CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-241

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

NDA 21-241
Ortho Tri-Cyclen Lo (norgestimate/ethinyl estradiol) Tablets
Johnson & Johnson Pharmaceuticals

This revised label is acceptable for Clin Pharm. Biopharm discipline.
Thanks,
Venkat

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jennifer L. Mercier
8/21/02 02:36:28 PM
CSO
for Venkat Jarugula

Ameeta Parekh
8/21/02 02:47:52 PM
BIOPHARMACEUTICS
Venkat had sent an email stating that the label was acceptable.

APPEARS THIS WAY
ON ORIGINAL

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA: [redacted]

Drug: Ortho Tri-cyclen Lo tablets

Sponsor: R.W. Johnson

Date of Submission: 08/25/00, 05/25/01, 05/31/01, 06/01/01

Type of Submission: Original NDA

Reviewer: Venkateswar R. Jarugula, Ph.D.

EXECUTIVE SUMMARY

OrthoTri-cyclen Lo is a combination oral contraceptive (OC) tablet containing norgestimate as progestin and ethinyl estradiol as estrogen and is indicated for the [redacted] OrthoTri-cyclen Lo tablet is to be taken once daily for 28 days of each menstrual cycle. It is a triphasic regimen, which involves a stepwise weekly increase in the dose of norgestimate (NGM) from weeks 1 through 3 (0.180 mg, 0.215 mg, 0.250 mg). The ethinyl estradiol (EE) dose remains constant at 0.025 mg. Placebo tablet is taken once daily during week 4. Previously approved OC products containing NGM and EE include Orthocyclen (NDA 19653) and OrthoTri-cyclen (NDA 19697, with higher dose of EE:35μg and same triphasic regimen of NGM).

Human pharmacokinetic and bioavailability section of the NDA consists of data collected from three primary studies and one supportive study utilizing Ortho Tri-cyclen Lo formulation and also additional supporting data from 10 supportive studies that utilized related hormonal products (NGM, 17dNGM, EE and /or estradiol) and relevant data from the literature. The primary studies provide information on the bioavailability of Ortho Tri-cyclen Lo tablets relative to an oral solution and on the multiple dose pharmacokinetics and dose proportionality. Additionally, a cross study population pharmacokinetic analysis to evaluate the effect of patient demographics on NGM and EE pharmacokinetics was conducted from the data of these four studies. The three primary studies and population pharmacokinetic analysis and relevant information from supportive studies are reviewed here.

The pharmacokinetics of NGM have been evaluated by measurement of its two major active metabolites, 17d-deacetylnorgestimate (17dNGM) and norgestrel (NG), since NGM is rapidly absorbed and extensively metabolized following oral administration and the systemic concentrations of unchanged parent compound, NGM are negligible.

The results of primary and relevant supportive studies submitted in Section 6 of the NDA are summarized as follows.

Following single oral administration of Ortho Tri-cyclen Lo, NGM and EE are rapidly absorbed. NGM is rapidly and extensively metabolized by first-pass mechanisms to two major active metabolites, 17dNGM and NG. Systemic concentrations of unchanged NGM are negligible. Peak concentrations of 17dNGM, NG and EE are obtained within 1 to 3 hours of administration. The systemic concentrations of 17dNGM and NG declined in biexponential manner with terminal half-lives of 20 – 30 hours and 50 to 80 hours respectively. EE levels also declined in a biexponential fashion with mean terminal half-life of 14 hours.

The average bioavailability of NGM (based on Cmax and AUC for 17dNGM and NG) from Orthotricyclen compared to oral solution of corresponding dosage ranges from 78% to 106% for low dose progestin and 65% to 84% for high dose progestin. The relative bioavailability of EE compared to oral solution ranged from 91% to 94%.

From a food effect study on a related formulation (Ortho-Prefest), it was shown that high-fat meal did not affect the AUC of 17d-NGM, and NG, and C_{max} of NG. However, C_{max} of 17d-NGM was lowered by 16% in presence of food. Food-effect on EE in Ortho Tricyclen LO formulation has not been studied.

Following multiple dosing of Ortho Tri-cyclen Lo for up to three cycles, the systemic concentrations accumulated by about 1.5 to 2 times for 17dNGM and by 1.5 times for EE as expected based on their respective terminal half-lives. However, the concentration of NG accumulated to significantly higher degree by about 4.5 to 14.5-fold with high variability. This high level of accumulation could be due to its binding to sexual hormone binding globulin (SHBG), the levels of which are significantly increased (2.5 to 3 times normal) by coadministration of EE.

Population analysis of pooled pharmacokinetic data following single administration of Ortho Tri-cyclen Lo showed that increasing body weight and body surface area were each associated with decreases in Cmax and $AUC_{0\text{-}24h}$ of 17dNGM , NG and EE. Increasing age was also associated with decrease in these parameters for 17dNGM and NG. These effects were statistically significant. However, only a small to moderate fraction (5-40%) of the overall variability may be explained by these covariates. Population pharmacokinetic analysis did not reveal any differences among Caucasians, African Americans and Hispanics.

Based on the data for clinical and biobatches, in vitro dissolution specifications should be modified as Q= [redacted] 20 minutes for both NGM and EE for all strengths. This recommendation was accepted by the sponsor.

RECOMMENDATION

The Human Pharmacokinetics and Bioavailability section of NDA 21241 is acceptable. The labeling comments should be conveyed to the sponsor as appropriate.

Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Ph.D., Team Leader _____

FT signed by Ameeta Parekh, Ph.D., Team Leader _____

cc: NDA 21241, HFD-580 (Willett, Mercier), HFD-870 (Malinowski, Parekh), CDR (B.Murphy for Drug).
CPB Briefing attendees: Drs. H. Malinwosky, J. Hunt, A. Parekh, and S. Al-Habet.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS SUMMARY

What is Ortho Tri-cyclen Lo and what is its mechanism of action?

