_{1/2} was two-fold higher (14 hrs versus 28 hours) after MD compared to SD studies. The sponsor explains that the difference is due to longer sampling time for MD study compared to SD studies, making 28 hours a more accurate t_{1/2} for EE. Based on the mean values of PK parameters (C_{av} , C_{min} , C_{max} , AUC₀₋₂₄), the accumulation of EE is negligible. With respect to ENG, however, the mean apparent clearance decreased as DSG dose increased from Phase 1 to 3, indicating lack of dose proportionality for this progestin. This change is reflected in the dose normalized PK parameters (see Table 4).

Sex hormone binding globulin and total testosterone concentrations were examined to determine if the CTR 77 regimen induced changes in these parameters. This study found that mean serum SHBG concentrations increased from a mean baseline concentration of 127.15 nmol/L on Day 1 of Cycle 3 to 169.23 nmol/L on Day 21 (33% increase). While mean total testosterone decreased from a baseline concentration of 565.35 pg/mL on Day 1 of Cycle 3 to 420.24 pg/mL by Day 21 (34% decreased).

In summary, both EE and ENG reached SS within each phase in ≤ 5 days. The data indicated that increased DGS (reflected in increased ENG plasma concentrations) does not alter EE pharmacokinetics. In contrast, ENG plasma concentrations (C_{av} , C_{min} , C_{max} , AUC₀₋₂₄) increased non-proportionally as DSG dose increased. The sponsor makes no speculation for the mechanism behind these observations. One explanation could be that since ENG is metabolized by CYP3A4, saturation of this enzyme has led to the observed decrease in apparent clearance. This study also indicates that CTR77 regimen results in lowering total testosterone concentrations, which could be one of the reasons for less androgenicity associated with desgestrol.

6.4 Bioequivalence

- *Is the to be marketed formulation the same as clinical formulation?*
- *If not, has there been a study performed to establish the bioequivalence between the two formulations?*

(V.16)

As mentioned earlier under Formulation (section 5), except for a few minor changes in the coating of the tablets, the to be marketed formulation is the same as the clinical trial formulation. However, the manufacturing site and batch sizes are different. Based on the SUPAC IR guidance, the changes mentioned under Formulation section can be categorized as level 2 SUPAC changes. According to the guidance, the sponsor is not required to conduct a BE study but is required to complete dissolution profiles in multiple media. This issue is further discussed under In Vitro Dissolution section.

6.5 Special Population

- *How are the pharmacokinetic parameters of CTR77 different in renally and hepatically impaired individuals? Any dose adjustment is required?*

The sponsor has performed no studies in hepatically and renally impaired patients. Given that sponsor believes DGS is converted to the active progestine entity, ENG, almost completely during first-pass metabolism. And that both EE and ENG are known to undergo enterohepatic recycling, it is expected that the pharmacokinetics to be altered in individuals with liver disease. With respect to renally impaired, mass-balance indicates that about 64% of total DGS dose and 55% of total EE dose are excreted renally, respectively. Indicating that the renal impairment may effect the PK of CTR 77. However, these values represent renal elimination of multiple metabolites of EE and DSG. Therefore, only under the assumption that the free concentration of the active entities, EE and ENG are remained unchanged in the renally impaired patients, it is reasonable to expect that renal impairment would have insignificant effect the PK of CTR77.

In the absence of studies that address hepatic and renal impairment, the possibility of higher than expected plasma concentrations of EE and ENG and or DSG in these special populations needs to be communicated to prescriber in the label. This information needs to be included under CLINICAL PHARMACOLOGY as well as PRECAUTION sections (see label).

6.6 Dose-Response

- *What is the rationale for the selected dose? How is the response measured?*
- *What is the dose-response relationship?*
- *What are the side effects associated with this class of drugs? How does CTR77 compare with those?*

(No study submitted)

As mentioned earlier, the combination of EE and DSG as an OC under different trade names has long been marketed in the US (e.g. Desogen® and Mircette®) as well as European (eg. Marvelon® and Mercilon®) markets. The differences between these marketed brands comprise of 1) the difference in the regimen, and 2) the doses and ratios of EE and DSG with respect to each other. Obviously all these products have shown to be able to prevent pregnancy in their clinical trials. Therefore, it is difficult to establish a straightforward relationship between dose and efficacy for combination OC drugs such as CTR 77. That is why a Phase 2, dose-finding study is not conducted in this NDA. A better relationship maybe established between dose (and / or concentration) and side effects such as breast tenderness, headache, weight gain, and nausea. However, quantitative exploration of these types of relationships are absent in most OC combinations, and CTR77 is not an exception. Generally, women using OCs, vary in their extent and the type of side effects they experience. To accommodate patients, physicians shift to totally different OC combination or simply stay with the same combination (product line) but different regimen. From marketing point of view, sponsors try to market as many efficacious combination and regimens as possible to accommodate their customers, hoping they do not switch to another vendor. Therefore, new regimens and combinations are not necessarily superior or inferior to the ones already in the market. They simply provide additional choices for those, whom for not understood reasons, experience different side effects.

6.7 Drug Interaction

The sponsor has performed no in vivo and/or in vitro drug-drug interaction studies. Since both DSG and EE are extensively metabolized, there is potential for metabolic drug interaction. The nature of these interactions could be induction or inhibition of the metabolism. The former could result in lack of efficacy (for EE) and the latter could result in toxicity (for EE) or lack of efficacy (for DGS). Therefore, the issue of drug interaction should be addressed. One way of addressing this issue is to conduct screening in vitro drug interaction studies with different components of CTR 77, namely EE, DSG as well as ENG, the active progestin.

For EE, the sponsor can refer to the published literature to identify the clinically significant inducers and inhibitors. The sponsor has done so by including some of the most known interaction interactions with OCs in the Drug Interaction section of the label. However, published information for drug interaction with DSG and ENG is rare to non-existent. Inhibition of CYP2C9 (major enzyme) and CYP2C19 (the minor enzyme) can result in increased DSG plasma concentration and decreased in ENG, the active metabolite (progestin) plasma concentration. This could result in failure of CTR77 and/or may result in increased in toxicity associated with DGS. Similarly, inhibition of CYP3A4, the enzyme metabolizing ENG could result in clinically significant increased ENG plasma concentration. Although according to the Pharm/Tox reviewer Dr. Raheja, toxicity associated with DSG and ENG at the proposed doses is not an issue. However, the induction of CYP3A4 could lead to opposite effect, leading to lack of efficacy.

Literature data indicate that CYP2C family is induced by ethanol, barbiturates and rifampin to a small degree⁴. The same inducers cause more significant decreased in plasma concentrations of CYP3A4 substrates (ENG and EE both are CYP3A4 substrates).

