breakfast on the tablet formulation. Tertiary objective was to determine the intra-subject variability when the tablet is given under fasted conditions on two different occasions.

**Results**

The absolute bioavailability of tegaserod was about 11-12%. There was a marked effect of fat rich breakfast on the pharmacokinetics with a reduction in $C_{max}$ of about 55% to 60% and in $AUC_{0-\infty}$ of about 53% to 58%. Interestingly, the two replicate fasting treatments were not bioequivalent.

**Table 1**. Summary of pharmacokinetic parameters.

| Parameter | 12 mg Tablet Fasted (Treatment A) | 12 mg Tablet Fed (Treatment B) | 3 mg IV Solution (Treatment C) | 12 mg Tablet Fasted (Treatment D) |
|---|---|---|---|---|
| $C_{max}$, ng/mL | 6.3 ± 1.5 | 2.5 ± 0.9 | 45.4 ± 9.2 | 5.5 ± 2.2 |
| $T_{max}$, hours | 1.1 ± 0.3 | 2.1 ± 0.8 | - | 1.5 ± 0.3 |
| $AUC_{0-\infty}$, ng hour/mL | 18.9 ± 4.9 | 8.0 ± 2.6 | 40.0 ± 7.9 | 17.1 ± 6.4 |
| CL/f, liter/hour | 675 ± 178 | 1665 ± 548 | 77 ± 15 | 799 ± 301 |
| $V_{ss}$, liter | - | - | 368 ± 223 | - |
| T1/2, hours | 7.7 ± 4.5 | 7.2 ± 2.3 | 10.8 ± 4.6 | 6.5 ± 3.2 |
| F (%) | 12 ± 2 | - | 100 | 11 ± 4 |

## STUDY W352 (Effect of Time of Food Intake)

**Study Type:** Food effect

**Protocol Title:** A randomized, open-label, two phase, five period, crossover study to evaluate the effect of the interval between meal and drug administration on the pharmacokinetics of SDZ HTF 919 in healthy subjects.

**NDA:** 21-200 **Submission Date:** 2/11/00 **Volume:** 1.63 **Protocol:** W352

**Clinical Investigators:** [redacted]

**Study Design**: Open-Label, single dose, randomized, five-treatment, five-period cross-over, at least one week washout period, over night fast of 12 hours. The meal composition was not described but the calorie content is about 600 calories.

**Subject Breakdown**

| **Demographics** | |
|---|---|
| Number | 19 Males, 1 female |
| Age (mean (range)) | 29 (18-41) |
| Weight (mean (range)) n=19 | 75 (58-113) |

**Formulation**

| **Treatment Group** | **Dose** | **Dosage Form** | **Strength** | **Lot** |
|---|---|---|---|---|
| 30 minutes prior to breakfast* | 12 mg | FMF Tablet | 6 mg | 1880895 |
| 15 minutes prior to breakfast | 12 mg | FMF Tablet | 6mg | 1880895 |
| 1 minute prior to breakfast | 12mg | FMF Tablet | 6 mg | 1880895 |
| as part of continued fast | 12 mg | FMF Tablet | 6 mg | 1880895 |
| 2.5 hours after breakfast | 12 mg | FMF Tablet | 6 mg | 1880895 |

600 calorie fat rich breakfast.

**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, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours after dosing.

Assay Method: [redacted]

**Labeling Claims**

When the drug was administered with food, the bioavailability of tegaserod [redacted] reduced by 40%-65% and $C_{max}$ by 20%-40%. Similar reductions in plasma concentration occurred when tegaserod [redacted] administered to subjects within 30 minutes prior to a meal. $T_{max}$

of tegaserod ——————— prolonged from approximately 1 hour to 2 hours when taken following a meal, but decreased to 0.7 hours when taken 30 minutes prior to a meal.

**Objective**: The primary objective of the study was to compare the pharmacokinetics and relative bioavailability when administered 30 and 15 minutes before the start of a meal. Secondary objective is to compare the pharmacokinetics and relative bioavailability when administered 30, 15, and 1 minute before the start of a meal, 2.5 hours after the start of a meal, and with a continued 4 hours post-dose fast.

**Results:**

In phase II clinical studies, drug intake occurred 30 to 60 minutes before meal time. Mean AUC and $C_{max}$ were reduced by 40-65% and 20-40%, respectively under all fed conditions relative to fasting conditions. There does not seem to be one optimum time for dosing among the tested times.

**Table 1**. Pharmacokinetic parameters 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

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## STUDY W351 (Multiple Dose Pharmacokinetics/Dose-Proportionality/Relative Bioavailability)

**Study Type:** Multiple dose pharmacokinetics/dose-proportionality/relative bioavailability

**Protocol Title:** A randomized, open-label, two-phase, five-period, crossover study to evaluate the dose-proportionality and steady state pharmacokinetics of SDZ HTF 919 in healthy subjects.

**NDA:** 21-200 **Submission Date:** 2/11/00 **Volume:** 1.60 **Protocol:** W351

**Clinical Investigators:** ———————

**Study Design**: Open-Label, two-phase, randomized, five-treatment, five-period cross-over, at least 4 day washout period, over night fast of 12 hours. Phase I and II are 3x3 and 2x2 balanced Latin square designs, respectively

**Subject Breakdown**

| **Demographics** | |
|---|---|
| Number | 18 Male and female subjects |
| Age (mean (range)) | 27 (21-36) |
| Weight (mean (range)) | 68 (52-90) |

**Formulation**

| **Treatment Group** | **Dose** | **Dosage Form** | **Strength** | **Lot** |
|---|---|---|---|---|
| 2 mg | 2 mg | FMI tablet | 2 mg | F010 0697 |
| 6 mg | 6 mg | FMI tablet | 6 mg | F011 0697 |
| 12 mg | 12 mg | FMI tablet | 6 mg | F011 0697 |
| 12 mg | 12 mg | FMF tablet | 6 mg | X1420695 |
| 12 mg | 12 mg | FMF tablet | —— | 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, 6, 8, 10, 12, and where applicable 18 and 24 hours after dosing.

Assay Method: ——

[ ]

**Treatment strategy**

During each period in Phase I, subjects received a single 2 mg (1x2 mg), 6 mg (1x6mg) or 12 mg (2x6mg) dose of tegaserod as FMI tablet on day 1, then twice daily for 5 days from day 2 onward. PK samples were drawn on day 1 for 12 hours after the first dose for the 2 mg dosing conditions, and for 24 hours after the first dose for the 6 mg and 12 mg dosing conditions. On day 7, subjects received a single morning dose after which PK samples were

drawn for 12 hours. After an interdose-interval of 4 to 10 days, subjects received the first dose of the next treatment period.