BACKGROUND

Ortho Tri-cyclen Lo is an oral contraceptive tablet formulation containing a progestin component, norgestimate (NGM) and an estrogen component, ethinyl estradiol (EE). The triphasic regimen of Ortho Tri-cyclen Lo involves a stepwise increase in NGM dose as shown below:

180 µg NGM/25 µg EE tablets (white)	Day 1 to 7
215 µg NGM/25 µg EE tablets (light blue)	Day 8 to 14
250 µg NGM/25 µg EE tablets (dark blue)	Day 15 to 21
Placebo tablets (green)	Day 22 to 28

Currently, R.W. Johnson markets two OC products containing NGM/EE. Orthocyclen (NDA 19653) was a monophasic regimen containing 250 µg NGM/35 µg EE tablets. Ortho Tri-cyclen (NDA 19693) was a triphasic regimen same as the OrthoTri-cyclen Lo of the current NDA except for higher EE dose of 35 µg.

MECHANISM OF ACTION

Estrogen and progestin combinations act as contraceptives by inhibiting gonadotropin secretion, which prevents ovulation. Additional actions of these hormones that decrease the likelihood of conception and implantation include changes in the cervical mucus, the endometrium, and tubal motility and secretions.

In general, it is believed that reducing the dose of estrogens and progestin without compromising on contraceptive efficacy would improve the tolerability and side-effect profile of the combination OC products. Sponsor claims that triphasic regimen offers advantage in view of lower total progestin dose per cycle leading to improved tolerability and better or equal cycle control.

FORMULATION

The to be marketed formulation and the clinical formulation used in phase III studies and the pivotal pharmacokinetic studies are essentially the same except for the different colorants used to distinguish the strengths of NGM in the final to be marketed formulation and the scale up of less than 10 times the size of clinical batches.
Sponsor used [redacted] s of NGM and EE for a dose finding study. Two BE studies (using a different formulation, Ortho Tricyclen containing 35 µg EE) covering the high and low progestin doses in combination with EE were submitted as supportive studies. Since the [redacted] was used only in dose finding study, these supportive bioequivalence studies are not reviewed here.

The composition of the commercial formulation of OrthoTri-cyclen L0 is given in Table 1.

Table 1: Quantitative Target Composition (mg/tablet)

Component	Reference	Role	180 µg NGM/ 25 µg EE	215 µg NGM/ 25 µg EE	250 µg NGM/ 25 µg EE
Norgestimate, [redacted]		Active	0.180	0.215	0.250
Ethinyl Estradiol, [redacted]	USP	Active	0.025	0.025	0.025
Lactose, [redacted]	NF	Diluent			
Microcrystalline Cellulose	NF	Diluent			
Croscarmellose Sodium	NF	Disintegrant			
Magnesium Stearate	NF	Lubricant			
Carnauba Wax	NF	Polishing Agent			
Purified Water[a]	USP	Film Coating			
[redacted]		Film Coating			
[redacted]		Film Coating			
[redacted]		Film Coating			

[a] Purified water is [redacted]

To support the scale up change and colorants used in the commercial formulation, sponsor submitted comparative dissolution profiles between clinical lot and commercial lots. Based on f_2 values (range: [redacted]) for the comparison, the dissolution of the clinical lots and the commercial lots is similar.

IN VITRO DISSOLUTION

The sponsor proposed the following dissolution method and specifications for [redacted] tablets.

Apparatus Type	USP 2, paddle
Medium	[redacted]
Volume	[redacted]
Speed of rotation	[redacted]
Proposed spec:	Q= [redacted] at 30 min for both NGM and EE for all strengths
Recommended spec:	Q= [redacted] at 20 min for both NGM and EE for all strengths

In vitro dissolution data for the batches used in clinical trials and pivotal bioavailability studies are included in Attachment E of Volume 1/Item 6 of NDA 21241 submission (page 168-170). The data provided by the sponsor for clinical/biobatches shows that the in vitro dissolution is rapid and more than [redacted] is dissolved by 20 minutes. So, the sponsor is recommended to modify the specs to Q = [redacted]% at 20 minutes for both NGM and EE. This recommendation was accepted by the sponsor.

Are the assay methods used for quantitation of NGM metabolites and EE adequate?

ANALYTICAL METHODOLOGY

The method for analysis of 17d-NGM and NG in human plasma and serum was developed and validated at [redacted] and the method for analysis of EE in human plasma and serum was developed and validated by [redacted] Serum/plasma concentrations of 17d-NGM and NG were assayed by a high performance liquid chromatographic method using mass spectrometric detection (LCMS). 17d-NGM, NG and internal standard were separated from human serum by a [redacted] extraction. The extract was [redacted] and the [redacted]. Analysis was accomplished by LCMS using [redacted]

Serum levels of EE were [redacted] EE along with its isotopically labeled internal standard, 17α-EE-$^{13}C_2$, was separated from serum by a [redacted] followed by [redacted] and [redacted] steps. The extract was [redacted] Analysis was accomplished by [redacted]

The limit of quantitation (LOQ) for the LCMS assay of 17dNGM and NG in human plasma was [redacted] respectively. Both compounds had a standard curve range of 0.1 to 2.5 ng/ml. The LOQ for [redacted] of EE in human plasma was [redacted] ng/ml and the standard curve was in the range of [redacted]

The intra-batch and inter-batch accuracy for 17-dNGM and NG in human plasma was [redacted] and that in human serum was [redacted]. For EE the intra-batch and inter-batch accuracies in human serum were [redacted] The intra-batch and inter-batch precision for 17-dNGM and NG was [redacted] in human plasma and [redacted] in human serum. For EE, these values were [redacted] in human serum.

The mean recovery of 17d-NGM and NG from human plasma ranged from [redacted] and [redacted] respectively. The mean recovery of EE from human serum was low in the range of [redacted]

Overall, the assay performance is found to be acceptable to characterize the pharmacokinetics of major metabolites of NGM (17d-NGM, NG) and EE following single and multiple dose administration of Ortho Tri-cyclen Lo tablets.

What is the relative bioavailability of NGM metabolites and EE from Ortho Tri-cyclen Lo formulation?