The sponsor can conduct in vitro studies with inducers and inhibitors of CYP2C and CYP3A4 in order to acquire indication of such interactions. The sponsor can then further pursue the in vivo drug interaction studies utilizing in vitro results. The sponsor is strongly encouraged to carry appropriate drug interaction studies that provide important information to the prescriber as well as consumer of CTR77.

In the absence of any drug interaction studies, the label should reflect the possible drug interactions with any of the active components of CTR77 (see label).

6.8 Population Pharmacokinetics

Not performed.

7 In Vitro Drug Release

- ***What is the purpose of using this dissolution method and setting in vitro dissolution specification?***
- ***Are the proposed method and dissolution specs acceptable?***
- ***Did the sponsor use clinical or pharmacokinetic batches (lots) to establish dissolution specification***

(Volume 16)

⁴ Handbook of Drug Metabolism. Edited by T. Woolf. Marcel Dekker, INC. 1999

The in vitro dissolution studies serve two purposes for this NDA. To assure the quality control (QC) in the manufacturing batches as well as providing justification for BE and BA waiver. Table 4 summarizes the proposed dissolution methods and specifications for the 0.100 mg DSG/0.025 mg EE, 0.125 mg DSG/0.025 mg EE and the 0.150 mg DSG/0.025 mg EE tablets included in CTR 77:

Table 4. Proposed Dissolution Method and Specifications for Combination DSG / Ethinyl Estradiol Tablets in CTR 77

Apparatus:	USP XXIII Dissolution Apparatus 2 (Paddle Method)
Medium:	_____
Volume:	_____
Temperature:	37°C ± 0.5°C
Paddle Speed:	_____
Specification DSG:	Not less than _____ (Q) of the labeled amount dissolved in 30 minutes
Specification EE:	Not less than _____ (Q) of the labeled amount dissolved in 30 minutes

This in vitro dissolution method and specifications are similar to the ones used for approved drugs Mircette® (20 µg EE/ 150 µg DSG) and Desogen® (30 µg EE/ 150 µg DSG). The use of surfactant, _____ as a concern of this reviewer since it increases the rate of dissolution. However, the use of _____ surfactant is justified by the sponsor in multiple submissions (see Feb 16, 1999 letter, IND 45548 # 46 and Nov. 10, 1998 # 42). Therefore, since:

- the proposed method is already approved for similar doses of EE and DSG, and
- the sponsor by providing information on the development of the method has justified the use of _____, furthermore,
- the drug is rapidly absorbed in vivo (t_{max} =1.1-1.6 hrs), and is highly permeable but not very soluble,

This reviewer finds the proposed method acceptable. However, based on the review of in vitro dissolution profiles provided in the Biopharm. section (reviewed by this reviewer) as well as Stability data provided in the CMC section (reviewed by Dr. Al-Hakim), it is decided that the current dissolution specifications are too wide. To assure the quality control and consistency between batches, this office recommended the sponsor to tighten the in vitro specifications to:

Not less than _____ (Q) of the labeled amount dissolved in 15 minutes

In a telephone conferencing with the sponsor on March 2, 2000; the sponsor agreed to use FDA recommendation for batches used in the in vitro release tests.

7.1 Biowaiver

As mentioned under BE and Formulation sections the main differences between the clinical trial formulation and the to-be-marketed formulation are the manufacturer, the batch size and the coating. The _____ and the to-be-marketed is manufactured by _____. The method of manufacture of a _____ Organon batch is based on the _____ production process of _____ with the following differences:

1

Based on the SUPAC IR guidance, these changes fall under categories of Level 2 changes with respect to Manufacturing, Changes in Batch Size, Site Change, and Composition Change. According to the guidance, no bioequivalence study is required. However, multi-point dissolution should be performed in water, 0.1 N HCL, and USP buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the clinical and to-be-marketed formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until of drug from the drug product is dissolved or asymptote is reached.

However, the sponsor has in vitro dissolution profiles in a single medium (see Table 4). During an IND review, via a T-con on March 8, 1999 Dr. Venkat Jarugula informed the sponsor of the SUPAC IR requirement, comprising of comparison of the in vitro dissolution profiles of the two formulations in the multi-media. In response, the sponsor indicated that they are unable to comply with the SUPAC requirements because they no longer have any of the original clinical formulation tablets. Subsequent to FDA request, submission of in vitro dissolution profiles were submitted and reviewed by Dr. Jarugula. In his review dated March 24, 1999 (IND 45,548-# 046), Dr. Jarugula finds sponsor's dissolution study in a single medium (0.05% Sodium lauryl sulfate in water) acceptable and supportive of BE waiver for the following reasons:

- The film coating used in both to be marketed and clinical formulations are water soluble. The proposed change is only in the amount of coating and the core of tablet remains the same. Hence, it is unlikely that the dissolution behavior of the two formulation to be significantly different in different aqueous media.
- In addition, since the amount of coating is reduced in the to be marketed formulation, the dissolution rate is expected to be slightly higher (if any) dissolution rate than the clinical trial formulation.
- If at all there is a change in *in vitro* dissolution, which may translate into a change in exposure, it should be noted that this might not be a concern because higher doses of these drugs have been approved as oral contraceptives.

Comparative dissolution studies were performed on CTR 77 tablets manufactured at and N.V. Organon. The following tables represent comparison of dissolution profiles of clinical (R5729, R5730, R5731) batches and to-be-marketed (083659001, 083660001, 083661001) batches. These batches refer to the following doses of DSG µg/EE µg respectively, 100/25, 125/25, and 150/25. In addition to the table, the dissolution plots are provided in the Figure attachment.

Table 5. Results of DSG and EE, USP dissolution of clinical and to-be-marketed (t-b-m) batches (mean of 12 tablets). The C.V. : 1.2-4.5%. Units : % dissolution.

Batch #	15 min		30 min		45 min		60 min	
	DSG	EE	DSG	EE	DSG	EE	DSG	EE
R5729								
083659001								
R5730								

083660001
R5731
083661001

Table 6. Similarity factor (f_2) used for the dissolution comparison between different batches.