In phase II, subjects received a single dose of 12 mg of tegaserod (2x6mg ——— as FMF form. Blood samples were drawn for 24 hours post-dose. The inter-dose interval was 4 to 10 days.

**Results**

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 of the FMI tablet.

The steady state pharmacokinetics after twice-daily multiple dosing for 5 consecutive days were same as single dose pharmacokinetics showing that were as no accumulation.

The single dose pharmacokinetics were not different for the administration of 2x6mg doses of FMI and FMF formulations.

**Table 1.** 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 |
| **$AUC_{0-\infty}$, 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 |
| **$AUC_\tau$, 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

**Table 2.** Relative bioavailability of FMI and FMF formulations.

| | Mean ratio FMF/FMI | 90% confidence interval |
|---|---|---|
| **$C_{max}$, ng/mL** | 1.07 | 86-122 |
| **AUC, hour* ng/mL** | 1.1 | 82-122 |

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## STUDY W101 (Safety and Tolerability of Single Doses)

**Study Type:** Safety and Tolerability

**Protocol Title:** A Study on the Safety and Tolerability of Single Rising Oral Doses of SDZ HTF 919 in Healthy Male Subjects.

**NDA:** 21-200 **Submission Date:** 2/11/00 **Volume:** 1.50 **Protocol:** W101

**Clinical Investigators:**

**Study Design**: Open-Label, double-blind, randomized, parallel group.

**Subject Breakdown**

| **Demographics** | |
|---|---|
| Number | 68 Male subjects |
| Age (mean (range)) | 24 (19-37) |
| Weight (mean (range)) | 73 (59-90) |

**Formulation**

| **Treatment Group** | **Dose** | **Dosage Form** | **Strength** | **Lot** |
|---|---|---|---|---|
| 0.5 mg | 0.5 mg | [ | 0.5 mg | X 230 1292 |
| 2.5 mg | 2.5 mg | | 5 x 0.5 mg | |
| 5 mg | 5 mg | | 5 mg | X 232 1292 |
| 10 mg | 10 mg | | 2 x 5 mg | |
| 25 mg | 25 mg | | 25 mg | X 233 1292 |
| 50 mg | 50 mg | | 2 x 25 mg | |
| 100 mg | 100 mg | | 100 mg | X 124 0693 |
| 200 mg | 200 mg | ] | 2 x 100 mg | |

**Analytical Methodology**

Plasma Sampling Times: blood samples for oral SDZHTF919 assay were collected at 0 hour (baseline), at 0.5, 1, 2, 4, 8, 10, 12, 24, 48, and 72 hours after dosing.

Assay Method:

[ ]

**Treatment strategy**

Eleven groups of nine subjects each (six on active medication, three on placebo) were planned to be investigated. Dose levels planned were: single oral administrations of 0.5 mg, 2.5 mg, 5.0 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, 700 mg, 1000 mg SDZ HTF 919. However, after the administration of 200 mg dose to five subjects, additional dosing was stopped due to serious adverse events.

**Results and Discussion**

Single oral administrations of SDZ HTF 919 were well tolerated up to 100 mg. However, twelve subjects reported minor gastrointestinal symptoms, namely one or two episodes of loose stool (n=11), abdominal pain (n=4) and/or flatulence (n=l). Loose stool occurred at all dose levels, whereas the other symptoms were only observed in the 100 mg group. In the 200 mg group, severe adverse events including diarrhea, loose stool and orthostatic hypotension occurred. Therefore, the study was terminated. All symptoms resolved spontaneously without therapeutic intervention. Typically, all adverse events were reported after the administration of the active drug. No clinically relevant changes were observed with respect to physical examination, as well as ECG and, at doses up to 100 mg, with regard to vital signs and psychometric testing. Laboratory evaluations including hematology, biochemistry and urinalysis remained stable over all dose levels.

The pharmacokinetics of SDZ HTF 919 appeared to be linear based on the $C_{max}$ and $AUC_{(0\text{-}12h)}$ versus dose relationships following the administration of 25 mg, 50 mg., 100 mg and 200 mg, respectively. The primary aim of this study was to investigate the safety and tolerability of the drug, with pharmacokinetic component intended to provide an early insight into the drug's pharmacokinetic characteristics. The low sensitivity of the method did not allow the reproducible detection of concentrations at the 0.5 and 2.5 mg doses. At the dose levels of 5 mg and 10 mg systemic plasma concentrations were just above the limit of quantitation being of only limited value for pharmacokinetic evaluations. The pharmacokinetic profiles of SDZ HTF 919 following the 50 mg administration did not reveal any differences between extensive and poor metabolizers for sparteine. The comparison of the plasma concentration and whole blood concentrations indicated SDZ HTF 919 to be distributed about equally throughout both biological fluids.

**Note**: 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). Therefore, the relative bioavailability of the FMF tablet appears to be considerably lower than that of the ——— form. An approximate estimate of about 48% is obtained by cross study comparison of the AUC's for ——— (AUC, 83 hour*ng/mL; dose, 100mg; study W105) and FMF tablet (AUC, 20.9 hour*ng/mL; dose, 12 mg; study W351)

**Table 1.** Gastrointestinal adverse events following single rising oral administrations of 0.5 mg up to 200 mg of tegaserod.

| SDZ HTF 919 Dose | Subject No. | Adverse Events [nx = incidence] | Severity | Onset Post Dose [h] | Duration |
|---|---|---|---|---|---|
| 0.5 mg | 14 | loose stool [2x] | moderate | 2.5, 5 | 2' |
| 2.5 mg | 29 | loose stool [2x] | moderate | 1.5, 3 | 2' |
| 5.0 mg | 31 | loose stool | moderate | 2 | 2' |
| 10 mg | 49 | loose stool | moderate | 1.5 | 10' |
| 25 mg | 51 | loose stool | mild | 4.5 | 2' |
| | 54 | loose stool | mild | 4.5 | 1' |
| 50 mg | 64 | loose stool | mild | 6 | 2' |
| | 67 | loose stool | moderate | 2 | 2' |
| 100 mg | 71 | abdominal pain | moderate | 3 | 10 h |
| | 72 | abdominal pain | mild | 4 | 20 h |
| | | flatulence | mild | 4 | 20 h |
| | | loose stool [2x] | moderate | 5.5, 6 | 2' |
| | 75 | abdominal pain | moderate | 0.5 | 2 h |
| | | loose stool | moderate | 2 | 2' |
| | 76 | abdominal pain | mild | 2 | 2 h |
| | | loose stool | mild | 4 | 2' |
| 200 mg | 82 | abdominal pain | moderate | 1 | 11 h |
| | | diarrhea [5x] | severe | 2 | 2.5 h |
| | 83 | abdominal pain | moderate | 0.25 | 3 h |
| | | diarrhea [4x] | severe | 0.5 | 4 h |
| | 85 | loose stool | severe | 2 | 5' |