BIOAVAILABILITY

Two phase I studies (NRGLOW-PHI-003, NRGLOW-PHI-004) were conducted to evaluate the relative bioavailability of [redacted] at lowest strength (180 µg NGM/25 µg EE) and highest strength (250 µg NGM/25 µg EE) in comparison to that of an oral solution. For the middle strength, comparative dissolution profiles were provided. The formulation used in these studies is identical to the one used in the Phase III clinical trial and the to be marketed formulation.

The two studies were designed as open-label, single center, randomized crossover studies with 24 healthy women in each study. The mean pharmacokinetic parameters of NGM metabolites (17dNGM and NG), and EE from these two studies are listed in the tables below.

Table 2: Arithmetic Mean (SD) Serum 17d-NGM Pharmacokinetic Parameters in Subjects Receiving 180 µg NGM and 25 µg EE in Solution and Tablet Formulations (Study NRGLOW-PHI-003, Study NRGLOW-PHI-004)

	180 µg NGM and 25 µg EE		250 µg NGM and 25 µg EE	
Parameter	Solution	Tablet	Solution	Tablet
C_{max} (ng/mL)	1.35 (0.36)	1.04 (0.25)	2.02 (0.49)	1.33 (0.38)
t_{max} (h)	1.23 (0.91)	1.67 (0.46)	1.06 (0.22)	1.88 (0.61)
$AUC_{0\text{-}24h}$[a] (ng·h/mL)	7.71 (1.27)	7.22 (1.62)	10.4 (2.11)	8.44 (1.87)
$AUC_{0-\infty}$[b] (ng·h/mL)	12.0 (3.79)	11.6 (3.77)	18.9 (6.23)	15.9 (6.60)
$AUC_{0\text{-}last}$ (ng·h/mL)	8.09 (2.35)	6.82 (3.15)	12.7 (4.65)	10.1 (3.94)
CL/F[b] (L/h)	16.6 (5.30)	17.3 (5.96)	15.1 (6.54)	18.3 (7.35)
$t_{1/2}$[b] (h)	21.7 (9.79)	22.4 (9.14)	32.0 (16.1)	31.4 (21.3)

[a] Fifteen of 24 subjects were included in the statistical analyses for this parameter.
[b] Twenty of 24 subjects were included in the statistical analyses for this parameter.

Table 3: Arithmetic Mean (SD) Serum NG Pharmacokinetic Parameters in Subjects Receiving 180 µg NGM and 25 µg EE in Solution and Tablet Formulations (Study NRGLOW-PHI-003)

	180 µg NGM and 25 µg EE		250 µg NGM and 25 µg EE	
Parameter	Solution	Tablet	Solution	Tablet
C_{max} (ng/mL)	0.35 (0.16)	0.36 (0.14)	0.65 (0.45)	0.56 (0.46)
t_{max} (h)	1.65 (0.96)	2.02 (0.63)	1.58 (0.78)	2.79 (2.19)
$AUC_{0\text{-}24h}$[a] (ng·h/mL)	4.68 (1.12)	4.48 (0.96)	8.19 (5.66)	8.04 (6.83)
$AUC_{0-\infty}$[b] (ng·h/mL)	28.7 (13.3)	23.5 (8.63)	35.8 (23.6)	31.0 (18.5)
$AUC_{0\text{-}last}$ (ng·h/mL)	6.44 (6.23)	5.94 (5.48)	12.8 (16.5)	11.1 (15.4)
CL/F[b] (L/h)	7.54 (3.41)	8.82 (3.94)	10.4 (7.46)	10.6 (6.11)
$t_{1/2}$[b] (h)	98.7 (52.6)	81.7 (33.6)	52.8 (27.2)	53.3 (19.4)

[a] Thirteen of 24 subjects were included in the statistical analyses for this parameter.
[b] Eleven of 24 subjects were included in the statistical analyses for this parameter.

Table 4: Arithmetic Mean (SD) Serum EE Pharmacokinetic Parameters in Subjects Receiving 180 µg NGM and 25 µg EE in Solution and Tablet Formulations (Study NRGLOW-PHI-003)

Parameter	180 µg NGM and 25 µg EE		250 µg NGM and 25 µg EE	
	Solution	Tablet	Solution	Tablet
C_{max} (pg/mL)	61.5 (15.8)	57.3 (18.9)	60.9 (18.9)	58.9 (21.4)
t_{max} (h)	1.56 (0.86)	1.60 (0.42)	1.29 (0.33)	1.40 (0.36)
AUC_{0-24h} (pg·h/mL)	460 (84.8)	431 (116)	418 (146)	404 (154)
$AUC_{0-\infty}$ (pg·h/mL)	612 (140)	584 (169)	545 (232)	532 (239)
AUC_{0-last} (pg·h/mL)	549 (139)	521 (167)	486 (223)	478 (232)
AUC_{0-t}[a] (pg·h/mL)	545 (134)	515 (174)	482 (222)	472 (228)
CL/F (L/h)	43.0 (10.1)	45.9 (11.9)	54.2 (22.7)	55.6 (22.8)
$t_{1/2}$ (h)	14.0 (3.12)	14.3 (2.94)	14.5 (4.56)	14.1 (4.28)

[a] AUC_{0-t} = area under the curve taken to the last time point for each subject that was common to both treatments.

Following single oral administration of Ortho Tri-cyclen Lo, NGM and EE are rapidly absorbed. NGM is rapidly and extensively metabolized by first-pass mechanisms to two major active metabolites, 17dNGM and NG. Systemic concentrations of unchanged NGM are negligible. Peak concentrations of 17dNGM, NG and EE are obtained within 1 to 3 hours of administration. The systemic concentrations of 17dNGM and NG declined in biexponential manner with terminal half-lives of 20 –30 hours and 50 to 80 hours respectively. EE levels also declined in a biexponential fashion with mean terminal half-life of 14 hours.

As shown in the above tables, all subjects were not included in the statistical analysis of AUC, Cl/F and t1/2 parameters because concentrations of analytes fell below quantitation limits prior to 24 hours or 36 hours of dosing.

