CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203505Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA #	203505
Submission Date	April 29, 2012
Brand Name	Osphena®
Generic Name	Ospemifene
Strength and Formulation; Regimen	60 mg; immediate release oral tablet; orally once daily taken with food
Sponsor	Shionogi Inc.
Proposed Indication	Treatment of Vulvar and Vaginal Atrophy due to Menopause
Submission Type	Original NDA; standard review
Relevant IND	67216
Clinical Pharmacology Reviewer	LaiMing Lee, PhD
Clinical Pharmacology Team Leader	Myong-Jin Kim, PharmD
OCP Division	Division of Clinical Pharmacology-3
OND Division	Division of Reproductive and Urologic Products

1 Executive Summary

The Clinical Pharmacology review of NDA 203505 (DARRTS, January 12, 2013) stated that NDA 203505 was acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert labeling. The final agreement was reached on February 25, 2013 and there are no pending issues from the Office of Clinical Pharmacology. The highlights of the prescribing information and Clinical Pharmacology relevant sections of the final agreed upon package insert labeling are included in Section 2 of this addendum.

1.1 Recommendation

The Division of Clinical Pharmacology-3, Office of Clinical Pharmacology finds the NDA 203505 acceptable.

2 Final Agreed Upon Package Insert Labeling

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

/s/

LAI M LEE
02/26/2013

MYONG JIN KIM
02/26/2013

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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Clinical Pharmacology Team Leader	Myong-Jin Kim, PharmD
Pharmacometrics Reviewer	Jiang Liu, PhD,
Pharmacometrics Team Leader	Yaning Wang, PhD
Pharmacogenomics Reviewer	Christian Grimstein, PhD
Pharmacogenomics Team Leader	Michael Pacanowski, PharmD, MPH
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products

A Required OCP Inter-Division Briefing was held on January 7, 2013 and was attended by Shiew-Mei Huang, E. Dennis Bashaw, Hae-Young Ahn, Julie Beitz, Theresa van der Vlught, Kellie Reynolds, Suresh Doddapaneni, Myong-Jin Kim, Lei Zhang, Ping Zhao, Chongwoo Yu, Hyunjin Kim, Li Li, Sayed Al Habet, Jihong Shon, Michael Pacanowski, Christian Grimstein, Jiang Liu, Yaning Wang, Hobart Rogers, Na Hyung Kim, Chinmay Shukla, and Jeff Bray. Other attendees participated via the call-in number.

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1 EXECUTIVE SUMMARY

Shionogi, Inc. is seeking approval of ospemifene (also referred to as FC-1271a) for the treatment of vulvar and vaginal atrophy (VVA) due to menopause, including moderate to severe symptoms of dyspareunia and/or vaginal dryness. Ospemifene is an estrogen receptor (ER) agonist/ antagonist.

Ospemifene is a solid, oval biconvex, white to off-white, film-coated immediate release (IR) oral tablet. The proposed dosing regimen is one 60 mg tablet orally once daily with food.

Currently approved pharmacological treatment options for VVA include systemic and topical (vaginal) estrogen products. Ospemifene is not approved for use in the US. If approved, ospemifene will be the first estrogen receptor agonist/antagonist and non-estrogenic product approved for the treatment of VVA. There are three estrogen receptor agonist/antagonists - tamoxifen, raloxifene, and toremifene - currently approved by the FDA. Tamoxifen (Nolvadex®, NDA 017970) and toremifene (Fareston®, NDA 020497) are approved for the treatment of breast cancer. Raloxifene (Evista®, NDA 020815) is approved for the treatment and prevention of osteoporosis in postmenopausal women.

The clinical program included 7 biopharmaceutics studies, 21 clinical pharmacology studies, 2 Phase II studies, and 3 Phase III studies (2 pivotal and 1 endometrial safety). Four biopharmaceutics (bioequivalence and food effect) studies, 13 clinical pharmacology (single and multiple dose PK, drug-drug interaction, hepatic and renal impairment) studies, and 1 Phase II study were reviewed by the Clinical Pharmacology Reviewer. A population PK study evaluating age, renal function, and race was conducted and submitted by the applicant; it was reviewed by Pharmacometrics Reviewer Jiang Liu. The risk for venous thromboembolism (VTE) in patients with Factor V Leiden was reviewed by Pharmacogenomics Reviewer Christian Grimstein.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) has reviewed NDA 203505 for ospemifene 60 mg oral tablets submitted to the Agency on April 29, 2012. We found this NDA acceptable from a Clinical Pharmacology perspective provided that an agreement is reached between the sponsor and the Division regarding the labeling language.

1.2 Phase IV Commitment/Requirement

None

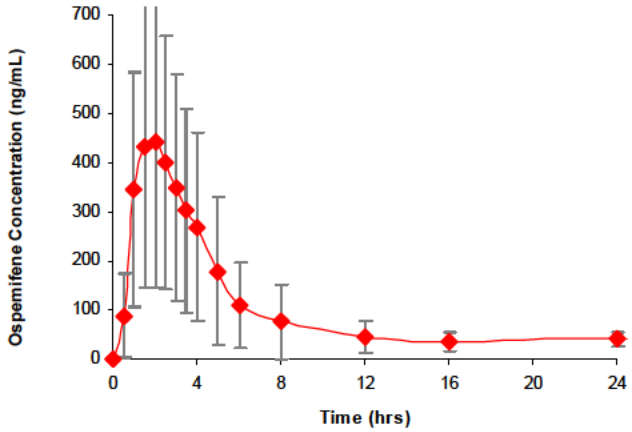
1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

During the clinical development program, there were several formulations (solution, capsule, and tablets) evaluated with multiple manufacturing sites [redacted] (b) (4) Penn Pharmaceuticals in the United Kingdom, [redacted] (b) (4) for the tablet formulations. Ospemifene 30 (Lot 0248A) and 60 mg tablets (Lot 0249A) were manufactured by Penn Pharmaceuticals for Phase 3 Study 15-50310. Ospemifene 60 mg tablets (Lot A07006) were manufactured by [redacted] (b) (4) for Phase 3 Study 15-50821. The to-be-marketed (TBM) ospemifene 60 mg tablets will be manufactured Penn Pharmaceuticals. The sponsor demonstrated bioequivalence (BE) under fasting conditions between the two formulations of 60 mg ospemifene used in the two Phase 3 studies.

PK Parameters Mean (SD) for Ospemifene	Formulation for Study 15-50821	Formulation for Study 15-50310	Geometric Mean Ratio (90% CI)
Cmax (ng/mL)	501 (305)	533 (304)	0.95 (0.83, 1.09)
$AUC_{0\text{-}96}$ (ng.hr/mL)	3661 (1728)	3781 (1795)	0.96 (0.89, 1.05)
$AUC_{0\text{-}inf}$ (ng hr/mL)	3982 (1913)	4165 (1970)	0.97 (0.88, 1.05)

Pharmacokinetic Characteristics

The following figure is the mean (SD) serum concentration-time profile of ospemifene following a single dose of 60 mg ospemifene, Penn Lot 0249A (TBM formulation), N=91, fasted (Study 15-51031).



Single Dose mean (SD) PK Parameters of Ospemifene 60 mg tablets (n=91, fasting, TBM formulation)

PK Parameter	Ospemifene (N=91)
$AUC_{0\text{-}96hr}$ (ng hr/mL)	3661 (1728)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	3982 (1913)
Cmax (ng/mL)	501 (305)
Tmax* (hr)	2.0 (1.0-24.0)
$T_{1/2}$ (hr)	26.4 (7.5)
λ_z (1/hr)	0.028 (0.007)

*median (min-max)

Dose-Response Relationship

Efficacy Endpoints

The four co-primary endpoints for the two 12-week pivotal Phase 3 studies are (1) change in percent parabasal cells; (2) change in percent superficial cells; (3) change in vaginal pH; and (4) change in most bothersome symptom (vaginal dryness and vaginal pain associated with sexual activity).

Efficacy

The dose-response relationships for the vaginal maturation indices using pooled data from the 3 placebo-controlled studies, and change in the severity of the most bothersome symptom of vaginal dryness and vaginal pain associated with sexual activity using pooled data from Studies 15-50310 and 15-50821 have been investigated. Dose-response relationships between each co-primary efficacy endpoint and dose were assessed with an ANCOVA model. Least-squares means were plotted against treatment group to produce dose-response curves for each endpoint. Ospemifene 60 mg QD demonstrated superiority over placebo for all co-primary endpoints. A

clear dose-related effect was observed in all objective primary endpoints, with ospemifene 60 mg/day being consistently more effective at treating VVA in postmenopausal women than ospemifene 30 mg/day. (Refer to the Pharmacometrics Review in the Appendix for additional details)

Primary Efficacy Summary: Mean Change from Baseline to Week 12/ LOCF in Study 15-50310; Modified ITT Population

	Ospemifene 30 mg	Ospemifene 60 mg	Placebo
% Superficial Cells	N = 257	N = 254	N = 247
- Baseline Mean (SD)	1.0 (1.53)	0.7 (1.35)	0.7 (1.26)
- Week 12 Mean (SD)	9.1 (11.85)	12.4 (15.63)	2.8 (8.20)
- Mean change from Baseline (SD)	8.1 (11.87)	11.7 (15.72)	2.1 (7.98)
- Lease Squares Mean (SE)	2.3 (0.79)	8.3 (0.78)	2.3 (0.79)
- P-value for Treatment Comparison[a]	<0.0001	<0.0001	-
% Parabasal Cells	N = 257	N = 254	N = 247
- Baseline Mean (SD)	40.2 (38.48)	40.6 (39.07)	38.8 (37.60)
- Week 12 Mean (SD)	16.9 (26.20)	9.0 (19.69)	42.5 (37.25)
- Mean change from Baseline (SD)	-2.3 (33.20)	-31.6 (38.60)	4.7 (35.68)
- Least Squares Mean (SE)	-23.1 (1.62)	-31.6 (38.60)	4.1 (1.64)
- P-value for Treatment Comparison[a]	<0.0001	<0.0001	-
Vaginal pH	N = 257	N = 254	N = 247
- Baseline Mean (SD)	6.36 (0.727)	6.38 (0.751)	6.36 (0.721)
- Week 12 Mean (SD)	5.66 (1.061)	5.37 (0.962)	6.24 (0.908)
- Mean change from Baseline (SD)	-0.67 (1.054)	-0.70 (1.065)	-0.12 (0.831)
- Least Squares Mean (SE)	-0.70 (0.058)	-0.99 (0.058)	-0.11 (0.058)
- P-value for Treatment Comparison[a]	<0.0001	<0.0001	-
Vaginal Dryness	N = 95	N = 113	N = 100
- Baseline Mean (SD)	2.5 (0.50)	2.5 (0.50)	2.4 (0.50)
- Week 12 Mean (SD)	1.3 (0.84)	1.1 (0.98)	1.5 (1.03)
- Mean Change from Baseline (SD)	-1.3 (0.92)	-1.3 (0.99)	-0.9 (0.97)
- P-value for Treatment Comparison[b]	P=0.0407	P=0.0136	-
Dyspareunia	N = 124	N = 110	N = 113
- Baseline Mean (SD)	2.6 (0.48)	2.6 (0.44)	2.7 (0.45)
- Week 12 Mean (SD)	1.5 (1.09)	1.4 (1.17)	1.8 (1.16)
- Mean Change from Baseline (SD)	-1.1 (1.02)	-1.4 (1.14)	-0.9 (1.13)
- P-value for Treatment Comparison[b]	0.0968	0.0012	-

Source: Adapted from the Clinical Reviewer Theresa van der Vlugt

Primary Efficacy Summary: Mean Change from Baseline to Week 12/LOCF (Dryness Stratum) in Study 15-50821; Modified ITT Population

	Ospemifene 60 mg	Placebo
% Superficial Cells	n =157	n = 150
- Baseline Mean (SD)	0.9 (1.44)	0.9 (1.48)
- Week 12/LOCF Mean (SD)	13.4 (15.39)	4.3 (9.12)
- Mean Change from Baseline (SD)	12.5 (15.39)	3.5 (9.02)
- Least Squares Mean (SE)	12.3 (1.03)	3.5 (1.06)
- P-value for Treatment Comparison[a]	<0.0001	-
% Parabasal Cells	n = 157	n =150
- Baseline Mean (SD)	46.2 (40.63)	45.7 (40.64)
- Week 12/LOCF Mean (SD)	14.5 (27.45)	41.8 (36.55)
- Mean Change from Baseline (SD)	-31.7 (37.16)	-3.9 (30.22)

- Least Squares Mean (SE) - P-value for Treatment Comparison[a]	-31.6 (2.13) <0.0001	-4.1 (2.19) -
Vaginal pH - Baseline Mean (SD) - Week 12 Mean (SD) - Mean Change from Baseline (SD) - Least Squares Mean (SE) - P-value for Treatment Comparison[a]	n = 157 6.25 (0.800) 5.33 (0.917) -0.92 (1.103) -0.96 (0.068) <0.0001	n = 150 6.26 (0.755) 6.03 (0.937) -0.24 (0.808) -0.25 (0.070) -
Vaginal Dryness - Baseline Mean (SD) - Week 12 Mean (SD) - Mean Change from Baseline (SD) - P-value for Treatment Comparison[b]	n = 157 2.5 (0.50) 1.2 (1.02) -1.3 (1.07) 0.0853	n = 150 2.5 (0.50) 1.4 (1.03) -1.1 (1.01) -

Source: Adapted from the Clinical Reviewer Theresa van der Vlugt

Safety

The most frequently reported drug-related adverse events were hot flushes, vaginal discharge, genital discharge, muscle spasm, and hyperhidrosis. Of the two Phase 3 studies, only Study 15-50310 included more than one dose (30 and 60 mg).

In the Phase 3 studies, the most common treatment-emergent adverse events (TEAEs) in ospemifene-treated patients were hot flush, urinary tract infection (UTI), and headache. The difference from placebo was 5.2% for hot flush, 1.6% for UTI and 0.5% for headache. Overall, there was no dose-related increase in TEAEs. Incidence of vaginal bleeding was low and none led to discontinuation from the study.

There was very little or no evidence of a dose-dependent relationship for adverse events (AEs) from the drug development program. In the QT study where there was a dose proportional increase in AUC from 60 to 240 mg, there were no differences in common AEs. Overall, for common AEs, there is no dose-safety correlation. For a serious and infrequent AE, endometrial change characterized by active proliferation and thickening, there were a few cases of dose-safety correlation in Phase 3 Study 15-50310. There was a dose-related increase in endometrial thickness (proliferative findings were observed in 3 patients in the 30 mg group, 5 patients in the 60 mg, and none in the placebo group).

Drug Substance Properties

Ospemifene has not been officially reviewed by the Biopharmaceutics Classification System (BCS) committee. The applicant believes ospemifene is a BCS Class 2 drug substance(low solubility and high permeability). At room temperature, ospemifene is highly insoluble in water and buffers over the pH range from 1.2 to 8.0. It is freely soluble in acetone, methylethylketone, methylisobutylketone, ethylacetate and tetrahydrofuran

Dose Proportionality

Cmax and $AUC_{0\text{-}24\ hr}$ increased in a less than dose-proportional manner in the range of 25 to 200 mg. Median Tmax was about 2 to 3 hrs. Elimination half-life was approximately 25.3 hrs as determined in the 200 mg dose group at Week 12. Enterohepatic recycling may be responsible for the long elimination half-life. Linearity was evident with doses 25, 50, and 100 mg for Cmax or AUC0-24hr. Dose proportionality was not established for single and multiple dosing. Accumulation for $AUC_{0\text{-}inf}$ was determined at Week 12 and ranged from 1.6 to 2.4 (average about 2.1) for doses 25 to 200 mg.

Metabolizing Enzymes

Based on in vitro study 15-4304 in human liver microsomes and recombinant human CYP enzymes, ospemifene is primarily metabolized by CYP3A4, 2C9, and 2C19 responsible for approximately 40 to 50%, ~25%, and ~25%, respectively, of its clearance. Therefore, the effect of ketoconazole, rifampicin, fluconazole, and omeprazole on the exposure of ospemifene was assessed in vivo in healthy postmenopausal women.

In vitro study 15-4318 in human liver microsomes suggests that ospemifene may be an inhibitor of CYP2B6, 2C9, and 2C19 with an IC_{50} value of approximately 7.8 μM, 10 μM, and 35 μM, respectively. The maximal concentration of ospemifene after 60 mg doses is approximately 3 μM. Therefore, in vivo studies using buproprion, warfarin, and omeprazole as substrates to assess the extent of ospemifene inhibition on CYP2B6, 2C9, and 2C19, respectively, were conducted.

The sponsor evaluated ospemifene as a potential substrate for transporters in a P-gp in vitro study. No in vivo transporter studies were conducted.

Intrinsic and Extrinsic Factors

The sponsor conducted studies to evaluate intrinsic and extrinsic factors that may affect the PK of ospemifene. These studies included, renal impairment, hepatic impairment, food effect, drug interactions with ketoconazole (a strong CYP3A4 inhibitor), rifampicin (a strong CYP3A4 inducer), fluconazole (a CYP3A4/CYP2C9/CYP2C19 inhibitor), and omeprazole (a CYP2C19 inhibitor and substrate). The sponsor conducted studies with warfarin (a CYP2C9 substrate), and bupropion (a CYP2B6 substrate) to assess the potential effect of ospemifene on CYP2C9 and CYP2B6 substrates.

Renal impairment on ospemifene PK

Severe renal impairment and End-Stage Renal Disease (ESRD) did not significantly impact the systemic exposure of a single 60 mg dose of ospemifene. In subjects with severe renal impairment and ESRD, mean Cmax, AUC_{0-t}, and AUC_{0-inf} for ospemifene were lower by 21%, higher by 19%, and higher by 20%, respectively. Half-life was the same at about 34 hrs in patients with severe renal impairment and ESRD and normal renal function subjects. These results are expected based upon the known clearance pathway for ospemifene, which is primarily through hepatic metabolism, and fecal and urinary excretion.

PK parameter*	Normal Renal Function (N=7)	Severe Renal Impairment + ESRD (N=8)	Severe/ESRD Renal Impairment versus Normal Renal Function PE (CI)**
AUC_{0-t} (ng hr/mL)	7567 ± 2296	9395 ± 3965	118.7 (0.84, 1.68)
AUC_{0-inf} (ng hr/mL)	8073 ± 2296	10141 ± 4144	119.6 (0.81, 1.76)
Cmax (ng/mL)	1106.1 ± 472.7	916.2 ± 525.2	78.6 (0.51, 1.22)
Tmax (hr)[1]	2 (1.0-6.0)	3.5 (2.0-8.0)	-
$T_{1/2}$ (hr)	33.6 ± 8.6	34.2 ± 6.1	103.0 (0.85, 1.25)
CL/F (mL/min)	132.3 ± 35.7	117.4 ± 56.8	83.6 (0.57, 1.23)

Severe (n=3), ESRD (n=5)
* mean ± SD
**point estimate and 90% CI of the least-squares geometric means ratio
[1]tmax: median and range

Hepatic impairment on ospemifene PK

Subjects with normal hepatic function and patients with mild hepatic impairment had similar mean Cmax, AUC_{0-t}, and AUC_{0-inf} for ospemifene. In patients with mild hepatic impairment,

mean Cmax, AUC_{0-t}, and AUC_{0-inf} for ospemifene were lower by 21%, 6.1%, and 9.1%, respectively.

Moderate hepatic impairment had a slightly greater effect on ospemifene exposure compared to mild hepatic impairment. Overall, the effect of moderate hepatic impairment was not significant following a single 60 mg dose of ospemifene. In patients with moderate hepatic impairment, mean Cmax was essentially the same. AUC_{0-t} and AUC_{0-inf} for ospemifene were higher by ~28%, compared to subjects with normal hepatic function. In the context of inter-subject variability of approximately 30%, the change in AUC_{0-inf} in patients with moderate hepatic impairment is not significant.

Genetics
The sponsor excluded Factor V Leiden (FVL) carriers from Phase 2 and Phase 3 clinical trials. Venous thromboembolism (VTE) risk is approximately 2-3 fold higher in FVL carriers compared to non-carriers, and further increased if other known risk factors are present. Based on the estimated prevalence of FVL and considering the increased risk associated with FVL, few/no additional VTE cases would have been observed if FVL carriers were included in Phase 2/3 trials. Therefore, current risk estimates are reasonable.

QT Prolongation
For ospemifene 60 mg, ΔQTcI was -2.8 ms and the 90% CI for ΔQTcI was - 4.3 to -1.2 ms. For the supratherapeutic dose 240 mg ospemifene, ΔQTcI was -3.5 ms and the 90% CI for ΔQTcI was -5.0 to -1.9 ms. The regulatory threshold of a 10 ms increase in QT was not exceeded; therefore, there is no safety concern for QT prolongation by ospemifene. For reference drug moxifloxacin 400 mg, ΔQTcI was 5.4 ms and the 90% CI for ΔQTcI was 3.2 to 7.5 ms.

Population PK
A two-compartment model with first-order absorption processes was selected. Inter-subject variability was assessed on each of the PK parameters using the exponential error structure. Based on the OBJ, exponential error model was chosen for intra-individual variability. Age, race, manufacturing sites, body weight, BMI, ALB, ALT, BILI, CREAT and CLcr were tested as a covariate on PK parameters of CL/F. Age, race, manufacturing sites, body weight, BMI and ALB were tested as a covariate on V2/F. Linear and power model were applied to test continuous covariates and categorical model was applied to test categorical covariates.

There was no covariate detected to have clinically relevant effect on ospemifene PK. The CL/F estimate (9.16 L/hr) and the inter-individual variability for CL/F (36.3%) under the fed condition are smaller compared to those under the fasted condition (16.9 L/hr for CL/F and 42.7% for the inter-individual variability for CL/F).

Effect of strong CYP3A4 inhibitor, ketoconazole, on ospemifene PK
Ketoconazole moderately increased the concentrations of ospemifene in healthy postmenopausal women treated with ketoconazole 400 mg once daily for 5 days prior to and 3 days after a single dose administration of ospemifene 60 mg.

The mean AUC_{0-inf} increased by 1.4-fold from 4578 to 6475 ng.hr/mL and Cmax increased by 1.5-fold from 644 to 872 ng/mL. Tmax was 2.5 hrs with ospemifene alone and with ketoconazole pre-treatment. Elimination half-life was similar at 24 hrs, respectively. Continued CYP3A4 inhibition was maintained by giving three additional doses of ketoconazole after ospemifene administration.

Effect of a strong CYP3A4 inducer, rifampicin, on ospemifene PK
Rifampicin moderately decreased ospemifene exposure in healthy postmenopausal women treated with rifampicin 600 mg daily for 5 consecutive days (Days 1-5 at approximately 4 pm and at least one hour before or two hours after a meal) prior to a single dose administration of ospemifene 60 mg (Day 6 at 8 am) under a fed condition.

The mean $AUC_{0\text{-}inf}$ was decreased by 58% from 4578 to 1854 ng.hr/mL and Cmax was decreased by 51% from 644 to 301 ng/mL. Tmax and elimination half-life remained essentially unchanged. Tmax was similar at ~ 3 hrs. Elimination half-life was similar at ~25 hrs. Rifampicin was not given after ospemifene administration on Day 6 and during the PK sampling period; therefore, enzyme induction by rifampicin may have been more significant. It is possible that ospemifene exposure may have been lowered more significantly if rifampicin was given during the PK sampling period.

Effect of a CYP2C19/2C9/3A4 inhibitor, fluconazole, on ospemifene PK
Fluconazole significantly increased ospemifene exposure in fourteen healthy postmenopausal women who received a single dose of ospemifene 60 mg (Day 5) with and without fluconazole pretreatment (400 mg on Day 1, 200 mg on Days 2-8).The effect of fluconazole on ospemifene exposure was apparent with ospemifene $AUC_{0\text{-}inf}$ increasing 2.7-fold from 4288 to 11932 ng.hr/mL after fluconazole pre-treatment. Cmax increased slightly by 1.7-fold from 650 to 1028 ng/mL and Tmax was similar at ~ 3 hrs. $T_{1/2}$ increased significantly from 25.0 to 42.9 hrs with fluconazole inhibition.

The applicant identified fluconazole as a potent CYP2C9 inhibitor. Based upon the classification of CYP inhibitors in the current FDA's Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (February 2012), fluconazole is an inhibitor of multiple enzymes - listed as a moderate CYP2C9, strong CYP2C19, and moderate CYP3A4 inhibitor. Despite the known inhibitory effects of fluconazole on CYP2C19 and CYP3A4, the sponsor selected fluconazole as the perpetrator drug in the study of CYP2C9 inhibition. Due to fluconazole's inhibitory effect on multiple CYP enzymes, it not possible to conclude that the pathway for ospemifene metabolism is solely through CYP2C9.

Effect of a moderate CYP2C19 inhibitor, omeprazole, on ospemifene PK
Once daily administration of omeprazole 40 mg at approximately 7 am on Days 1-4. On Day 5 (after an overnight fast) subjects took their fifth dose of omeprazole 40 mg at approximately 7 am followed by one tablet of ospemifene 60 mg was administered after a standard breakfast at 8 am. Omeprazole 40 mg was taken for three additional days at approximately 7 am to provide CYP2C19 inhibition during the blood sampling period for ospemifene PK

The effect of omeprazole on ospemifene exposure was less significant than with fluconazole with ospemifene $AU_{C0\text{-}inf}$ increasing 1.2-fold from 3949 to 4568 ng.hr/mL after omeprazole pretreatment. Cmax increased slightly from 560 to 657 ng/mL. Tmax was similar at ~ 3 hrs. $T_{1/2}$ was essentially unchanged at ~24 hrs

The applicant identified omeprazole as a strong CYP2C19 inhibitor. According to the above mentioned drug interaction guidance published in 2012, omeprazole is a moderate inhibitor of CYP2C19. The discrepancy in the categorization of omeprazole is likely due to the classification of inhibitors in the early guidance where omeprazole was listed as a strong CYP2C19 inhibitor.

Effect of food (low fat and high fat meal) on ospemifene PK
The two food effect studies (one with high-fat/high calorie food and one with low-fat/low calorie food) was conducted using ospemifene tablets manufactured by [redacted] (b) (4) Following administration of a light breakfast, the geometric mean ratio of ospemifene fed/fasted for Cmax was 2.3 and for $AUC_{0\text{-}72hr}$ was 1.9. Median Tmax of ospemifene was the same at 2.0 hrs under both fed and fasted conditions. Median $t_{1/2}$ of ospemifene remained relatively unchanged at 13.7 hrs under low fat, 13.6 hrs under high fat, and 14.6 hrs fasted conditions, respectively.

Following administration of a high fat breakfast, the geometric mean ratio of ospemifene fed/fasted for Cmax was 3.5 and for $AUC_{0\text{-}72hr}$ was 2.6. Median Tmax of ospemifene was the same at 2.0 hrs under both fed and fasted conditions. Median $t_{1/2}$ of ospemifene remained the same at 13.7 hrs under both fed and fasted conditions.

The sponsor conducted the above mentioned food effect studies in healthy young men using early development tablets (manufactured by [redacted] (b) (4)). To assess the effect of food on the to-be-marketed ospemifene tablets in postmenopausal women, a cross-study comparison using PK data gathered from 5 bioequivalence studies (1 under fed condition and 4 under fasted condition) was conducted by this reviewer. The PK parameters for ospemifene were similar across the four studies under fasted conditions. The results show that $AUC_{0\text{-}inf}$ and Cmax increased 1.7-fold and 2.3-fold, respectively, when ospemifene was administered with a high fat/high calorie meal. Tmax was similar at about 2 hrs. Half-life was similar and ranged from 24 to 29 hrs.

In the two pivotal Phase 3 clinical trials (Studies 15-50310 and 15-50821) and long-term endometrial safety study (Study 15-50718) ospemifene was administered with food (no specific type indicated). The proposed label states that ospemifene be taken with food.

Effect of ospemifene on warfarin, a CYP2C9 substrate, PK
This study was an open-label, balanced, two-period, and crossover design in 16 healthy postmenopausal women who were determined as rapid metabolizers of CYP2C9 (CYP2C9*1/*1 or CYP2C9*1/*2). A single dose of 10 mg warfarin as a probe drug with 10 mg vitamin K was administered at one hour after a standard breakfast without or with treatment of ospemifene on the 8^{th} day of its multiple treatment. A 60 mg tablet of ospemifene under fed condition after the breakfast was administered once daily for 12 days in the ospemifene treatment group.

Study results showed that the PK of *S*-warfarin was not influenced by multiple pre-treatment of ospemifene. The geometric mean ratio for *S*-warfarin was near unity for the primary PK parameters- 0.96 for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$, and 0.97 for Cmax.

Effect of ospemifene on omeprazole, a CYP2C19 substrate, PK
In a single dose, open-label, two-period, crossover study with a washout period of at least 2 weeks, twelve healthy postmenopausal women were given a single 20 mg dose of omeprazole (on Day 8) with and without pretreatment with 60 mg ospemifene with once daily dosing for 7 days (Days 1-7). Subjects genotyped as being homozygous as poor CYP2C19 metabolizers (possessing the CYP2C19*2/*2 genotype) were excluded from Study 15-50719. However, no other alleles were assayed. Ospemifene 60 mg tablets ([redacted] (b) (4) A07006) were used in this study.

The geometric mean ratios for both metabolic indices (omeprazole/5-hydroxyomeprazole) and for $AUC_{0\text{-}8hr}$ were 0.97 with and without ospemifene pretreatment with a 90% CI that ranged from 0.88 to 1.08. The near unity value for these metabolic indices suggest that ospemifene did not have a significant effect on the metabolism of omeprazole by CYP2C19.

There were limitations to this study including the significant time gap between ospemifene and omeprazole administration on Day 8 and subjects with various CYP2C19 alleles were not identified (subjects possessing the CYP2C19*2/*2 genotype were excluded from the study). Due to multiple deficiencies of the study design, the applicant failed to demonstrate that ospemifene does not affect the activity of CYP2C19 enzymes.

Effect of ospemifene on bupropion, a CYP2B6 substrate, PK
In an open-label, balanced, two-period, and crossover design, 16 healthy postmenopausal women who were not homozygous carriers of the CYP2B6*6 genotype were given food with 8 days of 60 mg ospemifene pretreatment followed by a single 150 mg tablet of buproprion. Ospemifene tablets (b) (4) A07006) were used in this study.

Ospemifene pretreatment had a small effect on bupropion (bupropion exposure was slightly lower); however, not significant enough to warrant dosing adjustments or precautionary statements. Arithmetic mean of the AUC and C_{max} values of bupropion tended to be lower in the period with pretreatment of ospemifene than the bupropion alone period. The t_{max} and $t_{½}$ of bupropion were similar between two periods. The point estimates of the LS geometric means ratio of C_{max}, AUC_t, AUC_{∞}, and $t_{½}$ of bupropion were 82.4%, 82.1%, 81.4% and 96.7%, respectively.

2 QUESTION-BASED REVIEW

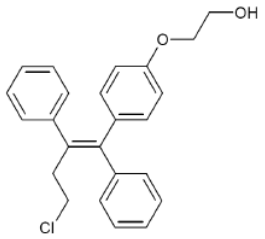
2.1 What pertinent regulatory background contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Shionogi is seeking approval of ospemifene for the treatment of VVA due to menopause. VVA is a condition associated with declining estrogen concentrations during menopause. Through binding to estrogen receptors in the vaginal walls, estrogen affects the thickening and maturation of vaginal mucosa and increased vaginal blood blow, lubrication, and mechanical sensitivity. Symptoms of VVA due estrogen insufficiency include vaginal dryness, burning, dyspareunia (vaginal pain associated with sexual intercourse), loss of vaginal secretions, leukorrhea, vulvar pruritus, feeling of pressure, bleeding and yellow malodorous discharge. The proposed dose and dosing regimen is 60 mg oral tablet to be taken once daily. Ospemifene should be taken with food. No dose adjustment is recommended.

2.2 GENERAL ATTRIBUTES OF THE DRUG

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

Ospemifene has a chemical name of Z-2-[4-(4-chloro-1,2-diphenyl-but-1-enyl)phenoxy]ethanol with a molecular weight of 378.90. The chemical formula is $C_{24}H_{23}ClO_2$. Ospemifene is practically insoluble in water and slightly soluble in acetone, methanol, ethanol, and DMSO. Ospemifene does not contain chiral structures. The drug substance is a white to off-white, crystalline powder and will be manufactured by (b) (4)



The to-be-marketed formulation is an immediate release, oval biconvex, white to off-white, film-coated tablet containing 60 mg ospemifene. The tablet will have one side engraved "60"and will be manufactured and released by Penn Pharmaceutical, United Kingdom. The table below summarizes the components and composition of the ospemifene 60 mg tablets used in the clinical development program. The applicant is seeking approval of the 60 mg tablet strength.

Core:	
Ospemifene	60.0 mg
Pregelatinized starch	(b) (4)
Mannitol	
Povidone	
Sodium starch glycolate	
Microcrystalline cellulose	
Colloidal silicone dioxide	
Magnesium stearate	
(b) (4)	
Film-coat:	
(b) (4)	
(b) (4)	

The tables below summarizes ospemifene formulations used during clinical development.

Study Objective	Study Design	Treatments (Dose, Route, Formulation) [Product ID]	Population	Protocol No.
Bioequivalence of ospemifene in tablet and capsule formulations and to evaluate the bioavailability of ospemifene	Open-label, randomized, three-sequence, three-period, crossover	Single 60 mg, oral, Fasted, Tablet [(b) (4)0107-852]; Capsules [(b) (4)002]; Solution [(b) (4)001]	Healthy male	1506004
Bioequivalence of two ospemifene 60 mg tablets	Open-label, randomized, multi-center, two-sequence, four-period, replicated-treatment, crossover	Single 60 mg, oral, Fasted, Tablet [Penn Pharma 0249A (commercial tablet)]; [(b) (4)85518]	Healthy postmenopausal female	15-50926
Bioequivalence of two ospemifene 60 mg tablets	Open-label, randomized, two-sequence, four-period, replicated-treatment, crossover	Single 60 mg, oral, Fasted, Tablet [Penn Pharma 0249A (commercial tablet)]; [(b) (4)85481]	Healthy postmenopausal female	15-51028
Bioequivalence of two ospemifene 60 mg tablets	Open-label, randomized, two-sequence, two-period, crossover	Single 60 mg, oral, Fed, Tablet [Penn Pharma 0249A (commercial tablet)]; [(b) (4)85481]	Healthy postmenopausal female	15-51029
Comparative BA study of five 60 mg ospemifene tablet batches	Open-label, randomized, five-sequence, five-period, crossover	Single 60 mg, oral, Fasted, Tablet [Penn Pharma 0249A (commercial tablet)]; [(b) (4)A10016, A10017, A10018, A10019]	Healthy postmenopausal female	15-51030
Bioequivalence of two ospemifene 60 mg tablets	Open-label, randomized, balanced, two-sequence, two-period, crossover	Single 60 mg, oral, Fasted, Tablet [Penn Pharma 0249A (commercial tablet)]; [(b) (4)A07006]	Healthy postmenopausal female	15-51031
Comparative BA study of ospemifene under fasted and high-fat fed conditions	Open-label, randomized, balanced, two-sequence, two-period, crossover	Single 60 mg, oral, Tablet [(b) (4)0107-852], Fasted; Fed (High-fat)	Healthy male	15-50208
Extension to 15-50208, to assess effects of a normal light breakfast on the bioavailability of ospemifene	Open-label, nonrandomized, one-period, one-treatment	Single 60 mg, oral, Tablet [(b) (4)0107-852], Fed (Low-fat);	Healthy male	15-50208-02

Study	Dose	Formulation	Population	Protocol No.
Single dose	10, 25, 50, 100, 200, 400, 800 (mg)	Gelatin capsules	Healthy male	3044001
Repeated dose	25, 50, 100, 200 (mg once daily)	Gelatin capsules	Healthy postmenopausal female	1506003
Single dose and steady state pharmacokinetics	60 (mg once daily)	Tablet	Healthy postmenopausal female	15-50927
Mass balance study	60 (mg) containing 20.2 MBq of (^{3}H)-ospemifene	Solution	Healthy postmenopausal female	15-50206
Effect of impaired hepatic function on ospemifene pharmacokinetics	60 (mg)	Tablet	Healthy or hepatic impaired postmenopausal female	15-50820
Effect of impaired hepatic function on ospemifene pharmacokinetics	60 (mg)	Tablet	Healthy or hepatic impaired postmenopausal female	15-50920
Effect of impaired renal function on ospemifene pharmacokinetics	60 (mg)	Tablet	Healthy or renal impaired postmenopausal female	15-50921
Drug-drug interaction; Effect of ospemifene on warfarin pharmacokinetics (CYP2C9 inhibition)	Racemic warfarin; 10 (mg), Ospemifene; 60 (mg once daily)	Tablet (Warfarin and Ospemifene)	Healthy postmenopausal female	15-50614
Drug-drug interaction; Effect of ospemifene on omeprazole pharmacokinetics (CYP2C19 and CYP3A4 inhibition)	Omeprazole; 20 (mg), Ospemifene; 60 (mg once daily)	Tablet (Omeprazole and Ospemifene)	Healthy postmenopausal female	15-50719
Drug-drug interaction; Effect of ospemifene on bupropion pharmacokinetics (CYP2B6 inhibition)	Bupropion; 150 (mg), Ospemifene; 60 (mg once daily)	Tablet (Bupropion and Ospemifene)	Healthy postmenopausal female	15-50825
Drug-drug interaction; Effect of rifampin and ketoconazole on ospemifene pharmacokinetics (CYP3A induction and inhibition)	Ospemifene; 60 (mg), Rifampin; 600 (mg once daily) / Ospemifene; 60 (mg), Ketoconazole; 400 (mg once daily)	Tablet (Ospemifene, Rifampin and Ketoconazole)	Healthy postmenopausal female	15-50716
Drug-drug interaction; Effect of fluconazole and omeprazole on ospemifene pharmacokinetics (CYP2C9 and CYP2C19 inhibition)	Ospemifene; 60 (mg), Fluconazole; 200 (mg once daily) / Ospemifene; 60 (mg), Omeprazole; 40 (mg once daily)	Tablet (Ospemifene), Capsule (Fluconazole), Gastro-resistant tablet (Omeprazole)	Healthy postmenopausal female	15-50823
Thorough QTc study	Placebo, Ospemifene; 60, 240 (mg once daily), Moxifloxacin; 400 (mg once daily)	Tablet (Placebo, Ospemifene and Moxifloxacin)	Healthy male and female	15-50824

2.2.2 What are the proposed mechanism of action and therapeutic indications?

The sponsor is seeking approval to market ospemifene for the treatment of VVA. Ospemifene is an estrogen receptor agonist/antagonist; it binds to human estrogen receptors (ERα and ERβ). Ospemifene and main metabolites 4-hydroxyospemifene (M1) and 4'-hydroxyospemifene (M2) cause estrogen-like effects on vaginal epithelium. Ospemifene improves symptoms of VVA by

changes induced to the vaginal epithelium (parabasal and superficial cells) and decrease in vaginal pH.

2.2.3 What are the proposed dosages and routes of administration?

The applicant is seeking approval of a 60 mg immediate release tablet to be given orally once daily with food.

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

Currently approved pharmacological therapies for VVA include systemic hormone therapy (oral estrogens) such as Premarin®, and topical (vaginal) estrogen products such as Synthetic Conjugated Estrogens, A® vaginal cream. Non-approved therapy includes non-hormonal lubricants and moisturizers such as K-Y Jelly®.

2.3 GENERAL CLINICAL PHARMACOLOGY

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and clinical studies used to support dosing or claims?

The clinical program included 7 biopharmaceutics studies, 21 clinical pharmacology studies, and 3 Phase III studies (2 pivotal and 1 endometrial safety). A population PK study evaluating age, renal function, and race was conducted. The proposed dosing instruction for ospemifene is 60 mg tablet administered orally once daily with food. No titration of dose is proposed by the applicant.

In the first Phase III trial (Study 15-50310), the doses were 30 mg and 60 mg and were administered as one 30 mg tablet (Penn Lot 0248A) or one 60 mg tablet (Penn Lot 0249A). Penn Pharmaceuticals manufactured the clinical trial ospemifene tablets for Study 15-50310 and will manufacture the commercial product. In the second Phase III trial (Study 15-50821), the dose was 60 mg and was administered as one 60 mg tablet (b) (4) Lot A07006). (b) (4) manufactured the clinical trial product for Study 15-50821. Patients were instructed to take ospemifene in the morning with food in both Phase III trials. The applicant demonstrated bioequivalence between 60 mg ospemifene tablets manufactured by Penn Pharmaceuticals (Penn Lot 0249A) and (b) (4) (Lot A07006) in Study 15-51031.

The majority of Phase I Clinical Pharmacology studies evaluating drug-drug interactions, intrinsic factors, extrinsic factors, and QT prolongation were conducted with ospemifene tablets (b) (4) Lot A07006) manufactured by (b) (4). With the exception of selected bioequivalence studies, subjects in the Phase III and Clinical Pharmacology studies were given a meal prior to ospemifene administration. Studies conducted with other formulations are noted in the respective sections of this QBR and Individual Study Reviews.

2.3.2 What is the basis for selecting the response endpoints (i.e. clinical endpoints or biomarkers) and how are they measured in clinical pharmacology and clinical studies?

The four co-primary efficacy endpoints in the pivotal Phase III trials are change from Baseline to Week 12 in the following (1) percentage of parabasal cells in the maturation index of the vaginal smear; (2) percentage of superficial cells in the maturation index of the vaginal smear; (3) vaginal pH; and (4) severity of the most bothersome symptom (MBS) of VVA of vaginal dryness (dryness) and vaginal pain associated with sexual activity (dyspareunia).

In the clinical pharmacology studies, the endpoints for the majority of studies were PK parameters of ospemifene. In some cases such as drug-drug interactions, the endpoints were PK parameters of the interacting drug.

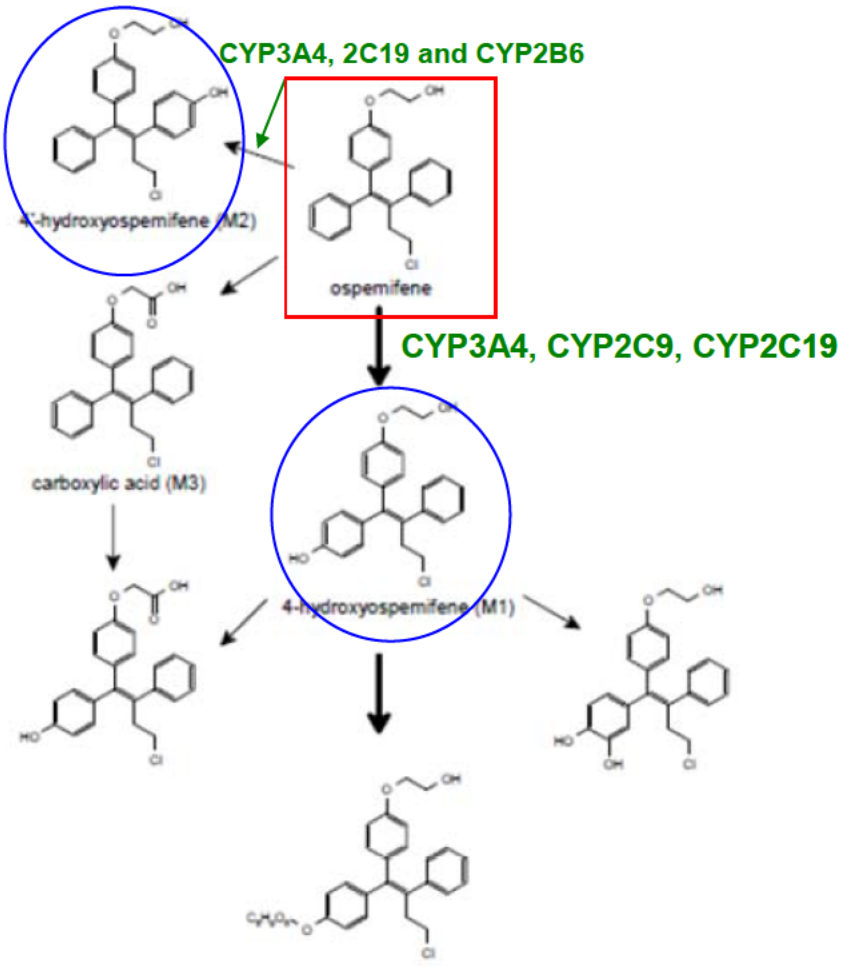
2.3.3 Are the active moieties in the serum and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

In an open-label study in six healthy postmenopausal women, the applicant evaluated the metabolism of a single oral solution dose of 60 mg ^{3}H-ospemifene (Study 15-50206). Metabolite profiling was done in human serum, urine, and feces. Blood, urine, and fecal samples were collected up 240 hrs after dosing. Ospemifene was extensively metabolized in humans. Fecal excretion was the major route of elimination of radioactivity. After oral dosing of ^{3}H-ospemifene through 240 hrs, approximately 75% (range 70 to 84%) of the radioactive dose was recovered in feces and 7% (5.5 to 10.1%) in urine. Recovery of total radioactivity in urine and feces was approximately 82%.

Plasma protein binding of ospemifene was 98.6%, 96.8%, and 95.0% at 2 hr, 6 hr, and 24 hr postdose, respectively.

Ospemifene is extensively metabolized to various metabolites, mainly by CYP3A4, CYP2C9, and CYP2C19 enzymes. 4-hydroxyospemifene (M1) and 4'-hydroxyospemifene (M2) are the two major metabolites with a serum concentration of approximately 25% and 7% of ospemifene, respectively. M1 and M2 have similar pharmacological activity to ERα and ERβ as ospemifene. PK parameters for M1 and M2 are not reported in this review due to their low systemic exposure relative to ospemifene.

The figure below is the proposed metabolic pathways of ospemifene in humans



2. 4 EXPOSURE-RESPONSE

2.4.1 Does the exposure-response (dose-response, concentration-response) relationship support evidence of effectiveness?

The applicant submitted data from two Phase III studies conducted in multiple centers in the United States to support the proposed indication, treatment of VVA in postmenopausal women. In the first Phase III trial (Study 15-50310), two doses (30 mg and 60 mg)were evaluated. The 30 mg tablets (Penn Lot 0248A) and 60 mg tablets (Penn Lot 0249A) were manufactured Penn Pharmaceuticals. In the second Phase III trial (Study 15-50821), one dose (60 mg) was evaluated. The 60 mg tablets ((b) (4) Lot A07006) was manufactured by (b) (4) .

The four co-primary endpoints for the two 12-weeek pivotal Phase 3 studies are (1) change in percent; (2) change in percent parabasal cells; change in percent superficial cells; (3) change in vaginal pH; and (4) change in most bothersome symptom (vaginal dryness and vaginal pain associated with sexual activity).

Primary Efficacy Summary: Mean Change from Baseline to Week 12/ LOCF in Study 15-50310; Modified ITT Population

	Ospemifene 30 mg	Ospemifene 60 mg	Placebo
% Superficial Cells	N = 257	N = 254	N = 247
- Baseline Mean (SD)	1.0 (1.53)	0.7 (1.35)	0.7 (1.26)
- Week 12 Mean (SD)	9.1 (11.85)	12.4 (15.63)	2.8 (8.20)
- Mean change from Baseline (SD)	8.1 (11.87)	11.7 (15.72)	2.1 (7.98)
- Lease Squares Mean (SE)	2.3 (0.79)	8.3 (0.78)	2.3 (0.79)
- P-value for Treatment Comparison[a]	<0.0001	<0.0001	-
% Parabasal Cells	N = 257	N = 254	N = 247
- Baseline Mean (SD)	40.2 (38.48)	40.6 (39.07)	38.8 (37.60)
- Week 12 Mean (SD)	16.9 (26.20)	9.0 (19.69)	42.5 (37.25)
- Mean change from Baseline (SD)	-2.3 (33.20)	-31.6 (38.60)	4.7 (35.68)
- Least Squares Mean (SE)	-23.1 (1.62)	-31.6 (38.60)	4.1 (1.64)
- P-value for Treatment Comparison[a]	<0.0001	<0.0001	-
Vaginal pH	N = 257	N = 254	N = 247
- Baseline Mean (SD)	6.36 (0.727)	6.38 (0.751)	6.36 (0.721)
- Week 12 Mean (SD)	5.66 (1.061)	5.37 (0.962)	6.24 (0.908)
- Mean change from Baseline (SD)	-0.67 (1.054)	-0.70 (1.065)	-0.12 (0.831)
- Least Squares Mean (SE)	-0.70 (0.058)	-0.99 (0.058)	-0.11 (0.058)
- P-value for Treatment Comparison[a]	<0.0001	<0.0001	-
Vaginal Dryness	N = 95	N = 113	N = 100
- Baseline Mean (SD)	2.5 (0.50)	2.5 (0.50)	2.4 (0.50)
- Week 12 Mean (SD)	1.3 (0.84)	1.1 (0.98)	1.5 (1.03)
- Mean Change from Baseline (SD)	-1.3 (0.92)	-1.3 (0.99)	-0.9 (0.97)
- P-value for Treatment Comparison[b]	P=0.0407	P=0.0136	-
Dyspareunia	N = 124	N = 110	N = 113
- Baseline Mean (SD)	2.6 (0.48)	2.6 (0.44)	2.7 (0.45)
- Week 12 Mean (SD)	1.5 (1.09)	1.4 (1.17)	1.8 (1.16)
- Mean Change from Baseline (SD)	-1.1 (1.02)	-1.4 (1.14)	-0.9 (1.13)
- P-value for Treatment Comparison[b]	0.0968	0.0012	-

Source: Adapted from the Clinical Reviewer Theresa van der Vlugt
NDA 203505, Addendum to Clinical Study Report for Study 15-50310 dated July 9, 2012, Table 14.9.2.1.2, Table 14.9.1.1.2, Table 14.9.3.1.2, Table 14.9.4.1.3, and Table 14.9.4.2.2.
[a]P-value was computed using ANCOVA where change from Baseline is response variable, Baseline assessment is the covariate, and treatment, uterus status (intact or not), and center are fixed effects.
[b]P-value was computed using Cochran-Mantel-Haenszel row mean score test controlling for uterus status (intact or not) and center.
Definitions: LOCF = last observation carried forward, ITT = intent-to-treat, SD = standard deviation.

Primary Efficacy Summary: Mean Change from Baseline to Week 12/LOCF (Dryness Stratum) in Study 15-50821; Modified ITT Population

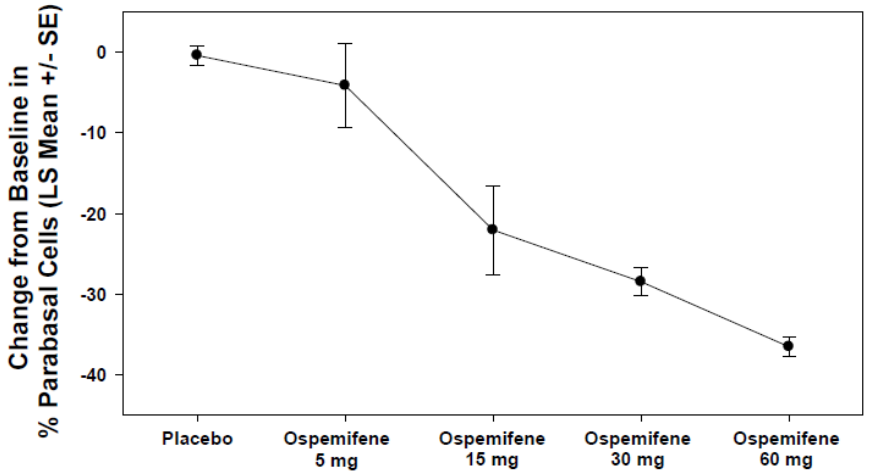
	Ospemifene 60 mg	Placebo
% Superficial Cells	n =157	n = 150
- Baseline Mean (SD)	0.9 (1.44)	0.9 (1.48)
- Week 12/LOCF Mean (SD)	13.4 (15.39)	4.3 (9.12)
- Mean Change from Baseline (SD)	12.5 (15.39)	3.5 (9.02)
- Least Squares Mean (SE)	12.3 (1.03)	3.5 (1.06)
- P-value for Treatment Comparison[a]	<0.0001	-
% Parabasal Cells	n = 157	n =150
- Baseline Mean (SD)	46.2 (40.63)	45.7 (40.64)
- Week 12/LOCF Mean (SD)	14.5 (27.45)	41.8 (36.55)
- Mean Change from Baseline (SD)	-31.7 (37.16)	-3.9 (30.22)

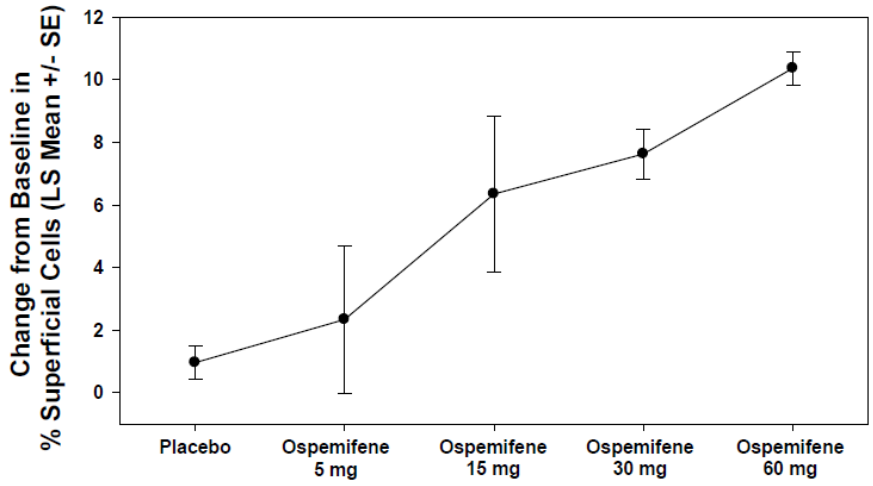
- Least Squares Mean (SE) - P-value for Treatment Comparison[a]	-31.6 (2.13) <0.0001	-4.1 (2.19) -
Vaginal pH - Baseline Mean (SD) - Week 12 Mean (SD) - Mean Change from Baseline (SD) - Least Squares Mean (SE) - P-value for Treatment Comparison[a]	n = 157 6.25 (0.800) 5.33 (0.917) -0.92 (1.103) -0.96 (0.068) <0.0001	n = 150 6.26 (0.755) 6.03 (0.937) -0.24 (0.808) -0.25 (0.070) -
Vaginal Dryness - Baseline Mean (SD) - Week 12 Mean (SD) - Mean Change from Baseline (SD) - P-value for Treatment Comparison[b]	n = 157 2.5 (0.50) 1.2 (1.02) -1.3 (1.07) 0.0853	n = 150 2.5 (0.50) 1.4 (1.03) -1.1 (1.01) -

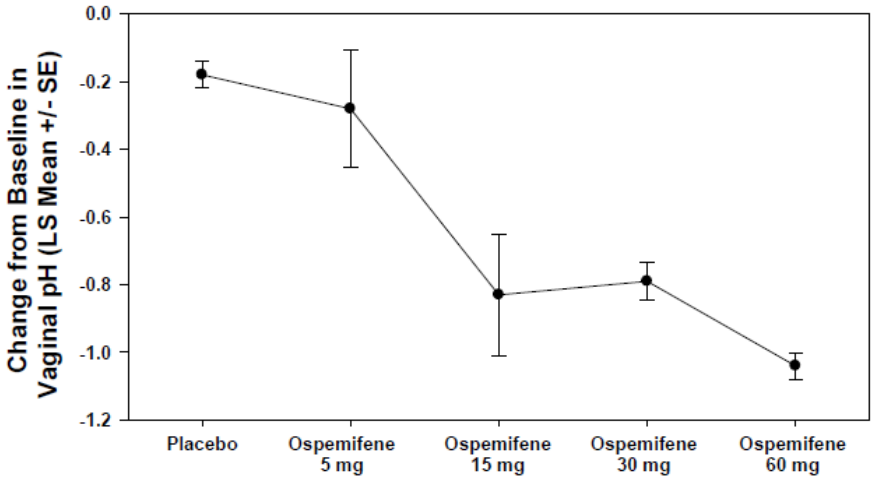
Source: Adapted from the Clinical Reviewer Theresa van der Vlugt
NDA 203505, Addendum to Study 15-50821 Clinical Study Report dated July 9, 2012, Table 14.9.1.2.2, Table 14.9.2.2.2, Table 14.9.3.2.2, and Table 14.9.4.3.2.
[a]P-value was computed using ANCOVA where change from Baseline is response variable, Baseline assessment is the covariate, and treatment and center are fixed effects.
[b]P-value was computed using Cochran-Mantel-Haenszel row mean score test controlling for center.
Definitions: LOCF = last observation carried forward, ITT = intent-to-treat, SD = standard deviation, SE = standard error.

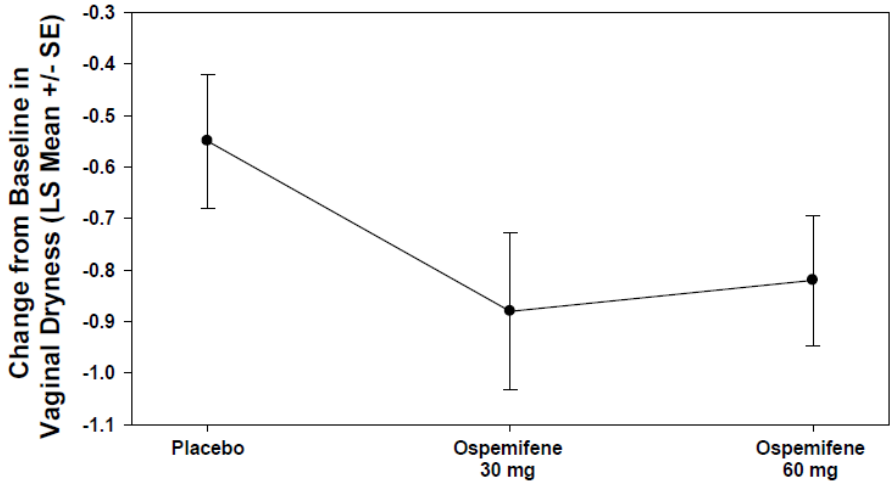
The dose-response relationships for the vaginal maturation indices using pooled data from the 3 placebo-controlled studies (15-50310, 15-50821 and 15-50718), and change in the severity of the most bothersome symptom of vaginal dryness and vaginal pain associated with sexual activity using pooled data from Studies 15-50310 and 15-50821 have been investigated. Dose-response relationships between each co-primary efficacy endpoint and dose were assessed with an ANCOVA model. Least-squares means were plotted against treatment group to produce dose-response curves for each endpoint. Ospemifene 60 mg QD demonstrated superiority over placebo for all co-primary endpoints. A clear dose-related effect was observed in all objective primary endpoints, with ospemifene 60 mg/day being consistently more effective at treating VVA in postmenopausal women than ospemifene 30 mg/day. (See Pharmacometrics Review by Jiang Liu in the Appendix)

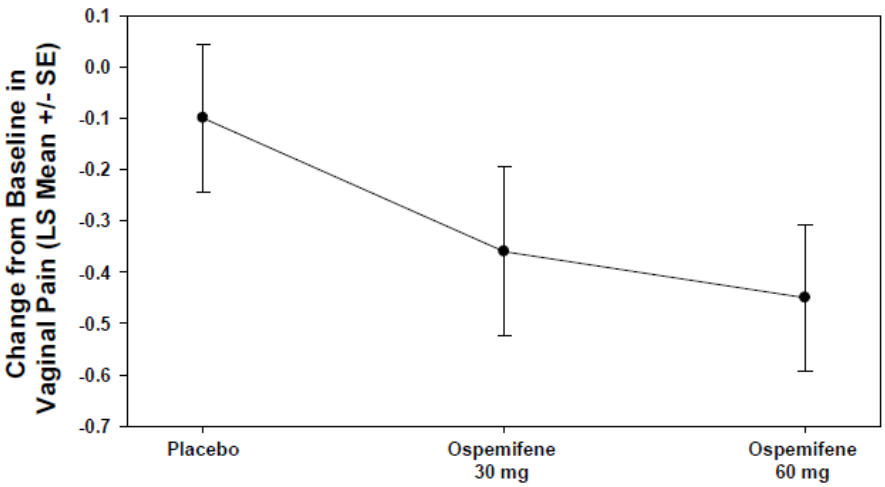
Change from Baseline to Week 12/LOCF in Co-Primary Efficacy Endpoints (ANCOVA Analysis of Pooled Data)











2.4.2 What are the characteristics of the dose (exposure)-response relationships for safety?

The most common TEAEs in ospemifene-treated subjects were hot flush, UTI, and headache. The difference from placebo was 5.2% for hot flush, 1.6% for UTI and 0.5% for headache. There was no dose-related increase in TEAEs. There were no occurrences of endometrial hyperplasia or carcinoma in the double-blind, Phase 2/3, placebo controlled studies. One simple hyperplasia (0.1%) was diagnosed 3 months after discontinuation of ospemifene 60 mg in the long-term 52-week study 15-50718. Incidence of vaginal bleeding was low and none led to discontinuation from the study. Concurred by the medical reviewer, no further exposure-response analysis for safety was needed. (See Pharmacometrics review by Jiang Liu in the Appendix.)

