CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

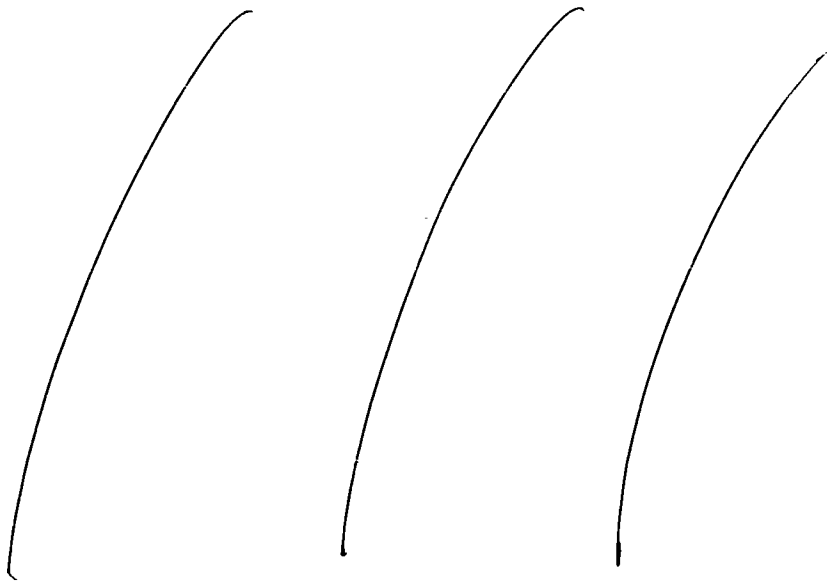
21-676

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MEMO TO FILE	
NDA	**21-676**
Submission Date	June 15, 2005
Brand Name	YAZ™
Generic Name	Drospirenone (DRSP) 3mg/Ethinyl Estradiol (EE) 0.02mg
Reviewer	Julie M. Bullock, Pharm.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Reproductive & Urologic Drug Products
Sponsor	Berlex, Inc.
Submission Type; Code	Standard
Dosing regimen	Once Daily
Indication	Oral Contraception

This memo addresses the Divisions proposed labeling changes for YAZ™. Only the relevant clinical pharmacology changes were included in this memo. The original NDA review was posted in DFS by Leslie Kenna, Ph.D. and the complete response was posted by Julie Bullock, Pharm.D..

1. Proposed Labeling Changes



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/s/

Julie Bullock
3/15/2006 08:18:13 AM
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Ameeta Parekh
3/16/2006 02:51:31 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review

NDA	**21-676 & 21-873**
Submission Date	December 22, 2004 June 15, 2004
Brand Name	YAZ™
Generic Name	Drospirenone (DRSP) 3mg/Ethinyl Estradiol (EE) 0.02mg
Reviewer	Julie M. Bullock, Pharm.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Reproductive & Urologic Drug Products
Sponsor	Berlex, Inc.
Submission Type; Code	Standard
Dosing regimen	Once Daily
Indication	21-676: Oral Contraception 21-873: Premenstrual dysphoric disorder (PMDD)

Briefing on November 18th attended by John Hunt, and Ameeta Parekh

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1 Executive Summary

YAZ is a 24-day oral contraceptive combination with 24 active tablets containing 3mg Drospirenone (DRSP) and 0.02 mg Ethinyl Estradiol (stabilized by betadex as a clathrate) and 4 inert film coated placebo tablets for use as an oral contraceptive and for the treatment of premenstrual dysphoric disorder.

YAZ tablets are a reduced estrogen version of YASMIN tablets (DRSP 3mg/EE 0.03mg) which were approved on May 11, 2001 for oral contraception (NDA 21-098). The main differences between YAZ and Yasmin® are below

	YAZ™	Yasmin®
Active Tablets	24	21
Placebo Tablets	4	7
Estrogen	0.02 mg EE as a betadex clathrate.	0.03 mg EE free steroid

Both YAZ and YASMIN contain DRSP, a novel progestin and derivative of 17α-spirolactone. DRSP possesses progestogenic and aldosterone-antagonist properties which differentiate DRSP from other currently marketed progestin's.

Berlex developed YAZ in the US under INDs 67,738 (oral contraceptives, OC) and 61,304 (premenstrual dysphoric disorder, PMDD). An NDA for the indication of oral contraception alone was submitted on October 16, 2003 (NDA 21-676; Reviewer: Leslie Kenna, Ph.D) and was found acceptable from a Clinical Pharmacology perspective. An approvable action was received on November 17, 2004 in which DRUDP stated in the approvable letter that the sponsor needed to demonstrate a clinical benefit for the 24-day regimen over that provided by the 21-day regimen to offset the increased potential risk associated with the additional 3 days of drospirenone/EE. The sponsor resubmitted a response to the NDA 21-676 approvable action on June 15, 2005. No new clinical pharmacology studies were submitted in the response to the approvable action

Berlex submitted a new NDA 21-873 on December 22, 2005 to demonstrate that the 24-day regimen is safe and effective for the secondary indication of the treatment of PMDD symptoms. PMDD is a medical disorder characterized by debilitating mood and behavioral changes, and frequently somatic complaints in the week preceding menstruation. The currently approved treatments for PMDD consist of various Selective Serotonin Re-uptake inhibitors which main indications are for the treatment of depression. The clinical development program of YAZ for the treatment of PMDD symptoms consists of two pivotal studies.

No new pharmacokinetic studies were submitted under NDA 21-873. Reference to NDA 21-676 was made for the Human Pharmacokinetics and Bioavailability section. During the initial review cycle for NDA 21-676 the NDA was deemed acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. In the NDA 21-873 for the PMDD indication, the sponsor has not made any changes which could impact the Clinical Pharmacology and Biopharmaceutics review. There has been no change in dose, nor has there in any change in drug formulation. The formulation used in the clinical trials was identical to the formulation used in NDA 21-676, which was equivalent to the to-be-marketed formulation.

In the original 21-873 NDA submission, the sponsor has provided the results of two large clinical trials:

- 304049: A multi-center, randomized, parallel group, study consisting of 2 qualifying menstrual cycles and 3 treatment cycles. The objective of this study was to evaluate the effectiveness of YAZ in the treatment of women with symptoms of PMDD. Primary efficacy variable was the change from baseline in the PMDD symptoms as measured by subject-recorded symptoms on the Daily Rating Severity of Symptoms (DRSP) scale. 450 subjects were randomized to YAZ or placebo.
- 305141: A multi-center, randomized, crossover study. A total of 64 subjects completed 2 qualification cycles, 3 treatment cycles with YAZ or placebo, a washout cycle, and 3 treatment cycles with YAZ or placebo. The objective of the study was to evaluate the effectiveness of YAZ in the treatment of women with symptoms of PMDD. The primary efficacy variable was the change from baseline in the PMDD symptoms as measured by the DRSP scale.

Refer to the NDA 21-676; YAZ for oral contraception for detailed information on the products clinical pharmacology and biopharmaceutics characteristics.

In addition please reference the submission made on March 31, 2005 for NDA 21-355 (Angeliq) which contains a Phase 1 drug-drug interaction study to evaluate the potential of DRSP to inhibit CYP3A4 using midazolam as a marker substrate for CYP3A4. The review of this study was completed by Julie Bullock, Pharm.D. (Review in DFS).

In brief, the study was a placebo controlled steady state crossover study to assess drospirenone's potential to inhibit CYP3A4. Each subject received DRSP 3mg or placebo to steady state and a single dose of midazolam was given on Days 7 and 9. The primary target variable was the mean of Days 7 and Day 9 AUC for Midazolam and its hydroxy-metabolite, 1-hydroxy-midazolam. The 90% confidence intervals for the geometric mean fell within the 80-125% confidence intervals needed for bioequivalence for AUC (see Table 1). A BE analysis for Cmax was not provided by the sponsor. An analysis using WinNonlin was performed by the reviewer and the average of Days 7 and 9 fell within the 90% confidence interval limit (see Table 2). The study concluded that DRSP at doses up to 3 mg per day does not potently inhibit CYP3A4 and that dose reductions for substrates of CYP3A4 would be clinically un-necessary.

TABLE 1: AUC 90% confidence intervals for assessment of bioequivalence

Primary target variable	Mean ratio	Lower confidence limit	Upper confidence limit
Mean of AUC(0-tlast) of MDZ at Day 7 and Day 9	97.9%	90.9%	105.4%
Mean of AUC(0-tlast) of 1'OH-MDZ at Day 7 and Day 9	96.1%	87.4%	105.8%

TABLE 2: Cmax 90% confidence intervals for assessment of bioequivalence (calculated by reviewer)

Primary target variable	Mean ratio	Lower confidence limit	Upper confidence limit
Mean of Cmax of MDZ at Day 7 and Day 9	101.9%	89.7%	115.7%
Mean of Cmax of 1'OH-MDZ at Day 7 and Day 9	97.1%	83.6%	112.8%

Recommendation

NDA 21-676, YAZ for Oral Contraception is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

NDA 21-873, YAZ for PMDD is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

Julie M. Bullock, Pharm.D.

Ameeta Parekh, Ph.D., Team Leader

APPEARS THIS WAY
ON ORIGINAL

2 Summary of Clinical Pharmacology and Biopharmaceutics

Refer to the review of YAZ for oral contraception NDA 21-676 by Leslie Kenna, Ph.D.

3 Detailed Labeling Recommendations

Changes to the label will be posted in DFS separately when complete.

4 Appendices

4.1 Cover Sheet and OCPB Filing / Review Form

Please see previous DFS submission by Julie Bullock

4.2 Review of YAZ for Oral contraception

Refer to previous submission to DFS for NDA 21-676 by Leslie Kenna

4.3 Review of Yasmin

Refer to a previous submission to DFS for NDA 21-098 by Venkat Jarugula.

4.4 Review of Study 036946

Refer to DFS review of Angeliq (NDA 21-355) complete response by Julie Bullock

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/s/

Julie Bullock
12/5/2005 01:50:17 PM
BIOPHARMACEUTICS

Ameeta Parekh
12/5/2005 01:56:46 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA	21-676
Product Trade Name	YAZ
Active Ingredients	Drospirenone (DRSP): 3.0 milligrams Ethinyl Estradiol (EE): 0.020 milligrams
Formulation	Oral tablet; Ethinyl Estradiol in a betadex clathrate
Product	24 active tablets; 4 inert tablets
Indication	Prevention of pregnancy
Sponsor	Berlex
Relevant Submission Dates	October 16, 2003, January 29, 2004, May 27, 2004, July 9, 2004
Type of Submission	Standard
Relevant NDAs	21-098, 21-355
Reviewer	Leslie Kenna, Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	DPE-II
ORM Division	Reproductive and Urologic Drug Products

I. Executive Summary

This product, Yaz, is an oral contraceptive regimen consisting of: (1) 24 active film coated tablets each containing drospirenone 3.0 mg and ethinyl estradiol 0.020 mg stabilized by betadex as a clathrate (molecular inclusion complex), and (2) 4 inert film coated conventional tablets.

Yaz is similar to a currently marketed product, Yasmin, which is also marketed by Berlex and indicated for the prevention of pregnancy. However, the currently marketed product (Yasmin) consists of: (1) 21 active film coated tablets each containing 0.030 mg ethinyl estradiol as a free steroid and 3.0 mg drospirenone, and (2) 7 inert film coated tablets.

Note the following three differences between Yaz (the product in this NDA) and Yasmin (the currently marketed product): (1) Yaz has a reduction of 0.010 mg in the dose of ethinyl estradiol (EE) relative to Yasmin (from 0.030 mg to 0.020 mg), (2) Yaz has a change in the formulation of EE (from a free steroid to a clathrate), and (3) Yaz has an increase in the duration of active tablet dosing (from 21 to 24 days). Note that data from clinical studies with Yaz were submitted in support of this application; efficacy is not evaluated on the basis of establishing bioequivalence with Yasmin.

The rationale for the magnitude of reduction in EE dose is based on information available for already marketed oral contraceptives. The stated purpose of the β-cyclodextrin clathrate formulation is to promote shelf stability of EE. The Sponsor claims that a 24-day regimen, rather than a 21-day regimen, was pursued to: (1) minimize symptoms associated with hormone-free intervals (such as premenstrual syndrome/premenstrual dysphoric disorder (PMS/PMDD) and acne), and (2) improve suppression of follicular

activity and ovulation inhibition via a shortened hormone-free interval. Substantiation of these claims is not the subject of this submission. The Sponsor has separate ongoing studies that are analyzing secondary indications such as premenstrual dysphoric disorder and acne.

Safety and efficacy of a 24-day Yaz regimen was demonstrated in a multi-center, open, uncontrolled study for 13 cycles in approximately 1000 healthy female volunteers aged 18 to 35 years. The primary efficacy variable was the number of unintended pregnancies as measured by the Pearl Index ("PI"). Secondary variables include cycle control parameters and bleeding pattern. Eleven pregnancies occurred during treatment yielding a PI of 1.41. This PI value lies within the generally accepted criteria for efficacy. Approved products have PI values as high as 2.39. According to the Medical Officer's review of this NDA, after the first cycle of use the amount of intracyclic bleeding remained generally within the 10-15% range (deemed acceptable).

To support the clinical pharmacology evaluation of this product, the Sponsor has submitted the results of a single bioavailability study, 5 human pharmacokinetics studies, a protein binding study and 2 uncontrolled pharmacodynamic studies. In this submission, reference is made to these new studies and to the approved NDA 21-098.

Reference is also made to NDA 21-355, a submission by this Sponsor (Berlex), for Angeliq tablets (1 mg or 3 mg DRSP / 1 mg Estradiol) indicated for the treatment of moderate to severe vasomotor symptoms, [redacted] and vulvar and vaginal atrophy in postmenopausal women. In NDA 21-355, the Sponsor submitted the results of: (1) a study of the effect of renal impairment and (2) a study of the effect of hepatic impairment on the pharmacokinetics of 3 mg DRSP. Note that the Sponsor received a Not-Approvable letter dated October 17, 2002 for NDA 21-355. The Sponsor submitted a complete response to the Not-Approvable letter on March 18, 2004, which received an Approvable letter on September 14, 2004.

Recommendation
This NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

Phase IV Commitments
None.

Briefing Details
An optional intra-division briefing was held on November 2, 2004 from 8:30-9:30 am in Parklawn 13B17.
In attendance were: Leslie Kenna, Ameeta Parekh, Hank Malinowski, John Hunt, Myong Jin Kim and Gerald Willett.

