CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-200

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-200	**Code:** 1P
Name: Zelmac™ (Tegaserod) Tablets	
Sponsor: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936	
Submission Type: Original NDA	**Submission Date:** February 11, 2000
Reviewer: Suresh Doddapaneni, Ph.D.	

SYNOPSIS

Tegaserod, a partial agonist of (5-HT_4) receptors, is intended to be used for the treatment of patients with constipation predominant Irritable Bowel Syndrome (C-IBS). The clinical pharmacology and biopharmaceutics aspects of the drug have been adequately characterized. Tegaserod tablets have an absolute bioavailability of about 10%. The absorbed tegaserod undergoes complete metabolism undergoing direct glucuronidation (to form the isomeric metabolites, M43.2/M43.8/M45.3) and does not have a cytochrome P450 component. It is not excreted unchanged in the urine. Tegaserod also undergoes presystemic hydrolysis, followed by oxidation and glucuronidation to form metabolites M29.0 and M7.0. M29.0 is the major of the three metabolites formed and does not have promotile activity. Tegaserod is highly protein bound to the extent of 98% to α_1-acid glycoprotein. Tegaserod exhibits linear pharmacokinetics at single and twice a day multiple doses up to 12 mg and does not accumulate. Age, gender, and weight have no effect on the pharmacokinetics. Dosage adjustment is not warranted in renal impairment. Inadequate and/or lack of data do not permit rationale dosage adjustment in moderate and severe hepatic impairment subjects. Food has significant effect on the bioavailability of tegaserod such that tegaserod has to be taken 30 minutes before food to mimic the clinical study conditions. No metabolic drug-drug interactions are expected when tegaserod is coadministered with other drugs. The dissolution method and proposed specifications are adequate. The to-be-marketed and clinical formulations were adequately linked through *in vivo* and *in vitro* data.

RECOMMENDATION

The Human Pharmacokinetics and Bioavailability section of original NDA 21-200 submitted on 2/11/00 is acceptable from the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics. The Clinical Pharmacology and Biopharmaceutics related labeling changes made to the sponsor's version should be conveyed as appropriate.

/S/ 7/11/00

Suresh Doddapaneni, Ph.D.
Clinical Pharmacologist, DPE II/OCPB

Concurrence by Shiew-Mei Huang, Ph.D. /S/ 7/11/00
Acting Division Director, DPEII/OCPB

CC:

NDA 21-200, HFD-180 (Division File, Levine), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Shiew-Mei Huang), Zom Zadeng (CDR).

TABLE OF CONTENTS

SUMMARY

1. What is the pharmacological class, scientific rationale, and intended use of tegaserod hydrogen maleate?

Tegaserod (also referred to as SDZ HTF 919) is a partial agonist of serotonin type-4 (5-HT_4) receptors located in the GIT without appreciable affinity for 5-HT_3 or dopamine receptors. In animals with normal or impaired GI motility, stimulatory effects were observed on gastric emptying, small intestine motility, as well as colonic transit and motility confirming its prokinetic action. Currently, this product is not approved in any country.

Tegaserod is intended to be used for the treatment of patients with constipation predominant Irritable Bowel Syndrome (IBS). It is expected to provide relief and improve the main symptoms such as; (i) improvement in abdominal discomfort and pain (ii) reduction in the number of days with significant abdominal discomfort and bloating (iii) reduction in the number of days with no bowel movements and (iv) reduction in the number of episodes with hard or very hard stool. The proposed dosage regimen is 6 mg bid.

2. What are the physicochemical properties of tegaserod substance and the composition of the to-be-marketed tablet formulation?

Tegaserod is a low solubility and low permeability drug and falls under class IV of the Biopharmaceutics Classification System.

Tegaserod hydrogen maleate is a white to off-white fine crystalline powder. The solubility's in water and all of the aqueous buffer solutions are very low (USP buffer pH 4.5, ——— w/v; pH 6.5, ——— w/v) and even the addition of surfactants to improve the solubility's resulted only in minor improvements. The best solubility is in PEG (——— .

Zelmac has been formulated as an immediate release tablet. The market formulations are 2 and 6 mg, whitish to slightly yellowish, marbled tablets. The ——— composition of both strengths and the function of each excipient in the formulation are shown in table 1. Although, the two strengths are ——————————— both have been evaluated in clinical trials.

Table 1. Composition of to-be-marketed tablets.

Ingredients	2 mg tablets (mg)	6 mg tablets (mg)	Function
Tegaserod —	2.77	8.31	Active substance
Poloxamer 188			
——— HPMC			
——— /PEG 4000			
Glyceryl monostearate			
Lactose monohydrate			
Crospovidone			
———			
Target tablet weight			

3. What does the mass balance studies contribute to understanding the disposition pathways of the drug, and the relative importance of these pathways in healthy volunteers and patients?

Tegaserod is a poorly absorbed drug based on the fact that only 27% of the orally administered dose was recovered in urine while 58% was recovered in feces (as unchanged tegaserod) by the end of 168 hours. The absorbed tegaserod undergoes extensive metabolism, as unchanged tegaserod was not detected in the urine. Metabolite M29.0, which is inactive, comprised the major metabolite.

Upto 24 hour of the dose excreted in the urine, metabolite M7.0 comprised about 7%, metabolite M29.0 comprised about 13%, and N-glucuronide metabolites (M43.2/M43.8/M45.3) comprised about 2%. Metabolite M29.0 shows negligible affinity to the 5-HT_4 receptor and is devoid of promotile activity in the dog.

4. What is known about the *in vitro* metabolism of the drug?

Tegaserod is neither a substrate nor an inhibitor of cytochrome P450 enzymes.

The metabolic pathway of tegaserod is schematically represented in figure 1. The biotransformation of tegaserod can be divided into two pathways-presystemic and systemic. The presystemic pathway is characterized by an initial nonenzymatic hydrolytic cleavage of the imine bond leading to the corresponding 5-methoxyindole-3-aldehyde. This initial hydrolysis is considerably fast at pH 2 and below, a situation commonly encountered in stomach. The aldehyde product is completely oxidized to the corresponding acid by aldehyde oxidase and partially or completely glucuronidated to form M29.0. The aldehyde product is also demethylated, oxidized and glucuronidated to form metabolite M7.0. *In vitro* experiments using human liver and intestinal slices did not show M29.0 and M7.0 metabolites.