Most frequent-occurring treatment-emergent adverse events (>3% of intent-to-treat subjects) by system class (Study 15-50310)

System Organ Class	Preferred Term	Ospemifene 30 mg (N=282)	Ospemifene 60 mg (N=276)	Placebo (N=268)
Infection and Infestations	Urinary Tract Infection*	20 (7.1%)	20 (7.2%)	8 (3.0%)
	Fungal Infection**	7 (2.5%)	9 (3.3%)	1 (0.4%)
	Sinusitis	6 (2.1%)	7 (2.5%)	10 (3.7%)
	Vulvovaginal Mycotic Infection	3 (1.1%)	11 (4.0%)	2 (0.7%)
Nervous System Disorders	Headache	17 (6.0%)	7 (2.5%)	14 (5.2%)
Musculoskeletal and Connective Tissue Disorders	Muscle Spasms	7 (2.5%)	11 (4.0%)	4 (1.5%)
Reproductive System and Breast Disorders	Vaginal Discharge	12 (4.3%)	11 (4.0%)	1 (0.4%)
Vascular Disorders	Hot Flush	27 (9.6%)	23 (8.3%)	9 (3.4%)

*Seven of 20 subjects with urinary tract infection in the ospemifene 30 mg group and 2 of 8 subjects in the placebo group were diagnosed on Day 1, indicating the infections were present before treatment was initiated.
**All "fungal infections" were likely vaginal infections.
Note: Counts reflect numbers of subjects reporting one or more adverse events that map to the MedDRA SOC/PT. At each level of summarization (PT), subjects reporting more than one TEAE were counted only once.
Source: Table 14.3.2.1 and Table 14.3.2.2

There was very little or no evidence of a dose-dependent relationship for AEs from the drug development program. In the QT study where there was a dose proportional increase in AUC from 60 to 240 mg, there were no differences in common AEs. Overall, for common AEs, there is no dose-safety correlation. For a serious and infrequent AE, endometrial change characterized by active proliferation and thickening, there were a few cases of dose-safety correlation. The information provided below are from one Phase 1 and three Phase 3 (two 12-week and one 52-week long-term safety) studies.

- In an early 12-week dose finding study (1506003) evaluating ospemifene capsules in a postmenopausal women. The histology data showed that ospemifene has an estrogenic effect on the endometrial thickness and there was a clear dose dependent relationship from 50 to 200 mg.
- In the first 12-week Phase 3 study (15-50310) evaluating doses 30 & 60 mg, most of the common AEs were more frequently reported by patients in the 30 mg group. The serious AEs (stroke and breast cancer) were reported by patients in the 30 mg group. Only two common AEs (muscle spasms and vulvovaginal infection) were higher in the 60 mg group, compared to the 30 mg group. However, there was a dose-related increase in endometrial thickness (proliferative findings were observed in 3 patients in the 30 mg group, 5 patients in the 60 mg, and none in the placebo group).
- In the second 12-week Phase 3 study (15-50821) evaluating 60 mg ospemifene, there were many more common AEs in the 60 mg group, compared to the placebo group. The most noticeable SAEs in this study were the 1 case of deep vein thrombosis, 2 cases of active endometrial proliferation, and increase in endometrial thickening.
- In the 52-week endometrial safety study (15-50718) with 60 mg ospemifene, there was one report of mild endometrial hyperplasia, one severe stroke, one moderate DVT, one severe cerebral hemorrhage, and one severe global amnesia.

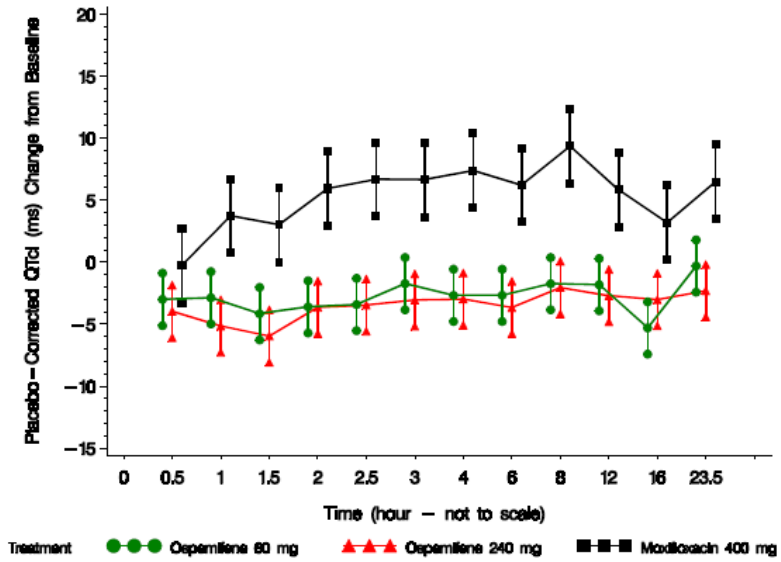
Overall, there appears to be no dose-response (safety) relationship for consider common AEs. However, for serious AEs, there appears to be suggestive evidence of endometrial change that is correlated with dose and long term use.

2.4.3 Does this drug prolong QT/QTc interval?

There was no effect of any of the two ospemifene doses (60 mg, 240 mg) on the QTc interval of any other electrocardiographic parameters, including heart rate, PR, or QRS interval.

A thorough QTc study was conducted in 200 healthy male and female subjects (50 subjects each arm: 25 women and 25 men) between 18 and 45 years of age. The total treatment duration was 7 days. Subjects were randomized to receive placebo daily, ospemifene 60 mg/day (b) (4) A07006; bioequivalent to the TBM), ospemifene 240 mg/day (supratherapeutic dose), or moxifloxacin (active control) after a high-fat breakfast. The 240 mg ospemifene dose covers the fold change that is expected with food administration.

Mean (±2 SEM) QTcI Placebo-Corrected Change from Baseline at Day 7 (N=200)



For ospemifene 60 mg, ΔQTcI was -2.8 ms and the 90% CI for ΔQTcI was - 4.3 to -1.2 ms. For the supratherapeutic dose 240 mg ospemifene, ΔQTcI was -3.5 ms and the 90% CI for ΔQTcI was -5.0 to -1.9 ms. The regulatory threshold of a 10 ms increase in QT was not exceeded; therefore, there is no regulatory concern for QT prolongation by ospemifene. For reference drug moxifloxacin 400 mg, ΔQTcI was 5.4 ms and the 90% CI for ΔQTcI was 3.2 to 7.5 ms.

2.4.4 Is the dose and dosing regimen selected by the applicant consistent with the known exposure-response relationship?

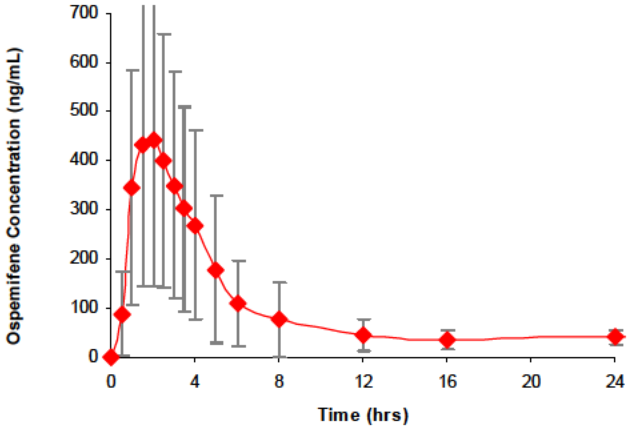
Pharmacometrics Reviewer Jiang Liu addresses the selection of dose in his review of the PopPK study.

2.5 WHAT ARE THE PK CHARACTERISTICS OF THE DRUG?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in postmenopausal women?

Ospemifene is extensively metabolized to various metabolites, mainly by CYP3A4, CYP2C9, and CYP2C19 enzymes. 4-hydroxyospemifene (M1) and 4'-hydroxyospemifene are the two major metabolites with a serum concentration of approximately 25% and 7% of ospemifene, respectively. M1 and M2 have similar pharmacological activity to ERα and ERβ as ospemifene. PK parameters for M1 and M2 are not reported in this review due to their low systemic exposure and overall effective pharmacological activity relative to ospemifene.

The following figure is the mean (SD) serum concentration-time profile of ospemifene following a single dose of 60 mg ospemifene, Penn Lot 0249A (TBM), fasted, N=91 (Study 15-51031).



Single Dose mean (SD) PK Parameters of Ospemifene 60 mg tablets (n=91, fasting, TBM formulation) (Study 15-51031)

PK Parameter	Ospemifene (N=91)
$AUC_{0\text{-}96\ hr}$ (ng hr/mL)	3661 (1728)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	3982 (1913)
Cmax (ng/mL)	501 (305)
Tmax* (hr)	2.0 (1.0-24.0)
$T_{1/2}$ (hr)	26.4 (7.5)
λ_z (1/hr)	0.028 (0.007)

*median (min-max)

No multiple dose PK data is available for ospemifene 60 mg tablets (Penn 0249A, TBM) manufactured by Penn Pharmaceuticals.

Of all available PK studies, Study 15-50927 was designed to obtain single and multiple dose PK for ospemifene. However the tablets used in Study 15-50927 was manufactured by [redacted] 85518), which is not the clinical product nor the TBM. [redacted] 85518 has been shown to be have lower exposure (20.7% lower in $AUC_{0\text{-}inf}$ and 34.4% lower in Cmax) compared to Penn 0249A (TBM) in Study 15-50926.

Following multiple oral doses of 60 mg ospemifene ([redacted] 85518), the median (range) Tmax was 3.0 (1-4) hrs for ospemifene and approximately 3.8 (1.5-24) hrs for 4-hydroxyospemifene and 3.5 (2-8) for 4'-hydroxyospemifene. There was a small peak after Tmax and approximately 24 hrs after ospemifene administration for ospemifene, 4-hydroxyospemifene, and 4'-hydroxyospemifene, suggesting enterohepatic recirculation. The mean $t_{1/2}$ for ospemifene was 29.1 hrs after multiple doses of ospemifene 60 mg. Assessment of steady-state was based upon $Cavg_{24hr}$ values after nine days of ospemifene administration; it appears that steady-state for ospemifene was reached by Day 7, possibly earlier.

Mean accumulation ratio (R_A) (90% CI) for ospemifene was 1.7 (1.5-1.9) for $AUC_{0\text{-}t}$ and 1.2 (1.1-1.4) for Cmax. For 4-hydroxyospemifene, mean accumulation ratio (90% CI) was 1.9 (1.6-2.3) for $AUC_{0\text{-}t}$ and 1.2 (0.9-1.5) for Cmax.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

The applicant evaluated the PK of ospemifene in healthy postmenopausal women, the target population.

2.6 INTRINSIC FACTORS

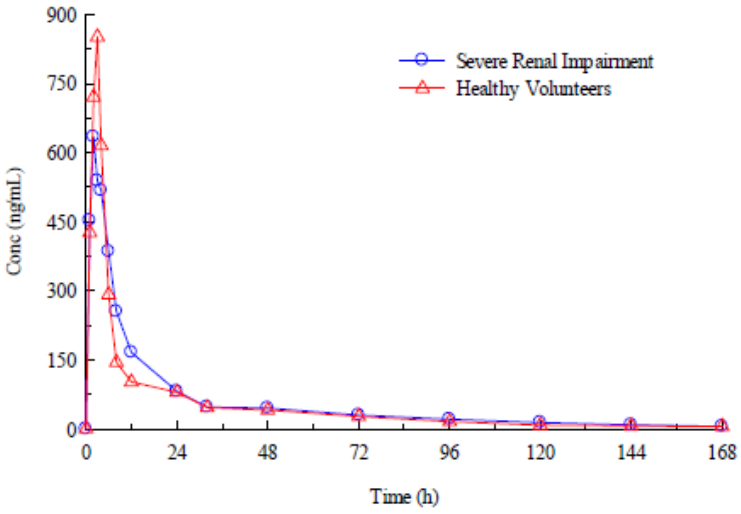
2.6.1 What intrinsic factors (organ dysfunction) influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Renal Impairment

The applicant evaluated the effects of severe renal impairment on the PK of ospemifene following a single oral dose of 60 mg ospemifene tablets (b) (4) A07006, bioequivalent to the TBM) following a high fat/high calorie breakfast in healthy postmenopausal women. The applicant conducted an abbreviated renal impairment study recruiting normal renal function subjects and severe renal impairment patients based upon the 1998 renal impairment guidance. The applicant was requested to re-classify the degree of impairment for all subjects and patients based upon the most recent 2010 renal impairment guidance. With the new reclassification scheme (eGFR), there were 6 normal, 1 mild, 3 severe, and 5 ESRD patients.

Severe renal impairment and ESRD did not significantly impact the systemic exposure of a single 60 mg dose of ospemifene. In subjects with severe renal impairment or ESRD, mean Cmax, AUC_{0-t}, and AUC_{0-inf} for ospemifene was lower by 21%, higher by 19%, and higher by 20%, respectively. Half-life was the same at about 34 hrs in patients with severe renal impairment and ESRD and normal renal function subjects. These results are expected based upon the known clearance pathway for ospemifene, which is primarily through hepatic metabolism, and fecal and urinary excretion.

The following is the serum concentration-time profile of ospemifene in subjects with normal renal function and patients with severe renal impairment based upon 1998 guidance (Study 15-50921).



The following table summarizes the PK parameters of ospemifene for subjects with normal renal function and patients with severe/ESRD renal impairment (data from Study 15-50921).

PK parameter*	Normal Renal Function (N=6)	Severe Renal Impairment + ESRD (N=8)	Severe/ESRD Renal Impairment versus Normal Renal Function PE (CI)**
AUC_{0-t} (ng hr/mL)	7567 ± 2296	9395 ± 3965	118.7 (83.8, 168.2)
AUC_{0-inf} (ng hr/mL)	8073 ± 2296	10141 ± 4144	119.6 (81.4, 175.9)
Cmax (ng/mL)	1106.1 ± 472.7	916.2 ± 525.2	78.6 (50.7, 121.8)
Tmax (hr)[1]	2 (1.0-6.0)	3.5 (2.0-8.0)	-
$T_{1/2}$ (hr)	33.6 ± 8.6	34.2 ± 6.1	103.0 (84.6,125.4)
CL/F (mL/min)	132.3 ± 35.7	117.4 ± 56.8	83.6 (56.9, 122.9)

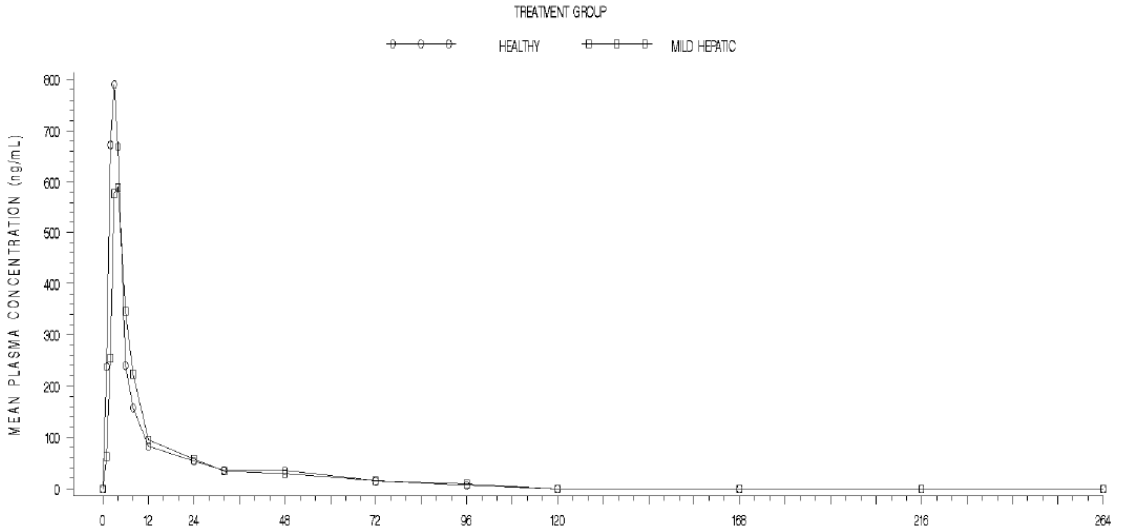
* arithmetic mean ± SD
**point estimate and 90% CI of the least-squares geometric means ratio
[1]tmax: median and range

Mild Hepatic Impairment

The applicant evaluated the effects of mild (Child-Pugh score 5-6) hepatic impairment on the PK of ospemifene following a single oral dose of 60 mg ospemifene tablets (b) (4) A07006, bioequivalent to TBM) following a high fat/high calorie breakfast in healthy postmenopausal women (Study 15-50820).

Subjects with normal hepatic function and patients with mild hepatic impairment had similar mean Cmax, AUC_{0-t}, and AUC_{0-inf} for ospemifene. In patients with mild hepatic impairment, mean Cmax, AUC_{0-t}, and AUC_{0-inf} for ospemifene were lower by 21%, 6.1%, and 9.1%, respectively. Half-life was prolonged from 28.2 hrs to 37.8 hrs in patients with mild hepatic impairment.

The following is the serum* concentration-time profile of ospemifene in subjects with normal hepatic function and patients with mild hepatic impairment (Study 15-50820).



*The figure above was taken from the sponsor's report which indicates plasma concentration in the y-axis. The report states blood samples were taken for determination of ospemifene in serum. Other clinical pharmacology studies report serum, not plasma, concentrations of ospemifene

The following table summarizes the PK parameters of ospemifene in for patients with mild hepatic impairment and normal hepatic function (data from Study 15-50820).

PK parameter*	Normal Hepatic Function (N=7)	Mild Hepatic Impairment (N=7)	Mild Hepatic Impairment Versus Healthy PE (CI)**
AUC_{0-t} (ng hr/mL)	6380 (27.2)	6090 (28.8)	0.94 (0.70, 1.26)
AUC_{0-inf} (ng hr/mL)	7190 (23.0)	6650 (27.7)	0.91 (0.66, 1.25)
Cmax (ng/mL)	970 (10.8)	787 (23.8)	0.80 (0.66, 0.96)
Tmax (hr)[1]	3.0 (2.0-4.0)	3.0 (2.0-6.0)	
$T_{1/2}$ (hr)	28.2 (42.9)	37.8 (47.7)	1.32 (0.88, 2.00)
CL/F (L/min)	9.77 (27.4)	10.5 (36.5)	1.06 (0.78, 1.42)

*arithmetic mean (CV%)
**point estimate and 90% CI of the least-squares geometric means ratio
[1]tmax: median and range

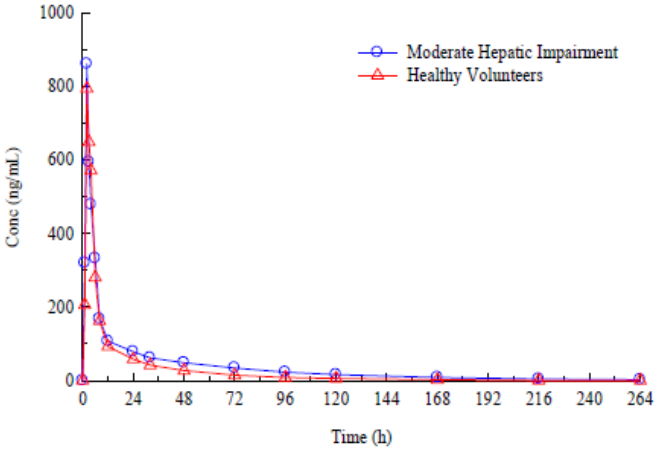
There was no significant effect of mild hepatic impairment on the serum protein binding of ospemifene at 3 hrs after dosing. At 3 hrs postdose, the mean free fraction was 1.65 and 1.21% in healthy subjects and mild hepatic impairment patients, respectively. At 24 hrs postdose, ospemifene free fraction was not quantifiable in healthy subjects and mild hepatic impairment patients.

Moderate Hepatic Impairment

Due to difficulties in recruitment of moderate hepatic impairment patients in Study 15-50820, the applicant conducted another study recruiting only subjects with normal hepatic function and patients with moderate impairment to Study 15-50920. The applicant did not evaluate the effect of severe hepatic impairment on PK of ospemifene.

Moderate hepatic impairment had a slightly greater effect on ospemifene exposure compared to mild hepatic impairment. Overall, the effect of moderate hepatic impairment was not significant following a single 60 mg dose of ospemifene. In subjects with moderate hepatic impairment, mean Cmax was essentially the same. AUC_{0-t} and AUC_{0-inf} for ospemifene were higher by ~28%, compared to subjects with normal hepatic function. In the context of inter-subject variability of approximately 30%, the change in AUC_{0-inf} in patients with moderate hepatic impairment is not significant. Half-life was prolonged from 35.0 hrs to 43.8 hrs in patients with moderate hepatic impairment.

The following is the serum concentration-time profile of ospemifene in subjects with normal hepatic function and patients with moderate hepatic impairment (Study 15-50920).



The following table summarizes the PK parameters of ospemifene for patients with moderate hepatic impairment and normal hepatic function (data from Study 15-50920).

PK parameter*	Normal Hepatic Function (N=8)	Moderate Hepatic Impairment (N=8)	Moderate Hepatic Impairment Versus Healthy PE (CI)**
$AUC_{0\text{-}t}$ (ng hr/mL)	6726 ± 1,661	9544 ± 4,457	1.28 (0.87, 1.90)
$AUC_{0\text{-}inf}$ (ng hr/mL)	6853 ± 1,677	9765 ± 4,592	1.29 (0.87, 1.90)
Cmax (ng/mL)	920 ± 219	1070 ± 643	1.01 (0.66, 1.55)
Tmax (hr)[1]	2.0 (1.0-4.0)	2.0 (2.0-6.0)	
$T_{1/2}$ (hr)	35.0 ± 8.57	43.8 ± 12.3	1.24 (0.98, 1.57)
CL/F (mL/min)	153 ± 31.8	138 ± 99.4	77.8 (0.53, 1.15)

* arithmetic mean ± SD
**point estimate and 90% CI of the least-squares geometric means ratio
[1]tmax: median and range

The unbound concentration was measureable in only 4 of 8 moderate hepatic impairment patients and 5 of 8 healthy subjects at 3 hrs, and only 1 healthy subject at 24 hrs. At 3 hrs, the percent bound was >99% in the 4 moderate hepatic patients and 5 subjects with normal function. At 24 hrs, the percent bound was 95.29% in the one subject with normal hepatic function. It appears that hepatic impairment does not affect protein binding of ospemifene.

Genetics

The sponsor excluded Factor V Leiden (FVL) carriers from Phase 2 and Phase 3 clinical trials. The Pharmacogenomics reviewer assessed whether (1) the risk estimation for venous thromboembolism (VTE) was biased due to exclusion of FVL carriers in Phase 2 and 3 trials and (2) whether screening for FVL is indicated for patients who are eligible for ospemifene therapy.

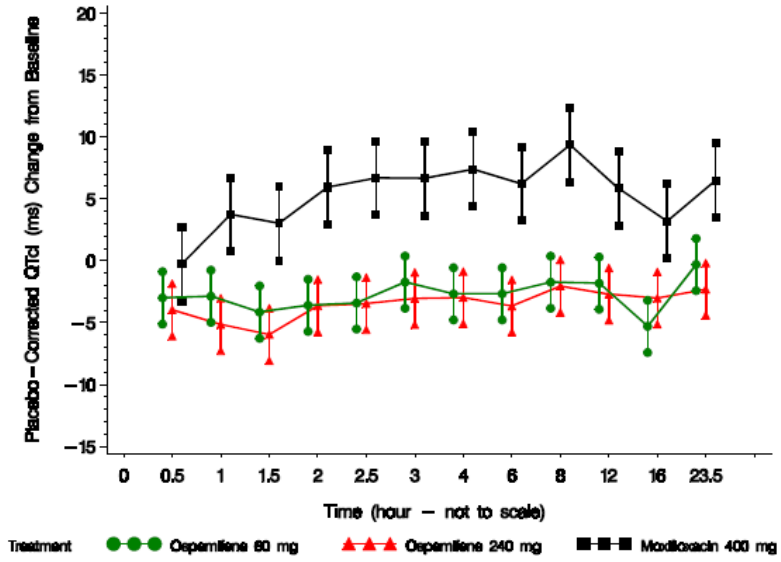
Known risk factors for developing a VTE include increased age, oral contraceptive/hormone replacement therapy/SERM therapy, smoking and inherited factors (e.g., FVL, prothrombin polymorphisms). VTE risk is approximately 2-3 fold higher in FVL carriers compared to non-carriers, and further increased if other known risk factors are present. Based on the estimated prevalence of FVL and considering the increased risk associated with FVL, few/no additional VTE cases would have been observed if FVL carriers were included in Phase 2/3 trials.

Therefore, current risk estimates are reasonable. Additionally, screening for FVL in patients being considered for ospemifene is not recommended given estimates that more than 1000 patients would need to be screened in order to prevent a single VTE. (See Pharmacogenomics review by Christian Grimstein in the Appendix.)

QT Prolongation

The applicant evaluated the effect of ospemifene on QT prolongation in a Phase 1, single-center, randomized, double-blind (except for moxifloxacin), parallel-group, active- and placebo-controlled trial in approximately 200 healthy male and female subjects between 18 and 45 years of age. The total treatment duration was 7 days, and subjects were randomized to receive placebo daily, ospemifene 60 mg/day, ospemifene 240 mg/day, or moxifloxacin 400 mg (positive control). Ospemifene 60 tablets (b) (4) A07006, bioequivalent to TBM) were used in the study and subjects were administered ospemifene after a high fat meal.

Mean (±2 SEM) QTcI Placebo-Corrected Change from Baseline at Day 7 (N=200)



For ospemifene 60 mg, ΔQTcI was -2.8 ms and the 90% CI for ΔQTcI was - 4.3 to -1.2 ms. For the supratherapeutic dose 240 mg ospemifene, ΔQTcI was -3.5 ms and the 90% CI for ΔQTcI was -5.0 to -1.9 ms. The regulatory threshold of a 10 ms increase in QT was not exceeded; therefore, there is no regulatory concern for QT prolongation by ospemifene. For reference drug moxifloxacin 400 mg, ΔQTcI was 5.4 ms and the 90% CI for ΔQTcI was 3.2 to 7.5 ms.

Population PK

A two-compartment model with first-order absorption processes was selected. Inter-subject variability was assessed on each of the PK parameters using the exponential error structure. Based on the OBJ, exponential error model was chosen for intra-individual variability. Age, race, manufacturing sites, body weight, BMI, ALB, ALT, BILI, CREAT and CLcr were tested as a covariate on PK parameters of CL/F. Age, race, manufacturing sites, body weight, BMI and ALB were tested as a covariate on V2/F. Linear and power model were applied to test continuous covariates and categorical model was applied to test categorical covariates.

There was no covariate detected to have clinically relevant effect on ospemifene PK. The CL/F estimate (9.16 L/hr) and the inter-individual variability for CL/F (36.3%) under the fed condition

are smaller compared to those under the fasted condition (16.9 L/hr for CL/F and 42.7% for the inter-individual variability for CL/F). Therefore, the population PK analysis supports the sponsor's proposal that ospemifene should be taken with food. (See Pharmacometrics review by Jiang Liu in the Appendix)

2.7 EXTRINSIC FACTORS

2.7.1 Drug-Drug Interactions

2.7.1.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Based on in vitro study 15-4304 in human liver microsomes and recombinant human CYP enzymes, ospemifene is primarily metabolized by CYP3A4, 2C9, and 2C19 responsible for approximately 40 to 50%, ~25%, and ~25%, respectively, of its clearance. Therefore, studies 15-50716 and 15-50823 were conducted to assess the effect of ketoconazole, rifampicin, fluconazole, and omeprazole on the exposure of ospemifene.

In vitro study 15-4318 in human liver microsomes suggests that ospemifene may be an inhibitor of CYP2B6, 2C9, and 2C19 with an IC_{50} value of approximately 7.8 μM, 10 μM, and 35 μM, respectively. The maximal concentration of ospemifene after 60 mg doses is approximately 3 μM. Therefore, in vivo studies using buproprion, warfarin, and omeprazole as substrates to assess the extent of ospemifene inhibition on CYP2B6, 2C9, and 2C19, respectively, were conducted.

The sponsor evaluated ospemifene as a potential substrate for transporters in a P-gp in vitro study. No in vivo transporter studies were conducted.

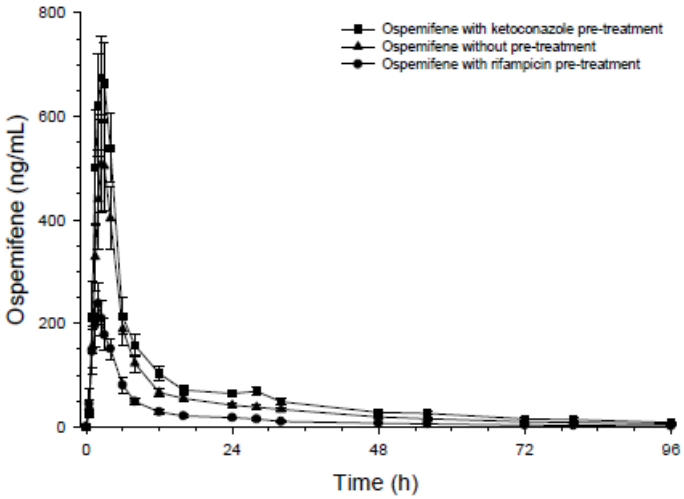
2.7.1.2 Is ospemifene a substrate of CYP enzymes? Is metabolism influenced by genetics?

Effect of ketoconazole (a strong CYP3A4 inhibitor) on ospemifene PK

The applicant evaluated the influence of multiple doses of strong CYP3A4 inhibitor ketoconazole on PK of ospemifene (Study 15-50716). This study was a single dose, open-label, randomized, three-period, crossover study (in same subjects and study with rifampicin, see below) with a washout period of at least 3 weeks and after an overnight fast of approximately 10 hrs. Twelve healthy post-menopausal women received ospemifene with and without pretreatment with rifampicin and ketoconazole. Ospemifene 60 mg tablets (Batch 0249A) manufactured by Penn Pharmaceuticals were used in this study.

Ketoconazole moderately increased the concentrations of ospemifene when subjects were treated with ketoconazole 400 mg once daily for 5 days prior to and 3 days after a single dose administration of ospemifene. The mean (%CV) $AUC_{0\text{-}inf}$ increased 1.4-fold from 4578 (33) to 6475 (32) ng.hr/mL and Cmax increased 1.5-fold from 644 (49) to 872 (27) ng/mL. Tmax was 2.5 hrs with ospemifene alone and with ketoconazole pre-treatment. Elimination half-life was similar with and without ketoconazole pre-treatment at 24.6 and 24.3 hrs, respectively. Continued CYP3A4 inhibition was maintained by giving three additional doses of ketoconazole after ospemifene administration.

The following figure is the mean (SE) concentration-time profiles for serum ospemifene with and without ketoconazole and rifampicin treatment.



The following table summarizes the PK parameters of ospemifene for subject given 60 mg ospemifene alone and 60 mg ospemifene + 400 mg ketoconazole.

PK parameter*	Ospemifene alone (N=12)	Ospemifene + Ketoconazole (N=12)
$AUC_{0\text{-}t}$ (ng hr/mL)	4381 (32.5)	6142 (29.8)
$AUC_{0\text{-}inf}$ (ng hr/mL)	4578 (33.0)	6475 (32.0)
Cmax (ng/mL)	644 (48.7)	872 (26.5)
Tmax (hr)[1]	2.5 (1.5-6.0)	2.5 (1.5-6.0)
$T_{1/2}$ (hr)	24.3 (16.9)	24.6 (21.7)

* mean (CV%)
[1]tmax: median and range

Effect of rifampicin (a strong CYP3A4 inducer) on ospemifene PK

Rifampicin moderately decreased ospemifene exposure when healthy postmenopausal women were treated with rifampicin 600 mg daily for 5 consecutive days (Days 1-5 at approximately 4 pm and at least one hour before or two hours after a meal) prior to a single dose administration of ospemifene 60 mg (Day 6 at 8 am) under a fed condition. Ospemifene 60 mg tablets (Batch 0249A) manufactured by Penn Pharmaceuticals were used in this study (Study 15-50716). The mean (%CV) $AUC_{0\text{-}inf}$ was decreased by 58% from 4578 (33.0) to 1854 (27.3) ng.hr/mL and Cmax was decreased by 51% from 644 (48.7) to 301 (32.9) ng/mL. Tmax and elimination half-life remained essentially unchanged. Tmax was 2.5 and 2.3 hrs with ospemifene alone and with rifampicin pre-treatment, respectively. Elimination half-life was similar with and without rifampicin pre-treatment at 25.5 and 24.3 hrs, respectively. Rifampicin was not given after ospemifene administration on Day 6 and during the PK sampling period; therefore, enzyme induction by rifampicin may have been more significant. It is possible that ospemifene exposure may have been lowered more significantly if rifampicin was given during the PK sampling period.

The following table summarizes the PK parameters of ospemifene for subject given 60 mg ospemifene alone and 60 mg ospemifene + 600 mg rifampicin.

PK parameter*	Ospemifene alone (N=12)	Ospemifene + Rifampicin (N=12)
AUC_{0-t} (ng hr/mL)	4381 (32.5)	1781 (27.4)
AUC_{0-inf} (ng hr/mL)	4578 (33.0)	1854 (27.3)
Cmax (ng/mL)	644 (48.7)	301 (32.9)
Tmax (hr)[1]	2.5 (1.5-6.0)	2.3 (1.0-6.1)
$T_{1/2}$ (hr)	24.3 (16.9)	25.5 (19.4)

* mean (CV%)
[1]tmax: median and range

Rifampicin is a moderate CYP2C8, moderate CYP2C9, moderate CYP2C19, and strong CYP3A4 inducer according to FDA's Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (February 2012). Because ospemifene is metabolized by multiple enzymes and rifampicin is an inducer of multiple enzymes, the exposure change to ospemifene due to rifampicin induction observed from this study cannot be attributed to CYP3A4 alone.

Effect of fluconazole (a CYP3A4/CYP2C9/CYP2C19 inhibitor) on ospemifene PK

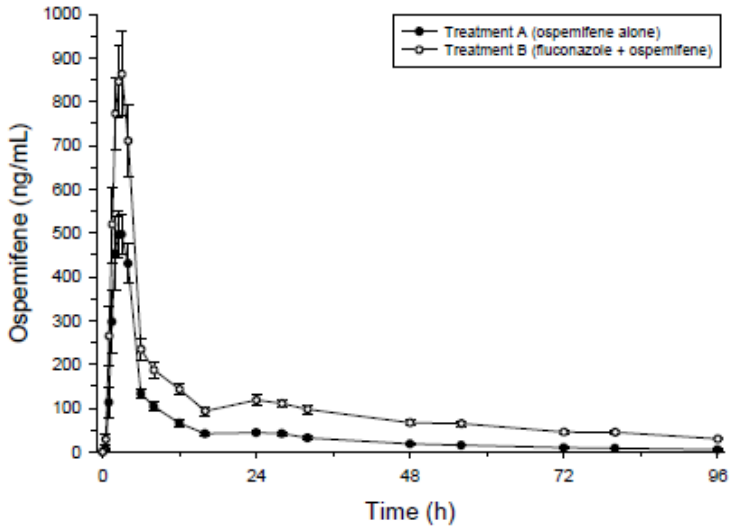
This was an open-label, randomized, three-way (two-way), crossover study with a washout period of at least 3 weeks and after an overnight fast of approximately 10 hrs. Fourteen healthy post-menopausal women received a single dose of ospemifene 60 mg (Day 5) with and without fluconazole pretreatment (400 mg on Day 1, 200 mg on Days 2-8) (Study 15-50823).

The effect of fluconazole on ospemifene exposure was apparent with ospemifene AUC0-inf increasing 2.7-fold from 4288 to 11932 ng.hr/mL after fluconazole pre-treatment. Cmax increased slightly by 1.7-fold from 650 to 1028 ng/mL and Tmax was similar (3.0 vs. 2.6 hrs w/o fluconazole pre-treatment). $T_{1/2}$ increased significantly from 25.0 to 42.9 hrs with fluconazole inhibition.

The applicant identified fluconazole as a potent CYP2C9 inhibitor. Based upon the classification of CYP inhibitors in the current FDA's Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (February 2012), fluconazole is an inhibitor of multiple enzymes - listed as a moderate CYP2C9, strong CYP2C19, and moderate CYP3A4 inhibitor. Despite the known inhibitory effects of fluconazole on CYP2C19 and CYP3A4, the sponsor selected fluconazole as the perpetrator drug in the study of CYP2C9 inhibition. Due to fluconazole's inhibitory effect on multiple CYP enzymes, it not possible to conclude that the pathway for ospemifene metabolism is solely through CYP2C9.

Mean* (CV%) PK Parameters for Ospemifene	With Fluconazole pretreatment	Without Fluconazole pretreatment	Geometric Mean Ratio (90% CI)
Cmax (ng/mL)	649.7 (38.0)	1027.9 (31.5)	1.66 (1.40, 1.97)
AUC_{0-96} (ng.hr/mL)	4098.4 (24.9)	9905.3 (28.6)	2.39 (2.15, 2.65)
AUC_{0-inf} (ng hr/mL)	4288.4 (24.0)	11931.9 (28.1)	2.74 (2.47, 3.03)
$T_{1/2}$ (hr)	25.0 (17.2)	42.9 (31.5)	1.66 (1.51, 1.82)
Tmax (hr)*	3.0 (32.7)	2.6 (31.0)	not available

*arithmetic mean



The following table summarizes the PK parameters of ospemifene for subject given 60 mg ospemifene alone and 60 mg ospemifene + 200 mg fluconazole.

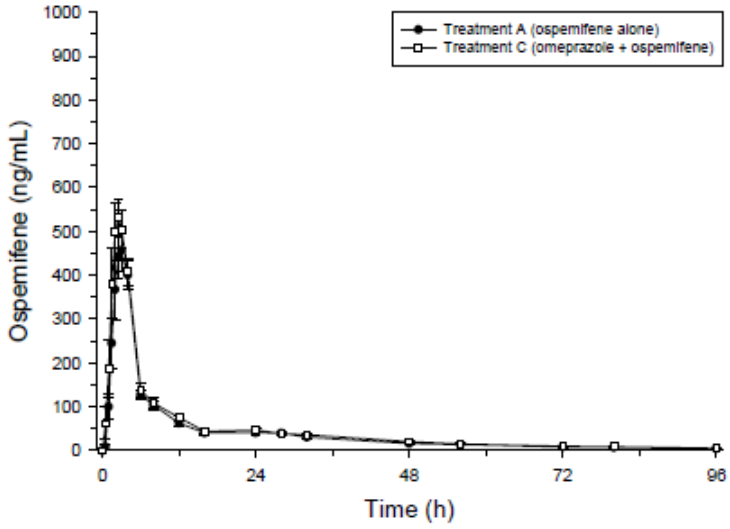
PK parameter*	Ospemifene alone (N=14)	Ospemifene + Fluconazole (N=14)
$AUC_{0\text{-}t}$ (ng hr/mL)	4098.4 (24.9)	9905.3 (28.6)
$AUC_{0\text{-}inf}$ (ng hr/mL)	4288.4 (24.0)	11931.9 (28.1)
Cmax (ng/mL)	649.7 (38.0)	1027.9 (25.1)
Tmax (hr)	3.0 (32.7)	2.6 (31.0)
$T_{1/2}$ (hr)	25.0 (17.2)	42.9 (31.5)

* mean (CV%)

Effect of omeprazole (a CYP2C19 inhibitor) on ospemifene PK

Once daily administration of omeprazole 40 mg at approximately 7 am on Days 1-4. On Day 5 (after an overnight fast) subjects took their fifth dose of omeprazole 40 mg at approximately 7 am followed by one tablet of ospemifene 60 mg was administered after a standard breakfast at 8 am. Omeprazole 40 mg was taken for three additional days at approximately 7 am to provide sufficient CYP2C19 inhibition during the blood sampling period for ospemifene PK (Study 15-50823).

The effect of omeprazole on ospemifene exposure was less significant than with fluconazole with ospemifene $AU_{C0\text{-}inf}$ increasing 1.17-fold from 3949 to 4568 ng.hr/mL after omeprazole pre-treatment. Cmax increased slightly from 560 to 657 ng/mL. Tmax was similar at ~ 3 hrs. $T_{1/2}$ was essentially unchanged at ~24 hrs.



The applicant identified omeprazole as a strong CYP2C19 inhibitor. According to the above mentioned drug interaction guidance published in 2012, omeprazole is a moderate inhibitor of CYP2C19. The discrepancy in the categorization of omeprazole is likely due to the classification of inhibitors in the early guidance where omeprazole was listed as a strong CYP2C19 inhibitor.

The following table summarizes the PK parameters of ospemifene for subject given 60 mg ospemifene alone and 60 mg ospemifene + 40 mg omeprazole.

PK parameter*	Ospemifene alone (N=14)	Ospemifene + Omeprazole (N=14)
$AUC_{0\text{-}t}$ (ng hr/mL)	3789.0 (28.7)	4362.3 (24.1)
$AUC_{0\text{-}inf}$ (ng hr/mL)	3948.4 (28.7)	4567.5 (24.7)
Cmax (ng/mL)	560.1 (36.2)	657.3 (28.8)
Tmax (hr)	3.1 (30.5)	2.5 (32.0)
$T_{1/2}$ (hr)	23.9 (15.9)	24.3 (30.2)

* arithmetic mean (CV%)

2.7.1.3 Is the ospemifene an inhibitor and/or inducer of CYP enzymes?

Is ospemifene a CYP2C19 inhibitor: effect on omeprazole?

This study was a single dose, open-label, two-period, crossover study with a washout period of at least 2 weeks. Twelve healthy postmenopausal women were given a single 20 mg dose of omeprazole (on Day 8) with and without pre-treatment with 60 mg ospemifene with once daily dosing for 7 days (Days 1-7). Subjects genotyped as being homozygous as poor CYP2C19 metabolizers (possessing the CYP2C19*2/*2 genotype) were excluded from Study 15-50719. However, no other alleles were assayed. Ospemifene 60 mg tablets ([(b) (4)] A07006) were used in this study.

The applicant states that in vitro studies suggest that ospemifene may be a weak CYP2C19 inhibitor with a Ki value of approximately 35 µM. Based on in vitro findings, the applicant conducted an in vivo study using omeprazole as a substrate to assess the extent of ospemifene inhibition on CYP2C19 and CYP3A4.

According to FDA's Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (February 2012), omeprazole

is a sensitive substrate for CYP2C19, not CYP3A4. The sponsor states omeprazole is a sensitive substrate of CYP2C19 and CYP3A4. The metabolism of omeprazole to 5-hydroxyomeprazole is catalyzed by CYP2C19, while omeprazole sulphoxidation is mediated by CYP3A4. The concentration ratio of omeprazole/5-hydroxyomeprazole from blood samples taken at 3 hrs was used as marker for CYP2C19 activity. The concentration ratio of omeprazole/omeprazole sulphone was used to assess CYP3A4 activity.

The geometric mean ratios for both metabolic indices (omeprazole/5-hydroxyomeprazole and omeprazole/omeprazole sulphone) and for $AUC_{0\text{-}8hr}$ were 0.97 or 1.0 with and without ospemifene pre-treatment with a 90% CI that ranged from 0.88 to 1.08. The near unity value for these metabolic indices suggest that ospemifene did not have an effect on the metabolism of omeprazole by CYP2C19. However, there were limitations to this study including the significant time gap between ospemifene and omeprazole administration on Day 8 (ospemifene was administered at least 12 hrs prior to omeprazole administration) and subjects with various CYP2C19 alleles were not identified (subjects possessing the CYP2C19*2/*2 genotype were excluded from the study). Additionally, omeprazole is not a sensitive substrate for CYP3A4; therefore, it is not possible to conclude that ospemifene will not affect drugs that are metabolized by CYP3A4 as suggested by the applicant. Due to multiple deficiencies of the study design, the applicant failed to demonstrate that ospemifene does not affect the activity of CYP2C19 and CYP3A4 enzymes.

The following table is the arithmetic and geometric mean (%CV) for the 3 hr conc time points and $AUC_{0\text{-}8hr}$ for omeprazole, 5-hydroxyomeprazole, and omeprazole sulphone.

Calculation based on	Parent/metabolite	Treatment	Arithmetic	Geometric
3 h concentrations	Omeprazole	A[1]	100.6 (135.1)	65.2 (106.3)
		B[2]	77.2 (98.2)	46.2 (158.1)
	5-hydroxyomeprazole	A[1]	106.1 (47.5)	97.5 (43.3)
		B[2]	82.4 (58.7)	71.0 (63.3)
	Omeprazole sulphone	A[1]	63.8 (59.5)	54.8 (61.5)
		B[2]	50.5 (59.2)	40.1 (97.0)
AUC_t	Omeprazole	A[1]	413.5 (63.2)	345.3 (71.2)
		B[2]	362.9 (62.1)	285.9 (94.5)
	5-hydroxyomeprazole	A[1]	452.7 (19.4)	444.9 (19.6)
		B[2]	396.6 (25.4)	378.1 (38.1)
	Omeprazole sulphone	A[1]	297.3 (60.6)	253.1 (65.1)
		B[2]	245.0 (53.0)	209.0 (71.1)

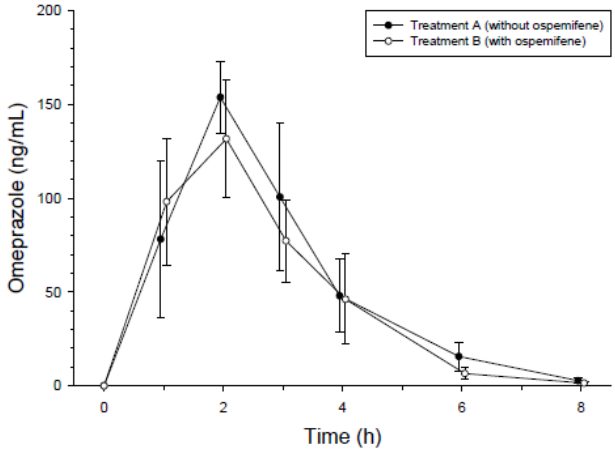
[1] Omeprazole without ospemifene
[2] Omeprazole with ospemifene
Source: Table 9.2.3

The following table is the geometric mean (%CV) of the metabolic ratios based on the 3 hr concentrations time point and $AUC_{0\text{-}8hr}$ for omeprazole/5-hydroxyomeprazole and omeprazole/omeprazole sulphone (sponsor's table 5, section 6.2.1)

Calculated from	Metabolic ratio	Treatment A [1]	Treatment B [2]
3h concentrations	Omeprazole / 5-hydroxyomeprazole	0.67 (78.4)	0.65 (98.7)
	Omeprazole / Omeprazole sulphone	1.19 (52.7)	1.15 (100.9)
AUC_t	Omeprazole / 5-hydroxyomeprazole	0.78 (59.0)	0.76 (61.5)
	Omeprazole / Omeprazole sulphone	1.36 (20.4)	1.37 (24.5)

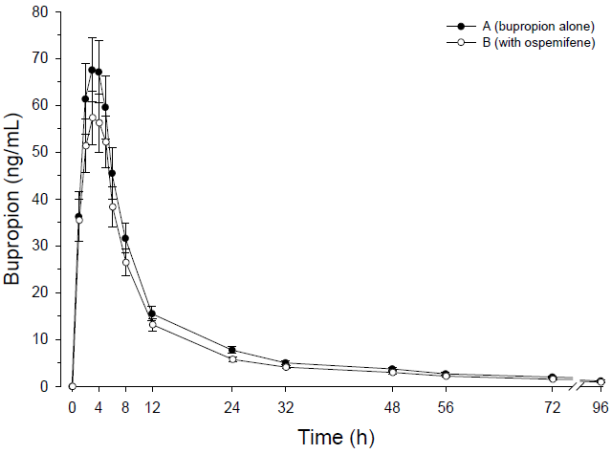
[1] Omeprazole without ospemifene
[2] Omeprazole with ospemifene
Source: Table 9.2.4

The following is the mean (SE) plasma concentration-time profiles for omeprazole



Is ospemifene a CYP2B6 inhibitor: effect on bupropion?

This study was an open-label, balanced, two-period, and crossover design in 16 healthy postmenopausal women who were not homozygous carriers of the CYP2B6*6 genotype. Subjects were given food with 8 days of 60 mg ospemifene pre-treatment followed by a single 150 mg tablet of buproprion. Ospemifene tablets (b) (4) A07006) were manufactured by (b) (4) for this study (Study 15-50825) and they were determined to be bioequivalent to the TBM.



Arithmetic mean and range of the AUC_t and $AUC_{0\text{-inf}}$ of hydroxybupropion were comparable between the periods with and without pretreatment of ospemifene. Cmax increased slightly in the period with ospemifene pre-treatment. The $t_{½}$ of hydroxybupropion was lower in the period with

pretreatment of ospemifene than the bupropion alone period. The point estimates of the LS geometric means ratio (90% CI) of Cmax, AUC_{0-t}, and AUC_{0-inf} were 116.1% (109.0, 123.7%), 101.0% (95.5, 106.8%), and 97.7% (92.1, 103.6%), respectively. With the exception of half-life, the point estimates were near unity and, thus, it can be concluded that ospemifene will unlikely affect substrates of CYP2B6.

Summary and statistical analysis of pharmacokinetic parameters of bupropion and hydroxybupropion after a single oral administration of 150 mg bupropion with or without 8 days multiple treatment of 60 mg ospemifene.

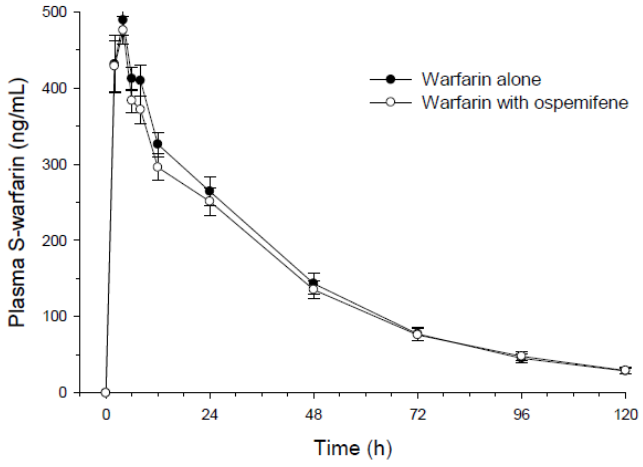
Parameters	Bupropion (n=16)		Geometric mean ratio (90% CI)	Hydroxybupropion (n=16)		Geometric mean ratio (90% CI)
	with ospemifene	without ospemifene		with ospemifene	without ospemifene	
C_{max} (ng/mL)	62.9 (40.4)	74.9 (36.6)	0.82 (0.75-0.91)	462 (29.0)	398 (30.6)	1.16 (1.09, 1.24)
t_{max} (hr) *	3 (1-5)	3.5 (1-5)	-	6.1 (5-8)	6.0 (5-24)	-
AUC_t (ng hr/mL)	0.70 (38.5)	0.85 (33.7)	0.821 (0.78, 0.87)	14.5 (31.7)	14.3 (28.1)	1.01 (0.96, 1.07)
AUC_∞(ng.hr/mL)	0.75 (38.5)	0.90 (32.3)	0.814 (0.77, 0.86)	15.2 (32.4)	15.5 (29.4)	0.98 (0.92, 1.04)
$t_{1/2}$ (hr)	29.5 (26.7)	30.8 (29.4)	0.97 (0.78, 1.21)	21.2 (18.0)	26.7 (18.8)	0.795 (0.75, 0.85)
CL/F (mL/hr)	230 (38.1)	185 (37.1)	1.23 (1.16, 1.30)	ND	ND	

(CV%), * median (min-max)

Is ospemifene a CYP2C9 inhibitor: effect on warfarin?

This study was an open-label, balanced, two-period, and crossover design in 16 healthy postmenopausal women who were determined as rapid metabolizers of CYP2C9 (CYP2C9*1/*1 or CYP2C9*1/*2). A single dose of 10 mg warfarin as a probe drug with 10 mg vitamin K was administered at one hour after a standard breakfast without or with treatment of ospemifene on the 8th day of its multiple treatment. A 60 mg tablet of ospemifene under fed condition after the breakfast was administered once daily for 12 days in the ospemifene treatment group. The ospemifene tablets used in this study (Study 15-50614) were manufactured by (b) (4) (Lot 0208-915). Subjects were given food with ospemifene administration. Inhibition potential by ospemifene on CYP2C9 was assessed by using the PK of S-warfarin.

Study results showed that the PK of *S*-warfarin and *R*-warfarin following a single dose 10 mg warfarin was not influenced by multiple pre-treatment of ospemifene.



Summary and statistical analysis of pharmacokinetic parameters of *S*-warfarin and *R*-warfarin after administration of 10 mg warfarin in the period with ospemifene pre-treatment and without pre-treatment.

PK Parameters	*S*-warfarin (n=16)		Geometric mean ratio (90% CI)	*R*-warfarin (n=16)	
	with ospemifene	without ospemifene		with ospemifene	without ospemifene
C_{max} (ng/mL)	497 (14.5)	513 (13.3)	0.97 (0.92, 1.02)	518 (15.2)	538 (15.4)
t_{max} (hr)	4 (2-6)	4 (2-8)	-	4 (2-6)	4 (2-8)
AUC_t (ng.hr/mL)	17.2 (27.4)	18.0 (28.3)	0.96 (0.90, 1.01)	26.2 (18.7)	27.8 (19.6)
AUC_∞(ng hr/mL)	18.5 (29.9)	19.2 (30.2)	0.96 (0.91, 1.02)	31.3 (21.7)	32.8 (23.1)
$t_{1/2}$ (hr)	30.4 (13.2)	29.2 (12.7)	1.04 (1.01, 1.08)	43.8 (17.1)	42.7 (15.6)
CL/F (mL/hr)	587 (29.2)	564 (27.5)	1.04 (0.98, 1.10)	334 (21.2)	320 (23.0)

Values are arithmetic means (CV%), t_{max} is median (range)

Based on both S- and R-warfarin, ospemifene did not affect the warfarin PK. The effect of ospemifene on the pharmacodynamic effects (i.e. prothrombin time) of warfarin was not assessed. It is unlikely that ospemifene will interfere with drugs that are metabolized by CYP2C9.

2.7.2.3 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

Based on in vitro study 15-4316 and 15-4317, ospemifene is not a significant P-glycoprotein substrate. No in vivo transporter study was conducted.

2.8 GENERAL BIOPHARMACEUTICS

2.8.1 Based on the biopharmaceutics classification system principles, in what class is this drug and formulation?

Ospemifene has not been officially reviewed by the BCS committee. The applicant believes ospemifene is a BCS Class 2 drug substance(low solubility and high permeability). At room temperature, ospemifene is highly insoluble in water and buffers over the pH range from 1.2 to 8.0. It is freely soluble in acetone, methylethylketone, methylisobutylketone, ethylacetate and tetrahydrofuran; soluble in ethanol, propanol, butanol, butylacetate, toluene and acetonitrile; very slightly soluble in isopropanol. The partition coefficient (log P) is 4.434 ± 0.376 at 25°C.

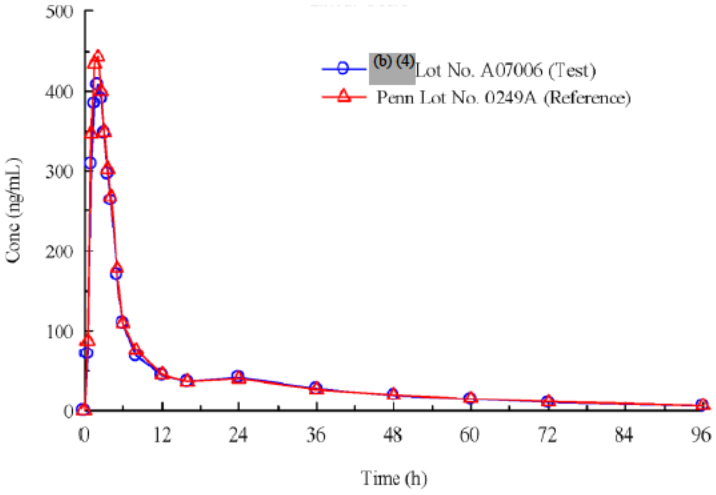
2.8.2 How is the proposed to-be-marketed formulation linked to the clinical trial formulation?

The proposed to-be-marketed ospemifene 60 mg tablets will be manufactured by Penn Pharmaceuticals, UK. There were two different clinical trial ospemifene tablets used in the two Phase 3 studies. For Phase 3 Study 15-50310, ospemifene 60 mg tablets (Penn Batch 0249A) manufactured by Penn Pharmaceuticals, UK were used exclusively in the trial. Similarly, for Phase 3 Study 15-50821, ospemifene 60 mg tablets (Lot A07006) manufactured by (b) (4) were used exclusively in the trial. In bioequivalence Study 15-51031, the applicant demonstrated bioequivalence between the one clinical trial tablets (manufactured by (b) (4)) and the to-be-marketed tablets (manufactured by Penn). The Phase 3 52-week safety extension study to assess endometrial safety (Study 15-50718) used ospemifene 60 mg tablets manufactured by both Penn and (b) (4)

The bioequivalence study was a randomized, open-label, two-way, crossover study in postmenopausal women under fasted conditions. Ninety-four subjects (91 subjects completed the study) were equally and randomly assigned to one of two treatment groups and were given a single 60 mg dose of ospemifene manufactured by Penn or (b) (4)

Pharmacokinetic results show that Penn and (b) (4) ospemifene formulations are comparable. The mean Cmax for Penn formulation and (b) (4) formulation was 533 and 501 ng/mL, respectively. The mean AUC_{0-t} for Penn formulation and (b) (4) formulation was 3781 and 3661 ng.hr/mL, respectively. The mean AUC_{0-inf} for Penn formulation and (b) (4) formulation was 4165 and 3982 ng.hr/mL, respectively. Median Tmax for Penn formulation and (b) (4) formulation was 2.0 hrs. Mean $T_{1/2}$ for Penn and (b) (4) formulations was 26.4 hrs.

The geometric mean ratio for Cmax, AUC_{0-t}, and AUC_{0-inf} was 0.95, 0.96 and 0.97, respectively. Although the Cmax for Penn tablets is higher than for (b) (4) tablets, the associated 90% CIs for Cmax, AUC_{0-t}, and AUC_{0-inf} all fell within 80% to 125%. Penn ospemifene 60 mg tablets (Lot No. 0249A) and (b) (4) ospemifene 60 mg tablets (Lot No. A07006) are bioequivalent.