Clinical	t-b-m	EE μ g/ DSG μ g	f_2 DSG	f_2 EE
R5729	083659001	25/100		
R5730	083660001	25/125		
R5731	083661001	25/150		
Clinical Batches		EE μ g/ DSG μ g	f_2 DSG	f_2 EE
R5729	R5730	25/100 vs. 25/125		
R5730	R5731	25/125 vs. 25/150		
R5731	R5729	25/150 vs. 25/100		
t-b-m Batches		EE μ g/ DSG μ g	f_2 DSG	f_2 EE
083659001	083660001	25/100 vs. 25/125		
083660001	083661001	25/125 vs. 25/150		
083661001	083659001	25/150 vs. 25/100		

The review of the in vitro dissolution in 0.05% Sodium lauryl sulfate (SLS) and water as medium indicates that there is no significant difference in the percent of DSG or EE dissolved at 15, 30, 45 or 60 minutes between the two formulations of CTR 77 tablets. The dissolution profiles were also compared using an equation that defines a similarity factor (f_2), resulting in values ≥ 74 .

Based on the similarity of the in vitro dissolution profiles and the reasons mentioned earlier, this reviewer concurs with the Dr. Jarugula conclusion and does not see the utility of additional bioequivalence (BE) studies. In addition, since the dissolution profiles were comparable for all three strengths of the combination tablets, based on 21 CFR 320.22 (d) (2), the submitted information is found sufficient to support the waiver for the BA study of the intermediate dose (25 μ gEE/125 μ gDSG).

8 Analytical Methodology

- *Is the analytical method selective and sensitive?*
- *Is there a validation for all the molecular entities measured in this NDA, EE, DSG, and ENG?*
- *How important is the assay validation and why?*
- *What analytical method was used for measurement of SHBG concentrations?*

(Vol. 17, 23 and 27)

Each of the three relative bioavailability studies had assay validation included as part of the study report. The results are summarized in this section of the review.

The parent drug progestin (desogestrel, DSG) was not assayed in any of the studies. Etonogestrel (ENG) and ethinyl estradiol concentrations were assayed by radio-immunoassay after _____ SHBG serum concentrations were determined by radioimmunoassay. _____ performed all analyses. Table 7 outlines the assay validation results for each of these chemical species. **Table 7. ENG assay validation (N=62-64).**

Nominal Conc. pg/mL	90	270	1080
Accuracy (%)			
Intra-assay Precision (%CV)			
Inter-assay Precision (%CV)			
The lower limit of quantitation was set to —			
Calibration standards 30-1440 pg/ml			
The percent cross-reactivity for various analytes was < 0.3%.			

EE assay validation (N=54-58).

Nominal Conc. pg/mL			
Accuracy (%)			
Intra-assay Precision (%CV)			
Inter-assay Precision (%CV)			
The lower limit of quantitation was set to —			
Calibration standards 1-48 pg/ml			
The percent cross-reactivity for various analytes <0.6%.			

SHBG assay validation (N=5-6).

Nominal Conc. pmol/mL	30.8	76.5	153
Accuracy (%)			
Intra-assay Precision (%CV)			
Inter-assay Precision (%CV)			
The lower limit of quantitation was set to —			
Calibration standards 10-250 pmol/ml			
The percent cross-reactivity for various analytes is not reported.			

The results of the assay validations indicate the adequate sensitivity of the assays.

It is important to note that desogestrel was not measured in these studies. In cases where the prodrug undergoes extensive first-pass metabolism, the plasma concentrations are very low. Often sponsors find it unnecessary to obtain plasma concentration of the prodrugs and are not concerned with developing sensitive assays for these species. In cases where the prodrug can be toxic at low plasma concentrations, measuring its concentration becomes an essential task. Desogestrel is metabolized to ENG, the active progestin via CYP2C9. Since there is variability associated with level of activity and concentration of this enzyme in the liver, desogestrel concentrations can also be variable. In addition, due to drug interaction the concentration of desogestrel may change. These changes can be associated with unwanted side effects (due to increased parent conc.) or lead to lack of efficacy (due to decreased metabolite, ENG conc.). In this case of DSG, however, (based on the review of Dr. Raheja, the Pharm-Tox reviewer) toxicological studies indicate that toxicity is not an issue with this prodrug.

9 Figures Attachment

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Study 92005 (SD study of 25 µg EE/ 100 µg DSG)

Note: The EE serum concentration curves (tablets and solution) end at 48 hours; after 48 hours, the EE levels were below the lower limit of quantitation.

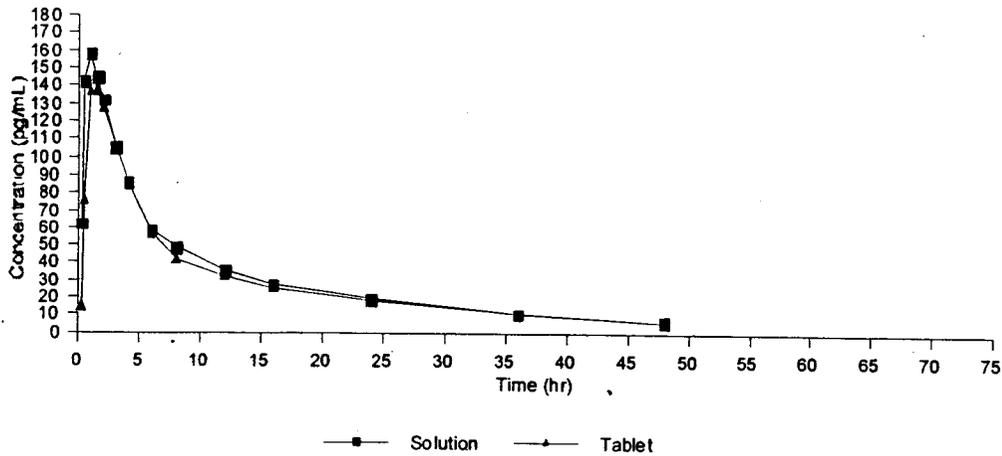
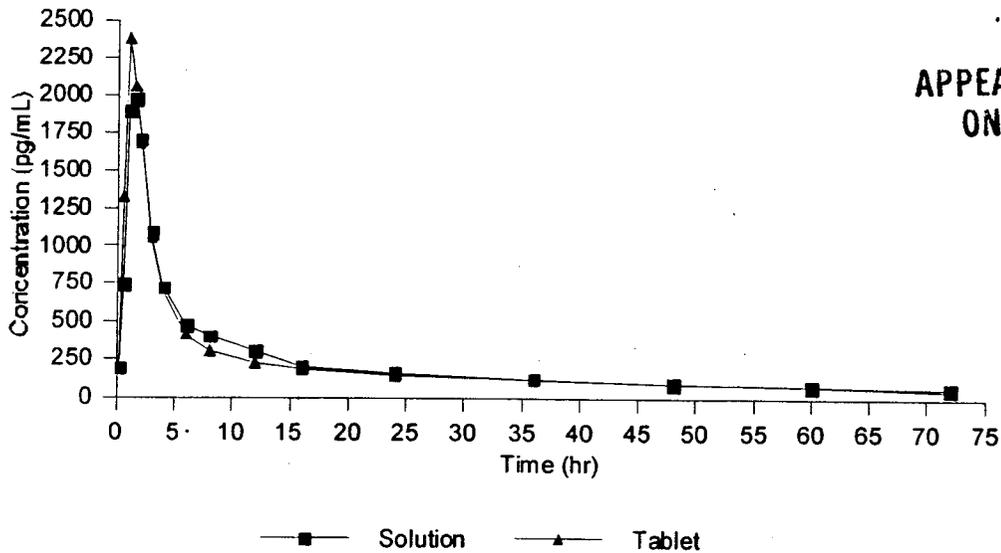


Figure 1. Mean Serum Concentration versus Time Curves for EE



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Figure 2. Mean Serum Concentration versus Time Curves for Etonogestrel, ENG.

