

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-287**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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NDA: 22287	Submission Date(s): December 28, 2007, April 28, 2008, May 5, 2008, May 22, 2008, May 30, 2008, July 11, 2008
Brand Name	<b>(b) (4)</b>
Generic Name	Dexlansoprazole
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OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology Products
Sponsor	TAP Pharmaceutical Products Inc
Submission Type; Code	Original
Formulation; Strength(s)	Delayed Release Capsules (30 mg, 60 mg, <b>(b) (4)</b> )
Indication	gastroesophageal reflux disease(GERD) , erosive esophagitis (EE)

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## 1 Executive Summary

### 1.1 Recommendation

The application is acceptable from the clinical pharmacology perspective provided the labeling comments are adequately addressed by the sponsor. (b) (4)

If the safety profiles of the drug are acceptable to the Division of Gastroenterology Products, our recommended dosing regimens for the proposed indications are as listed below.

Indication	Recommended dose	Frequency
Healing EE	60 mg	Once daily for up to 8 weeks
Maintenance of Healed EE	30 mg	Once daily*
Symptomatic GERD	30 mg	Once daily for up to 8 weeks

\*Controlled studies did not extend beyond 6 months. gastroesophageal reflux disease: GERD

### 1.2 Post-marketing Commitments

Under discussion

### 1.3 Regulatory Background

Lansoprazole (racemic mixture) has been approved for treating GERD and EE in several formulations (delayed release capsules, delayed release oral suspension, delayed release orally disintegrating tablets) via NDAs 20-406, 21-281, and 21-428. This is the original NDA to which dexlansoprazole MR is submitted for the indications of EE and GERD. Sponsor's rationale for developing dexlansoprazole (R-isomer) is that though both R and S isomers appeared to exhibit similar in-vitro pharmacological activities, dexlansoprazole has slower in-vivo metabolism than the S-isomer and that there is no in-vivo inversion of dexlansoprazole to its S-isomer. Lansoprazole is administered once a day, as is this product. It is unclear how the delayed-release formulation of dexlansoprazole would provide any further therapeutic benefit as compared to a immediate release formulation

### 1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Product: Dexlansoprazole, a proton pump inhibitor, is formulated in modified release (MR) capsules. The dexlansoprazole MR capsule contains two different types of enteric coated granules: (1) granules (b) (4) which provide 25% of the dexlansoprazole dose, release soon after entering the small intestine upon dissolution of the enteric coating at approximately pH  $\geq 5.5$ , and (2) granules ( ), which provide 75% of the dexlansoprazole dose, release farther along the GI tract upon dissolution of the enteric coating at approximately pH  $\geq 6.75$ . The sponsor's proposed oral dosing recommendations are as follows:

Indication	Recommended Dose	Frequency
Healing of EE	60 mg (b) (4)	Once daily for up to 8 weeks
Maintenance of Healed EE	30 mg (b) (4)	Once daily*
Symptomatic GERD	30 mg	Once daily for 4 weeks

\*Controlled studies did not extend beyond 6 months.

Pharmacokinetic characteristics:

Dexlansoprazole binds to human plasma proteins extensively (~96%) over the concentration range of 1-20 µg/ml. Following single oral dose in healthy subjects, plasma AUC<sub>(0-48)</sub> and C<sub>max</sub> of dexlansoprazole increased approximately dose proportionally between 30mg and 60mg, and less than dose proportionally between 60 mg and 120 mg. The half-life was 3-3.7hrs. Based on the results of several studies, CL/F was 6.1-8 L/h. Cross-study comparisons showed that patients with symptomatic GERD had higher mean dexlansoprazole AUC than healthy subjects (46% to approximately 76% higher).

Following repeated doses, plasma AUC<sub>(0-24)</sub> on Day 5 in healthy subjects for each individual dose was slightly higher (less than 10%) than that following single dose. The half-life was between 1.28 and 1.71hrs. Oral clearance after multiple dosing of 30 mg QD or 60 mg QD was 8.8 -11.45 L/h.

CYP2C19 polymorphism: Following single oral dose of 30 mg and 60mg, the heterozygous extensive metabolizers (EMs) (\*1/mutant allele) had approximately 2-fold and 1.3-fold higher C<sub>max</sub> and 2.2 fold and 1.4–fold higher AUC values than the homozygous EMs(\*1/\*1), respectively. At 90 mg and 120 mg, both C<sub>max</sub> and AUC were similar between these two groups. Poor metabolizers (PMs, mutant allele/mutant allele) had AUC values 2.96, 5.44, 4.67, 3.41, and 3.5 fold higher than EMs (homozygous and heterozygous EMs combined) when dosed with 15mg, 30mg, 60mg, 90mg, and 120 mg dexlansoprazole MR QD, respectively.

Food effect: When a single 90-mg dose was administered 30 minutes to 1 hour before or 30 minutes after the start of a high-fat meal, dexlansoprazole C<sub>max</sub> increased by 36 to 52% and AUC increased by 30-33% relative to administration while fasting. There were also effects of food on both t<sub>max</sub> and early-phase absorption. When drug was administered 30 minutes *after* a meal, early-phase absorption was significantly impaired and t<sub>max</sub> was delayed by 2-4 hours relative to administration before or meal or while fasting. When drug was administered *before* a meal, the rate of early-phase absorption is not affected relative to administration while fasting.

A separate, single-dose (60 mg) study in Japanese men who were CYP2C19 extensive metabolizers found that C<sub>max</sub> increased by 45% and AUC increased by 14% when dexlansoprazole was administered after a meal relative to fasting.

When the drug was administered 30 minutes to 1 hour before a high fat meal, there were no clinically significant differences in intragastric pH over the dosing interval between the fed and fasting regimens. When the drug was administered 30 minutes *after* a meal, there was a delay in the increase of gastric pH. Therefore, dexlansoprazole may be taken with or without food but there is a possible delay in onset of the effect if the drug is administered with or after a meal. In addition, there was no difference in

dexlansoprazole exposure when administered as an intact capsule or as granules sprinkled over applesauce.

Metabolism/Excretion: Human liver microsomes preferentially converted dexlansoprazole and lansoprazole to 5-hydroxylansoprazole over lansoprazole sulfone with formation of 5-hydroxylansoprazole correlating well with CYP2C19 activity, whereas formation of lansoprazole sulfone correlating well with CYP3A4 activity. In a mass balance study with [<sup>14</sup>C]dexlansoprazole, mean (SD) radioactivities recovered in urine and feces after 7 days were 37.2% (4.0%) and 44.4% (7.0%) of the administered dose, respectively. Dexlansoprazole was the major component in the plasma, accounting for over 70% of the plasma radioactivity. Dexlansoprazole was metabolized by oxidation, reduction, and conjugation to at least 19 metabolites with ten metabolites detected in plasma.

Drug drug interactions: Dexlansoprazole slightly inhibit in-vitro hepatic CYP 2C19 activity. A single dose of 5 mg of diazepam (a 2C19 substrate) was given after 11 days of 90 mg of dexlansoprazole MR QD, and no significant interaction was observed based on the AUC and C<sub>max</sub> values of diazepam and its metabolite nordiazepam.

In-vitro studies showed that lansoprazole is a CYP 1A1 and 1A2 inducer. A Single 400-mg IV dose of aminophylline dehydrate (315.2 mg anhydrous theophylline) was given after 9 days of dexlansoprazole MR 90 mg QD, and no interaction was observed based on the AUC and C<sub>max</sub> values of theophylline (1A2 substrate).

A single dose of 250mg phenytoin, a CYP2C9 substrate, was administered following 6 doses of dexlansoprazole 90mg. No significant interaction was observed based on the AUC and C<sub>max</sub> of phenytoin.

A single 25mg dose of warfarin, another CYP2C9 substrate, was administered following 6 doses of dexlansoprazole 90mg. No significant interaction was observed based on the AUC, C<sub>max</sub>, of R- and S-warfarin, INR<sub>max</sub>, and INR<sub>144</sub>.

Special populations:

The differences in the pharmacokinetics of dexlansoprazole between healthy subjects and patients with moderate hepatic impairment reached statistical significance for C<sub>max,u</sub>, AUC<sub>t</sub>, AUC<sub>∞</sub>, and AUC<sub>∞,u</sub>. Dose reduction in patients with hepatic impairment is recommended.

Dexlansoprazole exhibited higher AUC in the elderly (30.7% higher) or female subjects (40.6% higher) than in the young or male subjects, respectively, though the differences did not reach statistical significance. Dose adjustment may be needed for elderly or female patients.

QT effect: The QT/IRT review team concludes that “No significant QT prolongation effect of (b) (4) 90 mg and 300 mg) was detected in this TQT study.”

Exposure/response relationship: Following repeated dose for 5 days, intra-gastric pH values over the >4 to 9-hr or >9 to 12-hr or >12 to 16-hr or total 24-hr interval were similar between 60mg and 120 mg. No advantage in increasing intragastric pH was observed at doses higher than 60 mg. The mean percent time when intragastric pH exceeded 4 was similar between 60 and 120mg. Though the exposure increases with

dose between 30mg and 120mg, there is no clear pharmacodynamic response (intra-gastric pH & percent time of intra-gastric pH exceeded 4) and exposure relationship between 60mg and 120 mg.

Dose/efficacy relationship: Two clinical studies showed inconsistent observations of whether dexlansoprazole 60mg MR QD was more effective in healing EE than dexlansoprazole 30 mg QD. There is no statistical difference in overall EE healing rates between dexlansoprazole 60 mg MR QD and lansoprazole 90 mg MR QD regardless of severity. For maintenance of EE healing, similar efficacy was observed between 30 mg MR QD and 60 mg MR QD, and between 90 mg MR QD and 60 mg QD. In terms of treatment of GERD: Dexlansoprazole MR 30 mg QD and 60 mg QD were equally effective in relieving both daytime and nighttime heartburn combined and in relieving nighttime heartburn in subjects with symptomatic GERD.

Dose/Safety relationship: There is no dose/adverse events relationship. In healing EE study, one ischaemic coronary artery disorders observed for dexlansoprazole MR 90 mg QD but regarded as not treatment related. In GERD study, myocardial Infarction occurred in 2 subjects in the dexlansoprazole MR 30-mg treatment group 2 to 4 days after the last dose and one of these 2 subjects also experienced a cerebrovascular accident 7 days after the last dose. The sponsor concluded that these events were not related to study drug.

The review of OSE concludes that there is not dose/reponse (adverse events) relationship and states that "It does not seem likely that dexlansoprazole is a cause of cardiovascular disorders in the clinical trial data."

## 2 Question Based Review

### 2.1 General Attributes

#### 2.1.1 What is the proposed indication of (b) (4) ?

(b) (4) is a proton pump inhibitor (PPI) indicated for 1) healing (b) (4) of all grades of erosive esophagitis (EE), 2) Maintaining healing of EE (b) (4) (b) (4) 3) Treating (b) (4) heartburn (b) (4) associated with gastroesophageal reflux disease (GERD).

#### 2.1.2 What is the proposed mechanism of action of (b) (4) ?

Dexlansoprazole is a PPI that suppresses gastric acid secretion by specific inhibition of the (H<sup>+</sup>,K<sup>+</sup>)-ATPase in the gastric parietal cell. By acting specifically on the proton pump, dexlansoprazole blocks the final step of acid production.

#### 2.1.3 What are the proposed dosing regimens and route of administration?

(b) (4) is formulated in delayed release capsules for oral administration. The proposed dosing regimens for individual indications are listed below.

Indication	Recommended Dose	Frequency
Healing of EE	60 mg (b) (4)	Once daily for up to 8 weeks
Maintenance of Healed EE	30 mg	Once daily*
Symptomatic GERD	30 mg	Once daily for 4 weeks

\*Controlled studies did not extend beyond 6 months.

(b) (4)

#### 2.1.4 What is the regulatory background?

(b) (4)

#### 2.1.5 Why is dexlansoprazole (R-form of lansoprazole) selected over S-lansoprazole for clinical development?

Lansoprazole has a chiral center at the asymmetric sulfinyl group, and, therefore, has 2 enantiomers: R- and S-lansoprazole. The R-form is known as dexlansoprazole. Dexlansoprazole and S-lansoprazole have similar in-vitro specific inhibition of the (H<sup>+</sup>,K<sup>+</sup>)-ATPase enzyme system (proton pump) at the surface of the gastric parietal cell. Clinically, S-lansoprazole induces a lower suppression of gastric acid secretion than dexlansoprazole at an equivalent dose. The lower in-vivo pharmacodynamic (PD) effect of S-lansoprazole is due to its faster in-vivo clearance than dexlansoprazole. After oral administration of lansoprazole, dexlansoprazole is the predominant circulating enantiomer. Racemic conversion of dexlansoprazole to S-lansoprazole does not occur in humans, as no S-lansoprazole is detectable in plasma following oral administration of dexlansoprazole.

The sponsor conducted a study evaluating administration of lansoprazole 30 mg for 1 or 5 days, R-lansoprazole accounted for 85% and 90% of the total lansoprazole C<sub>max</sub> and AUC, respectively, compared to S-lansoprazole. Based on these data, dexlansoprazole (R-isomer) was selected for clinical development.

## **2.2 General Clinical Pharmacology**

### **2.2.1 What are the design features of the clinical pharmacology studies used to support dosing or label claims?**

The pharmacokinetic/pharmacodynamic (PK/PD) relationship of dexlansoprazole MR at different dose levels was determined in a Phase 1, randomized, open-label, single-center, multiple-dose, 4-period crossover study. The subjects received multiple doses of 60mg, 90mg or 120 mg of dexlansoprazole MR or 30 mg lansoprazole capsules. The results were summarized in table 3 of the proposed label. The results also demonstrated the increases with dose for the AUC and Cmax of dexlansoprazole MR.

For the labeling statement related to gastrin and enterochromaffin-like cells (neuroendocrine proliferation examined using chromogranin immunohistochemical stain), the sponsor summarized the results from 2 randomized, double-blind, multicenter, active-controlled, 3-arm studies.

The sponsor conducted an open-label, parallel-group study to evaluate the effect of moderate hepatic impairment on the PK and safety of dexlansoprazole MR (60 mg). Twenty four subjects (12 subjects with normal hepatic function and the rest with moderately impaired hepatic function) completed the study.

The effects of gender and age on the PK and safety of dexlansoprazole were investigated following administration of a 60 mg single oral dose of dexlansoprazole MR in an open-label, parallel-group study. Twenty four subjects (12 young subjects with 6 males and 6 females aged 18-40 and 12 elderly subjects with 6 males and 6 females aged 65 to 80) completed the study.

The drug-drug interactions were investigated using standard 2-way crossover studies with dexlansoprazole administered for 6 to 11 days and the probe administered as a single dose following at least 6 doses of dexlansoprazole. The probe used included diazepam, theophylline, warfarin and phenytoin.

The food effect studies were conducted as single-dose, crossover studies in healthy volunteers utilizing the standard high-fat breakfast.

The study designs of all the studies described above are acceptable to support the label claims. The clinical formulation is the same as the to-be-marketed formulation.

### **2.2.2 What are the design features of the clinical studies used to support dosing or label claims?**

Healing of EE (studies Study T-EE04-084 and Study T-EE04-085): Subjects with endoscopically proven EE were enrolled in the Phase 3 Studies. Both studies are randomized, double-blind, multicenter, active-controlled, 3-arm, 8-week studies. Subjects who were eligible for entry into the Treatment Period were randomized in a 1:1:1 ratio to receive one of the following treatments: dexlansoprazole MR 60 mg QD, dexlansoprazole MR 90 mg QD, or lansoprazole 30 mg QD.

The primary efficacy variable Study T-EE04-084 was the percentage of subjects who had complete healing of EE over 8 weeks as assessed by endoscopy. The secondary

efficacy variables were (1) the percentage of subjects who had complete healing of EE over 4 weeks as assessed by endoscopy and (2) the percentage of subjects with baseline EE Grade C or D (moderate or severe) who had complete healing of EE over 8 weeks as assessed by endoscopy.

The primary endpoint for Study T-EE04-085 was assessed using a closed testing procedure by first assessing noninferiority of the dexlansoprazole MR doses to lansoprazole. Those dexlansoprazole MR doses shown to be noninferior to lansoprazole were then tested for superiority to lansoprazole. Since 2 doses of dexlansoprazole MR were being evaluated, control of the overall significance level at 0.05 was accomplished using Hochberg's method for multiple comparisons.

Maintenance of Healing in Subjects with Healed Erosive Esophagitis:

Subjects who successfully completed Study T-EE04-084 or Study T-EE04-085 and had endoscopically proven healed EE were enrolled in Phase 3, randomized, double-blind, multi-center, placebo-controlled studies with a 6-month treatment period consisting of 4 visits (Day -1, Month 1, Month 3, and Month 6). Subjects who met the selection criteria were enrolled into the maintenance study at Day -1 and randomized in a 1:1:1 ratio to receive 1 of the following treatments: dexlansoprazole MR 30 mg QD, dexlansoprazole MR 60 mg QD, or placebo QD. The primary efficacy variable was the percentage of subjects who maintained healed EE over 6 months as assessed

Treatment of nonerosive gastroesophageal reflux disease

Subjects with symptomatic, endoscopically confirmed nonerosive GERD were enrolled in one of 2 identical Phase 3, randomized, double-blind, multicenter, placebo-controlled, 3-arm studies (T-GD04-082 or T-GD04-083). The studies consisted of 2 periods: a Screening Period, which lasted a minimum of 7 days and a maximum of 21 days, and a Treatment Period, which lasted 4 weeks. Subjects who were eligible for entry into the Treatment Period were randomized in a 1:1:1 ratio to receive one of the following treatments: dexlansoprazole MR 60 mg QD, dexlansoprazole MR 90 mg QD, or placebo QD. The primary efficacy variable was the percentage of days with neither daytime nor nighttime heartburn during treatment as assessed by daily electronic diary.

**2.2.3 What are the pharmacokinetics characteristics of dexlansoprazole?**

Plasma protein binding: Radiolabeled and nonradiolabeled dexlansoprazole were mixed to obtain the appropriate levels of radioactivity and dexlansoprazole concentrations. The protein binding of <sup>14</sup>C-dexlansoprazole in human plasma was evaluated by ultrafiltration at concentrations of 1, 5, 10, and 20 µg/mL. The extent of nonspecific binding to the ultrafiltration device was measured in triplicate in fortified buffer at concentrations of 1 and 20 µg/mL of <sup>14</sup>C-dexlansoprazole.

Table 1. Percentages of <sup>14</sup>C-dexlansoprazole unbound and bound at various concentrations in human plasma

Concentration ( $\mu\text{g/mL}$ )	Percent of Radioactivity				Standard Deviation
	Unbound		Bound		
	Individual	Mean	Individual	Mean	
1	3.76	3.72	96.2	96.3	0.1
	3.64		96.4		
	3.76		96.2		
5	3.51	3.65	96.5	96.4	0.2
	3.57		96.4		
	3.86		96.1		
10	3.76	3.66	96.2	96.3	0.1
	3.64		96.4		
	3.58		96.4		
20	3.76	3.87	96.2	96.1	0.1
	3.85		96.2		
	4.00		96.0		

The mean percentages of  $^{14}\text{C}$ -dexlansoprazole bound to human plasma proteins at 1, 5, 10, and 20  $\mu\text{g/mL}$  were 96.3, 96.4, 96.3, and 96.1%, respectively. There was no concentration dependence over the target concentration range of 1 to 20  $\mu\text{g/mL}$ .

The sponsor conducted three studies (T-P105-122, T-P-104-071 and T-P104-100) to determine the PK/PD of DEXLANSOPRAZOLE MR over the dose range of 30 mg to 120 mg. The sponsor did not provide information regarding the genotypes or phenotypes of CYP 2C19 of the subjects who participated in the studies. The results of these studies are summarized below to illustrate the single and multiple dose PK characteristics.

#### Single dose pharmacokinetics in healthy subjects

Table 2.1. Mean (CV%) pharmacokinetic parameters of dexlansoprazole after single dose (studies T-P105-122, T-P-104-071 and T-P104-100) in healthy subjects

Study	N	Dose	C <sub>max</sub> (ng/ml)/dose	AUC <sub>0-24</sub> (ng * hr/ml)/mg dose	CL/F (L/hr)
T-P105-122	43	30 mg	19.43(53)	97.71 (50)	12.72 (53)
	43	60 mg	20.14 (46)	98.09 (46)	12.13 (41)
T-P104-071	34	60 mg	21.50 (57)	99.22 (74)	--
	34	90 mg	19.87 (54)	96.26 (74)	--
	31	120 mg	20.37(42)	105.05 (75)	--
T-P104-100	40	90 mg	21.71(49)	124.7 (59)	9.93 (58%)
	40	120 mg	22.71 (51)	126.66 (56)	9.38 (47%)

After a single dose of 30mg, 60 mg, 90 or 120mg of dexlansoprazole MR, the half-life of dexlansoprazole ranged from 1.36-1.65 hrs, and its T<sub>max</sub> 4.38-5.53 hrs. The dose-normalized AUC and C<sub>max</sub> values were similar within each study, but differed slightly between the studies. The dose normalized pharmacokinetic results were similar for the 60-mg dose between studies T-P104-071 and T-P105-122. The dose-normalized pharmacokinetic results of study T-P104-071 were comparable to, but slightly lower

than, the respective results observed in study T-P104-100. Vz/F was not estimated for Study T-P104-071. The Day 1 mean (CV%) Vz/F of Study T-P105-122 was 30.87L (59%) for 30mg QD and was 32.67 (81%) for 60mg QD. The Day 1 mean (CV%) Vz/F of Study T-P104-100 was 28.47 L (78%) for 90mg QD and 27.2 (96%) for 120mg QD. Overall, these results demonstrated that AUC and Cmax values were approximately dose proportional between 30mg and 120mg.

Table 2.2 Cmax and AUC in CYP 2C19 PMs and EMs.

	C <sub>max</sub> (ng/mL)				AUC <sub>∞</sub> (ng-h/mL)			
	CYP2C19 Phenotype				CYP2C19 Phenotype			
	EM	EM (homozygous)	EM (heterozygous)	PM	EM	EM (homozygous)	EM (heterozygous)	PM
<b>15 mg Dexlansoprazole MR</b>								
N	6	2	4	6	6	2	4	6
Mean	269	192	308	665	1534	863	1870	6069
CV%	36	14	31	38	49	16	38	39
Min	173	173	239	312	764	764	946	2837
Median	245	192	274	636	1364	863	1962	6017
Maximum	446	210	446	1103	2608	962	2608	9930
<b>30 mg Dexlansoprazole MR</b>								
N	6	2	4	6	6	2	4	6
Mean	555	334	665	1443	2604	1431	3191	16769
CV%	35	38	15	33	42	24	24	39
Min	245	245	540	783	1188	1188	2132	7782
Median	597	334	674	1570	2621	1431	3415	16566
Maximum	772	442	772	1957	3804	1673	3804	24927
<b>60 mg Dexlansoprazole MR</b>								
N	6	4	2	6	6	4	2	6
Mean	1144	1039	1355	3057	5442	4822	6682	30834
CV%	22	24	3	28	38	39	35	19
Min	809	809	1328	1957	3014	3014	5006	24933
Median	1255	1042	1355	3048	5113	4479	6682	29364
Maximum	1382	1262	1382	4205	8357	7314	8357	38310
<b>90 mg Dexlansoprazole MR</b>								
N	6	3	3	6	6	3	3	6
Mean	1836	1858	1815	4501	9037	8348	9725	39886
CV%	33	49	18	32	32	53	4	12
Min	905	905	1468	2963	4245	4245	9318	33409
Median	1905	1967	1842	4176	9562	7769	9805	41294
Maximum	2702	2702	2134	6302	13031	13031	10053	45915
<b>120 mg Dexlansoprazole MR</b>								
N	6	4	2	6	6	4	2	6
Mean	2412	2316	2604	4474	12775	11270	15785	57449
CV%	19	24	7	52	31	34	14	17
Min	1759	1759	2482	2578	7715	7715	14243	42355
Median	2565	2290	2604	3757	13022	10461	15785	57007
Maximum	2923	2923	2726	9112	17326	16443	17326	73862

Source: Report TAK-390MR/CPH-001, Table 3.1, pages 159-167

Based on the single oral dose results of Study CPH-001 in which healthy subjects were genotyped for CYP2C19, Cmax in PMs showed dose proportionality between 15mg and 90 mg but remained similar between 90 mg and 120 mg, while the AUC was approximately dose proportional between 15 mg and 60 mg and failed so from 60 mg to 120 mg. In homozygous EMs Cmax and AUC was approximately dose proportional with high variation. In heterozygous EMs, Cmax was dose proportional between 15 mg and 60 mg but not between 60mg-120 mg, but AUC was dose proportional.

Table 2.3. Mean (SD) pharmacokinetic parameters of dexlansoprazole after single dose (Study CPH-001) in healthy subjects

	AUC0-48	Cmax	T1/2	CL/F
15 mg	3908 (3032)	445 (299)	3 (1.3)	7.5 (6.2)
30 mg	9818 (8722)	928 (627)	3.5 (2)	8 (7.7)
60 mg	18303 (14009)	1657 (1298)	3.2 (1.8)	7.2 (6.4)
90 mg	24712 (16827)	2389(1729)	3.3 (1.7)	6.8 (5.8)
120 mg	35010 (24256)	3161 (2127)	3.7 (2.2)	6.1 (4.9)

With the data from CYP2C 19 EMs and PMs combined above, the AUC and Cmax showed approximately dose proportional between 15 mg and 60 mg and less than dose proportional between 60 mg and 120 mg. Tmax was 5.5-7.1 hrs.

#### Multiple- dose pharmacokinetics in healthy subjects

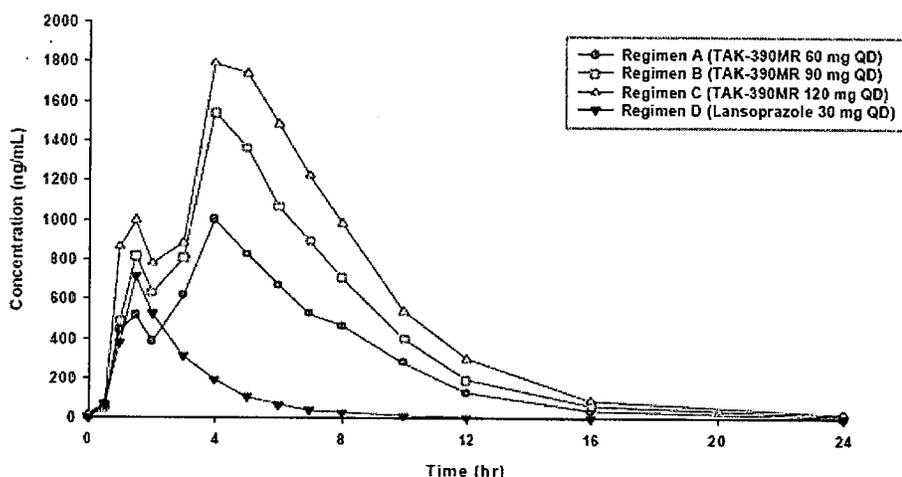
Table 3. Mean (CV%) pharmacokinetic parameters following 5-day administration (studies T-P105-122, T-P-104-071 and T-P104-100)

Study	N	dose	Cmax (ng/ml)/dose	AUC0-24 (ng * hr/ml)/dose	CL/F (L/hr)
T-P105-122	44	30 mg	21.94 (40%)	108 (48%)	11.29 (47%)
	43	60 mg	23.14 (53%)	108(48%)	11.62 (47%)
T-P104-071	34	60 mg	23.89 (49%)	108.35 (69%)	--
	34	90 mg	24.41 (42%)	106.21 (75%)	--
	30	120 mg	20.97 (46%)	110.17 (71%)	--
T-P104-100	40	90 mg	22.61 (48%)	127.81 (54%)	9.07(50%)
	40	120 mg	24.77 (44%)	138.49 ( 47%)	8.62 (59%)

For each study, the AUC values showed a trend of slightly higher on day 5 than day 1. These studies revealed that the values of half-life from day 1 and day 5 were 1.28-1.71hrs between 30mg and 120 mg. The Day 5 mean (CV%) Vz/F of Study T-P104-100 was 23.82 L (55%) for 90mg QD and was 23.0 (59%) for 120mg QD. The Day 5 mean (CV%) Vz/F of Study T-P105-122 was 25.37L (51%) for 30mg QD and was 32.9 L (91%) for 60mg QD. The tmax and Vz/F on day 1 and day 5 of study T-P105-122 ranged from 4.22 to 5.53 hrs, and 25.68-34.27 L, respectively.