Mean (SD) PK Parameters for Ospemifene	Study 15-50821 (b) (4) A07006)	Study 15-50310 (Penn 0249A)	Geometric Mean Ratio (90% CI)
Cmax (ng/mL)	501 (305)	533 (304)	0.95 (0.83, 1.09)
$AUC_{0\text{-}96}$ (ng.hr/mL)	3661 (1728)	3781 (1795)	0.96 (0.89, 1.04)
$AUC_{0\text{-}inf}$ (ng hr/mL)	3982 (1913)	4165 (1970)	0.97 (0.88, 1.05)
$T_{1/2}$ (hr)	26.4 (7.48)	26.4 (6.72)	
Tmax (hr)*	2.0 (1.0, 24.0)	2.0 (1.0, 8.0)	

* median (min, max)

2.8.3 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The two food effect studies were conducted using ospemifene tablets manufactured by (b) (4) (Batch 0107-852). There were 24 healthy Caucasian male subjects enrolled in an open-label, one-treatment, one-period, non-randomized study to evaluate the effect of high-fat food on ospemifene exposure (Study 15-50208). Twelve of the twenty-four subjects who were enrolled in the high-fat food effect study elected to participate in the low-fat food effect extension study (Study 15-50208-02). Because 12 subjects completed both the low-fat and high-fat food effect studies, the following PK results are based on 12 subjects. The effect of high-fat on ospemifene exposure from 12 and 24 subjects were similar.

Ospemifene is highly lipophilic (likely a BCS Class II) and will therefore be impacted by food and fat content. The results from the food effect studies show the significant impact of low-fat/low calorie and high-fat/high calorie food on ospemifene bioavailability.

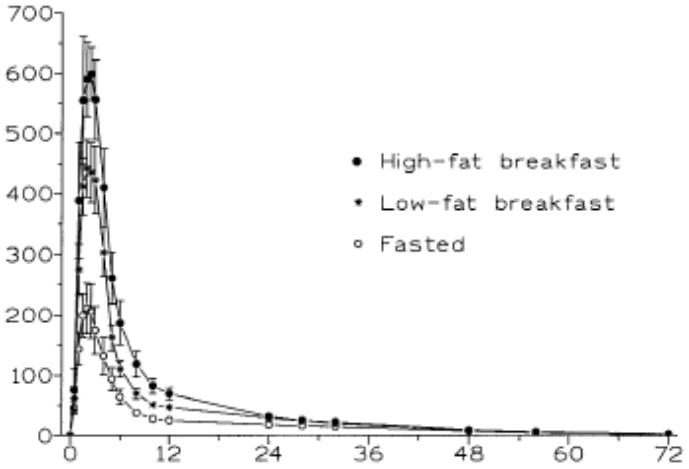
Following administration of a light breakfast (300 kcal; 70 kcal from fat), the geometric mean ratio of ospemifene fed/fasted for Cmax was 2.3 and for $AUC_{0\text{-}72hr}$ was 1.9. Median Tmax of ospemifene was the same at 2.0 hrs under both fed and fasted conditions. Median $t_{1/2}$ of ospemifene remained relatively unchanged at 13.7 hrs under low fat, 13.6 hrs under high fat, and 14.6 hrs fasted conditions, respectively.

Following administration of a high fat breakfast (860 kcal; 540 kcal from fat), the geometric mean ratio of ospemifene fed/fasted for Cmax was 3.5 and for $AUC_{0\text{-}72hr}$ was 2.6. Median Tmax of ospemifene was the same at 2.0 hrs under both fed and fasted conditions. Median $t_{1/2}$ of ospemifene remained the same at 13.7 hrs under both fed and fasted conditions.

The following table summarizes the mean (SD) PK parameters of ospemifene for subjects given 60 mg ospemifene under fasted, low-fat, and high-fat conditions (N=12)

PK parameter*	Fasted	Low-Fat	High-Fat
$AUC_{0\text{-}72}$ (ng.hr/mL)	1693 (53.0)	3045 (35.2)	4103 (35.3)
$AUC_{0\text{-}inf}$ (ng hr/mL)	1854 (50.3)	3106 (35.3)	4170 (35.6)
Cmax (ng/mL)	245 (52.3)	527 (26.7)	803 (25.3)
Tmax (hr)	2.0 (1-5)	2.0 (1-3)	2.0 (1-3)
$T_{1/2}$ (hr)	14.6 (26.3)	13.7 (22.6)	13.6 (15.3)

* mean (CV%)



The sponsor conducted the above mentioned food effect studies in healthy young men using early development tablets (manufactured by [redacted] (b) (4)). To assess the effect of food on the to-be-marketed ospemifene tablets in postmenopausal women, a cross-study comparison using PK data gathered from 5 bioequivalence studies (1 under fed condition and 4 under fasted condition) was conducted by this reviewer. The PK parameters for ospemifene were similar across the four studies under fasted conditions. The results show that $AUC_{0\text{-}inf}$ and Cmax increased 1.7-fold and 2.3-fold, respectively, when ospemifene was administered with a high fat/high calorie meal. Tmax was similar at about 2 hrs. Half-life was similar and ranged from 24 to 29 hrs.

Treatment Condition & Study Number*							
Mean PK Parameters for ospemifene	**Fed**** 1 15-51029 N=28	**Fasted** 1 15-50926 N=30	**Fasted** 2 15-51028 N=43	**Fasted** 3 15-51030 N-29	**Fasted** 4 15-51031 N=91	Fasted 1-4 Average	**Fed[1]/ Fasted[1-4]**
Cmax (ng/mL)	1197.78	527	493	527	533	520	**2.30**
Tmax (hrs)	2.5	2.3	2.5	2.0	2.0	2.2	1.14
AUC_{0-t} (ng hr/mL)	7188.45	4373	3729	3921	3781	3951	1.82
AUC_{0-inf} (ng hr/mL)	7521.19	4735	4077	4320	4165	4324.25	**1.74**
$T_{1/2}$ (hrs)	24.2	26.4	26.9	29.0	26.4	27.2	0.89
λz (1/hr)	0.0302	not analyzed	0.0273	0.0287	0.0279	0.0280	1.08

*ospemifene 60 mg tablets manufactured by Penn Pharmaceuticals (to-be-marketed formulation)
** high fat/high calorie meal

The effect of food on ospemifene exposure was also similar for another formulation. In a cross study comparison of ospemifene tablet manufactured by [redacted] (b) (4) (Lot 8541), AUC_{0-inf} and Cmax increased 2.1 -fold and 2.4-fold, respectively, when ospemifene was administered with a high fat/high calorie meal. Tmax was the same at 2.5 hrs. Half-life was similar at about 27 hrs.

Mean PK Parameters for ospemifene	**Fed**** 15-51029 N=28	**Fasted** 15-50928 N=43	**Fed/ Fasted**
Cmax (ng/mL)	955.14	391	**2.44**
Tmax (hrs)	2.5	2.5	1.00
AUC_{0-t} (ng hr/mL)	6684.54	3051	2.19
AUC_{0-inf} (ng hr/mL)	7119.36	3454	**2.06**
$T_{1/2}$ (hrs)	26.5	28.2	0.94
λz (1/hr)	0.0280	0.0266	1.05

*ospemifene 60 mg tablets manufactured by [redacted] (b) (4) (development formulation)
** high fat/high calorie meal

Overall, the effect of food on ospemifene exposure (AUC_{0-inf} and Cmax) increased 2-3-fold and there is no significant difference between low fat and high fat meals.

The two Phase 3 studies and long-term endometrial safety study were conducted with food (no specific type indicated) and the proposed dosing instruction states ospemifene be taken with food. This reviewer concurs with the dosing instruction recommendation to take ospemifene with food.

2.9 ANALYTICAL SECTION

2.9.1 What bioanalytical methods are used to assess drug concentrations? Briefly describe the methods and summarize the assay performance.

The analytical method used for ospemifene concentration determination in the majority of clinical pharmacology studies was LC-MS/MS after solid phase extraction of human serum samples.

2.9.2 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

The concentration range for the standard curve was from 1.0 to 750 ng/mL.

Nominal conc.	1.00	2.00	5.00	50.0	250	400	600	750
Accepted range	0.800-1.20	1.70-2.30	4.25-5.75	42.5-57.5	213-288	340-460	510-690	638-863
	St1	St2	St3	St4	St5	St6	St7	St8
Ospemifene	0.958	2.20	4.78	50.0	251	387	596	766
HM-187		2.23	4.62	48.8	251	382	604	764

Analyte	Slope (k)	Intercept (b)	Correlation (r)
Ospemifene	0.00183	-0.00027	0.9998
HM-187	0.000309	-0.00009	0.9997

2.9.3 What are the lower and upper limits of quantification (LLOQ/ULOQ)? What is the accuracy, precision and selectivity at these limits?

LLOQ and ULOQ for ospemifene was 1.0 ng/mL and 750 ng/mL, respectively.

Quality control samples were 1, 2, 3, 6, 150, and 600 ng/mL.

Validation parameter	Acceptance criteria
Selectivity	≤ 20% of LLOQ intensity
Calibration curve	75% / 6 standards within 85-115% (80-120% at LLOQ)
Intra-assay precision	15% / 20% at LLOQ
Intra-assay accuracy	85-115% / 80-120% at LLOQ
System suitability test	RSD < 6.00% / < 15% deviation

3 LABELING RECOMMENDATIONS

Detailed labeling recommendations will be incorporated into DRUP's proposed label.

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

Application Number	NDA 203505
Submission Date	25 April 2012
Drug Name	Ospemifene
Proposed Indication	Treatment of vulvar and vaginal atrophy associated with menopause
Clinical Division	Division of Reproductive and Urologic Products
Primary CP Reviewer	LaiMing Lee, PhD
Primary PM Reviewer	Jiang Liu, Ph.D.
Secondary CP Reviewer	Myong-Jin Kim, Pharm.D.
Secondary PM Reviewer	Yaning Wang, Ph.D.
Sponsor	Shionogi Inc.

1 SUMMARY OF FINDINGS

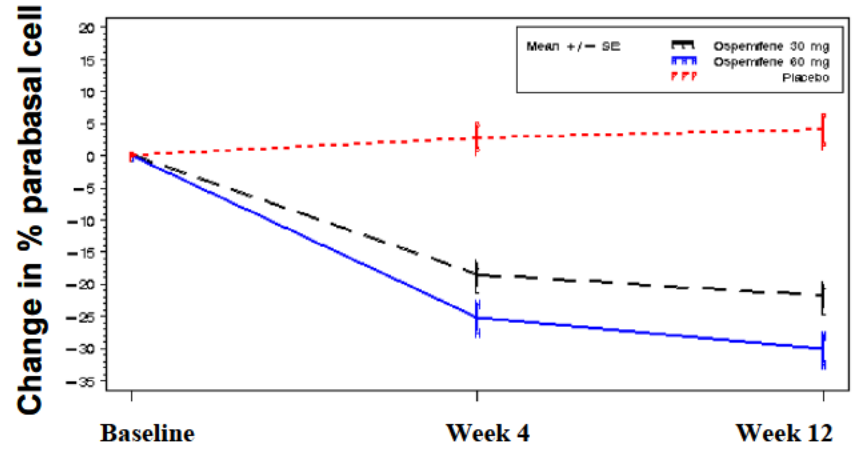
1.1 Key Review Questions

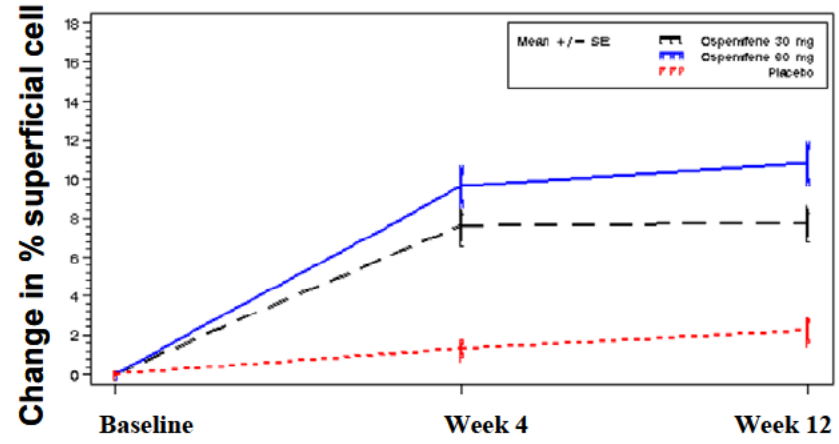
The purpose of this review is to address the following key questions.

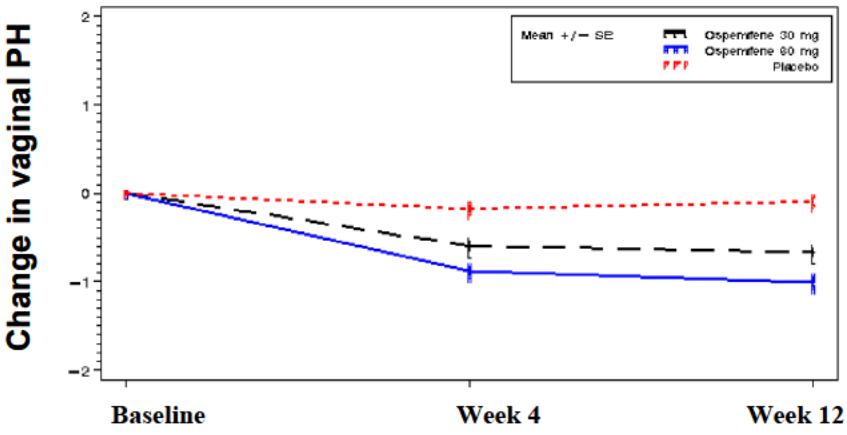
1.1.1 Does ospemifene dose/exposure-response for efficacy and safety support the proposed 60 mg QD dose?

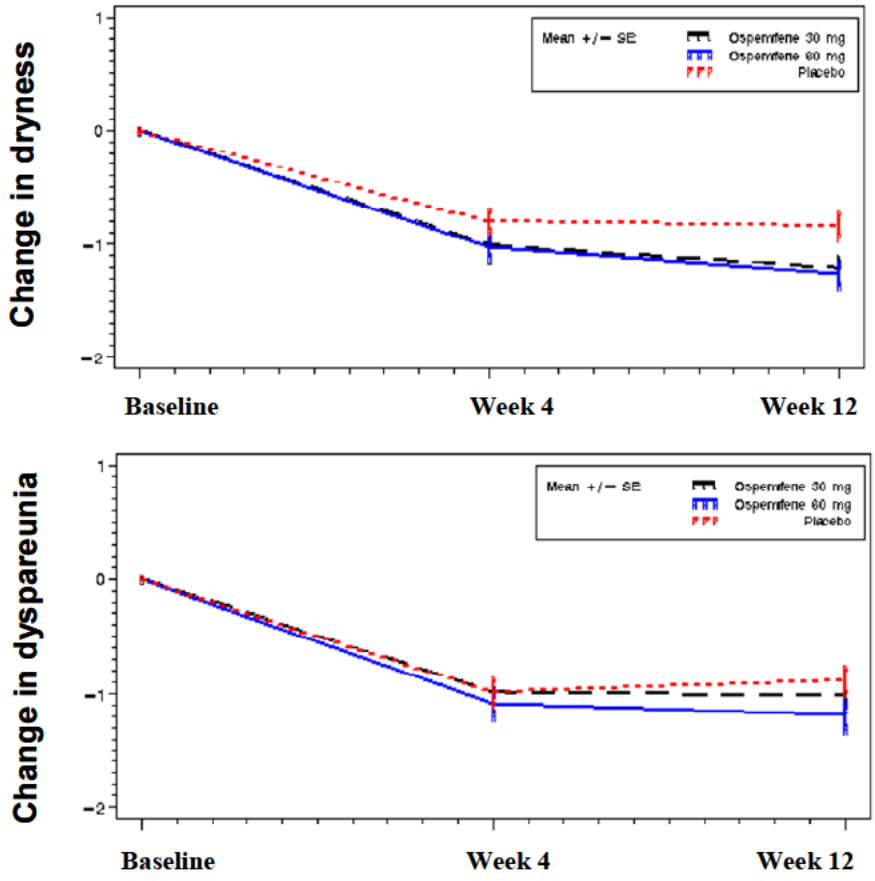
Yes. The sponsor completed three placebo-controlled Phase 3 trials (pivotal 12-week studies: 15-50310 and 15-50821 and supportive long-term 52-week study 15-50718) to support the use of the 60 mg QD dosing regimen for the treatment of vulvar and vaginal atrophy (VVA) associated with menopause. The primary efficacy endpoints measured at Week 12 in the pivotal studies were: the maturation index of vaginal epithelium (i.e., vaginal percent parabasal cells; percent superficial cells; and vaginal pH) and severity of the most bothersome VVA symptom (vaginal dryness or vaginal pain associated with sexual activity). The 60 mg QD ospemifene was consistently superior to the placebo in all of the Phase 3 clinical trials. And in Study 15-50310, the 60 mg QD group was also superior to the 30 mg QD for the vaginal maturation index endpoints (Figure 1).

Figure 1. The 60 mg Ospemifene Dose Was Superior to the Placebo in the Pivotal Phase 3 Study 15-50310 for All of the Co-Primary Efficacy Endpoints. The 60 mg Was Also Superior to the 30 mg for the Vaginal Maturation Index Endpoints



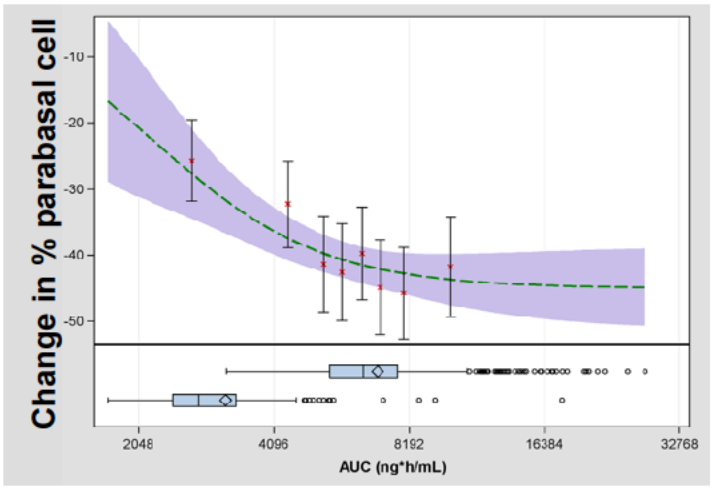


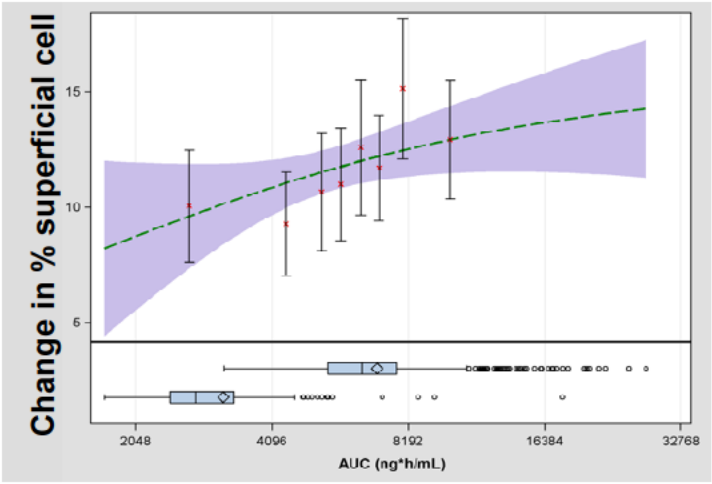


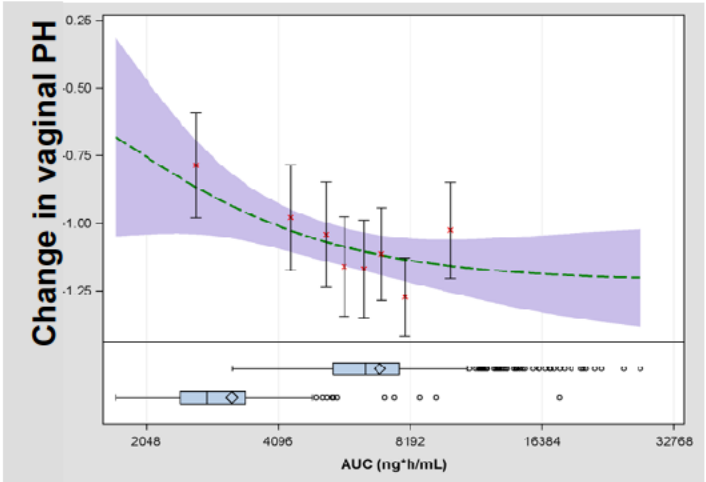


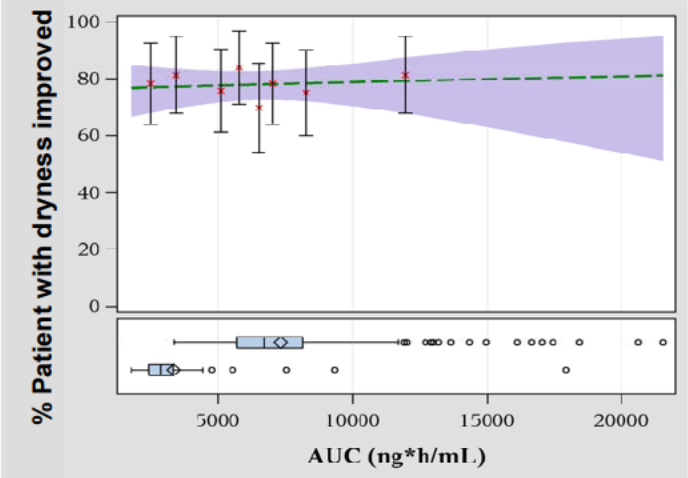
Exposure-response relationship for efficacy indicates that higher ospemifene exposure (AUC_{24_ss}) was associated with better vaginal maturation indices. However, doses higher than 60 mg do not seem to offer significant further advantage (Figure 2).

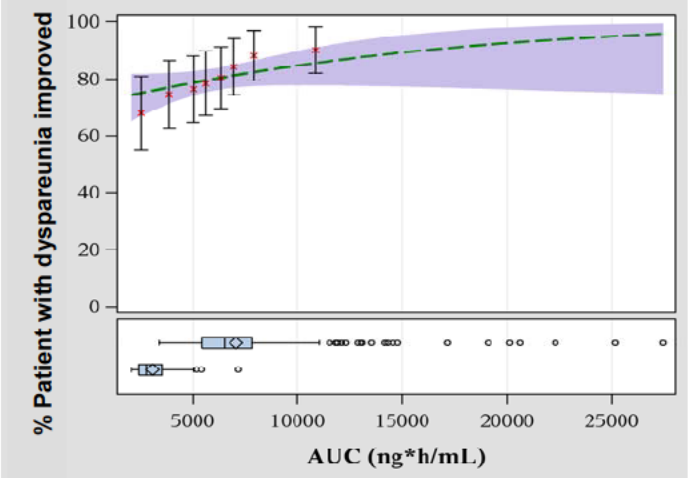
Figure 2. Ospemifene Exposure-Response for Efficacy at Week 12 Indicates Doses Higher than 60 mg Do not Seem to Offer Significant Further Advantage (Pooled Data from the Phase 3 Studies).











Exposure-response for safety: The 60 mg QD ospemifene regimen was well tolerated in the drug development. The most common TEAEs in ospemifene-treated subjects were hot flush, UTI, and headache. The difference from placebo was 5.2% for hot flush, 1.6% for UTI and 0.5% for headache. There was no dose-related increase in TEAEs. There were no occurrences of endometrial hyperplasia or carcinoma in the double-blind, Phase 2/3, placebo controlled studies. One simple hyperplasia (0.1%) was diagnosed 3 months after discontinuation of ospemifene 60 mg in the long-term 52-week study 15-50718. Incidence of vaginal bleeding was low and none led to discontinuation from the study. Concurred by the medical reviewer, no further exposure-response analysis for safety was needed.

1.2 Recommendations

The sponsor proposed 60 mg QD dosing regimen is acceptable from clinical pharmacology perspective.

2 PERTINENT REGULATORY BACKGROUND

This is the original submission of ospemifene (NDA 203505) that the sponsor is seeking approval of 60 mg tablet QD for the treatment of VVA associated with menopause.

Ospemifene is a selective estrogen receptor modulator (SERM), also called an estrogen receptor agonist/antagonist, which has an agonist effect on estrogen receptors in the vagina and bone, is neutral on the uterus and anti-estrogenic in breast tissue.

A total of 21 Phase 1 clinical pharmacology studies and 9 Phase 2/3 studies (7 double-blind, placebo-controlled studies) have been conducted. The primary efficacy was established in two Phase 3 pivotal studies: 15-50310 and 15-50821. Also the long-term Phase 3 study 15-50718 and the Phase 2 study 15-50717 provided supportive evidence (Table 1).

Table 1. Number of Randomized Subjects in Placebo-Controlled Clinical Efficacy Studies

Study Number	Treatment Duration	Placebo	Ospemifene					All Groups
			5 mg/ day	15 mg/ day	30 mg/ day	60 mg/ day	All	
15-50310	12 weeks	268	--	--	282	276	558	826
15-50717	12 weeks	34	33	29	30		92	126
15-50718	52 weeks	63	--	--	--	363	363	426
15-50821 – Dryness Stratum	12 weeks	154	--	--	--	160	160	314
15-50821 – Dyspareunia Stratum	12 weeks	302	--	--	--	303	303	605
Total Subjects		821	33	29	312	1,102	1,476	2,297

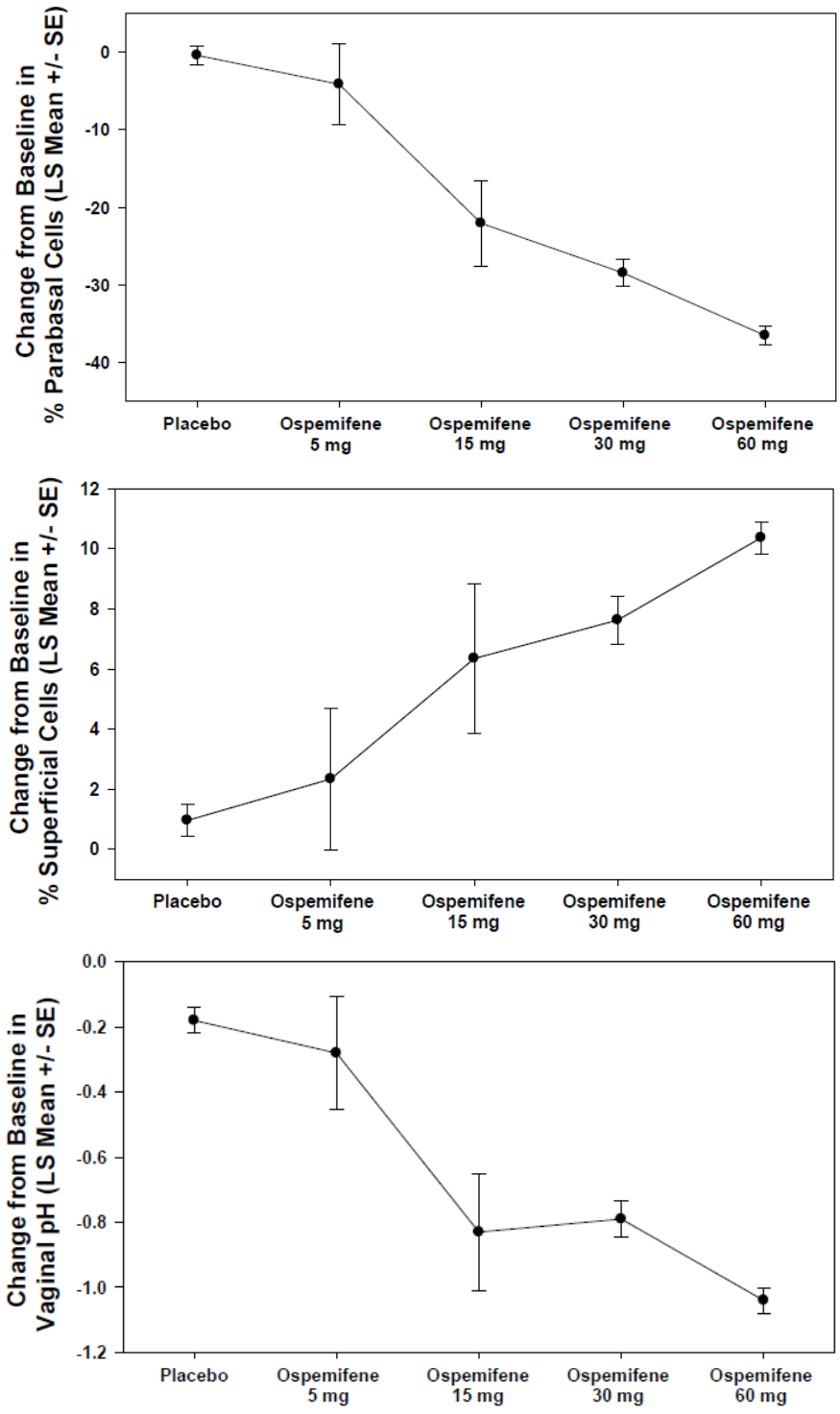
(Source: Sponsor's Integrated Summary of Efficacy: Table 1)

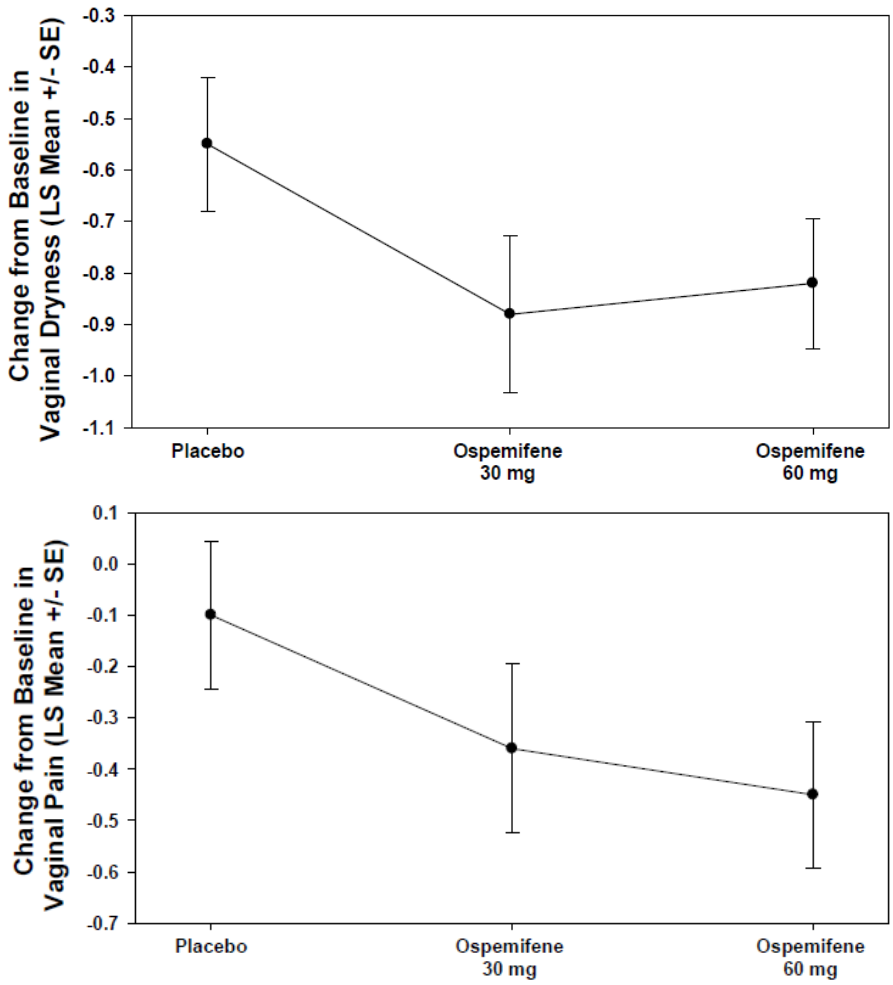
3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Dose response for efficacy

The dose-response relationships for the vaginal maturation indices using pooled data from the 3 placebo-controlled studies, and change in the severity of the most bothersome symptom (MBS) of vaginal dryness and vaginal pain associated with sexual activity using pooled data from Studies 15-50310 and 15-50821 have been investigated. Dose-response relationships between each co-primary efficacy endpoint and dose were assessed with an ANCOVA model. Least-squares means were plotted against treatment group to produce dose-response curves for each endpoint (Figure 3). Ospemifene 60 mg QD demonstrated superiority over placebo for all co-primary endpoints. A clear dose-related effect was observed in all objective primary endpoints, with ospemifene 60

Figure 3. Change from Baseline to Week 12/LOCF in Co-Primary Efficacy Endpoints (ANCOVA Analysis of Pooled Data)





(Source: Sponsor's Integrated Summary of Efficacy: Figure 32-36)

4 REVIEWER'S ANALYSIS

4.1 Objectives

Analysis objective was to assess the proposed 60 mg QD dose based on the exposure-response relationship for efficacy.

4.2 Methods

4.2.1 Software

SAS, R, and NONMEM were used for the reviewer's analyses.

4.2.2 Models and Results

4.2.2.1 Exposure-Response relationship for efficacy

The dataset of the exposure-response analyses for efficacy were pooled from the three pivotal Phase 3 studies 15-50310, 15-50821 and 15-50718. The exposure was the individual AUC_{24} at the steady state obtained from the population PK post-hoc estimation. Graphical visualization and non-linear regression modeling (Emax modeling for the objective vaginal maturation indices and logistic regression for the patients with improved MBS) were used to explore the effects of drug exposures and baseline characteristics on the clinical outcomes. The exposure-response relationship for each efficacy endpoint was explored independently. Our analysis results are consistent with the sponsor's dose-response findings: (1) higher ospemifene exposure (AUC_{24_ss}) was associated with better vaginal maturation indices; (2) higher exposure with doses more than 60 mg/day does not seem to offer significant further advantage; (3) the exposure-response relationship for MBS was relatively flat (Figure 2).

5 LISTING OF ANALYSES DATASET AND CODES

File Name	Description	Location in \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\
PPKPD.xpt	ER dataset for efficacy	\Ospemifene_NDA203505_JL\ER_Analyses\
ER.sas	ER for efficacy	\Ospemifene_NDA203505_JL\ER_Analyses\
quartilePlot_EmaxE0fixed.sas	ER plotting	\Ospemifene_NDA203505_JL\ER_Analyses\
quartilePlot_sigEmaxE0fixed.sas	ER plotting	\Ospemifene_NDA203505_JL\ER_Analyses\
quartilePlot_logistic2_v3.sas	ER plotting	\Ospemifene_NDA203505_JL\ER_Analyses\

APPENDIX - POPULATION PK ANALYSES OF OSPEMIFENE

6 SUMMARY OF FINDINGS

The final population PK model for orally administered ospemifene was a two-compartment model with first-order absorption processes. Age, race, manufacturing sites, body weight, mass index [BMI], albumin [ALB], alanine amino-transferase [ALT], bilirubin [BILI], serum creatinine [CREAT] and creatinine clearance [CLcr] calculated by Cockcroft-Gault formula did not have clinically relevant effect on ospemifene PK.

7 RESULTS OF SPONSOR'S ANALYSIS

The sponsor conducted a population pharmacokinetic analysis to:

1. Characterize the pharmacokinetics of ospemifene
2. Evaluate the effects of covariates on ospemifene exposure
3. Obtain individual post-hoc estimates of ospemifene exposure for exposure-response analysis

Two PPK analyses were conducted. One analysis contains ospemifene concentrations in phase 3 studies, phase 1 repeated dose study, and special population study as listed below. All subjects in the studies were postmenopausal women and took drug in the fed state.

- 1st Pivotal Phase 3 Study (15-50310)
- 2nd Pivotal Phase 3 Study (15-50821)
- 52 Week EU Study (15-50718)
- Phase 1 Steady-State PK Study (15-50927)
- EU Hepatic Study (15-50820)
- US Hepatic Study (15-50920)
- US Renal Study (15-50921)

The other analysis was based on the 4th Phase 1 BE Study (15-51031). All subjects in the study were postmenopausal women and took drug in the fasted state.

A total of 7332 ospemifene serum concentrations from 1089 subjects at 60 mg QD dosing and 171 concentrations from 171 subjects at 30 mg QD dosing were available for the PPK analysis (Table 2).

Table 2. Summary of Clinical Studies Used for the PPK Analysis

Study		Number of subjects	Number of serum samples	Dose	Manufacturing site	Time	Sampling
15-50310	Phase 3 Efficacy and Safety	171	171	30 mg	Penn	Actual blood sampling time and dosing time	Trough after 12 weeks of treatment
		171	171	60 mg			
15-50821	Phase 3 Efficacy and Safety	438	822	60 mg	(b) (4)		Post-dose at Week 4 Trough at Week 12
15-50718	Phase 3 Efficacy and Long-term Safety	328	1404	60 mg	Penn or (b) (4)		Trough at Week 12, 26 and 52 Post-dose (2-6 hrs and 8-12 hrs) at Week 39
15-50820	Phase 1 Effect of Impaired Hepatic Function	16	272	60 mg	(b) (4)	Scheduled blood sampling time and dosing time	0, 1, 2, 3, 4, 6, 8, 12, 24, 32, 48, 72, 96, 120, 168, 216 and 264 hrs
15-50920	Phase 1 Effect of Moderately Impaired Hepatic Function	16	271	60 mg			0, 1, 2, 3, 4, 6, 8, 12, 24, 32, 48, 72, 96, 120, 168, 216 and 264 hrs
15-50921	Phase 1 Effect of Severely Impaired Renal Function	16	256	60 mg			0, 1, 2, 3, 4, 6, 8, 12, 24, 32, 48, 72, 96, 120, 144 and 168 hrs
15-50927	Phase 1 Multiple Dose	12	456	60 mg			Day 1: 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16 and 24 hrs Trough at Day 7, 8 Day 9: 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 32, 48, 72, 96, 120 and 168 hrs
15-51031	Phase 1 Pivotal BE	92	3680	60 mg	Penn or (b) (4)		0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, 72 and 96 hrs

(Source: Sponsor's Population PK Report: Table 1)

7.1 Pharmacokinetics Model

A two-compartment model with first-order absorption processes was selected. Inter-subject variability was assessed on each of the PK parameters using the exponential error structure. Based on the OBJ, exponential error model was chosen for intra-individual variability. Age, race, manufacturing sites, body weight, BMI, ALB, ALT, BILI, CREAT and CLcr were tested as a covariate on PK parameters of CL/F. Age, race, manufacturing sites, body weight, BMI and ALB were tested as a covariate on V2/F. Linear and power model were applied to test continuous covariates and categorical model was applied to test categorical covariates.

The final PK parameter estimates for fed/fasted data are presented in Table 3/Table 4. There was no covariate detected to have clinically relevant effect on ospemifene PK. The CL/F estimate (9.16 L/hr) and the inter-individual variability for CL/F (36.3%) under the fed condition are smaller compared to those under the fasted condition (16.9 L/hr for CL/F and 42.7% for the inter-individual variability for CL/F). Therefore, the population PK analysis supports the sponsor's proposal that ospemifene should be taken with food.

Table 3. Estimated Population Pharmacokinetic Parameters of Ospemifene from the Final Pharmacokinetic Model (Fed Data)

	Units	Estimate	95 % Confidence Interval		
Pharmacokinetic model					
CL/F	(L/hr)	9.16	8.87	-	9.45
V2/F	(L)	34.3	30.1	-	38.5
Q/F	(L/hr)	16.4	14.5	-	18.3
V3/F	(L)	250	226	-	274
ka	(hr^{-1})	0.522	0.486	-	0.558
Inter-individual variability (CV%)					
CL/F	%	36.3			
V2/F	%	49.1			
Q/F	%	58.7			
V3/F	%	32.9			
ka	%	17.3			
Intra-individual variability (CV%)					
exponential	%	37.8			

(Source: Sponsor's Population PK Report: Table 6)

Table 4. Estimated Population Pharmacokinetic Parameters of Ospemifene from the Final Pharmacokinetic Model (Fasted Data)

	Units	Estimate	95 % Confidence Interval		
Pharmacokinetic model					
CL/F	(L/hr)	16.9	15.4	-	18.4
V2/F	(L)	60.8	53.4	-	68.2
Q/F	(L/hr)	22.3	18.8	-	25.8
V3/F	(L)	388	338	-	438
ka	(hr^{-1})	0.670	0.628	-	0.712
Inter-individual variability (CV%)					
CL/F	%	42.7			
V2/F	%	55.0			
Q/F	%	75.4			
V3/F	%	60.4			
ka	%	37.5			
Intra-individual variability (CV%)					
exponential	%	39.5			

(Source: Sponsor's Population PK Report: Table 12)

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA Number	203505
Submission Date	04/26/12
Applicant Name	Shionogi, Inc.
Generic Name	Ospemifene
Proposed Indication	Treatment of vulvar and vaginal atrophy (VVA) due to menopause
Primary Reviewer	Christian Grimstein, Ph.D.
Secondary Reviewer	Mike Pacanowski, Pharm.D., M.P.H.

Executive Summary

The sponsor excluded Factor V Leiden (FVL) carriers from Phase 2 and Phase 3 clinical trials. The review assessed whether 1) the risk estimation for venous thrombotic event (VTE) was biased due to exclusion of FVL carriers in Phase 2 and 3 trials and 2) whether screening for FVL is indicated for patients who are eligible for ospemifene therapy. VTE risk is ~2-3 fold higher in FVL carriers compared to non-carriers, and further increased if other known risk factors are present. Based on the estimated prevalence of FVL and considering the increased risk associated with FVL, few/no additional VTE cases would have been observed if FVL carriers were included in Phase 2/3 trials. Therefore, current risk estimates are reasonable. Additionally, screening for FVL in patients being considered for ospemifene is not recommended given estimates that more than 1000 patients would need to be screened in order to prevent a single VTE.

1 Background

Ospemifene is a selective estrogen receptor modulator (SERM). The proposed indication is for the treatment of vulvar and vaginal atrophy due to menopause. In Phase 2 and Phase 3 clinical trials of ospemifene, patients with FVL were excluded because FVL is considered a genetic risk factor for VTE. The purpose of this review is to evaluate whether risk estimation for VTE was biased in studies submitted to support registration because of this exclusion criterion and the potential implications for labeling.

2 Submission Contents Related to Genomics

The sponsor submitted data from the trials summarized below to support the safety of ospemifene. The safety population of interest for this review was derived from Phase 2 and 3 studies and consisted of 1892 patients who received ospemifene in 1) repeated doses up to 90 mg/day for 12 weeks; 2) up to 60 mg/day for 52 weeks (note that the proposed dose is 60 mg qd). Subjects were screened for FVL using FDA-cleared tests in Phase 2 and 3 studies and excluded if they were heterozygous or homozygous for FVL.

Table 1: Studies included in the Phase 2/3 safety database

Study	Population	Design	Objective
15-50615*	Post-menopausal women age 40- 70 with hot flashes	MC, R, DB, PG, PC	Safety, efficacy (hot flashes)
15-06002*	Healthy postmenopausal women with an intact uterus	R, DB, PG, PC	Effects on bone, vascular endothelium, lipid metabolism and endometrium
15-50717	Post-menopausal women age 40- 80 with VVA	MC, R, DB, PG, PC	Efficacy, safety of low dose ospemifene (VVA)
15-50310	Post-menopausal women age 40- 80 with VVA	MC, R, DB, PG, PC	Efficacy, safety (VAA)
15-50310x	Post-menopausal women from 15-50310 with an intact uterus	MC, R, DB, PG, PC	Long-term safety
15-50718	Post-menopausal women age 40- 80 with an intact uterus and VVA	MC, R, DB, PG, PC	Efficacy, safety (VAA)
15-50821	Post-menopausal women age 40- 80 years with VVA symptoms	MC, R, DB, PG, PC	Efficacy, safety (VAA)
1506001	Post-menopausal women	R, DB, PG, AC	Biomarkers of bone turnover; tolerability
15-50312	Post-menopausal women from 15-50310 without a uterus	MC, OL	Long-term safety

*not pertinent for proposed indication
MC: multi-center; R: randomized; DB: double-blind; PG: parallel-group; PC: placebo-controlled; AC: active-controlled; qd; once daily

Protocol deviations related to FVL status during Phase 2 and 3 in patients receiving ospemifene are presented in Table 2 (i.e., FVL heterozygotes were included in the respective study).

Table 2: FVL carriers that received ospemifene during Phase 2 and 3

Study	FVL status	days on study drug	Discontinued*	VTE reported
15-50310 (Phase3)	Heterozygous	57	Yes	No
	Heterozygous	104	No	No
15-50718 (Phase 3)	Heterozygous	84	Yes	No

*discontinued due to FVL status

The sponsor has not proposed any labeling related to FVL.

This review relies on data reported by the sponsor; no re-analysis was performed by the reviewer.

3 Key Questions and Summary of Findings

3.1 What evidence supports an increased risk of VTE in FVL carriers receiving SERM therapies?

Recent meta-analyses suggest an increased risk of VTE in FVL carriers that is even greater among those also receiving oral contraceptives (OCs) or hormone replacement therapy (HRT). However, the interaction between SERM therapy and FVL carriage is currently unclear given that few studies having only small numbers of cases are available.

FVL is a genetic characteristic marked by poor anticoagulant responses to activated protein C (APC) resulting from a glutamine to arginine substitution at the Arg506 APC cleavage site in the Factor V gene. This single amino acid substitution leads to Factor Va resistance to APC and subsequent increased thrombin generation [PMID: 21116184]. The FVL polymorphism is common in the US population. The prevalence of carrying at least one allele in whites is 5.3%; the prevalence is lower in other ethnicities (Hispanic Americans: 2.2%, Native Americans 1.3%, African Americans 1.2%, Asian Americans: 0.5 %;) [PMID: 9109469]. In the US population, homozygosity for FVL polymorphisms is uncommon at a frequency of 0.02% [PMID: 21116184].

The absolute risk for developing VTE in the general population is low (<1/1000 patient years) but increased if other risk factors are present. The absolute risk associated with FVL for developing a VTE is comparable to the absolute risk associated with other known risk factors (e.g. oral contraceptive (OC) use + increased age) (Table 3). VTE risk is exaggerated in the presence of more than one risk factor.

Table 3: Absolute risk associated with VTE risk factors

Risk factor	Absolute risk of VTE/1000 women patient years
age 15-34	0.27 - 0.75
age 34-55	0.74 - 1.23
OC + age 15-34	0.48 - 0.95
OC + age 35-55	1.7 - 4.1
FVL heterozygotes	~ 2
FVL homozygotes	~ 15
FVL carrier + OC use*	~ 18
FVL carrier + HRT*	~ 29

OC: oral contraceptive therapy; HRT: Hormone replacement therapy
* in first degree relatives symptomatic FVL carriers
Reported odds ratios are only estimates. Surveyed studies varied in population and some had low number of cases.
References: PMID: 21116184; PMID: 9521222; http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf

The reported relative risks for VTE associated with carriage of FVL and other factors based on published literature is summarized in Table 4 below. The magnitude of FVL-associated VTE risk is similar if not greater than other commonly recognized risk factors such as use of oral contraceptives, and smoking. Consistent with the findings presented above, the VTE risk conferred by FVL is similar other risk factors (compared to none; Table 4).

Table 4: Selected risk factors for VTE and associated relative risks

Risk factor	Odds ratio (95% CI) for VTE, relative to individuals without risk factor(s)
FVL	3.78 (2.22, 6.42)
Hormone replacement therapy	3.16 (1.9, 5.23)
Hormone replacement therapy + FVL	13.15 (4.28, 40.47)
Raloxifene	2.0 (0.9, 3.74)
Oral contraceptive therapy	3.10 (2.17, 4.42)
Oral contraceptives + FVL	15.62 (8.66, 28.15)
Smoking (current)	1.43 (1.26, 1.63)
Smoking (current) + FVL	5.05 (3.46, 7.38)

References: [PMID: 16595080, 17726684, 20569451]

Reported odds ratios are only estimates. Surveyed studies varied in population (e.g., age, indication) and had low case numbers.

Like OC or HRT therapy, SERM therapy is also associated with increased risk for VTEs. In women taking tamoxifen for adjuvant breast cancer therapy or raloxifene for osteoporosis, the risk for developing VTE was increased 1.9-3 fold compared to woman who took placebo, regardless of FVL status [PMID: 9747868, 10376571]. Similar to OC/HRT therapy, additional risk factors such as FVL may further increase the risk of developing a VTE under SERM therapy. The association of VTEs and tamoxifen therapy in FVL carriers was assessed in an early stage breast cancer trial in patients receiving adjuvant tamoxifen. FVL status was associated with increased risk for VTE (FVL heterozygotes vs. wild-type: OR 4.73, 95% CI 2.1-10.7) [PMID: 20554945]. However, no association of VTE with FVL and tamoxifen therapy was found in two other breast cancer prevention studies (that used a nested case-control design) [PMID: 14512389; 16818854].

3.2 Is the risk of VTE underestimated because FVL carriers were excluded from Phase 2 and 3 trials?

No, the risk estimation for VTE would not have changed significantly if FVL carriers were enrolled in clinical trials.

VTEs were reported in 2 patients receiving 60 mg ospemifene and 1 patient receiving placebo in Phase 2/3 studies. Estimates of the VTE incidence rate in patients receiving ospemifene or placebo is summarized in Table 5. According to the sponsor, all subjects with a VTE had other risk factors (i.e., prolonged immobilization or medication for deep vein thrombosis (DVT) prophylaxis that suggests previous history of VTE). The incidence of VTEs observed in ospemifene trials is in the range of what has been observed for lasofoxifene (2.9-3.8 VTE/1000 patient years) and raloxifene (2.0 VTE/1000 patient years [95% CI: 0.9, 3.74]) [PMID: 20569451, 20181970].

Table 5: VTE incidence in the safety and placebo treated population

	VTE event rate (%)		VTE Incidence/1000 patient years	
	Ospemifene	**Placebo**	**Ospemifene**	**Placebo**
All Phase 2/3	2/1892 (0.1%)	1/958 (0.1%)	NR	NR
Placebo controlled	2/1696 (0.1%)	1/958 (0.1%)	NR	NR
Phase 1, 2, 3	2/2471 (0.08%)	1/958 (0.1%)	2.12 (0.26, 7.67)	3.66 (0.09, 20.4)

NR: not reported

Assuming a FVL prevalence of 5% (prevalence in the Caucasian population), approximately 132 (2654*0.05) FVL carriers would be expected to have been excluded from Phase 2/3 clinical trials, 88 of whom would have been exposed to ospemifene. With an absolute incidence of 0.1% as observed in the trials and assuming a 5-fold increased risk of VTE in FVL patients receiving ospemifene (compared to non-FVL carriers), the incidence in FVL carriers would be approximately 0.5%. Given that only 88 FVL carriers would have been enrolled, it is unlikely that additional VTE cases would have been observed if FVL carriers were included in the trials (88*0.5% = 0.44 = <1 additional case).

3.3 Is screening for FVL feasible in patients eligible for ospemifene therapy?

No, routine screening for FVL in patients receiving ospemifene is not recommended in patients who have no additional risk factors because thousands of patients would need to be screened to prevent a single VTE.

Clinical guidelines currently do not recommend routine screening for FVL in patients receiving OCs, HRT or SERMs who have low/moderate risk for developing VTE [PMID: 22367731, 19470930, 22315276]. However, screening may be indicated in patients who have additional known VTE risk factors and are therefore at an increased risk for developing a VTE while on OC/HRT/SERM therapy.

The following provides an estimate of how many patients would need to be screened in order to prevent one VTE following ospemifene therapy, based on assumptions about the relative risk and VTE incidence. The background absolute VTE incidence, based on estimates from OC/HRT/SERM-treated patients, was simulated between 0.5-5/1000 patient years. Based on available meta-analyses relative risks associated with FVL were simulated between 2 and 20. Assuming FVL doubles or quintuples VTE risk in ospemifene-treated patients, several thousand patients would need to be screened to prevent a single VTE (Table 6). Therefore, routine screening for FVL in patients receiving ospemifene is not likely be practical. However, screening may be indicated in patients with additional risk factors known to be associated with VTEs (e.g. increased age, smoking, prior VTE) in whom risks are further enriched.

Table 6: Numbers need to screen (NNS) to prevent a VTE in the study population

		VTE incidence / 1000 patient-years			
		0.1	**0.5**	**1**	**5**
OR	**2**	200000	40000	20000	4000
	5	50000	10000	5000	1000
	10	22220	4444	2222	444
	15	14290	2857	1429	286
	20	10530	2105	1053	211

NNS: 1/ ([OR-1]*VTE incidence rate)/0.05 with estimated FVL prevalence: 5%
OR: Odds ratio

3.4 How have inherited thrombophilias been addressed in labeling for other SERMs?

The labeling for tamoxifen states that FVL screening is not recommended on the basis of a substudy of a breast cancer prevention trial. FVL screening is not addressed for other SERMs.

The tamoxifen labeling includes a Boxed Warning related to serious and life-threatening events, including pulmonary embolism and describes the increased incidence of thromboembolic events, including DVT and pulmonary embolism (PE), as observed during tamoxifen trials. Tamoxifen is contraindicated for women with history of DVT or PE. FVL and prothrombin mutation screening is explicitly not recommended. The labeling explicitly states the following: “In a subsmall study (N=81) of the NSABP P-1 trial, there appeared to be no benefit to screening women for Factor V Leiden and Prothrombin mutations G20210A as a means to identify those who may not be appropriate candidates for NOLVADEX therapy.”

The raloxifene labeling includes a Boxed Warning related to increased risk of deep vein thrombosis and pulmonary embolism and states that woman with active or past history of VTE should not take raloxifene. Raloxifene is contraindicated for patients with active or past history of venous thromboembolism, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. The labeling does not address FVL and prothrombin mutation screening.

Other hormonal agents such as oral contraceptives also generally do not recommend use in patients with active or history of deep vein thrombosis or pulmonary embolism. Third generation combination OCs (e.g. drospirenone/ethinyl estradiol) are contraindicated in women with known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders. FVL and prothrombin mutation screening is not explicitly recommended.

4 Summary and Conclusions

Known risk factors for developing a VTE include increased age, OC/HRT/SERM therapy, smoking and inherited factors (e.g., FVL, prothrombin polymorphisms). VTE risk is ~2-3 fold higher in FVL carriers compared to non-carriers, and further increased if other known risk factors are present.

The sponsor excluded FVL carriers from Phase 2 and Phase 3 clinical trials. We do not expect that additional VTE cases would have been observed if FVL carriers were included in Phase 2/3 trials based on estimates of the incidence of VTE and prevalence of FVL. Therefore, the risk estimation for VTE is reasonable.

Routine screening for FVL in patients receiving ospemifene is not recommended given estimates that more than 1000 patients would need to be screened in order to prevent a single VTE. However, FVL carriers receiving ospemifene may still be at greater risk for VTE (compared to FVL non-carriers) given the experience with other SERMs. Screening may be considered in patients with multiple risk factors known to be associated with VTEs (e.g. increased age, smoking, prior VTE).

5 Recommendations

No additional studies are recommended at this time. The proposed labeling, while not explicitly stated, is sufficient to address VTE risk/benefit considerations for women with risk factors for thromboembolic disease.

5.1 Post-marketing studies

None.

5.2 Label Recommendations

None.

NDA Number: 203505 **Applicant: Shionogi Inc.** **Stamp Date: April 25, 2012**

Drug Name: Ospemifene **NDA Type: Original**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X		
2	Has the applicant provided metabolism and drug-drug interaction information?	X		
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x		
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		x	n/a
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	X		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			n/a
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			n/a
11	Is the appropriate pharmacokinetic information submitted?	X		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X		
14	Is the clinical pharmacology and biopharmaceutical	X		

	section of the NDA indexed and paginated in a manner to allow substantive review to begin?			
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
17	Was the translation from another language important or needed for publication?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___YES_____

The following will be Clinical Pharmacology review issues to be conveyed to the Sponsor:

- The demonstration of bioequivalence between formulations Penn 5 and (b) (4) 5
- The in vivo drug interaction between ketoconazole, fluconazole or omeprazole and ospemifene
- Submit the results from the renal impairment study using the new classification scheme of renal impairment as described in FDA's Draft Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010)

Please submit the population PK (PPK) and PPK/PD datasets and their corresponding analysis codes to support the review process:

- All datasets used for model development and PPK/PD analyses should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any data point and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets. The flag of exclusion should be clearly explained in the define.pdf file.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- If applicable, a model development decision tree and/or table which gives an overview of modeling steps.

LaiMing Lee	May 15, 2012
Reviewing Clinical Pharmacologist	Date
Myong-Jin Kim	July 9, 2012
Team Leader/Supervisor	Date

Office of Clinical Pharmacology Filing Memo

NDA: 203505
Compound: Ospemifene
Sponsor: Shionogi Inc.

Submission Date: April 25, 2012
Filing Review Date: May 15, 2012
Reviewer: LaiMing Lee, PhD

Ospemifene is developed by Shionogi for the treatment of vulvar and vaginal atrophy (VVA) due to menopause, including moderate to severe symptoms of dyspareunia and/or dryness and physiological changes (parabasal cell, superficial cells, and pH). Ospemifene is a selective estrogen receptor modulator (SERM) and is also referred to as an estrogen receptor agonist/antagonist. Ospemifene has an agonist effect on estrogen receptor in the vagina and bone, is neutral on the uterus, and anti-estrogenic in breast tissue. It is a new molecular entity (NME) and, if approved, will be the first non-estrogenic agent for the treatment of VVA.

Ospemifene is a solid, oval biconvex, white to off-white, film coated immediate release (IR) oral tablet. The proposed dosing regimen is one 60 mg tablet once daily with food.

The clinical program includes 7 biopharmaceutics, 21 clinical pharmacology studies, and 3 Phase 3 studies (2 pivotal and 1 endometrial safety). A population PK study evaluating age, race, renal function, and race was conducted. There are 7 in vitro studies. In addition, the sponsor evaluated the effect of ospemifene on bone formation and resorption.

Based on in vitro studies (15-4304 and 15-4318) in human liver microsomes and recombinant human CYP enzymes, the sponsor believes ospemifene is primarily metabolized by CYP3A4, 2C9, and 2C19. M1 (4-hydroxyospemifene) and M2 (4'-hydroxyospemifene) are the active metabolites of ospemifene. According to the sponsor, both M1 and M2 have activities resembling those of ospemifene. M1 is the most abundant metabolite formed, comprising up to 75% of the metabolites, followed by M2 and M3 (carboxylic acid). They believe CYP3A4 is the principal contributor to the formation of M1, accounting for 40 to 50% of the formation, whereas CYP2C9 and CYP2C19 contribute the rest in equal share, and that other CYPs only have a negligible role in the metabolism of ospemifene to M1. CYP3A4 contributes about 45% of the formation of M2 with CYP2C19 and CYP2B6, contributing to the rest of the formation of this metabolite.

The sponsor evaluated the ability of ospemifene to inhibit CYP enzymes and found that ospemifene inhibited CYP2B6, CYP2C9, CYP2C19, CYP2C8 and CYP2D6 with IC50 values in the range of 7.8-49 μM. The peak concentration in postmenopausal women after repeated daily administration of 60 mg ospemifene and M1 was approximately 3 μM and 1-2 μM, respectively (in vitro study 15-50927). This concentration is lower than the concentrations inhibiting the enzyme specific reactions above. The enzyme inhibition potential of M1 and M2 has also been studied in vitro.

Due to significantly lower systemic exposures of M1 (25%) and M2 (7%) compared to ospemifene, the sponsor states that the pharmacological effects of ospemifene in humans are likely due to the parent compound. The sponsor conducted in vivo drug-drug interaction study to evaluate the effect of CYP3A4, CYP2C9, and CYP2C19 inhibitors on the metabolism of ospemifene and the effect of ospemifene on substrates of CYP3A4, 2C9, 2C19, and 2B6 enzymes.