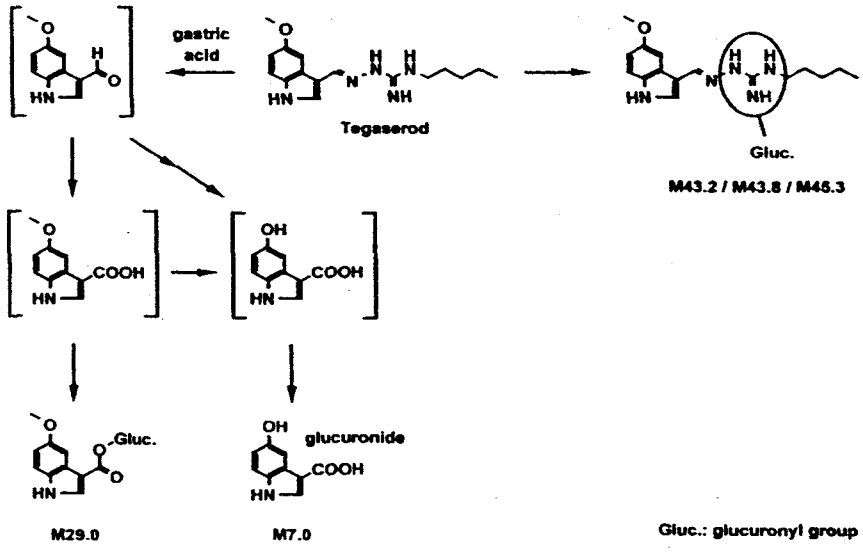
The systemic pathway consists of direct glucuronidation of the absorbed tegaserod to form the isomeric N-glucuronides M43.2/43.8/45.3.

Maximal tegaserod plasma concentrations following the recommended single 6 mg oral dose are in the range of 3-13 nM. The inhibitory concentrations of tegaserod towards 2C8, 2C9, 2C19, 2E1, and 3A were more than three orders of magnitude higher. With respect to 1A2 and 2D6, the inhibitory concentrations were more than 70-fold higher.

Table 2. Inhibitory potency of tegaserod towards the various CYP 450 isoforms.

Substrate	Isozyme	Pathway	IC_{50}/K_i
Phenacetin	1A2	O-deethylation	4 μM
Bufuralol	2D6	1 hydroxylation	1 μM
Paclitaxel	2C8	6-α-hydroxypaclitaxel	130 μM
Tolbutamide	2C9	4-hydroxylation	74 μM
S-mephenytoin	2C19	4-hydroxylation	153 μM
Chlorzoxazone	2E1	6-hydroxylation	100 μM
Cyclosporine A	3A	hydroxylation/N-demethylation	107 μM

Figure 1. Proposed tegaserod metabolic pathway.



Tegaserod is a substrate of Pgp. Theoretically, drug-drug interactions between another Pgp substrate/inhibitor and tegaserod are possible resulting in increased bioavailability. However, the sponsor considers that such an increase is limited by the moderate intrinsic permeability of tegaserod through Caco-2 cell monolayers when Pgp was inhibited by Cyclosporine.

5. What is the nature/extent of tegaserod plasma protein binding and does disease state/protein displacement by other drugs affect the its fraction free?

Tegaserod is bound to the extent of 98% in the concentration range of 20 to 20000 ng/mL primarily to α_1-acid glycoprotein. Protein binding did not change in subjects with hepatic and renal impairment. However, the sponsor states that because of the linearity in protein binding and large steady state volume of distribution, clinically relevant displacement interactions are unlikely.

6. What does the bioavailability and the pharmacokinetic parameters of ADME suggest about the drug?

The absolute bioavailability of tegaserod after oral administration is about 10% under fasting conditions (study W124). The mean values of plasma clearance, steady state volume of distribution, and terminal half-life after intravenous dosing are 77 liter/hour, 368 liters, and 11 hours, respectively (study W124).

The bioavailability of tegaserod was decreased by about 44% after pentagastrin pretreatment (median gastric pH <1) compared to no pretreatment (median gastric pH was 1.75). Bioavailability was also decreased by about 25% after omeprazole pretreatment (median pH >7.0) compared to no pretreatment. The major metabolite M29.0 levels were thrice as high after pentagastrin pretreatment. The M29.0 levels were negligible after omeprazole pretreatment. Essentially, under extreme acidic conditions, tegaserod's hydrolysis is promoted with decrease in tegaserod bioavailability and increase in M29.0 levels. On the other hand, under alkaline to neutral conditions, hydrolysis of tegaserod is decreased with decrease in systemic M29.0 levels. However, correspondingly tegaserod bioavailability is not enhanced as its solubility decreases significantly under these conditions.

7. Are the pharmacokinetics of the drug linear?

Tegaserod exhibits dose linearity in the dosage range tested in pivotal clinical trials.

In study W351, based on C_{max}, $C_{max,ss}$, and AUC, tegaserod exhibited dose-proportionality over the range of 2 to 12 mg administered as single and twice daily multiple doses (table 3).

8. Would tegaserod be expected to accumulate upon multiple dosing?

Tegaserod is not expected to accumulate upon multiple dosing up to 12 mg bid and its multiple dose pharmacokinetics are predictable from single dose data.

In study W351, the steady state pharmacokinetics after twice daily multiple dosing for 5 consecutive days of doses up to 12 mg bid tested in pivotal clinical trials were same as single dose pharmacokinetics.

Table 3. Tegaserod single and multiple dose pharmacokinetics.

	2mg FMI*	6 mg FMI	12mg FMI
Single dose			
C_{max}, ng/mL	0.9 ± 0.4	2.9 ± 1.1	6.3 ± 2.7
AUC, hour* ng/mL	4.4 ± 1.2	10.5 ± 4.6	20.1 ± 6.4
Multiple dose			
$C_{max,ss}$, ng/mL	0.7 ± 0.3	2.7 ± 1.2	5.6 ± 2.9
AUC_{τ}, hour* ng/mL	2.4 ± 1.3	8.9 ± 4.2	20.4 ± 14.0

*data for the 2 mg dose is not reliable because at several time points (6 hours and beyond), the concentrations were below LOQ

9. Is the pharmacokinetics different in patients?

The pharmacokinetics of tegaserod hydrogen maleate in IBS patients are comparable to those in healthy subjects.