Both AUCt and Cmax of dexlansoprazole from delayed release capsules were slightly higher (less than 10%) on day 5 than on day 1. One possible reason may be due to the fact that the average gastrointestinal transit time of food is close to 36 hrs or longer, and the delayed release capsule in the colon from the previous dosing was still releasing some residual amount of dexlansoprazole in the colon when a new capsule just began to release dexlansoprazole in the upper GI tract. The plasma concentration profiles of DEXLANSOPRAZOLE at different dose levels obtained from Study T-P104-071 are shown in the following figure,

Fig 1. Mean Concentration vs. Time Profiles for DEXLANSOPRAZOLE or Lansoprazole in Study T-P104-071 on Day 5



The concentration/time plots showed that the AUC of dexlansoprazole MR increased with dose between 60mg and 120 mg, and that T<sub>max</sub> remained similar among the three regimens (dexlansoprazole 60mg, 90mg and 120 mg MR QD).

#### Comparison of pharmacokinetics between healthy subjects and GERD patients

Table 4. Mean (CV%) pharmacokinetic parameters following 5-day administration (studies T-P105-122, T-P-105-129)

Study	N	dose	C <sub>max</sub> (ng/ml)/dose	AUC <sub>0-24</sub> (ng * hr/ml)/dose	t <sub>1/2</sub> hr
T-P105-122 (healthy subjects)	44	30 mg	21.94 (40%)	108 (48%)	1.52 (NA)
	43	60 mg	23.14 (53%)	108 (48%)	1.65 (NA)
T-P105-129 (GERD patients)	10	30 mg	26.6 (70%)	158 (108%)	2.52 (69%)
	12	60 mg	24.4 (42%)	190 (93%)	2.86 (76%)
	12	90 mg	21.9 (62%)	142 (96%)	2.86 (51%)

NA: Not available.

**Conclusion:** Overall, these results showed that C<sub>max</sub>, AUC<sub>t</sub> and AUC<sub>0-∞</sub> were dose proportional from 30mg to 120 mg. The results of Study CPH-001 (see section 2.2.7) revealed dose proportionality in EMs between 15mg and 120mg but slightly less so in PMs. The AUC of dexlansoprazole in patients with symptomatic GERD are higher (ranging from 46% to approximately 76% higher) than those in healthy subjects.

#### **2.2.4 How are lansoprazole, dexlansoprazole , and S-lansoprazole metabolized in-vitro?**

Individual in-vitro metabolisms of dexlansoprazole , S-enantiomer, and lansoprazole were studied using human hepatocyte microsomes with diclofenac (4'-hydroxylation), S-mephenytoin (4'-hydroxylation), and testosterone (6-beta-hydroxylation) as the substrate for CYP2C9, CYP2C19 and CYP3A4, respectively. Lansoprazole and its enantiomers were metabolized both by CYP 3A4 and by CYP 2C19, The results of metabolisms of these compounds by (1) recombinant human CYP2C19 and CYP3A4, and (2) human

liver microsomes from donors genotyped as CYP2C19 extensive metabolizers (EMs) or poor metabolizers (PMs) are summarized below.

Table 5. Km and Vmax for the 5-hydroxylation and sulfoxidation of racemic lansoprazole, dexlansoprazole, and (S)-lansoprazole by recombinant human CYP2C19 and CYP3A4

Test Article	Metabolite	Recombinant CYP2C19			Recombinant CYP3A4		
		Km (μM)	Vmax (pmol/min/pmol P450)	Vmax/Km (μL/pmol P450/min)	Km (μM)	Vmax (pmol/min/pmol P450)	Vmax/Km (μL/pmol P450/min)
Racemic lansoprazole	5-Hydroxy lansoprazole	0.433	2.93	6.77	44.8	4.51	0.101
	Lansoprazole sulfone	ND	ND	ND	51.0	41.7	0.818
	Total	NA	NA	6.77	NA	46.2	0.919
Dexlansoprazole	5-Hydroxy lansoprazole	4.11	20.4	4.96	71.6	9.50	0.133
	Lansoprazole sulfone	ND	ND	ND	59.8	14.4	0.241
	Total	NA	NA	4.96	NA	23.9	0.374
(S)-Lansoprazole	5-Hydroxy lansoprazole	0.278	1.95	7.01	101	6.97	0.0690
	Lansoprazole sulfone	ND	ND	ND	49.7	59.8	1.20
	Total	NA	NA	7.01	NA	66.8	1.27

Vmax/Km = *In vitro* intrinsic clearance  
 ND: Not detected. NA: Not Applicable

For the 5-hydroxylation of racemic lansoprazole by CYP2C19, the resulting Km and Vmax were  $0.433 \pm 0.011 \mu\text{M}$  and  $2.93 \pm 0.02 \text{ pmol/min/pmol P450}$ , respectively. For the 5-hydroxylation and sulfoxidation of racemic lansoprazole by CYP3A4, the resulting Km and Vmax were  $44.8 \pm 2.6 \mu\text{M}$  and  $4.51 \pm 0.12 \text{ pmol/min/pmol P450}$  and  $51.0 \pm 6.1 \mu\text{M}$  and  $41.7 \pm 3.5 \text{ pmol/min/pmol P450}$ , respectively. For the 5-hydroxylation of dexlansoprazole by CYP2C19, the resulting Km and Vmax were  $4.11 \pm 0.71 \mu\text{M}$  and  $20.4 \pm 2.6 \text{ pmol/min/pmol P450}$ , respectively. For the 5-hydroxylation and sulfoxidation of dexlansoprazole by CYP3A4, the resulting Km and Vmax were  $71.6 \pm 5.6 \mu\text{M}$  and  $9.50 \pm 0.60 \text{ pmol/min/pmol P450}$  and  $59.8 \pm 3.5 \mu\text{M}$  and  $14.4 \pm 0.5 \text{ pmol/min/pmol P450}$ , respectively. For the 5-hydroxylation of (S)-lansoprazole by CYP2C19, the resulting Km and Vmax were  $0.278 \pm 0.013 \mu\text{M}$  and  $1.95 \pm 0.03 \text{ pmol/min/pmol P450}$  (Table 1, Figure 9). For the 5-hydroxylation and sulfoxidation of (S)-lansoprazole by CYP3A4, the resulting Km and Vmax were  $101 \pm 18 \mu\text{M}$  and  $6.97 \pm 0.66 \text{ pmol/min/pmol P450}$  and  $49.7 \pm 6.7 \mu\text{M}$  and  $59.8 \pm 5.8 \text{ pmol/min/pmol P450}$ , respectively.

Metabolism of dexlansoprazole to 5-hydroxy metabolite by recombinant CYP2C19 showed much lower affinity and higher capacity than those of lansoprazole and (S)-lansoprazole. In terms of metabolism to 5-hydroxy metabolite by recombinant CYP 3A4, dexlansoprazole had lower affinity and higher capacity than lansoprazole, but higher affinity and higher capacity than (S)-lansoprazole. In terms of metabolism to lansoprazole sulfone by recombinant CYP 3A4, dexlansoprazole showed lower affinity and lower capacity than lansoprazole or (S)-lansoprazole. Recombinant CYP2C19 catalyzed only the formation of 5-hydroxylation metabolites.

Table 6. The *in vitro* intrinsic clearance (based on Vmax/Km) of racemic lansoprazole, dexlansoprazole and (S)-lansoprazole by recombinant human CYP3A4 and CYP2C19

Substrate	Vmax/Km for CYP3A4 ( $\mu\text{L}/\mu\text{mol P450}/\text{min}$ )			Vmax/Km for CYP2C19 ( $\mu\text{L}/\mu\text{mol P450}/\text{min}$ )
	5-Hydroxylansoprazole	Lansoprazole sulfone	Total	5-Hydroxylansoprazole
Racemic Lansoprazole	0.101	0.818	0.919	6.77
Dexlansoprazole	0.133	0.241	0.374	4.96
(S)-Lansoprazole	0.0690	1.20	1.27	7.01

Vmax/Km = *In vitro* intrinsic clearance or  $CL_{int}$

The rank order of intrinsic clearance ( $Cl_{int}$ ) by recombinant CYP2C19 was S-lansoprazole > lansoprazole > dexlansoprazole as shown above. Recombinant CYP3A4 converted all three substrates to both 5-hydroxylansoprazole and lansoprazole sulfone. The rank order of intrinsic clearance ( $Cl_{int}$ ) by recombinant CYP3A4 via the formation of sulfone metabolites was S-lansoprazole > lansoprazole > dexlansoprazole. Together with the study below, the findings suggested that (S)-lansoprazole is eliminated in the body faster than dexlansoprazole and that CYP2C19 contributed to dexlansoprazole to a greater extent than CYP3A4.

#### Metabolism by human liver microsomes

There were 4 donors and their CYP2C19 genotypes were determined. Donor H0257 and H0502 were homozygous for the non-functional CYP2C19\*2 allele (*i.e.*, \*2/\*2), and donors H0152 and H0503 were homozygous for the wild-type allele (\*1/\*1). Microsomes from Donors H0257 and H0502 showed extremely low rates of S-mephenytoin 4'-hydroxylation, confirming their phenotypic status as CYP2C19 PMs. Microsomes from Donors H0152 and H0503 showed high rates of S-mephenytoin 4'-hydroxylation, confirming their phenotypic status as CYP2C19 EMs. Human liver microsomes from EMs and PMs were pooled to determine the intermediate rate of metabolite formation.

Each of the three substrates was studied at 0.5 and 5.0  $\mu\text{M}$ . Human liver microsomes contain both CYP3A4 and CYP2C19 activities. The contribution of CYP3A4 to the 5-hydroxylation metabolite formation was estimated from the rate of microsomal sulfoxidation (which is only catalyzed by CYP3A4) and the ratio of 5-hydroxylation to sulfoxidation by recombinant CYP3A4. The contribution of CYP3A4 to the 5-hydroxylation reactions catalyzed by human liver microsomes was estimated by assuming that the ratio of 5-hydroxylation to sulfoxidation resulted from recombinant CYP3A4 is the same as that resulted from microsomal CYP3A4.

Table 7. Initial rate of metabolite formation from racemic lansoprazole, dexlansoprazole and (S)-lansoprazole by pooled (n=50) and individual human liver microsomes from donors genotyped as poor or extensive metabolizers of CYP2C19.

Sample	[Substrate]	5-Hydroxylansoprazole (pmol/mg protein/min)		Lansoprazole sulfone (pmol/mg protein/min)	
		Racemic Lansoprazole	Dexlansoprazole	Racemic Lansoprazole	Dexlansoprazole
EM1	0.5	39.0	20.7*	6.66	0
EM2		27.2	15.1*	15.4	1.84*
Pool		8.33	4.15*	9.68	1.37*
PM1		1.15	0.795*	4.82	0.838*
PM2		0.632*	0.510*	3.28	0.539*
EM1	5	73.8	85.6	29.6	5.32
EM2		70.1	70.7	118	27.6
Pool		31.9	26.4	88.3	17.2
PM1		11.4	8.48	41.1	10.1
PM2		7.34	5.66	25.9	6.20
					21.5

Initial rates are for 5 min incubations unless otherwise indicated

\*: Incubation time of 15 min

†: Incubation time of 30 min

"Pool": H0610, Pool of n=50, 0.7 mg/incubation

"EM": Extensive metabolizer, 0.35 mg/incubation

"PM": Poor metabolizer, 1.75 mg/incubation

EM1: H0152

EM2: H0503

PM1: H0257

PM2: H0502

Values are rounded to three significant figures.

Data are shown graphically in Figures 13-15.

Table 8. Estimate of the contribution of CYP3A4 to the 5-hydroxylation of 0.5  $\mu$ M racemic lansoprazole, dexlansoprazole and (S)-lansoprazole based on studies with recombinant CYP3A4 and CYP2C19

Substrate	[Substrate] ( $\mu$ M)	Sample	Rate of sulfoxidation (pmol/mg/min)	Ratio of sulfone to hydroxy by CYP3A4 ( $V_{max}/K_m$ ) $\S$	Estimated rate of 5-hydroxylation formation by microsomal CYP3A4 (pmol/mg/min)	Actual rate of 5-hydroxylation by microsomes (pmol/mg/min)	Estimated percent contribution of CYP3A4 to 5-hydroxylation
Racemic Lansoprazole	0.5	EM1	6.66	8.10	0.822	39.0	2.1%
		EM2	15.4		1.90	27.2	7.0%
		Pool	9.68		1.20	8.33	14.4%
		PM1	4.82		0.595	1.15	51.7%
		PM2	3.28		0.405	0.632	64.1%
		EM1	ND		ND	20.7	0%
Dexlansoprazole	0.5	EM2	1.84	1.81	1.02	15.1	6.8%
		Pool	1.37		0.757	4.15	18.2%
		PM1	0.838		0.463	0.795	58.2%
		PM2	0.539		0.298	0.510	58.4%
		EM1	0.964		0.0554	42.8	0.1%
		EM2	9.49		0.545	27.9	2.0%
(S)-Lansoprazole	0.5	Pool	6.02	17.4	0.346	9.44	3.7%
		PM1	3.68		0.211	1.18	17.9%
		PM2	2.32		0.133	0.597	22.3%

$\S$ : The ratio was based on a comparison of  $V_{max}/K_m$  values for the 5-hydroxylation and sulfoxidation by reactions catalyzed by recombinant CYP3A4. See Table 2.

"Pool": H0610, Pool of n=50, 0.7 mg/incubation

"EM": Extensive metabolizer, 0.35 mg/incubation

"PM": Poor metabolizer, 1.75 mg/incubation

EM1: H0152 EM2: H0503

PM1: H0257 PM2: H0502

Values are rounded to three significant figures.

Percent contribution values are rounded to one decimal place.

The contribution of CYP3A4 to the 5-hydroxylation of all three substrates was inversely related to CYP2C19. CYP3A4 contributed substantially to 5-hydroxylation in CYP2C19 PMs, but not in CYP2C19 EMs. The ratio of sulfoxidation to 5-hydroxylation, based on *in vitro* intrinsic clearance, was 8.1 for lansoprazole, 1.81 for dexlansoprazole, and 17.4 for (S)-lansoprazole. CYP3A4 contributed to a greater extent to the metabolisms of all three compounds in CYP2C19 PMs than in CYP2C19 EMs

Table 9. Correlation between CYP2C19 and CYP3A4 and the rate of 5-hydroxylation and sulfoxidation of racemic lansoprazole, dexlansoprazole and (S)-lansoprazole by human liver microsomes

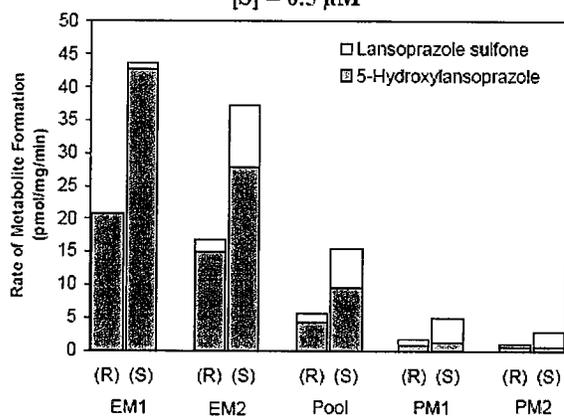
Substrate	[Substrate] ( $\mu\text{M}$ )	Correlation coefficient (r)			
		5-hydroxylation		Sulfoxidation	
		CYP2C19	CYP3A4	CYP2C19	CYP3A4
Racemic lansoprazole	0.5	0.977	-0.0255	0.316	0.984
	5	0.992	0.195	0.241	0.988
Dexlansoprazole	0.5	0.985	0.00274	0.899	1.000
	5	0.989	0.0657	0.162	0.994
(S)-Lansoprazole	0.5	0.964	-0.0825	0.892	0.999
	5	0.995	0.174	0.230	0.991

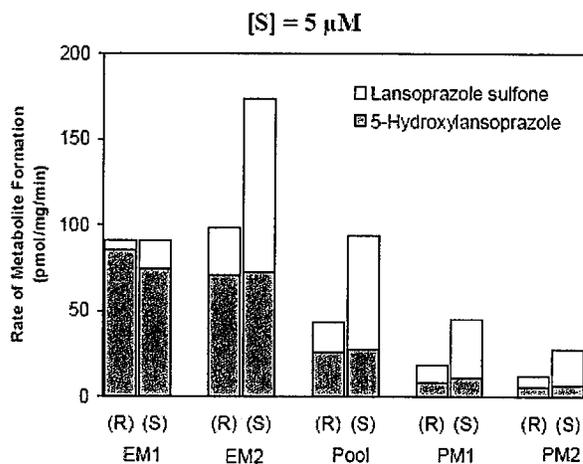
Marker activity for CYP2C19 = 5-Mephenytoin 4'-hydroxylation

Marker activity for CYP3A4 = Testosterone 6 $\beta$ -hydroxylation

For each substrate, formation of 5-hydroxylansoprazole correlated with CYP2C19 activity, whereas formation of lansoprazole sulfone correlated with CYP3A4 activity. S-lansoprazole was metabolized at about the same rate as racemic lansoprazole in the EM and PM liver microsomal samples, whereas dexlansoprazole was metabolized at a slower rate. Regardless of donor's CYP 2C19 genotypes, human liver microsomes preferentially converted all three substrates to 5-hydroxylansoprazole over lansoprazole sulfone.

Fig 2. Initial rate of metabolite formation from dexlansoprazole and (S)-lansoprazole (0.5 and 5  $\mu\text{M}$ ) by pooled (n=50) and individual human liver microsomes from donors genotyped as poor or extensive metabolizers of CYP2C19  
[S] = 0.5  $\mu\text{M}$





“Pool”: Pool of n=50 individual human liver microsomes, 0.7 mg/ incubation

“EM”: Extensive metabolizers, 0.35 mg/incubation

“PM”: Poor metabolizers, 1.75 mg/incubation

EM1 and EM2 = H0152 and H0503

PM1 and PM2 = H0257 and H0502

In general, (S)-lansoprazole was metabolized faster than dexlansoprazole by liver microsomes from both CYP2C19 EMs and PMs. The relatively slow metabolism of dexlansoprazole by human liver microsomes could be ascribed to a slightly slower metabolism by CYP2C19 and a markedly slower metabolism by CYP3A4. These *in vitro* results suggest that the *in vivo* clearance of dexlansoprazole would be lower, and hence its exposure (AUC and C<sub>max</sub>) would be higher than those of (S)-lansoprazole and racemic lansoprazole. Based on these results, the sponsor decided to develop dexlansoprazole into a new medication for treating EE and GERD.

### 2.2.5 Inhibition of CYP 2C19 enzyme activity by R-enantiomer and S-enantiomer ?

The CYP2C19 enzyme activity was determined using S-mephenytoin 4'-hydroxylation. Both R- and S-isomers had no inhibitory effect on the other CYP enzyme specific metabolic activities at concentrations up to 10  $\mu$ M. TAK-390 (R-isomer) and T-168391 (S-isomer) inhibited CYP2C19 by 45.5% and 94.5%, respectively.

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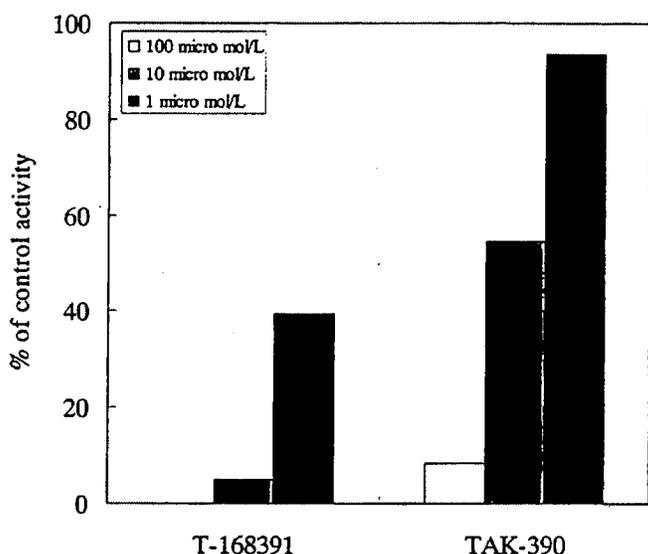


Figure 3. Mean inhibitory effect of TAK-390 and T-168391 on CYP2C19 specific activities (n=2)

Reviewer's comments: The C<sub>max</sub> in CYP2C19 poor metabolizers at 30 mg, 60 mg, 90 mg, and 120 mg dexlansoprazole MR QD were 1.4 µg, 3.1µg, 4.5 µg, and 4.5 µg, respectively (see 2C19 genotype results). The K<sub>m</sub> of 2C19-mediated metabolism of dexlansoprazole to 5-hydroxy lansoprazole is 4.1 µM, suggesting that dexlansoprazole does not have high CYP 2C19 binding affinity. The molecular weight of dexlansoprazole is 369.36. Based on the results in Figure 3, it is expected the inhibitory effect of dexlansoprazole is weak even at the highest dose, 120 mg MR QD.

### 2.2.6 Are R-enantiomer, S-enantiomer, and racemic lansoprazole inducers of cytochrome P450 expression in cultured human hepatocytes?

Human livers were perfused to harvest hepatocytes for in-vitro culture. This study compared lansoprazole with dexlansoprazole and with S-lansoprazole as the inducers of microsomal cytochrome P450 (CYP) enzyme activities in primary cultures of human hepatocytes. Cultured human hepatocytes were treated once daily for three consecutive days with dexlansoprazole, S-lansoprazole or lansoprazole. Cultures treated with dimethylsulfoxide (0.1% DMSO, v/v) served as negative controls, whereas those treated with omeprazole (100 µM), phenobarbital (750 µM), or rifampin (10 µM) served as positive controls. After the treatment period, microsomes were isolated and analyzed for the activities known to be specific for CYP1A2, 2B6, 2C9, 2C19 and 3A4 with the following specific substrates.

Table 10. Individual specific substrates for CYP1A2, 2B6, 2C9, 2C19 and 3A4

Enzyme	Substrate	Measurement
CYP1A2	Phenacetin	Phenacetin O-dealkylation
CYP2B6	Bupropion	Bupropion hydroxylation
CYP2C9	Diclofenac	Diclofenac 4'-hydroxylation
CYP2C19 S	Mephenytoin	S-Mephenytoin 4'-hydroxylation
CYP3A4	Testosterone	Testosterone 6β-hydroxylation

On average, treatment with omeprazole caused a 34.3-fold increase in CYP1A2 activity; phenobarbital caused an 11.4-fold increase in CYP2B6 activity, and rifampin caused a 2.17-fold increase in CYP2C9 activity, a 5.27-fold increase in CYP2C19 activity and a 5.71-fold increase in CYP3A4 activity.

Table 11. CYP induction in human hepatocytes treated with 10 and 25  $\mu$ M dexlansoprazole, S-lansoprazole or lansoprazole as a percent of positive control

Test article	CYP1A2 (omeprazole)	CYP2B6 (phenobarbital)	CYP2C9 (rifampin)	CYP2C19 (rifampin)	CYP3A4 (rifampin)
Dexlansoprazole	12.4% & 31.8%	10.8% & 24.5%	29.2% & 62.5%	4.45% & 9.27%	28.0% & 34.0%
S-Lansoprazole	9.50% & 23.2%	6.94% & 25.4%	17.9% & 41.9%	0.09% & 9.15%	32.4% & 46.0%
Lansoprazole	10.5% & 26.7%	9.31% & 20.9%	23.4% & 54.5%	4.41% & 12.3%	31.1% & 41.3%

- % inductions listed above are the results of 10  $\mu$ M followed by 25  $\mu$ M.

At 10  $\mu$ M, none of enantiomers or racemic mixture induced any of the CYP enzymes tested more than 35% of the positive control. At 25  $\mu$ M, the magnitudes of inducing CYP CYP1A2, 2B6, and 2C19 by these three compounds were less than 40% of the positive controls, while the inductions of CYP2C9 and CYP3A4 were 34.0 – 62.5% of the positive controls. At similar plasma levels, dexlansoprazole and S-lansoprazole administered as individual enantiomers would cause a similar degree of enzyme induction as racemic lansoprazole.

The typical observed maximum dexlansoprazole concentrations following oral administration of 30 mg to 90 mg modified-release formulation of dexlansoprazole are 1 to 6  $\mu$ M (that is < 2  $\mu$ M for 2C19 EMs and < 5  $\mu$ M for PMs), the sponsor's conclusion that the CYP induction effect of dexlansoprazole at the proposed doses may not be clinically relevant is acceptable.

### 2.2.7 What are the ADME characteristics of dexlansoprazole?

The sponsor conducted a mass balance study, in which after administration of dexlansoprazole MR 60 mg QD for 4 days the subjects were given on Day 5, after a 10-hr fasting, a single 60 mg oral dose of [14C]dexlansoprazole containing approximately 100  $\mu$ Ci. Six healthy male subjects (1 Black and 5 Whites) aged 18-55 years participated in the study. Subjects were genotyped for the genetic polymorphism of CYP 2C19. Five subjects were heterozygous CYP2C19 extensive metabolizers (\*2/wt) or homozygous CYP2C19 extensive metabolizers (wt/wt), and 1 subject was a homozygous CYP2C19 poor metabolizer (\*2/\*2).

Table 12. Pharmacokinetic parameter estimates for dexlansoprazole, 5-hydroxy dexlansoprazole, and dexlansoprazole sulfone following administration of a 60 mg [14C]dexlansoprazole on Day 5

	$t_{max}$ (h)	$C_{max}$ (ng/mL)	$AUC_{24}$ (ng.h/mL)	$t_{1/2}^c$ (h)

<b>Dexlansoprazole</b>				
Mean All Subjects	1.50	1176.17	6963.86	2.24 (1.64)
CV(%)	148	42	123	86
Mean <sup>a</sup> (101-105)	0.60	1001.4	3507.17	1.46 (1.43)
CV(%)	37	27	46	15
Subject 106 <sup>b</sup>	6.00	2050	24247.31	6.17
<b>5-Hydroxy Dexlansoprazole</b>				
Mean All Subjects	1.21	54.35	198.00	2.28 (1.84)
CV(%)	116	68	56	66
Mean <sup>a</sup> (101-105)	0.65	64.62	231.56	1.68 (1.63)
CV(%)	52	47	35	20
Subject 106 <sup>b</sup>	4.00	2.97	30.21	5.26
<b>Dexlansoprazole Sulfone</b>				
Mean All Subjects	1.50	57.03	918.60	7.88 (2.40)
CV(%)	150	200	239	134
Mean <sup>a</sup> (101-105)	0.60	10.43	23.68	7.79 (2.10)
CV(%)	86	49	76	152
Subject 106 <sup>b</sup>	6.00	290.00	5393.20	8.34

NA = not applicable.

- a Descriptive statistics of CYP2C19 extensive metabolizers (Subjects 101 to 105).
- b Individual values for Subject 106 CYP2C19 poor metabolizer.
- c Arithmetic mean (harmonic mean).
- d  $(AUC_{24} \text{ metabolite} / AUC_{24} \text{ dexlansoprazole}) \times 100\%$ .

There was an 8-fold difference in CL/F between extensive metabolizers (20.5 L/h) and the only poor metabolizer (Subject 106, 2.4 L/h). The mean Vz/F was 41.8 L for EMs and 21.4 L for Subject 106. Harmonic mean t<sub>1/2z</sub> was 1.43 hrs for EMs, and was 6.17 hrs (more than 4 fold higher) for Subject 106 (PM). The mean AUC<sub>24</sub> ratio of 5-hydroxy dexlansoprazole to dexlansoprazole was 8.8% for EMs and 0.1% for Subject 106, while for dexlansoprazole sulfone the corresponding ratio was 0.6% for EMs and 22.2% for Subject 106. This result suggested that metabolism by CYP3A was prominent for Subject 106 whose CYP2C19 activity was low.