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III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor has provided the results of a single bioavailability study, 5 human pharmacokinetics studies, a protein binding study and 2 uncontrolled pharmacodynamic studies to support a clinical pharmacology evaluation of this product in this submission. Specifically, the following study reports were submitted:

Bioavailability study

- Study B862:

  Open-label, randomized, crossover study to evaluate the relative bioavailability of ethinyl estradiol (EE) and drospirenone (DRSP) from two tablet formulations each containing 20 µg EE + 3 mg DRSP (SH T00186D and SH T00186A) in comparison with a [redacted] suspension of 40 µg EE + 6 mg DRSP after single oral administration in healthy postmenopausal volunteers

Pharmacokinetic studies

- Study A01222:

  Single dose pharmacokinetics of SH T00186D (3 mg drospirenone + 20 µg ethinyl estradiol) and of SH T00186E (1 mg, 3 mg and 6 mg drospirenone) after oral administration in young Caucasian women

- Study 03328:

  Two-center, open-label, non-randomized study to determine the multiple dose pharmacokinetics of SH T00186D (3 mg drospirenone + 20 µg ethinyl estradiol) after oral administration in a 21-day regimen in healthy young Caucasian and Japanese women

- Study 03773:

  Single dose pharmacokinetics of SH T00186D (3 mg drospirenone + 20 µg ethinyl estradiol) and of SH T00186E (1 mg, 3 mg and 6 mg drospirenone) after oral administration in young Japanese women

- Study BD09:

  Open-label, randomized, crossover study to assess the potential of drospirenone (DRSP) to inhibit Cytochrome P450 3A4 by evaluating the metabolic interaction between DRSP and simvastatin as model substrate in healthy postmenopausal volunteers

Study a11620:

Double-blind, randomized, crossover study to assess drospirenone's (DRSP) potential to inhibit Cytochrome P450 3A4 by evaluating the interaction between DRSP at steady state and single doses of the model substrate midazolam in healthy postmenopausal women

Protein binding study

- Study AW06:

  Determination of drospirenone serum protein binding in a study of the influence of SH T470 F, SH T 470 I, and SH T 470 K on parameters of the renin-angiotensin-aldosterone system (RAAS), electrolyte metabolism and lipid and carbohydrate metabolism.

Pharmacodynamic studies

- Study A11401:

  Multicenter, open-label, uncontrolled study to evaluate ovulation inhibition with SH T 00186 DB (0.02 mg ethinylestradiol-beta-cyclodextrin clathrate and 3 mg drospirenone) applied for two treatment cycles to 30 female Japanese subjects

- Study A09372

  Monocenter, open label, uncontrolled study to evaluate ovulation inhibition with SH T00186D (0.02 mg ethinylestradiol-beta-cyclodextrin clathrate) and 3 mg drospirenone), applied for two treatment cycles to 30 female volunteers

The following table summarizes the formulation of ethinylestradiol used in each of the Clinical Pharmacology studies. Note that the to-be-marketed and clinical formulations of EE were used in all but the protein binding study.

Study	Formulation	Idenfication	Batch	To-be-marketed EE formulation? (Clathrate)
B862	Ethinylestradiol (FS)* Ethinylestradiol (BC)** [redacted] (S)***	SH T00186A SH T00186D SH M00186A	AC032	Yes
A01222	Ethinylestradiol (BC)**	SH T00186D	H14501	Yes
03328	Ethinylestradiol (BC)**	SH T00186D	11004	Yes
03773	Ethinylestradiol (BC)**	SH T00186D	02002	Yes
BD09	DRSP	SH T00470R	NA	NA
A11620	DRSP	SH T00470R	NA	NA
AW06	Ethinylestradiol	SH T00470 F SH T00470 I SH T00470 K	NA	No
A09372	Ethinylestradiol (BC)**	SH T00186D	I16401	Yes
A11401	Ethinylestradiol (BC)**	SH T00186D	CL-2554	Yes

*FS = Free Steroid

**BC = Betadex Clathrate

***S = Suspension

Table 1. Formulation Used in Each of the Clinical Pharmacology Studies in this Submission.

The Sponsor has cross-referenced their NDA on Yasmin, 21-098. In this review, reference is made to the aforementioned studies, to the Approved NDA 21-098 (Yasmin 28 tablets), and to the Approvable (dated 9/14/04) NDA 21-355 (Angeliq tablets).

IV. Question Based Review

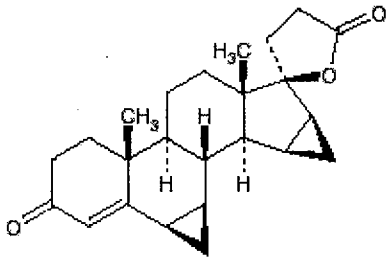
A. General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the product?

- Active Components

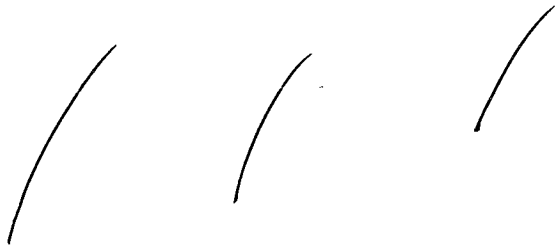
The structural formula for the components of Yaz are illustrated in Figure 1.

(A) Drospirenone



Molecular weight: 366.50

(B) Ethinyl Estradiol-β-cyclodextrin clathrate



(C) β-cyclodextrin

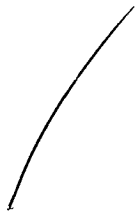


Figure 1. Structural Formulas of the Active Components of Yaz.

A clathrate, or a solid inclusion compound, is a crystalline compound consisting of molecules of two different types. One compound (considered the "guest") associates within the cavity of the second molecule (the "host"). The host-guest association depends on both: (1) weak physical bonds (e.g. Van der Waal's Forces, hydrophobic interactions) and (2) the geometric properties of the cavity; the molecules do not associate via ionic or covalent bonds. Drug-clathrate inclusion complexes have been used in pharmaceutical applications for the following purposes:

- Mask unpleasant tastes or odors
- Avoid incompatibility between ingredients of a formulation

• Increase stability to temperature, oxidation, photodegradation, etc.
• Increase aqueous solubility and enhance absorption
• Alter the appearance of the formulation
• Alter the rate of isomerization

Yaz is formulated using a β-cyclodextrin clathrate (Betadex NF) to protect the estradiol moiety from degradation. Cyclodextrins are cyclic oligosaccharides with six (α), seven (β) or eight (γ) glucose units. The β-cyclodextrin for Yaz is a

Other drugs which have incorporated cyclodextrins in their formulation include voriconazole, itraconazole, ziprasidone and alprostadil.

Note that the Sponsor has conducted a clinical trial of Yaz to demonstrate efficacy. Therefore, the evaluation of this product does not rely on demonstrating bioequivalence with the marketed product, Yasmin. Thus, the effect of this change in formulation on dissolution need not be evaluated in this regard.

• Physical Properties
Table 1 lists various physical properties of the active components of Yaz.

Characteristic	Drospirenone	Ethinyl Estradiol
Appearance		White to off-white powder
pKa	Neutral molecule; no acid-base properties in aqueous solutions (pH 1 to 12)	10.51 ± 0.03
Solubility		

Table 2: Physical and Chemical Characteristics of Drospirenone and Ethinyl Estradiol.

• Drug Product
Yaz, a combination product of drospirenone (DRSP) 3 mg and ethinyl estradiol (EE) 0.020 mg (as the β-cyclodextrin clathrate), is a film-coated, round, biconvex, 6 mm diameter tablet, colored light pink and with "DS" in a regular hexagon on one side. DRSP/EE tablets are packaged in a configuration containing 28 tablets (24 active and 4 inert tablets).

The inert tablets are film-coated, round, biconvex, 6 mm diameter tablets, colored white and with "DP" in a regular hexagon on one side.

Ethinyl estradiol as the free steroid is the pharmacologically active moiety of the ethinyl estradiol-β-cyclodextrin clathrate. When dissolved in water, the EE-β-cyclodextrin clathrate dissociates into its components EE and the ligand β-cyclodextrin. The dissociation rate constant of the EE-β-cyclodextrin complex was determined through *in vitro* stopped-flow conductometric studies of the competition reaction between sodiumdodecylsulfate and EE to form inclusion complexes with β-cyclodextrin. Under first order conditions the half-life of dissociation of the EE-β-cyclodextrin complex (1:1) was calculated to be 2.6 minutes.

2. What is the proposed mechanism of drug action and therapeutic indications?
Combination oral contraceptives act by suppression of ovulation and also lead to changes in the viscosity of cervical mucus which may inhibit sperm penetration.

3. What is the proposed indication, dosage and route of administration?
Yaz is indicated for the prevention of pregnancy.

Each monthly dosing regimen cycle consists of 1 active tablet taken orally once daily for 24 consecutive days followed by 1 inactive tablet taken orally once daily for 4 days. The tablets are to be taken in the morning or evening, but the interval between 2 tablets is to be as close as possible to 24 hours.

B. General Clinical Pharmacology

1. What are the general pharmacokinetic characteristics of the product?
The systemic clearance of DRSP is 1.5 ml/min/kg. Plasma concentrations of DRSP decline in a biphasic manner with a terminal half-life of about 30 hrs. The volume of distribution at steady-state (Vss) following I.V. administration is 4 L/kg, indicating that DRSP distributes well into the tissue. Approximately 38.5% of total radioactivity was excreted in urine and 44.3% in feces within 10 days following oral administration of 3.13.mg of 14C-DRSP. Since DRSP is well absorbed (absolute bioavailiability = 76 ± 13%), this suggests that biliary secretion may be an important mechanism of elimination. There is 2-3-fold accumulation at steady state.

DRSP was extensively metabolized; only trace amounts (1-2%) were excreted unchanged in urine and feces. About 20 metabolites were detected in urine and feces, each of the peaks accounting for less than 5% of the dose. Approximately 29-34% of radioactivity excreted in urine was excreted as glucuronide conjugates and 9-12% as sulfate conjugates. Approximately 5% of radioactivity excreted in feces was excreted as glucuronides and 12-15% as sulfates. Two major metabolites that could be identified, M11 (the acid form of DRSP formed by opening of the 21,17 carbolactone ring) and M14 (4,5 dihydro-DRSP-3-sulfate) are reported not to be pharmacologically active and are formed independently of the cytochrome P450 sytem.

DRSP is excreted into the breast milk, but the total intake ingested by the infant is only a small fraction of the dose and not likely to be of clinical significance. The fraction of DRSP excreted into breast milk is comparable to that observed for other progestens.

The bioavailability of EE is 40%. It distributes well with a Volume of 4-5 L/kg. The half life is 24 hours. There is approximately 2-fold accumulation at steady state. EE is highly metabolized. It is subject to hydroxylantion, methylation and conjugation in the small bowel.

Trace amounts of Cyclodextrin are absorbed. Cyclodextrins are resistant to stomach acid and pancreatic or salivary amylases. They are extensively hydrolyzed in the colon by the bacterial microflora to glucose and malto-oligosaccharides, which are then further fermented by anaerobic microorganisms in the colon to form short chain fatty acids and intestinal gases.

The pharmacokinetics of Yaz (3.0 milligrams DRSP + 0.020 milligrams Ethinyl Estradiol) and of 1 mg, 3 mg and 6 mg of drospirenone alone were investigated in a single dose study in young Caucasian women. The pharmacokinetic parameters of DRSP are tabulated below. The pharmacokinetic parameters for 3 mg drospirenone reported here are consistent with those reported in a study supporting the original submission of Yasmin (NDA 21-098). Note that there is a slight increase in CL/F for 3 mg DRSP when dosed with Ethinyl Estradiol relative to when dosed alone. This suggests that the clathrate formulation of ethinyl estradiol may exert a small influence the pharmacokinetics of drospirenone.

Pharmacokinetic parameter	Unit	Dose group			
		1 mg DRSP (N = 6)	3 mg DRSP (N = 6)	6 mg DRSP (N = 6)	3 mg DRSP + 20 µg EE2 (N = 18)
Cmax	ng/mL	9.85 (18.9%)	33.9 (20.4%)	62.5 (19.5%)	30.9 (27.0%)
tmax	h	1.25 (1 – 2)	1.5 (1 –2)	1.75 (1.5 – 2)	1.5 (1 – 4)
t1/2	h	25.5 (19.7%)	28.5 (16.4%)	26.3 (15.5%)	27.7 (18.4%)
AUC	ngxh/mL	140 (9.11%)	506 (21.5%)	1007 (20.7%)	458 (18.1%)
CL/F	mL/min	119 (9.03%)	98.7 (21.5%)	99.3 (20.6%)	109 (18.1%)

Cmax: maximum concentration of drug in serum after drug administration
tmax: time to reach maximum concentration following drug administration
t1/2: half-life of the last perceivable disposition phase
AUC: area under the concentration versus time curve from dosing time extrapolated to infinity
CL/F: total oral clearance

Table 3. Pharmacokinetic Parameters for Drospirenone After Dosing a Yaz Tablet and Various Doses of Drospirenone Alone.

The following table shows the pharmacokinetic parameters of ethinyl estradiol for Yaz obtained in this study.

	Tmax (hr)	Cmax	AUC_{0-24}	t½
EE2	1.5 hr (range: 1-4)	46.1 pg/mL (49.4%)	184 pg hr/mL (77%)	NA

Table 4. Pharmacokinetic Parameters for Ethinyl Estradiol After Dosing a Yaz Tablet.

2. What is the bioavailability of the product?

Based on reports in the literature, very small amounts of β-cyclodextrins are absorbed.

The relative bioavailability of EE and DRSP from two different tablet formulations, each containing 20 µg EE + 3 mg DRSP, was compared to a [redacted] suspension containing 40 micrograms EE + 6 mg DRSP in a crossover study in 18 postmenopausal women aged 48-75. The following test products were evaluated: two tablets of 20 µg EE-betadex clathrate/3 mg DRSP (**Test 1;** Yaz formulation), two conventional tablets of 20 µg EE as a free steroid/3 mg DRSP (**Test 2**), and an oral dose of a [redacted] suspension containing 40 µg EE/6 mg DRSP (Standard treatment, **ST**). A double dose was used to ensure analytic sensitivity for EE measurement.

The AUC and Cmax for EE and DRSP relative to a [redacted] suspension is provided below. The values of Test 1 vs Standard and Test 2 versus Standard are close to 100%, suggesting that dissolution does not affect the bioavailability of neither the free steroid nor the clathrate product. In addition, the values of Test 2 vs. Test 1 are close to 100% (all under 10%), suggesting that the free steroid and clathrate products have similar absorption.

Absolute bioavailability was not determined for Yaz. Absolute bioavailability for DRSP when dosed alone was previously determined as 76 ± 13%.

	Comparison		
Pharmacokinetic parameter	Test 1 vs ST[a]	Test 2 vs ST[a]	Test 2 vs Test 1[a]
EE, Cmax	100.9 (89.6-113.6)	105.8 (94.0-119.2)	104.9 (93.2-118.1)
EE, $AUC_{(0\text{-}tlast)}$	97.2 (85.3-110.7)	104.3 (91.6-118.8)	107.3 (94.2-122.3)
DRSP, Cmax	102.7 (93.5-112.9)	111.9 (101.8-122.9)	108.9 (99.1-119.6)
DRSP, $AUC_{(0\text{-}tlast)}$	107.0 (98.7-116.1)	108.2 (99.8-117.4)	101.1 (93.2-109.7)

Table 5. AUC and Cmax for EE and DRSP Relative to Standard [redacted] Suspension) with the 90% Confidence Interval. Test 1: Estradiol as a Betadex Clathrate. Test 2: Estradiol as a Free Steroid.

Note that the sponsor performed a similar experiment for Yasmin. Studies of the bioavailability of Yaz and Yasmin relative to the [redacted] suspension suggest that they may differ in terms of EE exposure. Following single dose administration of Yasmin, the bioavailability relative to a suspension of DRSP and EE was 107% and 117%, respectively (data in NDA 21-098). In contrast, as Table 5 showed, the bioavailability relative to a suspension of DRSP and EE for Yaz is 107.0% (98.7-116.1) and 97.2% (85.3-110.7), respectively. That is, there was a difference in average relative bioavailability of 20% for EE (less F for Yaz). Such a comparison across different studies, however, must be interpreted cautiously.