Tegaserod pharmacokinetics were assessed in-patients with C-IBS (Phase II safety trial- —— and —— (Phase III efficacy trial- B351) who were otherwise healthy. Steady state profiles (up to 6 hours post dosing) were obtained on day 29 at twice daily doses of 2 mg and 6 mg. In general, the pharmacokinetics in patients with C-IBS and —→ were comparable. However, the pharmacokinetics were different in patients when compared to healthy subjects. The $C_{max,ss}$ and AUC_{0-6} were 30% to 50% lower in patients. However, the pharmacokinetics in

healthy subjects were determined under fasting conditions whereas the pharmacokinetics in patients were determined under fed conditions. The dosing in patients occurred within 30 minutes before breakfast and the reductions in C_{max} and AUC under these conditions determined in the food effect study W352 were found to be of similar magnitude. Overall, it does not appear that the pharmacokinetics of tegaserod are different in patients.

10. Is there a concentration response or dose response relationship?

Data is not available to assess the existence of a concentration-response relationship. The dose-response seems to be shallow over the range of 4 mg/day to 12 mg/day with no difference between the doses.

PK/PD assessments were not conducted in phase III efficacy trials because local tegaserod concentrations were not accessible (local and systemic concentrations are believed to play a role) and the main efficacy variable was the subject's weekly global assessment of relief. Other study designs in phases I/II were considered too complex from a PD point of view to additionally include PK investigations or PK assessments were not made so as not to interfere with the primary PD objectives.

The phase III efficacy trials (studies B301, B307, and B351) evaluated 4 mg/day and 12 mg/day doses in relation to placebo. Both doses have similar response rates (primary efficacy variable of subject global assessment of relief) compared to placebo showing a flat dose-response relationship (table 4). Except for diarrhea, there was no difference in the incidence of adverse events between the treated and placebo groups or relationship to tegaserod dose. Diarrhea occurred during the first week of therapy.

Table 4. Subject global assessment of relief in efficacy trials.

	4mg	12 mg#	placebo
Study B301- Response Rate(N=881)	27.8 (299)	26.2 (294)	20.5 (288)
Study B307- Response Rate(N=841)	25.5 (282)	26.5 (275)	28.2 (284)
Study B351- Response Rate(N=799)	29.4 (265)	26.2 (267)	22.1 (267)

study B307, 4-12 mg.

11. From a pharmacokinetic perspective does the drug have adequate safety margin?

An eight fold safety margin (for serious adverse events to occur) for acute dosing relative to the proposed dosage regimen of 6 mg bid seems to exist for tegaserod tablet.

The safety, tolerability, and pharmacokinetics of tegaserod have been investigated up to about 100 mg (200 mg with the _____ doses) as single and multiple tablet doses.

Single oral administrations of tegaserod (in six subjects each) were well tolerated at 1.25, 2.5, 5, 5, 12.5, 25, and 50 mg doses of the tablet. One to two episodes of loose stool occurred at all dose levels whereas at the 50 mg dose level, episodes of flatulence and abdominal pain also occurred. In the 100 mg group, severe adverse events including diarrhea, loose stool

and orthostatic hypotension occurred. All symptoms resolved spontaneously without therapeutic intervention. Dose-linearity was observed with respect to C_{max} and AUC up to 100 mg.

Multiple oral administration of 50 mg tid given for two weeks were generally tolerated in all healthy male subjects. All eight subjects on active drug and one placebo subject reported loose stools. One to episodes of other adverse events such as flatulence, vomiting, nausea, epigastralgia, and headache (4 episodes) were also reported. All symptoms were transient, of mild to moderate severity and resolved without therapeutic intervention. Pharmacokinetic data showed that there was moderate accumulation with ratios between 1.5 and 1.7.

12. How was the performance of the to-be-marketed dosage form documented relative to the pivotal clinical trial dosage form?

The to-be-marketed and clinical trial formulations were adequately linked through comparative in vitro dissolution release profiles and an in vivo relative bioavailability study.

— different solid oral formulations were used in clinical studies. ——— formulations, ——————————————— and — tablet formulations, final market form (FMF) and final market image (FMI) were used to address the varying needs for safety/tolerability, PK, PD, and efficacy studies in healthy subjects and patient populations.

The ———was used in the single dose (from 2.5 mg to 200 mg) and multiple dose (100 mg tid) safety/tolerability studies. There is no direct bioavailability link between —and FMF dosage forms. However, the relative bioavailability of —compared to — is about 1.29 (study W105), while that of FMF compared to — is 1.29 (study W112). An approximate estimate of ——— bioavailability of 48% relative to FMF is obtained by cross study comparison of the AUC's.

The FMF is the tablet of the final qualitative and quantitative composition. The FMF and FMI possess the same qualitative and quantitative composition, but differ by a slight change in the manufacturing process.

The FMI (2 and 6 mg strengths) was used in phase III clinical studies (B301, B307, B351). FMI and FMF were adequately linked through bioavailability study W351 (formulations were bioequivalent) and *in vitro* dissolution data (f2 was more than 50).

13. What is the effect of food and how does it influence dosing recommendations?

Food decreases significantly the extent of absorption of tegaserod and available data indicates that dosing can be done 30 minutes before meals.

In study W352, mean AUC and C_{max} were reduced by 40-65% and 20-40%, respectively when a 600 calories breakfast was fed 30 minutes before meal, 15 minutes before meal, 1 minute before meal, and 2.5 hours after meal, relative to fasting conditions (table 5).

Study W124 employing a meal close to FDA recommended meal showed similar effect under fed conditions. There did not seem to be one optimum time for dosing among the tested times. In phase II clinical studies, drug intake occurred 30 minutes before morning and evening meals. Even though, there was decrease in C_{max} and AUC at this time, since this was how it was studied clinically, dosing can be done 30 minutes before meals.

Table 5. Pharmacokinetic parameters (mean ± SD) of tegaserod after different times of food intake relative to dosing.

Parameter	Fasted	30 minutes before meal	15 minutes before meal	1 minute before meal	2.5 hours after meal
C_{max}, ng/mL	4.4 ± 1.9	3.6 ± 1.9	2.6 ± 1.4	2.8 ± 1.0	2.8 ± 1.3
*T_{max}, hours	1.0	0.7	0.8	0.7	1.5
AUC, ng*hour/mL	12.8 ± 4.6	6.6 ± 2.9	5.7 ± 2.7	6.1 ± 2.9	7.7 ± 3.4

*median

14. Do special populations (gender, pediatric, geriatric) and disease state (renal and hepatic) require adjustments in the dosage regimen?