**Table 2.** Summary of pharmacokinetic parameters.

| | 25 mg | 50 mg | 100 mg | 200 mg |
|---|---|---|---|---|
| $C_{max}$, ng/mL | 6.5 ± 2.8 | 12.4 ± 3.0 | 17.0 ± 5.5 | 43.6 ± 11.2 |
| $C_{max}$/25mg | 6.5 ± 2.8 | 6.2 ± 1.5 | 4.3 ± 1.4 | 5.5 ± 1.4 |
| $AUC^*_{0\text{-}12}$, hour*ng/mL | 10.25 ± 6.0 | 24.4 ± 7.1 | 35.5 ± 13.8 | 74.8 ± 36.7 |
| $AUC_{0\text{-}12}$/25 mg | 10.25 ± 6.0 | 12.2 ± 3.6 | 8.9 ± 3.5 | 9.4 ± 4.6 |

* concentrations were not detectable past 8 hours.

## STUDY W106 (Safety and Tolerability of Multiple Doses)

**Study Type:** Safety and Tolerability

**Protocol Title:** A Study on the Tolerability and Pharmacokinetics of SDZ HTF 919 after Single and Multiple Oral Doses of 150 mg bid and 100 mg tid Given to Healthy Male Subjects.

**NDA:** 21-200 **Submission Date:** 2/11/00 **Volume:** 1.53 **Protocol:** W106

**Clinical Investigators:** [redacted]

**Study Design**: *Pilot Study*- Open label, single group. *Main Study*- Double blind, randomized, placebo controlled, parallel groups.

**Subject Breakdown**

| **Demographics** | |
|---|---|
| Number | 12 Male subjects |
| Age (mean (range)) | 25 (20-29) |
| Weight (mean (range)) | 69 (54-81) |

**Formulation**

| **Treatment Group** | **Dose** | **Dosage Form** | **Strength** | **Lot** |
|---|---|---|---|---|
| 100 mg tid | 100 mg tid | [redacted] | 25 mg<br>100 mg | X 233 1292<br>X 124 0693 |

**Analytical Methodology**

Plasma Sampling Times: For determination of SDZ HTF 919 single dose pharmacokinetics, plasma samples were taken before drug intake on day 1 and 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 9, 12, 18 and 24 hours thereafter. For determination of SDZ HTF 919 one-week multiple dose pharmacokinetics, plasma samples were collected before drug administration in the morning on day 8 and 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours thereafter. For determination of SDZ HTF 919 two-week multiple dose pharmacokinetics, plasma samples were collected before drug administration in the morning on day 15 and 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 9 and 12, 18, 24, 36, and 48 hours thereafter. Trough concentrations were determined immediately before the morning dose on days 4, 6, 10, and 12.

Assay Method: [redacted]

[redacted]

**Treatment strategy**

The study was initially designed to investigate the tolerability and pharmacokinetics of SDZ HTF 919 after single and multiple oral doses of 150 mg given twice-daily (bid) and 100 mg given thrice-daily (tid) for two weeks, in comparison to placebo, to 24

healthy male subjects. The subjects were to be divided into three groups of eight subjects each receiving either SDZ HTF 919 (group 1: 150 mg bid, group II: 100 mg tid) or placebo (group III). However, the Ethics Committee requested a pilot study with 150 mg SDZ HTF 919 before proceeding with the planned study as the 150 mg dose has not yet been investigated in the previous studies. However, following the first dose of 150 mg, severe loose stool was observed in one subject and consequently the 150 mg dose was dropped in the main study (no PK evaluation was done in the pilot study).

Therefore, in the main study, twelve subjects (SDZ HTF 919, n=8; placebo, n=4) received a single oral dose of 100 mg SDZ HTF 919 or placebo on day 1. On days 2 to 14 thrice-daily multiple oral doses of 100 mg SDZ HTF 919 or placebo were administered in 8-hour intervals, and a last dose was given in the morning on day 15. Both the active- and placebo-treated subjects received an additional placebo dose at 12 hours after the morning dose on days 2 to 14 to maintain the blinding. This was due to the initial plan to additionally investigate the 150 mg bid dose which was to be administered in 12-hour intervals.

**Results**

Single and thrice-daily multiple oral administrations of 100 mg SDZ HTF 919 given for two weeks were generally tolerated in all healthy male subjects. All eight subjects on active drug and one placebo subject reported adverse events such as loose stool (n=9) flatulence (n=2), vomiting (n=l), nausea (n=l), epigastralgia (n=l) and headache (n=4). All symptoms were transient, of mild to moderate severity and resolved without therapeutic intervention.