The bioavailability 17dNGM, NG and EE from the tablet formulation are slightly lower or similar to that of oral solution.

The average rate of absorption/formation (Cmax) of 17d-NGM and NG for the tablet relative to solution at lower dose strength ranged from 78 to 106% and the extent of absorption (AUC) ranged from 79 to 99%.

The average rate of absorption /formation of 17dNGM and NG from higher dose strength tablet relative to the oral solution was 65 to 84% and the extent of absorption was 79 to 83%.

The rate and extent of absorption of EE from the tablet formulations of both strengths were similar relative to the oral solution (91% for Cmax, 94% for AUC).

How does food affect the bioavilability of Ortho Tricyclen Lo tablets?

Food effect

No food effect study was submitted for Ortho Tricyclen Lo formulation. However, sponsor submitted a food effect study (ESTNRG-PHI-004) that was conducted for an approved NDA, Ortho-Prefest™ (NDA 21-040), which contains 90μg of NGM and 1 mg of 17β-estradiol (E_2). The NGM/E_2 formulation used in this study is similar (except for E_2 instead of EE) to Ortho Tricyclen Lo formulation, and since two tablets of Ortho-Prefest were dosed in the study, the dose of NGM is 180 μg, equivalent to the lowest NGM dose of present NDA. Thus the results of this study are applicable to NGM component in Ortho Tricyclen Lo formulation. The above mentioned food effect study has already been reviewed in NDA 21-040. Therefore only the relevant results are briefly summarized here.

The results of the food effect study with Ortho-Prefest showed that high fat meal did not affect the AUC of 17d-NGM, and NG. Food had no effect on the C_{max} of NG, but decreased the C_{max} of 17d-NGM by an average of 16%. However, this decrease in C_{max} is not considered clinically significant because the overall systemic exposure (AUC) of 17d-NGM, critical for chronically administered products like oral contraceptives, did not change in presence of high fat meal.

It should be noted the food-effect on EE component of Ortho Tricyclen Lo formulation has not been studied.

Currently, the proposed label does not mention anything about food effect. Sponsor has been requested to include food effect information in the Absorption section of the label.

Is there accumulation following multiple dosing? Are the pharmacokinetics of NGM dose proportional?

MULTIPLE DOSE/DOSE PROPORTIONALITY

The single and multiple dose pharmacokinetics of NGM and EE in Ortho Tri-cyclen Lo have been evaluated in two studies: Study NRGLOW-PHI-001 utilizing Ortho Tri-cyclen Lo, and study NRGLOW-PHI-002 utilizing a cyclophasic 28-day regimen that is not the subject of the current NDA. The later study is not reviewed here.

In study NRGLOW-PHI-001, 16 healthy, non-pregnant, female volunteers received the following regimen of Ortho Tri-cyclen Lo during each of three 28-day cycles:

NGM 180 μg/EE 25μg	Day 1 to 7
NGM 215 μg/EE 25μg	Day 8 to 14
NGM 250 μg/EE 25μg	Day 15 to 21
Placebo	Days 22 to 28

A comparison of single dose to multiple dose pharmacokinetic parameters was done using single dose obtained on Day 1of Cycle 1 and multiple dose data obtained from

Day 7 of Cycle 3. The mean serum levels and pharmacokinetic parameters are illustrated in the following Figures and Tables.

Table 5: Serum 17d-NGM Pharmacokinetic Parameters in Healthy Female Subjects Following Single Dose (Day 1 of Cycle 1) and Multiple Dose (Day 7 of Cycle 3) NGM/EE (180/25 µg) Tablets (Study NRGLOW-PHI-001)

Parameter	Arithmetic Mean (SD)		Cycle 3 Day 7:Cycle 1 Day 1 [a]		
				90% CI	
	Cycle 1 Day 1	Cycle 3 Day 7	Ratio (%)	Lower	Upper
C_{max} (ng/mL)	0.91 (0.27)	1.42 (0.43)	164	146	184
AUC_{0-24h} (ng·h/mL)	5.86 (1.54)	11.3 (3.18)	191	172	212
t_{max} (h)	1.78 (0.95)	1.76 (0.71)	--	--	--

[a] Geometric least squares mean ratio and 90% CI.

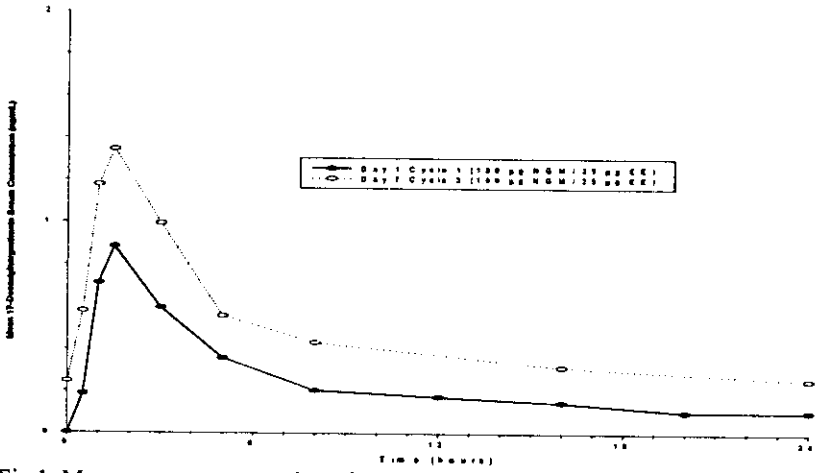

Fig 1. Mean serum concentration of 17dNGM following single and mutliple administartion Orhtotricylen 25 tablets.

Following multiple dosing of Ortho Tri-cyclen Lo for three cycles, mean serum levels of 17d-NGM accumulated by approximately 1.5 to 2-fold (164% for Cmax and 191% for AUC). This is similar to the level of accumulation predicted from single dose data, which is 2 to 2.5 fold.