3. How does Protein Binding Influence Drug Disposition?

In the Yasmin (the approved DRSP/EE free steroid product) NDA, DRSP was shown to be 94-97% bound to serum proteins. The free DRSP fraction was found to be unchanged over a 10-32 ng/ml concentration range (i.e. trough levels of a 2-4 mg multiple

administration dose range) and shown not bind to a significant extent to sex hormone-binding globulin (SHBG) or corticoid-binding globulin (CBG).

In this submission, the sponsor provided the results of a study of the effect of ethinyl estradiol on the induction of sex hormone-binding globulin (SHBG) or corticoid-binding globulin (CBG) after dosing DRSP 3 mg / EE free steroid (various doses). The study was a double blind, randomized parallel design in 80 females aged 18 to 34 years over 6 treatment cycles. The following regimens were tested:

- Microgynon (30 micrograms EE + 150 micrograms levonorgestrel)
- 3 mg DRSP + 15 micrograms EE2 free steroid Formulation K
- 3 mg DRSP + 20 micrograms EE2 free steroid Formulation I
- 3 mg DRSP + 30 micrograms EE2 free steroid Formulation F

Protein binding was determined on the last day of cycles 1, 3 and 6.

The following table reports the SHBG concentrations in serum over time.

Cycle	SH T 470 K	SH T 470 I	SH T 470 F	Microgynon
Pretreatment	60 ± 22	73 ± 33	81 ± 40	61 ± 25
1	197 ± 49	187 ± 59	205 ± 50	98 ± 34
3	190 ± 61	203 ± 70	205 ± 58	108 ± 39
6	186 ± 54	172 ± 61	220 ± 82	87 ± 42
Posttreatment	94 ± 35	89 ± 38	82 ± 42	61 ± 25

Table 6. Mean (+/- sd) SHBG Concentrations in Serum (nmol/L). Note that there were 21 days of active tablet dosed in each cycle.

The following table reports the CBG concentrations in serum over time.

Cycle	SH T 470 K	SH T 470 I	SH T 470 F	Microgynon
Pretreatment	42 ± 10	47 ± 11	48 ± 9	48 ± 13
1	81 ± 16	83 ± 16	97 ± 24	83 ± 12
3	75 ± 20	76 ± 20	104 ± 22	92 ± 23
6	66 ± 15	85 ± 25	97 ± 29	83 ± 27
Posttreatment	64 ± 46	55 ± 23	49 ± 14	47 ± 18

Table 7. Mean (+/- sd) CBG Concentrations in Serum (nmol/L). Note that there were 21 days of active tablet dosed in each cycle.

Table 6 and Table 7 suggest that there is an increase in SHBG and CBG in the serum of women treated with 15, 20 or 30 micrograms EE in combination of 3 mg DRSP. The change appears to correlate with ethinyl estradiol dose. There is up to a 3-fold change in SHBG and a 2-fold change in CBG within dosing cycles. The changes observed appear to plateau after a single dosing cycle for the duration studied.

Table 8, a comparison of the free fraction of DRSP as a function of dose and duration of exposure, suggests that the free fraction of DRSP when dosed with 20 micrograms Ethinyl Estradiol is slightly lower than when dosed with 30 micrograms Ethinyl

Estradiol. However, the values are within the measured variability of percent bound shown previously for DRSP (94-97%). The slight increase in the fraction unbound for the 30 microgram Estadiol dose does not correlate with the slight increase in SHBG and CBG, thus, the differences likely represent measurement error, not a physiological effect. Note that the free fraction is constant over the duration of dosing investigated. This suggests that there are no delayed effects on binding.

	20 microgram EE2 regimen	30 microgram EE2 regimen
Cycle 1	4.5 +/- 0.9%	4.8 +/- 1.2%
Cycle 3	3.9 +/- 0.8%	4.9 +/- 0.9%
Cycle 6	4.1 +/- 0.8%	4.6 +/- 0.7%

Table 8. Free Fraction of DRSP as a Function of Dose and Duration of Exposure.

Note that the 3 mg DRSP + 20 microgram EE regimen tested is not identical to the Yaz formulation since it is the free steroid, nor is it identical to the Yaz regimen because the sponsor dosed it for a total of 21 days with 7 days off treatment (instead of 24 days on treatment / 4 days off). Given that steady state levels of drug should be reached after 8 days of dosing, the effect on SHBG and CBG is expected stabilize by 3 weeks. Thus, this 21 day regimen is relevant for predicting the results of dosing for 24 days.

4. Do the PK parameters change with time following chronic dosing?
DRSP pharmacokinetics are dose proportional in the range of 1 – 10 mg following oral administration. Steady-state is achieved after 8 days of daily administration with accumulation ratios of 2 to 3 based on AUC comparison. This is consistent with a half life of 30 hours.

5. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?
In this submission for Yaz, the Sponsor notes that experience from marketed OCs supports the reduction of daily EE dose from 0.03 mg to 0.02 mg.

No dose-finding study to optimize the dose of DRSP or EE was performed specifically for this NDA, however, dose-finding studies for DRSP were submitted in NDA 21-098 for Yasmin. As noted in the Clinical Pharmacology review of NDA 21-098, Study A892 aimed to determine the minimum dose of DRSP sufficient for ovulation inhibition. A total of 48 healthy pre-menopausal women aged 19-35 years were randomized over 4 treatment groups (0.5, 1, 2 and 3 mg DRSP per day) and dosed for 21 days. The 3 mg DRSP dose over 21 days was determined as the minimum dose with ovulation-inhibition efficacy.

The EE dose in the currently marketed product Yasmin (0.03 mg) is a standard, compared with many other oral contraceptives. In Study A892 in NDA 21-098, the 0.03 mg dose EE was found to carry a lower frequency of intracyclic bleeding, compared to 15 and 20 μg. The EE dose in that study was administered for 21 days, as opposed to 24 days with Yaz.

Safety and efficacy of a 24 day Yaz regimen was demonstrated via a multi-center, open, uncontrolled study for 13 cycles in approximately 1000 healthy female volunteers aged 18 to 35 years. The primary efficacy variable was the number of unintended pregnancies as measured by the Pearl Index ("PI"). Secondary variables include cycle control parameters and bleeding pattern. Eleven pregnancies occurred during treatment yielding a PI of 1.41. This PI value lies within the generally accepted criteria for efficacy. Approved products have PI values as high as 2.39. According to the Medical Officer's review of this NDA, after the first cycle of use the amount of intracyclic bleeding remained generally within the 10-15% range (deemed acceptable).

Cycle control and safety of DRSP 3mg/EE 0.020 mg for a 21-day regimen was compared with Mercilon® (DSG 0.150 mg/EE 0.020 mg) for 7 cycles in a multicenter, open-label, randomized, parallel-group study (Report A09653). A total of 441 healthy female subjects enrolled in this study (220 in the DRSP 3 mg/EE 0.020 mg group, 221 in the Mercilon® group). Both treatments were demonstrated equivalently safe and efficacious for this shorter regimen, as compared to the 24-day regimen.

The effect of Yaz (DRSP 3 mg/EE 0.020 mg; 24-day regimen) compared with Mercilon® (DSG 0.150 mg/EE 0.020 mg) on plasma lipids, hemostatic variables, and carbohydrate metabolism was investigated in a single-center, open-label, randomized study (Report A09151). A total of 59 healthy female subjects were studied over 7 cycles (N=29 in the DRSP 3mg/EE 0.020 mg group, N=30 in the Mercilon® group). In addition to these parameters, bleeding pattern and pregnancy data were collected. Results for both study treatments showed comparable changes for lipid, carbohydrate, and hemostatic metabolism.

Two phase 2 studies of efficacy were performed to evaluate drug effect on ovulation inhibition. Study A11401 was an open-label, uncontrolled study to evaluate ovulation inhibition with Yaz when applied for two treatment cycles to 30 Japanese subjects. Duration of treatment was 2 cycles of 28 days duration having 21 active tablets in a 21 tablet blister, followed by a 7-day tablet-free interval. All volunteers in the per-protocol analysis group had an ovulation in the pretreatment cycle and all had ovulation inhibited during the treatment cycle. FSH values remained low during the follicular phase of the cycles 1 and 2 and the pronounced decrease in the second half of a normal ovulatory cycle was absent. No LH peak was observed in the middle of the cycles; E2 and progesterone levels were below the levels in the pretreatment cycle; progesterone levels remained at a low level throughout the treatment cycles. In the posttreatment cycle, the hormone levels returned to the pattern typical for ovulatory cycles and were comparable to the pretreatment cycle.

Study A09372 was of a similar design as Study A11401 except that it was conducted primarily in Caucasian volunteers. In this group, 92.9% of the volunteers included in the per-protocol (PP) analysis had follicular size ratings below that associated with ovulation. For 2 volunteers (PID 105, 128), Hoogland scores of 6 (potential ovulation) were assessed in treatment cycle 2. For PID 105, the results of the pharmacokinetic determination of the drospirenone blood levels suggest that no study medication was

taken in treatment cycle 2. For PID 128, the drospirenone blood levels were typical of a treatment cycle. The volunteer mentioned a history of cyst formation under OCs.

6. What is the effect of the product on QT interval?
The effect of Yaz on the QT interval has not been determined or addressed.

C. Intrinsic Factors
1. What is the effect of renal impairment on the pharmacokinetics of the product?
The effect of severe renal impairment has not been studied.

Based on the information in the Clinical Pharmacology review of the initial submission of NDA 21-355 for Angeliq, following multiple daily dosing of DRSP 3mg tablets for 14 days (to steady state levels), serum DRSP levels in a group with moderate renal impairment (CLcr, 30 - 50 mL/min) were on average 37 % higher compared to those in the group with normal renal function (CLcr, >80 mL/min). DRSP levels in subjects with mild renal impairment (creatinine clearance CLcr, 50-80 mL/min) were comparable to those in the group with normal renal function.

DRSP treatment did not show any clinically significant effect on serum potassium concentration. The reviewer noted that hyperkalemia was not observed in the study in five of the seven subjects who continued use of potassium sparing drugs during the study, but individual mean serum potassium levels increased by up to 0.33 mEq/L (to 4.67 mEq/L). The reviewer also noted that the potential exists for hyperkalemia in subjects with renal impairment whose serum potassium is in the upper normal range and who are concomitantly using potassium sparing drugs.

2. What is the effect of hepatic impairment on the pharmacokinetics of the product?
The effect of severe hepatic impairment has not been studied.

Based on the information in the Clinical Pharmacology review of the initial submission of NDA 21-355 for Angeliq, the exposure to DRSP in subjects with moderate hepatic impairment is about three times higher compared to normal subjects. This is consistent with DRSP being a drug which is extensively metabolized.

The reviewer of NDA 21-355 noted that one subject in the moderate hepatic impairment group experienced hyperkalemia beginning at 72 hours following DRSP administration. This subject had the highest AUC of DRSP in the group. It should be noted that this subject was taking K-Dur and her potassium levels were in the normal range until 72 hours after DRSP administration indicating that DRSP administration might have increased her serum potassium. Although no significant difference in serum potassium levels was found between the group of normal subjects and subjects with moderate impairment, the number of subjects (n=10) may be too small to detect significant difference. Since there is already a clinical concern for hyperkalemia with DRSP and the exposure of DRSP is higher in moderate hepatic impairment, the reviewer noted that labeling for Angeliq should recommend contraindication for liver dysfunction.

3. What is the effect of ethnicity on the pharmacokinetics of the product?
The pharmacokinetics of Yaz was investigated in N=48 young, healthy Caucasian (N=24) and Japanese (N=24) women, aged 20–35 years via a multiple dose study. The following plot suggests that there was no statistically significan difference in exposure between Caucasian and Japanese subjects.

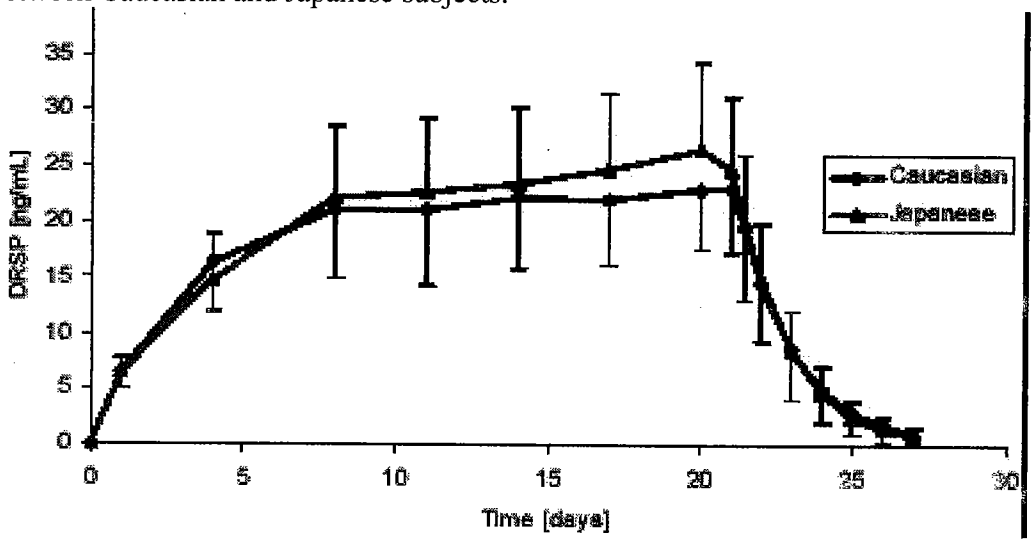


Figure 2. Mean Trough Levels of Drospirenone for Japanese vs. Caucasian Women After Single After Repeated Daily Dosing of Yaz for 21 Days.

4. What is the effect of Weight on the Product?
None of the subjects with "during treatment" pregnancies had a weight greater than 75kg. Thus, it appears that within the range of weights tested (up to 35 BMI), weight did not have a clinically relevant influence on exposure-response.

D. Extrinsic Factors
1. What is the effect of meals on the pharmacokinetics of the product?
A food effect study with Yaz was not performed. However, a food effect study was performed with the components of Yasmin.

The rate of absorption of DRSP and EE was influenced by food intake. A high fat meal reduced the Cmax of DRSP and EE by 40%. The extent of DRSP absorption remained unchanged, while that of EE was reduced by about 20%. Since clinical trials were conducted uncontrolled with respect to food intake, no specific dosing restrictions regarding food intake are recommended in the labeling.

The study was an open label, parallel, 2-treatment, 2-sequence design (N=16+16). Healthy premenopausal women, aged 19-36 years, were given a single dose of 2x3 mg DRSP and 2x30 µg EE once during fasting conditions and once 20 minutes after the start of a standardized high fat breakfast (2 fried eggs with 2 slices of bacon, 2 slices of fried toast bread each with 10 g butter, 100 g of hashed browns, 240 ml whole milk). Doses were administered on either days 4,5 or 6 of the menstrual cycle.