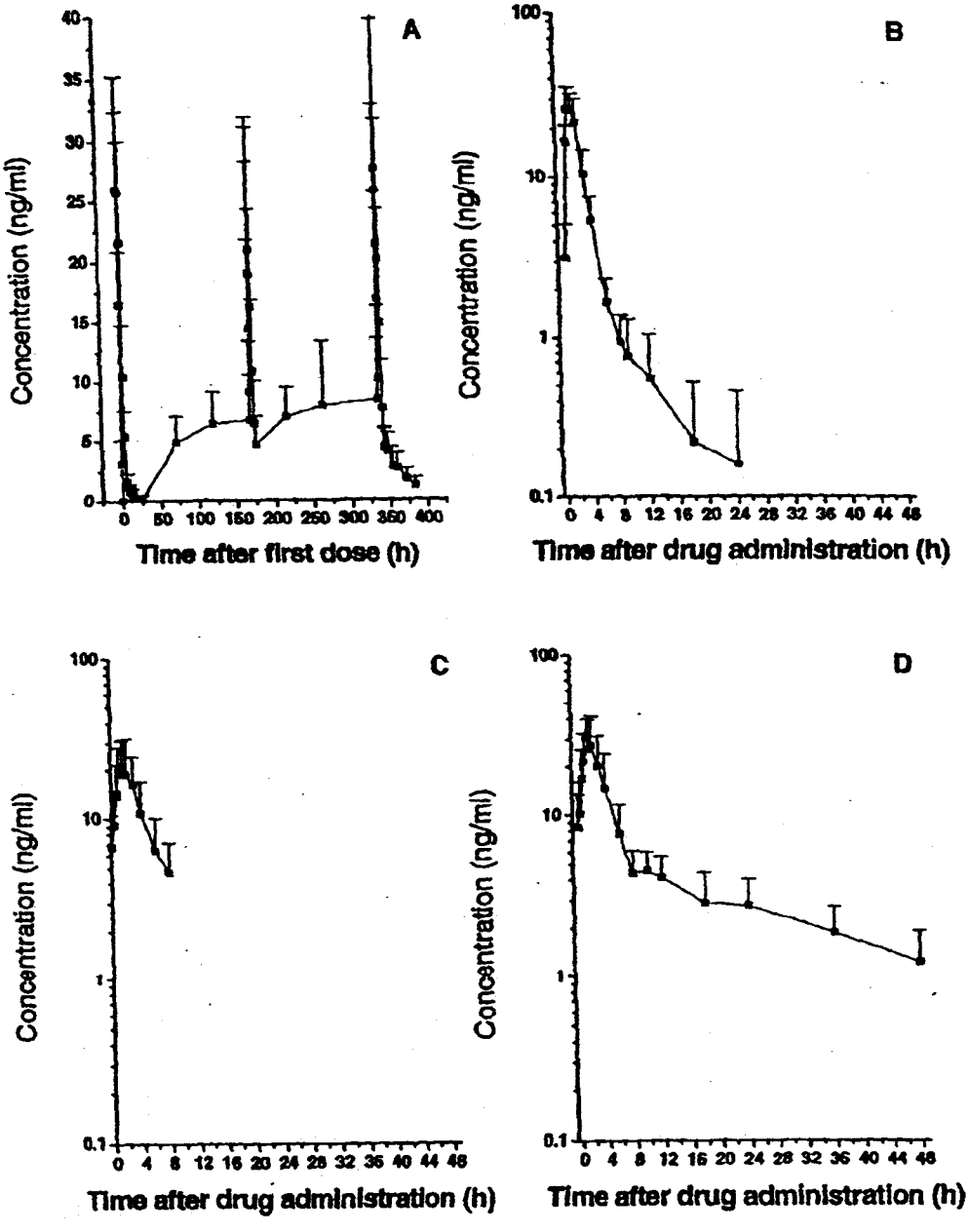
In both the *pilot* and *main* study no clinically relevant changes were observed on physical examination, ECG recordings, vital signs and laboratory evaluations.

Thrice-daily multiple dosing of 100 mg SDZ HTF 919 for 2 weeks: Plasma concentrations of SDZ HTF 919 peaked between on average 1.4 and 1.8 h post-dose with comparable values after single and multiple dosing. There was moderate accumulation with ratios between 1.5 and 1.7 based on exposure results. The terminal half-life was prolonged after thrice-daily multiple compared to the single dosing with on average 23 $\pm$ 7 h at day 15. Steady state was reached by day 8 in all subjects.

**Table 1.** Single and multiple dose pharmacokinetics of tegaserod

| Parameter | Day 1 | Day 8 | Day 15 |
|---|---|---|---|
| $C_{max}$, ng/mL | 29 ± 8 | 23 ± 10 | 29 ± 14 |
| AUC, hour* ng/mL | 78 ± 27 | 90 ± 46 | 114 ± 60 |
| $T_{max}$, hour | 1.4 ± 0.4 | 1.8 ± 0.6 | 1.8 ± 0.3 |

**Figure 1.** Single (A) and thrice-daily multiple dose (C day 8, D day 15) pharmacokinetics of 100 mg SDZ HTF 919 ——— (mean ± SD).



## STUDY W358 (Effect of Gastric pH Alterations)

**Study Type:** Gastric pH alterations.

**Protocol Title:** A randomized, open-label, single dose, three-period, crossover study to evaluate the effect of gastric pH alteration on the plasma concentrations of tegaserod and its major metabolite in healthy subjects.

**NDA:** 21-200 **Submission Date:** 2/11/00 **Volume:** 1.66 **Protocol:** W358

**Clinical Investigators:** [redacted]

**Study Design**: Randomized, open-label, single dose (tegaserod), three-period, crossover, at least one week washout period, over night fast of 12 hours.

**Subject Breakdown**

| **Demographics** | |
|---|---|
| Number | 18 Males |
| Age (mean (range)) | 33 (21-44) |
| Weight (mean (range)) | 78 (54-103) |

**Formulation**

| **Treatment Group** | **Dose** | **Dosage Form** | **Strength** | **Lot** |
|---|---|---|---|---|
| Tegaserod alone | 12 mg | FMI Tablet | 6 mg | F0110697 |
| Tegaserod + omeprazole + sodium bicarbonate | 12 mg | FMI Tablet | 6mg | |
| Tegaserod + Pentagastrin | 12 mg | FMI Tablet | 6 mg | |

**Analytical Methodology**

Gastric pH monitoring: every 15 minutes from 2 hours prior to dosing till 3 hours post dosing.

Plasma Sampling Times: blood samples for oral SDZHTF919 and M29.0 metabolite assay were collected at 0 hour (baseline), at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours after dosing.

Gastric Concentrations: gastric samples for SDZHTF919 and M29.0 metabolite were to be sampled according to the above schedule up to 3 hours (not done due to technical difficulties).

Assay Method: [redacted]

[redacted]

**Labeling Claims:**

[redacted] systemic exposure to tegaserod [redacted] was not [redacted] altered at neutral gastric pH values.

**Treatment strategy:**

Subjects received a single oral 40 mg (2 x 20 mg) dose of omeprazole (Prilosec®)

the evening prior to dosing, and on the morning of dosing, followed by 30 mL of 0.4 M sodium bicarbonate buffer (pH 4.5) to attain a gastric pH above 3.5, after which a single oral 12 mg (2 x 6 mg) dose of tegaserod was administered. The morning dose of omeprazole and the bicarbonate buffer were given approximately 2 hours and 0.5 hours before the tegaserod dose, respectively; 2) Subjects received a single subcutaneous 6 pg/kg dose of pentagastrin (Peptavlon®) to attain a gastric pH below 2 followed by a single oral 12 mg dose of tegaserod 30 minutes thereafter; or 3) Subjects received a single oral 12 mg dose of tegaserod without any pretreatment. In all periods, stomach pH was monitored using gastric pH probes. Subjects were only to be dosed when gastric pH's were within the required ranges for the respective treatment conditions. Gastric pH was monitored every 15 minutes starting 1 hour prior to administration of omeprazole or pentagastrin, and every 15 minutes thereafter, for at least 3 hours after administration of tegaserod.