Based on in vitro study 15-4316 and 15-4317, the sponsor states that ospemifene showed a high Caco-2 permeability and is not a significant P-glycoprotein substrate; no in vivo transporter study was conducted.

Formulation
The proposed drug product is an IR film-coated tablet. Phase 1 and 2 clinical studies were conducted with a capsule formulation. Batch 0249A (also referred to as "Penn 5") was manufactured at Penn Pharmaceutical Services in South Wales, UK and was used in the first pivotal Phase 3 clinical trial 15-50310. Batch A07006 (also referred to as [redacted] was manufactured at [redacted] and was used in the second pivotal Phase 3 clinical trial 15-50821. The sponsor conducted bioequivalence study 15-51031 comparing the bioequivalence of two 60 mg ospemifene tablets (Penn 5 and [redacted] manufactured by two different companies and manufacturing facilities. Penn 5 is the proposed to-be-marketed formulation.

Phase 3 Clinical Trials
The following is a brief description of the three completed Phase 3 clinical studies:

15-50310 (Phase 3) – 30 or 60 mg ospemifene doses; oral tablets; placebo; 12 weeks; ospemifene administered with food; Penn 5 clinical batch

15-50821 (Phase 3) – 60 mg ospemifene dose; oral tablets; placebo; 12 weeks; ospemifene administered with food; [redacted] clinical batch

15-50718 (Phase 3) – 60 mg ospemifene; oral tablets; placebo; long-term endometrial safety; 52 weeks; Penn 5 clinical batch

Efficacy Endpoints: 4 co-primary endpoints (parabasal cells, superficial cells, vaginal pH, most bothersome symptom). Most common drug-related adverse events were hot flushes, vaginal discharge, genital discharge, muscle spasm, and hyperhidrosis.

In the pivotal clinical trials (15-50310 and 15-50821) ospemifene tablets were administered with food. Sponsor states that dose selection for the Phase 3 trials was based on the results of the Phase 2 Studies 1506001 and 1506002 where the doses 30, 60, and 90 mg were evaluated.

Phase II Clinical Study
1506001 – dose finding; effects of ospemifene and raloxifene on bone formation; 30 mg gelatin capsule formulation; doses included 30, 60, or 90 mg once daily; 12 weeks; sponsor states that ospemifene had a positive effect on atrophic vaginal epithelium, reflected by changes in parabasal cells, intermediate cells, and superficial cells in the vaginal smear; most bothersome symptoms were not assessed.

1506002 – dose finding; effects of ospemifene on bone, vascular endothelium, lipid metabolism and endometrium; 30 mg gelatin capsule formulation; doses included 30, 60, or 90 mg once daily; administered with at least 200 mL of water; 12 weeks; sponsor states that ospemifene had a positive effect on atrophic vaginal epithelium, reflected by changes in parabasal cells, intermediate cells, and superficial cells in the vaginal smear;

15-50717 – dose-ranging study; doses included 5, 15, or 30 mg oral tablets; Penn 5 formulation; ospemifene once daily in the morning with food (both low and high fat food); there appears to be a dose dependent increase in adverse events such as headache, vaginal candidiasis, muscle spasm, and vaginal/genital discharge.

Phase I Biopharmaceutics Studies
1506004 – a relative bioavailability study; fasted condition; comparing bioavailability of ospemifene 60 mg tablet and capsule formulations ([redacted] Batch 0107-852 and [redacted] Batch 002)

15-50926 – first bioequivalence study; fasted condition; Penn 5 and [redacted] (b) (4) Batch 85518; the sponsor states bioequivalence was not met.

15-51028 – second bioequivalence study; fasted condition; Penn 5 and [redacted] (b) (4) Batch 85481; the sponsor states bioequivalence was not met.

15-51029 – third bioequivalence study; fed condition; Penn 5 and [redacted] (b) (4) Batch 85481; the sponsor states bioequivalence was not met.

15-51031 – fourth (pivotal) bioequivalence study; fasted condition; postmenopausal women; comparing bioequivalence of two 60 mg ospemifene tablets Penn 5 and [redacted] (b) (4) the sponsor states the two formulations are bioequivalent

Phase 1 Clinical Pharmacology Studies
The following is a brief description of the Phase 1 Clinical Pharmacology studies:

3044001 (former number 15-59501-01; single ascending dose, first-in-human) was an open-label, single dose, Phase I dose escalation study in 28 healthy male subjects with seven doses (10, 25, 50, 100, 200, 400, and 800 mg in gelatin capsules without any excipients) to evaluate the safety, tolerability, PK, and PD of ospemifene after a single administration after an overnight fast.

Median Tmax was 3 hrs and ranged from 1 to 6 hrs for all seven dose groups. Cmax increased in a dose-dependent (not dose proportional) manner. AUC was variable and did not correlate with dose.

1506003 (former number 3044002; multiple dose, once daily) was a multiple dose, double-blind, parallel group study in healthy postmenopausal women evaluating the safety, tolerability, PK, and PD (endometrial thickness, endometrial histology, lipid, hormone, and bone metabolism) of ospemifene 25, 50, 100, and 200 mg and placebo.

15-50927 (single and multiple dose, once daily) was a single and multiple dose, open-label, single group study in twelve healthy postmenopausal women. One 60 mg ospemifene tablet (Batch [redacted] (b) (4) 88518 manufactured at [redacted] (b) (4)) was administered once daily after a meal for 9 days.

15-50206 (mass balance) was a single dose, mass balance study in six healthy postmenopausal women given a 60 mg ^{3}H-ospemifene oral solution after an overnight fast.

Ospemifene was extensively metabolized, with a large number of metabolites present in plasma, urine and feces. The principal radioactive component in both plasma and feces was ospemifene and 4-hydroxyospemifene. Ospemifene and 4-hydroxyospemifene accounted for approximately 20% and 14% of the total radioactivity in serum, respectively, based on AUC ratios. The majority of radiolabelled material was excreted in the feces (~75% total radioactivity). Renal elimination appears to be minimal (~7%). Less than 0.2% of the ospemifene dose was excreted unchanged in urine.

15-50820 (hepatic impairment) was an open-label, single dose, parallel study in postmenopausal women with hepatic impairment (defined by the Child-Pugh score, mild, moderate) given 60 mg ospemifene after a standard meal. Subjects were age matched in the control group.

AUC0-inf and Cmax were about 0.9% and 21% lower, respectively, in subjects with mild hepatic impairment, compared to subjects with normal hepatic function.

AUC0-inf and Cmax were about 45% higher and 41% lower, respectively, in subjects with moderate hepatic impairment, compared to subjects with normal hepatic function.

15-50920 (hepatic impairment) was an open-label, single dose, parallel study in postmenopausal women with hepatic impairment (defined by the Child-Pugh score, moderate) given 60 mg ospemifene after a standard high fat/high calorie meal. Subjects were age and race matched in the control group. This study was conducted due to difficulties in recruiting patients with moderate hepatic impairment in Study 15-50820.

AUC0-inf and Cmax were about 29% and 1% higher, respectively, in subjects with moderate hepatic impairment, compared to subjects with normal hepatic function.

15-50921 (renal impairment) was an open-label, single dose, parallel group study in postmenopausal women with severe renal impairment (CrCl < 30 mL/min) given 60 mg ospemifene after a standard high fat/high calorie meal.

AUC0-inf and Cmax were about 20% higher and 21% lower, respectively, in subjects with severe renal impairment, compared to subjects with normal renal function.

15-50208 and 15-50208-02 (food effect) consisted of two sub-studies. The first sub-study was a randomized, open-label, two-sequence, two-period, crossover study designed to assess the effect of a high-fat meal on PK of ospemifene. The second sub-study was an open-label, one-period, one-treatment, non-randomized study designed to assess the effect of a low-fat meal on PK of ospemifene.

Following administration of a 60 mg ospemifene tablet, the AUC0-last and Cmax after a high-fat, high-calorie meal were about 2.8- and 3.6-fold higher, respectively, compared to the fasted state. The AUC0-last and Cmax after a light breakfast were about 1.9- and 2.3-fold higher, respectively, compared to the fasted state. The sponsor states that ospemifene should be given with food.

15-50716 (Effect of CYP3A4 inhibitor (ketoconazole) and CYP3A4 inducer (rifampin) on ospemifene) was an open-label, randomized, three-period, crossover study in 12 postmenopausal women administered with a single 60 mg dose of ospemifene following a meal with and without pre-treatment with rifampin and ketoconazole. Treatments include (1) 60 mg ospemifene after a standard meal as a single dose, (2) once daily administration of 600 mg rifampin in the fasted state for 5 days and 60 mg ospemifene after a standard meal on 6th day, and (3) once daily administration of 400 mg ketoconazole after a meal for 4 days and 400 mg ketoconazole and 60 mg ospemifene on 5th day followed by 3 days once daily administration of 400 mg ketoconazole.

Rifampin reduced the AUC0-inf and Cmax of ospemifene by 58% and 51%, respectively.

Ketoconazole increased the AUC0-inf and Cmax of ospemifene by 42% and 46%, respectively.

Tmax and $t_{1/2}$ were similar in all groups and was essentially unaffected by rifampin or ketoconazole.

15-50823 (Effect of CYP3A4/CYP2C9/CYP2C19 inhibitor (fluconazole) and CYP2C19 inhibitor (omeprazole) on ospemifene) was an open-label, randomized, two- and three-period, crossover study in 14 postmenopausal women administered with a single 60 mg dose of ospemifene following a meal with and without pre-treatment with fluconazole and omeprazole. The fluconazole treatment period included 200 mg fluconazole (400 mg on Day 1) administered once daily under fasted condition for 8 days and on the 5th day one tablet of 60 mg ospemifene was administered under fed condition. The omeprazole treatment period included 40 mg omeprazole administered once daily under fasted condition for 8 days

and on the 5th day one tablet of 60 mg ospemifene was administered under fed condition. Subjects were genotyped as extensive 2C9 and 2C19 metabolizers

Co-administration of fluconazole resulted in AUC0-inf increase of ospemifene by 174% by inhibiting CYP3A and CYP2C9 concomitantly. Fluconazole increased Cmax and $t_{1/2}$ by 66%. The sponsor states that ospemifene should not be used concomitantly with strong inhibitors of CYP3A and CYP2C9.

Co-administration of omeprazole (a CYP2C19 inhibitor) increased AUC0-inf of ospemifene by 17%. Omeprazole increased Cmax of ospemifene by 20% and did not affect $t_{1/2}$. The sponsor states that no dose-adjustment is required when ospemifene is co-administered with drugs that are inhibitors of only CYP2C19.

15-50614 (Effect of ospemifene on CYP2C9 (warfarin) is an open-label, two-period, crossover study in 16 healthy postmenopausal women given single dose of 10 mg warfarin with and without pre-treatment of 60 mg ospemifene once daily for 8 days following a meal.

The geometric least square means (90% CI) for test (warfarin + ospemifene)/reference (warfarin alone) ratio of S-warfarin AUC0-inf was 0.96 (0.91, 1.02). The sponsor states that repeated dosing of 60 mg ospemifene does not affect CYP2C9 activity. For Cmax, the LSM (905 CI) ratio was 0.97 (0.92, 1.02).

15-50719 (Effect of ospemifene on CYP2C19 and CYP3A4 (omeprazole)) was an open-label, two-period, crossover study in 12 postmenopausal women administered with a single 20 mg omeprazole with and without pre-treatment of once daily 60 mg ospemifene for 7 days. Women were genotyped as not being poor metabolizers of CYP2C19 were included in the PK analysis.

The ratios of the geometric means (90% CI) of the metabolic indices (with/without ospemifene) were 0.97 (0.77, 1.22) for 5- hydroxyomeprazole and 0.97 (0.66, 1.41) for omeprazole sulphone. The sponsor states that ospemifene does not have an effect on the metabolism of omeprazole and that repeat dosing of ospemifene does not significantly affect CYP2C19 and CYP3A4 activity.

15-50825 (Effect of ospemifene on CYP2B6 (bupropion)) is an open-label, two-period, two sequence, randomized, crossover study in 16 postmenopausal women administered a single 150 mg dose of bupropion with and without pre-treatment of once daily 60 mg ospemifene for 7 days. Subjects were genotyped as not being homozygous for CYP2B6*6.

The geometric mean AUC0-inf and Cmax of bupropion decreased by 19% and 18%, respectively, with ospemifene co-administration. The sponsor concludes that ospemifene has no impact on CYP2B6 activity and no dose modification is required if ospemifene and bupropion are co-administered.

15-50824 (thorough QTc) was a randomized, double-blind, active and placebo-controlled trial in 200 healthy male and female subjects (50 subjects each arm: 25 women and 25 men) between 18 and 45 years of age. The total treatment duration was 7 days. Subjects were randomized to receive placebo daily, ospemifene 60 mg/day, ospemifene 240 mg/day (supratherapeutic dose), or moxifloxacin (active control) after a high-fat breakfast.

The sponsor states that there was no effect of any of the two ospemifene doses on the QTc interval of any other electrocardiographic parameters, including heart rate, PR, or QRS interval.

Population PK (15-50310, 15-50821, 15-50718, 15-50927, 15-50820, 15-50920, and 15-9021) was conducted to evaluate the effects of demographic factors (i.e. body weight, CrCl, age, hepatic and renal function, on the PK of ospemifene based on the pooled data from Phase I and Phase III studies in

postmenopausal women under fed conditions. The sponsor states that no clear relationships were observed; no dose adjustment is required based on age, body weight, renal function, liver function or race.

Pivotal Bioequivalence Study 15-51031: Clinical Site (b) (4) and Analytical Site (b) (4)
On July 9, 2012, Michael Skelly, PhD, a pharmacologist in the Division of Bioequivalence and GLP Compliance Office of Scientific Investigations, informed the Clinical Pharmacology Review Team that (b) (4) was last inspected on 7/21/11 and covered NDA 22-113 and was classified NAI (No Action Indicated, no adverse observations). (b) (4) was last inspected on 5/10/11 (NDA 202-123) and 6/6/11 (NDA 202-133) and was also classified NAI. The Establishment Inspection Report (EIR) reviews are in DARRTS.

The (b) (4) studies for NDA 203-505, including the ones with failed BE outcomes, appear to have been done at approximately the same time as the ones covered by our inspections. Therefore, OSI does not have a separate reason to call for inspection and audit of these studies. According to your judgment, if you request inspections, we can arrange them in time for the PDUFA deadlines.

For tamoxifen and toremifene BE studies with similar analytical methodology and some pharmacokinetic features in common, we encountered variability like the ospemifene studies. The EIR Reviews (e.g., ANDA 74-539) and other records may not be available now, according to our record retention policies.

Based on Dr. Skelly's recommendation, discussion with Dr. Sam Hadiar (Chief, Bioequivalence Investigations Branch, Division of Bioequivalence and GLP Compliance, Office of Scientific Investigations), and preliminary review of the BE study, this reviewer feels no need to have an additional clinical site and analytical site inspection. Captain E. Dennis Bashaw, OCP DCP-3 Division Director, was informed of the above and supports that no additional inspection is necessary for this BE study.

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/s/

LAI M LEE
01/11/2013

JIANG LIU
01/11/2013

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01/12/2013

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BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	203-505	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	4/26/2012; 7/27/2012		
Division:	DRUP	**Acting Biopharmaceutics Team Leader:** Tapash Ghosh, Ph.D.	
Applicant:	Shionogi, Inc.	**Acting Biopharmaceutics Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	Osphena Tablets	**Date Assigned:**	5/21/2012
Generic Name:	ospemifene	**Date of Review:**	12/11/2012
Indication:	Treatment of vulvar and vaginal atrophy due to menopause, including dyspareunia and/or vaginal dryness	**Type of Submission:** 505(b)(1) Original NDA	
Formulation/strengths:	IR Tablet, 60 mg		
Route of Administration:	Oral		

SUMMARY

This submission is a 505(b)(1) New Drug Application for 60 mg Osphena (ospemifene) immediate release tablets. The proposed indication is for the treatment of vulvar and vaginal atrophy due to menopause, including dyspareunia and/or vaginal dryness.

The Biopharmaceutics information in this submission includes a drug product development section with the proposed dissolution method and acceptance criterion. The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion.

A. Dissolution Method

The proposed dissolution method is shown below.

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	50 rpm	900 mL	37 °C	2% SDS in water

The proposed dissolution method has adequate discriminating power, and therefore is deemed acceptable.

B. Acceptance Criterion

The proposed acceptance criterion is shown below.

Acceptance Criterion
Q = (b) (4) at 60 minutes

The dissolution acceptance criterion is deemed acceptable.

RECOMMENDATION:

1. Osphena (ospemifene) 60 mg strength immediate release tablets are recommended for approval from a Biopharmaceutics standpoint.
    - The following dissolution method and acceptance criterion is recommended for both strengths:
        i. Dissolution method: Apparatus II, 50 rpm agitation rate, 900 mL media volume, 37 °C, 2% SDS in water.
        ii. Dissolution acceptance criterion: Q = (b) (4) at 60 minutes.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader (acting)
Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto, Dr. Angelica Dorantes

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Substance

That Applicant asserts that ospemifene is classified as a BCS Class 2 drug substance (low solubility and high permeability). The structure of ospemifene is shown below in Figure 1.

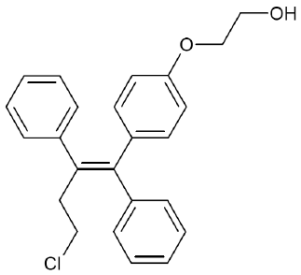


Figure 1. Chemical structure of ospemifene

Ospemifene is highly insoluble in water and buffers over the pH range from 1.2 to 8.0. The solubility of ospemifene does not change as a function of pH (refer to Table 1).

(b) (4)

The Applicant states that sink conditions were reached with the following surfactant concentrations: 2.0% SDS, (b) (4). They selected SDS as the surfactant for the final dissolution method because SDS is a common surfactant used in industry for dissolution methods. Sink conditions were met with a

surfactant concentration of 2.0% SDS with a sink volume of 850 mL, and ospemifene formulations were tested for dissolution in aqueous solutions containing 2.0% sodium dodecyl sulfate (SDS) during early development.

The solubility of ospemifene in 2% SDS at different pH as a function of time was studied (refer to Table 2). The solubility of ospemifene reached approximately 0.2 mg/mL level (sink conditions) in solutions at pH ranges of 1.2 - 8.0.

Table 2. Solubility of Ospemifene in 2% SDS at Different pHs

2% SDS Solution	Time	Solubility (mg/mL)
Unadjusted pH*	60 minutes	0.18
	20 hours	0.28
pH 1.2*	60 minutes	0.15
	20 hours	0.23
pH 4.5*	60 minutes	0.11
	20 hours	0.25
pH 6.8*	60 minutes	0.13
	20 hours	0.25
pH 8.0*	60 minutes	0.12
	20 hours	0.23

* Samples taken at different time-points during equilibrium at +37°C. Before measurement, samples were allowed to reach room temperature. Measurements by a spectrophotometer at 238 nm.

Reviewer's Assessment:

The data from Table 1 demonstrates that a surfactant is needed to achieve sink conditions. From Table 2, it can be seen that buffer + SDS does not provide sink conditions within the typical timeframe (e.g. 60 min) of the dissolution test for an IR solid dosage form tablet. Figures 2 and 3 below show that ospemifene does not achieve complete dissolution in these buffer + SDS ((b) (4) dissolved by 60 minutes).

Drug Product

Ospemifene 60 mg film-coated tablets are manufactured using conventional manufacturing methods. The manufacturing process consists of the following steps (b) (4) Early development work of the drug product was performed by (b) (4) and continued at Penn Pharmaceutical Services (Penn Pharma) and (b) (4) Penn Pharma was chosen as the commercial site.

The composition of ospemifene tablets is presented in Table 3.

Table 3. Composition of Ospemifene Tablets

Component	Quantity/Tablet (mg)	Function	Quality Standard
Ospemifene	60.0	Active	In-house
Pregelatinized starch (b) (4)	(b) (4)		NF
Mannitol			USP
Povidone (b) (4)			USP
Sodium starch glycolate			NF
Microcrystalline cellulose (b) (4)			NF
Colloidal silicon dioxide (b) (4)			NF
Magnesium stearate			NF
(b) (4)			In-house
			USP

[1] (b) (4)

2. Dissolution Method

The proposed dissolution method is shown in Table 4.

Table 4. Dissolution Test Conditions

Medium	2% SDS in water
Medium volume	900 mL
Temperature	37°C ± 0.5°C
Apparatus	USP Type 2, paddles
Rotation Speed	50 ± 2 rpm
Sample Volume	5 mL without replacement
Sample Measurement	UV absorbance @ 238 nm

The Applicant did not have sufficient data to support the adequacy of the proposed dissolution method. Therefore, the following IR comments were conveyed in the 74 day letter.

> **FDA Comment**
> There is insufficient data to support the adequacy of the proposed dissolution method (e.g. selected dissolution medium and surfactant are not justified). Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
> a. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters supporting the proposed dissolution method as the optimal test for your product (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.). The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least (b) (4) of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.
> b. Data to support the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent.

Selection of Dissolution Medium

The Applicant determined that the solubility of ospemifene should be 0.2 mg/mL in a dissolution medium to have sink conditions. They found that sink conditions are not reached using water or buffer solutions as dissolution medium. Therefore the addition of a surfactant to the medium was tested.

The Applicant performed dissolution experiments on the pivotal phase 3 study Batches 0249A and A07006 and larger scale batches made at (b) (4) using buffered solutions at pH 1.2, 4.5, 6.5 and 7.5 containing 2.0% of SDS. Figure 2a-d illustrates the dissolution profiles for these batches, and Table 5 lists the f2 similarity factors.

Figure 2 a-d. Dissolution Profiles of Ospemifene 60 mg Tablets Batches in Various Media (Apparatus II at 37°C with a paddle speed of 50 rpm)

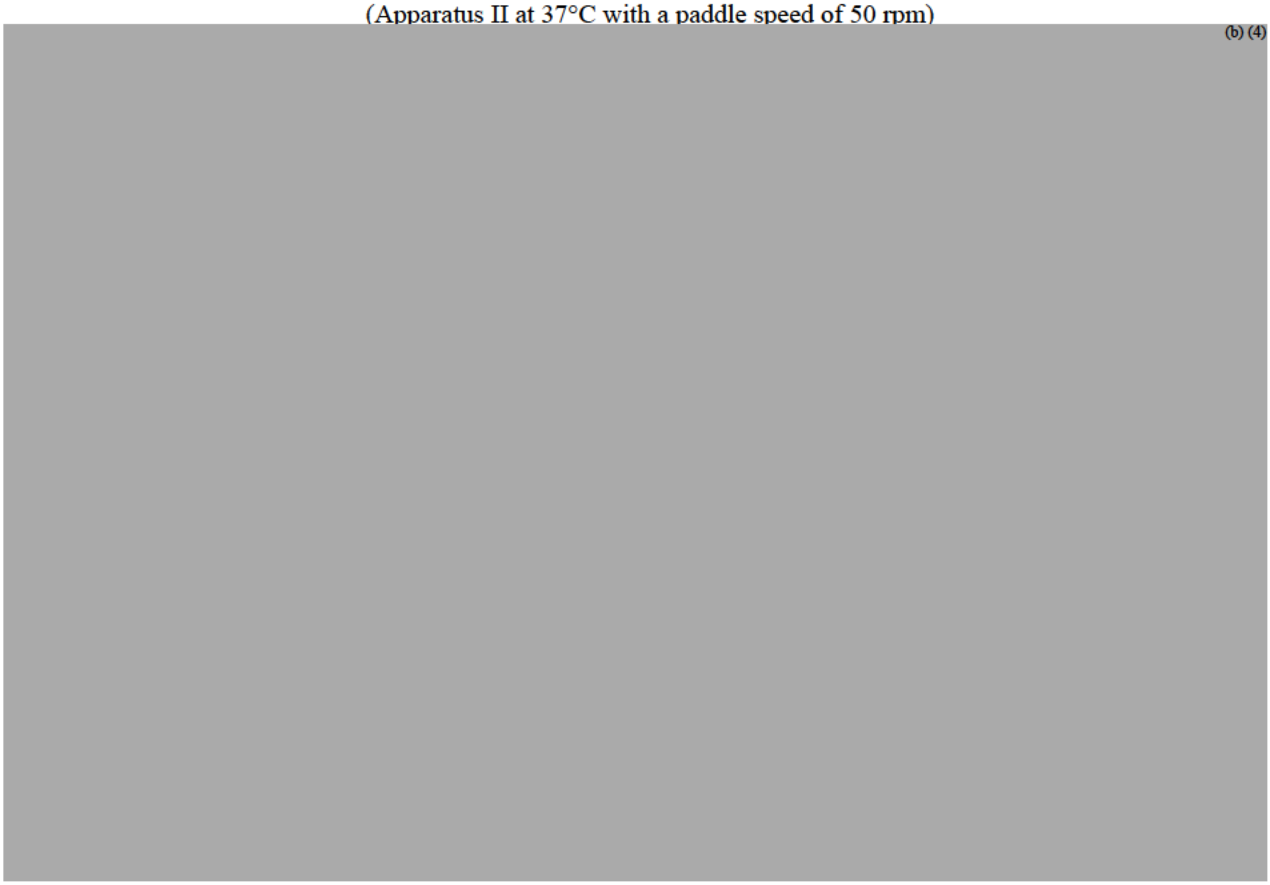


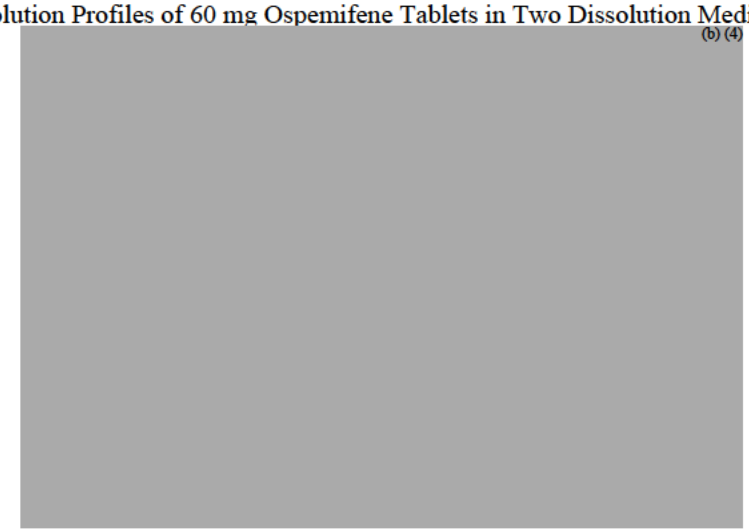
Table 5. Similarity Factors for Different Ospemifene 60 mg Batches in 2% SDS media at Various pH

Batches Compared	Similarity factor, f_2 pH 1.2	Similarity factor, f_2 pH 4.5	Similarity factor, f_2 pH 6.5	Similarity factor, f_2 pH 7.5
0249A vs. A07006	58	66	64	59
0249A vs. 85481	43	48	49	53
0249A vs. 85509	43	48	50	52
0249A vs. 85518	53	57	57	60
A07006 vs. 85481	35	42	41	43
A07006 vs. 85509	35	42	42	42
A07006 vs. 85518	43	49	48	50
85481 vs. 85509	96	97	96	97
85481 vs. 85518	57	63	69	68
85509 vs. 85518	59	64	69	66

The dissolution profiles of the pivotal phase 3 study Batches 0249A and A07006 were determined to be f2 similar (f2>50) in 2% SDS at different pHs. When the larger scale batches were compared to each other (Batches 85481, 85509 and 85518), they were determined to be similar in 2% SDS at different pHs. When the larger scale batches were compared to the pivotal phase 3 study Batches in 2% SDS at different pHs the dissolution profiles, they were not similar (f2<50), with the exception of Batch 85518 when compared with 0249A.

The Applicant tested two dissolution media, 2% SDS in water and pH 4.5 acetate buffered media, using Batch 0249A of ospemifene tablets 60 mg (refer to Figure 3).

Figure 3. Dissolution Profiles of 60 mg Ospemifene Tablets in Two Dissolution Media (Batch 0249A)



The Applicant determined that the two dissolution profiles are f2 similar (f2 = 54.5).

Reviewer's Assessment:

Figure 2 demonstrates that the dissolution of ospemifene is not pH dependent. From Table 5, it can be seen that pH 4.5 buffer + SDS can discriminate between some non-BE batches. However, ospemifene does not achieve complete dissolution in this media (b) (4) ***dissolved by 60 minutes). As shown in Figure 3, the drug product dissolves faster in 2% SDS in water (*** (b) (4) ***dissolved by 45 minutes). Sink conditions are reached with 2% SDS in water, but it takes 20 hours to reach sink conditions with pH 4.5 buffer+SDS. Therefore, the proposed dissolution media (including the surfactant and surfactant concentration) is acceptable.***

Selection of Paddle Speed

USP dissolution Apparatus 2 (paddle) was selected for ospemifene tablets 60 mg. The influence of paddle rotation speed on the dissolution of ospemifene tablets was studied in five different lots. Rotation speeds of 50 rpm and 100 rpm were used with a medium of 2% SDS in water (refer to Figures 4 and 5).

Figure 4. Dissolution Profiles of 60 mg Ospemifene Tablets in 2% SDS in Water (50 rpm speed)

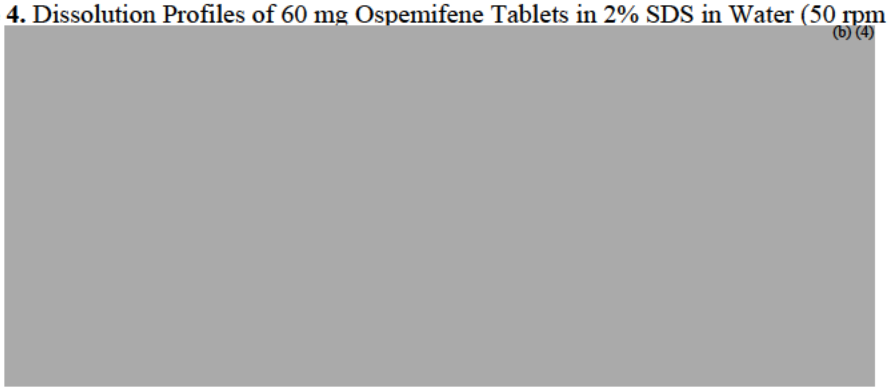
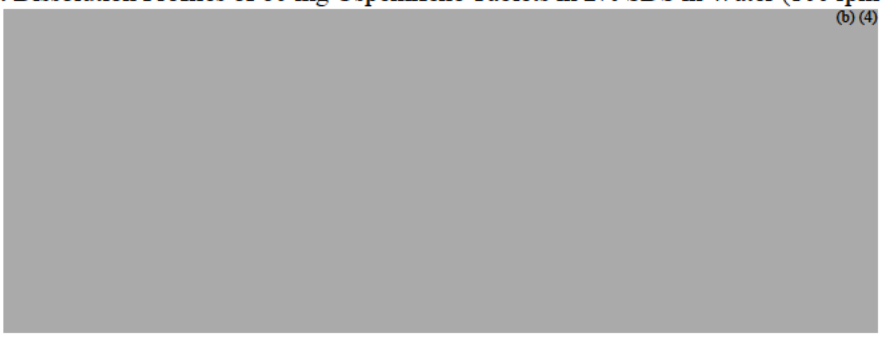


Figure 5. Dissolution Profiles of 60 mg Ospemifene Tablets in 2% SDS in Water (100 rpm speed)



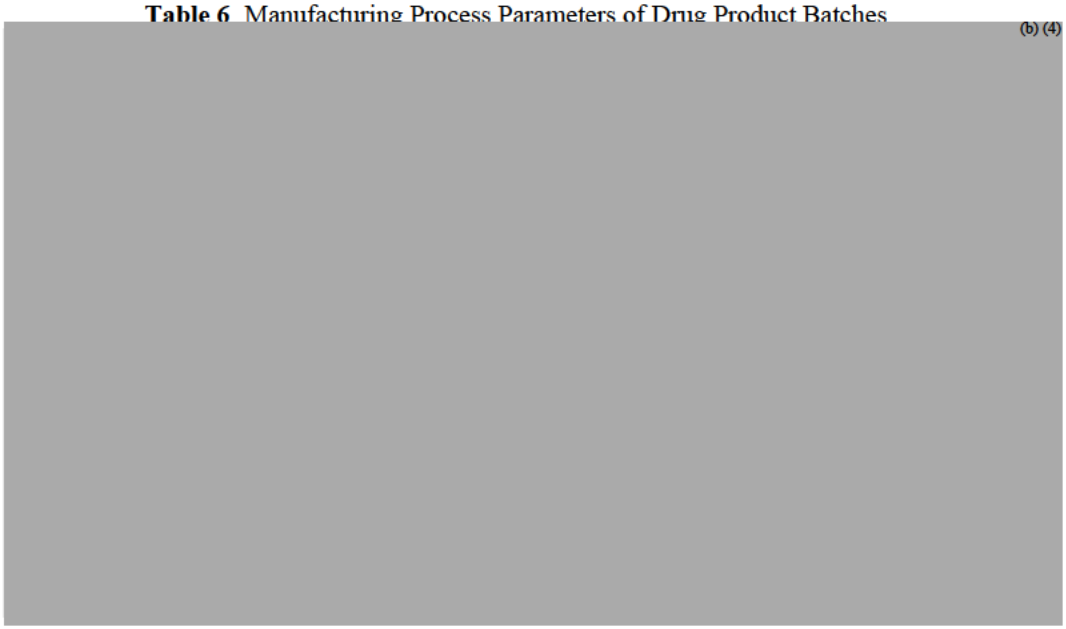
Reviewer's Assessment:

Figures 4 and 5 demonstrate that there is no significant difference in the effect that a paddle speed of 50 or 100rpm had on the dissolution profiles in 2% SDS in water. Therefore, the selection of 50 rpm paddle speed is acceptable for use with the proposed dissolution medium.

Discriminating Ability

The Applicant compared the dissolution profiles of batches of Ospemifene Tablets 60 mg manufactured utilizing the parameters specified in Table 6 to demonstrate the discriminating ability of the selected dissolution method. The profile comparisons are presented in Figures 6 and 7 below.

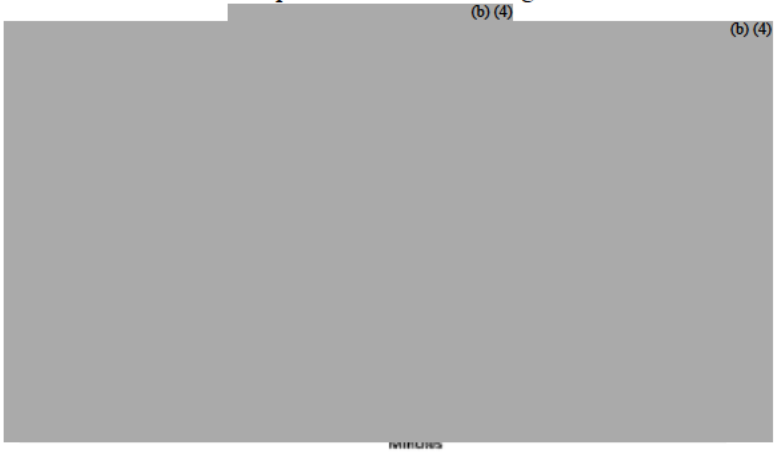
Table 6 Manufacturing Process Parameters of Drug Product Batches



(b) (4)

Figure 6 depicts the dissolution profiles obtained with ospemifene tablets 60 mg (b) (4) values in 2% SDS in water.

Figure 6 Dissolution Profiles of Ospemifene Tablets 60 mg Manufactured with Different (b) (4)



Particle Size

Figure 7 depicts the dissolution profiles obtained with ospemifene tablets 60 mg of (b) (4) in 2% SDS in water.

Figure 7. Dissolution Profiles of Ospemifene Tablets 60 mg Manufactured with Different Drug Substance (b) (4)

Reviewer's Assessment:

It appears that the proposed dissolution method can discriminate (b) (4). However, each batch had many manufacturing changes (b) (4) done together. Therefore, it is difficult to pinpoint which parameters the dissolution method can truly discriminate. This study would have been more informative if the Applicant manufactured batches that varied one parameter at a time, and tested compared the dissolution profiles of these batches.

However, the proposed dissolution method is able to detect manufacturing changes. Therefore, the discriminating ability of the proposed dissolution method is adequate. Thus, the proposed dissolution method is acceptable.

3. Dissolution Acdeptance Criterion

The proposed acceptance criterion is shown below.

Acceptance Criterion
Q = (b) (4) at 60 minutes

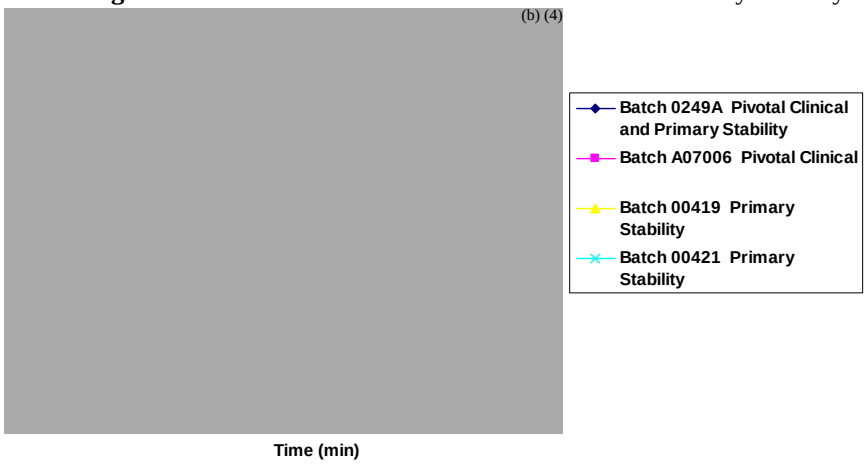
The Applicant did not have sufficient data to support the adequacy of the proposed dissolution data. Therefore, the following IR comments were conveyed in the 74 day letter.

FDA Comment
Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for your proposed product.

Applicant's Response
The dissolution profile data (raw data and mean values) for the following batches: 0249A (pivotal clinical and primary stability batch), A07006 (pivotal clinical batch), 004019 (primary stability batch), and 004021 (primary stability batch) in 2% SDS and water at 50 rpm are provided.

Dissolution profiles of the pivotal clinical and primary stability batches are displayed in Reviewer's Figure 1.

Reviewer's Figure 1. Dissolution Profiles of Pivotal Clinical and Primary Stability Batches



The mean dissolution data from stability batches are presented in Reviewer's Tables 1 and 2.

Reviewer's Table 1. Mean Dissolution Data from Stability Batches at 25° C/60% RH (HDPE Bottle)

(b) (4)

Reviewer's Table 2. Mean Dissolution Data from Stability Batches at 25° C/60% RH (Blister)

(b) (4)

Reviewer's Assessment:
Data from Reviewer's Figure 1 demonstrates that an acceptance criterion of Q (b) (4) ***minutes would have rejected Batch A07006, which is a pivotal clinical batch. Therefore, the proposed dissolution acceptance criterion is acceptable. The mean dissolution data from stability batches presented in Reviewer's Tables 1 and 2 further support that the proposed acceptance criterion is appropriate for this drug product.***

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/s/

KAREEN RIVIERE
12/11/2012

TAPASH K GHOSH
12/11/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW
(Individual Study Reviews)

NDA #	203505
Submission Date	April 29, 2012
Brand Name	Osphena®
Generic Name	Ospemifene
Strength and Formulation; Regimen	60 mg; immediate release oral tablet; orally once daily taken with food
Sponsor	Shionogi Inc.
Proposed Indication	Treatment of Vulvar and Vaginal Atrophy due to Menopause
Submission Type	Original NDA; standard review
Relevant IND	67216
Clinical Pharmacology Reviewer	LaiMing Lee, PhD
Clinical Pharmacology Team Leader	Myong-Jin Kim, PharmD
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products

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Individual Study Reviews

Study 1506003

Title: Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Orally Administered Repeated Doses of FC-1271a, Phase I

Objective: To investigate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of FC-1271a (ospemifene) during repeated oral administration. The PD variables were (1) endometrium thickness, endometrial biopsy, and cervical smear; (2) hormone (FSH and LH), lipid (HDL, LDL, and total cholesterol), and bone metabolism variables (S-PINP, S-PICP and S-OSTEO); and (3) climacteric symptoms. The sponsor's primary efficacy variables were endometrial thickness, serum LDL, serum LH, and serum FSH.

Methods: This was a double-blind, parallel group, repeat dose, Phase Ib study in healthy postmenopausal women with an average age of 61.0 years (SD 4.4 yrs). Oral doses of ospemifene were administered to 10 subjects (8 subjects with active drug and 2 subjects with placebo) for 12 weeks. The dose level was increased stepwise until hormonal or other PD effects or any clinically relevant adverse events were seen. The doses evaluated were 25, 50, 100, and 200 mg. Forty subjects enrolled; 38 subjects completed the study. Ospemifene was given in 25 and 50 mg gelatin capsules (size 1); the 100 and 200 mg groups received multiples of the 50 mg capsule. The study period was November 1995 to August 1996.

(b) (4) manufactured the capsules (Batches VL015L2, VL016L2, and XC005) for the study. Subjects were requested to take ospemifene capsule(s) with 250 mL of water each morning between 7 and 9 am. It appears that ospemifene was given under fasted condition as the study report does not state food was given with the study medication. Prior to the test day, subjects were requested to fast after an overnight starting at approximately at 10 pm.

Safety Monitoring: U-Prot, U-Gluc, U-Blood, U-pH, B-Eryt, B-Hb, B-Hcr, B-Leuc (neutrophils, lymphocytes, monocytes, eosinophils), B-Tromb, P-Na, P-K, S-Ca, S-Pi, S-Urea, S-Crea, S-Alb, total S-Prot, total S-Bil, S-Trigly, S-GT, S-ALAT, S-AFOS, and S-LDH were performed at screening and 4 days and 2, 4, 6, 8, 10, 12, and 16 weeks after ospemifene administration. Blood pressure and heart rate were measured using an automated sphygmomanometer at screening and 4 days and 12 weeks after ospemifene administration. Gynecological exams including ultrasound and measurement of endometrial thickness, cervical smear and endometrial biopsy were performed at baseline and at Week 12. Clinical visit took place after screening and at day 1 and 4, and 2, 4, 6, 8, 10, 12, and 16 weeks after ospemifene administration.

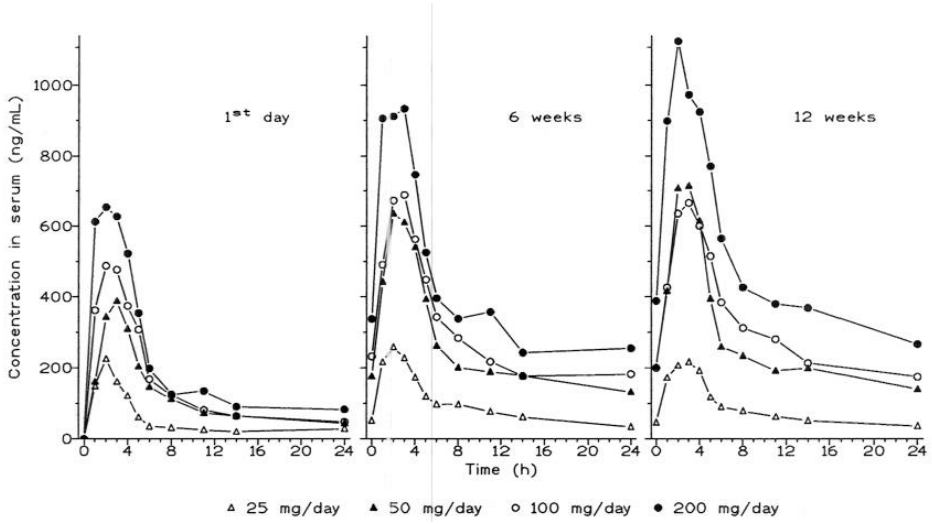
Pharmacokinetic Sampling: Blood samples were taken predose and 1, 2, 3, 4, 5, 6, 8, 11, 14, and 24 hrs postdose on Day 1 and at Week 6. Blood samples were taken predose and 1, 2, 3, 4, 5, 6, 8, 11, 14, 24, 28, 32, 36, and 48 hrs postdose at Week 12. The analysis of ospemifene concentrations were performed with HPLC with post-column photochemical activation and fluorescence detection.

Results and Reviewer's Comments: Cmax and $AUC_{0\text{-}24hr}$ increased in a less than dose-proportional manner in the range of 25 to 200 mg (for each dose group, N = 7 or 8). Median Tmax was about 2 to 3 hrs. Elimination half-life was approximately 25.3 hrs as determined in the 200 mg dose group at Week 12. Enterohepatic recycling may be responsible for the long elimination half-life. Linearity was evident with doses 25, 50, and 100 mg for Cmax and $AUC_{0\text{-}24hr}$. Dose proportionality was not established for single and multiple dosing. Accumulation for

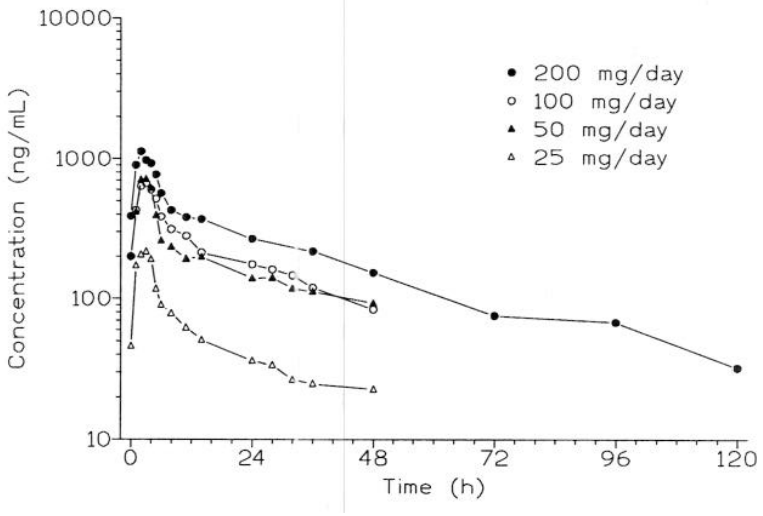
$AUC_{0\text{-inf}}$ was determined at Week 12 and ranged from 1.6 to 2.4 (average about 2.1) for doses 25 to 200 mg.

The PD effects of 60 mg ospemifene to-be-marketed tablets were not evaluated by the applicant. The applicant did not compare the exposure of the early development capsules to the to-be-marketed tablets in a relative bioavailability (BA) or bioequivalence (BE) study. To assess the applicability of these PD findings to the to-be-marketed dose and formulation, bioavailability of the 50 mg capsule was compared to the 60 mg tablet in a cross-study comparison. However, an empirical comparison can be made if we extrapolate the exposure from a 50 mg capsule to a 60 mg capsule. From this study, the exposure after administration of a single 50 mg capsule was 2727 ng.hr/mL for $AUC_{0\text{-inf}}$ and 476 ng/mL for Cmax. Adjusting for the dose increase, $AUC_{0\text{-inf}}$ and Cmax following a 60 mg capsule would be approximately 3272 ng.hr/mL and 571 ng/mL, respectively. Compared to a single dose to-be-marketed ospemifene 60 mg tablets (Penn 0249A) where $AUC_{0\text{-inf}}$ and Cmax are 3982 ng.hr/mL and 502 ng/mL (from bioequivalence study 15-51031), respectively, the exposure of the capsule and tablet formulations appear to be similar. Overall, the systemic exposure ($AUC_{0\text{-inf}}$ and Cmax) from a 50 mg capsule is similar to a 60 mg to-be-marketed tablet.

The following figure is the mean concentration-time profiles for ospemifene in serum after a single dose of ospemifene (25 mg – 200 mg) on Day 1, and multiple doses at Week 6 and Week 12 (N=7-8).



The following figure is the mean concentration-time profiles for ospemifene in serum after the last dose of ospemifene (25 mg – 200 mg) at Week 12 (N=8).



The following table is the mean (%CV) for the PK parameters of ospemifene in postmenopausal women after a single dose of ospemifene under a fasting condition.

Parameter	25 mg [1)]	50 mg [2)]	100 mg [1)]	200 mg [2)]
C_{max} (ng/mL)	244 (40.6)	476 (48.9)	619 (39.4)	823 (86.9)
t_{max} * (h)	2 (1-24)	2 (1-5)	2 (1-5)	2 (1-4)
AUC_{τ} (ng h/mL)	1176 (25.4)	2727 (32.3)	3446 (33.8)	4751 (70.7)

[1)] n=8, [2)] n=7, * median (range)

The following table is the mean (%CV) for the PK parameters of ospemifene in postmenopausal women at Week 6 after daily dosing of ospemifene.

Parameter	25 mg [1)]	50 mg [2)]	100 mg [1)]	200 mg [2)]
C_{max} (ng/mL)	295 (47.4)	750 (45.6)	721 (29.7)	1043 (36.6)
t_{max} * (h)	2 (1-6)	3 (2-4)	3 (2-3)	2 (1-3)
AUC_{τ} (ng h/mL)	2173 (35.2)	5941 (21.5)	6865 (22.5)	9523 (25.6)
$C_{av,ss}$ (ng/mL)	90.6 (35.3)	248 (21.4)	286 (22.5)	397 (25.6)
$C_{min,ss}$ (ng/mL)	33.6 (38.2)	113 (32.6)	154 (23.8)	210 (16.3)
PTF (%)	285 (39.0)	244 (36.3)	195 (18.6)	205 (20.5)
R_A (ratio)	1.84 (20.1)	2.28 (20.4)	2.12 (28.5)	2.33 (61.9)
$t_{½eff}$ (h)	19.2 (28.2)	28.8 (27.4)	25.9 (40.5)	30.9 (76.4)

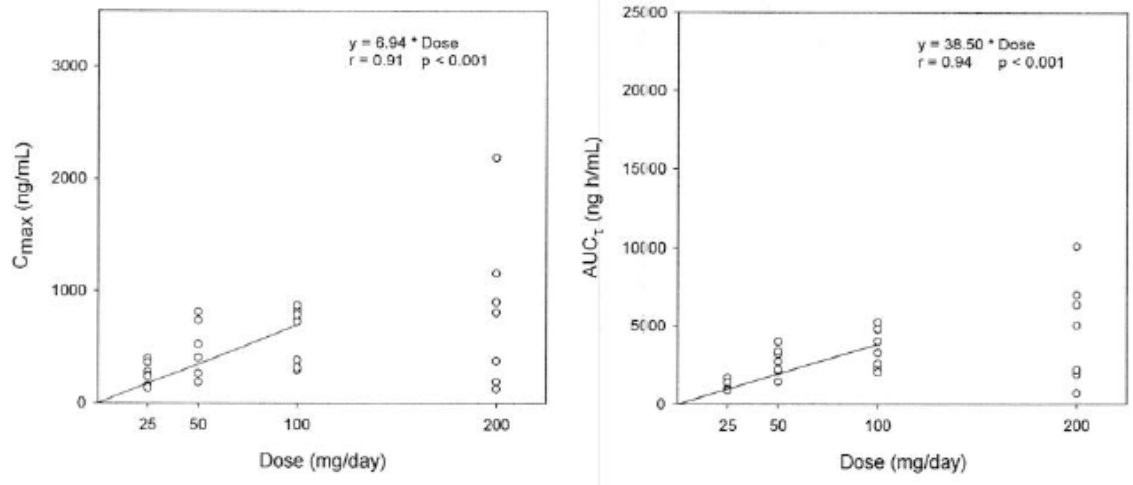
[1)] n = 8, [2)] n = 7, * median (range)

The following table is the mean (%CV) for the PK parameters of ospemifene in postmenopausal women at Week 12 after daily dosing of ospemifene.

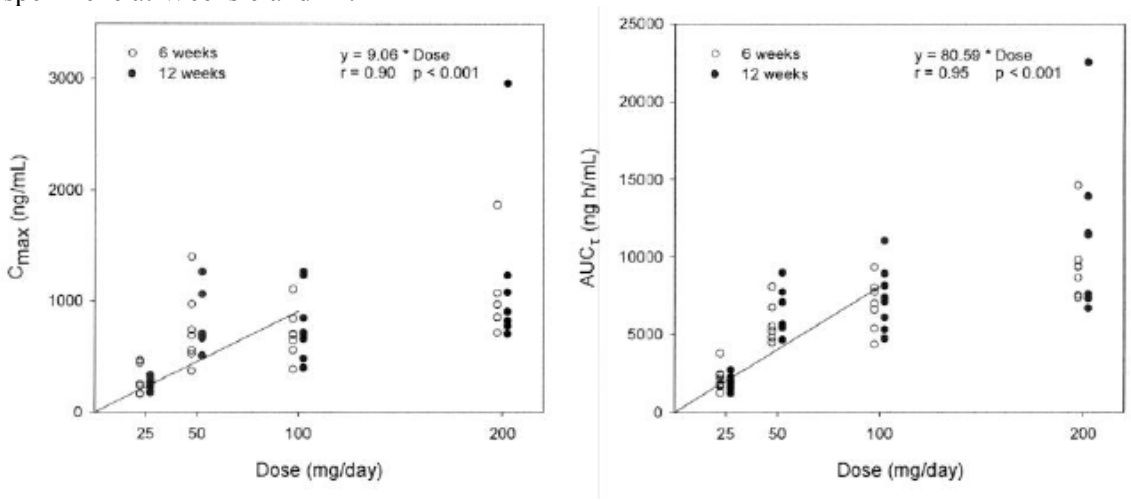
Parameter	25 mg [1)]	50 mg [2)]	100 mg [1)]	200 mg [2)]
C_{max} (ng/mL)	251 (22.2)	796 (33.2)	787 (40.1)	1211 (65.4)
t_{max} * (h)	3 (1-4)	3 (1-4)	2.5 (1-28)	3 (2-4)
AUC_τ (ng h/mL)	1943 (23.9)	6440 (23.8)	7340 (27.8)	11560 (47.9)
$C_{av,ss}$ (ng/mL)	81.0 (24.0)	268.4 (23.8)	306.0 (27.8)	481.9 (47.8)
$C_{min,ss}$ (ng/mL)	36.1 (41.4)	138.9 (34.0)	170.3 (18.4)	266.6 (51.0)
PTF (%)	274.1 (27.2)	244.1 (26.5)	197.4 (37.2)	190.0 (21.6)
R_A (ratio)	1.68 (17.6)	2.50 (29.4)	2.25 (28.4)	2.44 [4)] (40.8)
$t_{½eff}$ (h)	18.3 (29.0)	32.6 (38.3)	28.2 (39.1)	31.4 [4)] (54.3)
λ_z (h^{-1})	*0.0242* [3) †] *(52.3)*	*0.0260* [4) †] *(34.6)*	*0.0408* [3) †] *(41.5)*	0.0279 [4)] (14.9)
$t_{½}$ (h)	*37.0* [3) †] *(25.0)*	*30.2* [4) †] *(41.4)*	*19.9* [3) †] *(47.8)*	25.3 [4)] (13.8)
CL/F (L/h)	7.09 (21.1)	4.30 (36.9)	8.06 (31.2)	10.45 (45.3)
V_z/F (L)	*413* [3) †] *(45.1)*	*169* [4) †] *(20.1)*	*227* [3) †] *(24.1)*	402 [4)] (32.7)

[1)] n = 8, [2)] n =7, [3)] n = 4, [4)] n = 6, * median (range), † interpreted with caution, as the elimination half-life was determined over a period of less than two half-lives

The following figures are the individual Cmax and $AUC_{0\text{-}24hr}$ following a single dose of ospemifene.



The following figures are the individual Cmax and $AUC_{0\text{-}24hr}$ following daily dosing of ospemifene at Weeks 6 and 12.



In this Phase 1b study, the applicant evaluated the effectiveness of ospemifene in preventing bone loss due to estrogen deficiency. It was also believed that ospemifene may have beneficial effects on lipid metabolism and it may not cause undue stimulation of endometrium or breast. The following are the results:

The estrogenic effect of ospemifene on endometrial histology was absent in the 25 mg dose group. There appears to be a dose-dependent effect on the endometrium as ospemifene dose increased from 50 to 200 mg. As mentioned earlier, the exposure from a 50 mg capsule is likely to provide a lower exposure than a 60 mg to-be-marketed tablet. As such, the dose-dependent effect on the endometrium would include the proposed 60 mg dose.

The effect on LDL was noticeable in the all dose groups by Week 12. Postmenopausal women who received the 200 mg dose (n=7) showed a statistically significant difference after baseline adjustment compared to placebo (n=8) (p value = 0.0025). However, the effect of ospemifene on serum LDL at Week 16 (4 weeks after the last dose of ospemifene) was about the same as baseline for all dose groups.

For the hormonal variables evaluated, the applicant claims that ospemifene induces a dose-dependent effect on reducing serum LH and FSH with the greatest effect at 100 and 200 mg doses at Week 12. In general, this reviewer agrees with the applicant based upon review of the data but the effect of ospemifene on LH at Week 4 was greater in the 100 mg group, compared with the 200 mg group. As with LDL, the overall benefit of ospemifene on LH and FSH reversed back to baseline when subjects were no longer taking ospemifene.

The following table is a summary of the endometrial thickness (sponsor's table, section 4.3.2.1)

25 mg	At baseline	At week 12	50 mg	At baseline	At week 12	100mg	At baseline	At week 12
Subject	Class	Class	Subject	Class	Class	Subject	Class	Class
10	A	A	20	A	PCI	30	A	A
11	A	A	22	A	I	31	PCI	A
12	A	A	23	A	A	32	A	A
14	A	A	25	A	A	33	A	PCI
15	A	A	26	A	I	36	A	A
16	A	A	27	A	A	37	A	A
17	A	A	28	I	I	38	A	PCII
18	A	A	29	A	A	39	A	A

200 mg	At baseline	At week 12	Placebo	At baseline	At week 12
Subject	Class	Class	Subject	Class	Class
40	A	PCII	13	A	A
41	A	A	19	A	A
42	A	A	21	A	A
43	A	I	24	A	A
44	A	PCI	34	A	A
45	I	A	35	A	A
46	A	A	48	I	A
47	A	A	49	A	A

After completion of the Interim report, the endometrial samples were re-analysed using a same classification as in the Phase II study [Comparison of the SERMs FC-1271a and Raloxifene: Tolerability and Bone Turnover in Postmenopausal Women. Draft Study Report (1506001)]. The following classes were used: A=Atrophy (total atrophy or slight atrophy), I=Insufficient sample, PCI= Proliferative class I, PCII= Proliferative class II

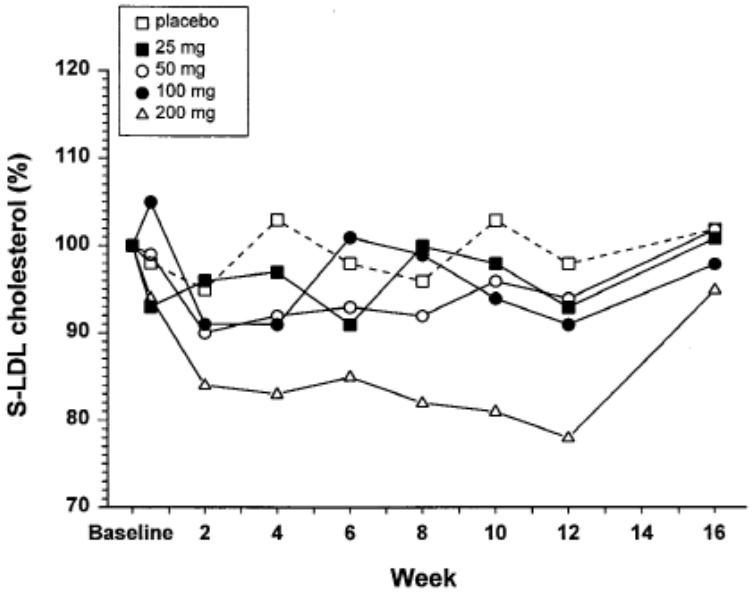
According to the applicant, ospemifene has a weak, dose-dependent, estrogenic effect on endometrial histology and is weaker than with estrogen replacement therapy. At the 25 mg dose, ospemifene showed no effect on endometrium – all subjects were atrophic at baseline and at Week 12. At the 50 mg dose, perceptible estrogen effect (PCI) was observed in one subject (Subject #20). At the 100 mg dose, one subject (Subject #33) showed PCI and one subject (Subject #38) showed moderate estrogen effect (PCII) at Week 12. The reverse was observed for Subject #31 who had PCI at baseline and atrophy at Week 12. At the 200 mg dose, one subject (Subject #40) had PCII and one subject (Subject #44) had PCI at Week 12. This reviewer concurs that ospemifene has an estrogenic effect on the endometrium.