Study 92006 (SD study of 25 µg EE/ 150 µg DSG)

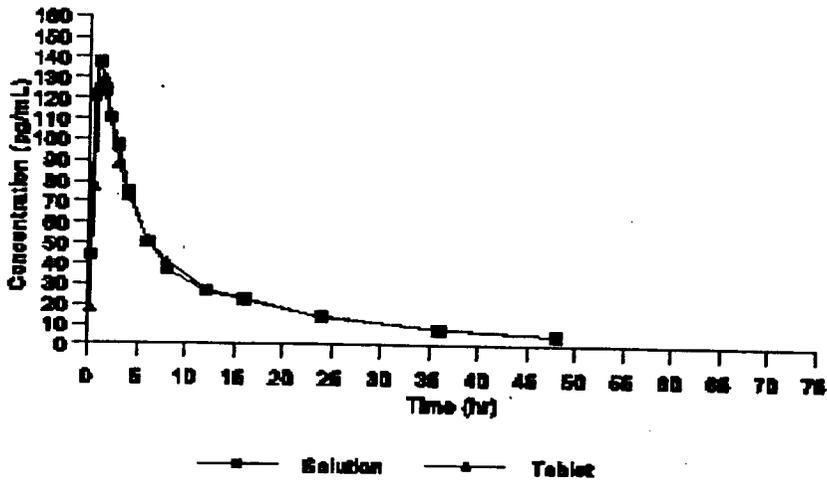
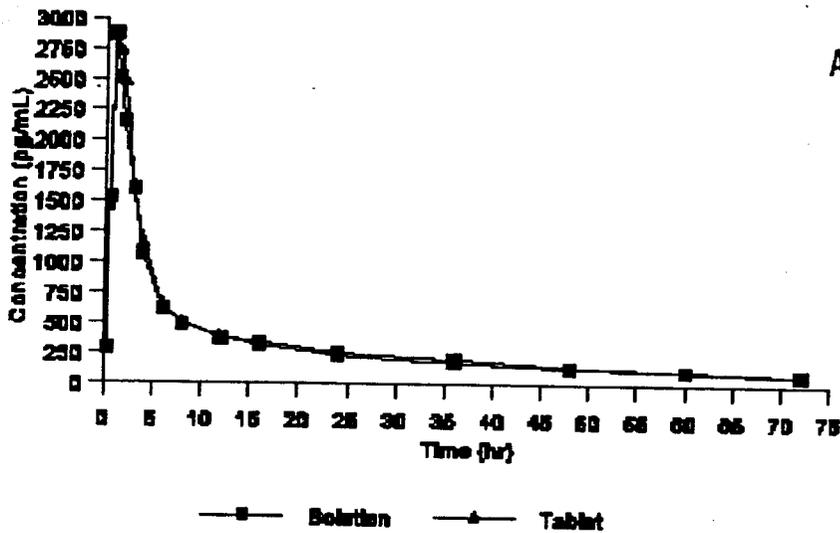


Figure 3. Mean Serum Concentration versus Time Curves for EE.



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Figure 4. Mean Serum Concentration versus Time Curves for Etonogestrel, ENG.

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WAS
DETERMINED
NOT
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| page

10 Study Synopsis Attachment

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Synopsis of individual studies

92005

Relative BA study at lowest dose

Title of the Study

A Single Dose, Randomized, Crossover Study Of The Bioavailability Of CTR 77 [0.100 mg Org 2969 (Desogestrel; DSG) + 0.025 mg EE] Relative To A Combination Solution.

Investigator

Study Center

Report/Publications

SDG Release Report 4742. There were no publications from this study.

Studied Period

June 26, 1995 - October 12, 1995

Clinical Phase

Phase I

Objective

The objective of this study was to determine the bioavailability of Org 2969 (desogestrel; DSG) and Org 224 (EE) in a 0.100 mg Org 2969 (desogestrel; DSG) plus 0.025 mg Org 224 (EE) CTR 77 tablet relative to a solution containing the same amount of Org 2969 (desogestrel; DSG) and Org 224 (EE).

Two tablets or two aliquots of solution, for a total dose of 0.200 mg Org 2969 + 0.050 mg Org 224, were administered in order to obtain adequate blood levels for measurement of both components for at least three half-lives. Since Org 2969 is rapidly converted to its active metabolite Org 3236 (etonogestrel), bioavailability was assessed by measuring Org 3236 serum concentrations rather than Org 2969 concentrations.

Methodology

Single-dose, open-label, randomized, 2-way crossover, single-site study.

Number of Subjects

Twenty-four subjects were enrolled. Twenty-two subjects completed the study and two subjects discontinued.

Diagnosis and Criteria for Inclusion

- Healthy non-smoking women in the age range of 18-50 years inclusive;
- Women who were willing to complete the entire study and observe all protocol requirements;
- Women who were willing to give voluntary informed (written) consent to participate in the study;
- Women who tested negative for drugs of abuse: cannabinoids, opiates, alcohol, cocaine, amphetamines, and benzodiazepines;
- Women who tested negative for human immunodeficiency virus (HIV) and Hepatitis B;
- Surgically sterile women, or women willing to use a non-hormonal barrier method of birth control; and
- Women who were willing to complete the Confidential Follow-up Form.

Test Product, Dose and Mode of Administration, Batch No.

- CTR 77 Tablets: Org 2969 (desogestrel) 0.100 mg/Org 224 (ethinyl estradiol) 0.025 mg
Dose: Single oral dose of two tablets Batch Number R5729

Duration of Treatment

One single dose in each of two consecutive cycles.

Reference Therapy, Dose and Mode of Administration, Batch No.