Table 6: Serum NG Pharmacokinetic Parameters in Healthy Female Subjects Following Single Dose (Day 1 of Cycle 1) and Multiple Dose (Day 7 of Cycle 3) NGM/EE (180/25 µg) Tablets (Study NRGLOW-PHI-001)

Parameter	Arithmetic Mean (SD)		Cycle 3 Day 7:Cycle 1 Day 1 [a]		
				90% CI	
	Cycle 1 Day 1	Cycle 3 Day 7	Ratio (%)	Lower	Upper
C_{max} (ng/mL)	0.32 (0.14)	1.64 (0.89)	460	381	557
AUC_{0-24h} (ng·h/mL)	2.44 (2.04)	27.9 (18.1)	1433	1092	1880
t_{max} (h)	2.00 (1.09)	1.90 (0.89)	--	--	--

[a] Geometric least squares mean ratio and 90% CI.

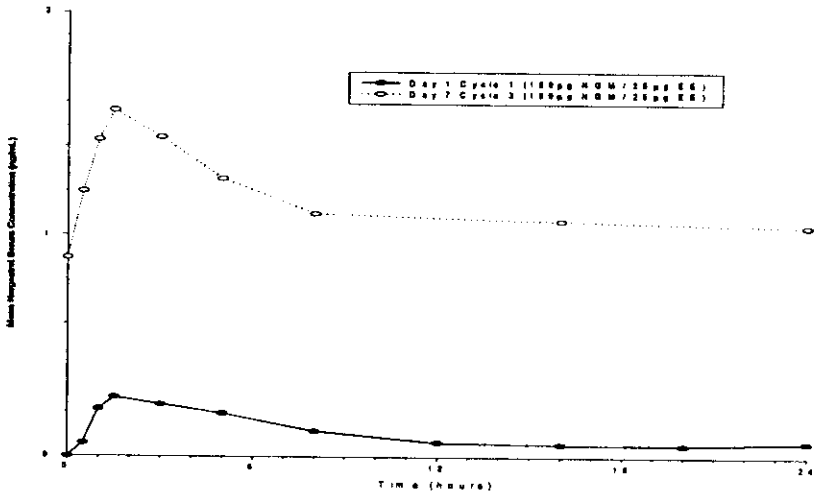

Fig 2. Mean serum concentrations of NG following single and multiple dose administration of Ortho Tri-cyclen Lo tablets

Mean serum levels of NG accumulatted by about 4.5 to 14.5 fold by Day 7 of Cycle 3 (460% for Cmax and 1433% for AUC) compared to Day 1 of Cycle 1. It should be noted that there was large variability in AUC values as evidenced by the large confidence intervals. The accumulation observed was much greater than that predicted (4 to 4.5 fold) from single dose pharmacokinetics.
This significant accummulation is likely due to the nonlinear pharmacokinetics exhibited by NG as a result of its binding to SHBG. Multiple dosing of EE induces marked elevations in SHBG levels which inturn cause NG levels to increase with multiple dosing of NGM/EE.

Table 7: Serum EE Pharmacokinetic Parameters in Healthy Female Subjects Following Single Dose (Day 1 of Cycle 1) and Multiple Dose (Day 7 of Cycle 3) NGM/EE (180/25 µg) Tablets (Study NRGLOW-PHI-001)

Parameter	Arithmetic Mean (SD)		Cycle 3 Day 7:Cycle 1 Day 1 [a]		
				90% CI	
	Cycle 1 Day 1	Cycle 3 Day 7	Ratio (%)	Lower	Upper
C_{max} (pg/mL)	55.6 (18.1)	91.1 (36.7)	157	141	174
$AUC_{0\text{-}24h}$ (pg·h/mL)	421 (118)	782 (329)	170	157	184
t_{max} (h)	1.66 (0.54)	1.32 (0.25)	--	--	--
CL/F (L/h)	49.8 (15.2)	37.7 (16.1)	75	69	81
$t_{1/2}$ (h)	12.6 (3.1)	15.0 (2.4)	126	113	139

[a] Geometric least squares mean ratio and 90% CI.

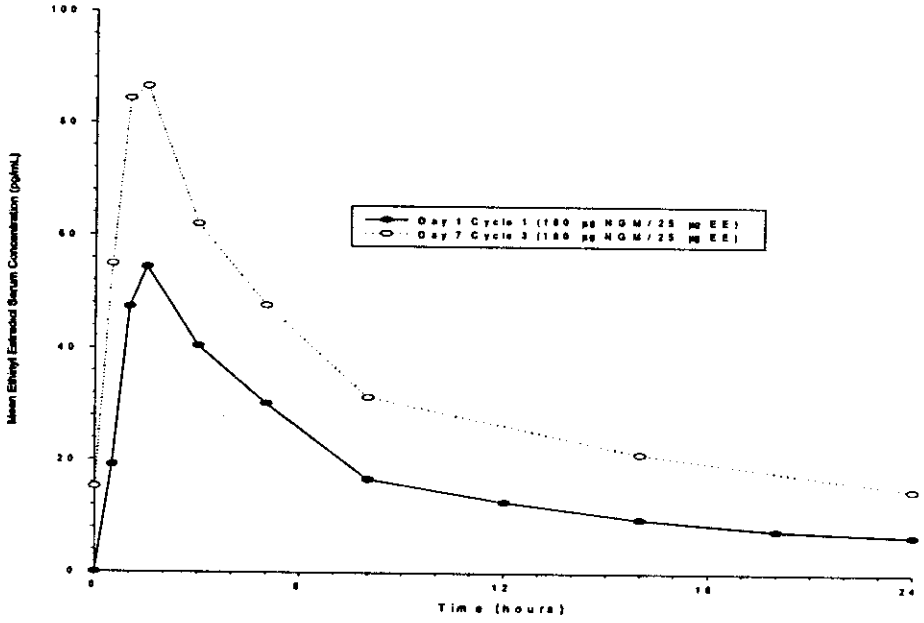

Fig 3. Mean serum concentrations of NG following single and multiple dose administration of Ortho Tri-cyclen Lo tablets

Steady-state serum EE levels on Day 7 of Cycle 3 accumulated by 157% for Cmax and 170% for AUC compared to those on Day 1 of Cycle 1. This level of accumulation is similar to the expected accumulation from single dose pharmacokinetics.