Table 13. Percent of urinary radioactivity following administration of a 60 mg oral dose of [14C]dexlansoprazole on day 5 to 6 healthy male subjects

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Subject(s)	101	102	103	104	105	106	Mean (SD) <sup>a</sup>	Mean (SD) <sup>b</sup>
	Urine (0-24 h)							
Dexlansoprazole	ND	ND	ND	ND	ND	ND	NA	NA
2-S-N-Acetylcysteinyl Hydroxybenzimidazole	(b) (4)	(b) (4)					1.58 (1.26)	1.46 (1.17)
2-S-N-Acetylcysteinyl benzimidazole	(b) (4)	(b) (4)					1.85 (0.76)	4.70 (7.04)
5-Glucuronyloxy Dexlansoprazole	(b) (4)	(b) (4)					14.1 (1.2)	12.3 (4.7)
5-Glucuronyloxy Dexlansoprazole Sulfide	(b) (4)	(b) (4)					10.8 (0.7)	9.80 (2.63)
5-Sulfonyloxy Dexlansoprazole Sulfide	(b) (4)	(b) (4)					3.09 (1.13)	2.90 (1.16)
4-Sulfonyloxy Dexlansoprazole	(b) (4)	(b) (4)					0.44 (0.20)	0.50 (0.26)
Percent Radioactivity in Urine Identified	(b) (4)	(b) (4)					86.1 (5.2)	85.2 (5.1)
Percent of Dose Radioactivity In Urine	(b) (4)	(b) (4)					37.2 (4.5)	37.2 (4.0)
Percent Dose Radioactivity Identified	(b) (4)	(b) (4)					31.9 (2.5)	31.6 (2.4)

ND = not detected; NA = not applicable.

a Mean and SD for Subjects 101 through 105.

b Mean and SD for Subjects 101 through 106.

Dexlansoprazole was not detected as in the urine of both CYP2C19 EMs and CYP2C19 PM. Approximately 81% to 94% of radioactivity excreted into urine as metabolites was tentatively identified. Glucuronide conjugates of the hydroxylated dexlansoprazole metabolites were the major metabolites in EM subjects, constituting approximately 25% of urinary radioactivity. The decreased ability to form the 5-hydroxylated metabolites in subject 106 (PM) resulted in a shift to products of glutathione conjugation (N-acetylcysteinyl products) contributing approximately 20% of urinary radioactivity.

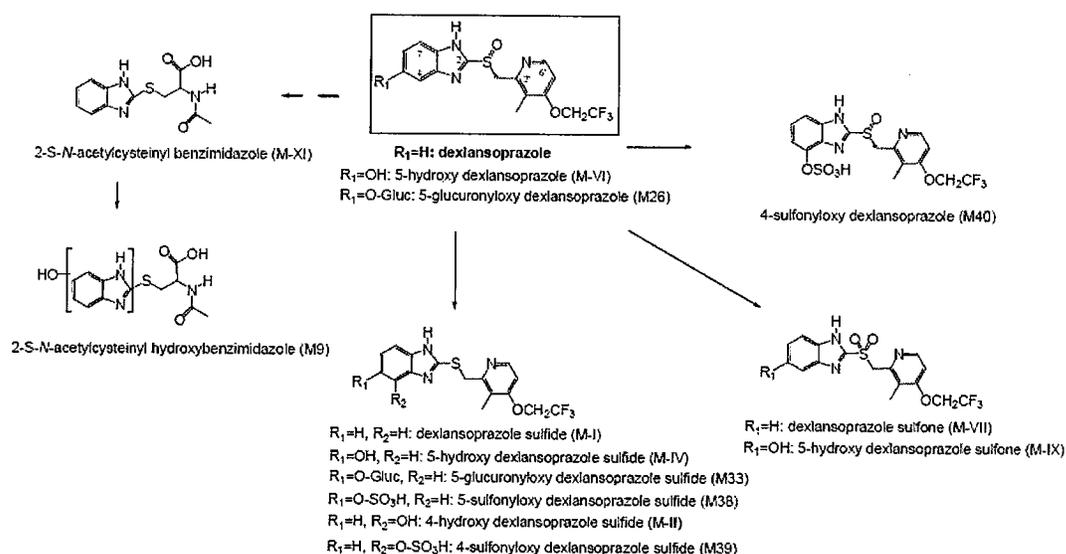
Table 14. Percent of fecal radioactivity following administration of a 60 mg oral dose of [14C]dexlansoprazole on day 5 to 6 healthy male subjects

Subject(s)	101 <sup>a</sup>	102 <sup>b</sup>	103 <sup>b</sup>	104 <sup>c</sup>	105 <sup>d</sup>	106 <sup>b</sup>	Mean(SD) <sup>e</sup>	Mean(SD) <sup>f</sup>
	Feces							
5-Hydroxy Dexlansoprazole Sulfide/Dexlansoprazole <sup>g</sup>	(b) (4)						24.2 (3.9)	22.9 (4.6)
5-Sulfonyloxy Dexlansoprazole Sulfide	(b) (4)						1.46 (2.93)	1.20 (2.68)
4-Sulfonyloxy Dexlansoprazole Sulfide	(b) (4)						0.75 (0.79)	0.60 (0.75)
5-Hydroxy Dexlansoprazole Sulfone	(b) (4)						0.76 (0.29)	0.90 (0.52)
4-Hydroxy Dexlansoprazole Sulfide	(b) (4)						0.43 (0.24)	0.60 (0.51)
Dexlansoprazole Sulfide	(b) (4)						5.66 (1.12)	5.60 (1.00)
Percent Radioactivity in Feces Identified	(b) (4)						71.3 (4.3)	71.9 (4.1)
Percent of Dose Radioactivity in Feces	(b) (4)						46.4 (5.5)	44.4 (7.0)
Percent of Dose Radioactivity Identified	(b) (4)						33.2 (5.5)	32.0 (5.8)

- a 0 to 48 hours.
- b 24 to 96 hours.
- c 24 to 72 hours.
- d 12 to 96 hours.
- e Mean and SD for Subjects 101 through 105.
- f Mean and SD for Subjects 101 through 106.
- g Coeluted with dexlansoprazole. MRM analyses of fecal samples from Subjects 101 and 103 showed that 5-hydroxy dexlansoprazole sulfide was the major coeluting component.

According to the sponsor, the major radioactive peak present in fecal homogenate profiles accounted for approximately 17% to 28% of dose radioactivity. Tandem mass spectrometry (MS/MS) analysis of this peak from Subjects 101 and 103 revealed the presence of dexlansoprazole and 5-hydroxy dexlansoprazole sulfide, indicating that 5-hydroxy dexlansoprazole sulfide was the predominant component. Based on these results, the metabolic pathway of dexlansoprazole is proposed below.

### Scheme 1 Proposed metabolic pathway of dexlansoprazole



**Conclusion:** Ninety eight (98%) of the dosed radioactivity was recovered in the excreta after 7 days and with nearly equal distribution between urine and feces. Dexlansoprazole was the major component in the plasma, accounting for over 70% of the plasma radioactivity. Dexlansoprazole was metabolized by oxidation, reduction, and conjugation to at least 19 metabolites. Ten metabolites were detected in plasma, with 5-glucuronyloxy dexlansoprazole and 5-hydroxy dexlansoprazole being the major metabolites. The radioactivity excreted in urine and feces consisted of up to 16 and 7 metabolites, respectively, with 5-glucuronyloxy dexlansoprazole and 5-glucuronyloxy dexlansoprazole sulfide being the major urinary metabolites, and 5-hydroxy dexlansoprazole sulfide and dexlansoprazole sulfide being the major fecal metabolites.

## 2.2.8 Exposure-response

### 2.2.8.1 What are the dose/efficacy and dose/safety relationships?

Treatment of endoscopically proven erosive esophagitis (EE): Study T-EE04-084 consisted of three treatment groups (N=680 for 60 mg dexlansoprazole MR QD, N=668 for 90mg dexlansoprazole MR QD, and N=690 for 30 lansoprazole mg QD). The 8-week treatment for healing of erosive esophagitis (EE) revealed that 60 mg QD and 90 mg QD were statistically significantly superior to the 30 mg QD regimen for healing of severe grades of EE (Grades C and D). The therapeutic gains over the 30 mg QD regimen were 14% and (b) (4) for 60 mg QD and 90 mg QD, respectively. The treatment-related serious adverse events were 4 and 2 in the dexlansoprazole MR 60 mg QD MR group and 90 mg QD MR group, respectively, and 5 in the lansoprazole 30 mg QD group.

Table 15. Comparison of EE healing rates

Week 8 Healing Rate/ Analysis	Dexlansoprazole MR		Lansoprazole 30 mg QD %	p-value		
	60 mg QD % (95% CI)	90 mg QD % (95% CI)		Dex MR 60 mg vs Lanso	Dex MR 90 mg vs Lanso	Dex MR 60 mg vs Dex MR 90 mg
Crude (Primary) <sup>a</sup>	(N=639)	(b) (4)	(N=656)	0.004 <sup>#</sup>	(b) (4)	(b) (4)
	85.3 (82.3, 87.9)	(b) (4)	79.0 (75.6, 82.0)			

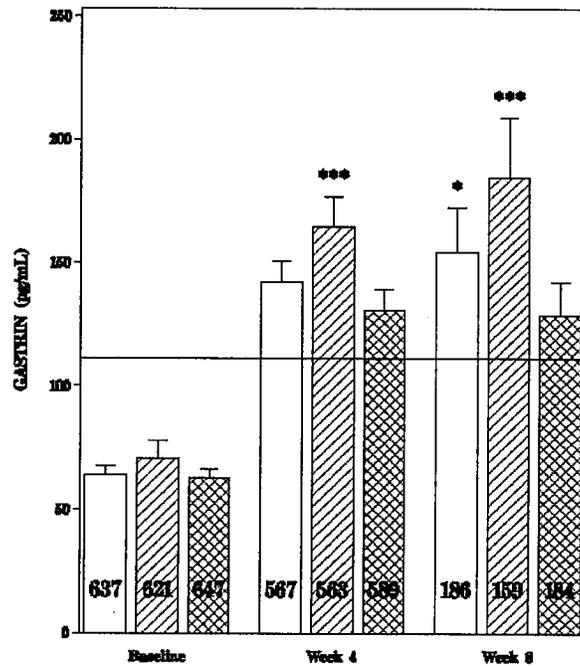
Based on the EE healing rates, there was no difference between the 90mg and 60 mg QD dexlansoprazole MR. Both dexlansoprazole MR doses showed therapeutic superiority than the 30 mg lansoprazole.

Table 16. Comparison of severe EE (Grades C and D) healing rates

Week 8 for C/D Healing Rate/ Analysis	Dexlansoprazole MR		Lansoprazole 30 mg QD %	p-value		
	60 mg QD % (95% CI)	90 mg QD % (95% CI)		Dex MR 60 mg vs Lanso	Dex MR 90 mg vs Lanso	Dex MR 60 mg vs Dex MR 90 mg
Crude (Primary) <sup>a</sup>	(N=182)	(b) (4)	(N=200)	0.002 <sup>#</sup>	(b) (4)	(b) (4)
	79.7 (73.1, 85.3)	(b) (4)	65.0 (58.0, 71.6)			

For severe grades of EE (Grades C and D), the healing rate was higher in the 60 mg QD dexlansoprazole treatment group than the other two treatment groups, though the statistical difference was only observed between the 60 mg QD MR and 30 mg lansoprazole treatment groups.

Fig 4. Mean Value of Gastrin at Each Visit



□: TAK MR 60 mg QD    ▨: TAK MR 90 mg QD    ▩: TAK MR 30 mg QD

Note: Error bars are  $\pm 2$  standard errors of the mean. The reference line provided is for the upper limit of normal from the central lab. The numbers reflected in the bars are the N's for each treatment group at the noted timepoints.

\*, \*\*, \*\*\* indicates statistical significance in the change from baseline compared to lansoprazole at the 0.05, 0.01, 0.001 level, respectively.

Gastrin is a hormone secreted by G cells (located in gastric pits), and it regulates gastric acid secretion as well as promotes gastric mucosal growth. Compared to lansoprazole 30 mg QD, the differences in mean changes in serum gastrin values from baseline were statistically significant at Weeks 4 and 8 for dexlansoprazole MR 90 mg QD and at Week 8 for dexlansoprazole MR 60 mg QD.

Table 17 Treatment-Emergent Serious Adverse Events

Subject No./ Gender/Age <sup>a</sup>	MedDRA High Level Term/ MedDRA Preferred Term	Day of Onset <sup>b</sup>	Duration <sup>c</sup>	Relationship to Study Drug	Alternative Etiology
<b>Dexlansoprazole MR 60 mg QD</b>					
12800003/F/59 <sup>d</sup>	Pain and Discomfort NEC/ <i>Non-cardiac Chest Pain</i>	20 (1)	3 days	Not related	Non-cardiac stress related pain
32118017/M/51 <sup>d</sup>	Transient Cerebrovascular Events/ <i>Transient Ischaemic Attack</i>	1 (0)	3 days	Not related	Underlying hypertension <sup>e</sup>
32957001/M/49 <sup>d</sup>	Coronary Artery Disorders NEC/ <i>Coronary Artery Disease</i>	66 (0)	10 days	Not related	Atherosclerosis CAD
32999003/M/74	Gastrointestinal Atonic and Hypomotility Disorders NEC/ <i>Gastroesophageal Reflux Disease</i>	46 (20)	2 days	Not related	Gastroesophageal reflux disease
<b>Dexlansoprazole MR 90 mg QD</b>					
8515013/F/33	Gastrointestinal Inflammatory Disorders NEC/ <i>Crohn's Disease</i>	12	4 days	Not related	Candida or Crohn's disease
9755050/M/85	Haemorrhoids and Gastrointestinal Varices (Excl Oesophageal)/ <i>Haemorrhoids<sup>f</sup></i>	3	4 days	Not related	Straining to have a bowel movement <sup>e</sup>

Note: Adverse events were coded using MedDRA version 10.0.

Excl = excluding; CAD=coronary artery disease; PCP=primary care physician; MRI=magnetic resonance imaging; HTN=hypertension; hrs=hours; Ong=ongoing; NEC=not elsewhere classified; F=female; M=male.

a Age at time of enrollment.

b Days postdosing are shown in parentheses.

c Duration is in days unless otherwise noted. If the event was ongoing, the day at which it was ongoing is shown in parentheses.

d Subject prematurely discontinued.

e Information reflected in the suspect adverse reaction report included in Section 14.3.3.3.

f Included 2 events, 1 event each of MedDRA low level terms Internal Haemorrhoids and Prolapsed Haemorrhoid.

No cardiovascular events were reported as related to study drug.

Conclusion: This study showed that both dexlansoprazole 60 mg and 90 mg MR QD were superior to 30 mg lansoprazole QD in healing EE regardless of severity, and that both resulted in similar rates of treatment-related serious adverse events.

Dexlansoprazole 90mg MR QD showed no therapeutic superiority in healing EE than dexlansoprazole 60 mg MR QD.

Study T-EE04-085 consisted of three treatment groups (N=194 for 60 mg dexlansoprazole MR QD, N=182 for 90mg dexlansoprazole MR QD, and N=194 for 30 mg lansoprazole mg QD).

Table 18 Summary of EE healing rates after a 8-week treatment

Week 8 Healing Rate/ Analysis	Dexlansoprazole MR		Lansoprazole	p-value		
	60 mg QD % (95% CI) (N=657)	90 mg QD % (95% CI) (b) (4)	30 mg QD % (95% CI) (N=648)	Dex MR 60 mg vs Lanso	Dex MR 90 mg vs Lanso	Dex MR 60 mg vs Dex MR 90 mg
Crude (Primary) <sup>a</sup>	86.9 (84.1, 89.4)	(b) (4)	84.6 (81.6, 87.3)	0.234	(b) (4)	(b) (4)

As compared to the lansoprazole 30mg QD regimen, both dexlansoprazole MR 90 mg QD and 60 mg QD regimens demonstrated higher healing rates, with 90 mg QD showing a statistically significantly higher healing rate.

Table 19 Summary of severe EE healing rates after a 8-week treatment

Week 8 for C/D Healing Rate/ Analysis	Dexlansoprazole MR		Lansoprazole	p-value		
	60 mg QD (%) [95% CI] (N=194)	90 mg QD (%) [95% CI] (b) (4)	30 mg QD (%) [95% CI] (N=190)	Dex MR 60 mg vs Lanso	Dex MR 90 mg vs Lanso	Dex MR 60 mg vs Dex MR 90 mg
Crude (Primary) <sup>a</sup>	77.8 (71.3, 83.5)	(b) (4)	78.9 (72.5, 84.5)	0.768	(b) (4)	(b) (4)

For subjects with moderate to severe EE (Grades C and D), dexlansoprazole MR 90 mg QD showed a higher healing rate than dexlansoprazole MR 60 mg QD while dexlansoprazole MR 60 mg QD and lansoprazole 30 mg QD resulted in similar healing rates. All 3 treatments were effective in relieving heartburn. Treatments with dexlansoprazole MR 60 mg QD and 90 mg QD up to 8 weeks were generally well tolerated and demonstrated a comparable safety profile to that of lansoprazole 30mg QD in this study.

Ten subjects experienced 11 nonfatal serious adverse events (SAEs). Three SAEs were considered possibly related to study drug: pain and discomfort (dexlansoprazole MR 60

mg QD), ischaemic coronary artery disorders (dexlansoprazole MR 90 mg QD), and facial cranial nerve disorders (lansoprazole 30 mg QD).

Conclusion: This study showed slightly different outcomes than study T-EE04-084 in that this study showed no difference between dexlansoprazole 60mg MR QD and lansoprazole 30 mg QD in treating moderate to severe EE. Furthermore, there was no statistical difference in overall EE healing rates between dexlansoprazole 60 mg MR QD and lansoprazole MR90 mg QD regardless of severity.

Based on the results of Study T-EE04-085 and Study T-EE04-084, dexlansoprazole MR90 mg QD was not therapeutically superior to dexlansoprazole MR60 mg QD in healing EE regardless of disease severity. It is inconclusive for those with moderate to severe EE whether dexlansoprazole MR 90mg QD results a statistically significant better efficacy than dexlansoprazole MR 60mg QD. (b) (4) a subject in the 90 mg QD regimen group developed ischaemic coronary artery disorders and no better therapeutic effects were observed from the 90-mg regimen than the 60-mg regimen (b) (4)

Maintenance of Healing in Subjects with Healed Erosive Esophagitis: A total of 445 subjects involved in the study with 147 patients receiving placebo, 140 patients receiving dexlansoprazole 30 mg MR QD, and 158 patients receiving dexlansoprazole 60 mg MR QD. The treatment duration was 6 months long (Study T-EE05-135).

Table 20 Summary the results of Maintenance Healed Erosive Esophagitis

Analysis/ Visit	Placebo % (95% CI)	Dexlansoprazole MR		p-values		
		30 mg QD % (95% CI)	60 mg QD % (95% CI)	Placebo vs Dex MR 30 mg	Placebo vs Dex MR 60 mg	Dex MR 30 mg vs Dex MR 60 mg
<b>Primary Crude Rates<sup>a</sup> with Prematurely Discontinued Considered Relapsed: ITT Primary Subjects</b>						
Month 6	14.3 (8.5, 21.9)	66.4 (57.4, 74.6)	(b) (4) (b) (4)	≤0.00001	(b) (4)	(b) (4)

CI=confidence interval; Dex MR=dexlansoprazole modified release.

<sup>a</sup> p-values are based on pairwise comparisons of the maintenance rates using Fisher's exact test.

<sup>†</sup> Dexlansoprazole MR treatment group is statistically significantly different from placebo using Hochberg's method at 0.0025 level.

The mean number of days on treatment was similar between the dexlansoprazole MR 30 mg QD and 60 mg QD treatment groups (136.6 and (b) (4) days, respectively) and much lower in the placebo treatment group (57.6 days).

Twenty-four subjects experienced adverse events that led, at least in part, to premature discontinuation from the study (14 in the placebo group, 4 in the 30 mg QD group, and 6 in the 60 mg QD group). The majority of these events were assessed as possibly or definitely related to study drug. The rates of adverse events that led to premature discontinuation were considered by the investigator to be possibly or definitely related to study drug were 10/17, 2/4, and 1/9 events in the placebo, dexlansoprazole MR 30 mg QD, and dexlansoprazole MR 60 mg QD treatment groups, respectively. No cardiovascular events were reported.

Conclusion: Assessed by endoscopy, similar percentages of subjects who were on either dexlansoprazole 30 mg MR QD or 60 mg MR QD had healed EE maintained over the 6-week period.

Two identical maintenance of healed EE studies were conducted (N=237 for Study T-EE04-086 and N=214 for Study T-EE04-087) and the data from both studies were combined and analyzed.

Table 21 Rates for Maintenance of Healed Erosive Esophagitis: Crude Rate Analysis and Time-to-Event Analysis

Analysis/ Visit	Placebo	Dexlansoprazole MR		Placebo vs Dex MR 60 mg	p-value	
		60 mg QD	90 mg QD		Placebo vs Dex MR 90 mg	Dex MR 60 mg vs Dex MR 90 mg
<b>Primary Crude Rates with Prematurely Discontinued Considered Relapsed: ITT Primary Subjects</b>						
	(N=112) % (95% CI)	(N=152) % (95% CI)	(N=138) % (95% CI)			
Month 1 <sup>a, d, e</sup>	30.4 (22.0, 39.8)	95.4 (90.7, 98.1)	(b) (4)	<0.00001 <sup>f</sup>	(b) (4)	
Month 3 <sup>b, d, e</sup>	16.1 (9.8, 24.2)	77.6 (70.2, 84.0)	(b) (4)	<0.00001 <sup>f</sup>		
Month 6 <sup>c, d, e</sup>	14.3 (8.4, 22.2)	66.4 (58.3, 73.9)	(b) (4)	<0.00001 <sup>f</sup>		
<b>Supportive Life Table Rates: ITT Subjects</b>						
	(N=140) % (95% CI)	(N=159) % (95% CI)	(N=152) % (95% CI)			
Month 1 <sup>a, d, f</sup>	38.6 (30.1, 47.2)	95.5 (92.2, 98.8)	(b) (4) (b)	<0.00001 <sup>f</sup>		
Month 3 <sup>b, d, f</sup>	27.2 (18.6, 35.9)	89.9 (85.0, 94.7)	(b) (4)			
Month 6 <sup>c, d, f</sup>	25.7 (17.0, 34.4)	86.6 (81.0, 92.3)	(b) (4)			

CI=confidence interval; Dex MR=dexlansoprazole modified release.

a Endoscopy showing no recurrence at Day 21 or later.

b Endoscopy showing no recurrence at Day 75 or later.

c Endoscopy showing no recurrence between Day 165 and Day 195; recurrences after Study Day 195 are moved to Study Day 195 in order to be included as a recurrences for Month 6.

d Subjects who prematurely discontinued with last endoscopy showing no recurrence are considered as recurred according to the methods described in Sections 9.7.1.7.1.1 and 9.7.1.7.1.2.

e p-values are based on pairwise comparisons of the maintenance rates using Fisher's exact test.

f p-values are based on pairwise comparisons of the maintenance functions using the log-rank test.

† Dexlansoprazole MR treatment group is statistically significantly different from placebo using Hochberg's method at 0.0025 level.

Table 22 Treatment-Emergent Serious Adverse Events

Subject No./ Gender/Age <sup>a</sup>	MedDRA High Level Term/ <i>MedDRA Preferred Term</i>	Day of Onset	Cumulative Study Day <sup>b</sup>	Duration	Relationship to Study Drug	Alternative Etiology
<b>Dexlansoprazole MR 60 mg QD</b>						
18128010/F/45 <sup>c</sup>	Uterine Disorders NEC/ <i>Endometriosis</i>	77	112	1 hour	Not related	Endometriosis
13239048/F/62 <sup>d</sup>	Pain and Discomfort NEC/ <i>Non-cardiac Chest Pain</i>	48	87	3 days	Not related	Bronchospasm; obesity; esophagitis
<b>Dexlansoprazole MR 90 mg QD</b>						
9624010/F/66 <sup>a,c</sup>	Breast and Nipple Neoplasms Malignant/ <i>Breast Cancer</i>	1	30	Chronic Condition	Not related	Family history of breast cancer
9677008/M/54 <sup>d</sup>	Non-site Specific Injuries NEC/ <i>Arthropod Bite</i>	89	116	18 days	Not related	Spider bite
12823011/F/28 <sup>d</sup>	Musculoskeletal and Connective Tissue Signs and Symptoms NEC/ <i>Musculoskeletal Discomfort</i>	126	152	29 days	Not related	Weight of breast tissue
18128038/M/62 <sup>a,d,e</sup>	Coronary Artery Disorders NEC/ <i>Coronary Artery Disease</i>	6 (1)	39	3 days	Not related	Past history of coronary artery disease
9172053/F/54 <sup>a,c</sup>	Acute and Chronic Pancreatitis/ <i>Pancreatitis</i>	149	180	6 days	Not related	Gallstones

Note: Adverse events were coded using MedDRA version 9.1. Days postdosing are in parentheses.

a Age at time of enrollment in the maintenance study.

b Cumulative study days since first dose in Study T-EE04-084 or T-EE04-085.

c SAE Category: Inpatient Hospitalization.

d SAE Category: Required Intervention.

e Subject prematurely discontinued.

No cardiovascular events were reported to be Study drug related.

Conclusion: The 90mg QD dose did not demonstrate treatment superiority over the 60mg QD dose.

Treatment of nonerosive gastroesophageal reflux disease: Though the sponsor conducted studies evaluating the efficacy of the 60mg QD and 90 mg QD regimens for treating GERD, those studies are not reviewed since the sponsor only claims the 30mg QD dose for this indication. A total of 947 subjects participated in the study. The results showed that 30mg dexlansoprazole MR QD and 60mg dexlansoprazole MR QD demonstrated similar clinical efficacy according to the percentage of days in the 4-week treatment period with neither daytime nor nighttime heartburn.

Table 23 Summary of the results of treating GERD.

Measurement	Placebo (N=310)	Dexlansoprazole MR	
		30 mg QD (N=312)	60 mg QD (N=307)
<b>Percentage of Days With Neither Daytime nor Nighttime Heartburn</b>			
Median	18.5	54.9	(b) (4)
Mean (SD)	25.0 (25.6)	50.3 (33.9)	
p-value Dexlansoprazole MR vs Placebo		<0.00001 <sup>†</sup>	
p-value Dexlansoprazole MR 30 mg vs 60 mg			

Note: p-values are based on pairwise comparisons using the Wilcoxon rank-sum test.

SD = standard deviation.

<sup>†</sup> Statistically significant difference versus placebo when using Hochberg's method of multiple comparisons to maintain a significance level of 0.0025.

In terms of the percentage of days in the 4-week treatment period with no nighttime heartburn, there was no statistically significant difference between 30mg dexlansoprazole MR QD and 60mg dexlansoprazole MR QD.

Table 24 Summary of the efficacy on treating nighttime heartburn.

Measurement	Placebo (N=308)	Dexlansoprazole MR	
		30 mg QD (N=311)	60 mg QD (N=307)
<b>Percentage of Days Without Nighttime Heartburn</b>			
Median	51.7	80.8	(b) (4)
Mean (SD)	47.1 (32.6)	67.6 (34.1)	
p-value Dexlansoprazole MR vs Placebo		<0.00001 <sup>†</sup>	
p-value Dexlansoprazole MR 30 mg vs 60 mg			

Note: p-values are based on pairwise comparisons using the Wilcoxon rank-sum test.  
SD = standard deviation.  
<sup>†</sup> Statistically significant difference versus placebo when using Hochberg's method of multiple comparisons to maintain a significance level of 0.0025.