- CTR 77 Solution: Org 2969 (desogestrel) 0.100 mg/Org 224 (ethinyl estradiol) 0.025 mg
Dose: Single oral dose of two aliquots Batch Number CO.03.95/A-1

Criteria for Evaluation Based on Org 3236 (etonogestrel; active metabolite of Org 2969) and Org 224 (ethinyl estradiol) serum concentrations, the peak concentration (C_{max}) and its time of occurrence (t_{max}), the area under the serum-concentration-versus-time-curve ($AUC_{0-\infty}$), the area under the serum-concentration-versus-time-curve from time 0 to the last time for which all subjects had measurable concentrations ($AUC_{0-t_{fix}}$), the elimination half-life ($t_{1/2}$) and the relative bioavailability (F), based on ($AUC_{0-\infty}$) and truncated relative bioavailability (F_{tr}), based on ($AUC_{0-t_{fix}}$) were calculated.

The assessment of safety was based on the incidence of adverse experiences, changes in vital signs, laboratory parameters, physical examination findings (general medical, breast, and pelvic examinations), and pregnancy outcome.

Statistical Methods

For pharmacokinetic parameters, descriptive statistics for Org 224 and Org 3236 serum concentrations included mean concentrations by time, together with their standard deviation, minimum and maximum. An analysis of variance for cross-over design was performed on log-transformed (base e) data to test for treatment-, sequence-, and period effects and to estimate the intrasubject variability. For all parameters, except t_{max} , the 95% two-sided confidence interval was calculated for the true ratio "test tablet/reference solution" using the estimated intrasubject variability. For t_{max} , the 95% non-parametric confidence interval was calculated for the true difference "test tablet-reference solution." In particular, an appropriate estimate of the mean relative bioavailability (F) was the ratio of the geometric mean of $AUC_{0-\infty,t}$ and $AUC_{0-\infty,s}$. The same holds true for the mean F_{tr} , for which the ratio of the geometric mean of $AUC_{0-t_{fix,t}}$ and $AUC_{0-t_{fix,s}}$ was appropriate as an estimate.

Descriptive statistics for demographics, vital signs, laboratory parameters, and SHBG concentrations were computed. Adverse experiences were tabulated by system-organ class and preferred terms.

SUMMARY

Twenty-four healthy female volunteers were enrolled in this study. Two subjects discontinued: Subject 18 withdrew from the study prior to Cycle 2 due to the adverse experiences of nausea and vomiting; Subject 20 discontinued due to non-compliance. A total of twenty-two subjects completed all study assessments.

The mean relative bioavailability (F) of Org 3236 from the tablets was found to be 99% (CI: 89% - 110%). Estimation of F based on truncated AUC resulted in comparable values: 103% (CI: 94% - 113%). C_{max} for the tablets (2429.55 ± 726.41 pg/mL) was slightly higher than for the solution (2095.91 ± 685.29 pg/mL). $t_{1/2}$ (34.29 ± 10.56 hr and 34.62 ± 16.32 hr for tablets and solution, respectively) and t_{max} (1.17 ± 0.33 hr and 1.34 ± 0.36 hr, respectively) were similar for both treatments.

The mean relative bioavailability (F) of Org 224 (EE) from tablets as compared to the solution was 92% (CI: 85% - 99%). Estimation of F based on truncated AUC resulted in comparable values; F_{tr} was 89% (CI: 83% - 94%). With respect to the other parameters, tablets and solution were also comparable: peak serum concentration (C_{max}) for the tablets (144.95 ± 54.71 pg/mL) was slightly smaller than for the solution (165.67 ± 58.53 pg/mL); elimination half-life ($t_{1/2}$) [14.90 ± 4.25 hr and 14.45 ± 4.93 hr for tablets and solution, respectively] and time to peak serum concentration (t_{max}) [1.26 ± 0.37 hr and 1.12 ± 0.38 hr, respectively] were similar for the two treatments.

The mean serum sex hormone binding globulin (SHBG) level (\pm SEM) decreased from $49.46 (\pm 4.51)$ nmol/L to $48.83 (\pm 3.67)$ nmol/L for tablets and from $44.79 (\pm 8.75)$ nmol/L to $42.56 (\pm 9.01)$ nmol/L for solution, after single dose administration. These slight changes were not considered to be clinically significant.

A total of 21 subjects (87.5% of the All-Subjects-Treated Group, N=24) reported at least one adverse experience. Nineteen of the 21 subjects reported an AE that was considered by the investigator to be at least possibly study drug-related. The most frequently reported AEs were nausea, headache, vomiting, and abdominal pain. All of the AEs, with the exception of a severe headache in one subject (13), were classified as mild to moderate in intensity. One subject (18) withdrew from the study due to the adverse experiences of nausea and vomiting. No serious adverse experiences (SAEs) were reported.

A total of six subjects (1, 3, 4, 13, 15, and 18) experienced changes from normal at baseline (screening) to abnormal at last measurement for physical examination parameters (which included general medical, breast, and pelvic examinations).

For general medical parameters, Subjects 4 and 13 both had a change from normal at baseline to abnormal at last measurement for skin; breast scars from implants (Subject 4) and small sebaceous cyst on right axilla (Subject 13).

For breast examination parameters, Subject 3 had changes in breast masses from none at baseline to present (left mass) at last measurement. Additionally, Subject 3 had changes in breast nodularity; from none at baseline to mild nodularity (rated "+" on the CRF) of the right breast at the last measurement. In contrast, Subject 1, who was listed as having nodularity of the left breast at baseline, had a change to no nodularity at the last measurement. None of the subjects experienced changes in nipple contour, nipple discharge, or overlying skin from baseline to the last measurement.

For pelvic examination parameters, three subjects had changes from normal at baseline to abnormal at the last measurement for Cervix Uteri (Subjects 1 and 15, endocervical polyp; Subject 18, residual menstrual debris). Subject 3 had a change (tilted to right) in Corpus Uteri and Subject 1 was reported to have external rectal hemorrhoidal tags at the last measurement. No subjects experienced changes from normal at baseline to abnormal at last measurement for vagina, adnexa, or vulva.

There appeared to be no clinically significant changes in blood pressure, heart rate, respiratory rate, body temperature, or laboratory parameters.

No pregnancies were reported.

CONCLUSIONS

Both Org 224 and Org 3236 (active metabolite of Org 2969) are readily available when administered as a 0.100 mg Org 2969 plus 0.025 mg Org 224 tablet. The bioavailability based on $AUC_{0-\infty}$ of the tablet relative to a solution containing the same amount of Org 224 and Org 2969 is 92% and 99% for Org 224 and Org 3236, respectively. Based on the $AUC_{0-t_{fix}}$, the bioavailability is 89% and 103% for Org 224 and Org 3236, respectively. The tablet and the solution are similar with respect to t_{max} and $t_{1/2}$. For Org 224, C_{max} is lower after administration of the tablets whereas for Org 3236, C_{max} is lower after administration of the solution.