2. What is the potential for drug interactions?

Based on information in the literature, the β-cyclodextrins are absorbed very little and primarily metabolically eliminated by the colonic microflora. Orally administered cyclodextrins have been shown to be nontoxic.

In vitro studies suggest that DRSP is metabolized only to a minor extent (4-7%) by cytochrome P450 enzymes, mainly by CYP 3A4. *In vitro*, DRSP exhibited no or minimum inhibition of CYP2D6 and 1A2, moderate inhibition of 2C9 (IC50=36.5 mM) and 3A4 (IC50=31.2 mM) and more potent inhibition of 2C19 (IC50=3.39 to 10.7 mM) and 1A1 (IC50=14.5 mM). The concentrations needed to inhibit 50% of CYP450 enzyme activity was approximately 14 (CYP2C19), 152 (CYP2C9) and 130 (CYP3A4) fold higher, respectively, than the steady-state Cmax of total DRSP (0.24 mM) following administration of Yasmin.

In vivo, DRSP at steady-state did not inhibit the pharmacokinetics of omeprazole, a classic 2C19 substrate, indicating that DRSP is not likely to interact with drugs metabolized by 2C19. DRSP also did not inhibit the formation of the omeprazole sulfone metabolite, a minor metabolic pathway, mediated by 3A4. Therefore, it is not likely an important substrate for these enzymes *in vivo*.

The two major metabolites observed in plasma, the open-ring acid form of DRSP and 4,5-dihydrodrospirenone-3-sulfate, are not pharmacologically active. These two metabolites are formed independently of the CYP enzyme system.

In this submission, the sponsor provided the results of two *in vivo* drug-drug interaction studies to investigate the effect of DRSP on the activity of CYP 3A4:

Simvastatin

Simvastatin (40 mg single dose) was used to investigate the effect of DRSP on drugs metabolized by CYP 3A4 in an open-label, crossover study in 24 postmenopausal women treated with 3 mg DRSP dosed to steady state (14 days). The sponsor noted that simvastatin is not expected to affect DRSP's metabolism, therefore, DRSP's pharmacokinetics were not investigated in this study.

The mean AUC(0-tlast) ratio of simvastatin with DRSP (Treatment B) relative to simvastatin alone (Treatment A) was 114.7%. The lower and upper limits of the corresponding 90% confidence interval were calculated to be 89.8% and 146.6%. The sponsor noted that the absence of a pharmacokinetic interaction between DRSP and simvastatin could not be concluded based on the statistical evaluation because the 90% confidence interval did not lie completely within the predefined equivalence interval. The sponsor conducted an additional study to investigate the interaction with CYP 3A4.

Midazolam:

The sponsor evaluated the effect of midazolam (MDZ) with and without DRSP co-administration to characterize the potential of DRSP to interact with CYP3A4 via a double-blind, randomized, crossover study in N=24 healthy post-menopausal women.

DRSP 3 mg (or Placebo) was dosed daily for 9 days of the study with a dose of midazolam (4 mg) coadministered on Day 7 and Day 9.

Steady state levels of DRSP were achieved by Day 7. Cmax, Tmax, and AUC of MDZ were similar regardless of whether it was dosed with DRSP or with placebo. The metabolic ratio of 1'OH-MDZ to MDZ was stable during treatment and was not different between DRSP and placebo treatment. This suggests that there is no clinically significant effect of DRSP on CYP 3A4.

Indomethacin
An open-label, randomized, crossover study was conducted in 32 healthy postmenopausal women, (aged 45- 75 years) to evaluate the potential of a 1mg E2/3 mg DRSP (Angeliq) combination to cause hyperkalemia after repeated oral coadministration with 150 mg (50 mg tid) indomethacin. Because DRSP is similar to spironolactone, the effect of E2/DRSP on the renal excretion of calcium was evaluated.

Thirty two healthy postmenopuasal women were randomly assigned to one of two sequences (AB, BA) of the following treatments:

Treatment A: 1 capsule of 50 mg indomethacin 3 times daily on Days 1 – 5
Total treatment phase: 8 days

Treatment B: 1 tablet of 1 mg E2/3 mg DRSP QD on Days 1- 17
Total treatment phase: 19 days.

Mean serum potassium levels were similar between the two treatments suggesting that multiple dose administration of a 1mg E2/3 mg DRSP combination with 150 mg/day of indomethacin does not cause hyperkalemia. Based on individual observations, more individuals with increased serum K values above normal range with E2/DRSP + indomethacin treatment were noted. Twelve volunteers (36.4%) had at least one potassium level above the upper limit of normal (4.4 mmol/l) with E2/DRSP + indomethacin in contrast to one volunteer (3.0%) with indomethacin alone. There was only one volunteer (her value: 5.82 mmol/l) who had a single potassium level above 5.5 mmol/l (hyperkalemic). This sample was hemolytic (plasma hemoglobin was 157.7 ⌈mol/l).

Since this study was performed in post-menopausal women, the results do not apply to this population.

3. What other co-medications are likely to be administered to the target patient population?
The target population is young, healthy women. Thus, no specific co-medications are anticipated.

E. General Biopharmaceutics
1. How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

In agreement with the Chemistry reviewer, the following dissolution specifications are recommended for both DRSP and EE.

Q= —in 30 minutes
Apparatus Type: Paddle
Media: Water
Volume: 900 mL
Speed of Rotation: 50 RPM

These are the same dissolution specs for DRSP as for Yasmin, however, the Q is increased for EE for Yaz compared to Yasmin. For Yasmin, the Q= — for EE at 30 minutes.

The following chart of dissolution shows that both components of the product dissolve quickly. The sponsor chose water as the dissolution medium because water allowed for equivalent or slightly better discrimination when compared to 0.1 N HCl and a pH 4.5 buffer solution.

	EE	DRSP
Water	94.1 (— at 15 min	91.4 (—) at 15 min
Water	89.8 (— at 15 min	88.8 (—) at 15 min
0.1 N HCl	96.6 — at 15 min	98.4 — at 30 min (30 min is 1st time point)
pH 4.5 Buffer	97.1 — at 15 min	87.9 (—) at 15 min

Table 9. Mean (Range) of Dissolution Data for the Active Ingredients of Yaz (Ethinyl Estradiol and Drospirenone).

2. Is the proposed to-be-marketed formulation identical to the pivotal clinical trial formulation?

The to-be-marketed immediate-release film-coated tablet formulation containing 0.020 mg EE (as EE- β-cyclodextrin-clathrate) and 3.0 mg DRSP (**SHT00186D**) is the same as the clinical trial formulation. Both were manufactured at the same site. The following table shows the quantitative composition of the drug product.

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Component	Active Tablets mg/tablet	Inert Tablets mg/tablet
Drospirenone,	3.000	-
Ethinyl Estradiol (as EE-β-CDC,	(= 0.020 EE)	-
Lactose Monohydrate, NF		
Starch, NF (Maize Starch)		
Magnesium Stearate, NF		
Povidone USP (25,000)		
Hypromellose, USP		
Talc, USP		
Titanium Dioxide, USP		
Ferric Oxide, red, NF		
Tablet Total	83.0000	82.0000

Table 10. Quantitative Composition of the Drug Product.

3. What are the assay methods for the determination of Drospirenone and Ethinyl Estradiol concentrations? How sensitive and specific are the assays?

Drospirenone

DRSP concentrations were determined in serum and plasma using radioimmunoassay (RIA). The RIA method is designed for the quantitative determination of DRSP based on the competitive antibody reaction with DRSP and tritium labeled DRSP. The method was demonstrated to be sensitive with a lower limit of quantification (LoQ) of 250 pg/mL. The accuracy of the radioimmunological determination was within the range of 80 to 120% of the nominal concentration. The intra- and inter- assay coefficients of variation were below 20 % for the QC at the LoQ and below 15 % at higher concentrations. DRSP was shown to be stable in serum samples stored for 8 days at about 4°C, for 24 h at room temperature and for 22 months at about .20°C. The cross-reactivity towards the 17β-isomer of DRSP was determined to be about 0.2 %.

Ethinyl Estradiol

EE concentrations were determined in serum using gas chromatography-mass spectrometry (GC-MS). The lower limit of quantitation (LOQ) in the matrix samples was established to be 10 pg/ml for the assay based on the results of method validation. The average recovery for liquid-liquid-extraction was 70%. The interassay precision varied from 6.4% to 14.5% over the calibration range 10 – 500 pg/ml measured with quality controls at five concentration levels. The interassay accuracy varied from 90% to 101% over the calibration range 10 – 500 pg/ml measured with quality controls at five concentration levels. Various stability tests were conducted in serum; freeze and thaw

stability, long term stability in serum and autosampler stability of processed serum samples. The repeatability of the GC-MS instrument was found to be good (CV% from 1.8% to 3.7%).

These evaluations indicate acceptable accuracy and precision of the methods.

4. Based on BCS principles, in what class is this drug and dosage form? What solubility, permeability and dissolution data support this classification?
Not applicable.

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V. Detailed Labeling Recommendations

Changes to the label have been discussed with the Sponsor.

VI. Appendices

A. Proposed Package Insert (Submitted separately to DFS by sponsor when NDA initially opened.)

B. Individual Study Reviews

Appended to this file.

C. Consult Review

None requested.

D. Cover Sheet and OCPB Filing/Review Form

Refer to a previous submission to DFS by Myong-Jin Kim.

E. Review of Yasmin (Drospirenone 3 mg + Ethinyl Estradiol 0.030 mg)

Refer to a previous submission to DFS for NDA 21-098 by Venkat Jarugula.

F. Review of Angeliq (Drospirenone 3 mg + Ethinyl Estradiol 1 mg)

Refer to a previous submission to DFS for NDA 21-355 by Venkat Jarugula.

Individual Study Reviews (18 Studies)

1. Study BD09 / 303741

Open-label, randomized, crossover study to assess the potential of drospirenone (DRSP) to inhibit Cytochrome P450 3A4 by evaluating the metabolic interaction between DRSP and simvastatin as model substrate in healthy postmenopausal volunteers

Conclusion

• Sponsor notes that the equivalence of both treatments, i.e. the absence of a pharmacokinetic interaction between simvastatin and DRSP, could not be concluded based on the 90% CI for ratio of means; mean change: 114.7% (90% CI: 89.8-146.6).

Aims

• Characterize DRSP's potential for drug-drug interactions with medications metabolized by pathways catalyzed by CYP3A4.

Methods

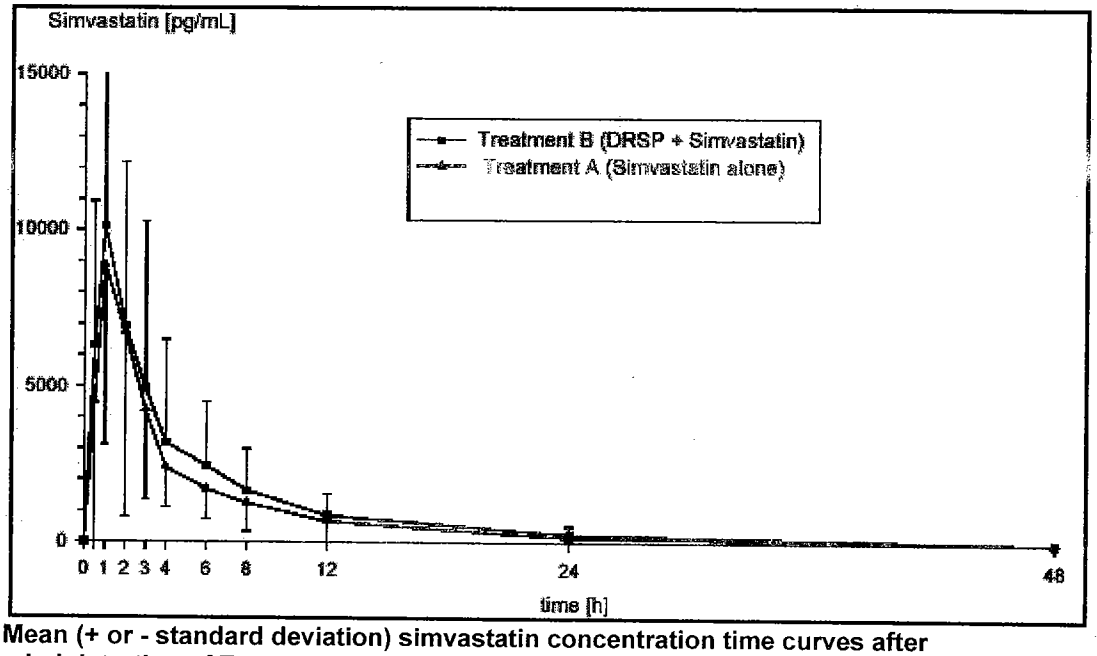
• Open-label, randomized, single center crossover study in N=24 postmenopausal women: 40-75 yrs
• Post-menopausal women selected because believed that: (a) elderly have the greatest potential for drug-drug interactions, (b) timing of dosing can be fixed with respect to the menstrual cycle.
• Two periods, two treatments (A = 40 mg simvastatin; B=3 mg DRSP for 14 days and 40 mg simvastatin on day 14), and two sequences (N=12: A then B; N=12 B then A)
• Single dose 40 mg simvastatin (1 tablet Zocor 40 mg)
• 3 mg DRSP Day1 1-14; 40 mg simvastatin Day 14
• "Simvastatin was chosen as a model substrate for CYP3A4 in accordance with the FDA guidance."
• "Simvastatin was not expected to affect DRSP's metabolism. Therefore, DRSP's pharmacokinetics were not investigated in this study."
• Postdose samples: 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 48 hours after dosing
• The terminal half-life of DRSP is 25-33 hours. Thus, a washout period of 14 days after multiple dosing of DRSP was chosen.
• Due to the short half-life of simvastatin washout period of 7 days
• Fasted intake
• DRSP, as potential CYP3A4 inhibiting agent, was given in the same dose as planned for clinical use. Administration for 14 days ensured steady-state conditions.
• Simvastatin: typical starting dose is 10 mg daily. If necessary the dose can be increased up to a maximum of 80 mg given once per day.