During the Treatment Period, 4 subjects (1: placebo, 2: dexlansoprazole MR 30 mg, 1: dexlansoprazole MR 60 mg) experienced 8 SAEs. These SAEs included Coronary Artery Occlusion, Myocardial Infarction, Cardiogenic Shock, Sepsis, Cerebrovascular Accident, Abdominal Pain Lower, and Haematochezia. The sponsor stated that "All events were single events experienced by 1 subject, with the exception Myocardial Infarction. Myocardial Infarction occurred in 2 subjects in the dexlansoprazole MR 30-mg treatment group 2 to 4 days after the last dose of study drug; 1 of these 2 subjects also experienced a Cerebrovascular Accident 7 days after the last dose of study drug. The SAEs showed no pattern in the type of event, and all were assessed by the investigator as not related to study drug." Though the sponsor claimed that the SAEs are not related to Study drug, myocardial infarction happened after the treatment stops. Since MI occurred shortly after the treatment stopped, it could not be ruled out that the incidence was treatment related.

Conclusion: Dexlansoprazole MR 30 mg QD and 60 mg QD were equally effective in relieving both daytime and nighttime heartburn combined and in relieving nighttime heartburn in subjects with symptomatic GERD. The occurrence of myocardial infarction at the 30 mg QD regimen is concerning. However, it is puzzling that no cardiovascular events were observed for the higher dose of 60 mg. It is unknown whether the 2 patients' past medical histories might have contributed to the MI occurrence.

Table 25 Recommendations based on the clinical efficacy studies discussed above:

Indication	Recommended dose	Frequency
Healing of EE	60 mg	Once daily for up to 8 weeks
Maintenance of Healed EE	30 mg	Once daily
Symptomatic GERD	30 mg	Once daily for 4 weeks

Long-term safety study: A total of 313 subjects participated in the study (153 received 60mg QD and 160 received 90 mg QD) for 12 months. The percentages of subjects with ≥1 treatment-related adverse event were 25% and 23% in the dexlansoprazole MR 60 mg QD and dexlansoprazole MR 90 mg QD groups, respectively. According to this study, treatment with dexlansoprazole MR at doses of 60 mg QD and 90 mg QD for up

to 12 months was generally well tolerated. However, the severe AEs observed in Study T-EE04-085 warrant continuing monitoring the long-term safety of dexlansoprazole MR.

### 2.2.8.2 What is the exposure/pharmacodynamic relationship?

Study T-P104-071 is a multiple-dose, 4-period crossover pharmacokinetic and pharmacodynamic study of three doses of dexlansoprazole MR, compared to those of 30 mg lansoprazole, each administered orally once a day for 5 days. Twenty eight males and 12 females, aged 18 to 55 years, participated in the study. The Day 1 and Day 5 dose normalized AUC<sub>0-∞</sub> and AUC<sub>0-24</sub> (ng h/mL) of 60mg, 90mg, and 120mg dexlansoprazole MR and 30 mg lansoprazole were 109, 112, 104, 110, 97, 113, 73, and 65, respectively. The lansoprazole immediate release capsules had lower AUC/dose than dexlansoprazole MR.

Table 26 Dose proportionality for DEXLANSOPRAZOLE MR regimens performed via 90% confidence intervals for the natural logarithm of dose-normalized C<sub>max</sub> and AUCs

Day	Parameter	Point Estimate	90% Confidence Interval
Day 1	Regimen B versus Regimen A		
	C <sub>max</sub> /Dose	0.8980	(0.7650-1.0542)
	AUC <sub>T</sub> /Dose	0.9323	(0.8483-1.0245)
	AUC <sub>24</sub> /Dose	0.9638	(0.8771-1.0591)
	Regimen C versus Regimen A		
	C <sub>max</sub> /Dose	1.0093	(0.8544-1.1924)
	AUC <sub>T</sub> /Dose	1.0480	(0.9501-1.1561)
	AUC <sub>24</sub> /Dose	1.0354	(0.9395-1.1410)
	Regimen C versus Regimen B		
C <sub>max</sub> /Dose	1.1240	(0.9539-1.3243)	
AUC <sub>T</sub> /Dose	1.1241	(1.0207-1.2381)	
AUC <sub>24</sub> /Dose	1.0742	(0.9749-1.1836)	
Day 5	Regimen B versus Regimen A		
	C <sub>max</sub> /Dose	1.0664	(0.9650-1.1785)
	AUC <sub>T</sub> /Dose	1.0463	(0.9769-1.1207)
	AUC <sub>24</sub> /Dose	1.0255	(0.9536-1.1028)
	Regimen C versus Regimen A		
	C <sub>max</sub> /Dose	0.9125	(0.8212-1.0141)
	AUC <sub>T</sub> /Dose	1.0473	(0.9741-1.1260)
	AUC <sub>24</sub> /Dose	1.0401	(0.9634-1.1229)
	Regimen C versus Regimen B		
C <sub>max</sub> /Dose	0.8557	(0.7707-0.9501)	
AUC <sub>T</sub> /Dose	1.0010	(0.9315-1.0756)	
AUC <sub>24</sub> /Dose	1.0142	(0.9422-1.0918)	

Note: Regimen A = 60 mg of TAK-390MR, Regimen B = 90 mg of TAK-390MR, and Regimen C = 120 mg of TAK-390MR.

The 90% confidence intervals for the point estimates of AUC or C<sub>max</sub> ratio between any pair of Regimens A, B, and C show the dose-proportionality of dexlansoprazole MR QD between 60 mg and 120 mg. The 90% CI of regimen B versus regimen A on Day 1 was slightly outside the 85%-125% acceptance range, so was that of regimen C versus regimen B on Day 5.

The pH monitoring unit (probe and recorder) was calibrated before and after each use using 2 standard pH buffers (pH 1.0 and pH 7.0). Intra-gastric pH was automatically sampled and recorded every 4 seconds over an interval of 24 hours. The median of these values over 15-minute intervals was calculated and used in all data analyses. The

intra-gastric pH was calculated over the following intervals of time relative to dosing: 0 to 4 hours, >4 to 9 hours, >9 to 12 hours, >12 to 16 hours, and >16 to 24 hours.

Table 27 Analysis of mean intra-gastric pH results

Day Interval	Mean <sup>a</sup> Intra-gastric pH for Each Dosing Regimen				Differences <sup>b</sup> (Significance) Between Dosing Regimens		
	A	B	C	D	A versus D	B versus D	C versus D
<b>Day 1</b>							
Total 24 hours	4.27	4.25	4.47	4.12	0.15	0.13	0.35*
0-4 hours	3.44	3.85	4.42	3.88	-0.44	-0.02	0.55
>4-9 hours	4.34	4.34	4.64	4.34	0.00	-0.00	0.30
>9-12 hours	4.99	5.06	4.99	4.69	0.30*	0.38**	0.31*
>12-16 hours	4.94	4.86	4.98	4.19	0.75***	0.67***	0.80***
>16-24 hours	4.98	4.71	5.32	4.45	0.53	0.26	0.87*
<b>Day 5</b>							
Total 24 hours	4.55	4.51	4.57	4.13	0.43***	0.39**	0.44***
0-4 hours	4.71	4.86	4.93	4.78	-0.07	0.08	0.15
>4-9 hours	4.88	4.79	4.87	4.31	0.57***	0.49***	0.57***
>9-12 hours	5.26	5.04	5.24	4.60	0.66***	0.44**	0.63***
>12-16 hours	4.37	4.48	4.66	3.57	0.79***	0.90***	1.09***
>16-24 hours	4.79	4.06	4.79	3.85	0.94	0.22	0.94

Note: Regimen A = 60 mg of TAK-390MR, Regimen B = 90 mg of TAK-390MR, Regimen C = 120 mg of TAK-390MR, and Regimen D = 30 mg of lansoprazole

a The estimates of the mean are least squares means, which took into account the possibility of period effects.

b The differences presented are the differences in least squares means.

\*, \*\*, \*\*\* Indicate statistical significance at the p = 0.05, 0.01, or 0.001 level, respectively.

On Day 5, regimens A, B, and C resulted in significantly higher pH than regimen D over the >4 to 9-hr, >9 to 12-hr, >12 to 16-hr, and total 24-hr intervals. The possible contributing factors were that 1) regimens A, B and C had two-fold, three-fold, and four-fold higher dose, respectively, than regimen D, and 2) that the former three regimens contained only the slower eliminated R-isomer while regimen D contained an equal amount of fast eliminated S-isomer and slower eliminated R-isomer. In terms of dexlansoprazole MR, intra-gastric pH values were similar among regimens A, B and C for both Days 1 and 5. No pharmacodynamic advantage was observed at doses higher than 60 mg of dexlansoprazole MR.

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Table 28 Analysis of Percent of Time Intra-gastric pH Exceeded 4

Day Interval	Mean <sup>a</sup> Percent of Time Intra-gastric pH Exceeded 4 for Each Dosing Regimen				Differences <sup>b</sup> (Significance) between Dosing Regimens		
	A	B	C	D	A versus D	B versus D	C versus D
<b>Day 1</b>							
Total 24 Hours	61.07	60.25	70.41	58.64	2.43	1.61	11.77**
0 to 4 Hours	36.01	51.86	58.68	48.32	-12.32	3.54	10.36
>4 to 9 Hours	66.62	70.00	81.08	65.00	1.62	5.00	16.08
>9 to 12 Hours	96.21	96.01	96.12	86.67	9.54**	9.34**	9.44**
>12 to 16 Hours	85.92	85.04	86.08	57.61	28.31***	27.43***	28.47***
>16 to 24 Hours	75.17	65.49	81.03	56.38	18.79	9.11	24.65*
<b>Day 5</b>							
Total 24 Hours	70.99	69.81	70.71	60.15	10.85**	9.67*	10.56**
0 to 4 Hours	76.19	80.56	79.71	81.18	-4.98	-0.61	-1.46
>4 to 9 Hours	84.74	82.29	85.53	66.23	18.52***	16.07**	19.30***
>9 to 12 Hours	95.85	90.86	97.21	77.01	18.84***	13.85***	20.20***
>12 to 16 Hours	71.09	69.51	76.99	43.07	28.02***	26.44***	33.91***
>16 to 24 Hours	71.24	54.51	67.27	42.34	28.89	12.17	24.92

Note: Regimen A = 60 mg of TAK-390MR, Regimen B = 90 mg of TAK-390MR, Regimen C = 120 mg of TAK-390MR, and Regimen D = 30 mg of lansoprazole

a The estimates of the mean are least squares means, which took into account the possibility of period effects.

b The differences presented are the differences in least squares means.

\*, \*\*, \*\*\* Indicate statistical significance at the p = 0.05, 0.01, or 0.001 level, respectively.

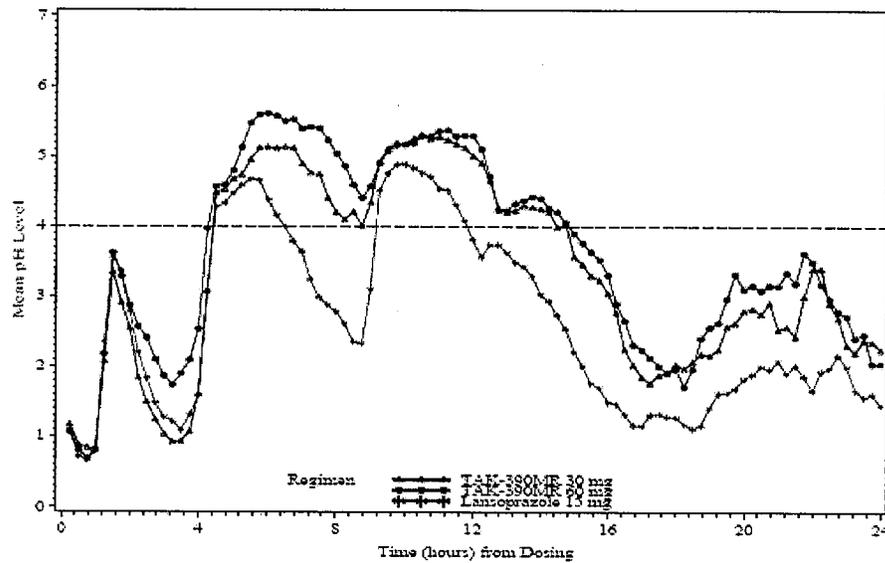
On day 1, the 120 mg regimen resulted in a slightly higher percent of time intra-gastric pH exceeded 4 than the 60 mg or 90 mg regimen. Although the AUC and C<sub>max</sub> increased dose proportionally between 60mg and 120 mg for Days 1 and 5 (as summarized in section 2.2.2- pharmacokinetic parameters of dexlansoprazole), the mean percent of time intra-gastric pH exceeded 4 following repeated dose for 5 days were similar between 60 and 120 mg dosage levels.

**Summary:** There is no clear exposure/response relationship. On Day 5, the results for mean intra-gastric pH and for mean percent of time intra-gastric pH exceeded 4 were similar across the dose regimens tested. Doses higher than 60 mg did not result in better pharmacodynamic outcomes.

**Study T-P105-122** (38 males and 7 females, aged 22-55) determines the pharmacokinetics and pharmacodynamics of dexlansoprazole and lansoprazole following oral administration of 30 mg or 60 mg dexlansoprazole MR or 15 mg lansoprazole for 5 days. The AUC and C<sub>max</sub> data are summarized in section 2.2.2- pharmacokinetic parameters of dexlansoprazole and showed dose proportionality for both days 1 and 5.

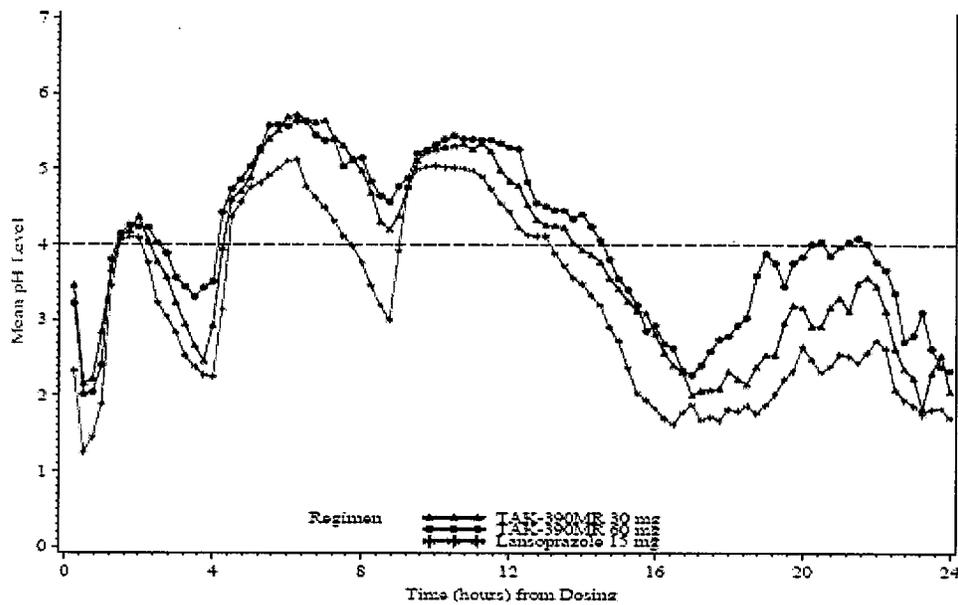
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Fig 5 Mean pH Measurements on Day 1 Based on 15-Minute Gastric pH Medians



Dexlansoprazole MR 60 mg increased the gastric pH to a greater extent than dexlansoprazole MR 30 mg over the >2 to 5-hr and >6 to 8-hr intervals after dosing. Both dexlansoprazole MR 60 mg and 30 mg had a better PD effect than 15 mg lansoprazole over > 6 to 8-hr and >11 to 24-hr after dosing. The pH-increasing effects of dexlansoprazole MR 60 mg and 30 mg were similar in the >10 to 24-hr interval after dosing. This interval seemingly corresponded to the times when stomach content from meals had been emptied. That is, the results in the >10 to 24-hr interval were not confounded by meals.

Fig 6 Mean pH Measurements on Day 5 Based on 15-Minute Gastric pH Medians



Dexlansoprazole MR 60 mg increased gastric pH to a greater extent than dexlansoprazole MR 30 mg at >2 to 5 hr and >18 to 22 hr intervals after dosing. Both dexlansoprazole MR 60 mg and 30 mg regimens had better PD effect than the 15 mg lansoprazole regimen over the >6 to 9-hr, >14 to 16-hr, and >18 to 22-hr intervals after dosing. These intervals appeared to correspond to the times when stomach content from meals had been emptied. The Day 5 results showed that dexlansoprazole MR resulted in higher night-time pH at 60 mg than at 30 mg.

Table 29 Analysis of mean intragastric pH results

Day Interval	The Mean <sup>a</sup> of the Mean Intragastric pH for Each Dosing Regimen			Differences <sup>b</sup> (Significance) Between Dosing Regimens		
	A	B	C	A versus C	B versus C	A versus B
Day 1						
Total 24 hours	3.34	3.64	2.63	0.71***	1.02***	-0.31**
0-4 hours	1.52	2.05	1.70	-0.18	0.36***	-0.53***
>4-9 hours	4.60	5.07	3.64	0.96***	1.43***	-0.47*
>9-12 hours	5.16	5.22	4.59	0.57***	0.63***	-0.06
>12-16 hours	4.04	4.15	2.87	1.16***	1.28***	-0.12
>16-24 hours	2.40	2.68	1.58	0.82***	1.10***	-0.28
Day 5						
Total 24 hours	3.67	3.94	3.21	0.47***	0.74***	-0.27*
0-4 hours	3.14	3.38	2.78	0.36*	0.61***	-0.24
>4-9 hours	5.00	5.09	4.27	0.73***	0.82***	-0.09
>9-12 hours	5.15	5.26	4.91	0.24*	0.35**	-0.11
>12-16 hours	3.81	4.01	3.31	0.50**	0.69***	-0.20
>16-24 hours	2.48	2.98	2.07	0.41	0.91***	-0.50

Note: Regimen A = 30 mg of TAK-390MR, Regimen B = 60 mg of TAK-390MR, and Regimen C = 15 mg of lansoprazole.

a The estimates of the mean are least squares means, which took into account the possibility of period effects.

b The differences presented are the differences in least squares means.

\*, \*\*, \*\*\* Indicate statistical significance at the p = 0.05, 0.01, or 0.001 level, respectively.

Dexlansoprazole MR 30 mg and 60 mg resulted in statistically significant higher pH values in several time intervals than the lansoprazole 15 mg regimen. This result is consistent with the result of Study T-P104-071. Numerical comparison reveals that the 60-mg MR dose resulted in higher intragastric pH than the 30-mg MR dose for both Days 1 and 5.

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Table 30 Analysis of percent of time intragastric pH exceeded 4

Day Interval	Mean <sup>a</sup> Percent of Time Intragastric pH Exceeded 4 for Each Dosing Regimen			Differences <sup>b</sup> (Significance) between Dosing Regimens		
	A	B	C	A versus C	B versus C	A versus B
Day 1						
Total 24 Hours	45	52	30	16***	22***	-6*
0 to 4 Hours	6	12	7	-2	5*	-7**
>4 to 9 Hours	73	85	49	24***	37***	-13*
>9 to 12 Hours	96	98	77	19***	21***	-2
>12 to 16 Hours	62	63	26	36***	37***	-2
>16 to 24 Hours	21	27	12	9**	14***	-5
Day 5						
Total 24 Hours	52	55	41	11***	14***	-3
0 to 4 Hours	29	36	25	4	11**	-7
>4 to 9 Hours	85	83	65	19***	18***	1
>9 to 12 Hours	97	94	88	8**	6*	2
>12 to 16 Hours	57	57	36	21***	21***	0
>16 to 24 Hours	24	32	18	6	14**	-8

Note: Regimen A = 30 mg of TAK-390MR, Regimen B = 60 mg of TAK-390MR, and Regimen C = 15 mg of lansoprazole

a The estimates of the mean are least squares means, which took into account the possibility of period effects.

b The differences presented are the differences in least squares means.

\*, \*\*, \*\*\* Indicate statistical significance at the p = 0.05, 0.01, or 0.001 level, respectively.

On day 1, the 60-mg dose resulted in higher mean percent of time intra-gastric pH exceeded 4 than the 30-mg dose, but not as consistently higher on Day 5.

**Summary:** Based on the AUC and Cmax and intragastric pH, there is a slight trend of response/exposure relationship observed between 30 mg MR and 60 mg MR. As compared to the 30-mg MR dose, the 60-mg MR dose resulted in better and longer-lasting effects in increasing intra-gastric pH.

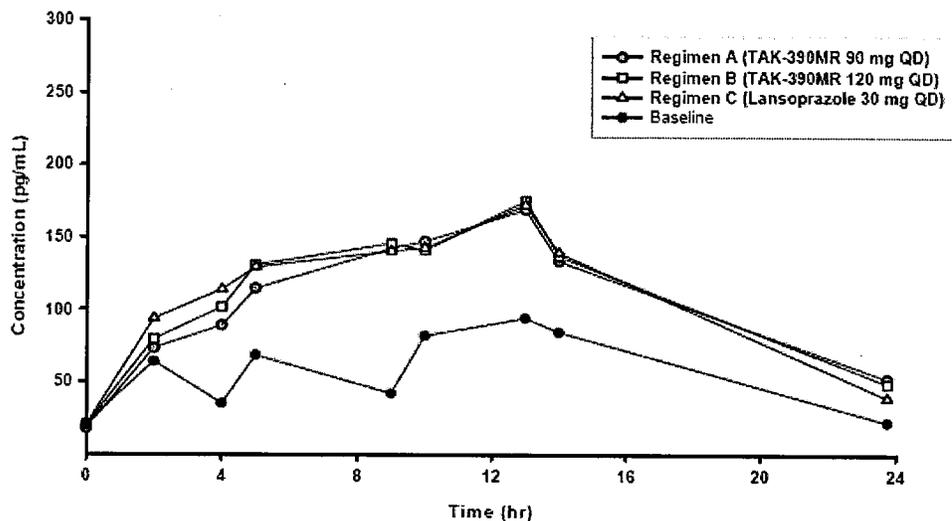
**Exposure/gastrin level**

Study T-P104-100 (36 males and 6 females, aged 18 to 54 years) was conducted to characterize the plasma gastrin and dexlansoprazole profiles following QD oral administration of dexlansoprazole MR or lansoprazole. A fasting gastrin level had to be within the clinically acceptable limits (0 to 200 pg/mL) for a subject to enter the study.

The AUC and Cmax data are summarized in section 2.2.2- pharmacokinetic parameters of dexlansoprazole and showed dose proportionality for both Days 1 and 5. The results of gastrin plasma profiles were compared and shown below.

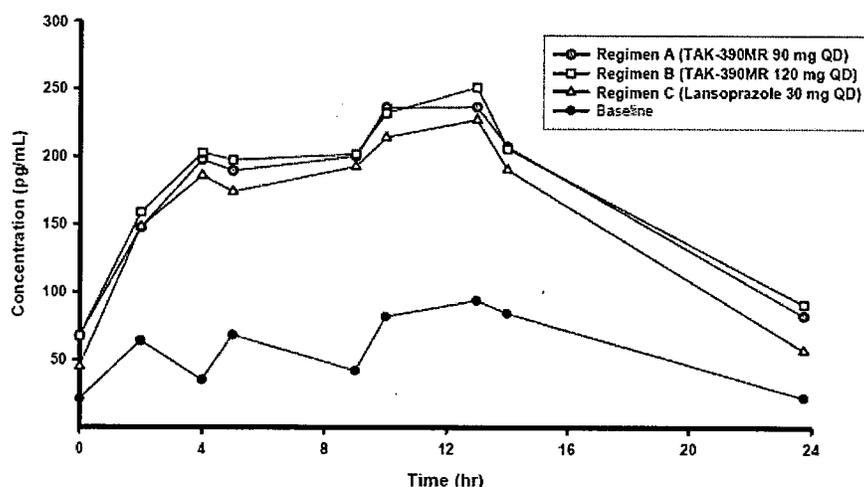
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Fig 7 Mean plasma concentration-time profiles of gastrin ( Day 1)



On Day 1, all three regimens increased the plasma concentrations of gastrin, and produced similar gastric levels in the >6 to 24 hr interval. Between 2 and 4 hrs following administration, lansoprazole 30 mg caused slightly higher gastrin levels than dexlansoprazole MR 90 mg and 120 mg. Apparently, immediate release capsules produced a quicker effect on gastrin secretion than delayed release capsules.

Fig 8 Mean plasma concentration-time profiles of gastrin (Day 5)



All three regimens increased the plasma concentrations of gastrin on Day 5 to a greater extent than on Day 1, as shown in Figures 6 and 7. There were minute differences between dexlansoprazole MR 90 mg and 120 mg in affecting the gastrin levels on Days 1 and 5, whereas these two dose regimens produced slightly higher gastrin levels than the lansoprazole 30 mg. Considering dexlansoprazole MR 90 mg and 120mg offered three fold and four fold higher dose, respectively, than regimen C, the latter two doses

did not produce higher gastric levels in a dose proportional manner than the 30 mg lansoprazole.

Table 31 Mean fasting gastrin concentrations at baseline and on days 5, 6, 8, and 12, by regimen

Day	Measure	Fasting Gastrin Concentration (pg/mL)		
		90-mg TAK-390MR	120-mg TAK-390MR	30-mg Lansoprazole
Baseline <sup>a</sup>	N	41	40	42
	Mean	17.6	20.1	20.3
	SD	5.84	11.07	12.62
5	N	41	41	41
	Mean	67.8***	67.3***	44.8***
	SD	47.91	53.19	33.14
6	N	41	41	41
	Mean	82.6***	91.0***	57.0***
	SD	66.2	72.9	46.7
8 <sup>b</sup>	N	24	26	28
	Mean	36.3*	40.6*	44.7**
	SD	30.41	30.14	52.63
12 <sup>b</sup>	N	25	28	28
	Mean	26.8	28.8	29.6
	SD	18.43	19.63	17.69

a Baseline represents the result obtained just prior to the first dose of each regimen.

b Day 8 and Day 12 samples were collected during Periods 1 and 2 only.

Note: P-values are from the ANOVA model utilizing all available data. Comparisons of the least-square means on Days 5, 6, 8, and 12 to the baseline were performed within each regimen.

\*, \*\*, and \*\*\* denote p-values of less than 0.05, 0.01, and 0.001, respectively.

The gastrin levels continuously increased up to Day 6 (1 day after the last dose) and then decline afterwards. According to the June-24-07 approved label of lansoprazole, it is stated that in over 2100 patients, median fasting serum gastrin levels increased 50% to 100% from baseline but remained within normal range after treatment with 15 to 60 mg of oral lansoprazole. These elevations reached a plateau within two months of therapy and returned to pretreatment levels within four weeks after discontinuation of therapy. As compared to lansoprazole, dexlansoprazole MR seems to offer a longer lasting effect on increasing the gastrin levels.

**Conclusion:** There was no apparent relationship between the plasma gastrin level and exposure of dexlansoprazole MR between 90 mg and 120mg. In terms of ingastric pH and mean percent of time intragastric pH exceeded 4, there was no exposure/response relationship between 60 mg and 120 mg either. The 60-mg dose may produce higher ingastric pH than the 30-mg dose, but there is no clear pharmacodynamic benefit for doses higher than 60 mg. In terms of study drug related adverse events reported in these three studies, there was no trend of higher incidence rates at higher doses. It is noteworthy that the number of subjects involved was small. Based on the results of clinical Study T-EE04-085 involving more than 2,000 subjects, there were severe adverse effects including ischaemic coronary artery disorders observed. Hence, doses higher than 60 mg QD may not be therapeutically beneficial.

### 2.2.9 Is there a relation between CYP 2C19 genotype and pharmacokinetics, pharmacodynamics, and adverse effects of dexlansoprazole ?

The sponsor genotyped the subjects for CYP2C19\*2, \*3, \*4, and \*5 alleles. Totally, seventy six subjects receiving dexlansoprazole MR at doses between 30mg and 90 mg

were genotyped for CYP2C19. These participants were from 4 separate Phase 1 single and multiple dose studies (Studies T-105-11, T-P105-119 and T-P106-141) in which full dexlansoprazole plasma concentration profiles were determined. Among these subjects, 75 were genotyped as extensive metabolizers (55 wt/wt, 19 \*2/wt, and 1 \*4/wt) and 1 was genotyped as poor metabolizers (\*2/\*2). Since there is only 1 PM genotype, it is impossible to statistically determine whether or not an association between CYP 2C19 genotype and dexlansoprazole pharmacokinetics/pharmacodynamics exists. There is no difference in dexlansoprazole AUC or Cmax between homozygous (wt/wt) and heterozygous (\*2/wt) EMs.