14.1. Hepatic Insufficiency

No dosage adjustment is warranted in the mild impairment group. However, inadequate data in the moderate impairment group and no data in the severe impairment group preclude any rationale dosage adjustments in these groups.

Consistent with the fact that tegaserod has a metabolic component to its overall elimination, the pharmacokinetics were changed in hepatic insufficiency subjects (study W251). In subjects with mild insufficiency a higher C_{max} (about 116% of that of healthy controls) and AUC_{0-tz} (about 131% of that of the healthy controls) were observed with no change in the time to median t_{max}. In the only single subject with moderate impairment, the C_{max} and AUC_{0-tz} were considerably higher (240% and 300% of that of healthy controls).

Since tegaserod is well tolerated up to a 50 mg equivalent tablet dose with dose-linearity demonstrated under the investigated dose range, the increase in drug exposure in the mild insufficiency group study is not expected to cause a safety problem.

14.2. Renal Failure

No dosage adjustment is warranted in subjects with any degree of renal impairment.

Consistent with the fact that unchanged tegaserod is not excreted in urine, the pharmacokinetics of tegaserod were similar in both healthy and severe renal impairment subjects (study W354).

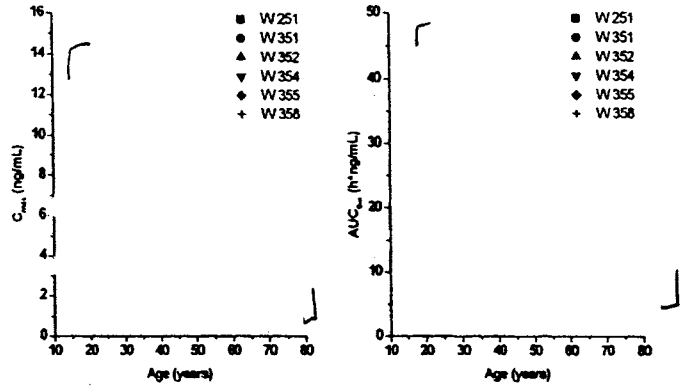
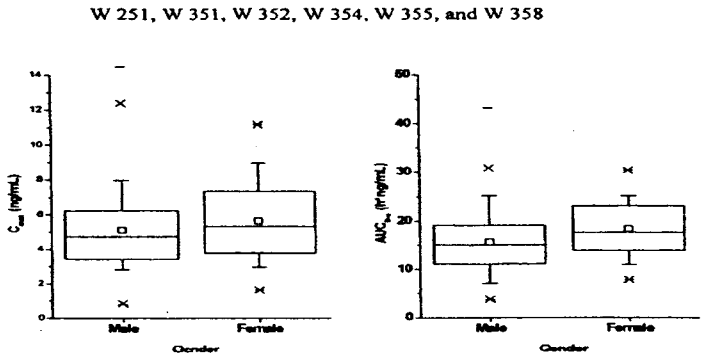


Figure 2. Relationship between C_{max} and $AUC_{0-\infty}$ versus age after a single administration of 12 mg dose of tegaserod to healthy subjects.

(a)



(b)

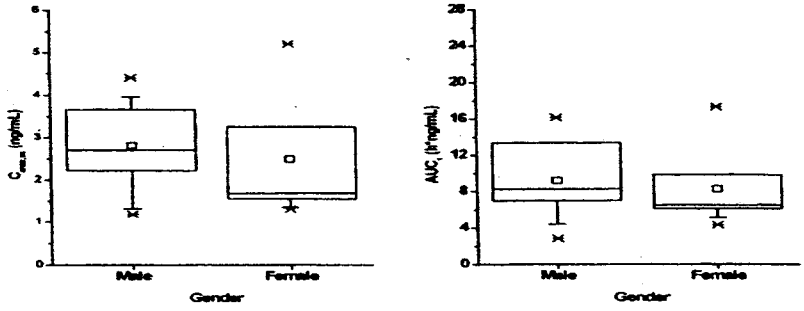


Figure 3. Box-Whisker plots of (a) C_{max} and $AUC_{0-\infty}$ after a single administration of 12 mg dose of tegaserod to healthy subjects from several studies (94 males and 40 females) and (b) $C_{max,ss}$ and AUC_{τ} after 6 mg bid doses of tegaserod to healthy subjects (11 males and 7 females) from study W351.

14.3. Gender & Elderly

There does not seem to be a consistent trend to indicate any significant gender or age effect.

Figure 2 shows the pooled C_{max} and AUC data as a function of age from several studies and there does not appear to be any specific trend to indicate that age affects the pharmacokinetics of tegaserod. Figure 3 shows the pooled C_{max} and AUC data as a function of gender from (a) several studies after single dose administration and (b) study W351 after multiple dose administration. There does not seem to be a definite trend to indicate any significant gender effect.

14.4. Pediatrics

The safety and effectiveness of tegaserod hydrogen maleate in pediatric patients below the age of 18 years have not been established.

[ ]

14.5. Race

Inadequate numbers among the different ethnic groups does not allow the assessment of race effect.

Sponsor pooled data from several studies and concluded that there was no race effect. However, the numbers from this analysis consists of 3 native Americans, 18 Blacks, 93 Caucasians, 11 Hispanics, and 8 Orientals for single dose data. For multiple dose data, the data was from 2 blacks, 13 Caucasians, and 3 Orientals. The multiple dose data in particular suggests substantial race effect. In light of the small number of subjects representing the different ethnic groups, concrete conclusions cannot be made regarding the absence or presence of a race effect.

14.5. Maternal/Fetal Ratio

Not determined.

14.6. Nursing mothers

Not determined in humans. However, the following statement is proposed in the package insert; *Tegaserod* ← *excreted in the milk of lactating rats with a high milk to plasma ratio.*

15. What was the significance of the drug-drug interaction studies and are dosage adjustments warranted?

Since, cytochrome P450 enzymes are not involved in the metabolism of tegaserod and tegaserod does not have appreciable inhibitory activity towards the various cytochrome P450 isozymes, studies exploring metabolic drug-drug interactions were not considered necessary.