Results

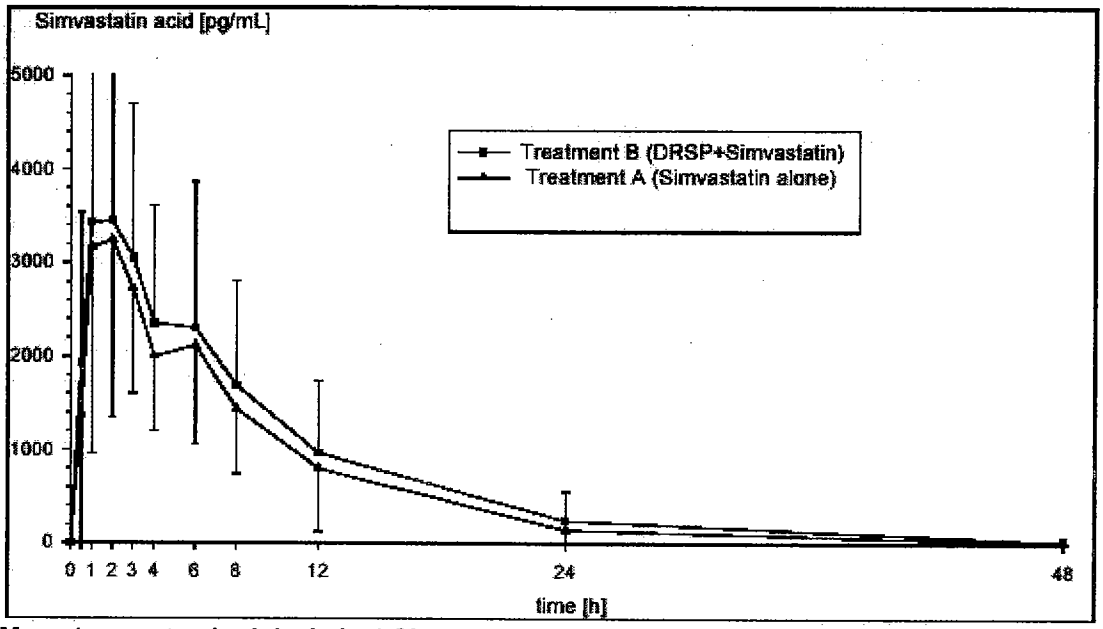
• Mean PK parameters of simvastatin alone versus in combination with DRSP:

	Simvastatin		Simvastatin acid	
Parameter	Treatment A	Treatment B	Treatment A	Treatment B
Cmax [pg/mL]	9250 (61.4%)	9507 (54.9%)	3811 (53.5%)	3832 (52.8%)
tmax [h]	1 (0.5-8)	1 (0.5-6)	2 (0.5-12)	2 (0.5-6)
t1/2 [h]	3.69 (36.8%);N=15	4.98 (40.6%);N=19	4.14 (41.3%);N=17	5.14 (39.2%);N=18
AUC(0-tlast) [pgxh/mL]	32232 (44.9%)	36978 (67.0%)	23553 (56.1%)	26390 (69.0%)
AUC [pgxh/mL]	35396 (47.9%);N=15	42787 (63.4%);N=19	28684 (45.4);N=17	28335 (72.5%);N=18

Mean pharmacokinetic parameters of simvastatin and simvastatin acid after oral administration of simvastatin alone (Treatment A) and in combination with DRSP (Treatment B) to 24 postmenopausal women. The geometric mean and geometric coefficient of variation (in parenthesis) are tabulated for all parameters except for tmax where the median and the range (in parenthesis) is given. The actual number of cases (N) used for calculation is shown, if it was less than 24.



Mean (+ or - standard deviation) simvastatin concentration time curves after administration of Treatments A or B to 24 postmenopausal women.



Mean (+ or . standard deviation) Simvastatin Acid Concentration Time Curves After Administration of Treatment A or B to 24 Postmenopausal Women.

	Mean Ratio (90% CI)
Simvastatin	114.7% (89.8,146.6)
Simvastatin acid	112.0% (90.4,138.9)

Mean ratio and confidence interval of AUC0-tlast for simvastatin and simvastatin acid. Equivalence of both treatments (i.e. the absence of a pharmacokinetic interaction between simvastatin and DRSP) could not be concluded.since the corresponding confidence interval does not lay completely within the equivalence interval of 70% and 143%.

• The AUC(0-tlast) of simvastatin instead of the total AUC was used as the primary target variable for the statistical evaluation, because the terminal half-life and thus the AUC could not be determined for all data sets. The mean AUC(0-tlast) ratio of simvastatin (Treatment B/Treatment A) was determined to be 114.7%. The lower and upper limits of the corresponding 90 % confidence interval were calculated to be 89.8 % and 146.6 %. The absence of a pharmacokinetic interaction between DRSP and simvastatin could not be concluded based on the statistical evaluation, because the 90 % confidence interval does not lie completely within the predefined equivalence interval of 70 % and 143 %.
• The analysis of the individual AUC(0-tlast) values revealed that 20 (83 %) of the subjects showed only small variations of the simvastatin AUC(0-tlast) resulting in less than either two-fold reduction or two-fold increase of this parameter after combined DRSP/simvastatin treatment. More than two-fold changes were observed in four subjects; two (8 %) showed an increase by factors of 2.4 and 7.7 and two (8 %) showed a decrease by factors of 2.6 and 4.4.
• The changes of the simvastatin AUC(0-tlast) observed by comparison of both treatments may be influenced by a high intra-individual variability of the simvastatin pharmacokinetics which can be assumed based on the considerable inter-individual variation of simvastatin pharmacokinetic parameters observed in this study. Overall, there was no consistent pattern in the effect of DRSP on simvastatin AUC(0-tlast): 11 subjects

showed an increase, 5 subjects showed a decrease, and 8 subjects showed essentially no effect (within ± 20 %).
• A total of 62 adverse events were reported in 21 of 24 volunteers (88%) during the treatment phase of the study. 51 of the 62 adverse events (82%), reported in 20 volunteers, were assessed as at least possibly related to the study drug. Headache was the most frequent treatment-related adverse event (17 AEs in 11 volunteers). The AEs assessed as possibly related to the study drug in more than one volunteer were headache, chills, sedation, skin disorders, sweating, and hot flushes. These AEs lasted between approximately one hour (vomiting) and almost 24 days (sore throat) and have in general been previously reported in clinical trials with DRSP or other progesterone preparations. The intensity of adverse events was assessed as mild for 43 adverse events, moderate for 17 adverse events, and severe for two adverse events (headaches). No deaths, serious adverse events, or other significant adverse events (AEs) occurred during the study. None of the volunteers prematurely ended the study due to an adverse event.
• Almost all 24 volunteers had at least one laboratory value outside the reference range in the final examination. However, most of these values exceeded the reference ranges only slightly and were not considered to be clinically significant.

2. Study B862 / 301780
Open-label, randomized, crossover study to evaluate the relative bioavailability of ethinylestradiol (EE) and drospirenone (DRSP) from two tablet formulations each containing 20 µg EE + 3 mg DRSP (SH T00186D and SH T00186A) in comparison with a — suspension of 40 µg EE + 6 mg DRSP after single oral administration in healthy postmenopausal volunteers

Aims
• Evaluate the relative bioavailability of EE and DRSP from two different tablet formulations, each containing 20 µg EE + 3 mg DRSP, compared to a — suspension (SH M00186A).
Test 1: SH T00186D: 2x (3 mg DRSP + 20 microgram EE in a betadex clathrate)
Test 2: SH T00186A: 2x (3 mg DRSP + 20 microgram EE as a free steroid)
— suspension: 40 micrograms EE + 6 mg DRSP

Methods
• Single center, open label, randomized treatment order, single dose, crossover study
• N=18 healthy, postmenopausal women, aged 48-75
• 3 periods; 3 treatments; 6 sequences
• 2 tablets for each test; 14 day washout for each test (half-life of EE: a range of 6 to 48 hours was reported for the disposition phase; half-life of DRSP: approximately 30 hours).
• The EE dose in the — suspension (40 µg per treatment) was chosen to ensure appropriate analytic sensitivity.
• Fasted intake; worst-case scenario since meals decrease drug exposure
• DRSP assay: lower limit of quantification (LOQ) was set to 0.2 to 0.5 ng/ml. Values below the lower limit were set to zero.
• EE assay: LOQ = 10.0 pg/mL
• Determination of serum levels of EE by gas chromatography-mass spectrometry (GC-

MS) at baseline and over 72 hours after single administration; determination of serum levels of DRSP by radioimmunoassay (RIA) up to 120 hours
• Primary target variables: area under the drug concentration-time curve [AUC(0-tlast)] for EE and DRSP
• Because the AUC of DRSP could not be determined properly for all 18 of the volunteers (e.g. the extrapolated part of the AUC was > 20 %), the AUC(0-tlast) was used as the primary target variable as predetermined in the study protocol.

Assay Validation
• The quantitative determination of DRSP in serum was performed using a radioimmunoassay. DRSP was extracted from serum with

s. The concentration of DRSP in serum samples was calculated by means of the pharmacokinetic LIMS software 3.7 (Schering AG) using a calibration curve as a reference.

• Individual assays were monitored for precision and accuracy using quality control samples which were analyzed under the same conditions as the samples of unknown DRSP concentration. The lower limit of quantification (LOQ) was set to 0.2 or 0.5 ng/ml depending on the accuracy results of quality controls in individual assays, using a sample volume of 100 µl. Values below the lower limit were set to zero.

Summary of DRSP Analytical Performance:

Nominal concentration	[ng/ml]	0.2	0.5	1.0	3.0
Mean measured concentration	[ng/ml]	0.205	0.519	1.08	3.39
Standard deviation	[ng/ml]	0.022	0.020	0.059	0.271
Inter-assay coefficient of variation	[%]	10.6	3.9	5.4	8.0
Mean accuracy	[%]	102	104	108	113
Mean intra-assay coefficient of variation	[%]	14	6	6	7

• EE was extracted from

GC/MS measurements were performed in the chemical ionization mode (negative ions) using ammonia as reagent gas.

Summary of EE Analytical Performance

Performance indicator	Value
Calibrated Range	10.0 – 500 pg/mL
Defined LOQ	10.0 pg/mL
Linearity (mean r^2 of the standard curves)	0.99417
Accuracy [bias %] (at the LOQ)	-0.1
Precision [cv %] (at the LOQ)	9.7
Accuracy [bias %] (at the lowest QC level)	0.2
Precision [cv %] (at the lowest QC level)	11.8

LOQ: lower limit of quantification

• The inter-assay accuracy and precision data were calculated from 39 sets of QC samples. The accuracy (expressed as bias) and the precision (expressed as coefficient of variation C.V.) data are shown below.

Nominal QC conc. [pg/mL]	20.0	80.0	400
Number	39	39	39
Mean (calc.)	20.0	81.0	399
s	2.37	7.87	42.3
C.V. [%]	11.8	9.7	10.6
Bias [%]	0.2	1.2	-0.3

s: standard deviation
C.V.: coefficient of variation

Relative Bioavailability with 90% CI.

Results

• Relative bioavailability of EE, from both the innovative EE-β cyclodextrin formulation (Yaz; SH T00186D) and the conventional EE formulation (SH T00186A), was nearly identical.

• The following table shows that the maximum EE concentrations and the time it took to reach these concentrations after oral administration were similar.

Parameter	[Unit]	Test 1	Test 2	Standard
Cmax	[pg/mL]	125 (22.8%)	120 (22.9%)	123 (27.2%)
tmax	[h]	1.5 (1.0 - 3.0)	1.0 (0.5 - 2.5)	1.0 (0.5 - 2.0)
AUC(0-24h)	[pg x h/mL]	934 (21.0%)*	868 (18.9%)**	845 (21.7%)**
AUC(0-tlast)	[pg x h/mL]	862 (44.8%)	843 (31.7%)	866 (37.6%)

Mean (CV or range) pharmacokinetic parameters of ethinylestradiol (EE) after single oral administration of 40 µg EE + 6 mg DRSP to 18 healthy postmenopausal volunteers.

Parameter	[Unit]	Test 1	Test 2	Standard
Cmax	[ng/mL]	87.1 (29.5%)	92.1 (26.9%)	82.7 (21.8%)
tmax	[h]	1.0 (1.0 - 4.0)	1.0 (0.5 - 2.0)	1.3 (1.0 - 2.0)
t1/2	[h]	36.6 (21.8%)*	34.4 (18.3%)**	34.3 (27.9%)**
AUC(0-24h)	[ng x h/mL]	567 (21.6%)	558 (19.7%)	522 (18.4%)
AUC(0-tlast)	[ng x h/mL]	1207 (24.4%)	1171 (22.9%)	1091 (16.3%)
AUC	[ng x h/mL]	1299 (25.0%)*	1242 (26.3%)**	1186 (15.4%)**

*: N = 16; **: N = 14

Mean (CV or range) pharmacokinetic parameters of drospirenone (DRSP) after single oral administration of 40 µg EE + 6 mg DRSP to 18 healthy postmenopausal volunteers

• 38 AEs were reported in 13 of the 18 volunteers during the treatment phase of the study. Six of the volunteers had AEs that were assessed as possibly related to the study drug (headache, peripheral edema, vaginal bleeding, and nocturia). A difference in the frequency or type of AE reported was not found for either the treatment formulation (MCS or tablet) or for the treatment period. No unexpected adverse drug reactions or serious adverse events were reported. None of the AEs were reported as being severe.

3. Study AW06 / KI92091 / ME90030

Determination of Drospirenone Serum Protein Binding in a Study of the Influence of SHT470F, SHT470I, and SHT470K on Parameters of the Renin-Angiotensin-Aldosterone System (RAAS), Electrolyte Metabolism and Lipid and Carbohydrate Metabolism

Aims

• Summarize the results of investigations into DRSP binding performed during a trial of 3 mg DRSP and 15, 20, or 30 micrograms EE2 when studied over 6 months in 80 female volunteers.

• Previously saw that 94-97% of drug bound to serum proteins. Here, lower EE2 dose.

Questions explored:

-Is EE2 mediated induction of SHBG and CBG altered?

-Is DRSP protein binding altered by a different EE2 dose?

Methods

• Double-blind, randomized trial in N=80 females aged 18-34 years

• 8 month study; 6 treatment cycles
• 4 Study arms; 20 subjects / treatment:
Microgynon (30 micrograms EE + 150 micrograms levonorgestrel)
3 mg DRSP + 15 micrograms EE2 "K"
3 mg DRSP + 20 micrograms EE2 "I"
3 mg DRSP + 30 micrograms EE2 "F"
• 21 days treatment; 7 days off
• Serum samples for protein binding on last day of tablet intake in cycles 1, 3, 6
• Proteins measured: sex hormone-binding globulin (SHBG), corticoid-binding globulin (CBG)
• Protein binding measured by ultrafiltration; [SHBG] & [CBG] determined w/ radioimmunology.

Results
• During treatment with DRSP/EE2 or levonorgestrel/EE2, levels of SHBG and CBG greater than pretreatment or posttreatment; indicates induction by EE2
• More SHBG induction with DRSP/EE2 than Microgynon; similar CBG induction
• No dose-relation between EE2 and CBG induction; max response may be reached
• Sponsor reports: "Problems in measuring SHBG. Can make no conclusions regarding EE2 dose and SHBG induction."

Cycle	SH T 470 K	SH T 470 I	SH T 470 F	Microgynon
Pretreatment	60 ± 22	73 ± 33	81 ± 40	61 ± 25
1	197 ± 49	187 ± 59	205 ± 50	98 ± 34
3	190 ± 61	203 ± 70	205 ± 58	108 ± 39
6	186 ± 54	172 ± 61	220 ± 82	87 ± 42
Posttreatment	94 ± 35	89 ± 38	82 ± 42	61 ± 25

Mean (+/- sd) SHBG Concentrations in Serum (nmol/L).

Cycle	SH T 470 K	SH T 470 I	SH T 470 F	Microgynon
Pretreatment	42 ± 10	47 ± 11	48 ± 9	48 ± 13
1	81 ± 16	83 ± 16	97 ± 24	83 ± 12
3	75 ± 20	76 ± 20	104 ± 22	92 ± 23
6	66 ± 15	85 ± 25	97 ± 29	83 ± 27
Posttreatment	64 ± 46	55 ± 23	49 ± 14	47 ± 18

Mean (+/- sd) CBG Concentrations in Serum (nmol/L).

• The following table suggests that the free fraction may be affected by the dose of EE2.