**Results and Discussion:**

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 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.

**Table 1**. Tegaserod pharmacokinetic parameters.

| Mean (±SD) and median tegaserod pharmacokinetics | | | | | |
|---|---|---|---|---|---|
| **Parameter** | **Tegaserod alone (A)** | **Tegaserod + Omeprazole (B)** | **Tegaserod + Pentagastrin (C)** | **90% CI (B/A)* p value** | **90% CI (C/A) * p value** |
| $C_{max}$ (ng/ml) | 4.2 ± 1.7 | 3.4 ± 1.2 | 2.5 ± 1.6 | (82%, 107%) | (40%, 69%) |
| | 3.8 | 3.4 | 2.4 | p = 0.209 | p < 0.001 |
| $t_{max}$ (h) (Median) | 1.0 | 1.0 | 1.8 | (-0.11h, 0.25) p = 0.488 | (0.295, 1.00) p = 0.003 |
| AUC $_{(0h-tz)}$ (ng·h/ml) | 10.9 ± 4.0 | 8.7 ± 3.4 | 6.5 ± 3.2 | (84%, 98%) | (45%, 69%) |
| | 10.9 | 8.2 | 6.7 | p = 0.069 | p < 0.001 |
| $t_{1/2\lambda z}$ (h) | 8.1 ± 9.1 | 6.1 ± 10.8 | 3.5 ± 3.1 | NA | NA |
| | 5.1 | 3.1 | 2.4 | | |

NA: not available; * based on Ln-transformed scale, treatment A is used as reference, CI and p value for $t_{max}$ based on median differences.

**Table 2**.. M29.0 pharmacokinetic parameters.

| Mean (±SD) and median tegaserod metabolite M29.0 pharmacokinetics | | | | | |
|---|---|---|---|---|---|
| **Parameter** | **Tegaserod alone (A)** | **Tegaserod + Omeprazole (B)** | **Tegaserod + Pentagastrin (C)** | **90% CI (B/A)** p value** | **90% CI (C/A)** p value** |
| $C_{max}$ (ng/ml) | 67.9 ± 58.0 | 4.3 ± 13.6 | 216 ± 85.7 | (2%, 10%) | (253%, 759%) |
| | 47.3 | 0.6 | 222 | p < 0.001 | p < 0.001 |
| $t_{max}$ (h) | 1.0*** | 1.0*** | 1.3*** | (-0.13, 1.38) p = 0.141 | (0.015, 0.50) p = 0.022 |
| AUC $_{(0h-tz)}$ (ng·h/ml) | 113 ± 100 | 9.0 ± 29.9 | 369 ± 165 | (1%, 7%) | (221%, 912%) |
| | 70.7 | 0.1 | 380 | p < 0.001 | p = 0.001 |
| $t_{1/2\lambda z}$ (h) | 5.3 ± 6.2 | 9.3* | 2.7 ± 2.0 | NA | NA |
| | 2.4 | 9.3 | 2.0 | | |
| $C_{max}$ Ratio[a] | 20.3 ± 33.9 | 1.4 ± 4.6 | 127 ± 139 | NA | NA |
| | 9.2 | 0.1 | 91.7 | | |
| AUC $_{(0h-tz)}$ Ratio[b] | 12.0 ± 17.4 | 1.0 ± 3.4 | 74.2 ± 79.6 | NA | NA |
| | 6.0 | 0.0 | 54.8 | | |

*n = 2; NA: not available; ** based on Ln-transformed scale, treatment A is used as reference, CI and p value for $t_{max}$ based on median differences.a $C_{max}$ ratio of metabolite M29.0 to tegaserod (molar basis); b $AUC_{(0h-tz)}$ ratio of metabolite M29.0 to tegaserod (molar basis); *** median.

**Figure 1.** *In vitro* pH dependent degradation of tegaserod (or formation of hydrolyti metabolite).

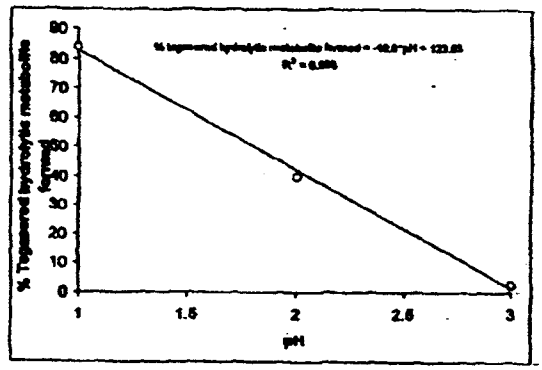
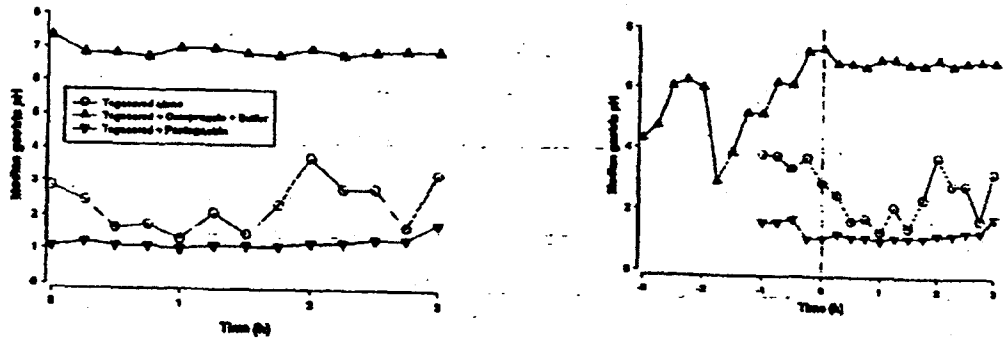



**Figure 2.** Median pH versus time profiles.

**(left: 0~3 h post-dose; right: -3~3 h)**



## STUDY W252 (Effect of Tegaserod on Digoxin)

**Study Type:** Drug-Drug Interaction.

**Protocol Title:** A open-label, randomized, two-period crossover study to evaluating the effects of multiple doses of SDZ HTF19 on the pharmacokinetics and pharmacodynamics of digoxin in healthy subjects.