However, dextromethorphan and theophylline were studied to confirm weak inhibitory potency of tegaserod towards CYP1A2 and CYP2D6 seen *in vitro* (see table 2). The effect of these two drugs on tegaserod pharmacokinetics was also assessed.

Effect of tegaserod on warfarin, digoxin, and oral contraceptives was investigated since the bioavailability of these narrow therapeutic agents can be affected secondary to the prokinetic pharmacologic effects of tegaserod. The full effect of these drugs on tegaserod pharmacokinetics was not assessed, as it was not deemed necessary.

15.1 Dextromethorphan

Dose adjustment of dextromethorphan is not necessary when tegaserod is coadministered with dextromethorphan.

Both, 6 mg bid tegaserod and 120 mg dextromethorphan pharmacokinetics were assessed alone and upon coadministration (study W360).

The mean values for C_{max} and $AUC_{0-\infty}$ of dextromethorphan after administration alone and after coadministration with tegaserod were similar with small differences between treatment means of 4% and 1% (higher after coadministration), respectively. Similar small reductions were seen in the C_{max} and $AUC_{0-\infty}$ (11% and 9%) of dextrorphan as well.

The mean values for C_{max} and $AUC_{0-\infty}$ of tegaserod after administration alone and after coadministration with dextromethorphan were slightly lower with differences between treatment means of 36% and 10%.

15.2. Theophylline

Dose adjustment of theophylline is not necessary when tegaserod is coadministered with theophylline.

A single dose of 600 mg of controlled release theophylline was either given alone or with 6 mg of tegaserod on day 2 of tegaserod dosing (study W359). A single dose of tegaserod was on day 1 followed by two doses 12 hours apart on day 2. Theophylline pharmacokinetics were not changed given alone or when coadministered with tegaserod (except t_{max} which decreased from a median of 8 hours to 6 hours on coadministration). For tegaserod, the C_{max} and AUC_{0-12} were increased by about 17% and 28%, respectively. However, this increase may in part can be attributed to the levels remaining from day 1 dosing.

15.3. Digoxin

Digoxin dosage need not be adjusted when coadministered with tegaserod.

On day 4 of tegaserod 6 mg bid administration for 6 days, 1 mg of digoxin was administered to healthy male and female volunteers.

A reduction of about 15% in C_{max} and $AUC_{0-\infty}$ of digoxin occurred following combination therapy compared to when given alone without any changes in the terminal half-life (study W252).

15.4. Warfarin

Dose adjustment warfarin is not necessary when coadministered.

On day 4 of tegaserod 6 mg bid administration for 7 days, 30 mg of warfarin was administered to healthy male and female volunteers (study W362).

The coadministration of tegaserod did not substantively alter the pharmacokinetic profile of R- or S-warfarin. . The 90% confidence intervals for log transformed C_{max} and $AUC_{0-\infty}$ were within the limits of —— No statistically significant changes in prothrombin time were seen.

No changes in trough concentrations of tegaserod were detected upon coadministration with warfarin compared to when tegaserod was given alone.

15.5. Oral Contraceptives

No alteration in oral contraceptive medication is necessary when tegaserod is coadministered.

Triphasil was given in combination with either 6 mg bid tegaserod or placebo for 28 days and the PK of ethinyl estradiol and levonorgestrel were assessed on day 21.

The pharmacokinetics of ethinyl estradiol and levonorgestrel were not changed upon coadministration with tegaserod (study W357). The 90% confidence intervals for log transformed $C_{max,ss}$, $C_{min,ss}$, and AUC_{0-12} were within —— limits. The progesterone concentrations measured on day 21 over the three menstrual cycle duration ranged from — — ng/mL with a mean of 0.44 ng/mL, well below the —ng/mL threshold allowing ovulation.

16. Does the dissolution test conditions and specifications appear to be appropriate to the physiological state, and related to *in vivo* conditions for BA and BE?

The proposed product dissolution release test method is as follows;
USP apparatus II (paddle); 50 rpm; deaerated purified water 500 mL, 37°C; minutes.

The proposed specification is;
Q= — at 30 minutes USP acceptance plan restricted to levels 1 and 2. At level 1, minimum percent of labeled amount dissolved is all six units individually more than ——— and at level 2 average of all units, more than — and for all units individually, more than ——
—

The solubility of tegaserod is pH dependent; below pH 3 it is rapidly degraded through hydrolytic breakdown. In USP buffer pH 4.5, dissolution was limited by low solubility of ——— (solubility volume of 4580 mL) and 900 mL of the medium were not enough to create sink conditions. Solubility at pH 7.5 was —— (solubility volume of 150 mL), —— (solubility volume of 222 mL) at pH 6.5, and —— (solubility volume of 24 mL) in the application medium purified water. Dissolution profiles were comparable for the 6 mg strength in

500 mL of water, 900 mL of buffer pH 6.5, and 900 mL of buffer pH 7.5 to attain sink conditions.

Table 3. Data from three representative batches.

Batch #	Units	Time (minutes)	Range	Mean % dissolved	% CV
X1880895	6	5	[	38.7	5.1
		15		96.2	1.3
		30		100.4	1.8
		60		101.8	1.7
X1420695	12	5		44.1	13.9
		15		100.0	5.3
		30		102.5	3.8
		60		103.2	3.6
F0110697	12	5		39.5	4.4
		15		98.3	2.8
		30		102.4	0.9
		60	]	102.6	1.1

17. Are the bioanalytical methods for *in vitro* studies, and subsequent clinical studies, specific, sensitive, reproducible and validated appropriately?

The bioanalytical methods used were specific, sensitive, and adequately validated.

Two different analytical methods, ——— were used for routine determination of tegaserod concentrations in plasma. A separate analytical]

[The three assay methodologies were fully validated and validation data are provided in each study report. Adequate information on ——— ——— were provided. In addition, complete information on the assay methodology used for the coadministered drugs was provided as well.

18. Is the Text Proposed in the Package Insert Accurately Reflect the Drug's Properties?

Note: Changes to the proposed language are indicated through strikethrough (deletions) and underlined (additions) text.

Pharmacokinetics

Absorption

——— peak plasma concentrations are reached approximately 1 hour after dosing. The absolute bioavailability of tegaserod ——— when administered to fasting subjects is

approximately 10%.

The pharmacokinetics are dose proportional over the 2 mg to 12 mg range given twice daily for 5 days. There was no clinically relevant accumulation of tegaserod hydrogen maleate in plasma when a 6 mg b.i.d. dose was given for 5 days.