It should be noted that the steady state serum levels of 17d-NGM and NG vary during the given cycle because of the step-wise weekly increase in dose of NGM (180 to 215 to 250 µg).

DOSE PROPORTIONALITY

The dose proportionality of NGM metabolites (17d-NGM and NG) was assessed using multiple dose data from the following treatment days of Cycle 3 (Study NRGLOW-PHI-001): Day 7 (180 µg NGM/25 µg EE), Day 14 (215 µg NGM/25 µg EE), Day 21 (250 µg NGM/25 µg EE). Dose proportionality was assessed by comparing dose-normalized Cmax (DN-Cmax) and dose-normalized $AUC_{0\text{-}24h}$ (DN-$AUC_{0\text{-}24h}$) for 17d-NGM and NG on Days 7, 14, and 21 of Cycle 3.

Table 8: Mean (SD) 17d-NGM and NG Pharmacokinetic Parameters in Healthy Female Subjects Following Days 7, 14, and 21 of Cycle 3 Treatments After Triphasic Administration of NGM/EE Tablets (Study NRGLOW-PHI-001)

Parameter	Arithmetic Mean (SD)		
	Cycle 3 Day 7 [a]	Cycle 3 Day 14 [a]	Cycle 3 Day 21 [a]
17d-NGM			
DN-C_{max} (ng/mL)	1.42 (0.43)	1.31 (0.33)	1.31 (0.39)
DN-$AUC_{0\text{-}24h}$ (ng·h/mL)	11.3 (3.18)	11.6 (3.13)	11.6 (3.44)
NG			
DN-C_{max} (ng/mL)	1.64 (0.89)	1.76 (0.95)	2.01 (1.02)
DN-$AUC_{0\text{-}24h}$ (ng·h/mL)	27.9 (18.1)	34.1 (20.8)	35.9 (19.9)

[a] Cycle 3 Day 7: 180 µg NGM/25 µg EE; Cycle 3 Day 14: 215 µg NGM/25 µg EE; Cycle 3 Day 21: 250 µg NGM/25 µg EE

Based on the dose normalized PK parameters (Cmax and AUC) shown above, and also based on the 90% confidence intervals for comparison between Day 7, 14 and 21 (not shown), it can be concluded that the exposure to 17d-NGM following multiple dosing of Ortho Tri-cyclen Lo for three cycles is dose proportional.

The exposure to NG was greater (about 40 to 50%) than dose proportional for Day 21 and Day 14 compared to Day 7. The data for NG has larger variability compared to that of 17d-NGM. The disproportional increase in exposure of NG with increase in dose of NGM may be due to the extensive protein binding of NG to SHBG and the increases in SHBG with chronic dosing of NGM/EE. As expected, no changes were observed for EE pharmacokinetics with increasing doses of NGM.

How does NGM/EE combination affect SHBG levels?

PHARMACODYNAMICS

Ethinyl estradiol is known to increase the concentrations of sexual hormone binding globulin (SHBG). In the multiple dose study, the serum levels of SHBG were measured at prestudy and on Day 1 and 21 of Cycles 1, 2 and 3.

Table 9: Mean (SD) Values of SHBG Serum Concentrations in Normal Female Subjects After Triphasic Multiple Administration of Norgestimate/Ethinyl Estradiol Tablets (Study NRGLOW-PHI-001)

	Mean (SD)													
	Prestudy		Cycle 1				Cycle 2				Cycle 3			
Parameter	Baseline		Day 1		Day 21		Day 1		Day 21		Day 1		Day 21	
SHBG (mmol/L)	62.3	(28.0)	50.6	(17.3)	133.5	(69.1)	101.4	(37.7)	146.5	(76.5)	96.6	(37.3)	158.5	(74.2)

As expected, SHBG levels were increased on Day 21 of Cycle 1, 2, and 3 relative to baseline and Day 1 of corresponding Cycle. Compared to baseline, there was about 2.5 to 3-fold increase in SHBG levels at the end of each Cycle. It should be noted that SHBG levels did not return to baseline at the end of each cycle because there is only seven days of pill free/placebo period in each Cycle. Comparison of SHBG values on Day 21 of Cycles 1, 2 and 3 showed no significant difference indicating that SHBG concentrations were at steady state by Day 21 of Cycle 1.

How does the disposition of Ortho Tri-cyclen Lo change in special populations?

SPECIAL POPULATIONS

Elderly: The pharmacokinetics of Ortho Tri-cyclen Lo have not been studied in geriatric population since this is not intended population to use this drug.

Pediatrics: Safety and efficacy of Ortho Tri-cyclen Lo have not been evaluated in subjects of postpubertal age under 16. Sponsor claimed that the safety and efficacy are expected to be the same for post pubertal adolescents under the age of 16 and for users of 16 years and older. There is no reason to believe that the pharmacokinetics of Ortho Tri-cyclen Lo would be different in post pubertal subjects under 16 and above 16 years.

Hepatic Impairment: The pharmacokinetics of Orthotricyclen have not been evaluated in subjects with hepatic impairment. However, as with other oral contraceptives, this drug is also contraindicated in women with liver dysfunction. Based on the information from literature, sponsor reported that the unbound fraction of EE was significantly higher in women with liver cirrhosis (1.51 ± 0.31; $p<0.01$) than in healthy volunteers (1.17 ± 0.12)

Renal Impairment: The pharmacokinetics of Ortho Tri-cyclen Lo have not been evaluated in women with renal impairment. However, based on literature information, peritoneal dialysis patients have decreased apparent oral clearance of EE leading to higher serum levels compared with women with normal renal function. The unbound fraction of EE was found to be significantly higher in women with renal failure (1.44 ± 0.11, $p<0.001$) than in healthy volunteers (1.17 ± 0.12).

Does the exposure to active components of Orthotricyclen change with covariates (Race, Bodyweight and Age)?