**NDA:** 21-200 **Submission Date:** 2/11/00 **Volume:** 1.80 **Protocol:** W252

**Clinical Investigators:** ———

**Study Design**: Randomized, open-label, single dose (tegaserod), two-period, crossover study

**Subject Breakdown**

| **Demographics** | |
|---|---|
| Number | 12 healthy (10M+2F) |
| Age (mean (range)) | 25 (21-32) |
| Weight (mean (range)) | 67 (60-81) |

**Formulation (FMI)**

| **Treatment Group** | **Dose** | **Dosage Form** | **Strength** | **Lot** |
|---|---|---|---|---|
| Digoxin | 1 mg | FMF Tablet | 6 mg | X1880895 |
| Digoxin + Tegaserod | 1 mg + 6 mg bid/5 days | FMF Tablet | 6mg | |

**Analytical Methodology**

Plasma Sampling Times: On study days 3 and 4 at 0, 1.5, and 2 hours post tegaserod dosing

Digoxin Plasma Sampling Times: blood samples for digoxin assay, on study day 1 of digoxin treatment and day 4 of digoxin + tegaserod treatment, were collected at 0 hour (baseline), at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, 72, 96, and 120 hours after dosing.

Assay Method: ———

Assay Method for Digoxin: ———

[ ]

**Rationale of the study**: Metoclopromide another prokinetic agent reportedly decreased the digoxin serum concentrations (about 31% decrease in $AUC_{0\text{-}24hours}$), especially digoxin formulations that have a low dissolution rate. Multiple doses of tegaserod were administered to bring it to its clinical effect.

**Results and Discussion**

A reduction of about 15% in $C_{max}$ and $AUC_{0\text{-}\infty}$ of digoxin occurred following combination therapy without any changes in the terminal half-life. The 90% confidence intervals for log transformed $C_{max}$ (0.73-0.96) and AUC (0.78-0.94) were outside the limits. The median $T_{max}$ was reduced from 1.5 hours to 1.0 hours. The mean post-dose plasma concentrations (1.5 and 2 hours) of tegaserod were increased by about 31% and 40%, respectively following coadministration with digoxin, compared to those on day 3. However, it should be noted that on day 3, only three subjects had detectable pre-dose concentrations whereas on day 4, ten subjects had detectable concentrations indicating that steady state may not have reached by day 3.

## STUDY W360 (Effect of Tegaserod on Dextromethorphan)

**Study Type:** Drug-Drug Interaction.

**Protocol Title:** A randomized, open-label, two-period crossover study to evaluate the effect of SDZ HTF19 on the pharmacokinetics of a cytochrome P450 2D6 prototype substrate, dextromethorphan in healthy subjects.

**NDA:** 21-200 **Submission Date:** 2/11/00 **Volume:** 1.79 **Protocol:** W360

**Clinical Investigators:** [redacted]

**Study Design**: Randomized, open-label, single dose (tegaserod), two-period, crossover study. Only extensive metabolizers were enrolled. Tegaserod 6 mg bid was given for 2 days and dextromethorphan was given on day 2 of tegaserod dosing. In the other arm, a single dose of 120 mg dextromethorphan was given.

**Subject Breakdown**

| **Demographics** | |
|---|---|
| Number | 20 healthy (12M+8F) |
| Age (mean (range)) | 37 (22-42) |
| Weight (mean (range)) | 75 (58-98) |

**Formulation (FMI)**

| **Treatment Group** | **Dose** | **Dosage Form** | **Strength** | **Lot** |
|---|---|---|---|---|
| Dextromethorphan | 120 mg | syrup | - | - |
| Dextromethorphan + Tegaserod | 120 mg + 6 mg bid/2 days | FMI Tablet | 6mg | |

**Analytical Methodology**

Plasma Sampling Times: on days 1 and 2, pre-dose, and 0.5, 1, 1.5, 2, 4, 8, 12 hours post tegaserod dosing.

Dextromethorphan Plasma Sampling Times: blood samples were collected at 0 hour (baseline), at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 after dosing.

Assay Method: [redacted]

Assay Method for Dextromethorphan and dextrorphan: [redacted]

[redacted]

**Rationale of the study**: *In vitro* studies have shown that tegaserod has potential to inhibit

CYP2D6 at relatively high concentrations ($IC_{50}$ of about 1 μM). This study is designed to determine the *in vivo* inhibitory potential. The proposed therapeutic dose of tegaserod produces significantly lower concentrations than are required to see the inhibition. Tegaserod was given 1 hour before dextromethorphan so as that peak tegaserod concentrations are achieved at the time of dextromethorphan dosing.

**Results and Discussion**

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. The 90% confidence intervals for log transformed $C_{max}$ (0.8-1.35) and $AUC_{0-\infty}$ (0.76-1.34) were outside the limits. 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%. The 90% confidence intervals for log transformed $C_{max}$ (0.44-0.92) and $AUC_{0-12}$ (0.44-0.94) were outside the limits.

Considerable variability was seen in the parameters of tegaserod, dextromethorphan and dextrorphan.

**Table 1**. Pharmacokinetic parameters of tegaserod and dextromethorphan (mean (%CV)).

| | **$C_{max}$, ng/mL** | | **AUC, ng* hour/mL** | |
|---|---|---|---|---|
| | **Alone** | **Coadministration** | **Alone** | **Coadministration** |
| **Tegaserod** | 1.5 (60) | 1.1 (59) | 4.7 (46) | 4.8 (40) |
| **Dextromethorphan** | 14.9 (87) | 15.1 (80) | 158 (136) | 145 (89) |
| **Dextrorphan** | 31 (51) | 35 (52) | 162 (38) | 177 (38) |

Median $t_{max}$ was not different between the treatments for tegaserod, dextromethorphan and dextrorphan.

## STUDY W360 (Effect of Tegaserod on Theophylline)

**Study Type:** Drug-Drug Interaction.

**Protocol Title:** A randomized, open-label, two-period crossover study to evaluate the effect of SDZ HTF19 on the pharmacokinetics of a cytochrome P450 prototype substrate, theophylline in healthy subjects.

**NDA:** 21-200 **Submission Date:** 2/11/00 **Volume:** 1.77 **Protocol:** W359

**Clinical Investigators:** [redacted]

**Study Design**: Randomized, open-label, single dose (pseudo steady state-tegaserod), two-period, crossover study. Tegaserod 6 mg single dose was given for day 1 and 6 mg bid on day 2 ,and 600 mg of Theo-Dur® (2x300 mg tablets) was given on day 2 of tegaserod dosing. In the other arm, a single dose of 600 mg Theo-Dur® (2x300 mg tablets) was given.