	20 microgram EE2 regimen	30 microgram EE2 regimen
Cycle 1	4.5 +/- 0.9%	4.8 +/- 1.2%
Cycle 3	3.9 +/- 0.8%	4.9 +/- 0.9%
Cycle 6	4.1 +/- 0.8%	4.6 +/- 0.7%

Free Fraction of DRSP as a Function of Dose and Duration of Exposure.

4. Study A11620 / 306946
Double-blind, randomized, crossover study to assess drospirenone's (DRSP) potential to inhibit Cytochrome P450 3A4 by evaluating the interaction between DRSP at steady state and single doses of the model substrate midazolam in healthy postmenopausal women

Aim

*Evaluate the *in vivo* effects of drospirenone (DRSP) on the catalytic activity of CYP3A4

Methods

*Use midazolam (MDZ) with and without DRSP co-administration to characterize the potential of DRSP to interact with CYP3A4

*Double-blind, randomized, crossover study in N=24 healthy post-menopausal women

*Regimen:

(A) Treatment

Day 1	Evening	2x 3mg DRSP
Days 2-6	Morning	3 mg DRSP
Day 7	Morning	3 mg DRSP + 4 mg MDZ
Day 8	Morning	3 mg DRSP
Day 9	Morning	3 mg DRSP + 4 mg MDZ

(B) Placebo

Day 1	Evening	2 PLAC
Days 2-6	Morning	1 PLAC
Day 7	Morning	1 PLAC + 4 mg MDZ
Day 8	Morning	1 PLAC
Day 9	Morning	1 PLAC + 4 mg MDZ

*Sample collection times: 0, 0.25; 0.5; 1; 1.5; 2; 3; 4; 5; 6; 8; 10; 12; 16 and 24 hours
MDZ / 1'OH-MDZ analysis: Day 7, Day 9
DRSP analysis: pre-dose on day 1 and day 6-9

*Measure plasma concentrations of MDZ and its 1-hydroxy metabolite (1'OHMDZ) via liquid chromatography-mass spectrometry method up to 24 hours

*Radioimmunological determination of DRSP in serum, before start of DRSP treatment and pre-dose samples on days 6, 7, 8, and 9.

*The analytes were isolated from human plasma by . The extract was quantitated by high performance liquid chromatography coupled to tandem mass spectrometric detection using multiple reaction monitoring. In order to monitor the assay quality, blank plasma and three quality control samples (blank plasma spiked with three different concentrations of midazolam and 1' –hydroxymidazolam) were analyzed within each assay.

*The lower limit of quantification (LLOQ) for the determination of midazolam and 1'-hydroxymidazolam in the human plasma samples was established to be 0.100 ng/mL based on the method validation. The LLOQ in the matrix samples for DRSP was established to be 200 pg/mL for the assay based on the results of the method validation.

Results

*The metabolic ratio of 1'OH-MDZ to MDZ was stable during treatment and was not different between DRSP and placebo treatment.

*The results for MDZ are summarized in the following table.

Treatment	day	Cmax [ng/mL]	tmax [h]	t1/2 [h]	AUC(0-tlast) [ngxh/mL]	AUC [ngxh/mL]
MDZ+DRSP	7	16.8 (45.3%)	0.5 (0.25-2)	6.30 (18.9%)[1]	45.4 (37.1%)	49.3 (37.0%)[1]
MDZ+DRSP	9	18.2 (35.6%)	0.5 (0.25-1)	6.61 (16.7%)[2]	46.4 (32.6%)	48.9 (33.4%)[2]
MDZ+Placebo	7	15.6 (40.1%)	0.5 (0.5-1.5)	6.38 (20.6%)[3]	44.4 (43.3%)	46.7 (41.1%)[3]
MDZ+Placebo	9	18.9 (51.0%)	0.5 (0.25-1)	6.32 (21.4%)[4]	48.9 (40.9%)	51.3 (42.7%)[4]
MDZ+DRSP	7+9*	--	--	--	46.0 (34.2%)	--
MDZ+Placebo	7+9*	--	--	--	47.0 (40.7%)	--

tmax = time to reach Cmax
t1/2 = terminal half-life
AUC(0-tlast) = area under the curve up to the last data point above the lower limit of quantitation
AUC = area under the curve up to infinity
[1]N = 20 subjects [2]N = 18 subjects [3]N = 21 subjects [4]N = 23 subjects
* mean of individual AUC(0-tlast) values calculated on day 7 and day 9 are average

Mean Pharmacokinetic parameters of MDZ with and without DRSP. Values are given as geometric means followed by the geometric coefficients of variation (CV) in parentheses, except for tmax, where the median and the range in parentheses are provided.

* Cmax of Midazolam was similar on Day 7 and Day 9, suggesting that steady state was reached during the study.
*In all pre-dose samples obtained on day 9, the concentration of MDZ was below the lower limit of quantification (LLOQ: 0.1 ng/mL) indicating that no MDZ from the previous treatment on day 7 remained in the body.
*The shape of the mean plasma level versus time profile of MDZ obtained on days 7 and 9 after oral administration of 4 mg MDZ in combination with placebo was similar to that obtained after MDZ + DRSP treatment. Accordingly, the pharmacokinetic parameters obtained after MDZ + placebo combination treatment were about the same on day 7 and day 9 with 15.6 ng/mL (40.1%) and 18.9 ng/mL (51.0%) for Cmax, 44.4 ngxh/mL (43.3%) and 48.9 ngxh/mL (40.9%) for the AUC(0-tlast), respectively.
*Note that at steady state, the Cmax of Midazolam was similar in subjects receiving MDZ + DRSP (18.2 ng/mL; 35.6% CV) as in subjects receiving MDZ with placebo (18.9; 51.0% CV). This suggests that metabolism of MDZ does not compete with the metabolism of DRSP. The primary target variable for statistical analysis was the mean of day 7 and day 9 AUC (0-tlast) of MDZ and its metabolite 1'OH-MDZ. The results of the statistical analysis (see table below) showed that the criteria to conclude equivalence between the treatments were fulfilled, since the 90% confidence limits lie within the equivalence range (70%, 143%) for both primary target variables.

Primary target variable	Mean ratio	Lower confidence limit	Upper confidence limit	Criterion
Mean of AUC(0-tlast) of MDZ at day 7 and 9	97.9 %	90.9 %	105.4 %	fulfilled
Mean of AUC(0-tlast) of 1'OH-MDZ at day 7 and 9	96.1 %	87.4 %	105.8 %	fulfilled

90%-confidence intervals for assessment of equivalence.

*In total, 142 adverse events were observed in 25 volunteers (crossover design): 73 AEs in 25 volunteers with MDZ + Placebo and 69 AEs in 25 volunteers with MDZ+ DRSP.
*With MDZ + Placebo, the maximum intensity was mild for 18 volunteers, moderate for 6 volunteers and severe for 1 volunteer. With MDZ+ DRSP, the maximum intensity was mild for 21 volunteers, moderate for 4 volunteers and severe for none of the volunteers. The 10 symptoms rated as moderate were back pain, abdominal pain lower, nausea, arthralgia, crying, venipuncture site hemorrhage, venipuncture site swelling, headache

and sedation (N=2). The one event assessed as severe was back pain (relationship to study drug: unlikely).

Background

*Of the CYP enzymes investigated, DRSP's greatest *in vitro* inhibitory effect was seen for CYP2C19, and to a much lesser extent, for CYP2C9 and CYP3A4.
*A drug-drug interaction study using simvastatin as a marker substrate for CYP3A4 (a daily oral intake of 3 mg DRSP and measurement at steady state) did not indicate a clinically relevant CYP3A4 inhibition. However, no final conclusion could be drawn from the study, because the number of the volunteers was too small to account for the high intra-subject variability of simvastatin pharmacokinetics (see earlier study reviewed).
*Compared to simvastatin, MDZ offers advantages such as exclusive metabolism via CYP3A4, less variability in pharmacokinetics, and a larger body of knowledge as a basis for valid interpretation of the results.
*Following oral administration, MDZ is almost completely absorbed from the gut and undergoes extensive presystemic metabolism by CYP3A4. Maximum concentrations occur approximately after 0.5 hours. The elimination half-life after oral dosing is approximately two hours.

5. Study A03773 / ME 300080

Single dose pharmacokinetics of SH T00186D (3 mg drospirenone + 20 µg ethinylestradiol) and of SH T00186E (1 mg, 3 mg and 6 mg drospirenone) after oral administration in young Japanese women

Aims

• Evaluate the pharmacokinetics of a single dose of Yaz (SHT00186D: 3 mg drospirenone + 20 µg ethinylestradiol) and examine the pharmacokinetics of different single doses of SH T00186E (1 mg, 3 mg and 6 mg drospirenone) including the dose dependency of drospirenone in Japanese women.

Methods

• Open-label, single dose study in N=36 Japanese women aged 20-35
• 18 received 3 mg DRSP + 20 microgram EE; 6 each received 1 mg, 3 mg, 6 mg DRSP
• Blood sampling until 8 days after study drug administration
• Volunteers fasted before dosing; worst-case exposure scenario

Results

• PK Parameters:

Pharmacokinetic parameter	Unit	Dose group			
		1 mg DRSP (N = 6)	3 mg DRSP (N = 6)	6 mg DRSP (N = 6)	3 mg DRSP + 20 µg EE (N = 18)
Cmax	ng/mL	13.0 (29.1%)	44.4 (20.7%)	92.6 (12.8%)	35.7 (31.4%)
tmax	h	1.25 (1 – 1.5)	1.0 (1 – 1.5)	1.5 (1 – 2)	1.5 (0.5 – 4)
t1/2	h	30.1 (33.8%)	24.2 (24.2%)	26.5 (20.5%)	26.6 (19.1%)
AUC	ngxh/mL	182 (28.2%)	458 (17.5%)	1051 (14.6%)	494 (16.7%)
CL/F	mL/min	91.3 (28.2%)	109 (17.5%)	95.2 (14.6%)	101 (16.7%)

Pharmacokinetic parameters of DRSP after single oral administration of different DRSP doses to young, healthy Japanese women. For the parameters Cmax, t1/2, AUC and CL/F, the geometric mean and the geometric coefficient of variation (in parentheses) are listed; for the parameter tmax, the median and range (in parentheses) is shown.

• Except for AUC, all PK Parameters in above table consistent with values in Study A03328. In this study, AUC is 494 ng hr/mL (CV = 16.7%); in Study A03228, AUC_{0-24} was 268 ng hr/mL. The smaller value likely represents a shorter collection period.
• 7 adverse events were observed in 7 out of 36 volunteers (19.4%). The adverse events were intermenstrual bleeding (4 volunteers in the 3 mg DRSP + 20 µg EE group; rated as probably related to treatment), headache (2 volunteers: 1 volunteer in the 3 mg DRSP + 20 µg EE group and 1 in the 6 mg DRSP group; rated as possibly related to treatment) and upper respiratory infection (1 volunteer in the 1 mg DRSP group; rated as not related to treatment). Six out of seven adverse events (85.7%) were assessed as mild, and one adverse event (upper respiratory infection) was rated as moderate in intensity. There were no deaths and no serious adverse events. All volunteers experiencing adverse events recovered completely.

6. Study A03328 / ME305103

Two-center, open-label, non-randomized study to determine the multiple dose pharmacokinetics of SH T00186D (3 mg drospirenone+ 20 µg ethinylestradiol) after oral administration in a 21-day regimen in healthy young Caucasian and Japanese women

Aims

• Primary: Determine the AUC(0-24h) of drospirenone (DRSP) on day 21 in Caucasian and Japanese women after daily oral administration of SH T00186D for 21 days
• Secondary: determine of the AUC(0-24h) of ethinylestradiol (EE2) on day 21 and all other pharmacokinetic parameters of DRSP and EE2 in Caucasian and Japanese women after daily oral administration of Yaz (SH T00186D) for 21 days and to assess safety laboratory parameters at defined time points.

Methods

• Two-center, open-label, parallel, non-randomized study of 3 mg DRSP + 20 micg EE in N=48 young, healthy Caucasian (N=24) and Japanese (N=24) women, aged 20–35 years.
• Samples were taken up to 24 hr after the first study drug administration

• Blood sampling for pharmacokinetic analyses of DRSP and EE2 was done up to 24 hr after the first study drug administration. On days 5, 9, 12, 15 and 18 pre- dose blood samples for analysis of DRSP was taken before study drug administration (trough levels). On day 21, blood samples for pharmacokinetic analyses of DRSP and EE2 were taken before (trough level) and up to 168 hr (DRSP) and 72 hr (EE2) after the last study drug administration, respectively.
• Dose in fasted state

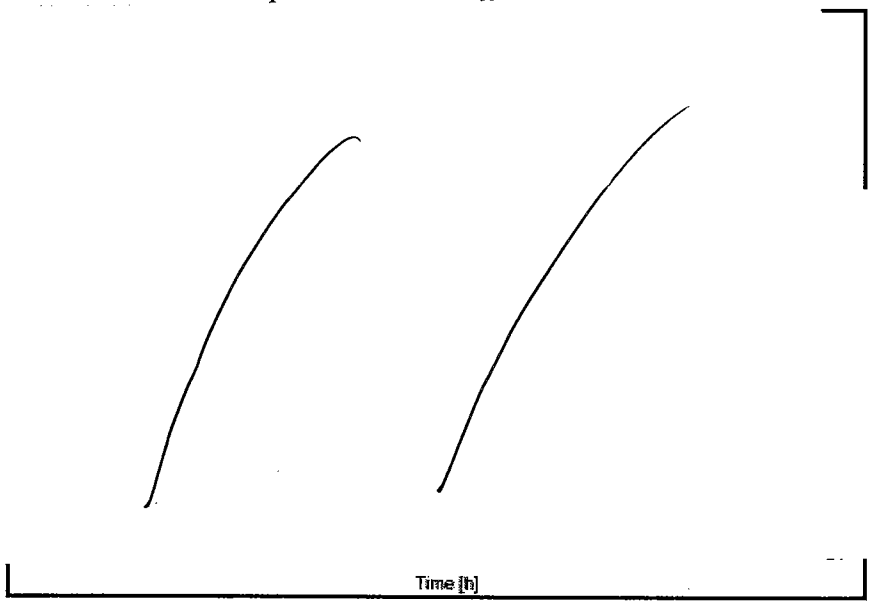
Results

• Drospirenone PK parameters:

	C_{max} [ng/mL]	t_{max} [h]	$t_{1/2}$[h]	AUC(0-24h) [ngxh/mL]	AUC [ngxh/mL]	R_A
day 1; Caucasian	38.4 (25.2%)	1.5 (1 - 2)	n.d.	268 (18.9%)	n.d.	n.d.
day 1; Japanese	38.9 (31.5%)	1.5 (1 - 2)	n.d.	271 (21.7%)	n.d.	n.d.
day 21; Caucasian	70.3 (14.5%)	1.5 (1 – 2)	30.8 (21.9%)	763 (17.4%)	1811 (32.7%)	2.8 (20.3%)
day 21; Japanese	78.9 (23.1%)	1.5 (1 – 2)	29.1 (17.7%)	803 (24.4%)	1852 (31.8%)	3.0 (15.1%)

Pharmacokinetic parameters of drospirenone after repeated daily oral administration of SH T00186D to young healthy Caucasian and Japanese women.