The following table is a summary of the results from the cervical smear (sponsor's table, section 4.3.2.1)

Karyopyknosis Index at baseline and after 12 weeks of treatment (mean±SD).					
STUDY GROUP	Visit	N	Karyopyknosis Index		
			1	2	3
25 mg	Baseline	8	39.4±44.3	59.4±44.1	1.3±2.3
	12 weeks	8	7.5±21.2	75.5±22.6	17.0±13.4
50 mg	Baseline	7	82.1±36.5	16.9±34.7	1.0±1.9
	12 weeks	7	0.0±0.0	75.4±17.0	24.6±17.0
100 mg	Baseline	8	50.0±44.1	45.0±41.7	5.0±4.6
	12 weeks	8	0.6±1.8	80.0±22.2	19.4±22.6
200 mg	Baseline	8	70.0±38.5	29.4±37.2	0.6±1.8
	12 weeks	8	0.0±0.0	76.9±11.6	23.1±11.6
placebo	Baseline	8	38.8±37.7	59.1±36.2	2.1±2.5
	12 weeks	8	54.1±44.0	44.1±42.8	1.8±2.2

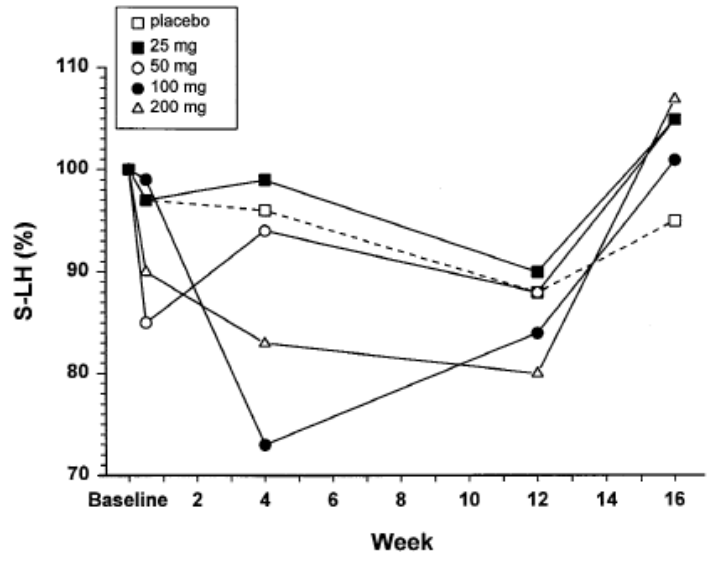
There was a shift in the Karyopyknosis indices that showed an estrogenic effect of ospemifene on vaginal epithelium.

The following figure summarizes the average change from baseline (%) for serum LDL cholesterol at four dose levels.



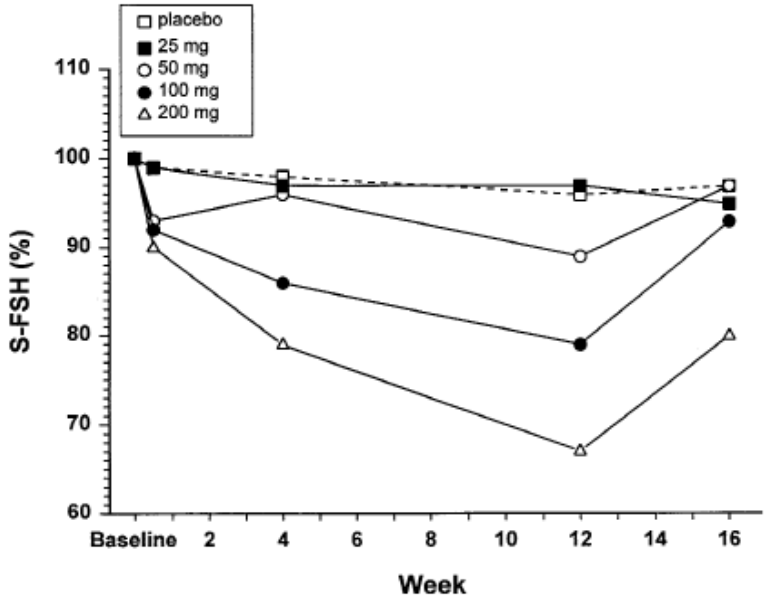
The sponsor states that there is statistically significant difference after baseline adjustment between the 200 mg dose group and placebo (p value = 0.0025) in serum LDL cholesterol. It appears that the effect on serum LDL was less significant with the lower dose groups. However, the effect of ospemifene on serum LDL at Week 16 (4 weeks after the last dose of ospemifene) was about the same as baseline for all dose groups.

The following figure summarizes the average change from baseline (%) for serum LH at four dose levels of ospemifene.



The maximum average reduction in serum LH was about 15 to 20% that achieved with the two highest doses 100 and 200 mg ospemifene at Week 12. After discontinuation of ospemifene treatment, LH values returned toward baseline values at Week 16 with some dose groups being higher than baseline values.

The following figure summarizes the average change from baseline (%) for serum FSH at four dose levels of ospemifene.



Ospemifene induced a dose-dependent decrease in serum FSH with doses 100 (N=8) and 200 mg (N=7) having the most significant effect compared to placebo (N=8) (p values 0.007 and 0.0001, respectively). The maximum average decrease in serum FSH was about 20 and 34% for 100 and 200 mg dose groups, respectively. Return to baseline values was observed in all dose groups at Week 16 when ospemifene treatment was discontinued.

The highest dose induced more adverse events compared to the other dose groups – 5 of 8 subjects in the 200 mg treatment group experienced hot flushes with one considered severe. The total numbers of adverse events were 9, 12, 11, and 26 for the 25, 50, 100, and 200 mg dose groups, respectively. The maximum tolerated dose was not reached in this study. Other adverse events included flu (most common), sweating, headache (possibly due to overnight fasting as stated by the sponsor), various body pains, insomnia, dizziness, depression, vaginitis, and leukorrhea.

Study 1506001

Title: Comparison of the SERMs FC-1271a and Raloxifene: Tolerability and Bone Turnover in Postmenopausal Women

Objectives: The objective of this study was to compare ospemifene (FC-1271a, former drug code) and raloxifene for safety, tolerability and effects on bone turnover during repeated oral administration in postmenopausal women using markers of bone turnover.

Methods: This was a randomized, parallel group, double-blind, active-controlled, repeated dose study. One hundred nineteen (118 started therapy) female subjects were randomized to one of the four following groups: 30 mg ospemifene (29 subjects), 60 mg ospemifene (30 subjects), 90 mg ospemifene (30 subjects), and 60 mg raloxifene (29 subjects). Subjects were postmenopausal with at least 12 months from the last spontaneous menstrual bleeding and age between 45 and 65 yrs with a BMI $\leq$ 30. Ospemifene 30 mg capsules manufactured by [redacted] (b) (4) were used in this study.

Primary Efficacy Variable: urinary NTX (U-NTX), serum PINP (S-PINP), and serum PICP (S-PICP) as markers of bone resorption (NTX) and formation (PINP and PICP).

Secondary Efficacy Variable: serum AFOS (S-AFOS), serum AFOS-BS (S-AFOS-BS), serum OSTEO (S-OSTEO), and urinary CTX (U-CTX) as markers of bone turnover, climacteric symptoms, endometrium thickness, endometrial histology, and lipid variables (S-TRIGLY, S-CHOL, S-LDL and S-HDL).

Ospemifene Concentration: Blood samples were collected after 12 weeks of treatment (+/- 3 days) after an overnight fast of at least 10 hrs for determination of ospemifene and raloxifene concentration.

Results: The applicant did not compare the exposure of [redacted] (b) (4) capsules to the to-be-marketed tablets in a relative BA or BE study. However, the exposures of these two formulations can be compared by conducting a cross study comparison using PK data from 2x30 mg [redacted] (b) (4) capsules from study 15-06004 and 1x60 mg to-be-marketed tablet from study 15-51031. From study 15-06004, the exposure after administration of a single 60 mg capsule [redacted] (b) (4) dose (given as 2x30 mg capsules) was 2130 ng.hr/mL for $AUC_{0\text{-}inf}$ and 277 ng/mL for Cmax. After a single dose to-be-marketed ospemifene 60 mg tablets, $AUC_{0\text{-}inf}$ and Cmax are 3982 ng.hr/mL and 502 ng/mL, respectively. The maximum concentration and the overall systemic exposure from the [redacted] (b) (4) capsules were approximately half of a 60 mg to-be-marketed tablet.

Ospemifene and 4-hydroxyospemifene concentration at week 12 (completion of study).
Note: in the following table, FC-1271a refers to ospemifene and TOR VI refers to the main metabolite 4-hydroxyospemifene; these codes were used early in development.

Table 8. Mean serum drug concentrations in study 1506001.

Study group	FC-1271a (ng/ml)		TOR VI (ng/ml)	
	Mean	SD	Mean	SD
30 mg FC-1271a (N = 25)*	208.7	163.0	53.3	26.2
60 mg FC-1271a (N = 25)	499.9	309.4	104.7	39.1
90 mg FC-1271a (N = 28)	648.9	548.7	131.0	68.9
Raloxifene (N = 28)	–	–	–	–

Raloxifene (N = 23)**	Raloxifene (ng/ml)	
	Mean	SD
	0.79	0.25

* Sample of subject 122 excluded from statistics (discontinued subject, no detectable drug concentration).
** Sample of subject 192 excluded from statistical calculations (result below quantitation limit).

Primary Efficacy Variables

Table 9. Primary efficacy variables, bone turnover, (mean±SD), study 1506001.

Variable	Sample	Study group			
		FC-1271a 30 mg	FC-1271a 60 mg	FC-1271a 90 mg	Raloxifene
U-NTX, normal range 5–65 nmol/ mmol Crea	Screening	65.7±37.8	75.0±43.6	69.2±59.3	56.3±29.4
	12 weeks	61.2±21.3	54.8±23.4	54.3±23.3	46.0±20.4
	14–16 weeks	59.2±21.6	59.3±21.2	66.5±31.3	49.5±20.7
S-PINP, normal range 19–84 µg/l	Screening	55.5±24.0	51.1±23.2	49.2±21.1	45.5±24.8
	12 weeks	57.1±18.7	48.9±17.0	44.4±14.8	50.1±21.9
	14–16 weeks	61.1±22.6	54.2±18.2	52.0±17.8	52.4±24.4
S-PICP, normal range 50–170 µg/l	Screening	150.0±38.9	125.0±35.6	136.1±45.2	129.2±35.7
	12 weeks	158.1±38.3	125.5±29.5	132.9±37.8	140.1±45.1
	14–16 weeks	162.3±43.1	136.8±31.6	144.2±45.3	147.6±49.8

NTX decreased in all study groups. PINP decreased with 60 and 90 mg ospemifene, while increased with 30 mg ospemifene and raloxifene. PICP decreased with 90 mg ospemifene, increased with 30 mg ospemifene and raloxifene but unchanged with 60 mg ospemifene.

Secondary Efficacy Variables: Bone Turnover Markers

Table 10. Secondary efficacy variables, bone turnover markers (mean±SD), study 1506001.

Variable	Sample	Study group			
		FC-1271a 30 mg	FC-1271a 60 mg	FC-1271a 90 mg	Raloxifene
S-AFOS, normal range 60–275 U/l	Screening	130.3±36.5	135.4±36.1	136.5±42.9	127.3±42.5
	12 weeks	142.0±37.6	137.5±37.6	135.6±45.4	134.6±43.8
	14–16 weeks	149.7±36.5	146.9±35.9	144.3±43.0	142.0±45.1
S-AFOS-BS, normal range 3.0–14 µg/l	Screening	10.0±3.5	9.9.±3.1	10.0±3.4	9.5±4.5
	12 weeks	11.0±3.6	10.2±2.9	10.1±3.2	10.0±4.7
	14–16 weeks	10.9±3.8	10.6±2.8	10.5±2.9	10.3±4.2
S-OSTEO, normal range 3.8–30 µg/l	Screening	31.2±12.2	30.0±11.1	30.2±13.1	26.9±11.4
	12 weeks	32.6±11.0	28.9±8.5	27.5±8.9	27.2±9.3
	14–16 weeks	35.5±10.1	32.1±8.7	33.8±11.0	30.8±9.8
U-CTX, normal range 40–680 µg/ mmol Crea	Screening	355.3±177.4	417.3±209.4	360.5±185.1	304.0±168.5
	12 weeks	359.1±175.1	360.7±186.5	325.5±171.1	299.4±171.1
	14–16 weeks	378.0±161.8	424.0±230.6	351.0±190.3	318.8±134.0

AFOS increased in the 30 and 60 mg ospemifene groups and raloxifene. 90 mg ospemifene did not result in an increase in AFOS. OSTEO decreased the most in the 90 mg ospemifene group but there was no difference between 90 mg ospemifene and raloxifene. CTX decreased in the 60 and 90 mg ospemifene groups and raloxifene but increased in the 30 mg ospemifene group.

Secondary Efficacy Variables: Endometrial Effects

Table 11. Secondary efficacy variables, endometrial effects, study 1506001.

Variable	Sample	Study group			
		FC-1271a 30 mg	FC-1271a 60 mg	FC-1271a 90 mg	Raloxifene
Endometrial thickness, mm	Screening	2.46±0.80	2.23±0.81	2.19±0.79	2.78±0.83
	12 weeks	2.79±1.15	2.66±1.01	2.71±1.43	2.69±1.64
Endometrial histology, proliferative*	Screening	0	1 (4.2%)	1 (3.6%)	4 (15.4%)
	12 weeks	0	2 (8.3%)	3 (11.5%)	2 (7.4%)

* other samples were atrophic or insufficient (reflecting atrophy), one screening sample in 60 mg FC-1271a group had signs of endometritis.

Endometrial thickness appeared to increase slightly from baseline with all three ospemifene groups, compared to raloxifene. However, at the end of 12 weeks, the endometrial thickness in subjects in all three ospemifene groups was similar to raloxifene group.

Secondary Efficacy Variables: Hormonal and Lipid Effects

Table 12. Secondary efficacy variables, hormonal and lipid effects (mean±SD), study 1506001.

Variable	Sample	Study group			
		FC-1271a 30 mg	FC-1271a 60 mg	FC-1271a 90 mg	Raloxifene
S-LH, post-menopausal 30–100 U/l	Screening	34.7±12.4	32.9±11.1	33.3±11.6	39.0±13.5
	12 weeks	32.6±12.5	30.3±10.8	28.0±11.1	37.0±13.9
	14–16 weeks	37.0±15.2	34.2±11.3	34.1±14.8	37.9±14.0
S-FSH, post-menopausal > 35 U/l	Screening	73.1±19.8	75.3±22.9	75.6±27.4	82.6±25.0
	12 weeks	68.9±20.9	64.6±21.2	59.9±20.8	72.7±23.5
	14–16 weeks	70.6±21.5	71.3±21.7	69.5±24.3	75.0±27.9
S-E_2, post-menopausal < 0.20 nmol/l	Screening	0.058±0.089	0.040±0.021	0.037±0.007	0.040±0.010
	12 weeks	0.036±0.008	0.045±0.028	0.042±0.014	0.049±0.050
	14–16 weeks	0.074±0.140	0.043±0.013	0.047±0.023	0.070±0.080
S-PTH, normal range 10–65 ng/l	Screening	31.7±10.0	31.6±11.7	31.5±9.3	30.3±13.3
	12 weeks	33.2±14.3	35.1±16.8	39.9±18.8	32.4±9.8
	14–16 weeks	33.3±13.4	34.3±13.3	37.1±19.4	36.5±12.7
S-SHBG, 20–125 nmol/l	Screening	68.6±29.7	66.1±27.8	68.6±24.1	69.5±35.8
	12 weeks	95.3±42.2	102.2±43.0	121.4±38.9	82.1±39.5
	14–16 weeks	72.2±31.0	74.4±33.7	78.8±30.7	72.8±35.0
S-IGF-1, 77–325 µg/l	Screening	142.7±47.3	137.4±34.8	139.2±60.8	144.3±55.9
	12 weeks	128.4±37.3	116.6±32.2	117.4±41.3	129.6±45.9
	14–16 weeks	151.1±55.1	146.0±37.0	151.3±58.1	138.9±42.4
S-LDL-Chol, < 3.5 mmol/l	Screening	4.02±0.75	3.71±0.86	3.68±1.13	3.74±0.95
	12 weeks	4.03±0.92	3.76±0.78	3.49±0.67	3.34±0.72
	14–16 weeks	4.29±0.90	4.18±0.93	3.94±0.94	3.64±0.71

FSH decreased significantly more with 90 mg than other dose groups or raloxifene. The 60 mg dose decreased FSH more than 30 mg group. SHBG increased with all ospemifene dose groups (dose response with 30, 60, and 90 mg), compared to raloxifene, with 90 mg dose having the greatest increase in SHBG.

Secondary Efficacy Variables: Climacteric Symptom – Hot Flushes

Table 13. Severity distribution of all hot flushes recorded in the individual study diaries during the study period, study 1506001 (all recorded hot flushes added up).

Severity of hot flushes	Study group			
	FC-1271a 30 mg	FC-1271a 60 mg	FC-1271a 90 mg	Raloxifene
Mild (% of all symptoms recorded)	37.21	59.57	37.58	27.92
Moderate (% of all symptoms recorded)	42.97	32.47	37.51	52.55
Severe (% of all symptoms recorded)	19.82	7.95	24.91	19.52

Overall, women in the 30 mg group had less adverse events, compared to the 60 and 90 mg groups. Women in the 60 mg group experienced less severe hot flushes compared to the other dose groups.

Study 15-50927

Title: Evaluation of the single dose and steady state pharmacokinetics of ospemifene in healthy postmenopausal women.

Objectives: To evaluate the single and multiple dose PK of ospemifene in healthy postmenopausal women.

Methods: This was an open-label, single group, single center study with one 60 mg ospemifene tablet administered once daily for 9 days in twelve healthy postmenopausal Finnish Caucasian females between 56 and 70 years of age. The mean (SD) age and weight were 62.3 (4.6) years and 66.8 (8.5) kg, respectively. A standard breakfast consisting of two slices of bread with ham, cheese, a few slices of cucumber and/or tomato and juice were given to subjects 30 min prior to drug administration. Ospemifene was administered with 200 mL tap water in an upright position under clinic supervision for Days 1 and 2; ospemifene was taken at home on Days 3-6; and ospemifene was administered under clinic supervision on Days 7 and 8. A single 60 mg dose was taken daily after a standard breakfast at approximately 8 am for a total of 8 days. Subjects fasted from 10 pm on Day 8 and reported to the clinic on the morning of Day 9 for extensive blood sampling for steady-state PK assessment.

Subjects were not allowed to take any prescription or non-prescription drugs, including herbal products and dietary supplements. Use of systemic estrogens and progestin replacement therapy, SERMs and strong CYP3A4 inducers and inhibitors was prohibited. Consumption of grapefruit or grapefruit products was forbidden starting at the screening visits (or at least 7 days before the first treatment) and continued until the last PK sampling.

The study drug for this study was (b) (4) Batch 85518 manufactured by (b) (4) . The (b) (4) tablets had a lower exposure - 20.7% lower in $AUC_{0\text{-}inf}$ and 34.4% lower in Cmax - compared to the to-be-marketed Penn tablets.

Pharmacokinetic Sampling: Blood samples were collected for determination of ospemifene, 4-hydroxyospemifene, and 4'-hydroxyospemifene in serum according to the following schedule: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, and 24 after the first ospemifene administration. For steady state and MD PK, blood samples were collected prior to Days 7 and 8, and prior to and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 32, 48, 72, 96, 120, and 168 hrs after the last dose of ospemifene on Day 9. Serum concentrations of ospemifene and metabolites were analyzed by LC-MS/MS at the bioanalytical lab of Hormos Medical.

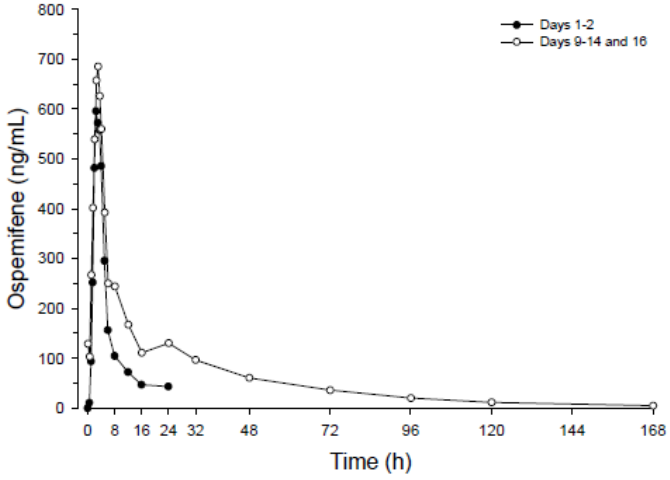
Results and Reviewer's Comments: Following single oral dose of 60 mg ospemifene, the median (range) Tmax was 2.8 (2-4) hrs for ospemifene and approximately 3.5 (2.5-4) hrs for 4-hydroxyospemifene and 4'-hydroxyospemifene. There was a small peak after Tmax and approximately 24 hrs after ospemifene administration for ospemifene, 4-hydroxyospemifene, and 4'-hydroxyospemifene, suggesting enterohepatic recirculation. The mean $t_{1/2}$ for ospemifene was 29.1 hrs after multiple doses of ospemifene 60 mg. Assessment of steady-state was based upon C_{24hr} values at Day 7-10. Mean (SD) C_{24hr} values were 121 (42), 123 (30), 129 (30), and 130 (41) ng/mL for ospemifene on Days 7, 8, 9, and 10, respectively. It appears that steady-state for ospemifene was reached by Day 7.

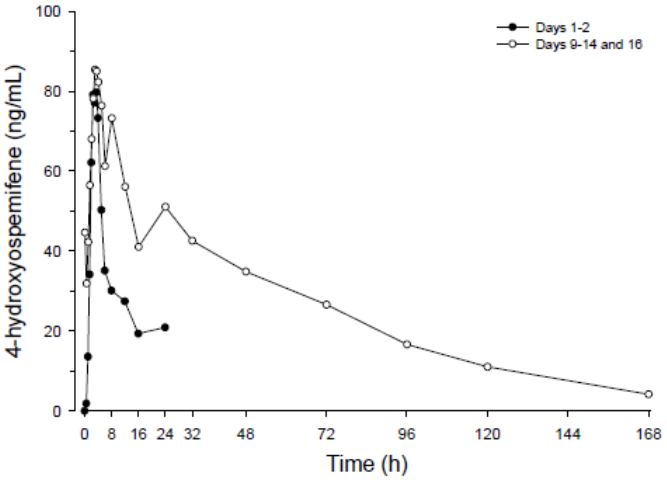
For ospemifene, mean accumulation ratio (90% CI) was 1.7 (1.5-1.9) for $AUC_{0\text{-}24hr}$ and 1.2 (1.1-1.4) for Cmax. For 4-hydroxyospemifene, mean accumulation ratio (90% CI) was 1.9 (1.6-2.3)

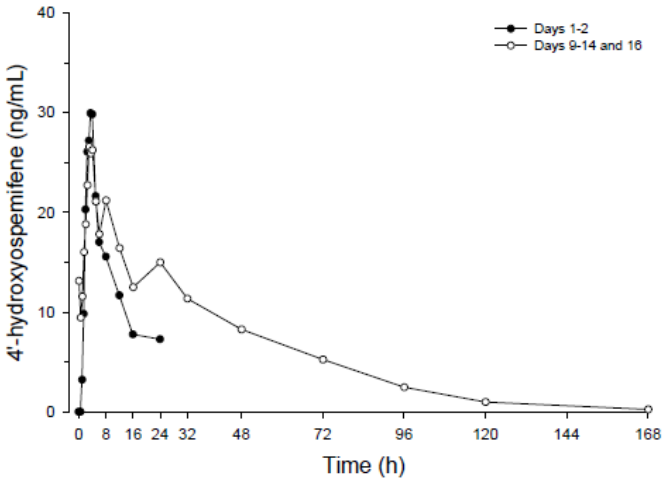
for $AUC_{0\text{-}24hr}$ and 1.2 (0.9-1.5) for Cmax. For 4'-hydroxyospemifene, mean accumulation ratio (90% CI) was 1.3 (1.1-1.6) for $AUC_{0\text{-}24hr}$ and 1.0 (0.8-1.2) for Cmax.

The applicant conducted a BE study (Study 15-50926) comparing (b) (4) Batch 85518 (tablets used in this study) to Penn Batch 0249A (to-be-marketed). It was concluded that the (b) (4) 85518 tablets and Penn 0249A tablets are not bioequivalent. The (b) (4) tablets had a lower exposure - 20.7% lower in $AUC_{0\text{-}inf}$ and 34.4% lower in Cmax - compared to the to-be-marketed Penn tablets.

The following figures are the mean concentration-time profiles for ospemifene and metabolites after single and multiple dose administration (figure 1, section 6.2.1).







The following are the mean (CV%) single and multiple dose (steady state) PK parameters of ospemifene, 4-hydroxyospemifene, and 4'-hydroxyospemifene (table 4, section 6.2.1).

Parameter		ospemifene	4-hydroxy-ospemifene	4'-hydroxy-ospemifene
C_{max} (ng/mL)	Single dose	654 (30.8)	85.7 (44.9)	31.0 (37.8)
	Steady state	785 (23.1)	102.3 (51.1)	30.1 (41.6)
t_{max} (hr) *	Single dose	2.8 (2-4)	3.3 (2.5-4)	3.5 (2.5-4)
	Steady state	3.0 (1-4)	3.8 (1.5-24)	3.5 (2-8)
AUC_τ (ng hr/mL)	Single dose	3236 (26.8)	732 (27.4)	297 (30.2)
	Steady state	5448 (19.7)	1435 (41.0)	400 (40.8)

* median (min-max); Source: Tables 9.2.3.1-9.2.3.3.

Note: AUCτ is the area under the concentration-time curve from 0-24 hrs

The following is the mean (CV%) multiple dose PK parameters of ospemifene, 4-hydroxyospemifene, and 4'-hydroxyospemifene (table 5, section 6.2.1).

Parameter	ospemifene	4-hydroxy-ospemifene	4'-hydroxy-ospemifene
AUC_∞ (ng hr/mL)	10433 (32.2)	4577 (39.3)	1091 (37.9)
$t_{½}$ (hr)	29.1 (14.5)	39.3 (21.6)	32.1 (27.3)
CL/F (L/hr)	6.30 (34.2)	NA	NA
V_z/F (L)	258 (27.2)	NA	NA
C_{min} (ng/mL)	93.7 (25.8)	27.8 (40.1)	8.9 (36.9)
C_{av} (ng/mL)	227 (19.7)	59.8 (41.0)	16.7 (40.8)
PTF (%)	311 (25.9)	121 (32.1)	125 (24.8)

Source: Tables 9.2.3.1-9.2.3.3.

The following is the accumulation index (R_A) (based on steady state/single dose) for AUC_{0-t} and Cmax for ospemifene, 4-hydroxyospemifene, and 4'-hydroxyospemifene (table 6, section 6.2.1).

Parameter	Statistics[1]	ospemifene	4-hydroxy-ospemifene	4'-hydroxy-ospemifene
R_A for AUC_τ	Ratio	1.702	1.903	1.317
	90% CI	1.551-1.869	1.556-2.328	1.101-1.575
	CV%	12.77	28.00	24.79
R_A for C_{max}	Ratio	1.222	1.190	0.964
	90% CI	1.087-1.374	0.925-1.532	0.784-1.186
	CV%	16.06	35.44	28.81

The following table is the metabolic ratios (metabolite/parent) for AUC0-t at steady state (table 7, section 6.2.1).

Parameter	Statistics[1]	4-hydroxyospemifene / ospemifene	4'-hydroxyospemifene / ospemifene
MR for AUC_τ	Ratio	0.252	0.070
	90% CI	0.218-0.292	0.062-0.081
	CV%	20.22	18.66

[1] Ratio of geometric means (metabolite / parent), 90% confidence interval (CI) for the ratio of geometric means and intra-subject coefficient of variation (CV%).
Source: Tables 9.2.6.1 and 9.2.6.2.

The following table is the summary of the C24 hr observed concentrations for ospemifene (table from section 9.2.2.1). This table is included to provide evidence for achieving steady-state.

Raw data summary statistics

Day	N	MEAN	SD	CV %	SEM	MIN	MEDIAN	MAX
Day 7	12	121.16	41.56	34.30	12.00	48.70	109.00	193.00
Day 8	12	123.35	29.72	24.10	8.58	63.00	128.50	168.00
Day 9	12	128.91	30.42	23.60	8.78	87.60	125.50	192.00
Day 10	12	130.26	40.92	31.42	11.81	64.10	117.00	199.00

Study 15-50206

Title: (^{3}H)-Ospemifene – A Study of the Absorption, Metabolism and Excretion Following a Single Oral Dose to Post-Menopausal Female Subjects

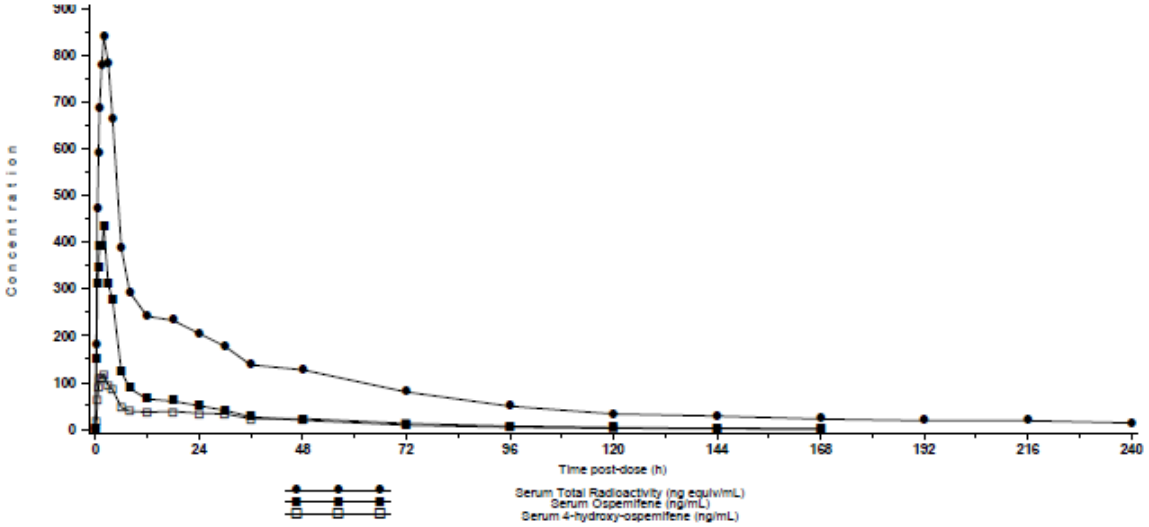
Objectives: The primary objectives of this study were (1) to evaluate the PK of total radioactivity, unchanged ospemifene, and the major metabolite 4-hydroxyospemifene following a single oral administration of (^{3}H)-ospemifene to healthy postmenopausal female subjects; (2) to obtain a mass balance by quantifying the urinary and fecal excretion of radioactivity; (3) to examine the pattern of metabolites in serum, urine, and feces; and (4) to determine ex vivo plasma protein binding of total radioactivity and ospemifene. The secondary objective was to determine the safety and tolerability of a single oral dose of ^{3}H-ospemifene in healthy postmenopausal female subjects.

Methods: This study was a single dose, open-label study in six healthy postmenopausal women with a mean age of 58 yrs (range: 54 to 61 yrs). Subjects were administered an oral solution (3.5 mL) of 60 mg containing 20.2 MBq (^{3}H)-ospemifene under fasted conditions. Subjects ingested 196.5 mL of tap water following ospemifene administration (total liquid volume of 200 mL was consumed at drug dosing).

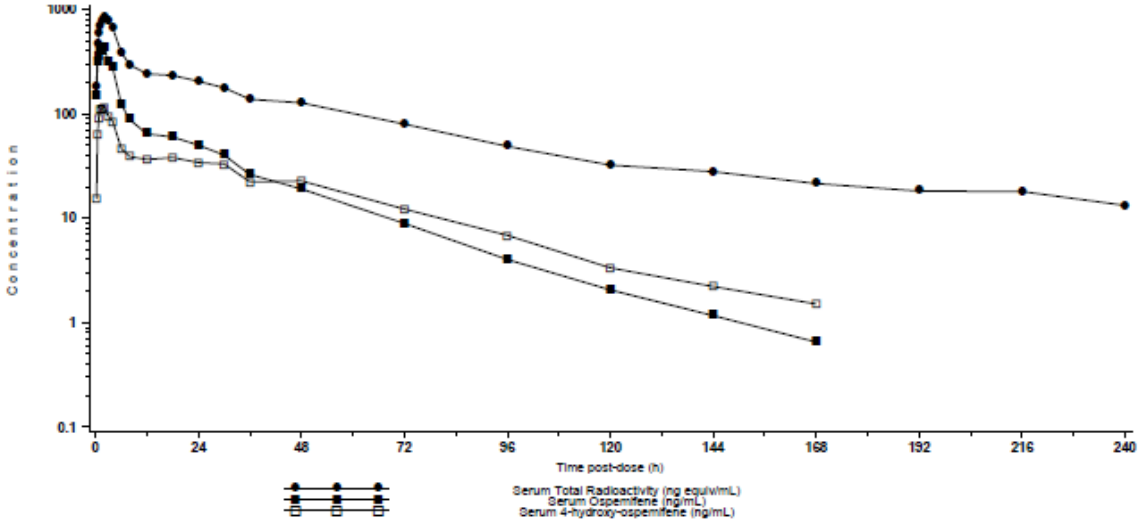
Blood, Urine, and Fecal Sampling: Blood samples were collected for total radioactivity, serum ospemifene and 4-hydroxyospemifene predose, 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240 hrs postdose. Urine samples were collected predose (-12 to 0 hrs), 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, 192 to 216, and 216 to 240 hrs postdose. Fecal samples were collected predose (-24 to 0), 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, 192 to 216, and 216 to 240 hrs postdose. Blood samples (30 mL) were collected at 2, 4, 6, 12, and 24 hrs postdose for protein binding and metabolite profiling.

Results and Reviewer's Comments: Ospemifene is primarily cleared by CYP metabolism with 18 to 25 radiolabelled metabolites recovered in serum, urine, and feces. The PK analysis of total radioactivity, serum ospemifene, and serum 4-hydroxyospemifene showed a mean Tmax to be 1.75, 1.5, and 1.75 (range: 0.75 to 3) hrs, respectively. The mean elimination half-life of ospemifene and 4-hydroxyospemifene was 24.5 and 29.0 hrs, respectively. Ospemifene and 4-hydroxyospemifene are highly protein bound with a mean value of approximately 98% (range: 93 to 98%). Fecal elimination accounted for approximately 75% of radioactivity elimination and 7% in urine over 240 hrs.

The following figure is the geometric mean of total radioactivity in serum (linear scale) (sponsor's figure A, section 11.1).



The following figure is the geometric mean of total radioactivity in serum (semi-log scale) (sponsor's figure B, section 11.1).

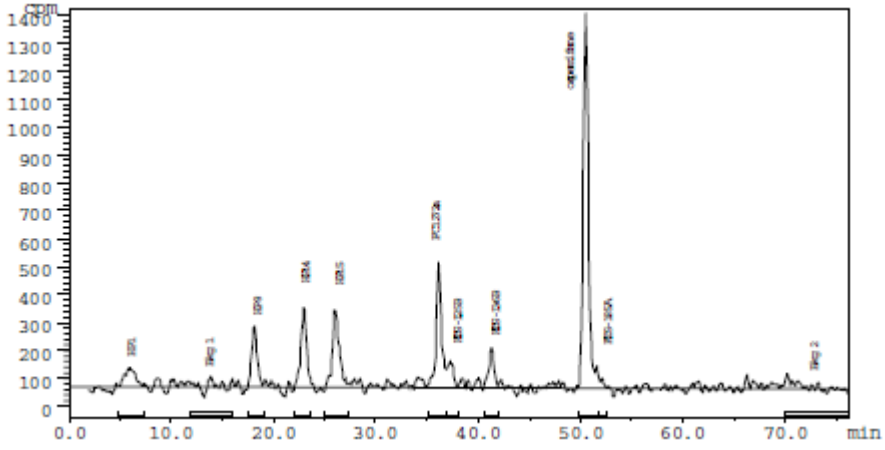


The following table is a summary of the PK parameters for total radioactivity, ospemifene, and 4-hydroxyospemifene in serum (sponsor's table F, section 11.1).

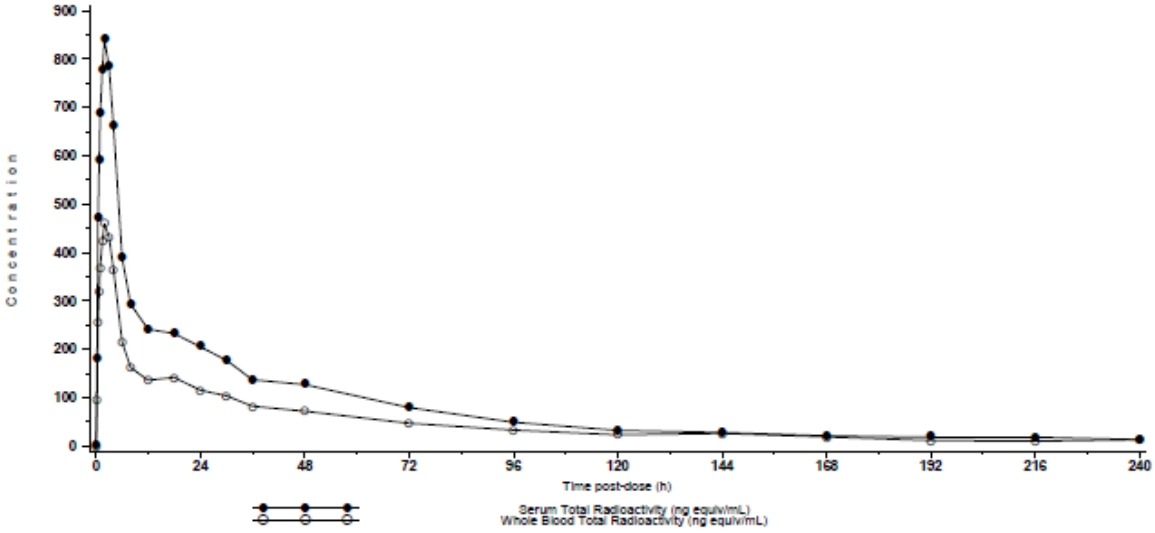
Parameter	Serum total radioactivity# (N=6)	Serum ospemifene (N=6)	Serum 4-hydroxy-ospemifene (N=6)
AUC(0-t_z) (ng.h/mL)	19837 (52.4)	4425 (63.3)	2789 (51.3)
AUC(0-∞) (ng.h/mL)	21829 (49.2)	4452 (63.3)	2870 (53.2)
C_{max} (ng/mL)	1014 (60.5)	612 (81.4)	139 (46.6)
t_{max}† (h)	1.75 (0.75-3.07)	1.50 (0.75-3.07)	1.75 (0.75-3.07)
$t_{½}$ (h)	98.5 (23.4)	24.5 (21.3)	29.0 (18.0)
MR1*	NC	NC	0.678 (0.204)
MR2*	NC	NC	0.246 (0.105)

Source: Section 14.2 (Tables 8 to 10)
Geometric mean (CV%) data are presented
Data presented as ng equivalent
† Median (min-max)
* Arithmetic mean (SD)
N = Number of subjects studied
MR1 = Metabolic ratio based on AUC(0-∞); MR2 = Metabolic ratio based on C_{max}
NC = Not calculated

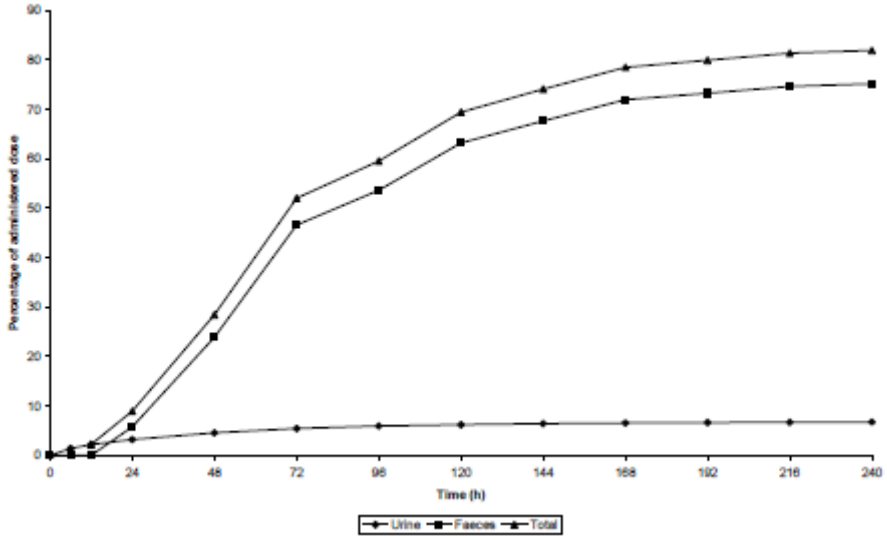
The following figure is the radioactivity of an extract of plasma at t=4 hrs postdose of a single oral administration of (^{3}H)-ospemifene in a healthy postmenopausal subject (sponsor's figure 7, page 463).



The following figure is the geometric mean of total radioactivity in serum and whole blood (linear scale) (sponsor's figure C, section 11.2).



The following figure is the arithmetic mean cumulative excretion of total radioactivity in urine and feces (sponsor's figure E, section 11.3).



The following table is the summary of total urinary and fecal excretion of total radioactivity (sponsor's table G, section 11.3).

Parameter	Urine (N=6)	Faeces (N=6)	Total excreta (N=6)
fe(0-240 h) (%)	6.77 (2.52)	75.19 (5.12)	81.96 (3.17)

Source: Section 16.1, Appendix 9
Arithmetic mean (SD) data are presented
N = Number of subjects studied

The following table is the summary of the plasma protein binding of total radioactivity, ospemifene, and 4-hydroxyospemifene (sponsor's table H, section 11.4).

Time post-dose (hours)	Total radioactivity (N=6)	Ospemifene (N=6)	4-hydroxy-ospemifene (N=6)
2	94.33 (6.11)	98.62 (0.35)	98.31* (0.78)
6	95.33 (1.04)	96.84* (1.66)	97.30* (1.27)
24	93.38 (2.73)	94.95* (2.13)	95.29 (1.82)

Source: Section 16.1, Appendix 9
Arithmetic mean (SD) data are presented
N = Number of subjects studied
* N=5

Study 15-50926

Title: Bioequivalence of Two 60 mg Ospemifene Tablet Batches – A Pharmacokinetic Study in Healthy Postmenopausal Females

Objectives: The objective of the study was to determine the bioequivalence of ospemifene 60 mg tablets manufactured at two different manufacturing sites (Penn Pharmaceuticals, UK and (b) (4) in healthy postmenopausal female subjects.

Methods: This study was a randomized, multi-center, open-label, two-sequence, four-period, replicate crossover study with single tablets from two different batches administered twice to each subject. Each treatment period was separated by a minimum of 7 days. On each dosing period, subjects swallowed one 60 mg tablet of ospemifene with approximately 240 mL of water at room temperature. All dose administrations were given under fasted condition. Thirty postmenopausal women with a mean age of 61.3 (range 48 to 79 yrs) were enrolled and completed the study.

Treatment A (Reference Product): Penn Pharmaceuticals; ospemifene 60 mg tablets, batch 0249A
Treatment B (Test Product): (b) (4); ospemifene 60 mg tablets, batch 85518

Pharmacokinetic Sampling: Blood samples for the determination of serum ospemifene concentrations were collected pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 32, 48, 56, 72 and 96 hrs post-dose.

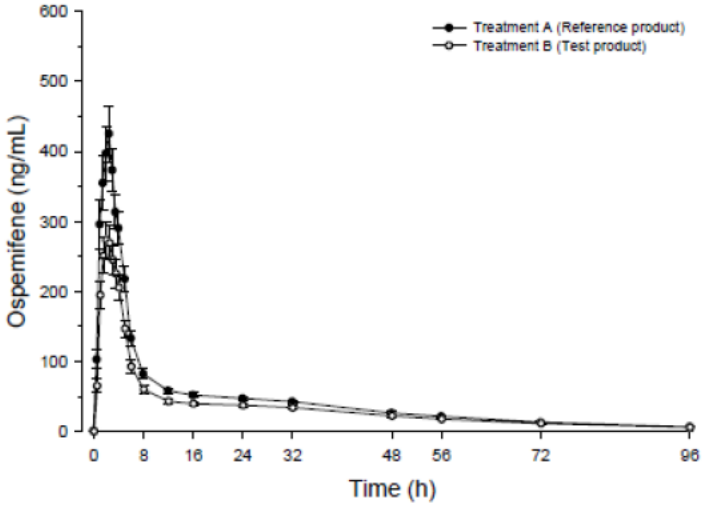
Results and Reviewer's Comments: The drug product formulation used in phase I PK Study 15-50927 in healthy postmenopausal women was manufactured by (b) (4) Batch 85518). (b) (4) Batch 85518 is not the to-be-market formulation, nor was it used in the Phase 3 clinical trials. The to-be-marketed formulation (Penn Batch 0249A) will be manufactured by Penn Pharmaceuticals. This BE study (Study 15-50926) under fasted conditions was conducted by the applicant to compare the exposure of two different tablet batches and to determine the bioequivalence of ospemifene 60 mg tablets manufactured at different manufacturing sites (b) (4) Batch 85518 and Penn Batch 0249A).

The sponsor did not demonstrate bioequivalence between Penn Batch 0249A (to-be-marketed) and (b) (4) Batch 85518 tablets. The test/reference ratios fell outside of the standard bioequivalence acceptance range of 0.80-1.25 and the confidence intervals (CIs) fell outside of 80-125%.

The exposure, as assessed by $AUC_{0\text{-}96hr}$, $AUC_{0\text{-}inf}$, and Cmax, for the (b) (4) tablets was lower by 24.7%, 20.7%, and 34.4%, respectively, compared to the Penn tablets. Mean (%CV) $AUC_{0\text{-}inf}$ was 4735 (48.0) and 3755 (48.0) for the Penn and (b) (4) tablets, respectively. Mean (%CV) Cmax was 527 (52.2) and 346 (54.0) for the Penn and (b) (4) tablets, respectively. The geometric mean ratio (90% CI) for $AUC_{0\text{-}96hr}$, $AUC_{0\text{-}inf}$, and Cmax was 0.74 (0.69-0.79), 0.79 (0.73-0.85), and 0.63 (0.56-0.72), respectively.

The number of subjects who experienced hot flushes was greater in subjects who received the Penn tablets with the higher ospemifene exposure. Other adverse events that were more prevalent in the Penn treatment group include anxiety, dizziness, lethargy, rhinorrhea, somnolence, and vomiting.

The following is the mean (SD) serum concentration-time profiles for Penn 5 (Treatment A) and (b) (4) Batch 85518 (Treatment B) formulations (sponsor's figure 1, section 6.2.1).



The following table is the mean (%CV) PK parameters for ospemifene in healthy postmenopausal women given Penn Batch 0249A (Tablet A) and (b) (4) Batch 85518 (Tablet B) (sponsor's table 6, section 6.2.1).

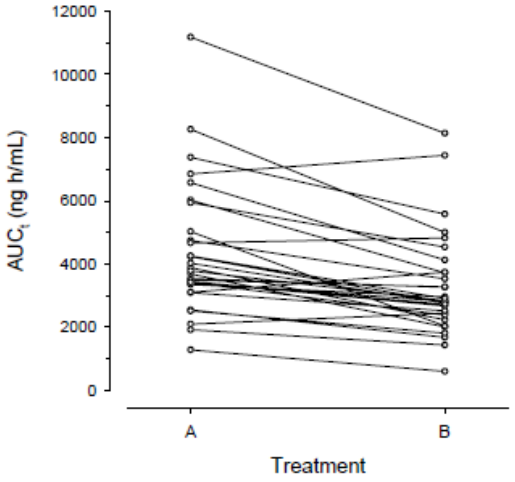
Parameter (mean over the two periods)	Tablet A (N=30)		Tablet B (N=30)	
	Mean	CV%	Mean	CV%
AUC_t (ng hr/mL)	4373	47.5	3295	49.7
AUC_∞ (ng hr/mL)[1]	4735	48.0	3755	48.0
C_{max} (ng/mL)	527	52.2	346	54.0
$t_{½}$ (hr)[1]	26.4	36.9	28.4	39.9
t_{max} (hr) *	2.3	1-4.3	2.5	1-4.5

The following table is the statistical analysis of bioequivalence for the primary PK parameters for Penn Batch 0249A and (b) (4) 85518 tablets (sponsor's table 7, section 6.2.2).

Parameter	Statistics[1]	Ospemifene
AUC_t	Ratio	0.740
	90% CI	0.690-0.794
	CV%	23.26
AUC_∞	Ratio	0.786
	90% CI	0.730-0.846
	CV%	23.57
C_{max}	Ratio	0.633
	90% CI	0.558-0.719
	CV%	43.42

[1] Ratio of geometric means (test / reference), 90% confidence interval (CI) for the ratio of geometric means and intra-subject coefficient of variation (CV%).

The following figure shows the individual mean AUC0-t values for ospemifene for Penn Batch 0249A (Tablet A) and [redacted] (b) (4) Batch 85518 (Tablet B) (sponsor's figure 3, section 6.2.2).



The following table is a summary of treatment-related adverse events following treatment of ospemifene 60 mg tablet given as Penn Batch 0249A (Tablet A) or [redacted] (b) (4) Batch 85518 (Tablet B) (sponsor's table 8, section 6.3.2).

Treatment-related Adverse Event	Treatment period with tablet A		Treatment period with tablet B	
	Events	Subjects	Events	Subjects
Headache	3[1]	3	4[2]	3
Hot flush	2	2	-	-
Nausea	1[3]	1	1	1
Abdominal pain upper	-	-	1	1
Anxiety	1	1	-	-
Diarrhoea	-	-	1	1
Dizziness	1	1	-	-
Fatigue	-	-	1	1
Lethargy	1	1	-	-
Oral herpes	-	-	1	1
Rhinorrhoea	1	1	-	-
Somnolence	1	1	-	-
Vomiting	1	1	-	-

[1] 2 moderate headaches and 1 mild headache
[2] 1 moderate headache and 3 mild headaches
[3] Moderate AE; All other AEs were mild
A total of 13 subjects had treatment-related AEs: 8 for tablet A, 3 for tablet B and 2 for both tablets

Study 15-51031

Title: A Phase 1 Bioequivalence Study of Two 60-mg Ospemifene Tablet Batches – A Pharmacokinetic Study in Healthy, Fasted Postmenopausal Females

Objectives: The primary objective of this study was to determine the bioequivalence of ospemifene 60 mg tablets manufactured at different manufacturing sites in healthy, fasted postmenopausal female subjects. The second objective of the study was to assess safety and tolerability of ospemifene in healthy postmenopausal women.

Methods: This was a randomized, open-label, two-sequence, two-period, crossover study in postmenopausal women. Ospemifene 60 mg tablets manufactured at two different sites (Penn Pharmaceuticals, United Kingdom (Penn; Lot No. 0249A) and (b) (4) ; Lot No. A07006)) were evaluated to determine bioequivalence. Penn tablets (Lot No. 0249A) are the proposed to-be-marketed products and they were used in the pivotal Phase 3 study 15-50310. (b) (4) tablets (Lot No. A07006) were used in the pivotal Phase 3 study 15-50821.

Ninety-four subjects were equally and randomly assigned to one of two treatment groups and were given a single 60 mg dose of ospemifene manufactured by Penn or (b) (4) There was a minimum of 14 days for washout between treatment periods. A single 60 mg ospemifene tablet was taken with 240 mL of room temperature water after an overnight fast of at least 10 hrs. Subjects fasted for 4 hrs after each drug administration and water consumption was restricted from 1 hr prior to dosing until 2 hrs postdosing.

Ninety-two subjects completed the study. Of the ninety-four subjects enrolled, 90 subjects were White, 3 subjects were Black or African-American, and 1 subject was American Indian/Alaskan Native. The mean (SD) age and weight was 60.2 (7.5) yrs and 72.9 (11.3) kg, respectively.

One subject from the Penn group was withdrawn from the study during Period 1 due to a positive test result for benzodiazepines at the Check-in visit. One subject from the (b) (4) group withdrew from the study during Period 1 due to adverse events (asthenia, circadian rhythm sleep disorder, and somnolence) that occurred 3.5 to 12.5 hrs postdose. Due to one major protocol violation (positive results on hepatitis B, hepatitis C, or HIV antibodies) by Subject 414, the final PK analysis was based on 91 subjects. Statistical analysis was conducted prior to the study; it was determined that a sample size of 89 subjects was expected to provide 80% power at $\alpha = 0.05$.

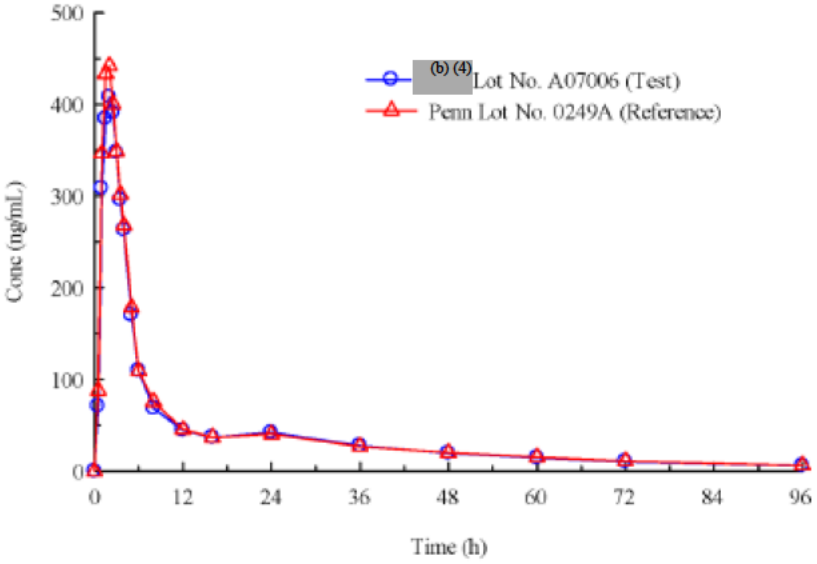
Pharmacokinetics Sampling: Blood samples for determination of serum ospemifene concentrations were collected immediately prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, 72, and 96 hrs postdose. Subjects were confined to the research center during the first 24 hrs after drug administration during the intensive blood sampling period and returned on an outpatient basis on Days 2-5 for additional blood draws and procedures. Ospemifene concentrations were determined by LC-MS/MS.

Results: Pharmacokinetic results show that Penn and (b) (4) ospemifene formulations are comparable. The mean (SD) Cmax for Penn formulation and (b) (4) formulation was 533 (304) and 501 (305) ng/mL, respectively. The mean (SD) AUC_{0-t} for Penn formulation and (b) (4) formulation was 3781 (1795) and 3661 (1728) ng.hr/mL, respectively. The mean (SD) AUC_{0-inf} for Penn formulation and (b) (4) formulation was 4165 (1970) and 3982 (1913) ng.hr/mL, respectively. Median Tmax for Penn formulation and (b) (4) formulation was 2.0 hrs. Mean $T_{1/2}$ for Penn formulation and (b) (4) formulation was 26.4 hrs.

The geometric mean ratio (90% CI) for Cmax, AUC_{0-t}, and AUC_{0-inf} was 0.95 (0.83, 1.09), 0.96 (0.88, 1.05) and 0.97 (0.88, 1.05), respectively. Although the Cmax for Penn tablets is higher than for (b) (4) tablets, the associated 90% CIs for Cmax, AUC_{0-t}, and AUC_{0-inf} all fell within 80% to 125%. This reviewer concurs with the sponsor's conclusion that the Penn tablets (Lot No. 0249A) and (b) (4) tablets (Lot No. A07006) are bioequivalent.

Adverse events after administration of ospemifene include headache, nausea, back pain, hot flush, and diarrhea. In general, the incidences were similar in both treatment groups; however, there is a noticeable difference in the incidences of headache (23 in the Penn group; 13 in the (b) (4) group) and more subjects effected (18 in the Penn group; 12 in the (b) (4) group) between the two treatment groups. It is unclear if the higher Cmax from the Penn group resulted in a higher incidence of headaches, compared to the (b) (4) group.

Mean Serum Ospemifene Concentrations After Administration of (b) (4) and Penn Pharmaceuticals 60-mg Tablets to Healthy Postmenopausal Women Under Fasted Conditions (Linear Scale)



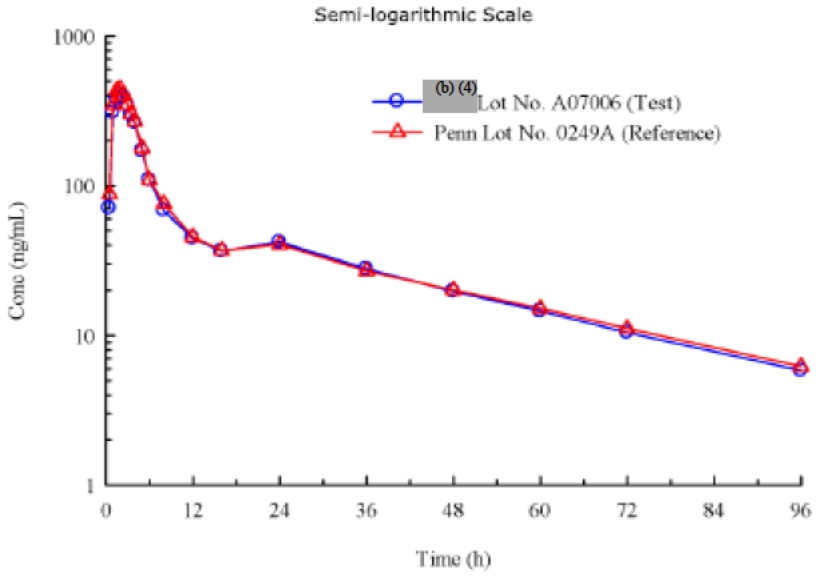


Table 11-1. Summary of Ospemifene Pharmacokinetic Parameters (Pharmacokinetic Analysis Population)

Parameter	N	(b) (4) *Test*	N	Penn Pharma *Reference*
C_{max} (ng/mL)				
Mean (SD)	91	501 (305)	91	533 (304)
T_{max} (hr)				
Median (min, max)	91	2.00 (1.00-24.0)	91	2.00 (1.00-8.00)
AUC_{0-t} (ng*hr/mL)				
Mean (SD)	91	3661 (1728)	91	3781 (1795)
AUC_{0-inf} (ng*hr/mL)				
Mean (SD)	83	3982 (1913)	83	4165 (1970)
$T_{1/2}$ (hr)				
Mean (SD)	83	26.4 (7.48)	83	26.4 (6.72)
λ_z (1/hr)				
Mean (SD)	83	0.0282 (0.0070)	83	0.0279 (0.0069)

Source: Table 15.2.5.1

Table 11-2. Statistical Analysis of Ospemifene Pharmacokinetic Data: [redacted] Relative to Penn Pharma Formulations (Pharmacokinetic Analysis Population)

Parameter (unit)	Geometric Means: [redacted] *Test* [Lot #A07006]	Geometric Means: Penn Pharma *Reference* [Lot#0249A]	Geometric Mean Ratio (90% CI)
C_{max} (ng/mL)	433.22	454.02	95.42 (83.21, 109.42)
AUC_{0-t} (ng*hr/mL)	3338.19	3463.19	96.39 (88.77, 104.67)
AUC_{0-inf} (ng*hr/mL)	3579.77	3709.14	96.51 (88.39, 105.38)

NOTE: Geometric mean ratio based on analysis of natural log-transformed data.
Source: Table 15.2.7.1

Study 15-50208

Title: Food Effect on Ospemifene Bioavailability in Healthy Male Subjects After Single Oral Administration

Objectives: The objective of this study was to assess the bioavailability and PK parameters of ospemifene and its main metabolite 4-hydroxyospemifene following a single oral dose of 60 mg ospemifene tablet after a high fat, high caloric meal.