Distribution

Tegaserod hydrogen maleate is approximately 98% bound to plasma proteins, predominantly alpha-1-acid glycoprotein. Tegaserod exhibited pronounced distribution into tissues following intravenous dosing with a volume of distribution at steady state of 368 ± 223 L.

Metabolism

Tegaserod is metabolized mainly via two pathways. The first is a presystemic acid catalyzed hydrolysis in the stomach followed by oxidation and conjugation which produces the main metabolite of tegaserod , 5-methoxyindole-3-carboxylic acid glucuronide. The main metabolite has negligible affinity for $5HT_4$ receptors,

The second metabolic pathway of tegaserod is direct glucuronidation which leads to generation of three isomeric N-glucuronides.

Elimination

The plasma clearance of tegaserod hydrogen maleate is 77±15 L/h with an estimated terminal half-life ($T_{1/2}$) of 11 ± 5 hours following intravenous dosing.

Special populations

[

]

Gender

[

]

Drug Interactions

In vitro drug-drug interaction data with tegaserod ——— indicated no inhibition of the cytochrome P450 isoenzymes CYP2C8, CYP2C9, CYP2C19, CYP2E1 and CYP3A4, whereas inhibition of CYP1A2 and CYP2D6 could not be excluded. However, in vivo, no clinically relevant drug-drug interactions have been observed with dextromethorphan (CYP2D6 prototype substrate), and theophylline (CYP1A2 prototype substrate). There was no effect on the pharmacokinetics of digoxin, oral contraceptives, and warfarin ——— The main human metabolite of tegaserod hydrogen maleate, 5-methoxyindole-3-carboxylic acid glucuronide, did not inhibit the activity of any of the above cytochrome P450 isoenzymes in in vitro tests.

Dextromethorphan: A pharmacokinetic ——— interaction study demonstrated that co-administration of tegaserod ——— and dextromethorphan did not change the pharmacokinetics of either compound to a clinically relevant extent. Dose adjustment of ———

[redacted] is not necessary when tegaserod [redacted] is combined with dextromethorphan. Therefore, [redacted] tegaserod [redacted] is not expected to alter the pharmacokinetics of drugs metabolized by CYP2D6 (e.g. fluoxetine, omeprazole, captopril).

Theophylline: A pharmacokinetic [redacted] interaction study demonstrated that co-administration of tegaserod [redacted] and theophylline did not affect the pharmacokinetics of theophylline [redacted] Dose adjustment of [redacted] theophylline is not necessary when tegaserod [redacted] is co-administered [redacted] Therefore, [redacted] tegaserod [redacted] is not expected to alter the pharmacokinetics of drugs metabolized by CYP1A2 (e.g. estradiol, omeprazole).

Digoxin: A pharmacokinetic [redacted] interaction study with digoxin demonstrated that concomitant administration of tegaserod [redacted] reduced peak plasma concentration and exposure of digoxin by approximately 15%. This reduction of bioavailability is not considered clinically relevant. When tegaserod [redacted] is co-administered with digoxin dose adjustment is unlikely to be required.

Warfarin: A pharmacokinetic and pharmacodynamic [redacted] interaction study with warfarin demonstrated no effect of concomitant administration of tegaserod [redacted] on warfarin pharmacokinetics and pharmacodynamics. Dose adjustment [redacted] of warfarin is not necessary when tegaserod [redacted] is co-administered [redacted]

Oral contraceptives:

[redacted] Co-administration of tegaserod [redacted] did not affect the steady state pharmacokinetics of ethinylestradiol and reduced peak concentrations and exposure of levonorgestrel by 8%. Tegaserod [redacted] is not expected to alter the risk of ovulation in subjects taking oral contraceptives. No alteration in oral contraceptive medication is necessary when tegaserod [redacted] is co-administered.

APPEARS THIS WAY
ON ORIGINAL

APPENDIX

APPEARS THIS WAY
ON ORIGINAL

STUDY W110 (Mass Balance)

Study Type: Mass Balance

Study Title: Evaluation of the absorption, distribution, metabolism and oral excretion of [^{14}C]SDZHTF 919 following a single oral administration to healthy male volunteers.

NDA: 21-200 **Submission Date:** 2/11/00 **Volume:** 1.65 **Protocol:** W110

Clinical Investigator: [redacted]

Study Design: Single dose, open-label.

Subject Breakdown

Demographics	
Number	4 healthy males
Age (mean (range))	59 ± 7
Weight (mean (range))	79 ± 6

Formulation

Treatment Group	**Dose**	**Dosage Form**	**Strength**	**Lot**
-	25 mg	[redacted]	25 mg	X 081 0694

Analytical Methodology

Plasma Sampling Times: blood samples for SDZHTF919 were collected at 0 hour (baseline), at 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 16, 20, and 24 hours after dosing. Blood samples for [^{14}C]SDZHTF 919 and potential metabolites were collected before dosing and at 0.33, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, 60, 84, 108, 120, 144, and 168 hours after dosing.

Urine Sampling Times: before dosing and at 0-8, 8-16, 16-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours.

Feces Sampling Times: Feces were collected for 168 hours following drug administration.

Assay Method: Plasma and urine samples were analyzed by [redacted] Fecal samples were analyzed by [redacted]

Labeling Claims

Approximately two-thirds of the orally administered dose of tegaserod [redacted] is excreted unchanged in the feces, with the remaining one-third excreted in the urine, primarily as the main metabolite.

Results and Discussion

Urinary excretion of radioactivity (0-168 hours) amounted to approximately 27 ± 12% of the dose. Majority of the dose (about 20%) was excreted in 0-8 hours. Unchanged tegaserod was not detectable in the urine. Fraction of urine (0-24 hours) showed that M7.0 comprised about 7%, M29.0 comprised about 13%, and N-glucuronides (M43.2/M43.8/M45.3) comprised about 2%.

Fecal excretion comprised about 58 ± 18% of the administered dose. Only unchanged tegaserod was detected in fecal extracts. Together, about 85% of the administered was recovered in urine and feces by the end of 168 hours.

Tegaserod levels were quantifiable up to 6 hours only (LOQ of ———). Therefore, terminal half-life was not calculated. Metabolites M29.0, M7.0, and N-glucuronides (M43.2/M43.8/M45.3) were detected in plasma. M29.0 comprised the major metabolite followed by M7.0. M29.0 reached the C_{max} in about 1.3 hours. The elimination half-life of total radioactivity was about 40.1 ± 17.4 hours.