A total of 49 subjects from phase III study (Study T-G104-088) were genotyped with only 1 subject genotyped as CYP2C19 \*2/\*2. So, no statistical analysis could be made to determine whether or not there is an association between the CYP2C19 genotype and the occurrence of adverse events related to dexlansoprazole.

In the April 28 amendment, the sponsor submitted a report of Study CPH-001 which consisted of single dose fasting study over the dose range of 15 mg to 120 mg and single dose food effect study, a total of 30 subjects genotyped as CYP2C19 EMs (wt/wt, \*2/wt, or \*3/wt) and 30 subjects genotyped as CYP2C19 PMs (\*2/\*2, \*2/\*3 or \*3/\*3) were enrolled in the ascending single dose portion of this study (6 EMs and 6 PMs per dose group).

Table 32 Dose and number of subjects in Steps 1 and 5

Step	Treatment group	Dose	# of Subjects <sup>1)</sup>
1	TAK-390MR 15 mg	One of TAK-390MR 15 mg capsules	12 (6 EMs, 6 PMs)
	TAK-390MR 15 mg placebo	One of TAK-390MR 15 mg placebo capsules	4 (2 EMs, 2 PMs)
2	TAK-390MR 30 mg	One of TAK-390MR 30 mg capsules	12 (6 EMs, 6 PMs)
	TAK-390MR 30 mg placebo	One of TAK-390MR 30 mg placebo capsules	4 (2 EMs, 2 PMs)
3	TAK-390MR 60 mg	One of TAK-390MR 60 mg capsules	12 (6 EMs, 6 PMs)
	TAK-390MR 60 mg placebo	One of TAK-390MR 60 mg placebo capsules	4 (2 EMs, 2 PMs)
4	TAK-390MR 90 mg	Two of TAK-390MR 45 mg capsules	12 (6 EMs, 6 PMs)
	TAK-390MR 90 mg placebo	Two of TAK-390MR 45 mg placebo capsules	4 (2 EMs, 2 PMs)
5	TAK-390MR 120 mg	Two of TAK-390MR 60 mg capsules	12 (6 EMs, 6 PMs)
	TAK-390MR 120 mg placebo	Two of TAK-390MR 60 mg placebo capsules	4 (2 EMs, 2 PMs)

1) EM: Extensive metabolizer; PM: Poor metabolizer.

Table 33 Dose, mode of administration and the number of subjects in step 6

Step	Study Drug	Dose / Mode of Administration <sup>1)</sup>		# of Subjects <sup>2)</sup>
		Period 1	Period 2	
6A	TAK-390MR 60 mg	Dosing one of TAK-390MR 60 mg capsule under fasting condition	Dosing one of TAK-390MR 60 mg capsule after breakfast	4 EMs
	TAK-390MR 60 mg placebo	Dosing one of TAK-390MR 60 mg placebo capsule under fasting condition	Dosing one of TAK-390MR 60 mg placebo capsule after breakfast	2 EMs
6B	TAK-390MR 60 mg	Dosing one of TAK-390MR 60 mg capsule after breakfast	Dosing one of TAK-390MR 60 mg capsule under fasting condition	4 EMs
	TAK-390MR 60 mg placebo	Dosing one of TAK-390MR 60 mg placebo capsule after breakfast	Dosing one of TAK-390MR 60 mg placebo capsule under fasting condition	2 EMs

1) The washout between period 1 and 2 was at least 1 week.

2) EM: Extensive metabolizer.

Table 34 Genotype and systemic exposure

	C <sub>max</sub> (ng/mL)				AUC <sub>0-∞</sub> (ng-h/mL)			
	CYP2C19 Phenotype				CYP2C19 Phenotype			
	EM	EM (homozygous)	EM (heterozygous)	PM	EM	EM (homozygous)	EM (heterozygous)	PM
<b>15 mg Dexlansoprazole MR</b>								
N	6	2	4	6	6	2	4	6
Mean	269	192	308	665	1534	863	1870	6069
CV%	36	14	31	38	49	16	38	39
Min	173	173	239	312	764	764	946	2837
Median	245	192	274	636	1364	863	1962	6017
Maximum	446	210	446	1103	2608	962	2608	9930
<b>30 mg Dexlansoprazole MR</b>								
N	6	2	4	6	6	2	4	6
Mean	555	334	665	1443	2604	1431	3191	16769
CV%	35	38	15	33	42	24	24	39
Min	245	245	540	783	1188	1188	2132	7782
Median	597	334	674	1570	2621	1431	3415	16566
Maximum	772	442	772	1957	3804	1673	3804	24927
<b>60 mg Dexlansoprazole MR</b>								
N	6	4	2	6	6	4	2	6
Mean	1144	1039	1355	3057	5442	4822	6682	30834
CV%	22	24	3	28	38	39	35	19
Min	809	809	1328	1957	3014	3014	5006	24933
Median	1255	1042	1355	3048	5113	4479	6682	29364
Maximum	1382	1262	1382	4205	8357	7314	8357	38310
<b>90 mg Dexlansoprazole MR</b>								
N	6	3	3	6	6	3	3	6
Mean	1836	1858	1815	4501	9037	8348	9725	39886
CV%	33	49	18	32	32	53	4	12
Min	905	905	1468	2963	4245	4245	9318	33409
Median	1905	1967	1842	4176	9562	7769	9805	41294
Maximum	2702	2702	2134	6302	13031	13031	10053	45915
<b>120 mg Dexlansoprazole MR</b>								
N	6	4	2	6	6	4	2	6
Mean	2412	2316	2604	4474	12775	11270	15785	57449
CV%	19	24	7	52	31	34	14	17
Min	1759	1759	2482	2578	7715	7715	14243	42355
Median	2565	2290	2604	3757	13022	10461	15785	57007
Maximum	2923	2923	2726	9112	17326	16443	17326	73862

Source: Report TAK-390MR/CPH-001, Table 3.1, pages 159-167

In general, heterozygous EMs had higher C<sub>max</sub> and AUC than homozygous EMs. Apparently, the mutation alleles caused lower CYP2C19 activity. PMs had AUC values 2.96, 5.44, 4.67, 3.41, and 3.5 fold higher than EMs when dosed with 15mg, 30mg, 60mg, 90mg, and 120 mg, respectively. PMs had C<sub>max</sub> values 2.47, 2.6, 2.7, 2.5, and 1.9 fold higher than EMs when dosed with 15mg, 30mg, 60mg, 90mg, and 120 mg, respectively. In homozygous EMs, the increase was more than dose proportional between 60 mg and 120 mg while in heterozygous EMs, the increase was slight less than dose proportional between 60 mg and 120mg. As both groups were combined together, the final outcome showed that in EMs, there was a dose proportional increase in C<sub>max</sub> as the dose increased from 15 mg to 120 mg. In PM subjects, the dose proportionality in C<sub>max</sub> was observed between 15 mg and 90 mg, but not between 90 mg to 120mg. Between 15 mg and 120 mg, EMs (homozygous or heterozygous) showed dose proportional increase in AUC while PMs showed slightly more than dose proportional increase.

The linear regression of dose versus C<sub>max</sub> or AUC was performed without forcing the line through the origin and the correlation coefficients are listed below.

Table 35 The correlation coefficients (r<sup>2</sup>) of linear regression of dose versus Cmax or AUC

Dose	EMs	Homozygous EMs	Heterozygous EMs	PMs
Cmax	0.999	0.9888	0.9943	0.9234
AUC	0.993	0.9928	0.9764	0.9876

Between 15 mg and 120 mg, there are slightly higher correlation coefficients in terms of the dose proportionality of Cmax or AUC in EMs, as compared to those in PMs.

Genotype and pharmacodynamics: No pharmacodynamic measurements were made in this study. In the pharmacodynamic studies, no subjects were genotyped.

Genotype and adverse events

Only 2 AEs were reported by 1 EM subject (wt/wt), and they were AST and ALT elevation occurring 7 days after dosing of dexlansoprazole 60 mg MR and were considered not treatment related. There is no association to conclude between CYP2C19 genotype and AEs due to the limited number of AEs..

According to the sponsor, in the combined nine phase 1 and 3 studies , 37% (75/202) and 75% (3/4) of the EMs and PMs (CYP2C19 genotypes), respectively, experienced treatment-emergent adverse events. Due to the small number of PMs, there is no association between CYP2C19 genotype and occurrence of adverse events observed. Dr. Stella Grosser (statistician) agreed to our conclusion and commented in her e-mail that “There appears to be no association statistically between genotype and AE's. A chi-square test for association gave a p-value of 0.12. Fisher's exact test, which is more appropriate here given the small numbers in the PM group, gave a p-value of 0.15. Both results are insignificant.”

In the wt/wt group, 3 out of 148 subjects experienced cardiac side effects and in the wt/\*2 group 0 out of 53 subjects experienced cardiac effects. Dr. Stella Grosser (statistician) commented that “There appears to be no association statistically between genotype and cardiac effects. A chi-square test for association gave a p-value of 0.30. Fisher's exact test, which is more appropriate here given the small numbers experiencing effects in both groups, gave a p-value of 0.40. Both results are far from significant.”

Reviewer's comments: In light of the severe adverse events observed in Study-EE-04 at higher doses and the higher percentage of patient experiencing AEs in Study CPH-001, though no statistical correlation with genotype was concluded, the question of association of AEs with CYP2C19 genotype remains to be investigated. There is a need for post-approval commitments to investigating whether or not such association exists.

**2.2.10 What is the pharmacokinetic characteristics of (b) (4) in patients with hepatic impairment?**

The effect of moderate hepatic impairment on the pharmacokinetics and safety of dexlansoprazole MR was evaluated in an open-label, parallel-group study. Twenty four subjects (12 subjects with normal hepatic function and 12 subjects with moderately impaired hepatic function) completed the study. There were six males and six females in

each of normal and hepatic impairment groups. The sponsor also conducted CYP2C19 genotyping using ABI TaqMan (Applied Biosystems, Foster City, California), and the results showed that 7 subjects were heterozygous (\*2/wild type [wt]) extensive metabolizers, and 17 subjects were homozygous (wt/wt) extensive metabolizers. Nine subjects were homozygous and 3 subjects were heterozygous in the normal hepatic function group, and 8 subjects were homozygous and 4 subjects were heterozygous in the impaired hepatic function group.

Subject 805 with normal hepatic function was genotyped heterozygous for CYP 2C19 (extensive metabolizer), but the pharmacokinetic results were similar to that of a CYP2C19 poor metabolizer. The blood of Subject 805 was re-genotyped for the \*2-\*5 alleles in addition to a recently developed assay for the \*6 allele, and the results confirmed the original result that Subject 805 had the \*2/wt genotype. It is unknown whether this subject might have some other mutations that would have caused the inconsistency in the relation of genotype and phenotype. This subject's data were included in data analysis.

The in vitro plasma protein binding of dexlansoprazole was determined by the addition of <sup>14</sup>C-dexlansoprazole into predose (blank) plasma samples obtained from subjects. The dexlansoprazole concentration studied was 5 µg/ml. The results are summarized below.

Table 36 Mean in vitro protein binding for [<sup>14</sup>C]dexlansoprazole in human plasma of normal and hepatically impaired subjects

Hepatic Group	Number of Subjects	Mean Unbound (% ± SD)
Normal	12	1.99 ± 0.16
Moderate Impairment	12	2.13 ± 0.40

Dexlansoprazole was extensively bound to human plasma protein. In vitro protein binding of dexlansoprazole in plasma was similar between subjects with moderately impaired hepatic function and those with normal hepatic function.

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Table 37 Summary of the pharmacokinetic parameter estimates for dexlansoprazole in normal and moderate hepatically impaired subjects following a single 60 mg oral dose of dexlansoprazole MR

Hepatic Group		$t_{max}$ (h)	$C_{max}$ (ng/mL)	$C_{max,u}$ (ng/mL)	$AUC_t$ (ng·h/mL)	$AUC_{\infty}$ (ng·h/mL)	$AUC_{\infty,a}$ (ng·h/mL)	CL/F (L/h)	$CL_{q/F}$ (L/h)	$t_{1/2z}^a$ (h)
Normal Function	N	12	12	12	12	12	12	12	12	12
	Mean	4.67	912.25	17.91	6425.22	7562.63	149.98	16.57	835.62	2.66 (1.56)
	SD	2.56	496.16	9.09	6734.88	9793.71	193.14	9.23	463.28	3.08
	CV(%)	55	54	51	105	130	129	56	55	116
Moderate Impairment	N	12	12	12	12	12	12	12	12	12
	Mean	4.92	1314.50	27.28	13555.93	16306.06	350.65	5.65	281.91	7.12 (4.36)
	SD	3.10	664.72	12.21	7443.17	9209.09	206.29	4.38	243.34	5.06
	CV(%)	63	51	45	55	56	59	77	86	71

<sup>a</sup> Arithmetic mean (harmonic mean).

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Following administration of a single oral dose of dexlansoprazole MR 60 mg, mean dexlansoprazole C<sub>max</sub> and C<sub>max,u</sub> in the moderately impaired hepatic function group were about 1.5-times higher in subjects with moderate hepatic impairment compared to those with normal hepatic function. Moderate impairment increased C<sub>max</sub>, AUC<sub>t</sub>, AUC<sub>∞</sub>, t<sub>1/2</sub> and unbound PK parameters of AUC<sub>∞,u</sub>, C<sub>max,u</sub>, AUC<sub>∞,u</sub> while decreasing CL/F and CL<sub>u</sub>/F (unbound CL/F). The AUC<sub>t</sub>, AUC<sub>∞</sub>, AUC<sub>∞,u</sub> and t<sub>1/2</sub> of dexlansoprazole were more than doubled due to hepatic impairment but the increases in C<sub>max</sub> and C<sub>max,u</sub> were less than 2 fold. The p-values comparing the normal hepatic function and moderate hepatic impairment groups were 0.832, 0.001, 0.056, 0.026, 0.004, 0.004, and 0.003 for t<sub>max</sub>, λ<sub>z</sub>, C<sub>max</sub>, C<sub>max,u</sub>, AUC<sub>t</sub>, AUC<sub>∞</sub>, and AUC<sub>∞,u</sub>, respectively. The differences in the PK parameters of dexlansoprazole between normal function and hepatic impairment reached statistical significance for C<sub>max,u</sub>, AUC<sub>t</sub>, AUC<sub>∞</sub>, and AUC<sub>∞,u</sub>. The sponsor also compared the pharmacokinetic parameters of inactive metabolites of dexlansoprazole: 5-hydroxy dexlansoprazole and dexlansoprazole sulfone; and the results are summarized below.

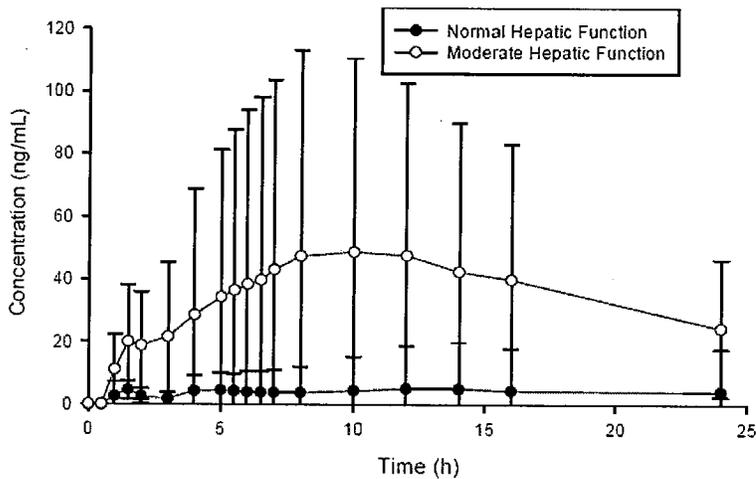
Table 38 Summary of the pharmacokinetic parameter estimates for 5-hydroxy dexlansoprazole and dexlansoprazole sulfone in normal and moderate hepatically impaired subjects following a single 60 mg oral dose of dexlansoprazole MR

Hepatic Function Group		t <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	AUC <sub>t</sub> (ng·h/mL)	AUC <sub>t</sub> <sup>a</sup> Ratio
<b>5-Hydroxy Dexlansoprazole</b>					
Normal Function	N	12	12	12	12
	Mean	4.54	36.30	189.92	0.05
	SD	3.09	20.13	108.66	0.02
	CV(%)	68	55	57	51
Moderate Impairment	N	12	12	12	12
	Mean	5.00	10.09	77.30	0.01
	SD	3.09	9.01	44.98	0.01
	CV(%)	62	89	58	106
<b>Dexlansoprazole Sulfone</b>					
Normal Function	N	12	12	12	12
	Mean	4.00	11.40	96.15	0.01
	SD	4.10	13.45	232.10	0.01
	CV(%)	103	118	241	138
Moderate Impairment	N	12	12	12	12
	Mean	8.63	54.60	840.52	0.05
	SD	4.42	64.61	963.58	0.04
	CV(%)	51	118	115	81

a Metabolite AUC<sub>t</sub> to dexlansoprazole AUC<sub>t</sub> ratio.

Fig 9 Mean plasma concentrations of dexlansoprazole sulfone versus time (linear) profile following administration of a single 60 mg oral dose of dexlansoprazole MR to subjects with normal or moderately impaired hepatic function

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The pharmacokinetic parameters of dexlansoprazole and 5-hydroxy dexlansoprazole were compared between the normal and moderate hepatic functions and the statistical results are shown below.

Table 39 Summary of statistical results

Parameter	p-value
<b>5-Hydroxy Dexlansoprazole</b>	
$t_{max}$ (h)	0.720
$C_{max}$ (ng/mL) <sup>a</sup>	0.003**
$AUC_0-t$ (ng·h/mL) <sup>a</sup>	0.088
$AUC_0-t$ Ratio <sup>a</sup>	0.008***
<b>Dexlansoprazole Sulfone</b>	
$t_{max}$ (h)	0.014*
$C_{max}$ (ng/mL) <sup>a</sup>	<0.001***
$AUC_0-t$ (ng·h/mL) <sup>a</sup>	<0.001***
$AUC_0-t$ Ratio <sup>a</sup>	<0.001***

a Natural logarithm values of the parameters were used in the analysis.

\*, \*\*, \*\*\* indicate p-values at the 0.05, 0.01, and 0.001 levels, respectively.

Sponsor's comments: Although exposure ratios of metabolite to parent drug decreased approximately 80% for the 5-hydroxy dexlansoprazole metabolite and increased about 8-times for the dexlansoprazole sulfone metabolite, the relative amounts of these inactive metabolites in plasma compared to parent drug were minimal ( $\leq 5\%$ ).

Table 40 Treatment-Emergent Adverse Events

MedDRA High-Level Term MedDRA Preferred Term(s)	Subjects with Normal Hepatic Function (N=12) n (%)	Subjects with Moderate Hepatic Impairment (N=12) n (%)
Total Subjects Reporting at Least 1 Adverse Event	1 (8)	4 (33)
Headaches NEC Headache	0	2 (17)
Flatulence, Bloating, and Distension Flatulence	1 (8)	0
Nasal Disorders NEC Epistaxis	0	1 (8)
Site Specific Injuries NEC Tooth Fracture	0	1 (8)

NEC = not elsewhere classified.

Cross-references: Statistical Table 14.3.1.3

Based on the adverse events reported, laboratory values, physical examinations, vital signs, and ECGs, there were more adverse events in the moderate hepatic impairment.

Sponsor's comments: Following an oral dose of dexlansoprazole MR 60 mg, mean plasma exposure (AUC) of total and unbound dexlansoprazole in the hepatically impaired group was approximately 2-times greater compared to subjects with normal hepatic function. Although differences in the metabolite-to-parent drug AUCt ratios between the hepatic function groups were found, the concentration of these inactive dexlansoprazole plasma metabolites were considered minor ( $\leq 5\%$ ) when compared to parent drug. No dosage adjustment for dexlansoprazole MR doses up to 60 mg is likely to be necessary for subjects with mild or moderate hepatic impairment.

Reviewer's conclusion: The differences in the PK parameters of dexlansoprazole between normal function and hepatic impairment reached a statistical significance for  $C_{max,u}$ ,  $AUC_t$ ,  $AUC_{\infty}$ , and  $AUC_{\infty,u}$  each. The mean  $C_{max}$  and AUCt of 5-hydroxy dexlansoprazole decreased by one half in moderate hepatic impairment group and the metabolite to parent drug ratio decreased from 0.05 to 0.01. The  $T_{max}$  of this metabolite was similar between these two groups. The  $T_{max}$ ,  $C_{max}$ , and AUCt of dexlansoprazole sulfone increased 2 fold, 4 fold and more than 3 fold, respectively, in moderate hepatic impairment group as compared to the normal hepatic function group. It is generally accepted that dose adjustment in patients with moderate hepatic impairment should take into considerations the changes in pharmacokinetics of dexlansoprazole. Based on the results of clinical Study T-EE04-085 involving more than 2,000 subjects, there were severe adverse effects including ischaemic coronary artery disorders observed. The higher exposure of dexlansoprazole in subjects with moderate hepatic impairment warrants careful evaluation by the physicians for appropriate dose adjustment.

#### **2.2.11 What are the impacts of age and gender on the pharmacokinetics of dexlansoprazole, 5-hydroxy dexlansoprazole, dexlansoprazole sulfone after an oral 60 mg of dexlansoprazole MR ?**

The effects of gender and age on the PK and safety of dexlansoprazole following administration of a single oral dose of dexlansoprazole MR 60 mg were studied in an open-label, parallel-group study. Twenty four subjects (12 young subjects aged 18-40 and 12 elderly subjects aged 65 to 80) completed the study. There were six males and six females in each of the young and elderly groups. Subjects were genotyped for

CYP2C19\*2, \*3, \*4, and \*5 alleles. CYP2C19 genotype testing indicated that all subjects enrolled in the study were extensive metabolizers, with 7 heterozygous extensive metabolizers (\*2/wt) and 17 homozygous extensive metabolizers (wt/wt). The mean ages of males and females were similar (48.4 ± 21.05 years and 49.7 ± 22.17 years, respectively), whereas the mean ages of young and elderly subjects were different, 29.1 ± 7.22 years and 69.0 ± 21.15 years, respectively.

***Gender effect***

**Pharmacokinetics of dexlansoprazole:** The in vitro plasma protein binding of dexlansoprazole was determined by adding 14C-dexlansoprazole into predose (blank) plasma samples obtained from subjects enrolled in this study. The concentration of 14C-dexlansoprazole studied 5 µg/mL. The extent of dexlansoprazole bound to plasma protein ranged from 95.3 to 97.6% and was similar between young and elderly subjects or between male and female subjects. The mean values of unbound (free) fraction of dexlansoprazole in human plasma were similar among all the subjects, ranging from 0.032 to 0.036.

Subject 119 (elderly female) had high dexlansoprazole AUC<sub>∞</sub> (30602 hr·ng/mL) compared with the rest of subjects, and her results contributed to the relatively higher mean exposure in the female subjects compared with the male subjects. This subject was a heterozygous CYP2C19 extensive metabolizer, suggesting that her high systemic exposure was not caused by poor CYP2C19-mediated metabolism of dexlansoprazole. It is unknown why her genotype and phenotype of CYP2C19 were inconsistent.

Table 41 Mean (%CV) plasma pharmacokinetic parameter estimates of dexlansoprazole, 5-hydroxy dexlansoprazole, and dexlansoprazole sulfone for male and female subjects

Gender Group (N=24)	t <sub>max</sub> (hr)	C <sub>max</sub> (ng/mL)	AUC <sub>t</sub> (hr·ng/mL)	AUC <sub>∞</sub> (hr·ng/mL)	t <sub>1/2t</sub> (hr) <sup>a</sup>
<b>Dexlansoprazole</b>					
Male Subjects (N=12)	5.58	1306	7339	7483	1.72
CV (%)	48	38	44	44	64
Female Subjects (N=12)	5.33	1703	10319	10685	1.87
CV (%)	41	46	66	71	54
<b>5-Hydroxy Dexlansoprazole</b>					
Male Subjects (N=12)	5.75	39.5	222	233	2.22
CV (%)	51	68	48	47	50
Female Subjects (N=12)	5.63	63.9	367**	377**	2.29
CV (%)	38	62	39	38	42
<b>Dexlansoprazole Sulfone</b>					
Male Subjects (N=12)	5.42	12.4	56.6	79.4	2.25
CV (%)	62	50	71	57	23
Female Subjects (N=11)	5.27	24.3	171	205	2.31
CV (%)	54	82	129	136	67

<sup>a</sup> Harmonic mean.

\*\* Statistical significantly different from that for male subjects (p < 0.01).

Mean CL/F(CV%) and Vz/F (CV%) of dexlansoprazole were 9.68 L/hr (45%) and 32.4 L (111%) for male subjects, respectively. Mean CL/F and Vz/F of dexlansoprazole were 7.84 L/hr (58%) and 23.7 L (73%) for female subjects, respectively. The harmonic mean tends toward the smallest value of the list of numbers while the arithmetic mean the largest value. The former is better for the mean value of rate parameters. Therefore it is appropriate for the sponsor to use harmonic mean values for t<sub>1/2</sub> values. No statistical differences in the pharmacokinetic parameters of dexlansoprazole were observed between male and female subjects (p >0.05 for both dexlansoprazole C<sub>max</sub> and AUC). Female subjects had higher C<sub>max</sub> and AUC values but lower CL/F and V<sub>d</sub> values than male subjects. The half-life and plasma-protein binding of dexlansoprazole were similar between the female and male subjects.

Pharmacokinetics of dexlansoprazole metabolites: The pharmacokinetic parameters of each of inactive metabolites, dexlansoprazole sulfone and 5-hydroxy dexlansoprazole, were higher in the female subjects than in the male subjects.

Age effect

Pharmacokinetics of dexlansoprazole: The results of the same study were analyzed for the age effect.

Table 42 Mean (%CV) plasma pharmacokinetic parameter estimates of dexlansoprazole, 5-hydroxy dexlansoprazole, and dexlansoprazole sulfone for young subjects (aged 18 through 40 Years) and elderly subjects (aged 65 through 80 years)

Subject Group (Years) N=24	t <sub>max</sub> (hr)	C <sub>max</sub> (ng/mL)	AUC <sub>t</sub> (hr·ng/mL)	AUC <sub>∞</sub> (hr·ng/mL)	t <sub>1/2</sub> <sup>a</sup> (hr)
<b>Dexlansoprazole</b>					
Young Subjects (18-40) N=12	4.50	1472	7655	7749	1.50
CV (%)	42	48	51	52	45
Elderly Subjects (65-80) N=12	6.42*	1538	10004	10419	2.23 <sup>†</sup>
CV (%)	40	43	65	70	54
<b>5-Hydroxy Dexlansoprazole</b>					
Young Subjects (18-40) N=12	4.88	44.5	240	246	1.89
CV (%)	49	71	53	52	39
Elderly Subjects (65-80) N=12	6.50	58.9	349*	365*	2.79 <sup>†</sup>
CV (%)	38	66	41	39	41
<b>Dexlansoprazole Sulfone</b>					
Young Subjects (18-40) N=11	3.91	16.3	78.8	114	2.07
CV (%)	71	80	110	82	68
Elderly Subjects (65-80) N=12	6.67*	19.7	141	172	2.45
CV (%)	41	90	149	157	61

<sup>a</sup> Harmonic mean

\* Statistically significantly different from young subjects (p <0.05).

<sup>†</sup> Statistically significantly different from young subjects (p <0.05) based on λ<sub>z</sub>.

Mean CL/F(CV%) and Vz/F (CV%) were 9.74 L/hr (50%) and 22.9 L (63%) for young subjects, respectively. Mean CL/F and Vz/F were 7.78 L/hr (52%) and 33.2 L (112%) for elderly subjects, respectively. The mean t<sub>max</sub> for dexlansoprazole in the young and elderly subjects was statistically significantly different (p = 0.048). Mean C<sub>max</sub> were

similar between the young and elderly subjects. The mean AUC $\infty$  in the elderly subjects was approximately 34% higher, as compared to the young subjects. The observed age differences in dexlansoprazole Cmax and AUC were not statistically significant (p >0.05). The results of Subject 119 (elderly female) were discussed above. The harmonic mean t1/2 values were 1.50 and 2.23 hours in the young and elderly subjects, respectively, showing a statistically significant difference (p = 0.045).