Methods: This was an open-label, randomized, two-treatment (fed vs fasted), two-period, two-sequence, single dose, crossover study. Twenty-four healthy Caucasian male subjects with a mean (SD) age of 23.8 (2.9) yrs and a mean (SD) weight of 76.6 (7.6) kg were enrolled and completed the study. A single dose of 60 mg ospemifene tablet ((b) (4) batch no. 0107-852) was given in the morning at approximately 8 am with 240 mL of tap water after an overnight fast of at least 10 hrs or after a standard high fat breakfast after an overnight fast of at least 10 hrs and consumed over 30 min before ospemifene administration. A standard lunch was served 4 hrs, a standard dinner was served 8 hrs, and a snack was served 11 hrs after ospemifene administration. Subjects were not permitted to drink water for one hr before and after drug administration. A washout period between the two treatment groups was at least two weeks.

The sponsor referred to the FDA draft guidance for the conduct of a food effect study. The composition of the high fat/high caloric meal (approximately 860 kcal) consisted of two eggs fried in butter, two strips of bacon, two slices of toast with butter, 60 g hash brown potatoes, and 240 mL of whole milk. The test meal provided approximately 150, 170, and 540 kcal from protein, carbohydrate, and fat, respectively.

Based on statistical analysis, the sponsor determined that 12 subjects per treatment period was needed to provide 80% power at $\alpha = 0.05$.

Ospemifene 60 mg tablets used in this study were manufactured by (b) (4) in Sweden (b) (4) Batch 0107-852). The components and composition of the (b) (4) tablets are the same as the TBM Penn tablets; the difference between the two tablets is in the manufacturing site.

Pharmacokinetics Sampling: Blood samples for determination of ospemifene and 4-hydroxyospemifene serum concentrations were collected immediately prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 28, 32, 48, 56, and 72 hrs postdose. Subjects were confined to the research center during the first 12 hrs after drug administration during the intensive blood sampling period and returned on an outpatient basis additional blood draws and procedures. Ospemifene and 4-hydroxyospemifene concentrations were determined by HPLC with fluorescence detection.

Results: Following administration of a high fat breakfast, the geometric mean ratio of ospemifene fed/fasted for Cmax was 3.6 and for AUC_{0-72} was 2.8. Median Tmax of ospemifene was the same at 2.0 hrs under both fed and fasted conditions. Median $T_{1/2}$ of ospemifene remained the same at 13.7 hrs under both fed and fasted conditions. Due to the influence of food (fat and caloric content) on the bioavailability of ospemifene, the sponsor recommends the concomitant administration of ospemifene with food in order to standardize ospemifene bioavailability. The two Phase 3 studies were conducted with food (no specific type indicated) and the proposed dosing instruction states ospemifene be taken with food.

The sponsor conducted the food effect studies (15-50208 and 15-50208-02) in healthy young men using tablets manufactured by [redacted] (b) (4). To assess the effect of food on the to-be-marketed ospemifene tablets in postmenopausal women, a cross-study comparison using PK data gathered from 5 bioequivalence studies (1 under fed condition and 4 under fasted condition) was conducted by this reviewer. The PK parameters for ospemifene were similar across the four studies under fasted conditions. The results show that $AUC_{0\text{-}inf}$ and Cmax increased 1.7-fold and 2.3-fold, respectively, when ospemifene was administered with a high fat/high calorie meal. Tmax was similar at about 2 hrs. Half-life was similar and ranged from 24 to 29 hrs.

Treatment Condition & Study Number*							
Mean PK Parameters for ospemifene	**Fed**** 1 15-51029 N=28	**Fasted** 1 15-50926 N=30	**Fasted** 2 15-51028 N=43	**Fasted** 3 15-51030 N-29	**Fasted** 4 15-51031 N=91	Fasted 1-4 Average	**Fed[1]/ Fasted[1-4]**
Cmax (ng/mL)	1197.78	527	493	527	533	520	**2.30**
Tmax (hrs)	2.5	2.3	2.5	2.0	2.0	2.2	1.14
$AUC_{0\text{-}t}$ (ng hr/mL)	7188.45	4373	3729	3921	3781	3951	1.82
$AUC_{0\text{-}inf}$ (ng hr/mL)	7521.19	4735	4077	4320	4165	4324.25	**1.74**
$T_{1/2}$ (hrs)	24.2	26.4	26.9	29.0	26.4	27.2	0.89
λz (1/hr)	0.0302	not analyzed	0.0273	0.0287	0.0279	0.0280	1.08

*ospemifene 60 mg tablets manufactured by Penn Pharmaceuticals (to-be-marketed formulation)
** high fat/high calorie meal

The effect of food on ospemifene exposure was also similar for another formulation. In a cross study comparison of ospemifene tablet manufactured by [redacted] (b) (4) (Lot 8541), $AUC_{0\text{-}inf}$ and Cmax increased 2.1 -fold and 2.4-fold, respectively, when ospemifene was administered with a high fat/high calorie meal. Tmax was the same at 2.5 hrs. Half-life was similar at about 27 hrs.

Mean PK Parameters for ospemifene	**Fed**** 15-51029 N=28	**Fasted** 15-50928 N=43	**Fed/ Fasted**
Cmax (ng/mL)	955.14	391	**2.44**
Tmax (hrs)	2.5	2.5	1.00
$AUC_{0\text{-}t}$ (ng hr/mL)	6684.54	3051	2.19
$AUC_{0\text{-}inf}$ (ng.hr/mL)	7119.36	3454	**2.06**
$T_{1/2}$ (hrs)	26.5	28.2	0.94
λz (1/hr)	0.0280	0.0266	1.05

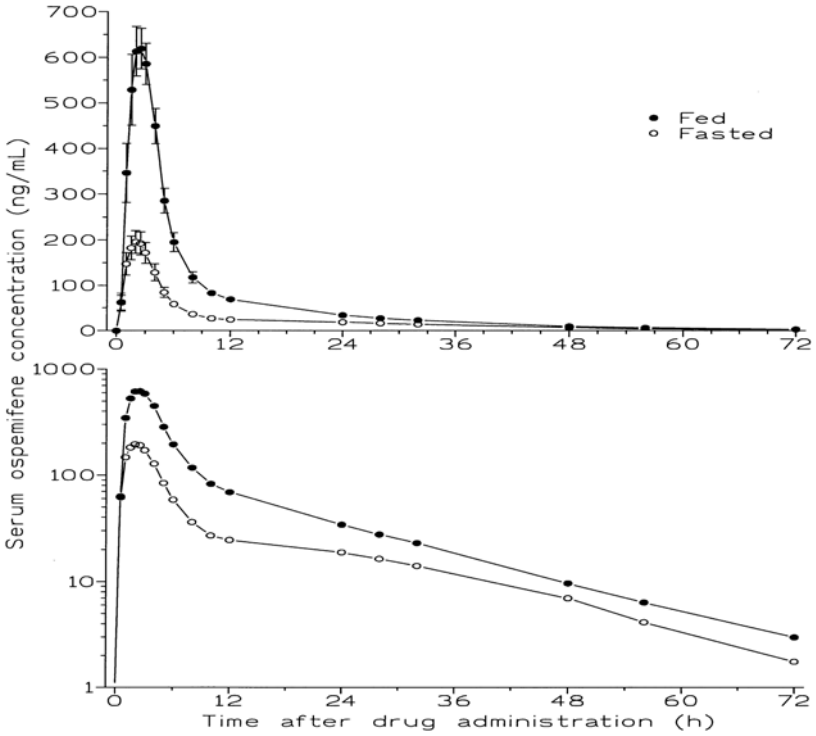
*ospemifene 60 mg tablets manufactured by [redacted] (b) (4) (development formulation)
** high fat/high calorie meal

Overall, the effect of food on ospemifene exposure ($AUC_{0\text{-}inf}$ and Cmax) increased 2-3-fold and there is no significant difference between low fat and high fat meals.

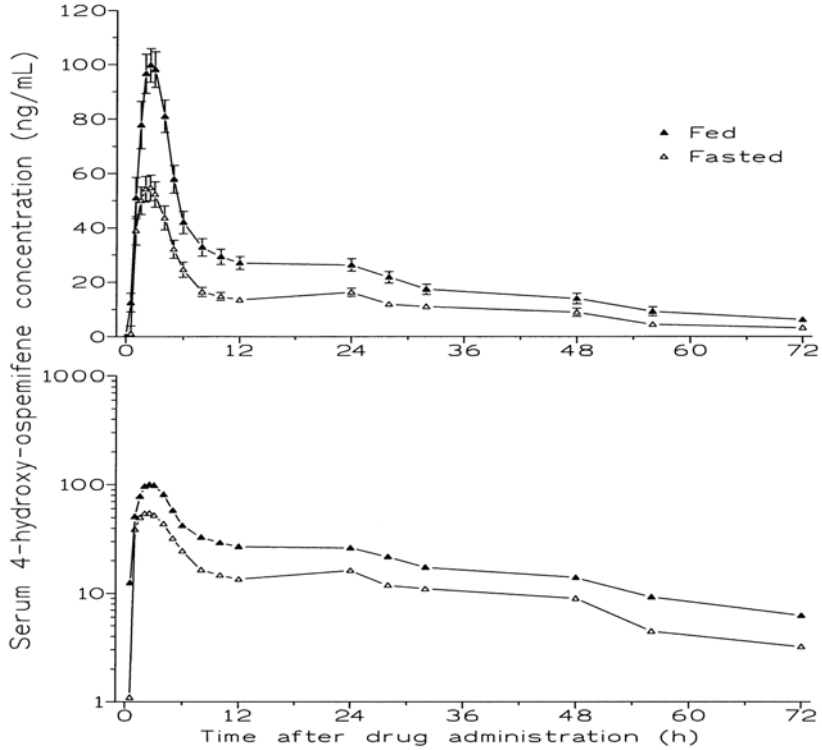
The two Phase 3 studies and long-term endometrial safety study were conducted with food (no specific type indicated) and the proposed dosing instruction states ospemifene be taken with food. This reviewer concurs with the dosing instruction recommendation to take ospemifene with food.

The sponsor reports two incidences of upper respiratory tract infection and 1 incidence of dizziness from 3 of 24 subjects. Two of the events occurred during the washout period and one after high fat food intake.

The following figures are the mean (SE) ospemifene concentration-time profiles (linear and semi-log scales) after administration of 60 mg ospemifene following an overnight fast and a high fat breakfast (n=24).



The following figures are the mean (SE) 4-hydroxyospemifene concentration-time profiles (linear and semilog scales) after administration of 60 mg ospemifene following an overnight fast and a high fat breakfast (n=24).



The following table is the mean (%CV) PK parameters of ospemifene and 4-hydroxyospemifene after administration of 60 mg ospemifene following an overnight fast and a high fat breakfast (n=24).

Parameter	ospemifene		4-hydroxy-ospemifene	
	Fasted	Fed	Fasted	Fed
C_{max} (ng/mL)	**243** (52.5)	**800** (26.1)	**64** (37.2)	**118** (23.7)
t_{max}† (h)	2.0 (1-5)	2.0 (1-4)	2.3 (1-5)	2.3 (1.5-4)
λ_z (h^{-1})	0.0566 [1)] (36.3)	0.0528 (18.9)	0.0288 [2)] (29.6)	0.0331 [3)] (35.2)
$t_{½}$ (h)	13.7 [1)] (33.4)	13.7 (21.8)	26.4 [2)] (35.1)	23.4 [3)] (34.7)
AUC_{0-72} (ng h/mL)	**1591** (46.6)	**4182** (30.3)	**881** (44.6)	**1541** (40.3)
$AUC_{0-\infty}$ (ng h/mL)	1703 [1)] (45.9)	4247 (30.5)	1043 [2)] (43.6)	1802 [3)] (41.2)
$\%AUC_{ex}$†	2.8 [1)] (0.8-9.7)	1.2 (0.4-4.0)	14.4 [2)] (11.3-33.9)	12.5 [3)] (4.3-22.4)

† Median (min-max); [1)] n=22 , [2)] n=9, [3)] n=14

Study 15-50208-02

Title: Food Effect on Ospemifene Bioavailability in Healthy Male Subjects After Single Oral Administration – Extension of the Study With the Effect of a Normal Light Breakfast

Objectives: The objective of this study was to assess the effects of a normal light breakfast on the bioavailability and PK parameters of ospemifene and its main metabolite 4-hydroxyospemifene following a single oral dose of 60 mg ospemifene tablet. This was an extension of the main food effect study 15-50208 in which healthy male subjects were given a high fat/high caloric meal.

Methods: This was an extension of the high fat food effect study 15-50208. This was an open-label, one-period, one-treatment, non-randomized study in twelve healthy Caucasian male subjects. The twelve subjects were recruited from the 24 healthy Caucasian male subjects who were enrolled in the original food effect study. The mean (SD) age of 23.8 (3.7) yrs and a mean (SD) weight of 76.3 (7.3) kg were enrolled and completed the study. A single dose of 60 mg ospemifene tablet was given in the morning at approximately 8 am with 240 mL of tap water after an overnight fast of at least 10 hrs or after a standard low fat breakfast after an overnight fast of at least 10 hrs and consumed over 30 min before ospemifene administration. A standard lunch was served 4 hrs, a standard dinner was served 8 hrs, and a snack was served 11 hrs after ospemifene administration. Subjects were not permitted to drink water for one hr before and after drug administration.

The composition of the light breakfast (approximately 300 kcal) consisted of two slices of toast with margarine, 6 slices of cucumber, 240 mL of non-fat milk, and 100 mL of orange juice. The test meal provided approximately 50, 180, and 70 kcal from protein, carbohydrate, and fat, respectively.

Ospemifene 60 mg tablets used in this study were manufactured by [redacted] (b) (4) in Sweden ([redacted] (b) (4) Batch 0107-852).

Pharmacokinetics Sampling: Blood samples for determination of ospemifene and 4-hydroxyospemifene serum concentrations were collected immediately prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 28, 32, 48, 56, and 72 hrs postdose. Subjects were confined to the research center during the first 12 hrs after drug administration during the intensive blood sampling period and returned on an outpatient basis additional blood draws and procedures. Ospemifene and 4-hydroxyospemifene concentrations were determined by HPLC with fluorescence detection.

Results: The following PK results comparing fasted vs. low-fat and fasted vs. high fat are based on 12 subjects who participated in the original food effect study (high fat/high calorie) and elected to enroll in this extension study. The subjects in this study received one treatment (light breakfast). For comparison purposes, the PK profiles and parameters from the same 12 subjects are shown in the figures and tables. The comparison of low-fat data from this extension study to fasted and high-fat data obtained from the earlier food effect study is not ideal because variability associated with two different studies can confound the findings and conclusions. However, all the PK parameters under fasted condition in both food effect studies are similar suggesting little variability between the two studies. For example, mean (%CV) for AUC_{0-72} was 1591 (46.6) and 1693 (53.0) ng.hr/mL in the high-fat (N=24) and low-fat (N=12) food effect study, respectively.

Following administration of a low-fat breakfast, the geometric mean ratio of ospemifene fed/fasted for Cmax was 2.3 and for AUC_{0-72} was 1.9. Based upon the results of same 12

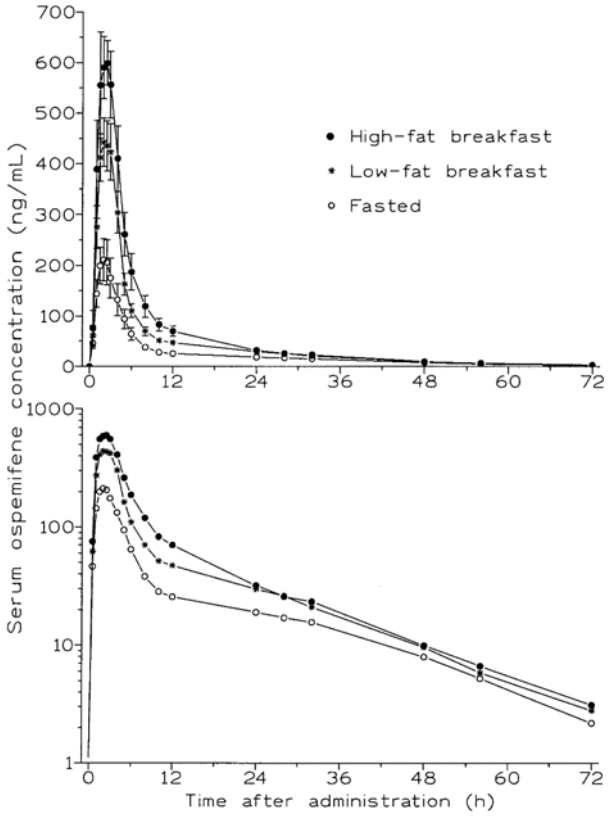
subjects, the geometric mean ratio of ospemifene fed/fasted for Cmax was 3.5 and for AUC_{0-72} was 2.6 following a high-fat meal. Median Tmax of ospemifene was the same at 2.0 hrs under both fed and fasted conditions. Median $T_{1/2}$ of ospemifene remained relatively unchanged at 13.7 hrs under low-fat, 13.6 hrs under high-fat, and 14.6 hrs under fasted conditions. The effect of high-fat on ospemifene exposure presented above in the extension study with 12 subjects were similar to those in 24 subjects from the earlier study where the high-fat meal resulted in a 3.6-fold increase in Cmax and 2.8-fold increase in AUC_{0-72}.

Based on the two food effect studies, AUC_{0-72} of ospemifene increased approximately 1.9- and 2.4- fold in the presence of low-fat and high-fat food, respectively. Cmax of ospemifene increased approximately 2.3- and 3.5- fold in the presence of low-fat and high-fat food, respectively. Food had a substantial effect on ospemifene bioavailability; however, low-fat and high-fat meals had nearly the same effect on ospemifene bioavailability.

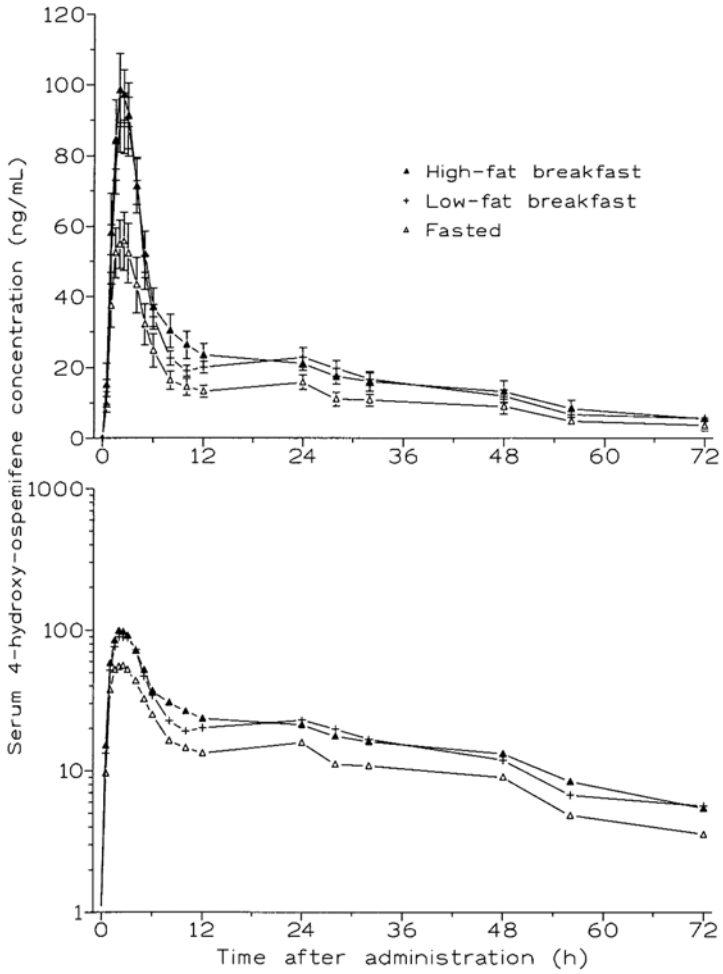
Ospemifene is highly lipophilic (likely a BCS Class II) and will therefore be impacted by food and fat content. The results from the food effect studies show the significant impact of low-fat/low calorie and high-fat/high calorie food on ospemifene bioavailability. The two Phase 3 studies were conducted with food (no specific type indicated) and the proposed dosing instruction states ospemifene be taken with food. This reviewer concurs with the dosing instruction recommendation to take food with ospemifene.

The applicant reports one incidence of adverse events – toothache.

The following figures are the mean (SE) ospemifene concentration-time profiles (linear and semilog scales) after administration of 60 mg ospemifene following an overnight fast, a low fat breakfast, and a high fat breakfast (N=12).



The following figures are the mean (SE) 4-hydroxyospemifene concentration-time profiles (linear and semilog scales) after administration of 60 mg ospemifene following an overnight fast, a low fat breakfast, and a high fat breakfast (N=12).



The following table is the mean (%CV) PK parameters of ospemifene and 4-hydroxyospemifene after administration of 60 mg ospemifene following an overnight fast, a low fat breakfast, and a high fat breakfast (N=12).

Parameter	ospemifene			4-hydroxy-ospemifene		
	Fasted	Low-fat	High-fat	Fasted	Low-fat	High-fat
C_{max} (ng/mL)	**256** (52.3)	**527** (26.7)	**803** (25.3)	**65.4** (43.2)	**99.2** (26.7)	**116** (26.8)
t_{max}† (h)	2.0 (1-5)	2.0 (1-3)	2.0 (1-3)	2.3 (1.5-5.0)	2.5 (1.0-3.2)	2.0 (1.5-3.1)
λ_z (h^{-1})	0.0505 [1] (26.3)	0.0527 (20.5)	0.0521 (13.9)	0.0280 [2] (31.4)	0.0290 [3] (26.2)	0.0273 [4] (28.5)
$t_{½}$ (h)	14.6 [1] (26.3)	13.7 (22.6)	13.6 (15.3)	27.3 [2] (37.3)	23.3 [3] (22.3)	26.5 [4] (28.9)
AUC_{0-72} (ng h/mL)	**1693** (53.0)	**3045** (35.2)	**4103** (35.1)	**879** (52.1)	**1311** (31.6)	**1391** (41.8)
$AUC_{0-\infty}$ (ng h/mL)	1854 [1] (50.3)	3106 (35.3)	4170 (35.6)	1013 [2] (48.9)	1491 [3] (25.6)	1637 [4] (28.0)
$\%AUC_{ex}$†	3.4 [1] (1.5-7.9)	1.8 (0.5-6.5)	1.3 (0.5-4.0)	16.9 [2] (13.6-33.9)	10.9 [3] (7.0-21.2)	13.9 [4] (7.5-22.4)

† Median (min-max); [1] n=11 , [2] n=6, [3] n=9, [4] n=8

Table 5. Statistics for the primary bioavailability parameters of ospemifene.

Comparison	Ratio estimate (%) and 90% CI	
	AUC_{0-72}	C_{max}
Low-fat vs. fasted	194 (159-237)	228 (181-287)
Low-fat vs. high-fat	74 (61-90)	66 (52-83)
High-fat vs. fasted	263 (215-321)	347 (275-438)

Study 15-50820

Title: Effect of impaired hepatic function on the pharmacokinetics of ospemifene in postmenopausal women

Study objectives:

- The primary objective of this study was to evaluate the PK of ospemifene, when the drug was given as a single 60-mg dose, in subjects with impaired hepatic function and in healthy control subjects.
- The secondary objectives were to evaluate the PK of the metabolites 4-hydroxyospemifene and 4'-hydroxyospemifene, and to assess the safety. Safety assessments included physical examination, safety laboratory tests, and adverse events.

Study design

- Open-label, single-dose, parallel-group, one-period, two-center PK study.
- Subjects
  : Planned (total 24) - 8 postmenopausal women with mild (Child-Pugh score 5-6) and 8 with moderate (Child-Pugh score 7-9) hepatic impairment, and 8 healthy demographically matched control subjects.
- Test product, dose, mode of administration
  : A 60-mg single dose of ospemifene (film-coated tablet manufactured by (b) (4) A07006) was administered orally after a standard breakfast
  : Proposed label recommends the prescribing dosage and administration method as 60 mg tablet orally once daily with food.
- Pharmacokinetic evaluation
  : Blood samples - before and 1, 2, 3, 4, 6, 8, 12, 24, 32, 48, 72, 96, 120, 168, 216, and 264 hours after drug administration
  : Serum concentrations of ospemifene and the metabolites 4-hydroxyospemifene and 4'-hydroxyospemifene were analyzed using a LC-MS/MS method.
  : Pharmacokinetic parameters of ospemifene and metabolites
  : Serum protein unbound fraction (fu) of ospemifene at 3 and 24 hours
- Safety evaluation
  : Adverse events
  : Safety laboratory at screening and the post-study visit
  : Vital signs at screening, before and 4 and 24 hours, and at the post-study visit

Study Population

- Subject disposition
  : Seven subjects with mild hepatic impairment and 7 healthy subjects were treated. Only two subjects with moderate hepatic impairment were enrolled. All subjects completed this study.
  : This study did not recruit the number of subjects initially planned (8 per group).
- Subjects' demography and characteristics
  : There was no significant difference of demographic data between healthy and mild hepatic impairment groups. Two subjects in moderate impairment group had lower weight (54.2 and 61.7 kg) and BMI (21.2 and 22.7 kg/m^2) than those of subjects in other groups (Range of mild group: 63.0-86.9 kg and 24.6-31.2 kg/m^2, healthy group: 65.0-84.2kg and 24.1-30.4 kg/m^2).
  : Two subjects in mild group were Black or other race and others were Caucasian.

Results

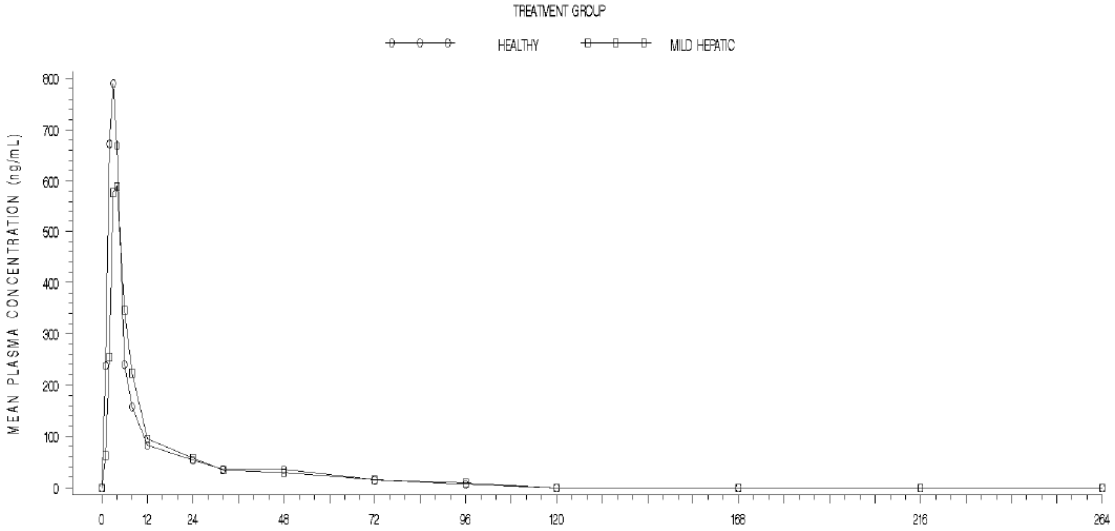
1. Pharmacokinetics

1) Ospemifene

Mild hepatic impairment

There were no PK parameters to show significant difference between the healthy and mild hepatic impairment groups, except for C_{max} (p=0.0478). Arithmetic mean of AUC_{0-t} and AUC_{0-inf} were similar between two groups, but C_{max} was lower and $T_{1/2}$ was longer in subjects with mild hepatic impairment than those in subjects with normal hepatic function. The point estimates of the LS geometric means ratio of C_{max}, AUC_{0-t}, AUC_{0-inf} and $T_{1/2}$ were 79.5%, 93.9%, 90.9% and 132.3%, respectively.

The serum concentration vs. time profile for ospemifene after a single oral administration of 60 mg ospemifene after standard breakfast.



*The figure above was taken from the sponsor's report which indicates plasma concentration in the y-axis. The report states blood samples were taken for determination of ospemifene in serum. Other clinical pharmacology studies report serum, not plasma, concentrations of ospemifene.

Summary and statistical analysis of ospemifene PK parameters.

PK parameters	Healthy subjects N = 7	Mild hepatic impairment N = 7	Moderate hepatic impairment N = 2	p-value[a]	Mild hepatic impairment vs Healthy subjects PE (CI)
C_{max} (ng/mL)	970 (10.8)	787 (23.8)	399 / 1113	0.0487	0.79 (0.66-0.96)
t_{max} (h)	3.0 (2.0-4.0)	3.0 (2.0-6.0)	2.0 / 3.0	0.4079	
$T_{1/2}$ (h)	28.2 (42.9)[b]	37.8 (47.7)[c]	69.9 / 37.8	0.2458	1.32 (0.88-2.00)
AUC_{0-t} (μg h/mL)	6.38 (27.2)	6.09 (28.8)	10.1 / 15.9	0.7122	0.94 (0.70-1.26)
AUC_{0-inf} (μg h/mL)	7.19 (23.0)[b]	6.65 (27.7)[c]	10.4 / 16.1	0.597	0.91 (0.66-1.25)
CL/F (L/h)	9.77 (27.4)	10.5 (36.5)	5.75 / 3.74	0.7463	1.06 (0.79-1.42)
V_z/F (L)	338 (27.9)[b]	519 (49.2)[c]	580 / 204	0.124	1.46 (0.97-2.19)
f_u_3h (%)	1.65 (27.1)	1.21 (70.0)	1.07 / 2.02	0.3468	0.79 (0.52-1.21)
f_u_24h (%)	BLQ (NC)	BLQ (NC)	1.42 / 1.80	NA	

Values are arithmetic means (CV%), t_{max} is median (range)

[a] p-value: probability of no mild hepatic impairment effect (ANOVA and Wilcoxon-Mann-Whitney test for t_{max}), [b] N = 5, and, [c] N = 6

BLQ = below the limit of quantification (< 2 ng/mL); NA = not applicable; NC = not calculated

PE and CI: point estimate and 90% CI of the least-squares geometric means ratio (ANOVA)

There was no significant effect of mild hepatic impairment on the protein binding of ospemifene at 3 hours after dosing.

Moderate hepatic impairment

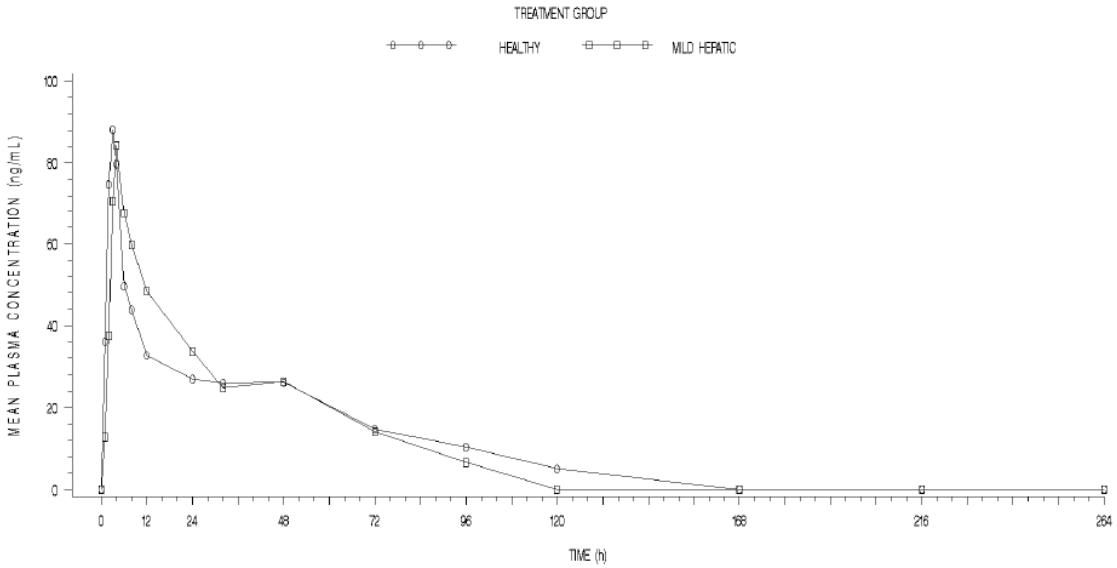
Two subjects with moderate hepatic impairment showed higher $T_{1/2}$, AUC_{0-t}, and AUC_{0-inf} values relatively than subjects in healthy and mild hepatic impairment groups. The C_{max} of 2 subjects appeared as both extreme values (399 and 1113 ng/mL, respectively) compared to the mean of other groups. Due to the low number of moderate hepatic subjects recruited for this specific study, no comments about how moderate hepatic impairment affects ospemifene exposure are discussed here. There is a second hepatic impairment study.

2) 4-Hydroxyospemifene

Mild hepatic impairment

Arithmetic mean values of C_{max}, AUC_{0-tz} and $AUC_{0-\infty}$ were similar between the two groups. The t_{max} was delayed and $T_{1/2}$ was shorter in subjects with mild hepatic impairment. The point estimates of the LS geometric means ratio of C_{max}, AUC_{0-t}, AUC_{0-inf}, and $T_{1/2}$ were 107.6%, 101.4%, 102.8%, and 63.7%, respectively.

The serum concentration versus time profile for 4-hydroxyospemifene after a single oral administration of 60 mg ospemifene after standard breakfast.



*The figure above was taken from the sponsor's report which indicates plasma concentration in the y-axis. The report states blood samples were taken for determination of ospemifene in serum. Other clinical pharmacology studies report serum, not plasma, concentrations of ospemifene.

Summary and statistical analysis of 4-hydroxyospemifene PK parameters.

Pharmacokinetic parameters	Healthy subjects N = 7	Mild hepatic impairment N = 7	Moderate hepatic impairment N = 2	p-value[a]	Mild hepatic impairment vs. Healthy subjects PE (CI)
C_{max} (ng/mL)	98.1 (44.1)	104 (38.3)	67.9 / 86.2	0.7581	1.08 (0.71-1.62)
t_{max} (hr)	3.0 (2.0-4.0)	4.0 (3.0-6.0)	12.0 / 3.0	0.0122	
$T_{1/2}$ (hr)	47.6 (44.7)[b]	30.0 (38.0)[d]	42.7 / 53.7	0.1174	0.64 (0.39-1.03)
AUC_{0-t} (μg hr/mL)	2.56 (48.4)	2.53 (35.8)	5.11 / 7.56	0.9523	1.01 (0.68-1.52)
AUC_{0-inf} (μg hr/mL)	3.12 (51.8)[c]	3.07 (28.8)[d]	5.58 / 7.96	0.9169	1.03 (0.63-1.68)

Values are arithmetic means (CV%), t_{max} is median (range)
[a] p-value: probability of no mild hepatic impairment effect (ANOVA and Wilcoxon-Mann-Whitney test for t_{max}), [b] N = 4, [c] N = 3, and [d] N = 6

PE and CI: point estimate and 90% CI of the least-squares geometric means ratio (ANOVA)

Moderate hepatic impairment

Two subjects with moderate hepatic impairment showed higher AUC_{0-tz} value relatively than subjects in healthy and mild hepatic impairment groups.

3) 4'-Hydroxyospemifene

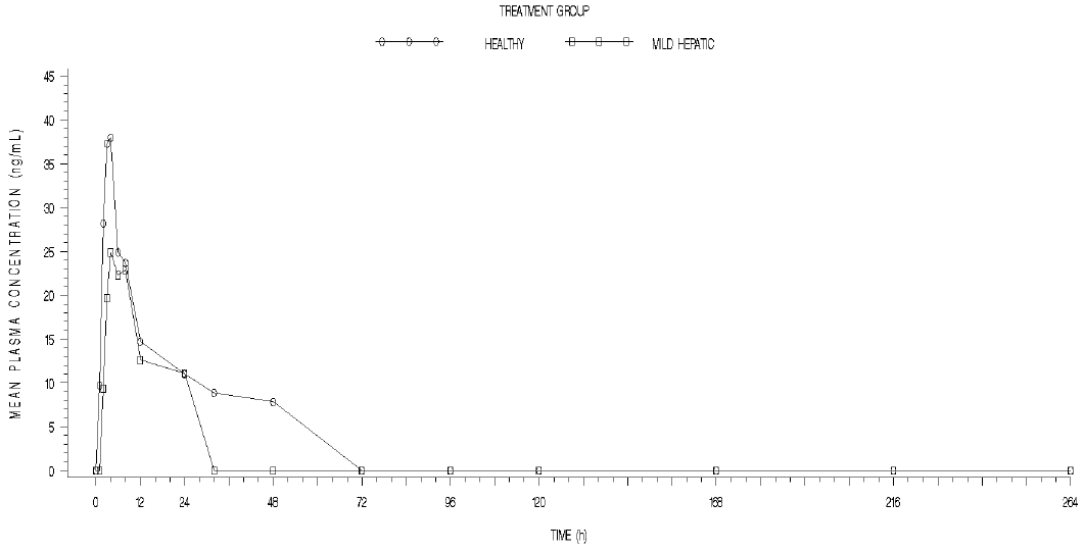
Mild hepatic impairment

The C_{max} and AUC_{0-tz} showed the lower tendency in mild hepatic impairment group than healthy group. The point estimates of the LS geometric means ratio of C_{max} and AUC_{0-tz} were 79.1% and 46.6%, respectively.

Moderate hepatic impairment

Two subjects with moderate hepatic impairment showed lower C_{max} value relatively than subjects in healthy and mild hepatic impairment group, but their AUC_{0-tz} values seemed not to be different from those of subjects in other groups.

The serum concentration vs. time profile for 4'-hydroxyospemifene after a single oral administration of 60 mg ospemifene after standard breakfast.



Summary and statistical analysis of 4'-hydroxyospemifene PK parameters.

PK parameters	Healthy subjects N = 7	Mild hepatic impairment N = 7	Moderate hepatic impairment N = 2	p-value[a]	Mild hepatic impairment vs. Healthy subjects PE (CI)
C_{max} (ng/mL)	40.7 (43.1)	32.7 (43.8)	13.9 / 18.6	0.3562	0.79 (0.51-1.22)
t_{max} (hr)	4.0 (2.0-8.0)	4.0 (3.0-8.0)	24.0 / 4.0	0.373	
$T_{1/2}$ (hr)	NC[b]	NC[c]	NC / NC	NA	
AUC_{0-t} (μg hr/mL)	0.769 (52.1)	0.425 (82.9)	0.512 / 0.824	0.0691	0.47 (0.24-0.92)
AUC_{0-inf} (μg hr/mL)	NC[c]	NC[d]	NC / NC	NA	

Values are arithmetic means (CV%), t_{max} is median (range)

[a] p-value: probability of no mild hepatic impairment effect (ANOVA and Wilcoxon-Mann-Whitney test for t_{max}), [b] N = 2, [c] N = 1, and [d] N = 0

NA = not applicable; NC = not calculated

PE and CI: point estimate and 90% CI of the least-squares geometric means ratio (ANOVA)

2. Safety

: Mild headache was the most common adverse events and observed in 5 of 16 subjects in all groups. No serious adverse events were reported.

: Subjects with mild or moderate hepatic impairment did not show higher incidence of adverse events than healthy group (Incidence of all treatment emergent AE: 4 of 7 subjects in healthy group and 0 of 7 and 2 in mild and moderate impairment groups).

: The clinical relevant changes or findings of laboratory abnormalities, physical examination, and vital sign over time were not reported during the study.

Sponsor's conclusion

· The PK of ospemifene seems not to be affected by mild hepatic impairment. Moderate hepatic impairment decreased CL/F by about 50% compared to healthy or mild hepatic impaired

subjects; however, no statistical test was done to confirm this effect because of the limited number of moderate hepatic impaired subjects (N = 2).

- The PK of 4-hydroxyospemifene and 4'-hydroxyospemifene seem not to be affected by mild hepatic impairment. Moderate hepatic impairment seems to increase and decrease the plasma exposure of 4-hydroxyospemifene and 4'-hydroxy- ospemifene, respectively, compared to healthy or mild hepatic impaired subjects. However, no statistical test was done to confirm this effect because of the limited number of moderate hepatic impaired subjects (N = 2).
- For a few subjects, correlations between some PK parameters of ospemifene or its metabolites and albumin and/or bilirubin were observed. However, no definite conclusions can be drawn with regard to these correlations (Data not shown in this report).
- Single dose administration of ospemifene 60 mg was generally safe and well tolerated in subjects with mild or moderate hepatic impairment.

Reviewer's comments

- The study design was acceptable to evaluate the effect of hepatic impairment on the PK of ospemifene and its major metabolites in target population, postmenopausal women, but the planned number of subjects for this study was not achieved.
- The subjects with mild hepatic impairment seem not to show clinical relevant change in the PK of ospemifene and its metabolites when compared with those in healthy subject group based on its PK variability in patient population and PK/PD relationships.
- Two subjects with moderate hepatic impairment tended to show higher exposure of ospemifene and 4-hydroxyospemifene in this study. However, it would not reach any conclusion due to limited number of subjects (N = 2).
- The correlation analysis between some PK parameters of ospemifene or its metabolites and the results of liver function test would give limited information, because limited number of subjects with moderate and no subject with severe hepatic impairment were included in this study.
- There was no significant safety concern after single dose administration of 60 mg ospemifene in postmenopausal women with or without hepatic impairment in this study.
- Even though serum samples were used for drug analysis of blood in this study, in clinical study report, some result was described as plasma concentration or plasma PK. It would not cause the problem to interpret results.

Study 15-50920

Title: Effect of moderately impaired hepatic function on pharmacokinetics of ospemifene in postmenopausal women

Study objectives:

- The primary objective of this study was to compare the PK of a single oral dose of ospemifene 60 mg in subjects with moderate hepatic impairment with those in demographically-matched healthy control subjects.
- The secondary aims of this study were to evaluate the PK of the metabolites 4-hydroxy-ospemifene and 4´-hydroxyospemifene and to assess the safety and tolerability of ospemifene.

Study design

- Open-label, single-dose, parallel-group, one-period, two-center safety and PK study
- Subjects
  : Eight postmenopausal women with moderate hepatic impairment (Child-Pugh score 7-9) and 8 healthy control subjects in demographically-matched
- Test product, dose, mode of administration
  : A 60 mg tablet single dose of ospemifene (film-coated tablet manufactured by (b) (4) A07006) was administered orally as a tablet after a standard breakfast (FDA standard meal defined as a high-fat/high-calorie meal)
- Pharmacokinetic evaluation
  : Blood samples: before and 1, 2, 3, 4, 6, 8, 12, 24, 32, 48, 72, 96, 120, 168, 216, and 264 hours after drug administration
  : Serum concentrations of ospemifene and the metabolites 4-hydroxyospemifene and 4'-hydroxyospemifene were analyzed using a LC-MS/MS method.
  : Pharmacokinetic parameters of ospemifene and metabolites
  : Serum protein unbound fraction (fu) of ospemifene and metabolites at 3 and 24 hours
- Safety evaluation
  : Adverse events
  : Safety laboratory at screening and the post-study visit
  : Vital signs at screening, before and 4 and 24 hours, and at the post-study visit
  : Physical examination at screening and the post-study visit

Study Population

- Subject disposition
  : Sixteen subjects were enrolled and all completed this study.
- Subjects' demography and medical history
  : There was no difference of demographic data between healthy and moderate hepatic impairment groups.

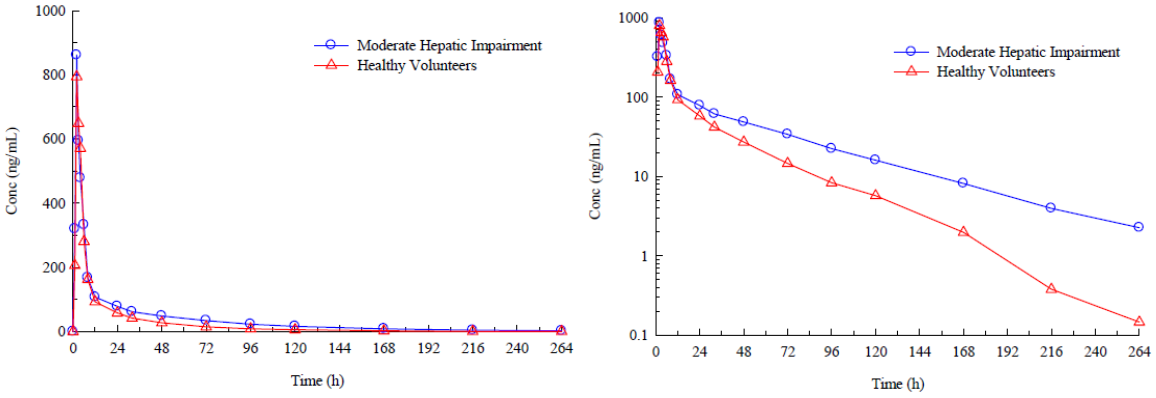
Results

1. Pharmacokinetics

1) Ospemifene

The mean serum concentrations of ospemifene in subjects with moderate hepatic impairment appeared to be higher than those in healthy control subjects.

The serum concentration vs. time profile for ospemifene after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women with moderate hepatic impairment and matched healthy subjects.



The PK parameters were more variable in subject with moderate hepatic impairment. Arithmetic mean of C_{max} was comparable between two groups. The $t_{½}$ in subjects with moderate hepatic impairment group seemed to be prolonged slightly. The values of AUC_{0-t} and AUC_{inf} tended to be higher in subjects with moderate hepatic impairment than in healthy subjects. The point estimates of the LS geometric means ratio of C_{max}, AUC_{0-t}, and AUC_{inf} were 101.1%, 128.4%, and 128.6% respectively.

Summary and statistical analysis of ospemifene PK parameters after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women with moderate hepatic impairment and matched healthy subjects.

Parameter*	Moderate hepatic Impairment N=8	Healthy subjects N=8	Moderate hepatic impairment vs. Healthy subjects PE (CI)**
C_{max} (ng/mL)	1070 ± 643	920 ± 219	1.01 (0.66-1.55)
T_{max} (hr)	2.0 (2.0 – 6.0)	2.01 (1.0 – 4.0)	
AUC_{0-t} (µg hr/mL)	9544 ± 4457	6726 ± 1661	1.28 (0.87-1.89)
AUC_{inf} (µg hr/mL)	9765 ± 4592	6853 ± 1677	1.29 (0.87-1.90)
λ_z (hr^{-1})	0.0170 ± 0.0049	0.0209 ± 0.0053	
$t_{½}$ (hr)	43.8 ± 12.3	35.0 ± 8.57	1.24 (0.98-1.57)
CL/F (mL/min)	138 ± 99.4	153 ± 31.8	0.78 (0.53-1.15)
Vz/F (L)	471 ± 266	448 ± 88.4	0.97 (0.71-1.32)

*Arithmetic mean ± standard deviation except T_{max} for which the median (range) is reported

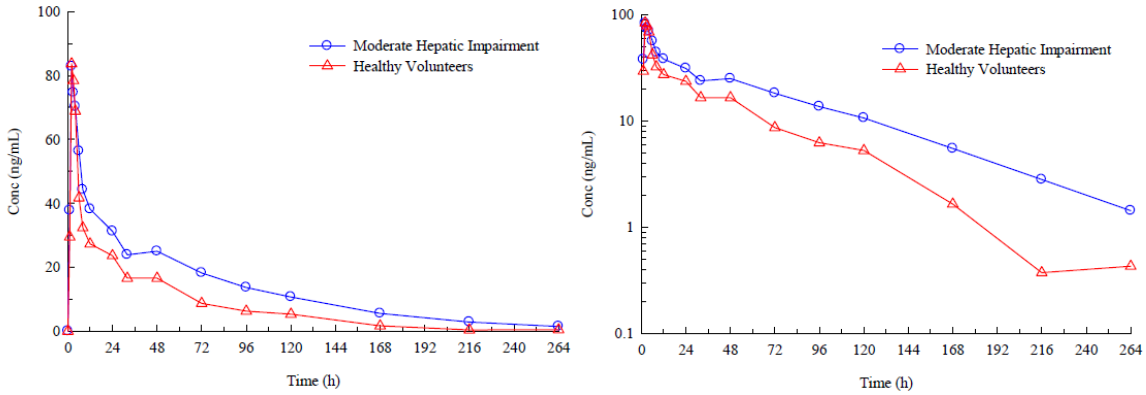
**point estimate and 90% CI of the least-squares geometric means ratio

Significant effect of moderate hepatic impairment on the protein binding of ospemifene was not observed in samples at 3 hours after administration. The free fraction concentration in most samples at 24 hours after administration was not measured.

2) 4-hydroxyospemifene

The mean serum concentrations of 4-hydroxyospemifene in subjects with moderate hepatic impairment appeared to be higher than those in healthy control subjects.

The serum concentration versus time profile for 4-hydroxyospemifene after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women with moderate hepatic impairment and matched healthy subjects.



Arithmetic mean of C_{max} was comparable between two groups. The $t_{½}$ in subjects with moderate hepatic impairment group seemed to be prolonged slightly. The values of AUC_{0-t} tended to be higher in subjects with moderate hepatic impairment than in healthy subject. The point estimates of the LS geometric means ratio of C_{max}, AUC_{0-t}, and $AUC_{inf,}$ were 103.3%, 163.3%, and 172.4% respectively.

Summary and statistical analysis of 4-hydroxyospemifene PK parameters after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women with moderate hepatic impairment and matched healthy subjects.

Parameter*	Moderate hepatic impairment n=8	Healthy subjects n=8	Moderate hepatic impairment vs. Healthy subjects PE (CI)**
C_{max} (ng/mL)	99.4 ± 47.2	93.3 ± 31.7	1.03 (0.70-1.53)
T_{max} (hr)	2.0 (2.0-6.0)	2.01 (2.0-4.0)	
AUC_{0-t} (ng hr/mL)	3497 ± 1773	2038 ± 882	1.63 (1.02-2.61)
AUC_{inf} (ng hr/mL)	3735 ± 1868	2075 ± 959	1.73 (0.98-3.02)
λ_z (hr^{-1})	0.0160 ± 0.0055	0.0206 ± 0.0105***	
$t_{½}$ (hr)	48.6 ± 18.2	40.4 ± 17.4***	1.24 (0.81-1.87)

*Mean ± standard deviation except T_{max} for which the median (range) is reported

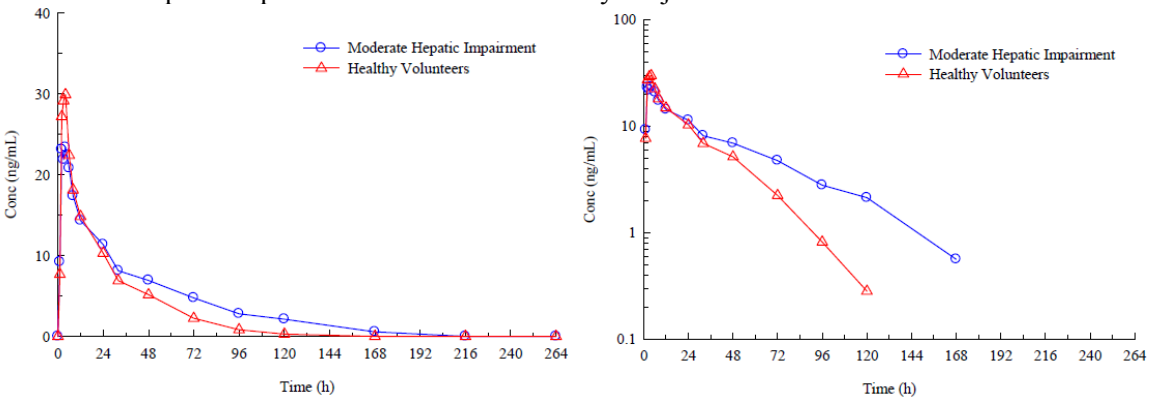
**point estimate and 90% CI of the least-squares geometric means ratio

*** n=5

3) 4'-hydroxyospemifene

The mean serum concentrations of 4'-hydroxyospemifene in subjects with moderate hepatic impairment appeared to be lower in the absorptive phase, but higher in the elimination phase than those in healthy control subjects.

The serum concentration vs. time profile for 4'-hydroxyospemifene after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women with moderate hepatic impairment and matched healthy subjects.



Arithmetic mean of most pharmacokinetic parameters was comparable between two groups. The point estimates of the LS geometric means ratio of C_{max}, AUC_{0-t}, and $AUC_{inf,}$ were 91.0%, 127.9%, and 107.9%, respectively.

Summary and statistical analysis of 4'-hydroxyospemifene PK parameters after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women with moderate hepatic impairment and matched healthy subjects.

PK Parameter*	Moderate hepatic impairment N=8	Healthy subjects N=8	Moderate hepatic impairment vs. Healthy subjects PE (CI)**
C_{max} (ng/mL)	30.2 ± 11.6	32.5 ± 09.7	0.91 (0.64-1.29)
T_{max} (hr)	3.50 (2.0-6.0)	3.5 (2.0-6.0)	
AUC_{0-t} (ng hr/mL)	881 ± 365	659 ± 238	1.28 (0.83-1.97)
AUC_{inf} (ng hr/mL)	1057 ± 473***	888 ± 189	1.08 (0.69-1.69)
λ_z (hr^{-1})	0.0191 ± 0.0084***	0.0201 ± 0.0084	
t½ (hr)	42.9 ± 18.4***	40.6 ± 17.9	1.06 (0.67-1.65)

*Arithmetic mean ± SD except Tmax for which the median [range] is reported

**point estimate and 90% CI of the least-squares geometric means ratio

*** n=7

Effect of hepatic impairment on protein binding

The unbound concentration was measureable in 4 of 8 moderate hepatic impairment patients and 5 of 8 healthy subjects with normal hepatic function at 3 hrs, and only 1 healthy subject with normal hepatic function at 24 hrs. At 3 hrs, the percent bound was >99% in the 4 moderate hepatic patients and 5 subjects with normal function. At 24 hrs, the percent bound was 95.29% in the one subject with normal hepatic function. It appears that hepatic impairment does not affect protein binding of ospemifene.

2. Safety

: Subjects with moderate hepatic impairment did not show higher incidence of adverse events than healthy subject group (incidence of all treatment emergent AE: 2 and 3 of 8 subjects in moderate impairment group and healthy group, respectively). Headache was the most common adverse event.

: The clinical relevant changes of laboratory abnormalities and vital sign over time were not reported during the study.

Sponsor's conclusion

- Oral administration of 60 mg of ospemifene with a high fat/high calorie meal resulted in minimal changes in exposure to ospemifene and 4′-hydroxyospemifene and an approximate 1.7-fold increase in exposure to 4-hydroxyospemifene in subjects with moderate hepatic impairment compared to demographically-matched healthy control subjects.
- This increase in 4-hydroxyospemifene exposure is not considered significant given that the concentration of the metabolite is a fraction of that of the parent.
- Therefore, this minor increase in exposure would not lead to a modification of dosing in patients with mild or moderate hepatic impairment.

Reviewer's comment

- The study design is acceptable to evaluate the effect of moderate hepatic impairment on the PK of ospemifene and its major metabolites in target population, postmenopausal women.
- Based on AUC parameters, the exposure of ospemifene tended to be increased (geometric mean of AUC_{inf} – 28%) in subjects with moderate hepatic impairment than in healthy control subjects. The reduction of elimination (metabolism) of ospemifene in subjects with moderate hepatic impairment would contribute to the increase in the exposure of ospemifene based on the tendency of half-life prolongation (Arithmetic mean value of moderate impairment and healthy groups was 43.8 (±12.3) and 35.0 (± 8.57) hour, respectively).
- Considerable increase (geometric mean of AUC_{inf} – 72%) in exposure of 4-hydroxyospemifene in subjects with moderate hepatic impairment was observed. PK of 4'-hydroxyospemifene was not influenced significantly by moderate hepatic impairment when compared with those in healthy subject group.
- There was no major safety concern after single dose administration of 60 mg ospemifene in postmenopausal women in this study regardless of hepatic function.
- These changes in exposures of ospemifene and its metabolites in subjects with moderate hepatic impairment are not clinically meaningful when considering the PK variability of ospemifene in patient population and its PK/PD relationships. Therefore, dose adjustment of ospemifene is not recommended for patients with moderate hepatic impairment.

Study 15-50921

Title: Effect of Severely Impaired Renal Function on the Pharmacokinetics of Ospemifene in Postmenopausal Women

Study objectives:
- The primary objective of this study was to compare the PK of a single oral dose of ospemifene 60 mg in subjects with severe renal impairment with those in demographically-matched healthy control subjects.
- The secondary aims of this study were to evaluate the PK of the metabolites 4-hydroxyospemifene and 4´-hydroxyospemifene and to assess the safety and tolerability of ospemifene.

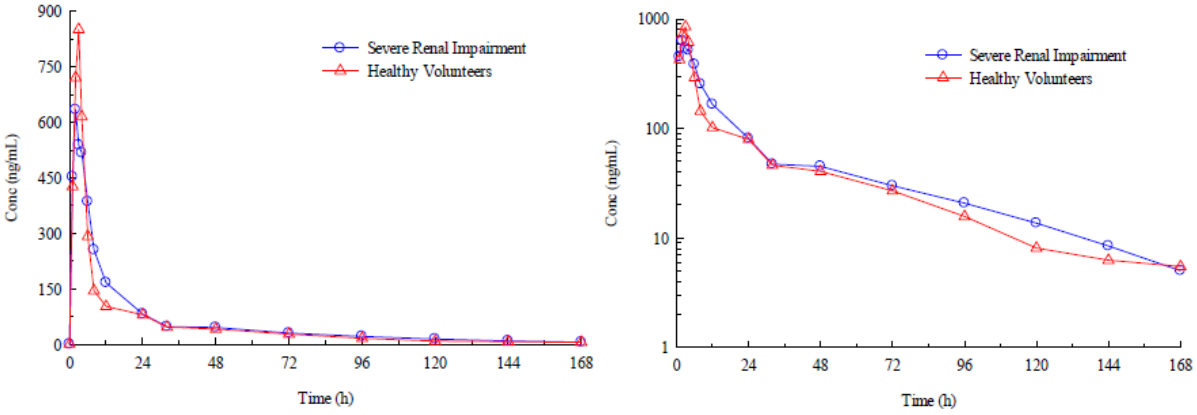
Study design
- Open-label, single-dose, parallel-group, one-period, 2-center safety and PK study
- Subjects
  : Eight postmenopausal women subjects with severe renal impairment (CLcr <30 mL/min based on the Cockcroft- Gault equation, not on dialysis state) and 8 demographically-matched healthy control subjects (CLcr >80 mL/min)
- Test product, dose, mode of administration
  : A single oral dose of ospemifene 60 mg tablet (film-coated tablet manufactured by (b) (4) A07006) following a standard breakfast (FDA standard meal defined as a high-fat, high-calorie meal)
- Pharmacokinetic evaluation
  : Blood samples - before and 1, 2, 3, 4, 6, 8, 12, 24, 32, 48, 72, 96, 120, 144, and 168 hours after dose
  : Urine samples – before and intervals of 0-6, 6-12, 12-24 hours, and 24-48 hours after dose
  : Serum protein unbound fraction (fu) of ospemifene at 3 and 24 hours
  : Serum concentrations of ospemifene and the metabolites 4-hydroxyospemifene and 4'-hydroxyospemifene were analyzed using a LC-MS/MS method.
  : Pharmacokinetic parameters of ospemifene and metabolites
- Safety evaluation
  : Adverse events
  : Safety laboratory at screening and the post-study visit
  : Vital signs at screening, before and 4 and 24 hours, and at the post-study visit

Study Population
- Subject disposition
  : Sixteen subjects were enrolled and all completed this study.
- Subjects' demography and medical history
  : There was no difference of demographic data between healthy and severe renal impairment groups.