**Subject Breakdown**

| **Demographics** | |
|---|---|
| Number | 18 healthy (9M+9F) |
| Age (mean (range)) | 32 (18-45) |
| Weight (mean (range)) | 72 (52-94) |

**Formulation (FMI)**

| **Treatment Group** | **Dose** | **Dosage Form** | **Strength** | **Lot** |
|---|---|---|---|---|
| Theophylline | 600 mg | FMI Tablet | - | - |
| Theophylline + Tegaserod | 600 mg + 6 mg bid/2 days | | 6mg | F0110697 |

**Analytical Methodology**

Plasma Sampling Times: on days 1 and 2, pre-dose, and 0.5, 1, 1.5, 2, 4, 8, and 12 hours post tegaserod dosing.

Theophylline Plasma Sampling Times: blood samples were collected at 0 hour (baseline), at 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, and 48 hours after dosing.

Assay Method: [redacted]

[redacted]

**Rationale of the study**: *In vitro* studies have shown that tegaserod has potential to inhibit CYP1A2 at relatively high concentrations ($IC_{50}$ of about 4 μM). This study is designed to determine the *in vivo* inhibitory potential. The proposed therapeutic dose of tegaserod produces

significantly lower concentrations than are required to see the inhibition. The sponsor admits to the low likelihood of significant change in pharmacokinetic or clinical profiles of the two compounds except for potential increased gastrointestinal motility.

**Results and Discussion**

The 90% confidence intervals for log transformed $C_{max}$ and $AUC_{0-\infty}$ of theophylline after administration alone and after coadministration with tegaserod were within the limits of —— The median $t_{max}$ decreased from 8 hours to 6 hours. However, this may not be clinically significant.

The mean values for $C_{max}$ and $AUC_{0-\infty}$ of tegaserod after coadministration with theophylline were higher compared to those after administration alone and with differences between treatment means of 36% and 16%. The 90% confidence intervals were outside the limits of —— This increase is mechanistically unexpected. However, it should be kept in mind that the data for tegaserod alone were from day 1 and for coadministration with theophylline were from day 2 following an additional dose.

## STUDY W362 (Effect of Tegaserod On Warfarin)

**Study Type:** Drug-Drug Interaction.

**Protocol Title:** A open-label, randomized, two-period crossover study evaluating the effects of multiple doses of SDZ HTF19 on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects.

**NDA:** 21-200 **Submission Date:** 2/11/00 **Volume:** 1.84 **Protocol:** W362

**Clinical Investigators:** ———

**Study Design**: Randomized, open-label, two-period, crossover study. Each subject received 6 mg tegaserod 6 mg bid for 7 days and 30 mg warfarin on day 4 for the coadministration treatment. A 21 day washout period separated the two treatments.

**Subject Breakdown**

| **Demographics** | |
|---|---|
| Number | 12 healthy (all males) |
| Age (mean (range)) | 30 (20-41) |
| Weight (mean (range)) | 75 (61-87) |

**Formulation (FMI)**

| **Treatment Group** | **Dose** | **Dosage Form** | **Strength** | **Lot** |
|---|---|---|---|---|
| Warfarin | 30 mg | FMI Tablet | 6 mg | F0110697 |
| Warfarin + Tegaserod | 30 mg + 6 mg bid/7 days | FMI Tablet | 6mg | |

**Analytical Methodology**

Plasma Sampling Times: On study days 3,4, 5, and 6 before tegaserod dosing and on study days 3 and 4, before and at 1, 1,5, and 2 hours post tegaserod dosing.

Warfarin Plasma Sampling Times: blood samples on day 4 of warfarin + tegaserod treatment and day 1 of warfarin alone treatments, were collected at 0 hour (baseline), at 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 48, 72, 96, 120, and 168 hours after dosing.

Assay Method: ———

Assay Method for Warfarin: ———

[ ]

**Rationale of the study**: Although metabolic interactions can be ruled out, the potential for a change in bioavailability of warfarin exists secondary to the prokinetic activity of tegaserod. 30 mg dose of warfarin was chosen for safety considerations. Multiple doses of tegaserod were administered to bring it to its clinical effect.

**Results and Discussion**

Two studies were conducted investigating the effect of tegaserod on warfarin

(studies W253 & W362). Due to sub optimal execution of study W253, the current study (W362) was initiated.

The coadministration of tegaserod did not substantially 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. 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.

**Table 1.** Pharmacokinetic parameters of warfarin after coadministration with tegaserod and alone.

| | R-Warfarin | | S-Warfarin | |
|---|---|---|---|---|
| | Alone | Coadministration | Alone | Coadministration |
| $C_{max}$, µg/mL | 1.8 (13) | 2.0 (18) | 1.9 (16) | 2.1 (19) |
| $AUC_{0-\infty}$, µg*hour/mL | 89.6 (17) | 93.9 (19) | 74.8 (33) | 74.4 (35) |

## STUDY W357 (Effect of Tegaserod on Oral Contraceptives)

**Study Type:** Drug-Drug Interaction.

**Protocol Title:** A double-blind, placebo controlled, randomized, three-period crossover study evaluating the effects of HTF 919 on the pharmacodynamics and pharmacokinetics of a triphasic oral contraceptive (Triphasil®-28) in healthy female subjects.

**NDA:** 21-200 **Submission Date:** 2/11/00 **Volume:** 1.86 **Protocol:** W357

**Clinical Investigators:** [redacted]

**Study Design**: Randomized, double-blind, placebo-controlled, three-period, crossover study. This study was conducted over three consecutive menstrual cycles in females who were on an established regimen of Triphasil®-28. During period 1, all subjects took only triphasil. During periods 2 & 3 the subjects received either tegaserod 6 mg bid or a matched placebo for 28 days. PK and PD variables were assessed on day 21 in periods 2 and 3.

**Subject Breakdown**

| **Demographics** | |
|---|---|
| Number | 61 healthy females |
| Age (mean (range)) | 25 (18-35) |
| Weight (mean (range)) | 64 (46-90) |

**Formulation (FMI)**

| **Treatment Group** | **Dose** | **Dosage Form** | **Strength** | **Lot** |
|---|---|---|---|---|
| Triphasil<br>Triphasil + Placebo | | | | 9978255 &<br>7813599 |
| Triphasil + Tegaserod | triphasil+ 6 mg bid/28 days | FMI Tablet | 6mg | F0110697 |

**Analytical Methodology**

Plasma Sampling Times for ethinyl estradiol, levonorgestrel, and tegaserod: On day 21 of periods 2 & 3, before dosing and at 0.5, 1, 1,5, 2, 2.5, 3, 4, 6, 8, and 12 hours post tegaserod dosing.

Assay Method: [redacted]

Assay Method for ethinyl estradiol & levonorgestrel: [redacted]

[redacted]

**Rationale of the study**: Although metabolic interactions can be ruled out, the potential for a change in bioavailability of ethinyl estradiol and levonorgestrel exists secondary to the prokinetic activity of tegaserod.