Pharmacokinetics of dexlansoprazole metabolites: The systemic exposure of 5-hydroxy dexlansoprazole was low, less than 5% of that of dexlansoprazole; as was that of dexlansoprazole sulfone. The elderly patients had higher mean tmax, Cmax, and AUC $\infty$  than the young subjects with the mean AUC $\infty$  reaching a statistically significance between these two age groups (p <0.05). The harmonic mean t1/2 values also showed a significant age difference (p <0.05). The observed differences in the mean AUC $\infty$  and t1/2 are not expected to be clinically relevant since the systemic exposure of the pharmacologically inactive 5-hydroxy dexlansoprazole is very low compared to that of the parent drug. The difference in the mean tmax of dexlansoprazole sulfone between the young and elderly subjects was statistically significant (p = 0.035). The statistically significant difference in the mean tmax is not expected to be clinically relevant either since the systemic exposure to the pharmacologically inactive dexlansoprazole sulfone was very low compared to that of the parent drug. The mean Cmax and AUC $\infty$  values were higher in the elderly than in the young, though no statistically difference was observed. The harmonic mean t1/2 values were slightly higher in elderly subjects.

Adverse effects observed

Table 43 Possibly or definitely treatment-related adverse events categorized by severity during the treatment period

MedDRA High Level Term MedDRA Preferred Term(s)	Subjects Grouped by Gender		Subjects Grouped by Age		All Subjects N=24 n (%)
	Male Subjects N=12 n (%)	Female Subjects N=12 n (%)	Young Subjects (18-40 Years) N=12 n (%)	Elderly Subjects (65-80 Years) N=12 n (%)	
Subjects Reporting at Least 1 Adverse Event	0	2 (17%)	0	2 (17%)	2 (8%)
Headaches NEC Headache	0	2 (17%) <sup>a</sup>	0	2 (17%) <sup>a</sup>	2 (8%) <sup>a</sup>

Note: Subjects with 1 or more AEs within a level of the MedDRA term were counted only once in that level and overall total. Adverse events were coded using MedDRA Version 8.1.

a Adverse events were considered possibly related to study drug and of mild severity.

The females or elderly subjects had higher incidence of adverse events as compared to the males or young subjects. However, this study did not reveal any concerning adverse events.

Sponsor's conclusion: The sponsor concluded that the observed age difference in the pharmacokinetic parameters is unlikely clinically relevant, based on no observed difference in the extent of plasma protein binding of dexlansoprazole, and no statistically significant difference in the systemic exposure to the unbound dexlansoprazole, between the young and elderly subjects. The sponsor concluded that no dose adjustment for elderly or female subjects is needed.

Reviewer's comments: The results of this study showed that (1) the observed gender differences in dexlansoprazole Cmax and AUC were not statistically significant (p >0.05),

(2) the pharmacokinetic parameters of each of inactive metabolites, dexlansoprazole sulfone and 5-hydroxy dexlansoprazole, were higher in female subjects than in male subjects, (3) the CL/F of dexlansoprazole was similar between heterozygous extensive metabolizers of CYP2C19 and homozygous extensive metabolizers, and (4) there was no statistically significance ( $p > 0.05$ ) in the observed age differences in dexlansoprazole C<sub>max</sub> and AUC. This study involved a small number of subjects. Dexlansoprazole exhibited higher AUC in the elderly (30.7% higher) or female subjects (40.6% higher) than in the young or male subjects, respectively. Based on the results of clinical Study T-EE04-085 involving more than 2,000 subjects, there were severe adverse effects including ischaemic coronary artery disorders observed. Therefore, the higher exposure of dexlansoprazole in females or the elderly, though not statistically significant, warrants careful evaluation by the physicians for appropriate dose adjustment.

### 2.2.12 What are the results of drug interaction studies?

Dexlansoprazole is metabolized by CYP2C19 and CYP3A4, and an in vitro study conducted by Takeda has shown that dexlansoprazole may inhibit CYP2C19 activity. There are four drug interaction studies conducted by the sponsor, concerning coadministration of dexlansoprazole MR with each of 1) warfarin, 2) phenytoin, 3) diazepam, and 4) theophylline.

Interaction with diazepam: Dexlansoprazole was shown to slightly inhibit hepatic CYP2C19 activity. Diazepam was primarily metabolized to nordiazepam by CYP2C19. Twenty subjects (13 males and 7 females) participated in the study, and nineteen completed the study. All 20 subjects had plasma concentration results and were included in the descriptive statistics for dexlansoprazole. The dexlansoprazole MR and placebo were administered in double-blind fashion, while diazepam was administered in an open-label fashion. Because metabolism of both diazepam and dexlansoprazole involves CYP2C19, each subject was genotyped for CYP2C19 alleles. The phenotypes of all but one of the subjects were extensive metabolizers of CYP2C19. Overall, 12 subjects were homozygous extensive metabolizers, 7 subjects were heterozygous extensive metabolizers. Subject 112 was a poor metabolizer.

Table 44 Summary of pharmacokinetic parameter estimates for diazepam and nordiazepam following a single oral dose of 5 mg of diazepam during each regimen

Regimen	Measure	t <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	AUC <sub>t</sub>		V <sub>d</sub> /F (L)	CL/F (L/h)	t <sub>1/2</sub> <sup>a</sup> (h)
				(ng·h/mL)	(ng·h/mL)			
Diazepam								
A	N	19	19	19	19	19	19	19
	Mean	0.91	165.82	3473.56	4395.43	100.46	1.31	61.18 (48.37)
	SD	0.41	38.86	936.74	1705.51	32.40	0.51	33.41
	%CV	45	23	27	39	32	39	55
B	N	19	19	19	19	19	19	19
	Mean	0.75	186.05	3388.61	4047.62	93.03	1.37	51.49 (42.69)
	SD	0.37	53.61	863.54	1262.22	29.61	0.47	19.67
	%CV	50	29	25	31	32	34	38

Regimen A = 90 mg of dexlansoprazole MR QD for 11 days plus a single dose of 5 mg of diazepam and Regimen B = placebo QD for 11 days plus a single dose of 5 mg of diazepam.

a Arithmetic mean (harmonic mean);

The mean t<sub>max</sub>, C<sub>max</sub>, AUC<sub>t</sub>, and AUC<sub>∞</sub> of diazepam were similar regardless diazepam was administered with placebo (Regimen B) or dexlansoprazole MR (Regimen A). Moreover, the mean V<sub>d</sub>/F, CL/F and t<sub>1/2</sub> of diazepam were similar

between regimen A and regimen B. The C<sub>max</sub> (1280 ng/mL) of dextansoprazole in Subject 112 was not the highest among all the subjects (maximum concentration range: 155 to 4150 ng/mL) but this subject did have the highest trough level (237 ng/mL), as compared to the other subjects (0 to 85.8 ng/mL, excluding Subject 112).

Table 45 Pharmacokinetic parameter estimates of nordiazepam

Regimen	Measure	t <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	AUC <sub>t</sub> (ng·h/mL)
A	N	19	19	19
	Mean	83.36	20.64	2217.24
	SD	36.31	6.62	551.21
	%CV	44	32	25
B	N	19	19	19
	Mean	74.54	21.48	2350.33
	SD	28.98	6.68	544.17
	%CV	39	31	23

The mean t<sub>max</sub>, C<sub>max</sub>, AUC<sub>t</sub>, and AUC<sub>∞</sub> of nordiazepam were similar no matter whether diazepam was administered with placebo (Regimen B) or dextansoprazole MR (Regimen A). The C<sub>max</sub>, AUC<sub>t</sub>, and AUC<sub>t</sub> of nordiazepam in Subject 112 were also the lowest when compared to those of EMs.

Table 46 Bioavailability of diazepam and nordiazepam with concomitant administration of dextansoprazole MR, relative to concomitant administration of placebo

Pharmacokinetic Parameter	Point Estimate	90% Confidence Interval
<b>Diazepam</b>		
C <sub>max</sub>	0.8881	(0.8255 - 0.9555)
AUC <sub>t</sub>	1.0206	(0.9860 - 1.0564)
AUC <sub>∞</sub>	1.0646	(1.0126 - 1.1193)
<b>Nordiazepam</b>		
C <sub>max</sub>	0.9524	(0.9140 - 0.9923)
AUC <sub>t</sub>	0.9284	(0.8804 - 0.9789)

Note: The point estimates and confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm-transformed data.

The 90% confidence intervals for the ratio of the mean C<sub>max</sub> and AUCs of diazepam and nordiazepam were all within the 0.80 to 1.25 acceptance range, indicative of the absence of interaction between dextansoprazole and diazepam. The sponsor concluded that multiple, once-daily oral doses of dextansoprazole MR90 mg had no effect on the pharmacokinetics of diazepam or nordiazepam, and that dextansoprazole does not significantly affect hepatic CYP2C19 activity.

Reviewer's comments: Based on the results and the adequacy of study design and data analysis, it is concluded there is no significant interaction between dextansoprazole and diazepam or between dextansoprazole and nordiazepam.

Table 47 Treatment-related adverse events experienced by ≥2 subjects in either regimen, by dosing regimen

MedDRA High Level Term MedDRA Preferred Term(s)	Regimen A N = 20	Regimen B N = 19
Total Subjects Experiencing at Least 1 Adverse Event	6 (30%)	8 (42%)
Disturbances in Consciousness NEC Somnolence	3 (15%)	5 (26%)
Neurological Signs and Symptoms NEC Dizziness	1 (5%)	2 (11%)
Asthenic Conditions Asthenia and Fatigue	1 (5%)	2 (11%)
Headaches NEC Headache	2 (10%)	0

Note: Regimen A = 90 mg of dexlansoprazole MR QD for 11 days plus a single dose of 5 mg of diazepam and Regimen B = placebo QD for 11 days plus a single dose of 5 mg of diazepam.

Based on the data provided by the sponsor, there was no clinically important difference in safety results observed between the dexlansoprazole MR plus diazepam regimen and the placebo plus diazepam regimen.

Interaction with theophylline: Theophylline metabolism (N-demethylation and 8-hydroxylation) is mainly catalyzed by CYP1A2. Theophylline has a narrow therapeutic index. In-vitro studies showed that lansoprazole is a CYP 1A1 and 1A2 inducer. The objective of this study was to evaluate the effect of multiple once daily doses of dexlansoprazole MR 90 mg on the pharmacokinetics of theophylline following a single intravenous (IV) dose of aminophylline. For both periods, on Days 1 and 9 of each period, subjects received dexlansoprazole MR 90 mg or placebo, and on Day 8 of each period, subjects received a single 400-mg IV dose of aminophylline plus dexlansoprazole MR 90 mg or placebo. N=10 for each regimen

Twenty subjects (8 males and 12 females) completed the study. In terms of genotypes, fourteen subjects were homozygous extensive metabolizers and 6 subjects were heterozygous extensive metabolizers.

Table 48 Summary of pharmacokinetic parameter estimates for theophylline following a Single 400-mg IV dose of aminophylline dehydrate (315.2 mg anhydrous theophylline)

Treatment	t <sub>max</sub> (hr)	C <sub>max</sub> (µg/mL)	C <sub>48</sub> (µg/mL)	AUC <sub>t</sub> (hr·µg/mL)	AUC <sub>∞</sub> (hr·µg/mL)	t <sub>1/2z</sub> (hr) <sup>a</sup>	CL (L/h)	V <sub>z</sub> (L)
<b>Regimen A</b>								
N	19	19	19	19	19	19	19	19
Mean	0.692	12.35	229.74	122.3	126.5	8.48 (8.20)	2.62	31.25
%CV	27	25	63	23	23	19	22	18
<b>Regimen B</b>								
N	19	19	19	19	19	19	19	19
Mean	0.649	11.66	275.32	126.6	131.8	9.26 (8.94)	2.51	32.89
%CV	23	22	67	22	23	19	23	21

<sup>a</sup> Arithmetic mean (harmonic mean).

%CV = percentage of coefficient of variation.

There was no significant difference between regimen A and regimen B in any of the pharmacokinetic parameters of theophylline, including T<sub>max</sub>, C<sub>max</sub>, AUC<sub>t</sub>, AUC<sub>∞</sub>, T<sub>1/2</sub>, CL, and V<sub>z</sub>.

Table 49 Assessment of the relative systemic exposure of theophylline in regimen A vs regimen B

Parameter	Regimen A vs Regimen B	
	Point Estimate	90% Confidence Interval
C <sub>max</sub>	1.05	(0.9650 – 1.1336)
AUC <sub>T</sub>	0.96	(0.9318 – 0.9975)
AUC <sub>∞</sub>	0.96	(0.9284 – 0.9917)

The ANOVA analysis indicated that the systemic exposure of theophylline resulting from regimens A and B were bioequivalent, as summarized below.

Table 50 Most frequent possibly or definitely treatment-related adverse events occurring in ≥2 subjects per regimen

MedDRA High-Level Term MedDRA Preferred Term(s)	Treatment Regimen	
	Regimen A (N=20) n (%)	Regimen B (N=20) n (%)
Subjects Reporting at Least 1 Adverse Event	3 (15)	8 (40)
Cardiac Signs and Symptoms NEC Palpitations	2 (10)	5 (25)
Neurological Signs and Symptoms NEC Dizziness	3 (15)	1 (5)
Nausea and Vomiting Symptoms Nausea Vomiting	1 (5)	2 (10)
Rate and Rhythm Disorders NEC Tachycardia	0	2 (10)

Note: AEs summarized occurred after first dose of study drug and not more than 30 days after last dose of study drug.

Note: Subjects with 1 or more AEs within a level of MedDRA term are counted only once in that level.

Note: n (%) are for HLTs.

Note: AEs coded using MedDRA version 9.0.

NEC = not elsewhere classified.

The sponsor's concluded that dexlansoprazole does not affect hepatic CYP1A2 activity in humans and, therefore, will not alter the metabolism of other drugs metabolized by this enzyme. No dose adjustment for theophylline is recommended by the sponsor when administered concomitantly with dexlansoprazole MR.

**Reviewer's comments:** There is no effect of oral dexlansoprazole MR on the systemic exposure of theophylline when administered as intravenous aminophylline. The study design used intravenous theophylline instead of an orally administered drug.

**Interaction with phenytoin:** For the phenytoin drug-drug interaction study, a standard Phase 1, single-center, double-blind, placebo-controlled, randomized, two-way crossover study was conducted. Healthy volunteers received a single 250mg dose of phenytoin following 6 days of dexlasoprazole. Sixteen males and females, aged 20-35, completed the study. Dexlansoprazole had no effect on phenytoin (2C9 substrate) C<sub>max</sub> and AUC. All 16 subjects had measurable plasma concentrations of both dexlansoprazole and phenytoin and were included in the descriptive statistics. Dexlansoprazole and placebo were administered in a double-blind manner while phenytoin administration was open-label. Subjects were genotyped for both CYP2C9 and 2C19 alleles. No subject was homozygous for either mutant allele; therefore, all subjects were considered by investigators to be extensive metabolizers by phenotype. Four subjects were heterozygous for 2C9\*2 allele and 3 other subjects were heterozygous for the 2C19\*2 allele.

Summary of PK parameter estimates for phenytoin following a single oral dose of 250mg administered with and without daily 90mg dexlansoprazole.

	$t_{max}$ (h)	$C_{max}$ ( $\mu\text{g/mL}$ )	$AUC_t$ ( $\mu\text{g}\cdot\text{h/mL}$ )	$AUC_{\infty}$ ( $\mu\text{g}\cdot\text{h/mL}$ )	$V_z/F$ (L)	CL/F (L/h)	$t_{1/2}^a$ (h)
<b>90 mg Dexlansoprazole MR &amp; 250 mg Phenytoin (Regimen A)</b>							
N	16	16	16	16	16	16	16
Mean	7.56	2.85	111.90	113.99	44.60	2.35	13.55 (13.14)
SD	5.33	0.61	27.04	28.53	10.51	0.73	2.46
CV (%)	70	21	24	25	24	31	18
<b>Placebo &amp; 250 mg Phenytoin (Regimen B)</b>							
N	16	16	16	16	16	16	16
Mean	9.16	2.92	113.41	115.62	43.75	2.29	13.65 (13.12)
SD	5.42	0.60	26.18	27.71	9.25	0.58	2.92
CV (%)	59	20	23	24	21	25	21

Regimen A: 90 mg dexlansoprazole MR once-daily for 9 consecutive days plus a single 250 mg dose of phenytoin.

Regimen B: Placebo once-daily for 9 consecutive days plus a single 250 mg dose of phenytoin.

The mean  $t_{max}$ ,  $C_{max}$ ,  $AUC_t$  and  $AUC_{\infty}$  of phenytoin were similar when administered with and without dexlansoprazole. The 90% confidence intervals for the ratio of phenytoin  $C_{max}$  and  $AUC_t$  were all within the 0.80 to 1.25 range, indicating no effect of dexlansoprazole on phenytoin PK. The sponsor concluded that multiple, one-daily oral doses of 90mg dexlansoprazole had no effect on the PK of phenytoin.

Bioavailability of phenytoin with dexlansoprazole relative to phenytoin with placebo.

Parameter	Point Estimate	90% Confidence Interval
$C_{max}$	0.9726	(0.8937 - 1.0584)
$AUC_t$	0.9820	(0.9380 - 1.0282)
$AUC_{\infty}$	0.9811	(0.9363 - 1.0281)

Note: The point estimates and confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm transformed data.

Reviewer's comments: Based on the results and the adequacy of the study design and data analysis, I conclude that there is no significant interaction between dexlansoprazole and phenytoin. Based on the data provided by the sponsor, there was no important difference in safety results between the dexlansoprazole and placebo groups.

Interaction with warfarin: For the warfarin drug-drug interaction study, a Phase 1, single-center, double-blind, placebo-controlled, randomized, two-way crossover study was conducted. Healthy volunteers received a single 25mg dose of warfarin following 6 days of dexlansoprazole. Nineteen males and females, aged 18-48, participated in the study. Eighteen subjects completed the study. Dexlansoprazole had no effect on warfarin (2C9 substrate)  $C_{max}$ ,  $AUC$ ,  $INR_{max}$ , or  $INR_{144}$  (the area under the  $INR$ -time curve from time 0 to 144 hours). In addition, subjects were genotyped for CYP2C9 and 2C19 alleles. One subject was found to be homozygous for the 2C19\*2 allele and classified as a poor metabolizer.

The following table is a summary of the PK estimates for R- and S-warfarin following a single 25mg oral dose.

Regimen		$t_{max}$ (h)	$C_{max}$ ( $\mu\text{g}/\text{mL}$ )	$AUC_t$ ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )	$AUC_{\infty}$ ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )	$t_{1/2}^a$ (h)	CL/F ( $\text{mL}/\text{h}$ )	$V_z/F$ (L)
<b>R-Warfarin</b>								
Regimen A	N	18	18	18	18	18	18	18
	Mean	1.03	1.65	73.03	85.07	49.04 (46.75)	304.69	20.96
	CV (%)	170	15	14	19	22	21	17
Regimen B	N	18	18	18	18	18	18	18
	Mean	1.76	1.52	71.05	82.15	48.81 (46.29)	314.29	21.63
	CV (%)	203	13	14	18	22	19	20
<b>S-Warfarin</b>								
Regimen A	N	18	18	18	18	18	18	18
	Mean	0.67	1.72	50.11	54.54	42.06 (40.48)	488.49	29.02
	CV (%)	37	17	23	26	21	26	25
Regimen B	N	18	18	18	18	18	18	18
	Mean	0.95	1.58	47.92	51.76	40.12 (38.90)	510.37	29.12
	CV (%)	47	16	21	24	18	25	26

Regimen A: 90 mg dexlansoprazole MR once-daily for 11 consecutive days plus a single oral 25 mg warfarin dose on Day 6.

Regimen B: Placebo once-daily for 11 consecutive days plus a single oral 25 mg warfarin dose on Day 6.

CV (%) = percent coefficient of variation.

a Arithmetic mean (harmonic mean).

The mean  $t_{max}$ ,  $C_{max}$ ,  $AUC_t$ ,  $AUC_{\infty}$ ,  $t_{1/2}$ , and CL/F of R- and S-warfarin were similar when administered with and without dexlansoprazole. The 90% confidence intervals for the ratio of R- and S-warfarin  $C_{max}$  and AUCs were all within the 0.80 to 1.25 range, indicating no effect of dexlansoprazole on warfarin PK. The sponsor concluded that multiple, one-daily oral doses of 90mg dexlansoprazole had no effect on the PK of warfarin.

Bioavailability of R- and S-warfarin with dexlansoprazole relative to warfarin with placebo.

Parameter	Point Estimate	90% Confidence Interval
<b>R-Warfarin</b>		
$C_{max}$	0.93	(0.8601 - 1.0027)
$AUC_t$	0.97	(0.9544 - 0.9936)
$AUC_{\infty}$	0.97	(0.9433 - 0.9923)
<b>S-Warfarin</b>		
$C_{max}$	0.93	(0.8397 - 1.0199)
$AUC_t$	0.96	(0.9325 - 0.9917)
$AUC_{\infty}$	0.95	(0.9232 - 0.9860)

Note: The point estimates and confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm transformed data.

The mean  $INR_{144}$  and  $INR_{max}$  for subjects administered either dexlansoprazole or placebo were not found to be statistically significantly different.

Regimen		INR <sub>144</sub> (N=18)	INR <sub>max</sub> (N=18)
Dexlansoprazole MR & Warfarin (Regimen A)	Mean	184.404	1.622
	SD	23.949	0.284
Placebo & Warfarin (Regimen B)	Mean	184.798	1.656
	SD	23.927	0.311
Difference in Least Square Means (Regimen A - Regimen B)		0.184	-0.019
p-value		0.910	0.362

The sponsor concluded that multiple, one-daily oral doses of 90mg dexlansoprazole had no effect on the PD of warfarin.

Sparse sampling of dexlansoprazole plasma concentrations were performed. The one subject who was a poor metabolizer was found to have elevated dexlansoprazole troughs (831 and 1030 ng/mL) relative to all other subjects (range, <5 to 211 ng/mL); however, the 4-hour level, an estimate of the peak, (1390 ng/mL) was within the range of other subjects (range, 319 to 1570 ng/mL).

Reviewer's comments: Based on the results and the adequacy of the study design and data analysis, I conclude that there is no significant interaction between dexlansoprazole and warfarin. Based on the data provided by the sponsor, there was no important difference in safety results between the dexlansoprazole and placebo groups.

### 2.2.13 What is the food effect on the pharmacokinetics and pharmacodynamics of Tavalon?

For the study of food effect on pharmacokinetics, a Phase 1, single-center, 4-sequence, 4-period crossover study was conducted in which volunteers received one 90mg capsule under each of 4 different feeding conditions. Twenty-eight healthy adult males and females aged 19-55 participated in the study. Twenty-five subjects completed the study.

Regimen	Feeding Conditions
A	After fasting for at least 10 hours, the subject received the 90-mg dose of TAK-390MR and continued to fast for an additional 4 hours before receiving a standard lunch.
B	After fasting for at least 9.5 hours, the subject had a standardized high-fat breakfast that was consumed within 25 minutes, and received the 90-mg dose of TAK-390MR 30 minutes after starting to eat the breakfast.
C	After fasting for at least 10 hours, the subject received the 90-mg dose of TAK-390MR and consumed a standard high-fat breakfast that started 30 minutes after dosing.
D	After fasting for at least 10 hours, the subject received the 90-mg dose of TAK-390MR and consumed a standard high-fat breakfast that started 1 hour after dosing.

Food has several effects upon the absorption of dexlansoprazole. The administration of dexlansoprazole after a high-fat meal increases C<sub>max</sub> by 36% and AUC by 33% relative to administration while fasting. Administration of dexlansoprazole 30 minutes to 1 hour before a meal increases C<sub>max</sub> by 40-52% and AUC by 30-33% relative to administration while fasting.

Summary of the effect of food on the pharmacokinetic parameter estimates for dexlansoprazole following a single oral 90mg dose.

Regimen	Measure	t <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	AUC <sub>t</sub> (ng·h/mL)	AUC (ng·h/mL)	t <sub>1/2z</sub> <sup>a</sup> (h)
A (90 mg TAK-390MR fasted)	N	27	27	27	27	27
	Mean	4.66	1811.85	9254.84	9665.43	1.54
	SD	2.41	903.19	8213.87	9773.30	-
	CV%	52	50	89	101	75
B (90 mg TAK-390MR 30 minutes after the start of a meal)	N	27	27	27	22	22
	Mean	7.66	2462.22	11615.41	12848.92	1.51
	SD	1.64	1205.51	9198.38	11774.74	-
	CV%	21	49	79	92	79
C (90 mg TAK-390MR 30 minutes before a meal)	N	27	27	27	24	24
	Mean	5.40	2770.56	12378.36	13516.12	1.68
	SD	4.90	1414.22	12672.69	15365.37	-
	CV%	91	51	102	114	63
D (90 mg TAK-390MR 1 hour before a meal)	N	27	27	27	23	23
	Mean	3.96	2549.26	12038.44	13473.25	1.94
	SD	2.48	1233.22	10327.86	12330.22	-
	CV%	63	48	86	92	56

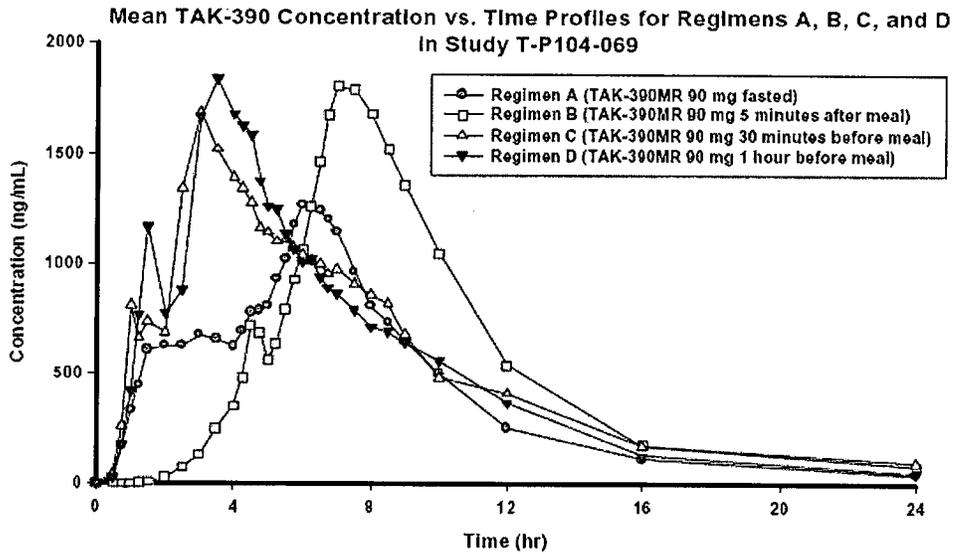
a Harmonic Mean

Point estimates and confidence intervals for dexlansoprazole under fed conditions relative to the fasted state.