Results
1. Pharmacokinetics

1) Ospemifene
: The mean serum concentrations of ospemifene appeared to be comparable between severe renal impairment and healthy control groups.

The serum concentration versus time profile for ospemifene after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women with severe renal impairment and matched healthy subjects.



Subjects with severe renal impairment tended to show lower C_{max} and more prolonged T_{max} than healthy control subjects. The values of t½ and AUC_{0-t} were comparable between subjects with severe renal impairment and healthy subjects. The point estimates of the LS geometric means ratio of C_{max}, AUC_{0-t}, and $AUC_{inf,}$ and t½ were 79.3%, 109.5%, 119.6% and 103.0%, respectively.

Summary and statistical analysis of ospemifene PK parameters after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women with severe renal impairment and matched healthy subjects.

PK Parameter*	Severe Renal Impairment N=8	Healthy Controls N=8	Geometric Mean Ratio (%) PE (90% CI)
C_{max} (ng/mL)	916 ± 525	1087 ± 441	0.79 (0.53-1.19)
T_{max} (hr)	3.5 (2.0–8.0)	2.0 (1.0–6.0)	-
AUC_{0-t} (ng hr/mL)	9395 ± 3965	8363 ± 3098	1.09 (0.77-1.56)
$AUC0-_{inf}$ (ng.hr/mL)	10141 ± 4144	8073 ± 2296	1.20 (0.81-1.76)
λz (hr^{-1})	0.0208 ± 0.0035	0.0215 ± 0.0041	-
t½ (hr)	34.2 ± 6.13	33.5 ± 8.61	1.03 (0.84-1.25)
CL/F (mL/min)	117 ± 56.8	132 ± 35.7	0.84 (0.57-1.23)
Vz/F (L)	343 ± 160	390 ± 173.4	0.86 (0.56-1.33)

* Mean ± SD except Tmax for which median (range) is reported.

: The protein bound percent at 3 hours after dosing was >99% in all serum samples which could be measured.

: Ospemifene concentrations in urine were detected in only 2 samples collected from 0 to 6 hours and 1 sample collected from 6-12 hours of subjects with renal impairment.

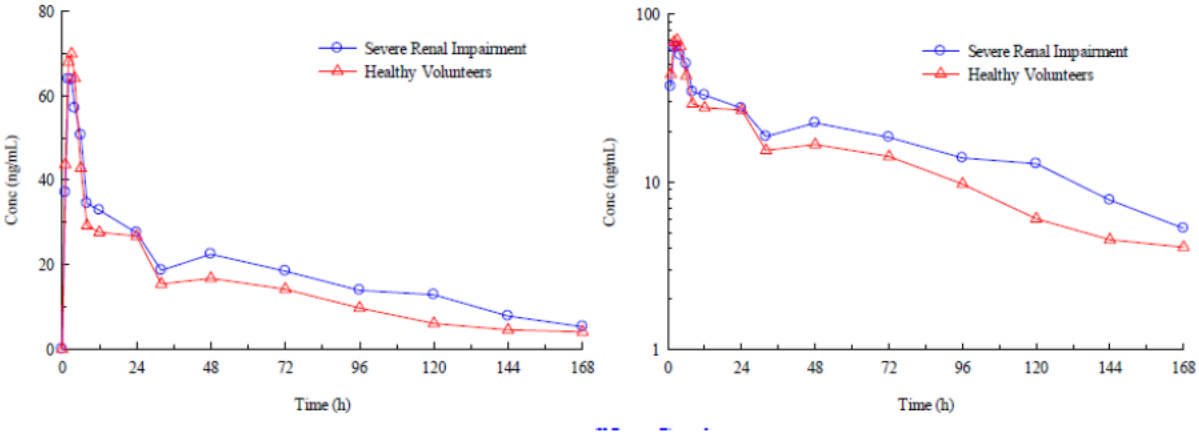
2) 4-hydroxyospemifene

: The mean serum concentrations of 4-hydroxyospemifene appeared to be higher slightly in subjects with severe renal impairment than healthy control group.

: Subjects with severe renal impairment tended to show lower C_{max} and more prolonged T_{max} than healthy control subjects. The values of t½ and AUC_{0-t} were similar between subjects with severe renal

impairment and healthy subjects. The point estimates of the LS geometric means ratio of C_{max}, AUC_{0-t}, AUC_{inf}, and $t_{½}$ were 82.3%, 101.7%, 122.6% and 102.9%, respectively.

The serum concentration versus time profile for 4-hydroxyospemifene after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women with severe renal impairment and matched healthy subjects.



Summary and statistical analysis of 4-hdyroxyospemifene PK parameters after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women with severe renal impairment and matched healthy subjects.

PK Parameter*	Severe Renal Impairment N=8	Healthy Subjects N=8	Geometric Mean Ratio (%) PE (90% CI)
C_{max} (ng/mL)	85.8 ± 51.4	89.9 ± 31.2	0.83 (0.50-1.38)
T_{max} (hr)	3.50 (1.0-24.0)	2.51 (1.0-6.0)	-
AUC_{0-t} (ng.hr/mL)	2998 ± 2153	2324 ± 251	1.02 (0.63-1.64)
AUC_{inf} (ng.hr/mL)	3697 ± 2410	2483 ± 220	1.23 (0.69-2.18)
λz (hr^{-1})	0.0185 ± 0.0068	0.0181 ± 0.0029	-
$t_{½}$ (hr)	42.0 ± 14.8	39.0 ± 5.93	1.03 (0.75-1.42)

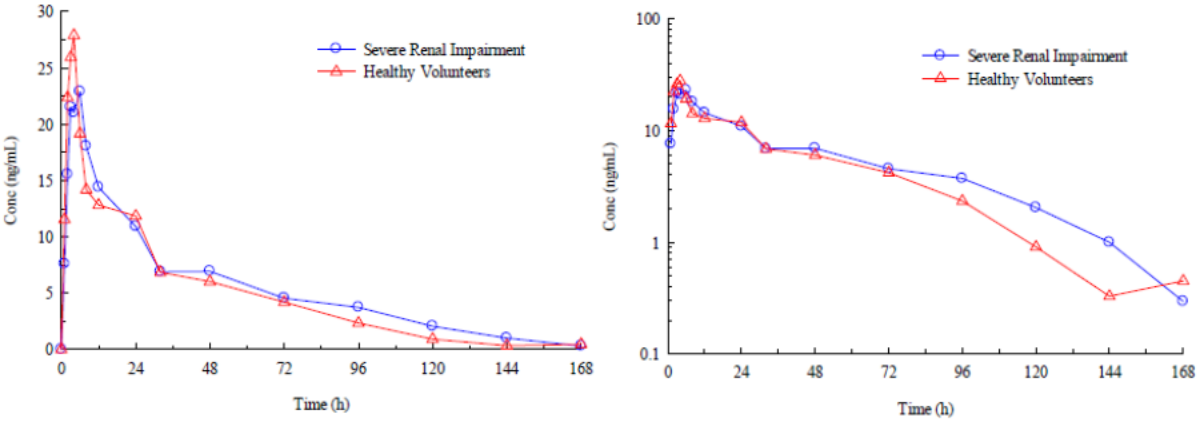
* Mean ± SD except T_{max} for which median (range) is reported.

3) 4'-hydroxyospemifene

: The mean serum concentrations of 4'-hydroxyospemifene appeared to be comparable between severe renal impairment and healthy control groups.

: Arithmetic mean of C_{max}, AUC_{0-t}, and AUC_{inf}, was similar between two groups. The values of $t_{½}$ tended to be shorter in subjects with severe renal impairment than healthy subjects. The point estimates of the LS geometric means ratio of C_{max}, AUC_{0-t}, and AUC_{inf}, and $t_{½}$ were 87.5%, 98.7%, 115.6% and 80.7%, respectively.

The serum concentration versus time profile for 4'-hydroxyospemifene after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women with severe renal impairment and matched healthy subjects.



Summary and statistical analysis of 4'-hydroxyospemifene PK parameters after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women with severe renal impairment and matched healthy subjects.

PK Parameter*	Severe Renal Impairment N=8	Healthy Subjects N=8	Geometric Mean Ratio (%) PE (90% CI)
C_{max} (ng/mL)	29.0 ± 15.0	30.9 ± 10.9	0.88 (0.57-1.34)
T_{max} (hr)	4.00 (3.0 – 24.0)	4.00 (2.0 – 6.0)	-
AUC_{0-t} (ng.hr/mL)	874 ± 458	778 ± 135	0.99 (0.67-1.45)
AUC_{0-inf} (ng hr/mL)	1169 ± 390	968 ± 171	1.16 (0.82-1.63)
λz (hr^{-1})	0.0210 ± 0.0059	0.0165 ± 0.0005	-
t½ (hr)	34.7 ± 7.3	42.1 ± 1.2	0.81 (0.66-0.99)

* arithmetic mean ± SD except Tmax for which median (range) is reported.

4) Reclassification of subjects and analysis based on new FDA guidance (2010, draft)
The sponsor submitted new report of Study 15-50921 as complete responses to FDA information request letter (7 Aug 2012).

4-1) Reclassification of subjects
The number of subjects in renal function groups according to the 1998 and 2010(draft) FDA guidance of PK in patients with impaired renal function. (Reconfiguration based on sponsor's complete response report)

	1998 Classification System		2010 Classification System			
Renal Function	CLcr†		CLcr*		eGFR**	
Normal	> 80 mL/min	8	≥ 90 mL/min	6	≥ 90 mL/min/1.73m^2	7
Mild impairment	50-80	0	60-89	2	60-89	1
Moderate impairment	30-50	0	30-59	0	30-59	0
Severe impairment	< 30	8	15-29	4	15-29	3
ESRD (not on dialysis)			<15 not on dialysis	4	<15 not on dialysis	5

* Estimated using the Cockroft-Gault Equation. ** Estimated using the MDRD equation in the 2010 FDA Guidance.

Two subjects and a subject who were in normal group were reclassified to mild impairment group based on CLcr (the Cockroft-Gault equation) and eGFR (the MDRD equation), respectively, according to the classification system to be described in new guidance (2010 draft).

4-2) Analysis of ospemifene pharmacokinetics based on CLcr
When comparing between combination group of severe renal impairment and ESRD and normal group of which 2 subjects were excluded due to reclassification to mild impairment group, descriptive statistic results of PK parameters were not different from those analyzed previously as grouping according to classic classification.

Summary and statistical analysis of ospemifene PK parameters after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women with severe renal impairment or ESRD and matched healthy subjects based on CLcr according to new classification. (Statistical results were generated by reviewer using Phoenix 6.3.0.395 program to display in equal format with them in previous report.)

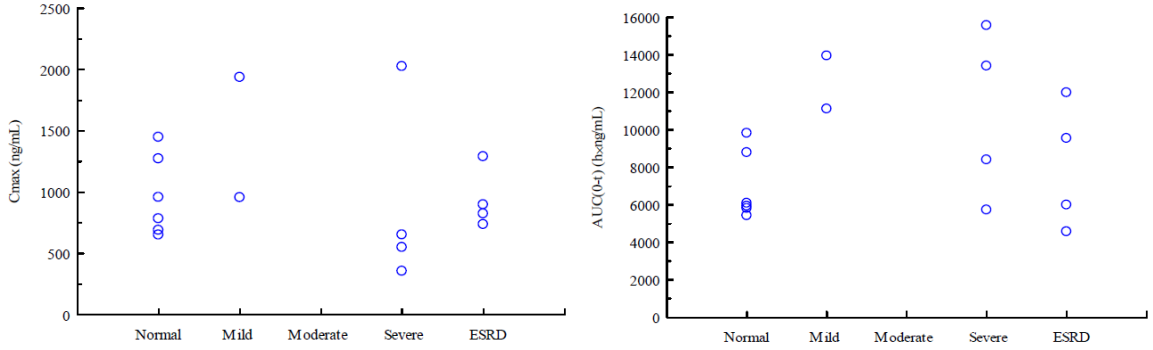
PK Parameter*	Severe Renal Impairment + ESRD N=8	Healthy Controls N=6**	Geometric Mean Ratio (%) PE (90% CI)
C_{max} (ng/mL)	916.16 ± 525.24	967.57 ± 327.03	0.87 (0.56-1.36)
T_{max} (hr)	3.5 (2.0-8.0)	2.0 (1.0-6.0)	-
AUC_{0-t} (ng.hr/mL)	9395 ± 3965	6975 ± 1824	1.27 (0.89-1.82)
AUC_{inf} (ng.hr/mL)	10141 ± 4144 (n=7)	7428 ± 1862 (n=5)	1.29 (0.86-1.94)
t½ (hr)	34.24 ± 6.13 (n=7)	33.65 ± 9.62 (n=5)	1.04 (0.83-1.28)
CL/F (mL/min)	117.38 ± 56.77 (n=7)	140.99 ± 31.88 (n=5)	0.78 (0.52-1.17)
Vz/F (L)	343.36 ± 159.56 (n=7)	416.78 ± 178.86 (n=5)	0.80 (0.50-1.27)

* arithmetic mean ± SD except T_{max} for which median (range) is reported.

** Two subjects who classified as a normal subject previously were excluded for this analysis as reclassified into mild impairment group.

Although its sample size was small, there was no trend to show the differences of PK parameters among renal function groups based on CLcr method according to new classification.

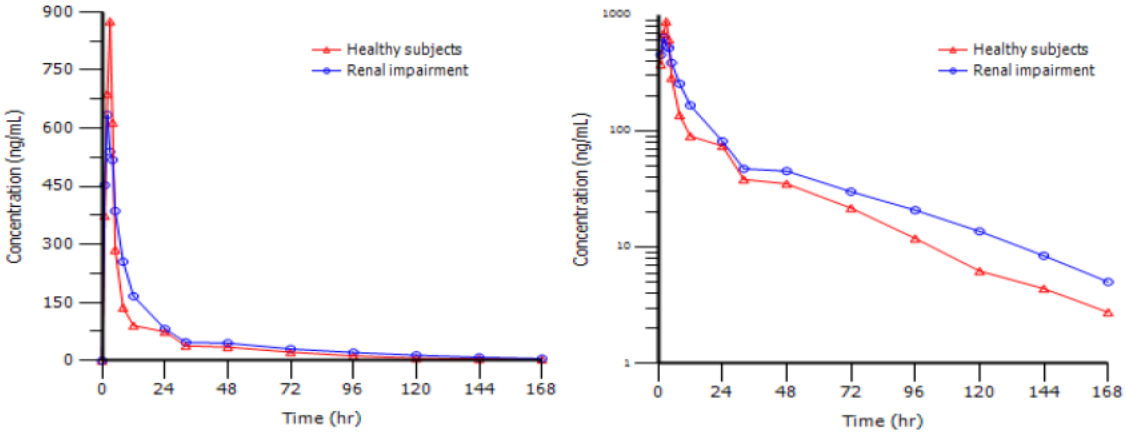
Plot of individual C_{max} and $AUC_{(0-t)}$ values in renal function groups based on CLcr according to new classification after oral administration of a 60mg ospemifene tablet after standard breakfast in postmenopausal women (sponsor's complete response report).



4-3) Analysis of ospemifene PK based on eGFR
When comparing between combination group of severe renal impairment and ESRD and normal group of which 1 subject was excluded due to reclassification to mild impairment group,

descriptive statistic results of pharmacokinetic parameters were not different from those analyzed previously as grouping according to classic classification.

The serum concentration versus time profile for ospemifene after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women patients (N=8) with severe renal impairment or ESRD and matched healthy subjects (N=7) (plot by this reviewer using the raw data).



Summary and statistical analysis of ospemifene PK parameters after a single oral administration of 60 mg ospemifene after standard breakfast in postmenopausal women with severe renal impairment or ESRD and matched healthy subjects based on eGFR according to new classification. (Statistical results were generated by reviewer using Phoenix 6.3.0.395 program to display in equal format with them in previous report.)

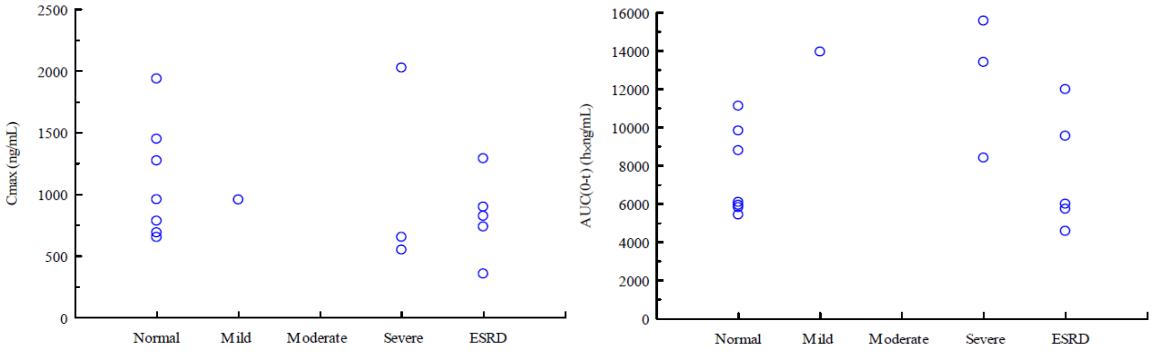
Parameter*	Severe Renal Impairment + ESRD N=8	Healthy Controls N=7**	Geometric Mean Ratio (%) PE (90% CI)
C_{max} (ng/mL)	916.16 ± 525.24	1106.08 ± 472.67	0.79 (0.51-1.22)
T_{max} (hr)	3.5 (2.0- 8.0)	2 (1.0-6.0)	-
AUC_{0-t} (ng.hr/mL)	9395 ± 3965	7567 ± 2296	1.19 (0.84-1.68)
AUC_{0-inf} (ng hr/mL)	10141 ± 4144	8073 ± 2296	1.20 (0.81-1.76)
t½ (hr)	34.24 ± 6.13	33.55 ± 8.61	1.03 (0.85-1.25)
CL/F (mL/min)	117.38 ± 56.77	132.25 ± 35.67	0.84 (0.57-1.23)
Vz/F (L)	343.4 ± 159.5	389.51 ± 173.36	0.86 (0.56-1.33)

* Mean ± standard deviation except Tmax for which median (range) is reported.

** One subject who classified as a normal subject previously were excluded for this analysis as reclassified into mild impairment group.

Although its sample size was small, there was no trend to show the differences of PK parameters among renal function groups based on eGFR method according to new classification.

Plot of individual C_{max} and $AUC_{(0-t)}$ values in renal function groups based on eGFR according to new classification after oral administration of a 60 mg ospemifene tablet after standard breakfast in postmenopausal women (sponsor's complete response report).



2. Safety

: Subjects with severe renal impairment did not show higher incidence of adverse events than healthy subject group; TEAEs were reported from 1 subject (back pain) with severe renal impairment and 2 healthy subjects (allergic rhinitis, headache).

: The clinical relevant changes of laboratory abnormalities and vital sign over time were not noted.

Sponsor's conclusion

- Oral administration of 60 mg of ospemifene with a high fat/ high calorie meal resulted in an approximate 20% increase in exposure to ospemifene and 4-hydroxyospemifene and an approximate 16% increase in exposure to 4′-hydroxyospemifene in subjects with severe renal impairment.
- Therefore, these minor increases in exposure would not lead to a modification of dosing in patients with mild, moderate, or severe renal impairment.
- Assessment based on CLcr and eGFR reclassified according to FDA's Draft Guidance (March 2010) suggests the lack of an effect of renal function on ospemifene PK. Therefore, no dose adjustment is required for renal function.
- A single dose of ospemifene 60 mg was safe and well tolerated in postmenopausal women with severe renal impairment and demographically-matched healthy control subjects.
- No deaths, other SAEs, or discontinuations due to AEs occurred during this study.
- TEAEs included back pain reported by 1 subject (12.5%) with severe renal impairment, rhinitis allergic reported by 1 healthy control subject (12.5%), and headache reported by 1 healthy control subject (12.5%).
- No clinically relevant changes were noted in clinical laboratory data or vital sign data.

Reviewer's comment

- The study design was acceptable to evaluate the effect of renal impairment on the PK of ospemifene and its major metabolites in target population, postmenopausal women, even though study was designed based on old classification of renal function grouping. Sponsor submitted additional report to reanalyze data based on reclassification according to new guidance.
- Subjects with severe renal impairment showed the tendency of lower C_{max} and more prolonged T_{max} when compared with healthy control subjects, whereas AUC_{0-inf} of ospemifene increased by approximately 20% in subjects with severe renal impairment, compared to healthy control subjects.

- The changes in the exposure of 4-hydroxyospemifene and 4'-hydroxyospemifene in subjects with severe renal impairment were not significant when compared with those in healthy subject group.
- The results reanalyzed by sponsor based on reclassification using CLcr (the Cockroft-Gault equation) and eGFR (the MDRD equation) according to new guidance were comparable to those originally submitted and did not support the significant effect of renal impairment on the disposition of ospemifene.
- There was no major safety concern after single dose administration of 60 mg ospemifene in postmenopausal women in this study regardless of renal function.
- The renal elimination of ospemifene and its metabolites was minimal as shown in mass balance study (Study 15-50206). This minor contribution of renal route excretion seems to cause the lack of the effect of renal dysfunction on the disposition of ospemifene.
- These minimal changes in exposures of ospemifene and its metabolites in subjects with severe renal impairment are not clinically meaningful when considering the PKvariability of ospemifene in patient population. Therefore, dose adjustment of ospemifene is not recommended for patients with mild, moderate, and severe renal impairment.

Study 15-50716

Title: Effect of Rifampicin and Ketoconazole on Ospemifene Pharmacokinetics – Study on Potential CYP3A4 Induction and Inhibition

Objectives: To evaluate the effects of rifampicin (a potent CYP3A4 inducer) and ketoconazole (a potent CYP3A4 inhibitor) on ospemifene PK

Methods: This was a single dose, open-label, randomized, three-period, crossover study with a washout period of at least 3 weeks and after an overnight fast of approximately 10 hrs. Twelve healthy post-menopausal women age 53-76 (mean 63 yo) years received ospemifene with and without pretreatment with rifampicin and ketoconazole. Ospemifene 60 mg tablets (Batch 0249A) were manufactured by Penn Pharmaceuticals (to-be-marketed formulation). Rifampicin 600 mg tablets (Rimapen), Orion Pharma, Finland and ketoconazole 200 mg tablets (Nizoral), Janssen-Cilag Oy, Finland were used in the study.

Treatment 1 (Ospemifene alone): one tablet of ospemifene 60 mg after a standard breakfast at approximately 8 am. The standard breakfast included two slices of bread with ham, cheese, a few slices of cucumber and/or tomatoes, and juice. Ospemifene was administered with 200 mL of tap water.

Treatment 2 (Ospemifene with rifampicin pre-treatment): once daily (one tablet) administration of rifampicin 600 mg at approximately 4 pm (at least one hr before a meal and two hrs after a meal) for 5 days; on the 6th day (after an overnight fast of approximately 10 hrs) one tablet of ospemifene 60 mg was administered after a standard breakfast at 8 am.

Treatment 3 (Ospemifene with ketoconazole pre-treatment): once daily administration of ketoconazole 400 mg (2 x 200 mg tablets) at 8 am after breakfast for 4 days; on the 5th day (after an overnight fast of approximately 10 hrs) two tablets of ketoconazole 200 mg and one tablet of ospemifene 60 mg were administered simultaneously with 200 mL water after a standard breakfast at 8 am. Ketoconazole administration once daily continued for an additional 3 days (Days 6, 7, and 8) to ensure sustained CYP3A4 inhibition during the PK sampling period for ospemifene concentrations.

Subjects were monitored by study personnel in sitting position or lying down for the first 4 hrs after ospemifene administration. A standard lunch was served 4 hrs after ospemifene administration (after the 4 hr sample was taken) and a standard dinner was served 8 hrs after ospemifene administration. An evening snack was given 12 hrs after ospemifene administration. Subjects were allowed to go home after the 16 hr blood sample was taken if the subject was feeling well and free of clinically significant adverse events. Subjects returned to the clinic the following day for the 24 hr blood sampling and subsequent samples.

Pharmacokinetic Sampling: Blood samples were taken for determination of serum ospemifene and 4-hydroxyospemifene concentrations at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 28, 32, 48, 56, 72, 80, and 96 hrs after ospemifene administration. Serum concentrations of ospemifene and hydroxyospemifene were determined with a validated LC-MS/MS method.

Results and Reviewer's Comments: Rifampicin is a moderate CYP2C8, moderate CYP2C9, moderate CYP2C19, and strong CYP3A4 inducer according to FDA's Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (February 2012). Rifampicin moderately decreased ospemifene exposure when subjects were treated with rifampicin for 5 consecutive days prior to a single dose

administration of ospemifene. The mean (%CV) $AUC_{0\text{-}inf}$ decreased by 58% from 4578 (33) to 1854 (27) ng.hr/mL and Cmax decreased by 51% from 644 (49) to 301 (33) ng/mL. Tmax and elimination half-life remained essentially unchanged. Tmax was 2.5 and 2.3 hrs with ospemifene alone and with rifampicin pre-treatment, respectively. Elimination half-life was similar with and without rifampicin pre-treatment at 25.5 and 24.3 hrs, respectively. Rifampicin was not given after ospemifene administration on Day 6 and during the PK sampling period; therefore, enzyme induction by rifampicin may have been more significant. It is possible that ospemifene exposure may have been lowered more significantly if rifampicin was given during the PK sampling period. Because rifampicin is a multi-enzyme inducer, the effect on ospemifene may be more significant if rifampicin was given with ospemifene on Day 6 and during the PK sampling period, which would be in alignment with the degree of inhibition by fluconazole (a multi-enzyme inhibitor).

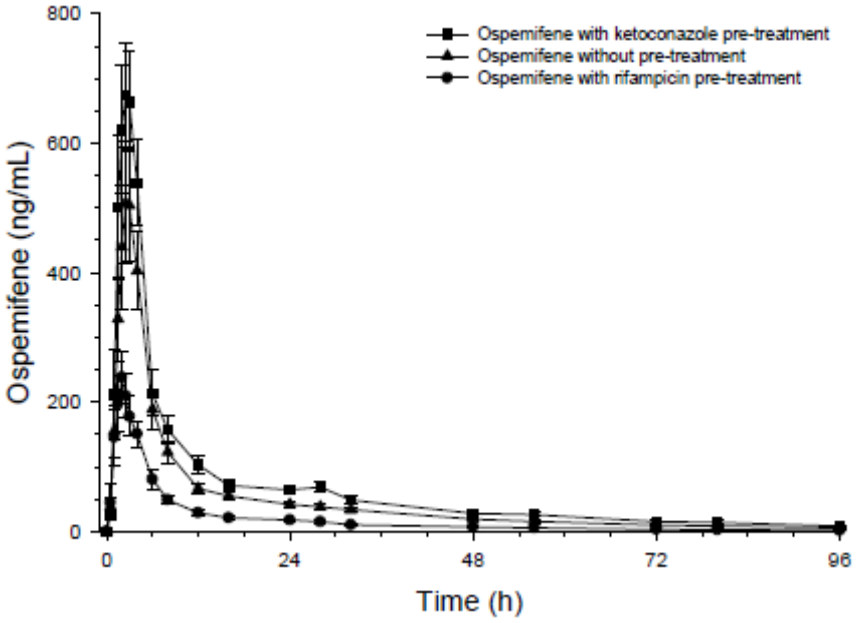
To achieve full CYP3A4 induction, rifampicin is typically dosed daily for 7 or more days. The subjects in this study received rifampicin once daily for 5 days; therefore, induction of CYP3A4 by rifampicin may not have been fully reached before ospemifene administration. In addition, rifampicin was not administered during the PK sampling period. It is possible that the reduction in ospemifene exposure may be more significant than reported by the applicant.

Ketoconazole is strong CYP3A inhibitor according to FDA's Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (February 2012). Ketoconazole moderately increased the concentrations of ospemifene when subjects were treated with ketoconazole 5 days prior to and 3 days after a single dose administration of ospemifene. The mean (%CV) $AUC_{0\text{-}inf}$ increased by 42% from 4578 (33) to 6475 (32) ng.hr/mL and Cmax increased by 46% from 644 (49) to 872 (27) ng/mL. Tmax (range) was 2.5 (1.5-6) hrs with ospemifene alone and with ketoconazole pre-treatment. Elimination half-life was similar with and without ketoconazole pre-treatment at 24.6 and 24.3 hrs, respectively. Continued CYP3A4 inhibition was maintained by giving three additional doses of ketoconazole after ospemifene administration. Food was given with ketoconazole which can adversely affect ketonazole absorption. If ketoconazole was given under fasted condition, CYP3A4 inhibition may be greater and ospemifene exposure may be higher than observed.

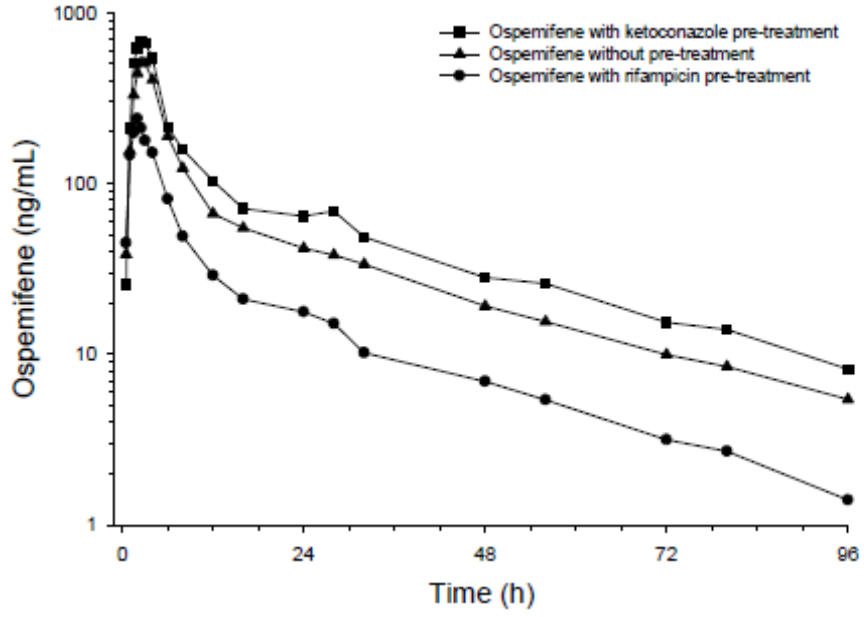
The sponsor concludes that the metabolism and elimination of ospemifene appears to be moderately affected by CYP3A4 activity; this reviewer does not concur for the reasons outlined above with regard to the study design.

Subjects who were given ketoconazole pre-treatment followed by ospemifene experienced more adverse events such as headache, nausea, dizziness, cold sweat, and insomnia. It is likely that the increased exposure to ospemifene due to CYP3A4 inhibition by ketoconazole resulted in a greater frequency of adverse events. Subject 006, a 75-year-old woman, suffered a severe adverse event (a transient cerebral ischemic attack) after receiving a single 60 mg dose of ospemifene after evaluation by a neurologist. It was later discovered that the subject had suffered a small brain infarction about 5 yrs earlier, which was not mentioned at the time of screening.

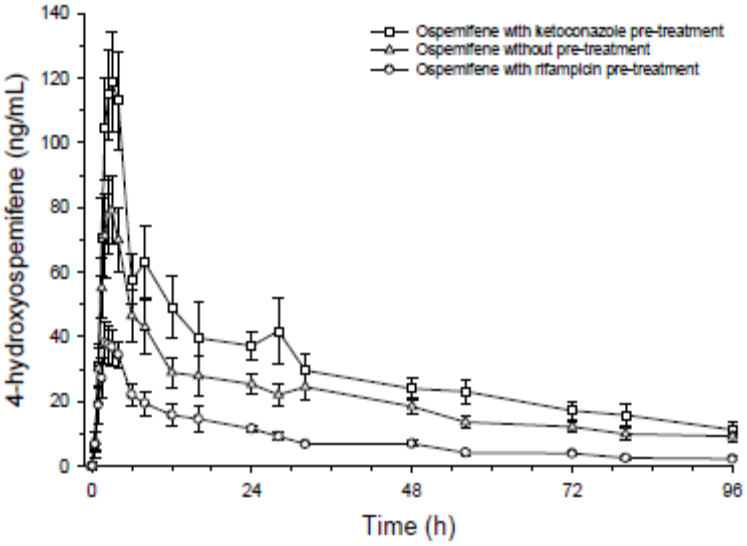
The following figure is the mean (SE) concentration-time profiles for serum ospemifene with and without ketoconazole and rifampicin treatment (linear scale, sponsor's figure 1, section 6.2.1).



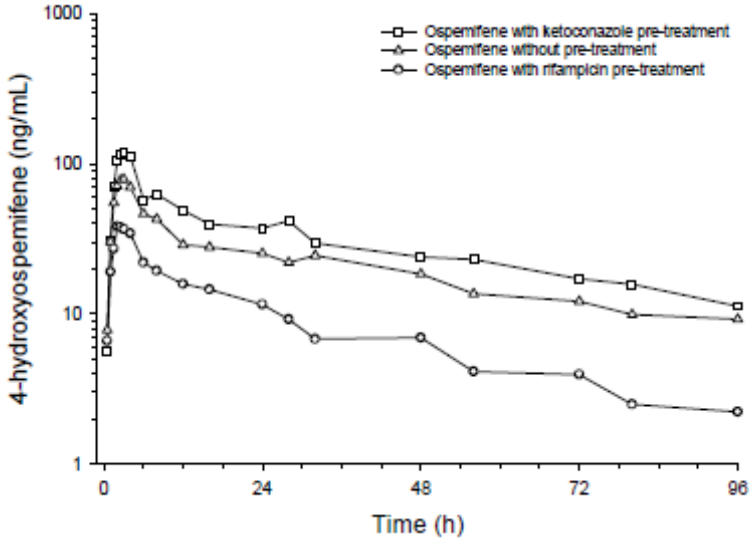
The following figure is the mean (SE) concentration-time profiles for serum ospemifene with and without ketoconazole and rifampicin treatment (semi-log scale, sponsor's figure 1, section 6.2.1).



The following figure is the mean (SE) concentration-time profiles for serum 4-hydroxyospemifene with and without ketoconazole and rifampicin treatment (linear scale, sponsor's figure 3, section 6.2.1).



The following figure is the mean concentration-time profiles for serum 4-hydroxyospemifene with and without ketoconazole and rifampicin treatment (semi-log scale, sponsor's figure 3, section 6.2.1).



The following are the mean (%CV) PK parameters of ospemifene (sponsor's table 4, section 6.2.1).

Parameter	Without pre-treatment	With rifampicin	With ketoconazole
AUC_∞ (ng hr/mL)	**4578** (33.0)	**1854** (27.3)	**6475** (32.0)
AUC_t (ng hr/mL)	4381 (32.5)	1781 (27.4)	6142 (29.8)
C_{max} (ng/mL)	644 (48.7)	301 (32.9)	872 (26.5)
t_{max} (hr) [1]	2.5 (1.5-6.0)	2.3 (1.0-6.1)	2.5 (1.5-6.0)
$t_{½}$ (hr)	24.3 (16.9)	25.5 (19.4)	24.6 (21.7)
CL/F (mL/hr)	15200 (49.1)	35307 (34.6)	10627 (49.2)

[1] Median (min-max). Source: Tables 9.2.1.2-9.2.1.7

The following is the mean (%CV) PK parameters of 4-hydroxyospemifene (sponsor's table 5, section 6.2.1).

Parameter	Without pre-treatment	With rifampicin	With ketoconazole
AUC_∞ (ng hr/mL)	2107 [2] (42.4)	1260 [2] (13.8)	2998 [3] (49.1)
AUC_t (ng hr/mL)	1971 (43.4)	779 (42.6)	2860 (51.0)
C_{max} (ng/mL)	88.1 (46.7)	47.7 (36.1)	135.0 (36.8)
t_{max} (hr) [1]	2.8 (1.5-6.0)	2.5 (1.0-8.0)	2.8 (1.5-4.0)
$t_{½}$ (hr)	30.2 [2] (25.0)	40.7 [2] (35.2)	33.5 [3] (35.5)

[1] Median (min-max), [2] N=5, [3] N=9. Source: Tables 9.2.2.2-9.2.2.6

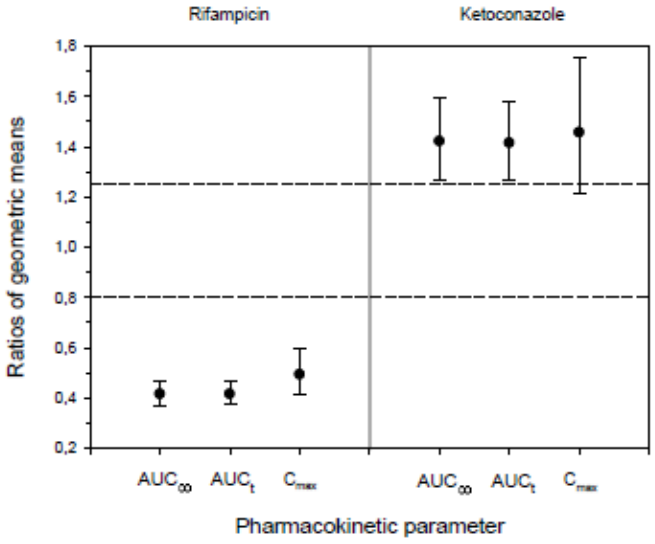


Figure 5. Ratios (ospemifene after treatment with rifampicin and ketoconazole vs ospemifene alone) of geometric means and their 90% confidence intervals for AUC_∞, AUC_t and C_{max} (N=12).

Table 7. Treatment-related AEs (N=15)

Treatment-related Adverse Event	Without pre-treatment[1]		With rifampicin[2]		With ketoconazole[3]	
	Events	Subjects	Events	Subjects	Events	Subjects
Headache	3	3	4	3	6	6
Nausea	1	1	1[a]	1	5	4
Diarrhoea	-	-	2	2	-	-
Dizziness	-	-	-	-	2	1
Cold sweat	-	-	-	-	1	1
Frequent bowel movements	-	-	1	1	-	-
Haematochezia	-	-	1[b,x]	1	-	-
Insomnia	-	-	-	-	1	1
Transient ischemic attack	1[x,x]	1	-	-	-	-

Statistical analysis of $AUC_{0\text{-}inf}$ for ospemifene with rifampicin or ketoconazole pre-treatment (sponsor's table 9.2.1.2).

```
Comparison of treatments

                                 Ratio      Lower 90%  Upper 90%
Comparison                       estimate   CL         CL
-------------------------------------------------------------------
Rifampicin pre-treatment vs.     0.415      0.370      0.465
no pre-treatment
Ketoconazole pre-treatment vs.   1.422      1.269      1.595
no pre-treatment
```

Statistical analysis of Cmax for ospemifene with rifampicin or ketoconazole pre-treatment (sponsor's table 9.2.1.4).

```
Comparison of treatments

                                 Ratio      Lower 90%  Upper 90%
Comparison                       estimate   CL         CL
-------------------------------------------------------------------
Rifampicin pre-treatment vs.     0.493      0.410      0.594
no pre-treatment
Ketoconazole pre-treatment vs.   1.457      1.211      1.754
no pre-treatment
```

Study 15-50823

Title: Effect of Fluconazole and Omeprazole on Ospemifene Pharmacokinetics – Study on Potential CYP2C9 and CYP2C19 Inhibition

Objectives: To evaluate the effects of a CYP2C9 inhibitor (fluconazole) and a CYP2C19 inhibitor (omeprazole) on ospemifene PK

Methods: This was a single dose, open-label, randomized, three-way, crossover study with a washout period of at least 3 weeks and after an overnight fast of approximately 10 hrs. Fourteen healthy post-menopausal women age 53-70 years (mean 63 years) received ospemifene with and without pre-treatment with fluconazole and omeprazole. Ospemifene 60 mg tablets (Batch A07006) were manufactured by (b) (4) (this is not the to-be-marketed formulation). Fluconazole 100 mg tablets (Diflucan) manufactured by Pfizer and omeprazole 20 mg tablets (Losec MUPS) manufactured by Astra Zeneca were used in the study.

The sponsor states that they had difficulties in recruiting subjects who were extensive metabolizers (EMs) with regard to both CYP2C9 and CYP2C19. Due to the stated recruiting difficulties, the study consisted of two groups: (1) EMs (N=9) with regard to both CYP2C9 and CYP2C19 who participated in three treatment periods (ospemifene alone, ospemifene with fluconazole pre-treatment, and ospemifene with omeprazole pre-treatment) and (2) EMs with respect to only one of the two CYP isozymes CYP2C9 (N=5) or CYP2C19 (N=5) who participated in two treatment periods (ospemifene alone and ospemifene with fluconazole pre-treatment or ospemifene alone and ospemifene with omeprazole pre-treatment).

Treatment 1 (Ospemifene alone): one tablet of ospemifene 60 mg after a standard breakfast at approximately 8 am. The standard breakfast included two slices of bread with ham, cheese, a few slices of cucumber and/or tomatoes, and juice. Ospemifene was administered with 200 mL of tap water.

Treatment 2 (Ospemifene with fluconazole pre-treatment): once daily administration of fluconazole 400 mg (4 x 100 mg capsules) at approximately 7 am on Day 1 at the study clinic, followed by 200 mg (2 x 100 mg capsules) at approximately 7 am on Days 2-4 at home. On Day 5 (after an overnight fast of approximately 10 hrs) subjects took their fifth dose of fluconazole 200 mg (2 x 100 mg capsules) at approximately 7 am followed by one tablet of ospemifene 60 mg was administered after a standard breakfast at 8 am. Fluconazole 200 mg (2 x 100 mg capsules) was taken for three additional days at approximately 7 am to provide sufficient CYP2C9 inhibition during the blood sampling period for ospemifene PK. On all days fluconazole was administered with 200 mL tap water.

Treatment 3 (Ospemifene with omeprazole pre-treatment): once daily administration of omeprazole 40 mg (2 x 20 mg tablets) at approximately 7 am on Day 1 at the study clinic, followed by 40 mg (2 x 20 mg tablets) at approximately 7 am on Days 2-4 at home. On Day 5 (after an overnight fast of approximately 10 hrs) subjects took their fifth dose of omeprazole 40 mg (2 x 20 mg tablets) at approximately 7 am followed by one tablet of ospemifene 60 mg was administered after a standard breakfast at 8 am. Omeprazole 40 mg (2 x 20 mg tablets) was taken for three additional days at approximately 7 am to provide sufficient CYP2C19 inhibition during the blood sampling period for ospemifene PK. On all days omeprazole was administered with 200 mL tap water.

Subjects were monitored by study personnel in sitting position or lying down for the first 4 hrs after ospemifene administration. A standard lunch was served 4 hrs after ospemifene

administration (after the 4 hr sample was taken) and a standard dinner was served 8 hrs after ospemifene administration. An evening snack was given 12 hrs after ospemifene administration. Subjects were allowed to go home after the 16 hr blood sample was taken if the subject was feeling well and free of clinically significant adverse events. Subjects returned to the clinic the following day for the 24 hr blood sampling and subsequent samples.

Pharmacokinetic Sampling: Blood samples were taken for determination of serum ospemifene and 4-hydroxyospemifene concentrations at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 28, 32, 48, 56, 72, 80, and 96 hrs after ospemifene administration. Serum concentrations of ospemifene and hydroxyospemifene were determined with a validated LC-MS/MS method.

Results and Reviewer's Comments: The effect of fluconazole on ospemifene exposure was apparent. Ospemifene $AUC_{0\text{-}inf}$ increased 2.7-fold (geometric mean ratio). The arithmetic mean for $AUC_{0\text{-}inf}$ increased from 4288 to 11932 ng.hr/mL after fluconazole pre-treatment. Ospemifene Cmax increased 1.7-fold (geometric mean ratio). The arithmetic mean for C_{max} increased from from 650 to 1028 ng/mL after fluconazole pre-treatment. Tmax was similar (2.6 hrs with vs. 3.0 hrs without fluconazole pre-treatment). Although the $T_{1/2}$ increased significantly from 25.0 to 42.9 hrs with fluconazole inhibition, the PK profiles were similar.

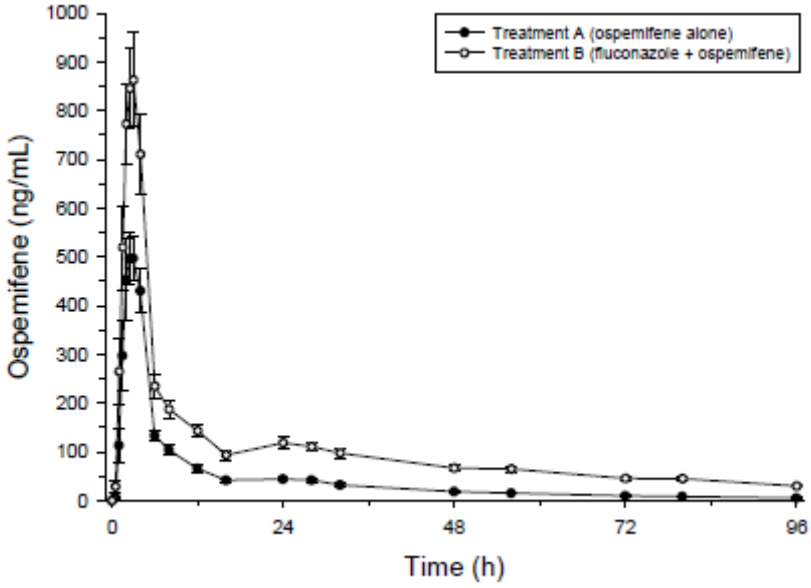
Subjects in this study received fluconazole once daily for 4 days before ospemifene administration.

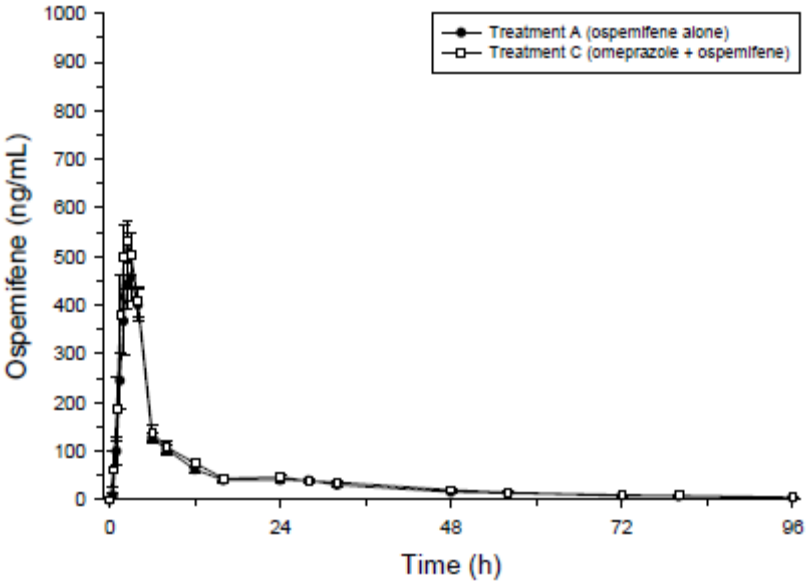
The sponsor identified fluconazole as a potent CYP2C9 inhibitor. Based upon the classification of CYP inhibitors in the current FDA's Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (February 2012), fluconazole is an inhibitor of multiple enzymes - listed as a moderate CYP2C9, strong CYP2C19, and moderate CYP3A4 inhibitor. Despite the known inhibitory effects of fluconazole on CYP2C19 and CYP3A4, the applicant selected fluconazole as the perpetrator drug in this study to evaluate CYP2C9 inhibition and its impact on ospemifene exposure. There is no commonly accepted drug that acts as a strong and specific inhibitor of CYP2C9.

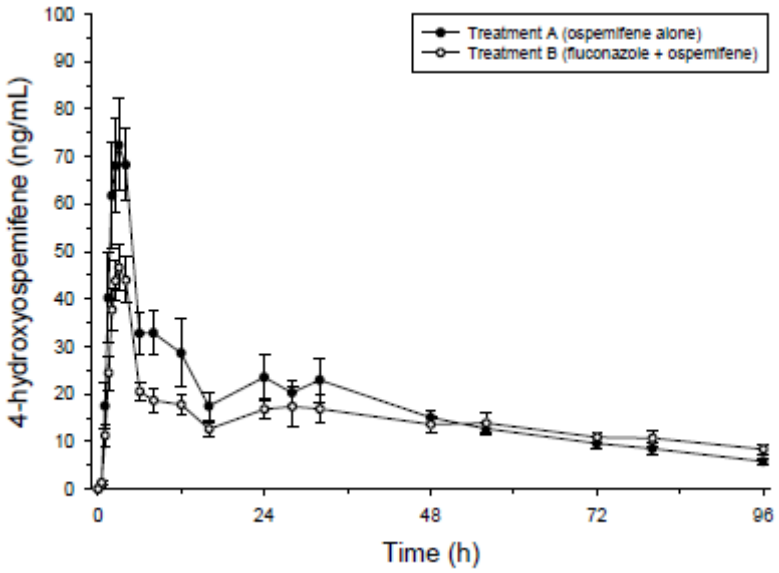
The sponsor identified omeprazole as a strong CYP2C19 inhibitor. According to the above mentioned drug interaction guidance published in 2012, omeprazole is a moderate inhibitor of CYP2C19. The discrepancy in the categorization of omeprazole is likely due to the classification of inhibitors in the early guidance where omeprazole was listed as a strong CYP2C19 inhibitor.

The effect of omeprazole on ospemifene exposure was apparent (though less significant compared with fluconazole). Ospemifene $AUC_{0\text{-}inf}$ increased 1.2-fold (geometric mean ratio). The arithmetic mean for $AUC_{0\text{-}inf}$ increased from 3949 to 4568 ng.hr/mL after omeprazole pre-treatment. Cmax increased 1.2-fold (geometric mean ratio). The arithmetic mean for C_{max} increased from 560 to 657 ng/mL. Tmax was similar (2.5 hrs with vs. 3.1 hrs without omeprazole pre-treatment). $T_{1/2}$ was essentially unchanged (24.2 hrs with vs. 23.9 hrs without omeprazole pre-treatment).

Subjects in this study received omeprazole once daily for 4 days before ospemifene administration.







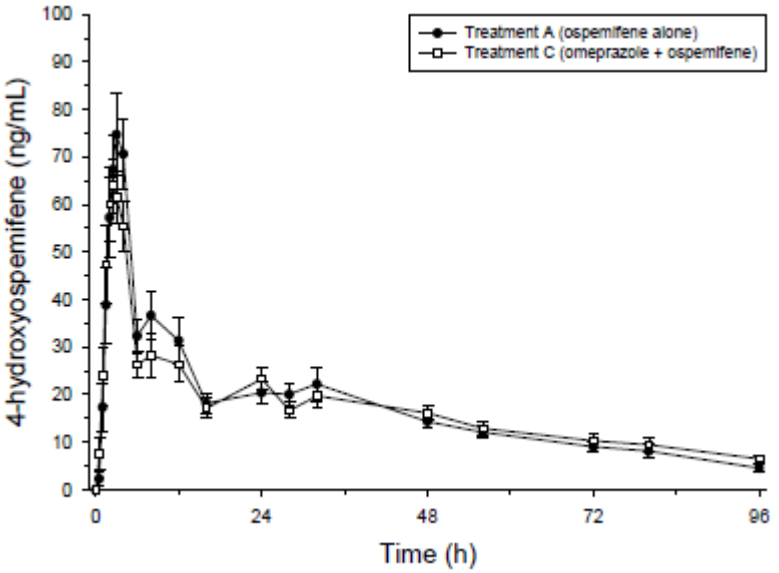


Table 4. Mean (CV%) pharmacokinetic parameters of ospemifene (N=14).

Parameter	Without pre-treatment	With fluconazole	Without pre-treatment	With omeprazole
AUC_{∞} (ng hr/mL)	4288.4 (24.0)	11931.9 (28.1)	3948.4 (28.7)	4567.5 (24.7)
AUC_t (ng hr/mL)	4098.4 (24.9)	9905.3 (28.6)	3789.0 (28.7)	4362.3 (24.1)
C_{max} (ng/mL)	649.7 (38.0)	1027.9 (25.1)	560.1 (36.2)	657.3 (28.8)
$t_{½}$ (hr)	25.0 (17.2)	42.9 (31.5)	23.9 (15.9)	24.2 (30.2)
t_{max} (hr)	3.0 (32.7)	2.6 (31.0)	3.1 (30.5)	2.5 (32.0)

Table 5. Mean (CV%) pharmacokinetic parameters of 4-hydroxyospemifene (N=14).

Parameter	Without pre-treatment	With fluconazole	Without pre-treatment	With omeprazole
AUC_{∞} (ng hr/mL)	2069.8 (40.1)[1]	1949.0 (41.9)[2]	1900.7 (31.0)[3]	1826.1 (26.7)[1]
AUC_t (ng hr/mL)	1649.9 (44.1)	1376.4 (43.6)	1608.2 (34.1)	1593.7 (32.6)
C_{max} (ng/mL)	80.9 (47.8)	50.0 (34.2)	81.7 (40.0)	72.6 (32.4)
$t_{½}$ (hr)	34.9 (42.4)[1]	45.5 (21.8)[2]	30.0 (33.7)[3]	31.6 (19.4)[1]
t_{max} (hr)	3.2 (27.1)	4.7 (145.3)	3.1 (29.0)	3.0 (53.0)

[1] N=10, [2] N=7, [3] N=11. Source: Table 9.2.2

Statistical analysis of $AUC_{0\text{-inf}}$ for ospemifene with fluconazole pre-treatment (sponsor's table 9.2.1.2)

Geometric means

Treatment	Estimated mean	Lower 95% CL	Upper 95% CL
A (ospemifene alone)	4132.51	3542.78	4820.41
B (with fluconazole)	11306.60	9693.08	13188.71

Comparison of treatments

Comparison	Ratio estimate	Lower 90% CL	Upper 90% CL
B vs. A	2.736	2.468	3.033

Statistical analysis of $AUC_{0\text{-inf}}$ for ospemifene with omeprazole pre-treatment (sponsor's table 9.2.1.2)

Geometric means

Treatment	Estimated mean	Lower 95% CL	Upper 95% CL
A (ospemifene alone)	3748.78	3206.21	4383.17
C (with omeprazole)	4388.61	3753.43	5131.28

Comparison of treatments

Comparison	Ratio estimate	Lower 90% CL	Upper 90% CL
C vs. A	1.171	1.070	1.280

Statistical analysis of Cmax for ospemifene with fluconazole pre-treatment (sponsor's table 9.2.1.4)

Geometric means

Treatment	Estimated mean	Lower 95% CL	Upper 95% CL
A (ospemifene alone)	601.04	488.57	739.41
B (with fluconazole)	997.22	810.61	1226.79

Comparison of treatments

Comparison	Ratio estimate	Lower 90% CL	Upper 90% CL
B vs. A	1.659	1.395	1.973

Statistical analysis of Cmax for ospemifene with omeprazole pre-treatment (sponsor's table 9.2.1.4)

Geometric means

Treatment	Estimated mean	Lower 95% CL	Upper 95% CL
A (ospemifene alone)	531.85	440.72	641.84
C (with omeprazole)	638.19	528.83	770.16

Comparison of treatments

Comparison	Ratio estimate	Lower 90% CL	Upper 90% CL
C vs. A	1.200	1.002	1.437

Table 9. Treatment-related AEs

Treatment-related Adverse Event	Without pre-treatment[1]		With fluconazole[2]		With omeprazole[3]	
	Events	Subjects	Events	Subjects	Events	Subjects
Headache	4	4	5	3	2	2
Diarrhoea	1	1	1	1	4	2
Abdominal pain	-	-	-	-	2	1
Dyspepsia	-	-	1	1	-	-
Flatulence	-	-	1	1	-	-
Haematuria	-	-	1[xx]	1	-	-
Hot flush	1	1	-	-	-	-
Migraine	1	1	-	-	-	-
Sleep disorder	-	-	1	1	-	-
Vomiting	1	1	-	-	-	-

Study 15-50719

Title: Effect of Ospemifene on Omeprazole Pharmacokinetics – Study on CYP2C19 and CYP3A4 Inhibition by Ospemifene

Objectives: The objective of the study was to evaluate the effect of ospemifene on omeprazole (a CYP2C19 substrate) PK in postmenopausal women who are not CYP2C19 poor metabolizers (PMs). The applicant states that in vitro studies suggest that ospemifene may be a weak CYP2C19 inhibitor with a Ki value of approximately 35 µM. Based on in vitro findings, the sponsor conducted an in vivo study using omeprazole as a substrate to assess the extent of ospemifene inhibition on CYP2C19 and CYP3A4.

Methods: This study was an open-label, two-period, crossover study with a washout period of at least 2 weeks. Subjects were given a single 20 mg dose of omeprazole with and without pre-treatment with 60 mg ospemifene with once daily dosing for 7 days. Fourteen Finnish Caucasian healthy postmenopausal women age 50-67 years (mean 59.6 yo) were enrolled in the study. Two subjects discontinued – one due to scheduling issue before receiving medication and one due to adverse event (urinary tract infection) after receiving all 7 doses of ospemifene. Subjects genotyped as being homozygous as CYP2C19 PMs (possessing the CYP2C19*2/*2 genotype) were excluded from the study.

Ospemifene 60 mg tablets (Batch A07006) were manufactured by (b) (4) (this is not the to-be-marketed formulation). Omeprazole 20 mg tablets (Losec MUPS enterotablets) manufactured by Astra Zeneca were used in the study.

Treatment 1: One 20 mg tablet of omeprazole was administered with 200 mL of water in the morning after an overnight fast of at least 10 hrs.

Treatment 2: One 60 mg tablet of ospemifene was administered once daily for 7 days with 200 mL of water at approximately 4 pm after eating a light meal. On the 8th day, a single dose of one 20 mg tablet of omeprazole was administered with 200 mL of water in the morning after an overnight fast of at least 10 hrs; ospemifene was not given on Day 8.

Pharmacokinetic Sampling: Blood samples for determination of plasma omeprazole, 5-hydroxyomeprazole, and omeprazole sulphone concentrations were drawn predose and 1, 2, 3, 4, 6, and 8 hrs after omeprazole administration. Blood samples for ospemifene and 4-hydroxyospemifene concentrations were collected predose and 3 and 8 hrs after omeprazole administration. According to the description of the study design, subjects received ospemifene for 7 days. According to the applicant's flow chart of schedule of events, subjects received 8 days of ospemifene pretreatment; however, the compliance data showed that omeprazole was administered at approximately 8 am on Day 8 and the last ospemifene tablet was self-administered at home at approximately 4 pm on Day 7. Therefore, this reviewer concludes that a time gap of at least 12 hrs existed between ospemifene and omeprazole administration.

Results and Reviewer's Comments: According to FDA's Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (February 2012), omeprazole is a sensitive substrate for CYP2C19, not CYP3A4. The applicant states omeprazole is a sensitive substrate of CYP2C19 and CYP3A4. The metabolism of omeprazole to 5-hydroxyomeprazole is catalyzed by CYP2C19, while omeprazole sulphoxidation is mediated by CYP3A4. The concentration ratio of omeprazole/5-hydroxyomeprazole from blood samples taken at 3 hrs was used as marker for CYP2C19 activity.