Table 1. Summary of results.

Metabolite/ Parent drug (n.q.=not quantifiable)	**C_{max} (pmol/mL)**	**Ratio (metabol. to parent drug) molar**	**Urinary excretion % of dose**	**Fecal excretion % of dose**
M7.0	209 ±178	8:1	7.1 ± 8.5	n.q.
M29.0	404 ± 247	16:1	12.7 ± 4.7	n.q.
N-glucuronides : (M43.2/M43.8/M45.3)	108 ± 38	4:1	1.9 ± 1.3	n.q.
SDZ HTF 919	25.7 ± 5.5			
(from metabolite profiles)			n.q.	at least 34

The fate of the Pentylaminoguanidine (PAG) side chain of tegaserod was investigated in male mice following a single oral dose of 20 mg/kg [^{14}C]tegaserod labeled at the guanidine carbon atom (study P98-2187, volume 1.46). Urine, feces, plasma were sampled at periodic intervals. After exsanguination of the mice, wall and content of stomach, duodenum, jejunum, and ileum were collected. After 24 hours post-dose, about 89% of the dose was already excreted. After 72 hours 97% was excreted (82% in feces and 15% in urine).

PAG forms condensation products with endogenous (or food derived) keto-acids (pyruvate, alpha-keto glutarate and others). PAG itself was hardly detectable in the GIT (tissues and contents). These were found in the GIT tissues of animals and seem to be formed in the stomach and do not seem to be catalyzed. These compounds are excreted in the urine and as such seem to be absorbed systemically to some extent.

STUDY W251 (Hepatic Impairment)

Study Type: Hepatic Impairment

Protocol Title: A single dose, parallel group study of the pharmacokinetics of SDZ HTF 919 in patients with liver dysfunction (hepatic cirrhosis) and healthy control subjects matched for age, sex, and weight.

NDA: 21-200 **Submission Date:** 2/11/00 **Volume:** 1.73-74 **Protocol:** W251

Clinical Investigators: [redacted]

Study Design: Single dose, open-label, parallel group study in 12 liver cirrhosis subjects and 12 healthy subjects.

Subject Breakdown

Demographics	Control Group	Hepatic Impairment Group
Number	12	12
Age (mean (range))	54 (38-68)	55 (42-68)
Weight (mean (range))	83 (67-98)	71 (67-108)

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Control Group & Hepatic Impairment group	12 mg	FMF Tablet	6 mg	X142 0695

Analytical Methodology

Plasma Sampling Times: blood samples for SDZHTF919 and metabolite assay (only in cirrhotics) were collected at 0 hour (baseline), at 0.33, 0.67, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, and 48 hours after dosing. Plasma protein binding was determined at 0 and 1.5 hours post-dose.

Assay Method: [redacted]

Labeling Claims:

[redacted]

Results:

Two studies (W118 and W251) were initiated to examine the effect of hepatic impairment. Study W118 was discontinued after only one subject was enrolled with no plasma sample collection.

In the current study, 11 subjects were in the mild insufficiency category while 1 subject was in the moderate category.

Oral administration of 12 mg dose of tegaserod in subjects with mild hepatic insufficiency (cirrhosis) resulted in a higher peak mean concentration (about 116% of that of healthy controls) and AUC_{0-tz} (about 131% of that of the healthy controls) with no change in the time to median t_{max}.

In the one subject with moderate insufficiency, the C_{max} and AUC_{0-tz} were considerably higher (240% and 300% of that of healthy controls).

Since the metabolite concentrations were not measured in healthy controls, no comparative assessment with the metabolite concentrations in healthy controls could be made. Since SDZ HTF 919 is well tolerated up to a 60 mg equivalent tablet dose and dose-linearity was demonstrated under the dose range investigated, the increase in drug exposure in the mild impairment group study is not expected to cause a safety problem. Therefore, no dosage adjustment is warranted in the mild insufficiency group. However, inadequate data in the moderate insufficiency group and no data in the severe insufficiency group preclude any rationale dosage adjustments in these groups.

Table 1. Single-dose pharmacokinetics of 12 mg of tegaserod (FMF tablet) in subjects with hepatic impairment compared to healthy controls.

Parameter Mean ± SD	Mild Impairment Subjects (n = 11)	Controls (n = 12)
t_{max} (h)[a]	1.0	1.01
C_{max} (ng/mL)	4.8 ± 1.8	4.13 ± 1.3
AUC_{0-tz} (h·ng/mL)	14.3 ± 7.7	10.9 ± 4.9
$AUC_{0-\infty}$ (h·ng/mL)	18.5 ± 7.4 (n=7)	13.4 ± 6.0 (n=7)
$t_{½}$ (h)	8.6 ± 5.9	5.9 ± 4.2

[a] median

APPEARS THIS WAY
ON ORIGINAL

STUDY W354 (Renal Impairment)

Study Type: Renal Impairment

Protocol Title: A single dose, open-label, parallel group study to evaluate the pharmacokinetics of SDZ HTF 919 in subjects with severe renal insufficiency and healthy controls matched for age, weight, height and sex.

NDA: 21-200 **Submission Date:** 2/11/00 **Volume:** 1.75 **Protocol:** W354

Clinical Investigators: [redacted]

Single Dose: Yes **Parallel Group**: Yes **Other Design**: Single dose, Open-Label.

Subject Breakdown

Demographics	Control Group	Severe Renal Impairment Group
Number	10	10
Age (mean (range))	45 (27-67)	45 (27-68)
Weight (mean (range))	76 (57-103)	71 (53-105)

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
Control Group Severe Renal Impairment group	12 mg	FMF Tablet	6 mg	KN X142 0695

Analytical Methodology

Plasma Sampling Times: blood samples for SDZHTF919 assay were collected at 0 hour (baseline), at 0.33, 0.67, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, and 48 (renal impairment group only) hours after dosing.

Dialysate Sampling Times: pre-dialysis (24 hours post-dose), during dialysis, post-dialysis.

Assay Method: [redacted]

[redacted]

Labeling Claims

[redacted]

Pharmacokinetic Results:

Consistent with the fact that unchanged tegaserod is not excreted in urine, the pharmacokinetics of tegaserod were similar in both healthy subjects and subjects with severe renal impairment. Overall, the data suggest that dose adjustment is not needed in subjects with any degree of renal impairment. The major metabolite, M29.0 levels were not quantified as it was considered to be inactive.