Parameter	Point Estimate	90% Confidence Interval
Regimen B (Test) versus Regimen A (Reference)		
C <sub>max</sub>	1.3772	(1.1752 - 1.6138)
AUC <sub>t</sub>	1.3723	(1.2443 - 1.5135)
AUC <sub>∞</sub>	1.3744	(1.2527 - 1.5079)
Regimen C (Test) versus Regimen A (Reference)		
C <sub>max</sub>	1.5520	(1.3244 - 1.8186)
AUC <sub>t</sub>	1.3376	(1.2128 - 1.4752)
AUC <sub>∞</sub>	1.3469	(1.2319 - 1.4727)
Regimen D (Test) versus Regimen A (Reference)		
C <sub>max</sub>	1.3628	(1.1652 - 1.5939)
AUC <sub>t</sub>	1.2773	(1.1595 - 1.4070)
AUC <sub>∞</sub>	1.3457	(1.2308 - 1.4713)

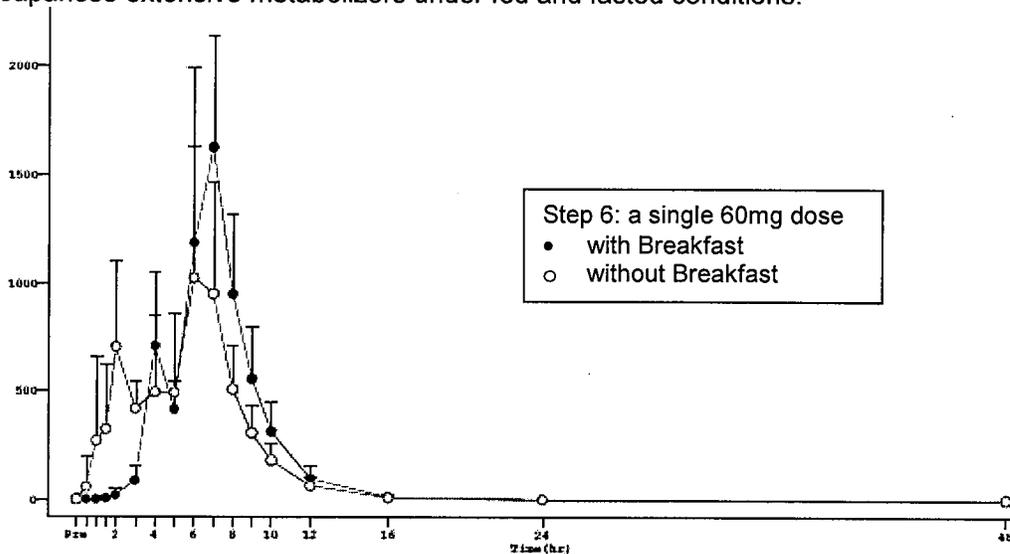
There are also effects of food on both t<sub>max</sub> and early-phase absorption. When drug is administered 30 minutes *after* a meal, early-phase absorption is significantly impaired and t<sub>max</sub> is delayed by 2-4 hours relative to administration before or meal or while fasting. When drug is administered *before* a meal, the rate of early-phase absorption is not affected relative to administration while fasting.

Mean plasma concentration-time profiles of dexlansoprazole administered under fasted or various fed conditions.



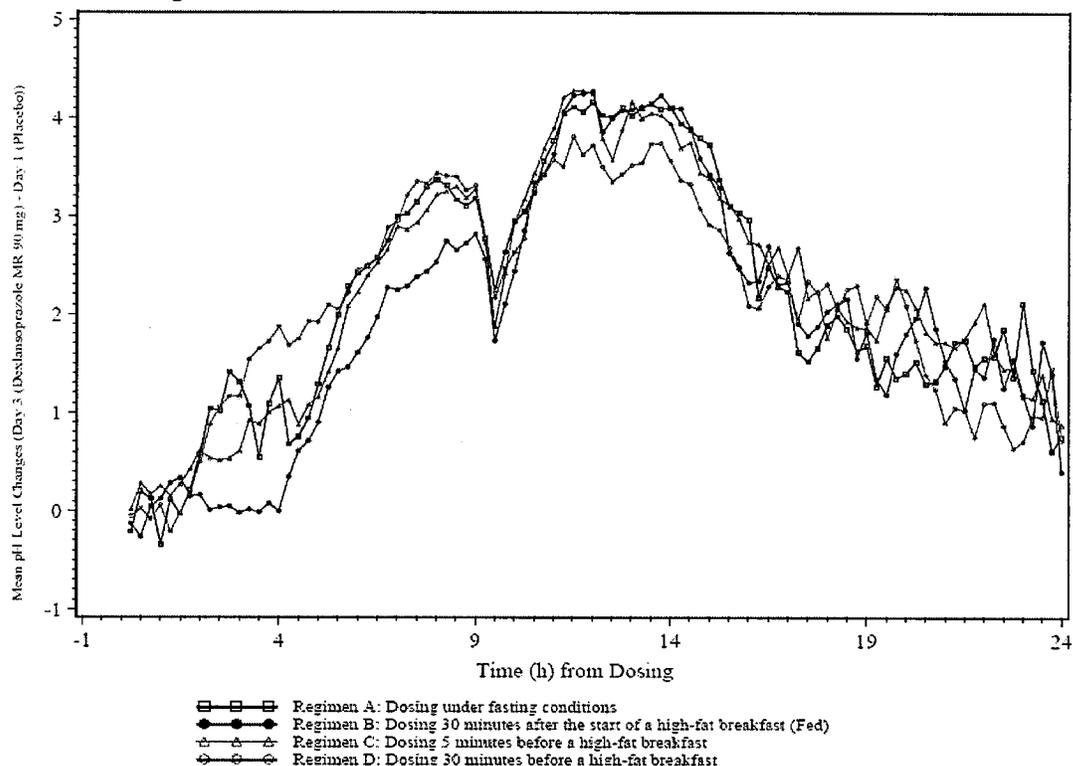
A second food-effect study, CPH-001, was conducted in 12 Japanese males in order to characterize the pharmacokinetic parameters of dexlansoprazole in CYP2C19 Extensive Metabolizers (EMs). [Genotype analysis was not performed in the previous trial; however, the subjects were mostly (80%) Caucasian, in whom the poor metabolizer phenotype is very unlikely to be present.] Unlike the previous study, subjects received a dose of 60mg dexlansoprazole and there were only two feeding conditions in this study. Subjects either took dexlansoprazole under fasted conditions or after breakfast. For fed subjects, like the study in Caucasians,  $t_{max}$  was delayed by 2 hours and  $C_{max}$  increased by 45% relative to fasting subjects. The  $AUC_{\infty}$  in Japanese EMs was increased by 14%, less than the increase observed in Caucasians (34-37%), although this is a cross-study comparison. When adjusted for dose,  $C_{max}$  was increased by 7-13% and  $AUC_{\infty}$  was decreased by 16-34% in Japanese EMs relative to Caucasians.

Mean plasma concentration-time profiles of dexlansoprazole administered to male Japanese extensive metabolizers under fed and fasted conditions.



Study T-P106-146 was conducted to investigate the effects of food on the pharmacodynamics of dexlansoprazole. A single, 90mg dexlansoprazole dose was administered to 48 healthy men and women under 4 different feeding conditions. Subjects were administered dexlansoprazole in the fasted state, 30 minutes after a meal, 5 minutes before a meal, or 30 minutes before a meal. On days when the subjects received dexlansoprazole or placebo, intragastric pH was sampled every 4 seconds over the 24-hour dosing interval.

Mean pH changes between treatment with 90mg dexlansoprazole and placebo over the 24-hour dosing interval.



The percentage of time intragastric pH was >4 over the 24 hour dosing interval was 57% when administered after food compared to 64% in the fasting group. Similarly, when administered 5 or 30 minutes before a meal, the percentage of time intragastric pH was >4 over the 24 hour dosing interval was 62% and 66%, respectively. The difference in PD parameters was driven largely by the periods 0-4 and 4-9 hours post-dose. Regimen B does not demonstrate a significant change in pH for 4 hours after dosing. This correlates with the delayed absorption and decreased bioavailability of the Type 1 granules designed to release drug upon entry into the duodenum. The four feeding regimens have less variation 9 or more hours after dosing. This time period corresponds to the time following the administration of dinner to all subjects.

Percentage of time that intragastric pH exceeded 4 during the 24-hour dosing interval following administration of 90mg dexlansoprazole or placebo.

Analysis	Result for Each Dosing Regimen				p-value <sup>a</sup> for Pairwise Comparisons		
	A	B	C	D	Regimen B versus Regimen A <sup>b</sup>	Regimen C versus Regimen A <sup>b</sup>	Regimen D versus Regimen A <sup>b</sup>
Day 1 (Placebo)	17	18	16	19	0.897	0.548	0.547
Day 3 (Dexlansoprazole MR)	64	57	62	66	0.003**	0.222	0.544
Change from Baseline (Day 3 minus Day 1)	47	39	46	47	0.018*	0.642	0.993

Note: Regimen A = dosed under fasting conditions, Regimen B = dosed 30 minutes after the start of a high-fat breakfast, Regimen C = dosed 5 minutes before a high-fat breakfast, and Regimen D = dosed 30 minutes before a high-fat breakfast.

a The p-values are from an ANOVA with effects for regimen, sequence, period, and subject nested within sequence.

b Regimen A was defined as the reference regimen.

\*, \*\*, \*\*\* indicate  $p \leq 0.05$ , 0.01, or 0.001, respectively.

For the mean intragastric pH and change from baseline over the 24-hour dosing interval, the only statistically significant differences were between Regimens B and A; however, these differences were not greater than 8%. Overall, the pharmacodynamic results suggest there are no clinically relevant differences between the various regimens.

Summary of the effect of food on the pharmacokinetic parameter estimates for dexlansoprazole following a single oral dose 90mg dose of dexlansoprazole.

Regimen	Measure	$t_{1/2}$ (h)	$t_{max}$ (h)	$C_{max}$ (ng/mL)	$AUC_t$ (ng·h/mL)	$AUC_{\infty}$ (ng·h/mL)	$V_z/F$ (L)	$CL/F$ (L/h)	$t_{1/2}^a$ (h)
A	N	46	46	46	46	37	37	37	37
	Mean	0.87	5.38	1485.63	6996.26	7057.65	39.59	16.65	1.82 (1.49)
	SD	0.61	1.94	808.09	3738.70	3749.13	28.33	8.54	1.09
	%CV	70	36	54	53	53	72	51	60
B	N	46	46	46	46	37	37	37	37
	Mean	1.91	7.63	1824.96	7998.50	8157.18	27.81	13.44	1.54 (1.25)
	SD	0.87	1.84	658.85	3855.53	3992.02	18.72	5.65	0.76
	%CV	45	24	36	48	49	67	42	50
C	N	46	46	46	46	37	37	37	37
	Mean	0.49	5.94	1653.00	7974.69	8198.13	24.09	13.26	1.40 (1.20)
	SD	0.66	2.45	717.73	3751.38	3909.87	9.97	5.59	0.68
	%CV	136	41	43	47	48	41	42	49
D	N	46	46	46	46	37	37	37	37
	Mean	0.53	4.73	1597.09	7447.75	7970.43	33.77	14.17	1.71 (1.39)
	SD	0.49	2.84	760.88	3843.37	4014.52	32.31	6.98	1.05
	%CV	92	60	48	52	50	96	49	61

Note: Regimen A = dosed under fasting conditions, Regimen B = dosed 30 minutes after the start of a high-fat breakfast, Regimen C = dosed 5 minutes before a high-fat breakfast, and Regimen D = dosed 30 minutes before a high-fat breakfast.

a Arithmetic mean (harmonic mean).

Bioavailability of dexlansoprazole following a single oral dose of dexlansoprazole under fed conditions relative to administration while fasting.

Pharmacokinetic Parameter	Point Estimate	90% Confidence Interval
<b>Regimen B (Test) versus Regimen A (Reference)</b>		
C <sub>max</sub>	1.3065	1.1735 - 1.4547
AUC <sub>t</sub>	1.1901	1.1249 - 1.2591
AUC <sub>∞</sub>	1.2050	1.1449 - 1.2683
<b>Regimen C (Test) versus Regimen A (Reference)</b>		
C <sub>max</sub>	1.1684	1.0494 - 1.3009
AUC <sub>t</sub>	1.1910	1.1257 - 1.2600
AUC <sub>∞</sub>	1.2096	1.1484 - 1.2740
<b>Regimen D (Test) versus Regimen A (Reference)</b>		
C <sub>max</sub>	1.1165	1.0026 - 1.2432
AUC <sub>t</sub>	1.0903	1.0305 - 1.1535
AUC <sub>∞</sub>	1.1483	1.0887 - 1.2112

Note: Regimen A = dosed under fasting conditions, Regimen B = dosed 30 minutes after the start of a high-fat breakfast, Regimen C = dosed 5 minutes before a high-fat breakfast, and Regimen D = dosed 30 minutes before a high-fat breakfast.

Note: The point estimates and confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm-transformed data.

Sponsor's comments: Although an increase in dexlansoprazole plasma concentrations were observed when administered under various fed conditions relative to fasting, no relevant differences between the regimens with regard to intragastric pH were observed. The sponsor suggests that dexlansoprazole can be administered without regard to food or the timing of food.

Reviewer's comments: The difference in intragastric pH over the 24-hour dosing interval when dexlansoprazole is administered after a high-fat meal relative to fasting is ≤ 8%. This difference is driven by the nine-hour period after dosing. Dosing 30 minutes after a high-fat meal was least effective in increasing intragastric pH during this time period. Following the first 9 hours; however, all regimens appear to have a similar effect upon intragastric pH.

#### 2.2.14 What is the bioavailability of the granules relative to the intact capsule?

In order to compare the exposure of granules sprinkled over applesauce to that of the intact capsule, the sponsor conducted a randomized, 2-treatment, 2-period, 2-sequence, crossover, single-dose, bioavailability/bioequivalence study. Sixty healthy males and females, aged 19-49, participated in the study. Fifty-one subjects completed the study.

Summary of dexlansoprazole pharmacokinetic parameter estimates following administration of a single 90mg dose of dexlansoprazole capsules and granules.

Regimen	Measure	t <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	AUC <sub>t</sub> (ng·h/mL)	AUC <sub>∞</sub> (ng·h/mL)	λ <sub>z</sub> (h <sup>-1</sup> )	t <sub>1/2z</sub> <sup>a</sup> (h)	CL/F (L/h)	V <sub>z</sub> /F (L)
A	N	50	50	50	49	49	49	49	49
	Mean	4.71	1840.76	10127.04	10416.48	0.43	2.08 (1.62)	12.92	32.16
	%CV	48	54	68	71	48	57	62	48
B	N	50	50	50	49	49	49	49	49
	Mean	4.73	1966.78	10736.08	11093.38	0.43	2.14 (1.63)	12.14	31.20
	%CV	44	56	72	75	47	60	62	58

Note: Regimen A = Granules from a single capsule of 90 mg of dexlansoprazole MR administered orally sprinkled over 1 tablespoon of applesauce. Regimen B = A single, intact capsule of 90 mg of dexlansoprazole MR administered orally.

a Arithmetic mean (harmonic mean).

Summary of point estimates and confidence intervals of the C<sub>max</sub> and AUC administered as granules relative to intact capsules.

Pharmacokinetic Parameter	Point Estimate	90% Confidence Interval
	Regimen A versus Regimen B	
C <sub>max</sub>	0.94	(0.8695 - 1.0225)
AUC <sub>t</sub>	0.95	(0.8943 - 0.9998)
AUC <sub>∞</sub>	0.94	(0.8898 - 0.9951)

Note: Regimen A = Granules from a single capsule of 90 mg of dexlansoprazole MR administered orally sprinkled over 1 tablespoon of applesauce. Regimen B = A single, intact capsule of 90 mg of dexlansoprazole MR administered orally.

There is no difference in bioavailability between the granules administered with one tablespoon of applesauce and the intact capsule administered with water. The 90% confidence intervals for C<sub>max</sub> (86%-102%), AUC<sub>t</sub> (89%-99%), and AUC<sub>inf</sub> (88%-99%) were well within the range for bioequivalence. Other PK parameters including t<sub>max</sub>, CL/F, and V/F were also similar between the groups.

Sponsor's comments: This sponsor concluded that there was no difference in dexlansoprazole exposure when dexlansoprazole is administered as intact capsules or sprinkled over applesauce.

Reviewer's comments: Based on the results and the adequacy of the study design, I conclude that there is no difference in dexlansoprazole exposure when administered intact or as granules.

#### 2.2.15 What are the population pharmacokinetic characteristics of (b) (4)

The sponsor submitted a population pharmacokinetic analysis and concluded that the age and gender are not significant covariates to affect the exposure of dexlansoprazole. The results are not reviewed and will not be included for the product labeling based on the following reasons: 1) more serious adverse events are observed at higher dose, 2) the increases in exposure in elderly or female subjects are substantial and concerning. It is unknown when dexlansoprazole is used by the public whether there will be a higher occurrence rate of adverse events in elderly or female patients due to their higher exposure, 3) CYP 2C19 contributes to a large extent the high variability in the pharmacokinetics of dexlansoprazole, but the association between CYP2C19 genotype and occurrence of adverse events is not clear.

### 2.3 Intrinsic Factors

CYP2C19 genotype/phenotype, 3A4 phenotype, age, gender, hepatic functions may affect the exposure of dexlansoprazole MR and consequently its efficacy and treatment-related adverse events. Notably, the data accumulated so far show that CYP2C19 genotype and hepatic function are two significant biomarkers for the systemic exposure of dexlansoprazole MR. There are still unknown genetic characteristics of CYP2C19 concerning the observations of some heterozygous genotype subjects exhibiting PM phenotype.

## 2.4 General Biopharmaceutics

### 2.4.1 Is the to-be-marketed formulation identical to the one used for the phase 3 efficacy trial?

Yes. The to-be-market formulation and clinical formulation are the same dexlansoprazole MR capsules.

### 2.4.2 What is the delivery system designed for (b) (4)

Dexlansoprazole modified release (MR) capsules (dexlansoprazole MR capsules) contain two different types of enteric coated granules: (1) granules (b) (4) release soon after entering the small intestine upon dissolution of the enteric coating at approximately pH  $\geq 5.5$  which provide 25% of the dexlansoprazole dose, and (2) granules (b) releases farther along the GI tract upon dissolution of the enteric coating at approximately pH  $\geq 6.75$  which provide 75% of the dexlansoprazole dose.

(b) (4)



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**2.4.3 What is the to-be-marketed formulation?**

Quantitative Composition of Dexlansoprazole-(b) (4) Granules(b) (dexlansoprazole MR Granules(b) ) for 30 mg Capsules and Dexlansoprazole-(b) (4) Granules(b) (dexlansoprazole MR Granules(b) ) for 60 mg (b) (4) Capsule

Component	Quantity per Capsule (mg)		(b) (4)
	30 mg	60 mg	
(b) (4)	(b) (4)		
Sugar Spheres (500µm to 710µm)			
Magnesium Carbonate			
Sucrose			
Low-Substituted Hydroxypropyl Cellulose			
Hydroxypropyl Cellulose			
(b) (4)			
(b) (4)			
Hypromellose 2910			
Talc			
Titanium Dioxide			
(b) (4)			
(b) (4)			
Titanium Dioxide			
Talc			
Methacrylic Acid Copolymer(b) (4)			
Polyethylene Glycol 8000			
Polysorbate 80			
(b) (4)			
(b) (4)			
Colloidal Silicon Dioxide			
Talc			
<b>SUB TOTAL</b>	<b>80</b>	<b>58</b>	<b>87</b>
(b) (4)			

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Quantitative Composition of Dexamisoprazole (b) (4) Granules (b) (dexamisoprazole MR Granules (b) ) for 30 mg, 60 mg (b) (4)

Component	Quantity per capsule (mg)		
	30 mg	60 mg	(b) (4)
<b>CORE GRANULES</b>	(b) (4)		
TAK-390			
Sugar Spheres (500 µm to 710 µm)			
Magnesium Carbonate			
Sucrose			
Low-Substituted Hydroxypropyl Cellulose			
Hydroxypropyl Cellulose			
(b) (4)			
<b>MIDDLE LAYER (PROTECTIVE LAYER)</b>			
Hypromellose 2910			
Talc			
Titanium Dioxide			
(b) (4)			
<b>ENTERIC LAYER-H</b>			
Talc			
Methacrylic Acid Copolymer (b)			
Methacrylic Acid Copolymer (b)			
Triethyl Citrate			
(b) (4)			
(b) (4)			
<b>LUBRICATION</b>			
Talc			
Colloidal Silicon Dioxide			
<b>SUB TOTAL</b>	105	210	315
(b) (4)			

## 2.5 Analytical Section

### 2.5.1 What analytical methods were used to assess dexlansoprazole and its metabolites and were the analytical assay methods adequately validated?

Quantitation of plasma, urine, fecal samples: Previous clinical studies demonstrated no bioinversion from dexlansoprazole (the R-(+)-enantiomer) to the S-(-)-enantiomer of lansoprazole. Plasma, urine, and fecal concentrations of dexlansoprazole, 5-hydroxy dexlansoprazole, dexlansoprazole sulfone, and other metabolites were determined using a validated liquid chromatography assay with mass spectrometric detection. Briefly, plasma samples were spiked with the deuterated internal standards dexlansoprazole-d4, 5-hydroxy dexlansoprazole-d4, and dexlansoprazole sulfone-d4, and extracted using a liquid-liquid extraction procedure. The extracted samples were analyzed by LC-MS/MS using positive ion monitoring in multiple reaction monitoring (MRM) mode. Radioactivity

was determined using (b) (4) scintillation fluid by counting for at least 5 minutes or 100000 dpm.

Validation of analytical assays for individual studies

Study	Analytes	r for Standard curves	Mean Deviation for back-calculated standard concentrations	Mean Deviation for QC standard concentrations	Dilution variation
Mass Balance study T-P105-141	dexlansoprazole	10.0 to 2000 ng/mL ≥0.9966	AD: -5.5% to 4.0%	AD: -4.0% to 3.0% CV: ≤10.1%	CV: ≤1.7% AD: -1.3%
	5-hydroxy dexlansoprazole	1.00 to 200 ng/mL ≥0.9956	AD: -5.0% to 4.0%	AD: -5.0% to -2.0% CV: ≤10.1%	NA
	dexlansoprazole sulfone	2.00 to 400 ng/mL ≥0.9973	AD: -5.3% to 4.4%	AD: 0.3% to 2.0% CV: ≤10.1%	NA
DDI t-p-105-139	dexlansoprazole	5 to 1200 ng/mL. ≥0.9952	AD: 0.6% to 10.8% CV: 0.6% to 5.2%.	CV: ≤3.1% AD: ≤6.1%,	NA
	theophylline	200 to 50000 ng/mL. ≥0.9983	AD: 0.00% to 1.66% CV: 1.55% to 4.16%.	300, 750, and 25000 ng/mL CV: ≤8.00% and AD%: ≤6.17%,	NA
DDI t-p-105-134	dexlansoprazole	5.00 to 1200 ng/mL. ≥0.9961	AD: 8.3% to 5.0%.	CV: ≤5.1% AD: -3.7% to 2.0%,	NA
	diazepam	1- 500 ng/mL ≥0.9948	AD: -12.0% - 4.8% CV: 2.1% to 4.6%.	CV: ≤6.0% AD: ≤6.7%,	NA
	nordiazepam	1- 500 ng/mL ≥0.9951	AD: -11.0%-4.5% CV: 2.1% - 5.9%	CV: ≤4.9% AD: ≤5.3%,	NA

		r for Standard	Mean Deviation for	Mean Deviation for	Dilution variation
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		curves	back-calculated standard concentrations	QC standard concentrations	
T-P105-129 Dexlansoprazole Population kinetics		5.00 to 1200 ng/mL ≤ 0.9949	AD: 0.0-8.3% CV%:2.2- 4.7%	15.0-2400 ng/mL; CV: ≤20.9%, AD: ≤ 3.9	CV: 3.2 AD: -0.2%- 0.8%
T-GI04-088 Population kinetics		5.00 to 1200 ng/mL ≥ 0.9980	AD: 0.3-3% CV%:1.1- 3.8%	15.0-2400 ng/mL; CV: ≤35.2%, AD: ≤ 10.7%	CV% ≤49.3% AD: - 12.9%- 0.8%

		r for Standard curves	Mean Deviation for back-calculated standard concentrations	Mean Deviation for QC standard concentrations	Dilution variation
T-P105-115 hepatic	dexlansoprazole	0 to 2000 ng/mL, ≥0.9995	AD:-1.5% to 1.3%	CV:≤3.8% AD: 5.7% to 9.0%	CV:≤0.7% AD: 5.3%
	5-hydroxy dexlansoprazole	1.0 to 200 ng/mL, ≥0.9987	AD:-2.5% to 3.0%	CV:≤3.8% AD: 1.3% to 5.3%	CV:≤0.7% AD: -0.7% %
	dexlansoprazole sulfone	2.0 to 400 ng/mL ≥0.9992	AD:-1.3% to 1.8%	CV:≤3.8% AD: 5.7% to 9.0%	CV:≤0.7% AD: 1.0%
T-P104-069 (feeding time and 90 mg)	60 mg, 120 mg QD for 5 days  dexlansoprazole	5.00 to 1200.00 ng/mL. ≥0.9933	AD: 0.0-1.1% and CV: 2.7- 4.8%.	15.00, 100.00, 900.00, 2400.00 ng/mL CV: ≤7.8% AD: ≤1.2%,	2400 ng/mL 1:5 and 1:10) CV: ≤8.8% AD: 12.1%.
T-p-104-071	60 mg, 90 mg, or 120 mg(5 days) PK and PD dexlansoprazole	5.00 to 1200.00 ng/mL ≥0.9909	AD: 0.0 to 1.6% CV: 3.1 to 5.5%.	15.0, 100, 900, and 2400 ng/mL. CV: ≤7.8% AD: ≤1.2%	2400 ng/mL 1:5 and 1:10  CV: ≤5.6% AD: ≤1.3%
T-P104-	90 mg and 120	5.00 to	AD: 0.0% to	100 ng/mL	900 ng/mL

100	mg, PK and gastrin (5 days)  dexlansoprazole	1200.00 ng/mL. ≥0.9924	1.0%  CV: 3.1% to 5.8%.	and 900 ng/mL  CV: ≤12.1% AD: ≤3.2%	1:2, 2400 ng/mL 1:5 and 1:10 CV: ≤14.7% AD: ≤3.9%
T-P105-119 60mg, age, gender**	dexlansoprazole	10.0 to 2000 ng/mL) ≥0.9991	3.1%	30.0, 300, and 1500 ng/mL AD: 6.0% CV:3.5%	*
	5-hydroxy dexlansoprazole	1.00 to 200 ng/mL), ≥0.9985	4.4%	6.00, 60.0, and 300 ng/mL AD: 11.3% CV: 4.4%	*
	dexlansoprazole sulfone	2.00 to 400 pg/mL). ≥0.9988	3.3%	3.00, 30.0, and 150 ng/mL AD: 4.0% CV:2.7%	*

AD(% bias): absolute deviation; \*: no report; \*\*: The organic supernatant was analyzed using a (b) (4) (b) (4) & plasma samples at (b) (4)

Study	Analytes	Range of Standard Curve (ng/mL)	Precision (%)	Accuracy (%)	Dilution Variation
T-P104-069	TAK-390	5.00-1200.00 $r^2 \geq 0.9933$	≤7.8	-1.2 to 0.7	CV: ≤8.8%
T-P106-146	TAK-390	5.00-1200.00 $r^2 \geq 0.9957$	≤ 4.7	-2.3 to 1.3	CV: ≤5.0%
T-P106-148	TAK-390	5.00-1200.00 $r^2 \geq 0.9982$	< 3.9	-0.8% to 1.3	CV: ≤16.2%
T-P105-133	TAK-390	5.00-1200.00 $r^2 \geq 0.9974$	≤3.1	-2.3% to 3.0	CV: ≤6.0%
T-P105-132	TAK-390	5.00-1200.00 $r^2 \geq 0.9972$	< 3.2	-2.8% to 3.3	CV: 5.6%

### Analysis of gastrin

Plasma concentrations of gastrin were determined using a validated sensitive and specific DPC Immulite 2000 procedure. The standard curves was established with 5 concentrations of gastrin ranging from 31.0 to 1151.0 pg/mL. The LLOQ with a 0.35-mL plasma sample was 31.00 pg/mL. The back-calculated values for the calibration standards of gastrin resulted in mean absolute deviations from theoretical concentrations of 1.2% to 10.9% and coefficients of variation of 4.1% to 38.6%. The coefficients of variation at standard concentrations of 325.0 pg/mL and 767.0 pg/mL were 38.6% and

19.4%, respectively, due to an anomalous value for each concentration in one analytical batch (GAS\_005). The other standard samples had acceptable coefficients of variation of 4.1% to 6.9%. Plasma QC samples analyzed with each analytical run had coefficients of variation and absolute deviations from nominal concentrations of  $\leq 4.6\%$  and  $\leq 2.8\%$ , respectively.