No serious adverse experiences were reported

**APPEARS THIS WAY
ON ORIGINAL**

92006

Relative BA study at highest dose

Title of the Study

A Single Dose, Randomized, Crossover Study Of The Bioavailability Of CTR 77 [0.150 mg Org 2969 (Desogestrel;DSG) + 0.025 mg EE] Relative To A Combination Solution.

Investigator

Study Center

Report/Publications

SDG Release Report 4626. There were no publications from this study.

Studied Period

June 28, 1995 - September 8, 1995

Clinical Phase

Phase I

Objective

The objective of this study was to determine the bioavailability of Org 2969 (desogestrel; DSG) and Org 224 (EE) in a 0.150 mg Org 2969 (desogestrel; DSG) plus 0.025 mg Org 224 (EE) CTR 77 tablet relative to a solution containing the same amount of Org 2969 (desogestrel; DSG) and Org 224 (EE).

Two tablets or two aliquots of solution, for a total dose of 0.300 mg Org 2969 + 0.050 mg Org 224, were administered in order to obtain adequate blood levels for measurement of both components for at least three half-lives. Since Org 2969 is rapidly converted to its active metabolite Org 3236 (etonogestrel), bioavailability was assessed by measuring Org 3236 serum concentrations rather than Org 2969 concentrations.

Methodology

Single-dose, open-label, randomized, 2-way crossover, single-site study.

Number of Subjects

Twenty-four subjects were enrolled. Twenty-two subjects completed the study and two subjects discontinued.

Diagnosis and Criteria for Inclusion

- Healthy non-smoking women in the age range of 18-50 years inclusive;
- Women who were willing to complete the entire study and observe all protocol requirements;
- Women who were willing to give voluntary informed (written) consent to participate in the study;
 - Women who tested negative for drugs of abuse: cannabinoids, opiates, alcohol, cocaine, amphetamines, and benzodiazepines;
 - Women who tested negative for human immunodeficiency virus (HIV) and Hepatitis B;
 - Surgically sterile women, or women willing to use a non-hormonal barrier method of birth control; and
 - Women who were willing to complete the Confidential Follow-up Form.

Test Product, Dose and Mode of Administration, Batch No.

CTR 77 Tablets: Org 2969 (desogestrel) 0.150 mg/Org 224 (ethinyl estradiol) 0.025 mg

Dose: Single oral dose of two tablets Batch Number R5731

Duration of Treatment

One single dose in each of two consecutive cycles.

Reference Therapy, Dose and Mode of Administration, Batch No.

CTR 77 Solution: Org 2969 (desogestrel) 0.150 mg/Org 224 (ethinyl estradiol) 0.025 mg

Dose: Single oral dose of two aliquots Batch Number CO.04.95/B-1

Criteria for Evaluation

Based on Org 3236 (etonogestrel; active metabolite of Org 2969) and Org 224 (ethinyl estradiol) serum concentrations, the peak concentration (C_{max}) and its time of occurrence (t_{max}), the area under the serum-concentration-versus-time-curve (AUC_0), the area under the serum-concentration-versus-time-curve from time 0 to the last time for which all subjects had measurable concentrations (AUC_{0-tfix}), the elimination half-life ($t_{1/2}$) and the relative bioavailability (F), based on (AUC_0) and truncated relative bioavailability (F_{tr}), based on (AUC_{0-tfix}) were calculated.

The assessment of safety was based on the incidence of adverse experiences, changes in vital signs, laboratory parameters, physical examination findings (general medical, breast, and pelvic examinations), and pregnancy outcome.

Statistical Methods

For pharmacokinetic parameters, descriptive statistics for Org 3236 and Org 224 serum concentrations included mean concentrations by time, standard deviation, minimum and maximum. An analysis of variance for cross-over design was performed on log-transformed (base e) data to test for treatment-, sequence-, and period effects and to estimate the intrasubject variability. For all parameters, except t_{max} , the 95% two-sided confidence interval was calculated for the true ratio "test tablet/reference solution" using the estimated intrasubject variability. For t_{max} , the 95% non-parametric confidence interval was calculated for the true difference "test tablet-reference solution." In particular, an appropriate estimate of the mean relative bioavailability (F) was the ratio of the geometric mean of AUC_{0-1} and AUC_{0-5} . The same holds true for the mean F_{tr} , for which the ratio of the geometric mean of $AUC_{0-tfix,1}$ and $AUC_{0-tfix,5}$ was appropriate as an estimate.

Descriptive statistics for demographics, vital signs, laboratory parameters, and SHBG concentrations were computed. Adverse experiences were tabulated by system-organ class and preferred terms.

SUMMARY

Twenty-four healthy female volunteers were enrolled in this study. Two subjects discontinued for personal reasons after receiving the first dose of study drug. A total of 22 subjects completed all study assessments.

The mean relative bioavailability (F) of Org 3236 (etonogestrel) from tablets as compared to the solution was 100% (CI: 88% - 114%). Estimation of F based on the truncated AUC resulted in comparable values; F_{tr} was 100% (CI: 90% - 110%). With respect to the other parameters, tablets and solution were also comparable: peak serum concentration (C_{max}) for the tablets (3161.82 ± 1037.23 pg/mL) was slightly higher than for the solution (3072.27 ± 1343.14 pg/mL); elimination half-life ($t_{1/2}$) for the tablets (33.76 ± 15.27 hr) was comparable to the solution (32.81 ± 11.04 hr); and time to peak serum concentration (t_{max}) for the tablets (1.37 ± 0.55 hr) was similar to the solution (1.28 ± 0.57 hr).

The mean relative bioavailability (F) of Org 224 (EE) from tablets as compared to the solution was 98% (CI: 90% - 106%). Estimation of F based on the truncated AUC resulted in comparable values; F_{tr} was 100% (CI: 93% - 108%). With respect to the other parameters, tablets and solution were also comparable: peak serum concentration (C_{max}) for the tablets (137.02 ± 40.86 pg/mL) was slightly lower than for the solution (149.13 ± 56.54 pg/mL); elimination half-life ($t_{1/2}$) for the tablets (16.37 ± 4.80 hr) was slightly shorter than for the solution (17.12 ± 4.01 hr); and time to peak serum concentration (t_{max}) was similar for both the tablets and the solution, 1.29 ± 0.42 hr and 1.19 ± 0.50 hr, respectively.