Compared to the healthy control group, in subjects with severe renal impairment the mean apparent elimination half-life was prolonged. This change is probably not of clinical relevance, because of the small sample size (n=6), marked inter-subject variability, and errors in extrapolating the terminal half-life.

The dialysis clearance of tegaserod could not be determined in study W 354 because dialysate concentrations all were below the LOQ (hemodialysis was performed between 24 hours and 36 hours post dose). However, based on the large distribution volume of tegaserod and its extensive binding to plasma proteins it is unlikely that tegaserod could be removed efficiently by dialysis.

Table 1. Single-dose pharmacokinetics of 12 mg of tegaserod (FMF tablet) in subjects with severe renal impairment compared to healthy controls.

Parameter Mean ± SD (n = 10 per group)	Subjects with severe renal impairment[c]	Controls
t_{max} (h)[a]	1.0	1.0
C_{max} (ng/mL)	4.6 ± 2.3	5.1 ± 2.2
AUC_{0-tz} (h·ng/mL)	14.6 ± 8.5	14.3 ± 7.1
$AUC_{0-\infty}$ (h·ng/mL)	17.7 ± 7.1[b]	16.0 ± 6.8[b]
$t_{½}$ (h)	14.1 ± 12.0[b]	8.5 ± 5.0[b]
Creatinine clearance (mL/min/1.73m^2)	< 15	> 80

[a] Median, [b]n = 6, [c]7 of 10 subjects with renal impairment were anuric

APPEARS THIS WAY
ON ORIGINAL

STUDY W355 (Effect of Age and Gender)

Study Type: Effect of Age and Gender.

Title: An open-label, single oral dose, parallel group study to Evaluate the pharmacokinetics of SDZHTF919 in young and elderly subjects matched for height, weight, and sex.

NDA: 21-200 **Submission Date:** 2/11/00 **Volume:** 1.70-1.71 **Protocol:** W355

Clinical Investigator:

Single Dose: Yes **Parallel Group**: Yes **Other Design**: Open-Label.

Subject Breakdown

Demographics	18-40 years		65-85 years	
Number	10 Male	10 Female	10 Male	10 Female
Age (mean (range))	26 (19-32)	25 (18-39)	71 (68-76)	71 (67-77)
Weight (mean (range))	81 (66-95)	65 (54-76)	82 (65-95)	64 (52-73)

Formulation

Treatment Group	Dose	Dosage Form	Strength	Lot
All Groups	12 mg	FMI Tablet	6 mg	FIM-F011 0697

Analytical Methodology

Plasma Sampling Times: blood samples for SDZHTF919 assay were collected at 0 hour (baseline), at 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours after dosing.

Assay Method:

[ ]

Labeling Claims

Gender has no effect on the pharmacokinetics of tegaserod.

Results:

The single dose pharmacokinetics were similar in the young female, young male, and elderly male subjects. There was evidence of a small increase in systemic exposure in the elderly female subjects compared to the other groups. The mean C_{max} and AUC_{∞} were 20 and 26% lower in the young female than elderly female subjects. The magnitude of these changes is within the variability in the pharmacokinetic parameters of HTF 919. There was no evidence of a difference in exposure based on sex. In HTF 919 therapy there is no need for dose adjustment based on sex or age.

Table 1. Pharmacokinetic parameters of tegaserod in young female, elderly female, young male, and elderly male subjects.

Parameter	young male	young female	elderly male	elderly female
age (years)	26 ± 4	25 ± 7	71 ± 3	71 ± 4
t_{max} (hour)	1.0	1.0	1.0	1.0
C_{max} (ng/mL)	5.5 ± 3.1	5.2 +_1.3	5.1 ± 1.9	6.5 ± 2.3
$AUC_{0\text{-}tz}$ (hour*ng/mL)	11.8 ± 6.5	12.8 ± 3.9	12.7 ± 4.7	17.3 ± 6.1
AUC_{∞} (hour*ng/mL) an=4, bn=6, Cn=7	16.5 ± 7.7[a]	15.7 ± 3.0[b]	15.1 ± 3.0[a]	19.2 ± 6.9[c]

STUDY W124 (Absolute Bioavailability/Food Effect)

Study Type: Absolute bioavailability/food effect

Protocol Title: A study on the absolute bioavailability, the intra-individual variability and the effect of food on the pharmacokinetics of SDZ HTF 919 when given as a single oral dose of 12 mg and as a single intravenous dose of 3 mg to healthy male subjects.

NDA: 21-200 **Submission Date:** 2/11/00 **Volume:** 1.56 **Protocol:** W124

Clinical Investigators: ———————————

Study Design: Open-Label, single dose, randomized, four-treatment, four-period cross-over, at least one week washout period, over night fast of 12 hours.

Food Content:

150 mL orange juice, two rolls, 20 gm butter, 25 gm marmalade, two fried eggs, two slices of bacon, and 200 mL of whole milk within 0.5 hour before drug intake.

Subject Breakdown

Demographics	
Number	10 Males
Age (mean (range))	24 (19-31)
Weight (mean (range))	73 (59-93)

Formulation

Treatment Group	**Dose**	**Dosage Form**	**Strength**	**Lot**
Treatment A (po fasted)	12 mg	FMF Tablet	6 mg	X 104 0595
Treatment B (po fed)	12 mg	FMF Tablet	6mg	X 104 0595
Treatment C (IV)	3 mg	IV solution	1 mg/mL	Y 274 1094
Treatment D (po fasted)	12 mg	FMF Tablet	6 mg	X 104 0595

Analytical Methodology

Plasma Sampling Times: blood samples for oral SDZHTF919 assay were collected at 0 hour (baseline), at 0.33, 0.67, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 32, and 48 hours after dosing. Blood samples for IV SDZHTF919 assay were collected at 0 hour (baseline), at 0.25, 0.5, 0.67, 0.75, 0.83, 1, 1.33, 1.66, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 32, and 48 hours after dosing.

Assay Method: ——

[ ]

Labeling Claims

The absolute bioavailability of tegaserod ———— when administered to fasting subjects is approximately 10%.

Objective: The primary objective of the study was to determine the absolute bioavailability of the final marketed tablet formulation. Secondary objective is to determine the effect of high fat