• Concentration-time profile after a single dose of DRSP in Caucasian women



Individual and mean DRSP concentrations in serum after single dose administration of SH T00186D in Caucasian women on day 1 (N = 23).

• Concentration-time profile after a single dose of DRSP in Japanese women:

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1 Trade Secret / Confidential

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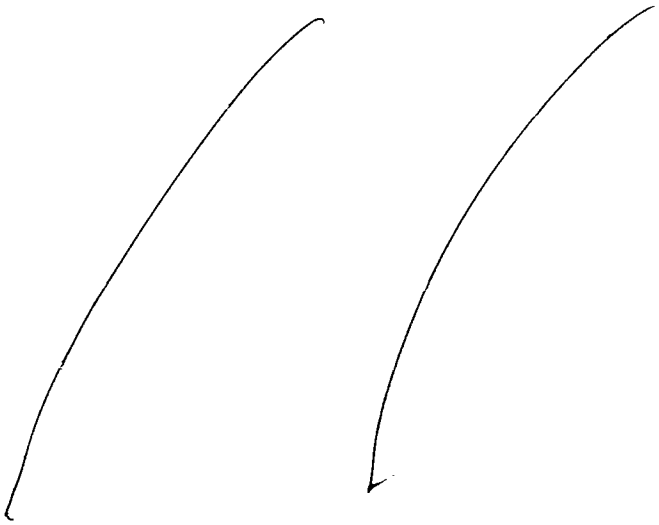


Individual and mean DRSP concentrations in serum after multiple dose administration of SHT00186D in Japanese women on day 21 (N = 24).

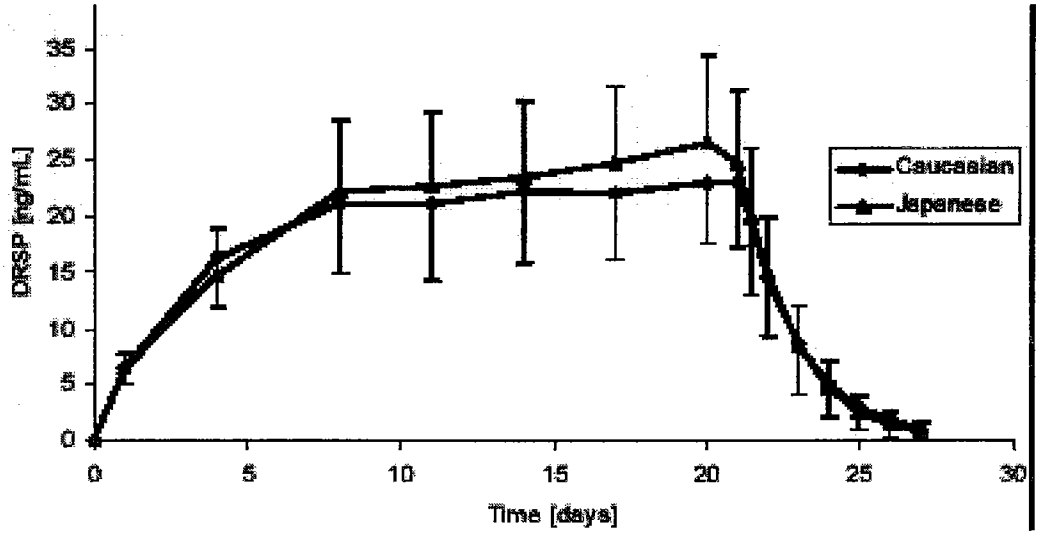
• Greater variability in Caucasian women may be due to 2 subjects data

• The accumulation ratio based on the ratio of the AUC(0-24h) on day 21 to the AUC(0-24h) on day 1 was calculated to a mean value of 3.0 (15.1%).

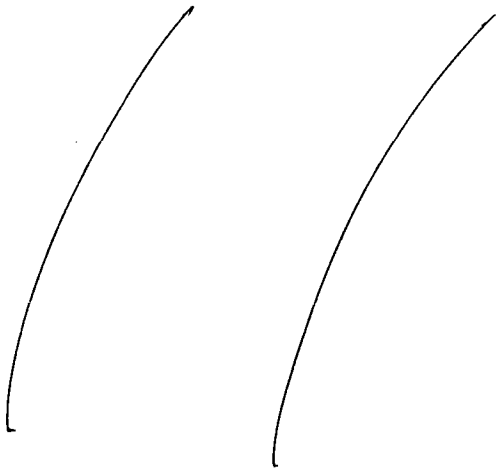
• EE PK parameters:

	C_{max} [pg/mL]	t_{max} [h]	AUC(0-24h) [pgxh/mL]	AUC(0-t_{last}) [pgxh/mL]	R_A
day 1; Caucasian	32.8 (44.9%)	1.5 (1 – 2.2)	108 (51.8%)	n.d.	n.d.
day 1; Japanese	32.5 (52.3%)	1.5 (1 – 2)	96.5 (79.3%)	n.d.	n.d.
day 21; Caucasian	45.1 (34.7%)	1.5 (1 – 2)	220 (57.4%)	206 (63.3%)	2.04 (45.6%)
day 21; Japanese	51.1 (53.4%)	1.25 (1 – 2)	225 (75.9%)	203 (83.9%)	2.33 (40.8%)

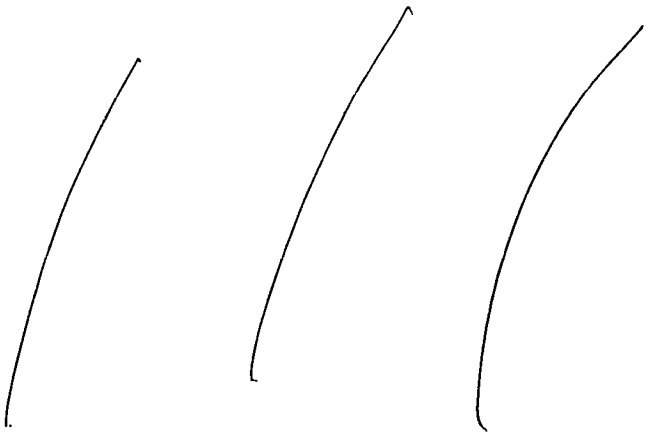
Pharmacokinetic parameters of ethinylestradiol after repeated daily oral administration of SHT00186D to young healthy Caucasian and Japanese women.



Mean Trough Levels of Drospirenone for Japanese vs. Caucasian Women After Single After Repeated Daily Dosing of Yaz for 21 Days.



Individual and mean SHBG concentrations in serum after multiple dose administration of SHT00186D in Caucasian young healthy women over a treatment period of 21 days.



Individual and mean SHBG concentrations in serum after multiple dose administration of SHT00186D in Japanese young healthy women over a treatment period of 21 days.

• Greater exposure in EE and DRSP for Japanese versus Caucasian volunteers. May be due to weight.

• The ratio of the geometric means (Japanese women/Caucasian women) of the AUC(0-24h) of DRSP on day 21 was 1.05 with 90% confidence limits of 0.95 to 1.17. The ratio of the geometric means (Japanese women/Caucasian women) of the AUC(0-24h) of EE2 on day 21 was 1.02 with 90% confidence limits of 0.76 to 1.38. These data indicate equivalence between both ethnic groups with respect to the daily systemic DRSP exposure measured by AUC(0-24h) at steady state.

• DRSP approaches plateau after 8 days of treatment. The pharmacokinetic profiles over the treatment period of 21 days suggest that steady state pharmacokinetics of DRSP are achieved within that treatment period and that no changes are expected with a treatment period exceeding 21 days.

• All volunteers entering the study had at least one adverse event from which they recovered completely. In total, there were 94 adverse events in 48 volunteers. Sixty-five adverse events occurred in the Caucasian group and 29 in the Japanese group. The most common study drug related adverse events were withdrawal bleeding occurring in 37 volunteers (17 Caucasians, 20 Japanese), headache in 13 volunteers (Caucasians only), intermenstrual bleeding in 12 volunteers (4 Caucasians, 8 Japanese) and dysmenorrhea in 5 volunteers (Caucasians only). All drug-related adverse events were of mild or moderate intensity.

7. Study A01222 / ME304326

Single dose pharmacokinetics of SH T00186D (3 mg drospirenone + 20 µg ethinylestradiol) and of SH T00186E (1 mg, 3 mg and 6 mg drospirenone) after oral administration in young Caucasian women

Aims

• Evaluate PK of a single dose of Yaz (SHT00186D; 3 mg DRSP + 20 micrograms EE2) in Caucasian women.

• Evaluate the PK of different single doses of SHT00186E (DRSP: 1 mg, 3 mg, 6 mg) in Caucasian women.
• Compare PK of a single dose of Yaz (SHT00186D; 3 mg DRSP + 20 micrograms EE2) in Caucasian women to that collected in Japanese women.
• Compare the PK of different single doses of SHT00186E (DRSP: 1 mg, 3 mg, 6 mg) in Caucasian women to that collected in Japanese women.

Methods
• Open-label, dose-escalation, parallel design in 36 women aged 20-35
• Regimens tested:

A	3 mg DRSP+20 µg EE2 betadex clathrate	1 tablet SH T00186D	N=18
B	1 mg DRSP	1 tablet SH T00186E	N=6
C	3 mg DRSP	3 tablets SH T00186E	N=6
D	6 mg DRSP	6 tablets SH T00186E	N=6

• DRSP and EE2 PK measured until 168 and 72 hours post-dose, respectively (0.5,1,1.5,2,4,6,8,10,12,16,24,34,48,72,96,120,144,168 hrs)
• Study drugs were administered cycle-dependently, i.e. at the beginning of the volunteer's individual menstrual cycle, in order to reduce intrinsic (hormonal) influences on pharmacokinetics
• Fasted from 9 pm the evening before study drug administration

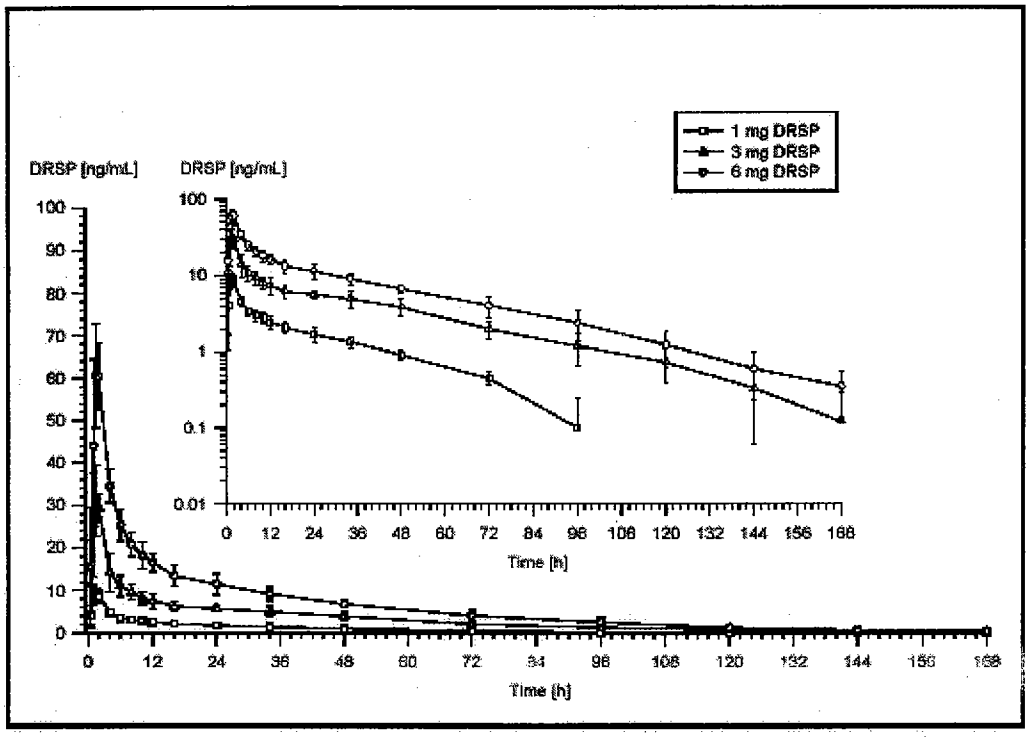
Results
• Pharmacokinetic parameters of DRSP tabulated below:

Pharmacokinetic parameter	Unit	Dose group			
		1 mg DRSP (N = 6)	3 mg DRSP (N = 6)	6 mg DRSP (N = 6)	3 mg DRSP + 20 µg EE2 (N = 18)
Cmax	ng/mL	9.85 (18.9%)	33.9 (20.4%)	62.5 (19.5%)	30.9 (27.0%)
tmax	h	1.25 (1 – 2)	1.5 (1 –2)	1.75 (1.5 – 2)	1.5 (1 – 4)
t1/2	h	25.5 (19.7%)	28.5 (16.4%)	26.3 (15.5%)	27.7 (18.4%)
AUC	ngxh/mL	140 (9.11%)	506 (21.5%)	1007 (20.7%)	458 (18.1%)
CL/F	mL/min	119 (9.03%)	98.7 (21.5%)	99.3 (20.6%)	109 (18.1%)

Cmax: maximum concentration of drug in serum after drug administration
tmax: time to reach maximum concentration following drug administration
t1/2: half-life of the last perceivable disposition phase
AUC: area under the concentration versus time curve from dosing time extrapolated to infinity
CL/F: total oral clearance

Comments on above table:
1. Dose linearity in Tmax, Cmax and t½
2. Greater than proportional increase in AUC as DRSP dose increase from 1 mg to 3 mg
3. Decrease in CL/F as DRSP dose increased from 1 mg to 3 mg
4. Cmax, Tmax and t½ of 3 mg DRSP equivalent when dosed alone and when dosed w/ 20 micrograms EE2

• The following plot represents the PK for the 3 doses of DRSP graphically:



Mean (± standard deviation) DRSP serum concentration time profiles after single oral administration of 1, 3 or 6 mg DRSP to groups of 6 young, healthy volunteers.