The mean serum SHBG level (\pm SEM) Cycle 1 to Cycle 2, decreased from $73.10 (\pm 12.06)$ nmol/L to $66.94 (\pm 9.81)$ nmol/L for tablets and decreased from $51.21 (\pm 6.30)$ nmol/L to $45.80 (\pm 5.77)$ nmol/L for solution, after single dose administration.

A total of 19 subjects (79.2% of the All-Subjects-Treated Group, N=24) reported at least one adverse experience. Fifteen of the 19 subjects reported an AE that was considered by the investigator to be at least possibly study drug-related. The most frequently reported AEs were headache, vaginal bleeding, nausea, and breast pain. Only two of

the AEs (vaginal bleeding and headache) were classified as moderate in intensity; the remaining AEs were all classified as mild in intensity. No serious adverse experiences (SAEs) were reported.

A total of two subjects (17 and 24) experienced changes from normal at baseline (screening) to abnormal at last measurement for physical examination parameters (which included general medical, breast, and pelvic examinations).

For general medical parameters, Subject 17 had a change from normal at baseline (screening) to abnormal at last measurement for lymph nodes (enlarged anterior cervical nodes).

For pelvic examination parameters, Subject 24 had a change from normal at baseline (screening) to abnormal at last measurement for vagina (mild menses).

For breast examination parameters, none of the subjects experienced changes in nodularity, nipple contour, nipple discharge, overlying skin, or masses from baseline to the last measurement.

There appeared to be no clinically significant changes in blood pressure, heart rate, respiratory rate, body temperature, or laboratory parameters.

No pregnancies were reported.

CONCLUSIONS

Both Org 224 and Org 3236 (active metabolite of Org 2969) are readily available when administered as a 0.150 mg Org 2969 plus 0.025 mg Org 224 CTR 77 tablet. The bioavailability based on AUC_0 of the tablet relative to a solution containing the same amount of Org 224 and Org 2969 is 98% and 100% for Org 224 and Org 3236, respectively. Based on $AUC_{0-t_{fix}}$, the bioavailability is 100% and 100% for Org 224 and Org 3236, respectively. For both Org 224 and Org 3236, no statistically significant differences between tablets and solution were found with respect to C_{max} , t_{max} , and $t_{1/2}$.

No serious adverse experiences were reported.

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92004 Steady-State study with the proposed dosing regimen

Title of the Study

An Open-Label, Single Center, Pharmacokinetic Study of a Triphasic Combination Oral Contraceptive, CTR 77

Investigator

Study Center

Report/Publication

SDR Release Report 4975. There were no publications from this study.

Studied Period

June 29, 1995 - December 12, 1995

Clinical Phase

Phase I

Objectives

The objective of the study was to first determine that the steady-state was reached for Org 3236 (etonogestrel, the active metabolite of Org 2969) and Org 224 (EE) within each dosing phase. Once the steady-state was attained, the objective was to determine that Org 3236 (etonogestrel) steady-state serum levels were proportional to the Org 2969 (desogestrel; DSG) dose (linear kinetics) during Cycle 3 of CTR 77 treatment and that Org 224 (EE) steady-state serum levels were similar under different co-administered Org 2969 (desogestrel; DSG) doses during Cycle 3 of CTR 77 treatment (dose equivalency).

Methodology

Open-label, single center, pharmacokinetic study.

Number of Subjects (total and for each treatment)

Twenty-four subjects were enrolled. Twenty-one subjects completed the study and three subjects discontinued.

Diagnosis and Criteria for Inclusion

- Healthy non-smoking women in the age range of 18 - 50 years inclusive;
- Women who were willing to be available for study visits, willing to use a Sunday-start OC regimen, and to continue the study drug for three consecutive cycles;
- Women who tested negative for drugs of abuse: cannabinoids, opiates, alcohol, cocaine, amphetamines, and benzodiazepines;
- Women who tested negative for human immunodeficiency virus (HIV) and Hepatitis B;
- Women who were between 80% and 130% of the ideal body weight (Metropolitan Height and Weight Tables);
- Women in whom pregnancy was ruled out before the start of the study;
- Women who were willing to give voluntary informed (written) consent to participate in the study; and
- Women who were willing to complete the Confidential Follow-up Form.

Test Product, Dose and Mode of Administration, Batch No.

Days 1-7: 0.100 mg Org 2969 (desogestrel; DSG) + 0.025 mg Org 224 (EE); Batch No. R5729
Days 8-14: 0.125 mg Org 2969 (desogestrel; DSG) + 0.025 mg Org 224 (EE); Batch No. R5730
Days 15-21: 0.150 mg Org 2969 (desogestrel; DSG) + 0.025 mg Org 224 (EE); Batch No. R5731
Days 22-28: Placebo; Batch No. R5728

Duration of Treatment

Three consecutive cycles.

Reference Therapy, Dose and Mode of Administration, Batch No.

None

Criteria for Evaluation

From the measured Org 3236 and Org 224 serum concentrations the following pharmacokinetic parameters were derived: i) the (dose normalized) pre-dose concentration ($C_{min,t}$), ii) the (dose normalized) minimum steady-state

concentration ($C_{ss,min}$), iii) the (dose normalized) peak concentration (C_{max}), iv) the time to peak concentration (t_{max}), v) the (dose normalized) area under the serum level versus time curve from zero to 24 hr after administration (AUC_{0-24}), vi) the (dose normalized) average drug concentration during a dosing interval at steady-state (C_{av}), vii) the degree of fluctuation at steady-state (DF), viii) the elimination half-life ($t_{1/2}$), ix) the apparent serum clearance (CL), and x) the apparent serum clearance per kg body weight (CL/kg).

Blood samples were collected during Cycle 3. Pre-dose samples were taken on Days 1, 5, 6, 7, 12, 13, 14, 19, 20, and 21. Serial blood samples up to 24 hr after drug administration on Days 7, 14, and 21 were taken 15 and 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after drug administration. Additional blood samples after drug administration on Day 21 were taken 36, 48, 60, and 72 hours after administration.

The study monitored all routine safety parameters including vital signs, complete physical examination (including breast and pelvic examination, and Pap smear), blood chemistry, hematology, urinalysis, and adverse experiences.

Statistical Methods

The following descriptive statistics were calculated: mean, standard deviation (SD), coefficient of variation [CV (%)], minimum, median, maximum. The first step of the statistical analysis was to determine if and when steady-state had been reached within each dosing phase. To that end, a repeated-measures analysis of variance with one within-subject factor (TIME) was performed per phase on the log-transformed normalized pre-dose concentrations ($n-C_{min,t}$). The contrast transformation indicated at which time point the pre-dose concentrations ceased to change.