POPULATION PHARMACOKINETICS

The effects of race, age, body weight and body surface area on the pharmacokinetics of NGM (17d-NGM and NG) and EE were evaluated by analyzing the data pooled from four pharmacokinetic studies (NRGLOW-PHI-001, -002, -003, and –004). Single dose parameters for 17d-NGM, NG and EE were used for evaluation demographic effects since these were common across all four studies, and hence could be pooled. Thus, in the two multiple dose studies (NRGLOW-PHI-001, and –002), only pharmacokinetic parameters from Day1, Cycle 1 (single-dose data) were used in this analysis. The pooled data include 50 Caucasians, 21 Hispanics and 8 African American women.

A two-stage approach to population pharmacokinetic analysis was used. For the first stage, individual pharmacokinetic parameters for EE and the NGM metabolites, 17d-NGM and NG were obtained by pooling from data-rich clinical pharmacokinetic studies (two-single dose studies : NRGLOW-PHI-003 and -004, and the single-dose phase of two multiple dose studies:NRGLOW-PHI-001 and 002). The relationship between pharmacokinetic parameters and the demographic factors as covariates (race, age, body weight and body surface area) was analyzed using regression models. The pharmacokinetic parameters that were analyzed include Cmax and AUC for 17d-NGM and NG; and Cmax, AUC, apparent clearance (Cl/F) and apparent volume of distribution (Vd/F) and terminal half-life for EE.

Sponsor stated that single dose parameters were used for this analysis because these were common across all four studies and hence could be pooled.

The statistical analysis was carried out in two ways: 1. With race, age and body weight as predictors and 2. With race, age and body surface area as predictors. Log-transformed PK parameters were used in regression models with race as categorical predictor; and age and BWT or BSA as continuous predictors. The regression models were run using other transformations (such as square root or log) of PK parameters or covariates to evaluate whether the r^2 would improve. For the final analysis, log of PK parameters was used in linear regression analysis, since log transformation gave highest R^2 values. The p-values associated with each covariate from log-linear regression analysis are listed in the following table. The effect of bodyweight and age on the systemic exposure ($AUC_{0\text{-}24h}$) of 17d-NGM, NG and EE following single dose administration of Orthotricyclen is shown in Fig.

Table 10: P-values for regression analysis (Race, age, body weight effects)

Analyte	Parameter	Age	Weight	Race	R^2
17d-NGM	AUC_{0-24h} 0.028(-)		<0.001(-) 0.737	0.417	
	Cmax	0.016(-)	<0.001(-)	0.909	0.204
NG	AUC_{0-24h} 0.850		<0.001(-) 0.666	0.297	
	Cmax	0.542	0.010 (-)	0.877	0.129
EE	AUC_{0-24h} 0.538		<0.001(-) 0.916	0.193	
	CL/F	0.563	0.014	0.838	0.086
	Cmax	0.903	<0.001(-)	0.878	0.193
	$T_{1/2}$	0.879	0.163	0.818	0.04

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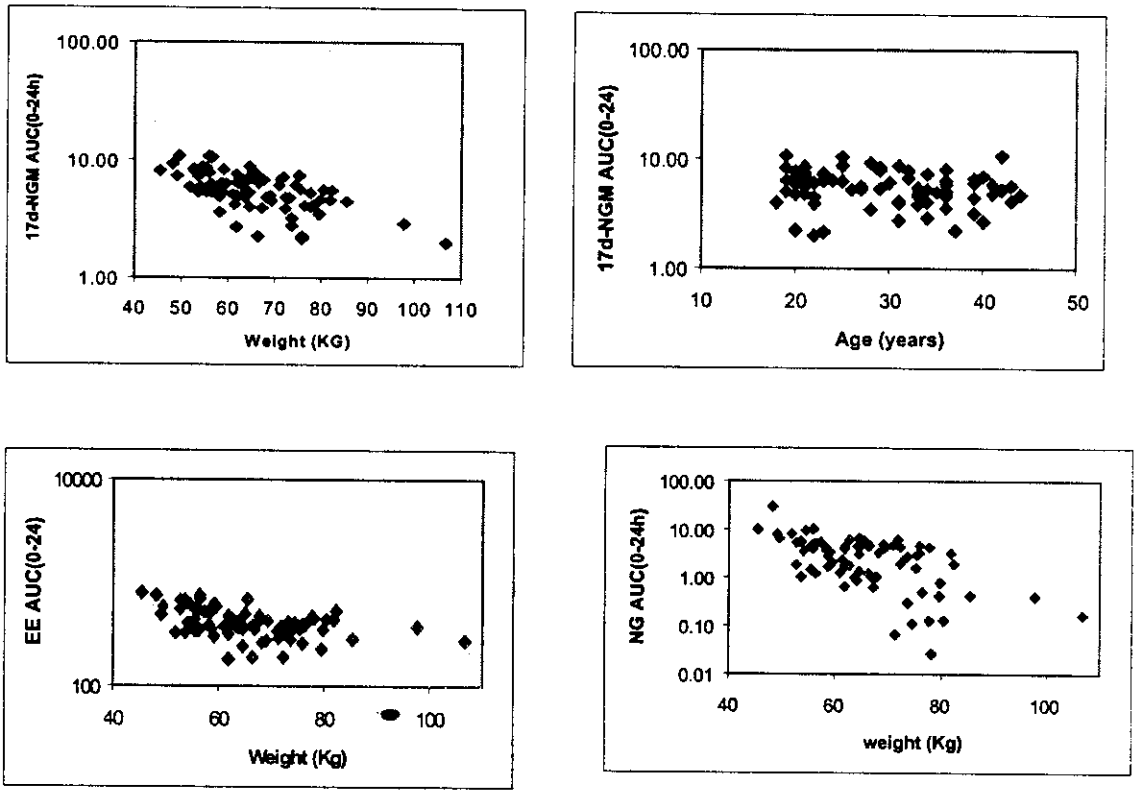

Fig.4. Effect of covariates on systemic exposure of 17d-NGM, NG and EE following single administration of Orthotricyclen (180 µg NGM/25 µg EE) tablets.