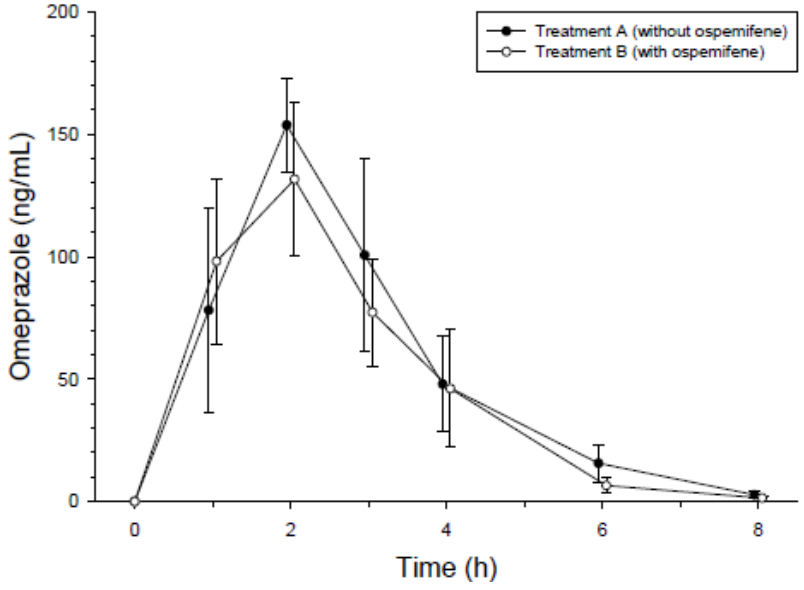
The concentration ratio of omeprazole/omeprazole sulphone determined from the 3 hr sample was used to assess CYP3A4 activity. The ratio of omeprazole/omeprazole sulphone is used in the scientific community as an index of CYP3A4 activity because CYP3A4 is a secondary pathway for omeprazole metabolism; however, this approach has not validated and has not been included in the 2012 drug interaction guidance.

The applicant states that the omeprazole film-coated tablet containing enteric-coated granules is expected to reach peak concentrations within 2-3 hrs and a single blood sample taken at 3 hrs after omeprazole intake can reliably determine both the CYP2C19 and CYP3A4 activities. The 3 hr time point has not been validated. Additionally, mean Cmax for omeprazole was reached at 2 hrs (see PK profile and concentration data below). To capture the maximum concentrations of omeprazole, 5-hydroxyomeprazole, and omeprazole sulphone, blood draws should have been taken at 2 hrs, not 3 hrs.

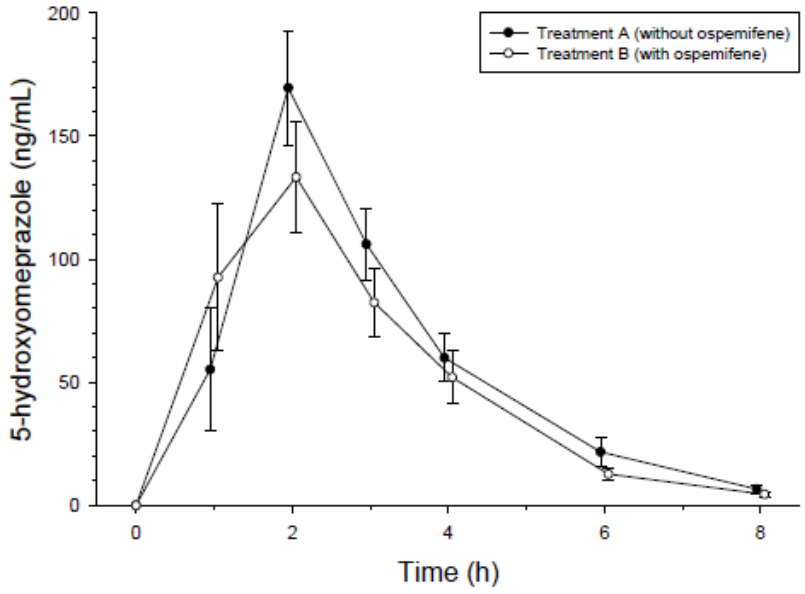
The geometric mean ratios for both metabolic indices (omeprazole/5-hydroxyomeprazole and omeprazole/omeprazole sulphone) at the 3 hr time point and for $AUC_{0\text{-}8hr}$ were 0.97 or 1.0 with and without ospemifene pre-treatment with a 90% CI that ranged from 0.67 to 1.41 (see table below).

Although the variability was significant (CV greater than 30%), the near unity value for these metabolic indices suggests that ospemifene did not have an effect on the metabolism of omeprazole by CYP2C19. However, there were limitations to this study including the significant time gap between ospemifene and omeprazole administration on Day 8 (ospemifene was administered at least 12 hrs prior to omeprazole administration) and subjects with various CYP2C19 alleles were not identified (subjects possessing the CYP2C19*2/*2 genotype were excluded from the study). Additionally, omeprazole is not a sensitive substrate for CYP3A4; therefore, it is not possible to conclude that ospemifene will not affect drugs that are metabolized by CYP3A4 as suggested by the applicant. Due to multiple deficiencies of the study design, the applicant failed to demonstrate that ospemifene does not affect the activity of CYP2C19 and CYP3A4 enzymes.

The following are the mean (SE) plasma concentration-time profiles for omeprazole (sponsor's figure 1a, section 6.2.1)



The following is the mean (SE) plasma concentration-time profiles for 5-hydroxyomeprazole (sponsor's figure 1b, section 6.2.1)



The following is the mean (SE) plasma concentration-time profiles for omeprazole sulphone (sponsor's figure 1c, section 6.2.1)

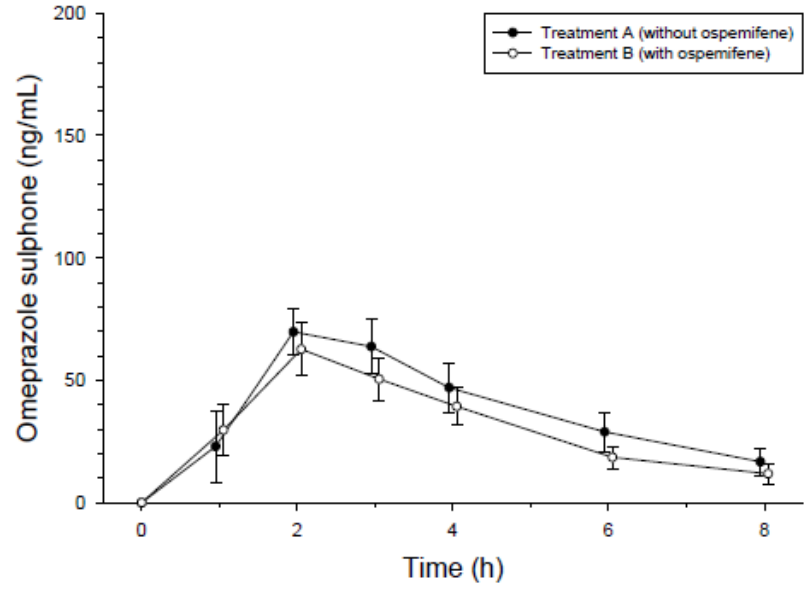


Table 9.2.1 Summary of omeprazole, 5-hydroxyomeprazole and omeprazole sulphone concentrations (ng/mL)

Omeprazole

Nominal time (h)	Treatment	N	Mean	SD	CV %	SE	Min	Q1	Median	Q3	Max	Geometric Mean	Geometric CV %
Zero sample	A	12	0.0	0.0		0.0	0.0	0.0	0.0	0.0	0.0		
	B	12	0.0	0.0		0.0	0.0	0.0	0.0	0.0	0.0		
1h	A	12	78.1	145.1	185.8	41.9	0.0	4.0	19.0	95.2	511.0	29.5	454.7
	B	12	98.1	116.8	119.1	33.7	0.0	19.0	63.3	124.2	379.0	73.7	145.3
2h	A	12	153.7	65.9	42.9	19.0	62.3	100.5	146.0	205.5	276.0	140.6	47.4
	B	12	131.6	107.9	82.0	31.2	0.0	67.2	84.1	214.0	385.0	116.5	73.5
3h	A	12	100.6	135.8	135.1	39.2	17.1	44.7	63.3	87.1	520.0	65.2	106.3
	B	12	77.2	75.8	98.2	21.9	11.2	13.9	53.9	116.5	253.0	46.2	158.1
4h	A	12	47.9	67.4	140.8	19.5	2.9	7.8	24.4	52.5	234.0	22.3	212.2
	B	12	46.1	83.0	180.1	24.0	2.1	3.2	21.9	44.0	301.0	16.6	300.5
6h	A	12	15.6	26.4	169.4	7.6	0.0	0.0	2.8	21.4	80.9	8.9	348.9
	B	12	6.5	10.9	167.9	3.1	0.0	0.0	3.3	8.3	39.2	6.2	119.8
8h	A	12	2.7	4.9	177.9	1.4	0.0	0.0	0.0	4.1	13.0	6.4	118.2
	B	12	1.4	3.3	237.7	1.0	0.0	0.0	0.0	1.5	11.6	2.7	129.1

5-hydroxyomeprazole

Nominal time (h)	Treatment	N	Mean	SD	CV %	SE	Min	Q1	Median	Q3	Max	Geometric Mean	Geometric CV %
Zero sample	A	12	0.0	0.0		0.0	0.0	0.0	0.0	0.0	0.0		
	B	12	0.0	0.0		0.0	0.0	0.0	0.0	0.0	0.0		
1h	A	12	55.2	86.8	157.3	25.1	0.0	3.6	19.2	59.7	277.0	19.7	442.4
	B	12	92.6	103.2	111.5	29.8	0.0	19.7	45.0	151.5	340.0	48.3	359.1
2h	A	12	169.6	80.7	47.6	23.3	36.5	124.0	173.0	222.0	328.0	146.7	69.4
	B	12	133.3	79.1	59.4	22.8	0.0	80.1	133.5	183.5	290.0	128.0	61.3
3h	A	12	106.1	50.4	47.5	14.6	51.0	81.4	91.9	122.0	239.0	97.5	43.3
	B	12	82.4	48.4	58.7	14.0	20.5	56.0	63.2	109.5	200.0	71.0	63.3
4h	A	12	59.9	33.2	55.4	9.6	27.8	37.1	47.8	76.1	143.0	53.3	51.5
	B	12	52.0	37.5	72.0	10.8	17.2	29.6	38.6	60.3	149.0	42.9	69.8
6h	A	12	21.7	21.0	96.7	6.1	7.0	8.7	12.6	27.8	64.2	15.5	93.5
	B	12	12.7	7.6	60.4	2.2	4.2	7.5	11.1	15.1	28.8	10.8	64.4
8h	A	12	6.6	6.2	94.1	1.8	1.8	2.9	3.8	9.5	18.0	4.8	93.5
	B	12	4.5	3.5	78.4	1.0	1.4	2.1	3.8	5.2	14.2	3.6	75.8

Omeprazole sulphone

Nominal time (h)	Treatment	N	Mean	SD	CV %	SE	Min	Q1	Median	Q3	Max	Geometric Mean	Geometric CV %
Zero sample	A	12	0.0	0.0		0.0	0.0	0.0	0.0	0.0	0.0		
	B	12	0.0	0.0		0.0	0.0	0.0	0.0	0.0	0.0		
1h	A	12	23.0	50.5	220.1	14.6	0.0	0.6	3.4	19.5	179.0	9.6	337.9
	B	12	29.7	36.2	121.9	10.4	0.0	4.3	13.2	45.5	101.0	20.5	169.6
2h	A	12	69.8	33.3	47.8	9.6	13.6	47.9	71.7	92.4	131.0	60.0	71.7
	B	12	62.7	38.2	61.0	11.0	0.0	42.0	60.7	80.4	127.0	59.0	69.6
3h	A	12	63.8	37.9	59.5	11.0	25.5	35.3	48.9	93.0	138.0	54.8	61.5
	B	12	50.5	29.9	59.2	8.6	5.3	25.7	43.7	78.5	97.9	40.1	97.0
4h	A	12	47.0	34.7	73.7	10.0	12.1	18.2	39.5	63.3	135.0	37.1	84.1
	B	12	39.3	27.1	68.9	7.8	10.5	15.3	32.4	57.7	97.8	30.9	87.3
6h	A	12	28.9	27.2	94.3	7.9	3.5	6.5	23.2	42.5	94.2	18.2	146.0
	B	12	18.5	15.5	83.7	4.5	3.1	5.0	14.1	30.5	49.5	12.4	128.1
8h	A	12	16.7	19.5	116.6	5.6	1.0	2.4	12.1	23.4	69.6	8.7	209.0
	B	12	11.8	14.1	120.1	4.1	1.3	1.7	7.5	17.1	50.3	6.1	198.9

NOTE: A = without ospemifene, B = with ospemifene
NOTE: Values below lower limit of quantitation (LLOQ) were set to zero. LLOQ was 1.0 ng/mL.

The following table is the arithmetic and geometric mean (%CV) for the 3 hr concentrations time point and $AUC_{0\text{-}8hr}$ for omeprazole, 5-hydroxyomeprazole, and omeprazole sulphone (sponsor's table 4, section 6.2.1)

Calculation based on	Parent/metabolite	Treatment	Arithmetic	Geometric
3 h concentrations	Omeprazole	A[1]	100.6 (135.1)	65.2 (106.3)
		B[2]	77.2 (98.2)	46.2 (158.1)
	5-hydroxyomeprazole	A[1]	106.1 (47.5)	97.5 (43.3)
		B[2]	82.4 (58.7)	71.0 (63.3)
	Omeprazole sulphone	A[1]	63.8 (59.5)	54.8 (61.5)
		B[2]	50.5 (59.2)	40.1 (97.0)
AUC_t	Omeprazole	A[1]	413.5 (63.2)	345.3 (71.2)
		B[2]	362.9 (62.1)	285.9 (94.5)
	5-hydroxyomeprazole	A[1]	452.7 (19.4)	444.9 (19.6)
		B[2]	396.6 (25.4)	378.1 (38.1)
	Omeprazole sulphone	A[1]	297.3 (60.6)	253.1 (65.1)
		B[2]	245.0 (53.0)	209.0 (71.1)

[1] Omeprazole without ospemifene
[2] Omeprazole with ospemifene
Source: Table 9.2.3

The following table is the geometric mean (%CV) of the metabolic ratios based on the 3 hr concentrations time point and $AUC_{0\text{-}8hr}$ for omeprazole/5-hydroxyomeprazole and omeprazole/omeprazole sulphone (sponsor's table 5, section 6.2.1)

Calculated from	Metabolic ratio	Treatment A [1]	Treatment B [2]
3h concentrations	Omeprazole / 5-hydroxyomeprazole	0.67 (78.4)	0.65 (98.7)
	Omeprazole / Omeprazole sulphone	1.19 (52.7)	1.15 (100.9)
AUC_t	Omeprazole / 5-hydroxyomeprazole	0.78 (59.0)	0.76 (61.5)
	Omeprazole / Omeprazole sulphone	1.36 (20.4)	1.37 (24.5)

[1] Omeprazole without ospemifene
[2] Omeprazole with ospemifene
Source: Table 9.2.4

The following table is the geometric mean ratio for the 3 hr concentrations time point and $AUC_{0\text{-}8hr}$ for omeprazole/5-hydroxyomeprazole and omeprazole/omeprazole sulphone with and without ospemifene pre-treatment (sponsor's table 6, section 6.2.1)

Calculated from	Metabolic ratio	B vs. A[2]
3 h concentrations	Omeprazole / 5-hydroxyomeprazole	0.97 (0.77-1.22)
	Omeprazole / omeprazole sulphone	0.97 (0.67-1.41)
AUC_t	Omeprazole / 5-hydroxyomeprazole	0.97 (0.88-1.08)
	Omeprazole / omeprazole sulphone	1.00 (0.88-1.15)

[1] Ratio of geometric means and 90% confidence interval (CI) for the ratio of geometric means
[2] Omeprazole with ospemifene / Omeprazole without ospemifene
%-changes can be obtained by subtracting 1 from the ratio and 90% CI
Source: Table 9.2.4

Study 15-50614

Title: Effect of ospemifene on *S*-warfarin pharmacokinetics study on CYP2C9 inhibition by ospemifene

Objective: The objective of the present study was to evaluate a possible inhibitory effect of ospemifene on *S*-warfarin (a sensitive CYP2C9 substrate) metabolism and pharmacokinetics.

Method: This study was conducted in open-label, balanced, two-period, and crossover design in 16 healthy postmenopausal women who were determined as CYP2C9 EMs (CYP2C9*1/*1 or CYP2C9*1/*2).

· Test product, dose, method of administration:
A single dose (2 tablets of 5 mg) of 10 mg warfarin (racemate) as a probe drug with 10 mg vitamin K were administered at one hour after a standard breakfast without (treatment A) or with (treatment B) treatment of ospemifene on the 8th day of its multiple treatment. A 60 mg tablet of ospemifene (manufactured by (b) (4) AB, Lot 0208-915) was administered once daily after breakfast during 12 days in the period of ospemifene pretreatment (treatment B). The treatment periods were separated by a drug free interval of at least 3 weeks.

· Pharmacokinetic evaluation:
Blood samples for pharmacokinetics of warfarin were collected at before and 2, 4, 6, 8, 12, 24, 48, 72, 96 and 120 hours after warfarin administration. Blood samples for determination of serum ospemifene and metabolite concentrations were collected at before the 6th, 7th and 8th doses of ospemifene.

The plasma concentrations of *S*- and *R*-warfarin were analyzed using a validated LC-MS/MS method. The serum concentrations of ospemifene and 4-hydroxyospemifene were analyzed using a validated LC-MS/MS method. PK parameters of *S*- and *R*-warfarin were calculated. The $AUC_{0\text{-}inf}$ of S-warfarin was regarded as the primary parameter to assess the inhibitory potential on CYP2C9 activity.

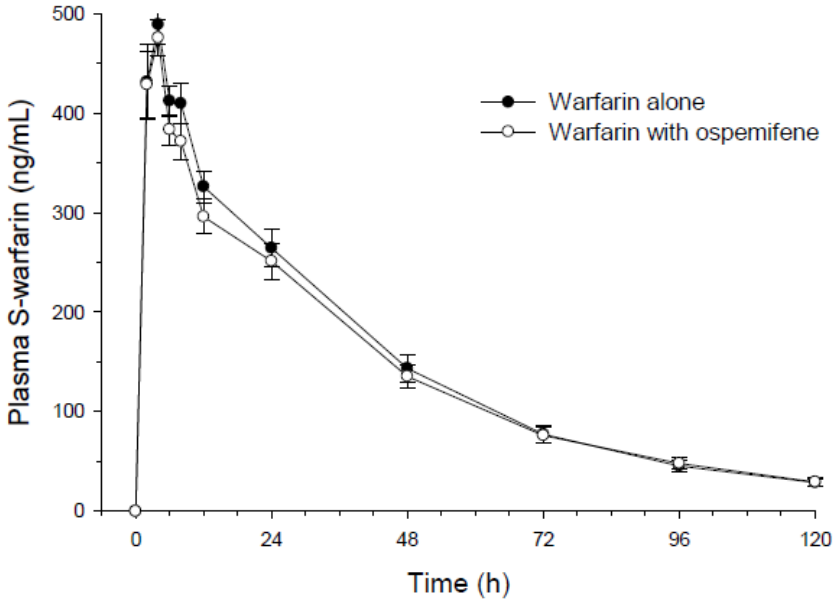
· Safety evaluation:
Adverse events were monitored during the study periods. The safety laboratory determinations were conducted at screening and post-study examinations.

Results

1. Study Population:
All 16 subjects completed the study. The age of subjects ranged from 51.8 to 71.0 and mean weight and BMI were 68.0 (±7.3) kg and 25.3 (±2.4) kg/m^2. Twelve of subjects had CYP2C9*1/*1 and 4 had CYP2C9*1/*2.

2. Pharmacokinetic results
The mean concentration-time profiles of *S*-warfarin were similar between warfarin only period without ospemifene and pretreatment period with multiple doses of ospemifene. Arithmetic mean or range of PK parameters of *S*-warfarin including C_{max}, t_{max}, $t_{1/2}$, AUC_t, AUC_∞, and CL/F were similar between two treatment periods. The point estimates of the geometric means ratio of C_{max}, AUC_t, and AUC_∞ were 96.8%, 95.5% and 96.3%, respectively. The 90% CI of geometric means ratio for $AUC_{0\text{-}inf}$ ranged from 90.9% to 102.0%. Arithmetic mean or range of PK parameters of *R*-warfarin were also similar between two periods.

The plasma concentration versus time profile of *S*-warfarin after administration of 10mg warfarin in the period with and without 60 mg ospemifene multiple pretreatment.

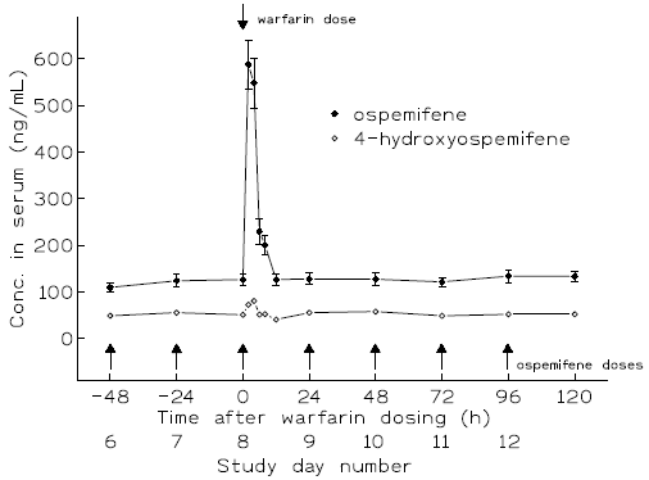


Parameters	*S*-warfarin (N=16)		Geometric mean ratio (90% CI)	*R*-warfarin (N=16)	
	with ospemifene	without ospemifene		with ospemifene	without ospemifene
C_{max} (ng/mL)	497 (14.5)	513 (13.3)	0.97 (0.92-1.02)	518 (15.2)	538 (15.4)
t_{max} (hr)	4 (2-6)	4 (2-8)	-	4 (2-6)	4 (2-8)
AUC_t (µg hr/mL)	17.2 (27.4)	18.0 (28.3)	0.96 (0.90-1.01)	26.2 (18.7)	27.8 (19.6)
$AUC_{0\text{-inf}}$ (µg.hr/mL)	18.5(29.9)	19.2 (30.2)	0.96 (0.91-1.02)	31.3 (21.7)	32.8 (23.1)
$t_{1/2}$ (hr)	30.4 (13.2)	29.2 (12.7)	1.04 (1.01-1.08)	43.8 (17.1)	42.7 (15.6)
CL/F (mL/hr)	587 (29.2)	564 (27.5)	1.04 (0.98-1.10)	334 (21.2)	320 (23.0)

3. The concentrations of ospemifene and 4-hydroxyospemifene

In the period of ospemifene pretreatment, the concentrations of ospemifene and 4-hydroxyospemifene were observed to reach the steady state already on the 7th day.

Mean concentration-time curves of ospemifene and 4-hdyroxyospemifene in serum after daily administration of 60 mg before and after warfarin dosing (N=16)



4. Safety

The number of treatment-emergent AEs was 58 (38 in the period with ospemifene pretreatment and 20 in the period without pretreatment), of which 32 (9 in mild group; 23 in moderate group) were considered to have a positive causal relationship to the study treatments.

The most abundant AE was headache to be reported 16 times by 8 subjects in the period with ospemifene pretreatment and 9 times by 8 subjects in the period without pretreatment.

Sponsor's conclusion

- The results of the primary PK parameter, AUC_{∞} of *S*-warfarin, as well as the results of all secondary PK parameters of *S*- and *R*-warfarin, demonstrated unequivocal equivalence when evaluated with standard bioequivalence methods.
- Thus, the study did not indicate the existence of a PK interaction between ospemifene and warfarin. It is concluded that ospemifene, administered orally at 60 mg/day, does not inhibit CYP2C9 activity.
- There were no SAEs in this study. The most frequently reported AE during the ospemifene period, headache, has been reported in previous studies.

Reviewer's comment

- The study design is acceptable to evaluate the effect of multiple treatment of ospemifene on the PK of **S**-warfarin as a CYP2C9 probe drug in target population, postmenopausal women.
- Study results showed that the PK of *S*-warfarin was not influenced by multiple pretreatment of ospemifene.
- There was no significant safety concern in this study. Headache, most common AE, was more frequent in the period with ospemifene pretreatment than without pretreatment.
- The applicant did not study the effect of ospemifene on multiple doses of warfarin.
- The effect of ospemifene on the PD effects (i.e. prothrombin time) of warfarin was not assessed. Based on the PK data, it is unlikely that ospemifene will interfere with drugs that are metabolized by CYP2C9. The applicant did not study the PD (INR and/or PT) of warfarin.

Study 15-50825

Title: Effect of ospemifene on bupropion pharmacokinetics–Study on CYP2B6 inhibition by ospemifene

Objective: The objective of the present study was to evaluate the possible effect of ospemifene on the PK of bupropion, a sensitive CYP2B6 substrate.

Method: This study was conducted in open-label, balanced, two-period, and crossover design in 16 healthy postmenopausal women who were not homozygous carriers of the CYP2B6*6 genotype.

Test product, dose, method of administration:

Treatment A (bupropion alone period) - A single dose of 150 mg bupropion (Zyban®, film-coated sustained release formulation) as a probe drug of CYP2B6 was administered at 8 am after overnight fast.

Treatment B (the period with pretreatment of ospemifene) - A 60 mg tablet of ospemifene (film-coated tablet manufactured by (b) (4) A07006) was administered once daily for seven days at 5 pm after a meal. On the 8th day, administration of bupropion for PK study was conducted in same method as treatment A and the last ospemifene dose was administered at 5 pm.

The treatment periods were separated with a drug free interval of at least 2 weeks.

Pharmacokinetics evaluation:

Blood samples for PK of bupropion were collected at before and 1, 2, 3, 4, 5, 6, 8, 12, 24, 32, 48, 56, 72 and 96 hours after bupropion administration.
Sampling for the steady state C_{min} of ospemifene and 4-hydroxyospemifene was collected at 1 hour prior to and 24 hours after last ospemifene dosing (8 and 32 hours blood sampling time-points after bupropion dosing, respectively). Sampling for C_{max} was collected at 3 hours after last ospemifene dosing (12 hours blood sampling time-point after bupropion dosing).
The plasma concentrations of bupropion and hydroxybupropion were analyzed using a validated LC-MS/MS method.

PK parameters of bupropion and hydroxybupropion which is known as a selective marker of CYP2B6 activity were calculated. Sponsor suggested that the AUC_{∞} of hydroxybupropion was regarded as the primary parameter and other PK parameters of hydroxybupropion and bupropion were considered secondary.

Safety evaluation

Adverse events were monitored during the study periods. The safety laboratory determinations were conducted at screening and post-study examinations.

Results

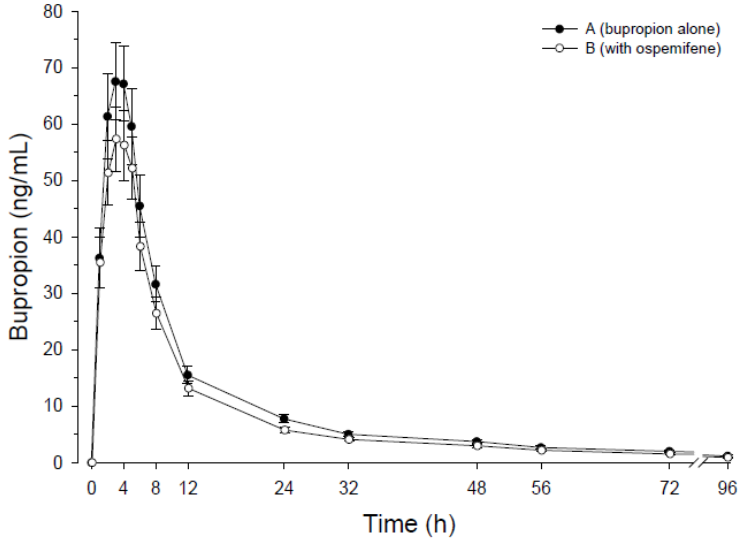
1. Study Population:

All 16 subjects completed the study. The age of subjects ranged from 50.9 to 70.4 and mean weight and BMI were 67.0 (±6.3) kg and 24.6 (±2.2) kg/m^2. All subjects who were homozygous CYP2B6*6 genotype (classified as a CYP2B6 PM) were excluded from the study.

2. Pharmacokinetic results:

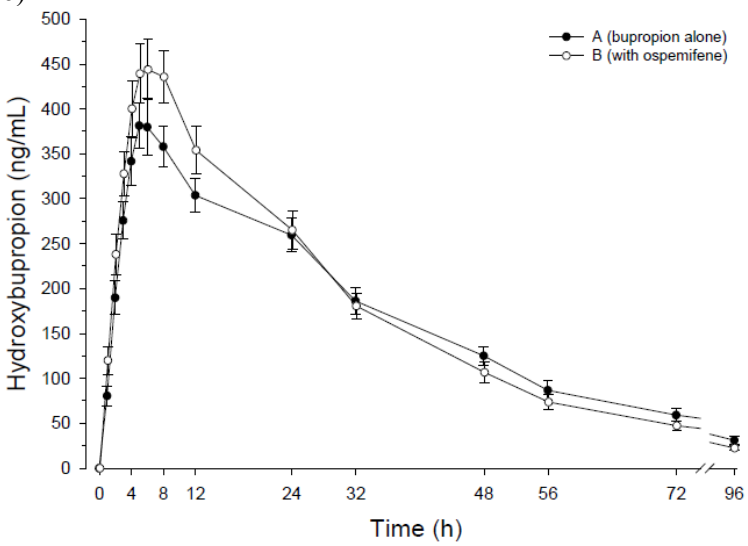
The mean plasma concentrations of bupropion were slightly lower in the ospemifene pretreatment period than that in the bupropion alone period.

The plasma concentration versus time profile of bupropion after a single oral administration of 150 mg bupropion with or without 8 days multiple treatment of 60 mg ospemifene (N=16)



Arithmetic mean of the AUC and C_{max} values of bupropion tended to be lower in the period with pretreatment of ospemifene than the bupropion alone period. The t_{max} and $t_{½}$ of bupropion were similar between two periods. The point estimates of the LS geometric means ratio (90% CI) of C_{max}, AUC_t, $AUC_{o\text{-}inf}$, and $t_{½}$ of bupropion were 0.82 (0.75, 0.91), 0.82 (0.78, 0.87), 0.81 (0.77, 0.86), and 0.97 (0.78, 1.21), respectively.

The plasma concentration versus time profile of hydroxybupropion after a single oral administration of 150 mg bupropion with or without 8 days multiple treatment of 60 mg ospemifene (N=16)



The mean plasma concentrations of hydroxybupropion were slightly higher in the ospemifene pretreatment period than that in the bupropion alone period.

Arithmetic mean and range of the AUC_t and AUC_∞ of hydroxybupropion were comparable between the periods with and without pretreatment of ospemifene, but the Cmax was increased in the period with ospemifene pretreatment. The t½ of hydroxybupropion tended to be lower in the period with pretreatment of ospemifene than the bupropion alone period. The point estimates of the LS geometric means ratio (90% CI) of C_{max}, AUC_t, AUC_∞, and $t_{½}$ were 1.16 (1.09, 1.24), 1.01 (0.96, 1.07), 0.98 (0.92, 1.04), and 0.80 (0.75, 0.85), respectively.

PK Parameters	Bupropion (N=16)		Geometric mean ratio (90% CI)	Hydroxybupropion(N=16)		Geometric mean ratio (90% CI)
	with ospemifene	without ospemifene		with ospemifene	without ospemifene	
C_{max} (ng/mL)	62.9 (40.4)	74.9 (36.6)	0.82 (0.75-0.91)	462 (29.0)	398 (30.6)	1.16 (1.09-1.24)
t_{max} (hr) *	3 (1-5)	3.5 (1-5)	-	6.1 (5-8)	6.0 (5-24)	-
AUC_t (µg hr/mL)	0.70 (38.5)	0.85 (33.7)	0.82 (0.78-0.87)	14.5 (31.7)	14.3 (28.1)	1.01 (0.96-1.07)
$AUC_{0\text{-}inf}$ (µg.hr/mL)	0.75 (38.5)	0.90 (32.3)	0.81 (0.77-0.86)	15.2 (32.4)	15.5 (29.4)	0.98 (0.92-1.04)
$t_{1/2}$ (hr)	29.5 (26.7)	30.8 (29.4)	0.97 (0.78-1.21)	21.2 (18.0)	26.7 (18.8)	0.80 (0.75-0.85)
CL/F (mL/hr)	230 (38.1)	185 (37.1)	1.23 (1.16-1.30)	ND	ND	

The mean (SD) steady-state C_{min} concentrations of ospemifene at Days 8 and 9 were 128.5 (40.1) ng/mL and 154.2 (62.5) ng/mL, respectively. The mean (SD) C_{max} concentration (at 3 hours after last ospemifene dosing) was 815.8 (286.4) ng/mL.

3. Safety

There were 43 treatment-emergent AEs (TEAE) during the study. There were no severe cases. The number of AEs that were considered to have a positive causal relationship with ospemifene was 10: headache (3), photophobia (2), constipation (1), erythema (1), hot flush (1), nausea (1) and pain in extremity (1).

Sponsor's conclusions

- Based on the results of this study, there was no evidence of CYP2B6-mediated metabolic drug interactions by ospemifene. The results of the primary PK parameter AUC∞ of hydroxybupropion demonstrated unequivocal equivalence: the 90% CI of the AUC ratio from 0.92 to 1.04 was well within the standard BE acceptance range. Corresponding results were obtained for the Cmax ratio, with a 90% CI from 1.09 to 1.24. The remaining secondary PK parameters further supported the absence of a PK interaction.
- There were no deaths, SAEs nor discontinuations due to adverse events during the study. The most frequently reported AE during the study, headache, has been reported in previous studies on ospemifene. In conclusion, both ospemifene and bupropion were well tolerated and safe.

Reviewer's comments

- The C_{min} and C_{max} concentrations of ospemifene after 8 days pretreatment ensured that its steady state was achieved when compared with results observed in other PK studies of ospemifene multiple treatment. The C_{min} concentrations of ospemifene at day 9 after the administration of bupropion tended to be higher than those measured at day 8 before bupropion dosing and observed in another study of ospemifene multiple treatment (in Study 15-50614

warfarin interaction study, the mean (SD) C_{min} was 128.2 (±50.5) ng/mL at Day 9 after 8 days pretreatment of ospemifene). This result may provide a possibility that bupropion can affect the disposition of ospemifene even though in vitro metabolism studies suggested that CYP2B6 contributes to the metabolism of ospemifene little or in minor portion.

- Study results showed that the PK of hydroxybupropion was not influenced significantly by multiple pretreatment of ospemifene. In particular, the AUC values of hydroxybupropion were similar between periods with and without ospemifene pretreatment. The multiple treatment of 60 mg ospemifene seemed to have no inhibitory effect on bupropion hydroxylation as a marker of CYP2B6 activity. However, the exposure, C_{max} as well as AUC, of bupropion appeared to be lower in the bupropion alone period than the ospemifene pretreatment period. PK mechanism to cause this result is not fully understood.
- The optimal administration method for maximum exposure of ospemifene could have been considered in the study design to evaluate the effect of ospemifene, as a potential competitive inhibitor of CYP2B6, on the disposition of bupropion.
  - Bupropion was administered at 8 am separately from ospemifene to be taken at 5 pm. Co administration or administration in short interval of ospemifene with bupropion would have been optimal to assure the maximum exposure of ospemifene.
  - Ospemifene was treated for 8 days. Last dosing of ospemifene was just administered on the day for bupropion PK study, even though blood samples were collected to 96 h after administration of bupropion. The implication of results derived from this study can be limited because dosing scheme to assure the maximum exposure of ospemifene in the study design was not considered well enough.
- There was no significant safety concern in this study.

APPENDIX

Component of [redacted] Gelatin Capsules Used for Clinical Studies (Module 2.7.1, Table 1)

Clinical Studies	Phase I		Phase II
Formulation	**25 mg [redacted] gelatin capsule**	**50 mg [redacted] gelatin capsule**	**30 mg [redacted] gelatin capsule**
Lot Number(s) (Manufacturer)	VL015L2	VL016L2, XC005L2	001, 002 [redacted]
Components			
Ospemifene	25 mg	50 mg	30.00 mg
[redacted]			
Pregelatinized starch			
Magnesium stearate			
[redacted]			
[redacted] gelatin capsule			

[1] [redacted]

Component of Film-Coated Tablets 5, 15, 30, 60 mg and Placebo Used for Clinical Studies (Module 2.7.1, Table 2)

Formulation	5 mg film-coated tablet	15 mg film-coated tablet	30 mg film-coated tablet	60 mg film-coated tablet	Placebo film-coated tablet
Lot Number(s) (Manufacturer(s))	A07005 [redacted]	0247A (Penn)	0248A (Penn)	0107-852, 0208-915 [redacted] 0249A (Penn), A07006, A10016, A10017, A10018, A10019, 85481, 85518, [redacted]	0246A (Penn) 85207 [redacted]
Core:					
Ospemifene	5.0 mg	15.0 mg	30.0 mg	60.0 mg	--
Lactose monohydrate	[redacted]				
Pregelatinized starch					
Mannitol					
Povidone					
Sodium starch glycolate					
Microcrystalline cellulose					
Colloidal silicone dioxide					
Magnesium stearate					
[redacted]					
Film-coat:					
[redacted]					
[redacted]					

[2] Consists of Hypromellose, Titanium dioxide, Lactose monohydrate, [redacted] and Triacetin [redacted]

Penn: Penn Pharmaceutical Services, UK

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

/s/

LAI M LEE
02/22/2013

MYONG JIN KIM
02/22/2013

NDA Number: 203505 **Applicant: Shionogi Inc.** **Stamp Date: April 25, 2012**

Drug Name: Ospemifene **NDA Type: Original**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X		
2	Has the applicant provided metabolism and drug-drug interaction information?	X		
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x		
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		x	n/a
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	X		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			n/a
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			n/a
11	Is the appropriate pharmacokinetic information submitted?	X		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X		
14	Is the clinical pharmacology and biopharmaceutical	X		

	section of the NDA indexed and paginated in a manner to allow substantive review to begin?			
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
17	Was the translation from another language important or needed for publication?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___YES_____

The following will be Clinical Pharmacology review issues to be conveyed to the Sponsor:

- The demonstration of bioequivalence between formulations Penn 5 and (b) (4)
- The in vivo drug interaction between ketoconazole, fluconazole or omeprazole and ospemifene
- Submit the results from the renal impairment study using the new classification scheme of renal impairment as described in FDA's Draft Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010)

Please submit the population PK (PPK) and PPK/PD datasets and their corresponding analysis codes to support the review process:

- All datasets used for model development and PPK/PD analyses should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any data point and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets. The flag of exclusion should be clearly explained in the define.pdf file.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- If applicable, a model development decision tree and/or table which gives an overview of modeling steps.

LaiMing Lee	May 15, 2012
Reviewing Clinical Pharmacologist	Date
Myong-Jin Kim	July 9, 2012
Team Leader/Supervisor	Date

Office of Clinical Pharmacology Filing Memo

NDA: 203505
Compound: Ospemifene
Sponsor: Shionogi Inc.

Submission Date: April 25, 2012
Filing Review Date: May 15, 2012
Reviewer: LaiMing Lee, PhD

Ospemifene is developed by Shionogi for the treatment of vulvar and vaginal atrophy (VVA) due to menopause, including moderate to severe symptoms of dyspareunia and/or dryness and physiological changes (parabasal cell, superficial cells, and pH). Ospemifene is a selective estrogen receptor modulator (SERM) and is also referred to as an estrogen receptor agonist/antagonist. Ospemifene has an agonist effect on estrogen receptor in the vagina and bone, is neutral on the uterus, and anti-estrogenic in breast tissue. It is a new molecular entity (NME) and, if approved, will be the first non-estrogenic agent for the treatment of VVA.

Ospemifene is a solid, oval biconvex, white to off-white, film coated immediate release (IR) oral tablet. The proposed dosing regimen is one 60 mg tablet once daily with food.

The clinical program includes 7 biopharmaceutics, 21 clinical pharmacology studies, and 3 Phase 3 studies (2 pivotal and 1 endometrial safety). A population PK study evaluating age, race, renal function, and race was conducted. There are 7 in vitro studies. In addition, the sponsor evaluated the effect of ospemifene on bone formation and resorption.

Based on in vitro studies (15-4304 and 15-4318) in human liver microsomes and recombinant human CYP enzymes, the sponsor believes ospemifene is primarily metabolized by CYP3A4, 2C9, and 2C19. M1 (4-hydroxyospemifene) and M2 (4'-hydroxyospemifene) are the active metabolites of ospemifene. According to the sponsor, both M1 and M2 have activities resembling those of ospemifene. M1 is the most abundant metabolite formed, comprising up to 75% of the metabolites, followed by M2 and M3 (carboxylic acid). They believe CYP3A4 is the principal contributor to the formation of M1, accounting for 40 to 50% of the formation, whereas CYP2C9 and CYP2C19 contribute the rest in equal share, and that other CYPs only have a negligible role in the metabolism of ospemifene to M1. CYP3A4 contributes about 45% of the formation of M2 with CYP2C19 and CYP2B6, contributing to the rest of the formation of this metabolite.

The sponsor evaluated the ability of ospemifene to inhibit CYP enzymes and found that ospemifene inhibited CYP2B6, CYP2C9, CYP2C19, CYP2C8 and CYP2D6 with IC50 values in the range of 7.8-49 μM. The peak concentration in postmenopausal women after repeated daily administration of 60 mg ospemifene and M1 was approximately 3 μM and 1-2 μM, respectively (in vitro study 15-50927). This concentration is lower than the concentrations inhibiting the enzyme specific reactions above. The enzyme inhibition potential of M1 and M2 has also been studied in vitro.

Due to significantly lower systemic exposures of M1 (25%) and M2 (7%) compared to ospemifene, the sponsor states that the pharmacological effects of ospemifene in humans are likely due to the parent compound. The sponsor conducted in vivo drug-drug interaction study to evaluate the effect of CYP3A4, CYP2C9, and CYP2C19 inhibitors on the metabolism of ospemifene and the effect of ospemifene on substrates of CYP3A4, 2C9, 2C19, and 2B6 enzymes.

Based on in vitro study 15-4316 and 15-4317, the sponsor states that ospemifene showed a high Caco-2 permeability and is not a significant P-glycoprotein substrate; no in vivo transporter study was conducted.

Formulation
The proposed drug product is an IR film-coated tablet. Phase 1 and 2 clinical studies were conducted with a capsule formulation. Batch 0249A (also referred to as "Penn 5") was manufactured at Penn Pharmaceutical Services in South Wales, UK and was used in the first pivotal Phase 3 clinical trial 15-50310. Batch A07006 (also referred to as [redacted] was manufactured at [redacted] and was used in the second pivotal Phase 3 clinical trial 15-50821. The sponsor conducted bioequivalence study 15-51031 comparing the bioequivalence of two 60 mg ospemifene tablets (Penn 5 and [redacted] manufactured by two different companies and manufacturing facilities. Penn 5 is the proposed to-be-marketed formulation.

Phase 3 Clinical Trials
The following is a brief description of the three completed Phase 3 clinical studies:

15-50310 (Phase 3) – 30 or 60 mg ospemifene doses; oral tablets; placebo; 12 weeks; ospemifene administered with food; Penn 5 clinical batch

15-50821 (Phase 3) – 60 mg ospemifene dose; oral tablets; placebo; 12 weeks; ospemifene administered with food; [redacted] clinical batch

15-50718 (Phase 3) – 60 mg ospemifene; oral tablets; placebo; long-term endometrial safety; 52 weeks; Penn 5 clinical batch

Efficacy Endpoints: 4 co-primary endpoints (parabasal cells, superficial cells, vaginal pH, most bothersome symptom). Most common drug-related adverse events were hot flushes, vaginal discharge, genital discharge, muscle spasm, and hyperhidrosis.

In the pivotal clinical trials (15-50310 and 15-50821) ospemifene tablets were administered with food. Sponsor states that dose selection for the Phase 3 trials was based on the results of the Phase 2 Studies 1506001 and 1506002 where the doses 30, 60, and 90 mg were evaluated.

Phase II Clinical Study
1506001 – dose finding; effects of ospemifene and raloxifene on bone formation; 30 mg gelatin capsule formulation; doses included 30, 60, or 90 mg once daily; 12 weeks; sponsor states that ospemifene had a positive effect on atrophic vaginal epithelium, reflected by changes in parabasal cells, intermediate cells, and superficial cells in the vaginal smear; most bothersome symptoms were not assessed.

1506002 – dose finding; effects of ospemifene on bone, vascular endothelium, lipid metabolism and endometrium; 30 mg gelatin capsule formulation; doses included 30, 60, or 90 mg once daily; administered with at least 200 mL of water; 12 weeks; sponsor states that ospemifene had a positive effect on atrophic vaginal epithelium, reflected by changes in parabasal cells, intermediate cells, and superficial cells in the vaginal smear;

15-50717 – dose-ranging study; doses included 5, 15, or 30 mg oral tablets; Penn 5 formulation; ospemifene once daily in the morning with food (both low and high fat food); there appears to be a dose dependent increase in adverse events such as headache, vaginal candidiasis, muscle spasm, and vaginal/genital discharge.

Phase I Biopharmaceutics Studies
1506004 – a relative bioavailability study; fasted condition; comparing bioavailability of ospemifene 60 mg tablet and capsule formulations [redacted] Batch 0107-852 and [redacted] Batch 002)

15-50926 – first bioequivalence study; fasted condition; Penn 5 and [redacted] (b) (4) Batch 85518; the sponsor states bioequivalence was not met.

15-51028 – second bioequivalence study; fasted condition; Penn 5 and [redacted] (b) (4) Batch 85481; the sponsor states bioequivalence was not met.

15-51029 – third bioequivalence study; fed condition; Penn 5 and [redacted] (b) (4) Batch 85481; the sponsor states bioequivalence was not met.

15-51031 – fourth (pivotal) bioequivalence study; fasted condition; postmenopausal women; comparing bioequivalence of two 60 mg ospemifene tablets Penn 5 and [redacted] (b) (4) the sponsor states the two formulations are bioequivalent

Phase 1 Clinical Pharmacology Studies
The following is a brief description of the Phase 1 Clinical Pharmacology studies:

3044001 (former number 15-59501-01; single ascending dose, first-in-human) was an open-label, single dose, Phase I dose escalation study in 28 healthy male subjects with seven doses (10, 25, 50, 100, 200, 400, and 800 mg in gelatin capsules without any excipients) to evaluate the safety, tolerability, PK, and PD of ospemifene after a single administration after an overnight fast.

Median Tmax was 3 hrs and ranged from 1 to 6 hrs for all seven dose groups. Cmax increased in a dose-dependent (not dose proportional) manner. AUC was variable and did not correlate with dose.

1506003 (former number 3044002; multiple dose, once daily) was a multiple dose, double-blind, parallel group study in healthy postmenopausal women evaluating the safety, tolerability, PK, and PD (endometrial thickness, endometrial histology, lipid, hormone, and bone metabolism) of ospemifene 25, 50, 100, and 200 mg and placebo.

15-50927 (single and multiple dose, once daily) was a single and multiple dose, open-label, single group study in twelve healthy postmenopausal women. One 60 mg ospemifene tablet (Batch [redacted] (b) (4) 88518 manufactured at [redacted] (b) (4) was administered once daily after a meal for 9 days.

15-50206 (mass balance) was a single dose, mass balance study in six healthy postmenopausal women given a 60 mg ^{3}H-ospemifene oral solution after an overnight fast.

Ospemifene was extensively metabolized, with a large number of metabolites present in plasma, urine and feces. The principal radioactive component in both plasma and feces was ospemifene and 4-hydroxyospemifene. Ospemifene and 4-hydroxyospemifene accounted for approximately 20% and 14% of the total radioactivity in serum, respectively, based on AUC ratios. The majority of radiolabelled material was excreted in the feces (~75% total radioactivity). Renal elimination appears to be minimal (~7%). Less than 0.2% of the ospemifene dose was excreted unchanged in urine.

15-50820 (hepatic impairment) was an open-label, single dose, parallel study in postmenopausal women with hepatic impairment (defined by the Child-Pugh score, mild, moderate) given 60 mg ospemifene after a standard meal. Subjects were age matched in the control group.

AUC0-inf and Cmax were about 0.9% and 21% lower, respectively, in subjects with mild hepatic impairment, compared to subjects with normal hepatic function.

AUC0-inf and Cmax were about 45% higher and 41% lower, respectively, in subjects with moderate hepatic impairment, compared to subjects with normal hepatic function.

15-50920 (hepatic impairment) was an open-label, single dose, parallel study in postmenopausal women with hepatic impairment (defined by the Child-Pugh score, moderate) given 60 mg ospemifene after a standard high fat/high calorie meal. Subjects were age and race matched in the control group. This study was conducted due to difficulties in recruiting patients with moderate hepatic impairment in Study 15-50820.

AUC0-inf and Cmax were about 29% and 1% higher, respectively, in subjects with moderate hepatic impairment, compared to subjects with normal hepatic function.

15-50921 (renal impairment) was an open-label, single dose, parallel group study in postmenopausal women with severe renal impairment (CrCl < 30 mL/min) given 60 mg ospemifene after a standard high fat/high calorie meal.

AUC0-inf and Cmax were about 20% higher and 21% lower, respectively, in subjects with severe renal impairment, compared to subjects with normal renal function.

15-50208 and 15-50208-02 (food effect) consisted of two sub-studies. The first sub-study was a randomized, open-label, two-sequence, two-period, crossover study designed to assess the effect of a high-fat meal on PK of ospemifene. The second sub-study was an open-label, one-period, one-treatment, non-randomized study designed to assess the effect of a low-fat meal on PK of ospemifene.

Following administration of a 60 mg ospemifene tablet, the AUC0-last and Cmax after a high-fat, high-calorie meal were about 2.8- and 3.6-fold higher, respectively, compared to the fasted state. The AUC0-last and Cmax after a light breakfast were about 1.9- and 2.3-fold higher, respectively, compared to the fasted state. The sponsor states that ospemifene should be given with food.

15-50716 (Effect of CYP3A4 inhibitor (ketoconazole) and CYP3A4 inducer (rifampin) on ospemifene) was an open-label, randomized, three-period, crossover study in 12 postmenopausal women administered with a single 60 mg dose of ospemifene following a meal with and without pre-treatment with rifampin and ketoconazole. Treatments include (1) 60 mg ospemifene after a standard meal as a single dose, (2) once daily administration of 600 mg rifampin in the fasted state for 5 days and 60 mg ospemifene after a standard meal on 6th day, and (3) once daily administration of 400 mg ketoconazole after a meal for 4 days and 400 mg ketoconazole and 60 mg ospemifene on 5th day followed by 3 days once daily administration of 400 mg ketoconazole.

Rifampin reduced the AUC0-inf and Cmax of ospemifene by 58% and 51%, respectively.

Ketoconazole increased the AUC0-inf and Cmax of ospemifene by 42% and 46%, respectively.

Tmax and $t_{1/2}$ were similar in all groups and was essentially unaffected by rifampin or ketoconazole.

15-50823 (Effect of CYP3A4/CYP2C9/CYP2C19 inhibitor (fluconazole) and CYP2C19 inhibitor (omeprazole) on ospemifene) was an open-label, randomized, two- and three-period, crossover study in 14 postmenopausal women administered with a single 60 mg dose of ospemifene following a meal with and without pre-treatment with fluconazole and omeprazole. The fluconazole treatment period included 200 mg fluconazole (400 mg on Day 1) administered once daily under fasted condition for 8 days and on the 5th day one tablet of 60 mg ospemifene was administered under fed condition. The omeprazole treatment period included 40 mg omeprazole administered once daily under fasted condition for 8 days

and on the 5th day one tablet of 60 mg ospemifene was administered under fed condition. Subjects were genotyped as extensive 2C9 and 2C19 metabolizers

Co-administration of fluconazole resulted in AUC0-inf increase of ospemifene by 174% by inhibiting CYP3A and CYP2C9 concomitantly. Fluconazole increased Cmax and $t_{1/2}$ by 66%. The sponsor states that ospemifene should not be used concomitantly with strong inhibitors of CYP3A and CYP2C9.

Co-administration of omeprazole (a CYP2C19 inhibitor) increased AUC0-inf of ospemifene by 17%. Omeprazole increased Cmax of ospemifene by 20% and did not affect $t_{1/2}$. The sponsor states that no dose-adjustment is required when ospemifene is co-administered with drugs that are inhibitors of only CYP2C19.

15-50614 (Effect of ospemifene on CYP2C9 (warfarin) is an open-label, two-period, crossover study in 16 healthy postmenopausal women given single dose of 10 mg warfarin with and without pre-treatment of 60 mg ospemifene once daily for 8 days following a meal.

The geometric least square means (90% CI) for test (warfarin + ospemifene)/reference (warfarin alone) ratio of S-warfarin AUC0-inf was 0.96 (0.91, 1.02). The sponsor states that repeated dosing of 60 mg ospemifene does not affect CYP2C9 activity. For Cmax, the LSM (905 CI) ratio was 0.97 (0.92, 1.02).

15-50719 (Effect of ospemifene on CYP2C19 and CYP3A4 (omeprazole)) was an open-label, two-period, crossover study in 12 postmenopausal women administered with a single 20 mg omeprazole with and without pre-treatment of once daily 60 mg ospemifene for 7 days. Women were genotyped as not being poor metabolizers of CYP2C19 were included in the PK analysis.
The ratios of the geometric means (90% CI) of the metabolic indices (with/without ospemifene) were 0.97 (0.77, 1.22) for 5- hydroxyomeprazole and 0.97 (0.66, 1.41) for omeprazole sulphone. The sponsor states that ospemifene does not have an effect on the metabolism of omeprazole and that repeat dosing of ospemifene does not significantly affect CYP2C19 and CYP3A4 activity.

15-50825 (Effect of ospemifene on CYP2B6 (bupropion)) is an open-label, two-period, two sequence, randomized, crossover study in 16 postmenopausal women administered a single 150 mg dose of bupropion with and without pre-treatment of once daily 60 mg ospemifene for 7 days. Subjects were genotyped as not being homozygous for CYP2B6*6.

The geometric mean AUC0-inf and Cmax of bupropion decreased by 19% and 18%, respectively, with ospemifene co-administration. The sponsor concludes that ospemifene has no impact on CYP2B6 activity and no dose modification is required if ospemifene and bupropion are co-administered.

15-50824 (thorough QTc) was a randomized, double-blind, active and placebo-controlled trial in 200 healthy male and female subjects (50 subjects each arm: 25 women and 25 men) between 18 and 45 years of age. The total treatment duration was 7 days. Subjects were randomized to receive placebo daily, ospemifene 60 mg/day, ospemifene 240 mg/day (supratherapeutic dose), or moxifloxacin (active control) after a high-fat breakfast.

The sponsor states that there was no effect of any of the two ospemifene doses on the QTc interval of any other electrocardiographic parameters, including heart rate, PR, or QRS interval.

Population PK (15-50310, 15-50821, 15-50718, 15-50927, 15-50820, 15-50920, and 15-9021) was conducted to evaluate the effects of demographic factors (i.e. body weight, CrCl, age, hepatic and renal function, on the PK of ospemifene based on the pooled data from Phase I and Phase III studies in

postmenopausal women under fed conditions. The sponsor states that no clear relationships were observed; no dose adjustment is required based on age, body weight, renal function, liver function or race.

Pivotal Bioequivalence Study 15-51031: Clinical Site (b) (4) and Analytical Site (b) (4)
On July 9, 2012, Michael Skelly, PhD, a pharmacologist in the Division of Bioequivalence and GLP Compliance Office of Scientific Investigations, informed the Clinical Pharmacology Review Team that (b) (4) was last inspected on 7/21/11 and covered NDA 22-113 and was classified NAI (No Action Indicated, no adverse observations). (b) (4) was last inspected on 5/10/11 (NDA 202-123) and 6/6/11 (NDA 202-133) were also classified NAI. The Establishment Inspection Report (EIR) reviews are in DARRTS.

The (b) (4) studies for NDA 203-505, including the ones with failed BE outcomes, appear to have been done at approximately the same time as the ones covered by our inspections. Therefore, OSI does not have a separate reason to call for inspection and audit of these studies. According to your judgment, if you request inspections, we can arrange them in time for the PDUFA deadlines.

For tamoxifen and toremifene BE studies with similar analytical methodology and some pharmacokinetic features in common, we encountered variability like the ospemifene studies. The EIR Reviews (e.g., ANDA 74-539) and other records may not be available now, according to our record retention policies.

Based on Dr. Skelly's recommendation, discussion with Dr. Sam Hadiar (Chief, Bioequivalence Investigations Branch, Division of Bioequivalence and GLP Compliance, Office of Scientific Investigations), and preliminary review of the BE study, this reviewer feels no need to have an additional clinical site and analytical site inspection. Captain E. Dennis Bashaw, OCP DCP-3 Division Director, was informed of the above and supports that no additional inspection is necessary for this BE study.

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

/s/

LAI M LEE
07/09/2012

MYONG JIN KIM
07/09/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	203-505
Submission Date	April 26, 2012
Product name, generic name of the active	Osfena (ospemifene)
Dosage form and strength	IR Tablet, 60 mg
Indication	Treatment of vulvar and vaginal atrophy due to menopause, including dyspareunia and/or vaginal dryness
Applicant	Shionogi, Inc.
Clinical Division	DRUP
Type of Submission	505(b)(1) Original NDA
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Biopharmaceutics Supervisor (acting)	Richard Lostritto, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		
3.	Does the application contain the dissolution method development report?	x		See Attachment. More information/data will be requested from the Applicant.
4.	Is there a validation package for the analytical method and dissolution methodology?	x		
5.	Does the application include a biowaiver request?		x	Not Applicable.
6.	Is there information provided to support the biowaiver request?		x	Not Applicable.
7.	Does the application include an IVIVC model?		x	Not Applicable.
8.	Is information such as BCS classification mentioned, and supportive data provided?	x		The Applicant claims that ospemifene is a BCS Class 2 drug substance.
9.	Is information on mixing the product with foods or liquids included?		x	Not Applicable.
10.	Is there any in *vivo* BA or BE information in the submission?	x		BA/BE data were included to support the bioequivalence of Phase I/II and Phase III products as well as drug product manufactured from different manufacturing sites (these information/data will be reviewed by OCP).
11.	Is information linking the commercial and phase 3 formulations included?	x		The commercial and phase 3 formulation are the same.

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
12.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
13.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	-	-	Not Applicable.
14.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		IR comments will be sent to the Applicant in the 74 day letter. The comments are outlined in the Attachment.

{See appended electronic signature page}
Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment
06/28/12
Date

{See appended electronic signature page}
Sandra Suarez-Sharp, Ph.D.
Biopharmaceutics Team Leader (acting)
Office of New Drug Quality Assessment
06/28/12
Date

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

ATTACHMENT

Biopharmaceutics Information:

The Biopharmaceutics information in this submission includes a drug product development section with the proposed dissolution method and acceptance criterion.

The proposed dissolution method:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	50 rpm	900 mL	37 °C	2% SDS in water

The proposed dissolution acceptance criterion:

Acceptance Criterion
Q = (b) (4) at 60 minutes

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion.

To aid the review of the Applicant's submission, the following comments will be conveyed to the Applicant:

1. There is insufficient data to support the adequacy of the proposed dissolution method (e.g. selected dissolution medium and surfactant are not justified). Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:

    a. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters supporting the proposed dissolution method as the optimal test for your product (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.). The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least (b) (4) of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.

    b. Data to support the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent.

2. Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for your proposed product.

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

/s/

KAREEN RIVIERE
06/28/2012

SANDRA SUAREZ
06/28/2012