The second step of the analysis was to investigate dose proportionality. Under the assumption of linear kinetics, the parameters $n-C_{max}$, $n-AUC_{0-24}$, $n-C_{av}$, $n-C_{ss,min}$, DF, and t_{max} are dose-independent. To that end, a repeated-measures analysis of variance with one within-subject factor (PHASE) was performed on the log-transformed parameter values (except for t_{max}). For t_{max} , Friedman's non-parametric test was performed.

In the analysis of Org 224 pharmacokinetic parameters, it is more appropriate to talk about "dose equivalency" in case of a statistically non-significant PHASE effect than "dose proportionality" because the Org 224 dose in the three dosing phases is the same.

Descriptive statistics were computed for demographics, extent of exposure, SHBG concentrations, laboratory parameters, and vital signs. Subjects with abnormalities in physical examination (including breast and pelvic examination) and cervical Pap smear which were not present at baseline were identified. For breast examination, if there were changes in the nodularity categories, the worst of left and right nodularity was used. Adverse experiences were tabulated by system-organ class and preferred terms.

SUMMARY

Twenty-four healthy female volunteers were enrolled in this study and received at least one dose of study drug. Three subjects discontinued (one subject due to a drug-related AE, one subject due to a non drug-related reason, and one subject due to personal reasons). A total of 21 subjects completed all study assessments.

Mean pharmacokinetic parameters for Org 3236 (active metabolite of Org 2969) and Org 224 during Dosing Phases 1, 2, and 3 of Cycle 3 are summarized in the following table:

Parameter		Org 3236 (etonogestrel)			Org 224 (EE)		
		100/25 (Phase 1)	125/25 (Phase 2)	150/25 (Phase 3)	100/25 (Phase 1)	125/25 (Phase 2)	150/25 (Phase 3)
t_{max} (hr)	n	21	20	21	21	20	21
	Mean	1.62	1.14	1.52	1.45	1.18	1.19
	SD	0.72	0.33	0.75	0.82	1.20	0.68
C_{max} (pg/mL)	n	21	20	21	21	20	21
	Mean	2163.33	3241.50	3855.71	85.42	91.27	90.09
	SD	856.40	1296.53	1273.07	51.66	52.17	48.22

C _{ss,min} (pg/mL)	n	21	21	21	21	21	21
	Mean	525.83	815.17	1111.83	15.35	17.79	17.54
	SD	222.23	356.55	543.28	8.35	10.71	9.18
C _{av} (pg/mL)	n	21	20	21	21	20	21
	Mean	816.70	1220.60	1603.70	27.54	30.22	29.44
	SD	313.95	442.79	650.03	12.02	16.12	13.70
DF (%)	n	21	20	21	21	20	21
	Mean	212.38	211.98	191.86	252.83	246.71	248.10
	SD	84.45	85.43	104.66	89.76	69.05	91.13
t _{1/2} (hr)	n	n.a.	n.a.	21	n.a.	n.a.	17
	Mean	n.a.	n.a.	37.09	n.a.	n.a.	28.23
	SD	n.a.	n.a.	14.77	n.a.	n.a.	10.47
Apparent CL (L/hr)	n	21	20	21	21	20	21
	Mean	6.11	5.08	4.64	43.49	41.74	42.51
	SD	2.26	1.89	1.63	15.00	15.45	18.70
n- C _{max} (pg/mL/ g)	n	21	20	21	21	20	21
	Mean	21.63	25.93	25.70	3.42	3.65	3.60
	SD	8.56	10.37	8.49	2.07	2.09	1.93
n- AUC ₀₋₂₄ (pg hr/mL/ g)	n	21	20	21	21	20	21
	Mean	196.01	234.36	256.59	26.44	29.01	28.26
	SD	75.35	85.01	104.00	11.54	15.48	13.16

n.a. - not applicable

For clinical pharmacology parameters, mean serum SHBG concentration increased from 127.15 nmol/L on Day 1 to 169.23 nmol/L on Day 21. Mean serum total testosterone concentration decreased from 565.35 pg/mL on Day 1 to 420.24 pg/mL on Day 21. Descriptive statistics were not computed for Free Testosterone because most of the serum concentrations were below the lower limit of quantitation of the assay.

Five selected laboratory parameters were statistically analyzed (paired t-test) with the following results: statistically significant changes from baseline to last measurement occurred in the following analytes: cholesterol increased by 25.09 mg/dL; while decreases occurred for glucose (-4.70 mg/dL), hematocrit (-1.50 %), and hemoglobin (-0.52 gm/dL). A statistically non-significant increase of 19.65 mg/dL occurred for triglycerides. None of the changes noted for selected laboratory parameters were apparently clinically significant.

Seven subjects (29.2% of the All-Subjects-Treated Group, N=24) reported at least one adverse experience. Three of the seven subjects reported AEs that were considered by the investigator to be at least possibly study drug-related. The most frequently reported AE was headache (2 subjects, 7702 and 7706). Subject 7719 withdrew from the study due to a drug-related AE (depression). No serious adverse experiences (SAEs) were reported.

Only one subject experienced any changes in physical examination parameters. Subject 7714 experienced a change from normal at baseline (screening) to abnormal at last measurement for skin (scars on left wrist and elbow from surgery).

There were no subjects who experienced changes from normal at baseline (screening) to abnormal at last measurement for breast or pelvic examination parameters. No changes in Pap smears, from normal to abnormal, were reported for any subject.

For vital signs, based on descriptive statistics, it appeared that there were no clinically significant changes in heart rate, respiratory rate, or body temperature. Based on paired t-test analyses, no statistically significant differences were found for body weight, BMI, and systolic and diastolic blood pressure.

CONCLUSIONS

Org 3236

During Phases 1 and 3 of CTR 77 treatment, steady-state was reached at any rate after 4 days of treatment. During Phase 2 of CTR 77 treatment, steady-state was reached after 5 days of treatment. Consequently, steady-state was reached at least after 5 days of CTR 77 treatment for all phases. A mean minimum steady-state concentration of approximately 526 pg/mL, 815 pg/mL, and 1112 pg/mL was observed for Phases 1, 2, and 3, respectively.

Comparing Phases 1, 2, and 3 with each other indicated a decreased clearance during Phases 2 and 3, presumably due to time-dependent kinetics.

Org 224

During Phases 1, 2, and 3 of CTR 77 treatment, steady-state was reached at any rate after 4 days of treatment within each phase with a mean minimum steady-state concentration of approximately 15.4 pg/mL, 17.8 pg/mL, and 17.5 pg/mL for Phases 1, 2, and 3, respectively.

Comparing Phases 1, 2, and 3 with each other, the data suggested dose equivalency.

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