For 17d-NGM, regression analysis showed that race effect was not significant for either $AUC_{0\text{-}24h}$ or Cmax. However, the effect of age and BWT were significant with BWT being most significant. Therefore, the model was refitted for Cmax and $AUC_{0\text{-}24h}$ without race effect.

For NG, both race and age were not significant for either Cmax or $AUC_{0\text{-}24h}$. The model was refitted with only BWT effect.

For EE, none of the effects were significant for t1/2. (it should be noted that there was a high degree of variability in t1/2 due to some of the terminal blood concentration falling below LOQ.

Both age and race were not significant for Cmax, AUC and CL/F of EE. So, the model was refitted using BWT for these parameters. Similar effects were noted when BSA was used in the analysis in place of BWT.

Using the final regression models, the PK parameters of 17d-NGM, NG and EE were predicted for various age and BWT/BSA ranges.

It should be noted that although the age factor turned out to be statistically significant in the regression model for 17dNGM, the effect seems to be much less compared to the bodyweight factor (see Fig 4).

Table 11. Predicted changes in PK parameters with change in Age (from 30 years), BWT (from 65Kg) and BSA ($1.7m^2$)

Analyte	Parameter	Age (↑5 years)	BWT (↑10Kg)	BSA (↑$0.3m^2$)
17d-NGM	$AUC_{0\text{-}24h}$	↓5-6%	↓19%	↓36%
	Cmax	↓5-6%	↓9%	↓20%
NG	$AUC_{0\text{-}24h}$	NE	↓46%	↓74%
	Cmax	NE	↓12%	↓25%
EE	$AUC_{0\text{-}24h}$	NE	↓12%	↓24%
	Cmax	NE	↓13%	↓25%

It should be noted that R^2 values associated with regression were small (0.2 to 0.4) indicating that only up to 40% variability in PK parameter was explained by these covariates. Nonetheless, the trend towards decrease in PK parameters (especially for 17d-NGM) with increase BWT/BSA and age is statistically significant. These decreasing trends were reported in the Clinical Pharmacology section of the labeling, where sponsor

also stated that these effects were not observed in the clinical trials. The latter statement needs to be verified by the Medical and statistical reviews of the NDA.

Do NGM and its metabolites inhibit CYP 450 isozymes? If so, what is the potential of OrthoTricyclen to interact with coadministered CYP 450 substrates?

IN VITRO DRUG INTERACTION

The ability of NGM, 17d-NGM, NG, 3-keto NGM and EE to inhibit the major CYP450 enzymes (CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4/5 and 4A9/11) were evaluated using human liver microsomes. These studies were previously submitted to Ortho-Prefest NDA and the results are briefly summarized here.

To evaluate the potential of these steroids as reversible inhibitors of P450 activity, human liver microsomes were incubated with marker substrates (at concentrations equal to K_m and 4X K_m) in the presence or absence of each steroid at clinically relevant concentration ranging from [redacted] mM. To evaluate mechanism based inhibition potential, human liver microsomes were incubated for 0 to 10 minutes with the steroids prior to the addition of the marker substrate. The concentration of steroid in this experiment corresponded to the highest concentration that caused less than 20% reversible inhibition of p450 activity at a substrate concentration equal to K_m. Where ever possible, known reversible or mechanism based inhibitors of P450 activity were included as positive controls.

Table 12. In Vitro inhibition constants (K_I, μM)

CYP 450 Isozyme	17d-NGM	NGM	NG	3-keto NGM	EE
1A2	34.1	>90	>90	>90	17.7
2A6	>90	>90	40.3	>90	15.8
2C9	11.1	60.9	40.6	5-15[a]	5-15[a]
2C19	5.9	14.3	42.8	>90	14.8
2D6	10.4	3.52	>90	82.9	11.9
2E1	>90	>90	>90	>90	>90
3A4/5	11.3	20.2	51.2	16.1[b]	5.78
4A9/11	>90	>90	>90	>90	>90

[a] Mixed inhibition, [b] Noncompetitive inhibition

The results of this study suggest that NGM and its metabolites and EE can inhibit a variety of Cyp450 isozymes. However, clinically relevant total concentrations of these steroids from Ortho Tri-cyclen Lo administration at steady state (0.004 to 0.009 μM) are much lower than the K_i values for these inhibitions indicating that the potential for these interactions in vivo is low.

What are the serum protein binding characteristics of 17dNGM and NG?

PROTEIN BINDING

The protein binding characteristics of 17dNGM, NGM and NG in serum have been assessed in ex-vivo in women who received three cycles of either Orthocyclen or Ortho-tricyclen. The bound and unbound fractions were determined by equilibrium dialysis after spiking the serum with radiolabeled 17dNGM and NG.

Table 13: Protein Binding of 17d-NGM and NG (Percentage Bound)

Contraceptive Product	17d-NGM Mean (SD)	NG Mean (SD)
ORTHO-CYCLEN® (N = 18)		
Day 1 of Cycle 1	98.7 (0.09)	98.3 (0.3)
Day 21 of Cycle 3	98.6 (0.07)	98.8 (0.2)
ORTHO TRI-CYCLEN® (N = 20)		
Day 1 of Cycle 1	98.8 (0.2)	98.4 (0.5)
Day 21 of Cycle 3	98.7 (0.1)	99.0 (0.2)

In these studies, 17d-NGM and NG were highly bound to serum proteins (98.3 to 99.0%). The protein binding of 17d-NGM did not change significantly during dosing, since this molecule does not bind to SHBG. However, there was a statistically significant increase ($p<0.001$) in the binding of NG during three cycles of administration. The mean free fraction of NG decreased from 1.72% on Day 1 of Cycle 1 to 1.2% on Day 21 of Cycle 3 for Orthocyclen study (similar decrease was noted for Orthotricyclen also). Sponsor attributed this increase to an increased binding to SHBG, as a result of SHBG induction caused by coadministered EE. Although statistically significant, these differences are within the range of assay variability and thus should be interpreted with caution.

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I concur.

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