**Results and Discussion**

The pharmacokinetics of ethinyl estradiol and levonorgestrel were not changed upon coadministration with tegaserod (tables 1 & 2). 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.

Tegaserod concentrations are available only when coadministered with triphasil and not when administered alone, as such the effect of triphasil on tegaserod's pharmacokinetics cannot be assessed (an effect is not expected).

**Table 1.** Pharmacokinetic parameters (mean ± SD) of ethinyl estradiol after coadministration with tegaserod and placebo.

| | Triphasil + Tegaserod | Triphasil + Placebo |
|---|---|---|
| $C_{max,ss}$, pg/mL | 108 ± 38 | 111 ± 42 |
| $C_{min,ss}$, pg/mL | 23.4 ± 14.9 | 27.7 ± 20.7 |
| $T_{max,ss}$, hour | 1.8 ± 0.7 | 1.5 ± 0.6 |
| $AUC_{0-12}$, pg*hour/mL | 737 ± 277 | 751 ± 309 |

**Table 2.** Pharmacokinetic parameters (mean ± SD) of levonorgestrel after coadministration with tegaserod and placebo.

| | Triphasil + Tegaserod | Triphasil + Placebo |
|---|---|---|
| $C_{max,ss}$, ng/mL | 7.4 ± 2.6 | 8.0 ± 2.8 |
| $C_{min,ss}$, ng/mL | 3.3 ± 1.4 | 3.6 ± 1.5 |
| $T_{max,ss}$, hour | 1.6 ± 0.8 | 1.4 ± 0.6 |
| $AUC_{0-12}$, ng*hour/mL | 58.4 ± 21.3 | 63.3 ± 21.3 |

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## STUDY B351 (Pharmacokinetics in C-IBS Patients)

**Study Type:** Efficacy.

**Protocol Title:** A randomized, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of SDZ HTF19 at two dose levels and placebo in subjects with constipation-predominant irritable bowel syndrome.

**NDA:** 21-200 **Submission Date:** 2/11/00 **Volume:** 1.162 **Protocol:** B351

**Study Design**: Randomized, double blind, placebo controlled, parallel group.

**Formulation (FMI)**

| Treatment Group | Dose | Dosage Form | Strength | Lot |
|---|---|---|---|---|
| Tegaserod | 2 mg bid/28 days | FMI Tablet | 2 mg | F0100697 |
| Tegaserod | 6 mg bid/28 days | FMI Tablet | 6mg | F0110697 |

**Analytical Methodology**

Plasma Sampling Times: On days 29, up to 6 hours post-dosing.

Assay Method: [redacted]

[redacted]

**Results and Discussion**

The pharmacokinetics were different in patients when compared to healthy subjects from study W351. The $C_{max,ss}$ and $AUC_{0-6}$ were 30% to 50% lower in patients. 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.

**Table 1.** Multiple dose pharmacokinetics of tegaserod 2 mg and 6 mg bid assessed on day 29 in patients.

| | 2 mg | 6 mg |
|---|---|---|
| **$C_{max,ss}$, ng/mL** | 0.5 ± 0.3 | 1.7 ± 0.7 |
| **$C_{min,ss}$, ng/mL** | <LOQ | 0.17 ± 0.12 |
| ***$T_{max,ss}$, hour** | 0.7 | 1.0 |
| **$AUC_{0-6}$, hour*ng/mL** | 1.2 ± 0.5 | 4.3 ± 1.8 |

* median

**Table 2.** Multiple dose pharmacokinetics of tegaserod 2 mg and 6 mg bid assessed on day 7 in healthy volunteers.

| | 2 mg | 6 mg |
|---|---|---|
| **$C_{max,ss}$, ng/mL** | 0.7 ± 0.3 | 2.7 ± 1.2 |
| **$C_{min,ss}$, ng/mL** | <LOQ | 0.11 ± 0.07 |
| ***$T_{max,ss}$, hour** | 1.0 | 0.8 |
| **$AUC_{0-6}$, hour*ng/mL** | 2.1 ± 1.0 | 7.7 ± 3.3 |

* median

## STUDY B254 (Pharmacokinetics in ——→ Patients)

**Study Type:** Efficacy.

**Protocol Title:** A randomized, double-blind, placebo-controlled, multiple dose study to assess the safety and tolerability of three ascending dose levels of SDZ HTF19 and placebo in subjects with ——————

**NDA:** 21-200 **Submission Date:** 2/11/00 **Volume:** 1.184 **Protocol:** B254

**Study Design**: Randomized, double blind, placebo controlled, parallel group.

**Formulation (FMI)**

| Treatment Group | Dose | Dosage Form | Strength | Lot |
|---|---|---|---|---|
| Tegaserod | — mg bid/28 days | FMI Tablet | —— | X103 0595 |
| Tegaserod | 2 mg bid/28 days | FMI Tablet | 2 mg | X141 0695 |
| Tegaserod | 6 mg bid/28 days | FMI Tablet | 6mg | X142 0695 |

**Analytical Methodology**

Plasma Sampling Times: On days 29, up to 6 hours post-dosing.

Assay Method: ——

[ ]

**Results and Discussion**

The pharmacokinetics were different in patients when compared to healthy subjects from study W351. The $C_{max,ss}$ and $AUC_{0-6}$ were 30% to 50% lower in patients. 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.

**Table 1.** Multiple dose pharmacokinetics of tegaserod 2 mg and 6 mg bid assessed on day 29 in patients.

| | 2 mg | 6 mg |
|---|---|---|
| **$C_{max,ss}$, ng/mL** | 0.5 ± 0.3 | 1.9 ± 1.4 |
| **$C_{min,ss}$, ng/mL** | <LOQ | 0.13 ± 0.14 |
| ***$T_{max,ss}$, hour** | 0.7 | 1.0 |
| **$AUC_{0-6}$, hour*ng/mL** | 1.0 ± 0.7 | 3.8 ± 1.9 |

* median

**Table 2.** Multiple dose pharmacokinetics of tegaserod 2 mg and 6 mg bid assessed on day 7 in healthy volunteers.

| | 2 mg | 6 mg |
|---|---|---|
| **$C_{max,ss}$, ng/mL** | 0.7 ± 0.3 | 2.7 ± 1.2 |
| **$C_{min,ss}$, ng/mL** | <LOQ | 0.11 ± 0.07 |
| ***$T_{max,ss}$, hour** | 1.0 | 0.8 |
| **$AUC_{0-6}$, hour*ng/mL** | 2.1 ± 1.0 | 7.7 ± 3.3 |

* median