- Difference in parameters for 1 mg likely due to falling below LOQ.
- DRSP serum concentrations decreased biphasically at all three dose levels
- The (geometric) mean Cmax values increased dose-dependently from 9.85 ng/mL (CV: 18.9 %) after administration of 1 mg DRSP to 33.9 ng/mL (CV: 20.4 %) and further to 62.5 ng/mL (CV:19.5 %) after administration of 3 and 6 mg DRSP.
- The following shows the DRSP concentration-time plot for the Yaz tablet

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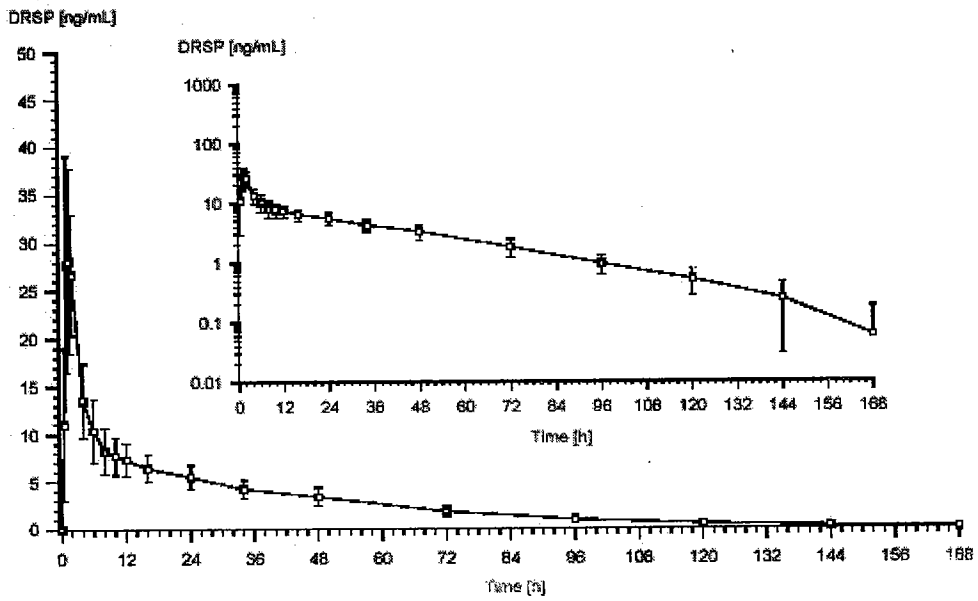
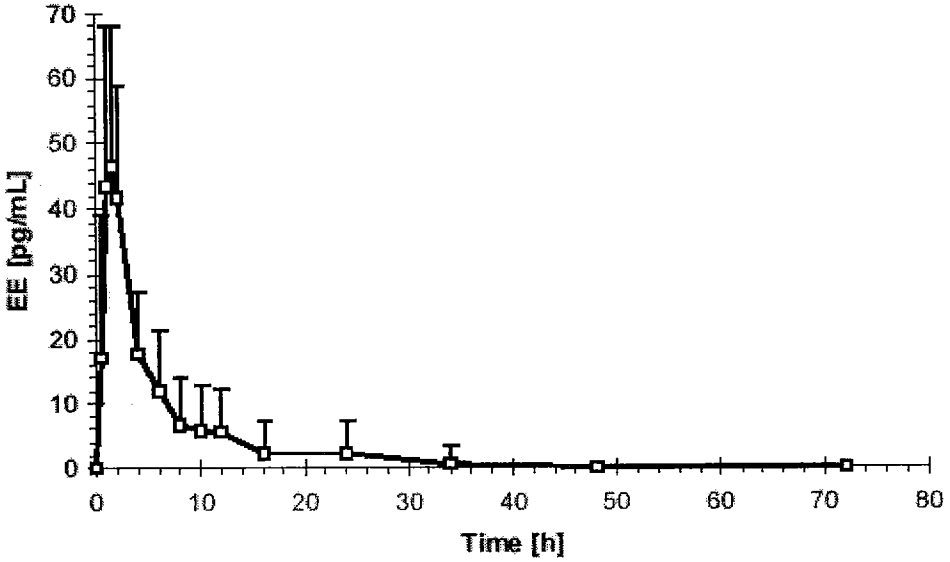


Mean (± standard deviation) DRSP serum concentration time profiles after single oral administration of 1 tablet SH T00186D to 18 young, healthy volunteers.

• Pharmacokinetic parameters of EE2 and DRSP when Yaz dosed tabulated below:

	Tmax (hr)	Cmax	AUC_{0-24}	t½	CL/f
EE2	1.5 hr (range: 1-4)	46.1 pg/mL (49.4%)	184 pg hr/mL (77%)	NA	
DRSP	1.5 hr (range: 1-4)	30.9 ng/mL (27%)	458 ng hr / mL (18.1%)	27.7 hr (18.4%)	109 mL/min (18.1%)

• Plot of PK of EE after administration of Yaz:



Mean (+ standard deviation) ethinylestradiol serum concentration time profiles after single oral administration of 1 tablet SH T00186D to 18 young, healthy volunteers.

• Adverse events in 14 of 36 volunteers (38.9%); 8 adverse events assessed as being possibly related to the study drug (N=6 headache, N=1 dizziness, N= 1 laboratory test abnormal). There were no deaths and no serious adverse events.

8. Study A11401
Multicenter, open-label, uncontrolled study to evaluate ovulation inhibition with SH T00186DB (0.02 mg ethinylestradiol-beta-cyclodextrin clathrate and 3 mg drospirenone) applied for two treatment cycles to 30 female Japanese subjects

Aim
• Assess the ovulation inhibitory effect of the treatment with SH T 00186 DB (0.02 mg EE betadex in combination with 3 mg DRSP) in Japanese women.
• Primary objective: Determine the proportion of volunteers with ovulation inhibition in cycle 2 assessed by Hoogland score.
• Secondary objective: Measurement of follicular development and the assessment of endogenous hormones (follicle-stimulating hormone (FSH), luteinizing hormone (LH), E2, and progesterone).

Methods
• Duration of treatment: 2 cycles, 28 days each (21 active tablets in a 21 tablet blister, followed by a 7-day tablet-free interval)
• N=30 Japanese females 20-35 planned; Analyzed: 23 (FAS=full analysis set), 18 (PP)
• Tablet intake started on the first day of menstrual bleeding at the beginning of the first medication cycle.
• No control group
• No PK data collected

Results
• Demographics of study volunteers:

	N	Mean	SD
Age [years]	23	27.9	4.2
Height [cm]	23	154.2	5.2
Weight [kg]	23	50.2	5.8
BMI [kg/m^2]*	23	21.2	2.2

*BMI calculated : weight [kg] / height [m^2]

• Protocol deviations were reported for all 24 randomized volunteers. The most common protocol deviations were time schedule deviation observed in 21 (87.5%) of all enrolled volunteers, followed by the presence of procedure deviation in 12 (50.0%) volunteers, inclusion/exclusion error at study entry in 2 (8.3%) volunteers, excluded concomitant treatment in 1 (4.2%) volunteer, and treatment deviation in 1 (4.2%) volunteer. The protocol deviations were assessed as minor or major according to their potential to

interfere with the primary efficacy variable. A total of 6 volunteers (PID 100, PID 107, PID 114, PID 115, PID 118, and PID 128) had protocol deviations assessed as major and were excluded from PP.

• Primary Response Analysis:

	PP	FAS
Women included in analysis set	18	23
Missing values in Hoogland score (treatment cycle 2)	0	4
N	18	19
Number of women with ovulation inhibition in cycle 2 (percentage in parenthesis)	18 (100%)	19 (100%)
Exact lower one-sided 95% confidence limit	84.67%	85.41%

• 100% of the volunteers in the PP and 87.0% of the volunteers in the full analysis set (FAS) had an ovulation in the pretreatment cycle. In treatment cycle 2, ovulation was inhibited in 100% of the volunteers of the PP and FAS.

• No woman included in the PP (n=18) as well as in the FAS (n=23) had a Hoogland score of 6 in treatment cycle 2, thus the estimated proportion was 100 % (lower exact one-sided 95% confidence limit 84.67 %) in the PP and 100 % (lower exact one-sided 95% confidence limit 85.41 %) in the FAS.

• Secondary Response Analysis: Maximum Follicle Size by Cycle

	N	Mean (mm)	SD	Median (mm)	Min (mm)	Max (mm)
Pretreatment	23	17.17	5.71	17.70		
Cycle 1	23	10.16	4.41	9.80		
Cycle 2	21	13.30	9.26	10.90		
Posttreatment	21	17.95	10.58	16.50		

*0.00= no follicles were seen on TVU

• Mean maximum follicle size in the FAS was 17.17 mm in the pretreatment cycle. In cycle 1, the mean maximum size in the FAS decreased to 10.16 mm and reached a mean maximum size of 13.30 mm in treatment cycle 2, suggesting the inhibition of the follicular development. In the posttreatment cycle, the mean maximum size of 17.95 mm in the FAS were reached which was comparable to the pretreatment cycle value.

• FSH values remained low during the follicular phase of the cycles 1 and 2 and the pronounced decrease in the second half of a normal ovulatory cycle was absent. No LH peak was observed in the middle of the cycles; E2 and progesterone levels were below the levels in the pretreatment cycle; progesterone levels remained at a low level throughout the treatment cycles. In the posttreatment cycle, the hormone levels returned to the pattern typical for ovulatory cycles and were comparable to the pretreatment cycle.

• A total of 73 AEs were reported in 21 volunteers (91.3%) at the end of the study. The 3 most frequently reported AEs were laboratory test abnormality (12 AEs in 12 volunteers, 52.1%), headache (12 AEs in 5 volunteers, 21.7%), and abdominal pain (9 AEs in 5 volunteers, 21.7%).

• 12 volunteers had treatment related AEs and 6 volunteers had unrelated AEs. For 11 (47.8%) volunteers, the maximum treatment relationship of their AEs was assessed as possible, and for 1 volunteer (4.3%) the maximum treatment relationship of her AE was assessed as probable. The 3 most frequent treatment-related AEs were abdominal pain in 3 volunteers (13%), headache in 2 volunteers (8.7%), and ovarian cysts in 2 volunteers (8.7%). The maximum intensity of AEs was assessed as severe in 1 volunteer (4.3%), moderate in 4 volunteers (17.4%), and mild in 13 volunteers (56.5%). A total of 8 volunteers (34.8%) fully recovered from their AEs and 10 volunteers (43.5%) had not recovered from their AEs until the end of the study.
• One AE led to study discontinuation. The volunteer PID 100 discontinued the study after cycle 1 due to irregular bleeding and abdominal discomfort.
• One volunteer experienced weight loss (from 50 kg to 43 kg during the study) considered as clinically significant by the investigator.

9. Study A09372
Monocenter, open label, uncontrolled study to evaluate ovulation inhibition with SH T00186D (0.02 mg ethinylestradiol-beta-cyclodextrin clathrate) and 3 mg drospirenone), applied for two treatment cycles to 30 female volunteers

Aim
• Assess the ovulation inhibitory effect of the treatment with Yaz (SH T00186D; 0.02 mg ethinylestradiol betadex in combination with 3 mg drospirenone).
• Primary objective: Determine the proportion of volunteers with ovulation inhibition in cycle 2 assessed by the Hoogland score using transvaginal ultrasonography and hormone measurement (E2 and progesterone).
• Secondary objectives: Measurement of follicular development and the assessment of endogenous hormones (follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and progesterone).

Methods
• Duration of treatment: 2 cycles, 28 days each (21 active tablets in a 21 tablet blister, followed by a 7-day tablet-free interval)
• Cumulative maximum dosage over 2 cycles:
Ethinylestradiol betadex: 0.84 mg
Drospirenone: 126 mg
• Tablet intake started on the first day of withdrawal bleeding at the beginning of the first medication cycle.
• N=30 female volunteers planned aged 18-35 years; Analyzed 30 (FAS=full analysis set); 28 (PP=per-protocol)
• No control group
• Hoogland Score:

Code	Activity	Size of the follicle-like structure (mm)	Progesterone (serum, nmol/l)	Estradiol (serum, nmol/l)
1	No activity	< 10	--	--
2	Potential activity	10 – 13	--	--
3	Non-active follicle-like structure	> 13	--	≤ 0.1
4	Active follicle-like structure	> 13	≤ 5	> 0.1
5	Luteinized unruptured follicle	> 13, persisting	> 5	> 0.1
6	Ovulation	> 13, ruptured	> 5	> 0.1

Results

• Demographics of participants:

	N	Mean	SD	Min	Median	Max
Age [years]	30	23.8	2.6	18	24.0	29
Weight [kg]	30	62.34	7.76	50.4	61.90	86.8
Height [cm]	30	166.6	4.7	156	167.5	173
BMI [kg/m^2]	30	22.5	2.9	18	22.0	29

• Primary Efficacy variable: Hoogland score <6 in treatment cycle 2.

	PP	FAS
Women included in analysis set	28	30
Missing values in Hoogland score (treatment cycle 2)	0	1
N	28	29
Number of women with ovulation inhibition	26	27
Percentage of women with ovulation inhibition	92.9%	93.1%
Exact lower one-sided 95% confidence limit	79.2%	79.8%

• 92.9% of the volunteers included in the PP (N = 28) and 93.1% of the volunteers included in the FAS (N = 30) had a Hoogland score of less than 6. The corresponding exact lower one-sided 95% confidence limit was 79.2% in the PP and 79.8% in the FAS.

• For 2 volunteers (PID 105, 128), Hoogland scores of 6 (potential ovulation) were assessed in treatment cycle 2. For PID 105, the results of the pharmacokinetic determination of the drospirenone blood levels suggest that no study medication was taken in treatment cycle 2. For PID 128, the drospirenone blood levels were typical of a treatment cycle. The volunteer mentioned a history of cyst formation under OCs.

• Secondary Outcome Variable: Maximum Follicle Size in mm

TT 16 **Maximum follicle size by cycle in mm - PP**

Maximum follicle size	Pre-cycle (N = 28)	Treatment cycle 2 (N = 28)	Post-treatment cycle (N = 28)
Median	18.70	8.95	18.35

TT 17 **Maximum follicle size by cycle in mm - FAS**

Maximum follicle size	Pre-cycle (N = 30)	Treatment cycle 2 (N = 29)	Post-treatment cycle (N = 29)
Median	18.40	8.90	18.00

• The median of the maximum follicle size was smaller under treatment as compared to the pre- cycle and reached a median maximum size of 8.95 mm in treatment cycle 2 for the PP and of 8.90 mm for the FAS, thus demonstrating the inhibition of the follicular development. In the post-treatment cycle, median maximum sizes of 18.35 mm in the PP and of 18.00 mm in the FAS were reached which were comparable to the pre-cycle values.
• Under treatment with SHT 00186D, the hormone pattern was different from that pre-cycle, where ovulation was observed. A suppression of gonadotropins was observed: FSH values did not show the pronounced decrease in the second half of the cycle; there was no LH peak in the middle of the cycle; estradiol and progesterone levels were considerably below the levels in the pre-cycle. Progesterone levels remained at a low level throughout the entire treatment cycle. In the post-treatment cycle, the course of hormone levels changed to the pattern typical for ovulatory cycles.
• A total of 72 AEs were reported in 24 (80%) volunteers at the end of the study.
• The 3 most frequently occurring AEs were upper respiratory infections (16 AEs in 15 volunteers, 50.0%), headache (11 AEs in 9 volunteers, 30.0%), and breast engorgement (4 AEs in 4 volunteers, 13.3%).
• For 5 (16.7%) volunteers a treatment relationship was assessed as being possible, and for 3 volunteers (10%) the treatment relationship was assessed as probable. The most frequently treatment-related AEs were breast engorgement, assessed as related in 4 volunteers (13.3%) and headache in 2 volunteers (6.7%).
• The maximum intensity of AEs was assessed as moderate in 17 volunteers (56.7%), mild in 7 volunteers (23.3%) and, presumably, severe in 20%. Most of the volunteers 23 (76.7%) recovered completely from their AEs and 1 volunteer (3.3%) recovered with residual side effects by the end of the study. This volunteer had an accidental injury. No volunteer prematurely discontinued the study medication due to AE.
• No death or SAE occurred in the course of the study.
• None of the other safety parameters measured in the study including laboratory examinations, physical and gynecological examinations, vital signs, and weight gave rise to any safety concerns.

10. Assay LE00607-20909
Pre-Study Validation of a GC-MSD Assay for the Quantitative Determination of Ethinylestradiol (EE2) in Human Serum

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