Genotyping: CYP2C19 genotyping using ABI TaqMan (Applied Biosystems, Foster City, California). TaqMan is routinely used in genotyping. The PCR method used is acceptable.

**Conclusion:** All the analytical assay methods are acceptable and adequately validated for lansoprazole, its metabolites, and gastrin.

**Bioanalytical sites**

Per reviewer's request on May 1, 2008, the sponsor confirmed the May 5, 2008 correspondence that "No pharmacokinetic assays for any of the studies submitted in this NDA were performed at (b) (4) ," and provided a comprehensive list of the clinical studies performed by TAP, bioanalytical sites, and associated validation reports, as attached below.

Study	Title	Analyte/Matrix	Bioanalytical Site	Validation Report(s)
M01-309	Comparative Pharmacokinetics and Pharmacodynamics of TAK-390 (20 and 30 mg), T-368391 (30 mg), and Lansoprazole (30 mg) in Healthy Subjects	Dexlansoprazole/Plasma, S-lansoprazole/Plasma	(b) (4) (b) (4) (b)	
C02-004	Pharmacokinetics and Pharmacodynamics of TAK-390 (60 and 90 mg), Esomeprazole (40 mg), and Lansoprazole (30 mg) in Healthy Subjects	Dexlansoprazole/Plasma, Lansoprazole/Plasma	(b) (4) (b)	(b) (4)
T-P104-069	A Phase I, Randomized, Open-Label, Single-Dose, Four-Period Crossover Study Comparing the Pharmacokinetics of a 90 mg Modified-Release TAK-390 Formulation Administered Orally Under Fed and Fasting Conditions in Healthy Subjects	Dexlansoprazole/Plasma	(b) (4) (b)	(b)
T-P104-071	A Phase I, Randomized, Open-Label, Four-Period Crossover, Multiple-Dose Single-Center Study to Evaluate the pharmacokinetics, Pharmacodynamics and Safety Following Administration of 60 mg, 90 mg and 120 mg Oral Doses of a Modified Release Formulation of TAK-390 and 30 mg Oral Doses of Lansoprazole in Healthy Subjects	Dexlansoprazole/Plasma, Lansoprazole/Plasma	(b) (4)	
T-P104-092	A Phase I, Randomized, Double-Blind, Four-Period Crossover Study to Assess the Effects on the Cardiac QT Interval of a Single Dose of TAK-390MR (90 mg and 300 mg) with a Placebo Control and Avelox <sup>®</sup> 400 mg as an Active Control in Healthy Subjects	Dexlansoprazole/Plasma  Moxifloxacin/Plasma		
T-P104-100	A Phase I, Randomized, Open-Label, Crossover, Single-Center Study to Measure Plasma Gastrin Levels Following Administration of 90-mg and 120-mg Oral Doses of a Modified-Release Formulation of TAK-390 and a 30-mg Oral Dose of Lansoprazole in Healthy Subjects	Plasma, Dexlansoprazole/Plasma, Lansoprazole/Plasma		
T-P105-115	A Phase I, Open-Label, Parallel Study to Evaluate the Pharmacokinetics and Safety of a Single Oral Dose of Dexlansoprazole MR (60 mg) in Subjects With Normal or Moderately Impaired Hepatic Function	Dexlansoprazole/Plasma, S-Hydroxy dexlansoprazole/Plasma, Dexlansoprazole sulfone/Plasma		

Study	Title	Analyte/Matrix	Bioanalytical Site	Validation Report(s)
T-P105-119	A Phase 1, Open-Label, Parallel Study to Evaluate the Effect of Gender and Age on the Pharmacokinetics and Safety of a Single Oral Dose of Dexlansoprazole MR 60 mg	Dexlansoprazole/Plasma, 5-Hydroxy dexlansoprazole/Plasma, Dexlansoprazole sulfone/Plasma	(b) (4)	
T-P105-122	A Phase 1, Single-Center, Randomized, Open-Label, Three-Period Crossover, Multiple-Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety Following Administration of Oral Doses of TAK-390MR (30 mg and 60 mg) and Lansoprazole 15 mg in Healthy Subjects	Dexlansoprazole/Plasma, Lansoprazole/Plasma		
T-P105-129	A Phase 1, Single-Center, Randomized, Open-Label, Parallel-Group, Multiple-Dose Study to Evaluate the Pharmacokinetics and Safety of Dexlansoprazole MR (30 mg, 60 mg, and 90 mg) in Subjects with Symptomatic, Nonerosive Gastroesophageal Reflux Disease (GERD)	Dexlansoprazole/Plasma		
T-P105-132	A Phase 1 Two-Way Crossover Study to Assess the Effect of Multiple Oral Doses of Dexlansoprazole MR on the Single Oral Dose Pharmacokinetics and Pharmacodynamics of Warfarin	Dexlansoprazole/Plasma (R)- and (S)-Warfarin/Plasma		
T-P105-133	A Phase 1, Double-Blind, Placebo-Controlled, Two-way Crossover Study to Assess the Effect of Multiple Oral Doses of 90 mg Dexlansoprazole MR on the Pharmacokinetics of Phenytoin Following a Single Oral Dose of 250 mg Phenytoin	Dexlansoprazole/Plasma  Phenytoin/Plasma		
T-P105-134	A Phase 1, Double-Blind, Placebo-Controlled, Two-Way Crossover Study to Assess the Effect of Multiple Oral Doses of Dexlansoprazole MR on Diazepam Pharmacokinetics Following a Single Oral Dose of Diazepam	Dexlansoprazole/Plasma  Diazepam/Plasma, Desmethyl Diazepam/Plasma		

Study	Title	Analyte/Matrix	Bioanalytical Site	Validation Report(s)
T-P105-139	A Phase 1, Double-Blind, Placebo-Controlled, Two-way Crossover Study to Assess the Effect of Multiple Oral Doses of Dexlansoprazole MR on the Pharmacokinetics of Theophylline Following a Single Intravenous Dose of Aminophylline	Dexlansoprazole/Plasma  Theophylline/Plasma	(b) (4)	
T-P105-141	A Phase 1, Open-Label Study to Assess the Absorption, Distribution, Metabolism and Excretion of Orally Administered [ <sup>14</sup> C]Dexlansoprazole in Healthy Subjects	Dexlansoprazole/Plasma, 5-Hydroxy dexlansoprazole/Plasma, Dexlansoprazole sulfone/Plasma		
T-P105-146	A Phase 1, Open-Label, Single-Dose, Four-Way Crossover Study to Assess the Effect of the Timing of Food on the Pharmacokinetics and Intra-gastric pH of Dexlansoprazole Following a Single Oral Dose of 90-mg Dexlansoprazole MR	Dexlansoprazole/Plasma		
T-P105-148	A Phase 1, Open-Label, Two-Way Crossover Study to Assess the Bioavailability of Dexlansoprazole MR 90 mg When the Capsule Contents Are Administered Sprinkled Over Applesauce Relative to a Single Oral Dose of Dexlansoprazole MR 90 mg Intact Capsule Administered Orally	Dexlansoprazole/Plasma		
T-P105-149	A Phase 1, Open Label, Three-Way Crossover Study to Compare the Bioavailability, Pharmacokinetics, and Safety of Dexlansoprazole After Single Oral Doses of Three Dexlansoprazole MR 90 mg Capsule Formulations	Dexlansoprazole/Plasma		

### 3 Detailed Labeling Recommendations

#### Section 12.3

In the first paragraph of section 12.3,

The statement of "Dexlansoprazole is eliminated with a half-life of approximately 1 to 2 hours in healthy subjects and in patients with symptomatic GERD." should be changed to "Dexlansoprazole is eliminated with a half-life of approximately 1 to 3 hours in patients with symptomatic GERD..

(b) (4)

(b) (4)

(b) (4)

Distribution: The statement of "Plasma protein binding of dexlansoprazole ranged from 96.1% to 98.8% in healthy subjects and was independent of concentration from 0.01 to 20 mcg per mL." should be revised to (b) (4)

The statement of The apparent volume of distribution ( $V_z/F$ ) after multiple doses in symptomatic GERD patients was 40.3 L." should be changed to (b) (4)

(b) (4)

(b) (4)

#### Section 12.5

The statement of "Population pharmacokinetic analyses indicate that the pharmacokinetics of dexlansoprazole in patients with symptomatic GERD are similar to those in healthy subjects, and are not affected by age, gender, race or body mass index." should be deleted.

The statement of "No adjustment for (b) (4) is necessary for patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with (b) (4)

(b) (4) (b) in patients with severe hepatic impairment (Child-Pugh Class C). A (b) (4)

*Geriatric Use:*

The statement of "Although the terminal elimination half-life of dexlansoprazole is increased in geriatric subjects compared to younger subjects (2.23 and 1.5 hours, respectively), this difference is not clinically relevant." should be revised to "Although the terminal elimination half-life of dexlansoprazole is statistically significantly longer in geriatric subjects compared to younger subjects (2.23 and 1.5 hours, respectively), this difference is not clinically relevant."

A statement of "Dexlansoprazole exhibited higher systemic exposure (AUC) in the elderly (b) (4) ) than in the young. (b) (4)

Gender: A statement of "Dexlansoprazole exhibited higher systemic exposure (AUC) in female subjects (b) (4) ) than in male subjects. (b) (4)

## 12.6 Drug-Drug Interactions

The statement "Furthermore, clinical drug-drug interaction studies have shown that (b) (4) does not affect the pharmacokinetics of diazepam, phenytoin, or theophylline." should be changed to (b) (4)

The following statements regarding warfarin are found in sections 7.2, and section 12.6, respectively: "Co-administration of (b) (4) 90 mg and warfarin 25 mg did not affect the pharmacokinetics of warfarin or INR (see Clinical Pharmacology (12.6). However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time." And "In a study of 20 healthy subjects, co-administration of (b) (4) 90 mg once daily for 11 days with a single 25 mg oral dose of warfarin on day 6 did not result in any significant differences in the pharmacokinetics of warfarin or INR compared to administration of warfarin with placebo. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly (see Drug Interactions (7.2))." **The first statement is nearly identical to the statement in the lansoprazole label and the second statement is an accurate description of the warfarin study. Therefore, these statements are adequate to describe the possible risks of warfarin despite the negative results of the drug-drug interaction study.**

## 4 Appendices

### 4.1 Proposed labeling

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### 4.2 Individual Study Reviews

Please see appendix 4.2.1

### 4.3 OCP Filing/Review Form

Please see appendix 4.2.2

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Appendix 4.2.1 Individual Study Review

Study T-P104-071 Pharmacokinetics and pharmacodynamics

<b>Name of Company:</b> TAP Pharmaceutical Products Inc. <b>Name of Finished Product:</b> TAK-390MR <b>Name of Active Ingredient:</b> R-(+)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole					
<b>Title of Study:</b> A Phase 1, Randomized, Open-Label, Four-Period Crossover, Multiple-Dose Single-Center Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety Following Administration of 60 mg, 90 mg and 120 mg Oral Doses of a Modified Release Formulation of TAK-390 and 30 mg Oral Doses of Lansoprazole in Healthy Subjects					
<b>Investigator:</b> (b) (4)					
<b>Study Center:</b> (b) (4)					
<b>Publication (reference):</b> None					
<b>Study Period:</b> Date of First Dose: 27 July 2004 Date of Last Procedure: 04 October 2004			<b>Phase of Development:</b> 1		
<b>Objective(s):</b> The objectives of this study were to evaluate the pharmacokinetics and pharmacodynamics of TAK-390 and lansoprazole following a single dose (Day 1) and multiple doses (Day 5) of 60 mg, 90 mg, or 120 mg of TAK-390MR formulation and 30 mg of lansoprazole capsules and to evaluate the safety of 60 mg, 90 mg, or 120 mg of TAK-390MR formulation following once daily oral administration for 5 consecutive days.					
<b>Methodology:</b> This was a Phase 1, randomized, open-label, multiple-dose, single-center, 4-period crossover study. The study was designed to assess the safety, pharmacokinetics, and pharmacodynamics of 3 different doses of TAK-390MR, compared to those of 30 mg of lansoprazole, each administered orally once daily (QD) for 5 consecutive days to healthy subjects. Subjects were randomly assigned to the sequence in which they received each of the 4 different regimens identified below.					
Regimen A: 60 mg of TAK-390MR administered QD for 5 consecutive days with 240 mL of water. Regimen B: 90 mg of TAK-390MR administered QD for 5 consecutive days with 240 mL of water. Regimen C: 120 mg of TAK-390MR administered QD for 5 consecutive days with 240 mL of water. Regimen D: 30 mg of lansoprazole administered QD for 5 consecutive days with 240 mL of water.					
At study completion, each subject had received all 4 regimens as shown:					
<b>Regimen Sequences</b>					
<b>Sequence</b>	<b>Number of Subjects</b>	<b>Period 1</b>	<b>Period 2</b>	<b>Period 3</b>	<b>Period 4</b>
1	10	Regimen A	Regimen D	Regimen B	Regimen C
2	10	Regimen B	Regimen A	Regimen C	Regimen D
3	10	Regimen C	Regimen B	Regimen D	Regimen A
4	10	Regimen D	Regimen C	Regimen A	Regimen B
On Day -1 of each period, subjects were confined to the testing unit, and they remained confined until all study procedures were completed on Day 6 of each period. During each period, dosing began at approximately 0900 hours on Days 1 through 5. A washout interval of at least 5 days separated the last dose of one period from the first dose of the consecutive period. At study completion, a subject had received five 60-mg, five 90-mg, and five 120-mg doses of TAK-390MR and five 30-mg doses of lansoprazole. Safety was monitored through adverse event reports, concomitant medication usage, 12-lead electrocardiograms (ECGs), physical examinations, vital sign assessments, and laboratory evaluations. The pharmacokinetic and pharmacodynamic profiles of TAK-390 administered as the modified-release formulation and of lansoprazole were assessed during the study through blood sampling for pharmacokinetic analysis and intragastric pH monitoring for pharmacodynamic analysis. Plasma					

concentrations of TAK-390 and lansoprazole were determined using validated LC/MS/MS assay methods, and pharmacokinetic parameters for TAK-390 and lansoprazole in plasma were estimated using standard noncompartmental methods.				
Number of Patients (planned and analyzed): 40 planned; 40 analyzed				
Diagnosis and Main Criteria for Inclusion: Male and female subjects between 18 and 55 years of age, inclusive, in general good health.				
Test Product, Dose and Mode of Administration, Batch Number:				
<b>Test Product</b>	<b>Dose</b>	<b>Mode of Administration</b>	<b>Lot Number</b>	<b>Manufacturer</b>
TAK-390MR Capsules	60 mg	Oral	Z540G012	Takeda Pharmaceutical Company Limited
TAK-390MR Capsules	90 mg	Oral	Z540D023	Takeda Pharmaceutical Company Limited
TAK-390MR Capsules	120 mg (as two 60-mg capsules)	Oral	Z540G012	Takeda Pharmaceutical Company Limited
Duration of Treatment: During the 4 crossover periods, each subject was to receive single, daily doses 60 mg, 90 mg, and 120 mg of TAK-390MR for 5 consecutive days and 30 mg of lansoprazole once daily for 5 consecutive days. The crossover periods were separated by washout intervals of at least 5 days.				
Reference Therapy, Dose and Mode of Administration, Batch number:				
<b>Reference Product</b>	<b>Dose</b>	<b>Mode of Administration</b>	<b>Lot Number</b>	<b>Manufacturer</b>
Lansoprazole Capsules	30 mg	Oral	016782E22	Takeda Pharmaceutical Company Limited
<p><b>Criteria for Evaluation:</b></p> <p><b>Efficacy:</b> Efficacy was not assessed in this study.</p> <p><b>Pharmacokinetics:</b> Plasma concentrations of TAK-390 or lansoprazole were determined at MDS Pharma Services (US) Inc. (Lincoln, NE) using validated LC/MS/MS assay methods. The lower limit of quantitation was 5 ng/mL. Pharmacokinetic parameters for TAK-390 or lansoprazole in plasma were estimated using standard noncompartmental methods. The pharmacokinetic parameters included the observed maximum plasma concentration (<math>C_{max}</math>); the time to reach the observed maximum concentration (<math>t_{max}</math>); the apparent terminal elimination rate constant (<math>\lambda_z</math>); the half-life of the apparent terminal elimination phase (<math>t_{1/2z}</math>); and the area under the plasma concentration-time curve (AUC) from time zero to the last measurable concentration (AUC<sub>t</sub>), to 24 hours (AUC<sub>24</sub>), and to infinity (AUC<sub>∞</sub>).</p> <p><b>Pharmacodynamics:</b> Pharmacological responses were measured for each of the regimens on Days 1 and 5 of each period with 24-hour intragastric pH recording. The intragastric pH was evaluated using the average pH over the entire 24-hour postdose interval, as well as the following intervals of time relative to dosing: 0-4 hours, &gt;4-9 hours, &gt;9-12 hours, &gt;12-16 hours, and &gt;16-24 hours. For these intervals, the percent of time that the intragastric pH was &gt;3, &gt;4, &gt;5, or &gt;6 was also determined. Plasma gastrin concentrations were assessed at specified timepoints on Days 1 and 5 of each period.</p> <p><b>Safety:</b> Safety was monitored by assessing adverse events, concomitant medication usage, clinical laboratory variables, physical examinations, ECGs, and vital signs.</p>				

**Statistical Methods:****Efficacy:**

Efficacy was not assessed in this study.

**Pharmacokinetics:**

For each regimen, TAK-390MR or lansoprazole plasma concentration data and pharmacokinetic parameter estimates were tabulated and descriptive statistics computed. The assessment of dose proportionality for Regimens A, B, and C was performed via 90% confidence intervals for the central values obtained within the framework of the ANOVA from natural logarithm of dose-normalized  $C_{120\text{min}}$ ,  $AUC_{0-4}$ , and  $AUC_{0-24}$ . The assessment of dose proportionality was performed on both Days 1 and 5, separately. The ANOVA model utilized in this study contained the following factors: sequence, subjects nested within sequence, period, and regimen. The factor of subjects nested within sequence was considered random, and all others were fixed. Pairwise comparisons between Days 1 and 5 were performed for each of Regimens A, B, and C, separately.

**Pharmacodynamics:**

Descriptive statistics for each of the pharmacodynamic parameters were tabulated. For each of Days 1 and 5, the effect of the 4 dose regimens were compared with an ANOVA model that included effects for sequence, subject nested within sequence, period and regimen. The analysis was carried out on average pH (based on 15-minute medians) during each of the 24-hour postdose intervals and over each of the following intervals of time relative to dosing: 0-4 hours, >4-9 hours, >9-12 hours, >12-16 hours, and >16-24 hours. The percent of time that intragastric pH exceeded 3, 4, 5, or 6 was also analyzed. Within the ANOVA framework, pairwise comparisons of the regimens were performed. Plasma gastrin concentrations at specified timepoints on Days 1 and 5 of each period were summarized.

**Safety:**

All subjects who received at least 1 dose of study drug were included in the analyses of safety. Treatment-emergent adverse events were summarized for each regimen and overall. Baseline and after-dose values and mean change from baseline to postdose were summarized by regimen for clinical laboratory variables and for vital signs. Subjects with laboratory or vital sign results that met the predefined criteria for potentially concerning values were identified.

**Summary-Conclusions:****Efficacy Results:**

Efficacy was not assessed in this study.

**Pharmacokinetic Results:**

Noncompartmental pharmacokinetic parameter estimates for TAK-390 or lansoprazole following oral administration of 60-mg, 90-mg, or 120-mg doses of TAK-390MR or a 30-mg dose of lansoprazole once daily on Days 1 and 5 are summarized in the following table:

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Plasma Pharmacokinetic Parameter Estimates for TAK-390 or Lansoprazole on Days 1 and 5 Following Oral Administration of 60 mg, 90 mg, or 120 mg of TAK-390MR or 30 mg of Lansoprazole								
Regimen	Day	Measure	$t_{max}$ (h)	$C_{max}$ (ng/mL)	$AUC_t$ (ng·h/mL)	$AUC_{\infty}$ or $24^a$ (ng·h/mL)	$AUC/Dose^{a,b}$	$t_{1/2}^c$ (h)
A (60 mg of TAK-390MR)	1	N	34	34	34	30	109	30
		Mean	5.03	1290.18	5995.01	6533.50		1.49
		CV%	44	57	74	77		77
	5	N	34	34	34	30	112	30
		Mean	4.51	1433.65	6372.74	6720.34		1.39
		CV%	51	49	75	73		46
B (90 mg of TAK-390MR)	1	N	35	35	35	30	104	30
		Mean	5.01	1774.89	8564.47	9375.69		1.57
		CV%	51	54	74	72		61
	5	N	34	34	34	33	110	33
		Mean	4.93	2196.71	9751.12	9938.42		1.28
		CV%	38	42	69	68		51
C (120 mg of TAK-390MR)	1	N	32	32	32	28	97	28
		Mean	5.53	2427.81	12446.74	11677.40		1.36
		CV%	46	42	75	57		94
	5	N	30	30	30	29	113	29
		Mean	4.22	2516.60	13220.13	13574.32		1.44
		CV%	46	46	71	69		69
D (30 mg of lansoprazole)	1	N	31	31	31	27	73	27
		Mean	1.71	839.77	2040.85	2179.12		1.23
		CV%	29	40	82	82		52
	5	N	31	31	31	30	65	30
		Mean	1.54	844.65	1885.85	1949.17		1.11
		CV%	22	45	82	79		54

a  $AUC_{\infty}$  for Day 1,  $AUC_{24}$  for Day 5; b Dose normalized AUC (ng·h/mL/mg); c Harmonic Mean

The initiation of absorption of TAK-390 was rapid following oral administration of 60 mg, 90 mg, or 120 mg of TAK-390MR, with mean plasma concentrations of approximately 450-850 ng/mL reached within 1.5 hours. After that, mean plasma concentrations declined to approximately 400-600 ng/mL at about 3 hours postdose before rising again. Mean  $C_{max}$  ranged from about 1290 to 2430 ng/mL on Day 1 and from approximately 1430 to 2520 ng/mL on Day 5, while  $t_{max}$  ranged from 5.0 to 5.5 hours postdose on Day 1 and from 4.2 to 4.9 hours postdose on Day 5. Approximate dose proportionality was observed for mean  $C_{max}$  and AUC values following oral administration of 60 mg, 90 mg, and 120 mg of TAK-390MR. The plasma exposure of TAK-390 on Day 5 was generally similar to that observed on Day 1. As expected, administering the 120-mg dose of TAK-390MR as two 60-mg capsules did not appear to affect the dose proportionality of mean  $C_{max}$  or mean AUC of TAK-390. The dose-normalized AUC (AUC/Dose) was much smaller for lansoprazole compared to the TAK-390MR regimens, which is understandable considering TAK-390 is the more metabolically stable enantiomer of lansoprazole. In addition, the use of different formulations (ie, delayed-release capsules for lansoprazole versus modified-release capsules for TAK-390) may have affected the dose-normalized AUC results. The TAK-390/lansoprazole concentration versus time profiles on both Days 1 and 5 were very similar for the first 2 hours following oral administration of 90 mg or 120 mg of TAK-390MR and 30 mg of lansoprazole, indicating similar initial absorption for these 3 regimens. The pharmacokinetics of lansoprazole following oral administration of 30-mg lansoprazole delayed-release capsules QD for 1 or 5 days were consistent with historic data.

The slopes of terminal phases were similar for all 4 regimens, with terminal half-lives of 1.11 to 1.57 hours (harmonic mean). Variability associated with the pharmacokinetic parameters was similar for all 4 regimens, with CV% values ranging from 40% to 57% for  $C_{max}$  and 57% to 82% for AUC.

The assessment of dose proportionality for Regimens A, B, and C on Day 1 and Day 5 performed via 90% confidence intervals for the central values obtained within the framework of the ANOVA from natural logarithm of dose-normalized  $C_{max}$ , AUCs are summarized in the following table.

**Dose Proportionality for TAK-390MR Regimens Performed via 90% Confidence Intervals for the Natural Logarithm of Dose-normalized  $C_{max}$  and AUCs**

Day	Parameter	Point Estimate	90% Confidence Interval
Day 1	Regimen B versus Regimen A		
	$C_{max}/Dose$	0.8980	(0.7650-1.0542)
	$AUC_7/Dose$	0.9323	(0.8483-1.0245)
	$AUC_{24}/Dose$	0.9638	(0.8771-1.0591)
	Regimen C versus Regimen A		
	$C_{max}/Dose$	1.0093	(0.8544-1.1924)
	$AUC_7/Dose$	1.0480	(0.9501-1.1561)
	$AUC_{24}/Dose$	1.0354	(0.9395-1.1410)
	Regimen C versus Regimen B		
	$C_{max}/Dose$	1.1240	(0.9539-1.3243)
	$AUC_7/Dose$	1.1241	(1.0207-1.2381)
	$AUC_{24}/Dose$	1.0742	(0.9749-1.1836)
Day 5	Regimen B versus Regimen A		
	$C_{max}/Dose$	1.0664	(0.9650-1.1785)
	$AUC_7/Dose$	1.0463	(0.9769-1.1207)
	$AUC_{24}/Dose$	1.0255	(0.9536-1.1028)
	Regimen C versus Regimen A		
	$C_{max}/Dose$	0.9125	(0.8212-1.0141)
	$AUC_7/Dose$	1.0473	(0.9741-1.1260)
	$AUC_{24}/Dose$	1.0401	(0.9634-1.1229)
	Regimen C versus Regimen B		
	$C_{max}/Dose$	0.8557	(0.7707-0.9501)
	$AUC_7/Dose$	1.0010	(0.9315-1.0756)
	$AUC_{24}/Dose$	1.0142	(0.9422-1.0918)

Note: Regimen A = 60 mg of TAK-390MR, Regimen B = 90 mg of TAK-390MR, and Regimen C = 120 mg of TAK-390MR

The 90% confidence intervals for the ratio of the central values between any pair of Regimens A, B, and C demonstrated approximate dose-proportionality for doses between 60 mg and 120 mg of TAK-390MR QD for 1 or 5 days of dosing. On Day 1, the 90% confidence intervals for the ratio of the central values of  $AUC_7/Dose$  and  $AUC_{24}/Dose$  between any pair of Regimens A, B, and C were within the bioequivalence range of 0.80 to 1.25. The 90% confidence intervals for the ratio of the central values of  $C_{max}/Dose$  between Regimens C and A were within the bioequivalence range of 0.80 to 1.25, between Regimens B and A the lower bound of the 90% confidence interval was slightly below the lower bioequivalence limit of 0.80, and between Regimens C and B the upper bound of the 90% confidence interval was slightly above the upper bioequivalence limit of 1.25. These results were probably due to the slightly higher  $C_{max}/Dose$  level of Regimen B. On Day 5, most of the 90% confidence intervals for the ratio of the central values between any pair of Regimens A, B, and C were within the bioequivalence range of 0.80 to 1.25 for  $C_{max}/Dose$ ,  $AUC_7/Dose$ , and  $AUC_{24}/Dose$ . The lower bound of the 90% confidence interval for the ratio of the central values for  $C_{max}/Dose$  was slightly below the lower bioequivalence limit of 0.80 between Regimens C and B.

In addition, pairwise comparisons between Days 1 and 5 were performed for each of Regimens A, B, and C. For Regimen A, the 90% confidence intervals for the ratio of the central values for Day 5 relative to Day 1 were within the bioequivalence range of 0.80 to 1.25 for  $AUC_t$  and  $AUC_{\infty \text{ or } 24}$  but were slightly above the upper bioequivalence limit of 1.25 for  $C_{\text{max}}$ . For Regimen B, the 90% confidence intervals for the ratio of the central values for Day 5 relative to Day 1 were within the bioequivalence range of 0.80 to 1.25 for  $AUC_{\infty \text{ or } 24}$  but were above the upper bioequivalence limit of 1.25 for  $C_{\text{max}}$  and  $AUC_t$ . For Regimen C, the 90% confidence intervals for the ratio of the central values for Day 5 relative to Day 1 were within the bioequivalence range of 0.80 to 1.25 for  $C_{\text{max}}$ ,  $AUC_t$ , and  $AUC_{\infty \text{ or } 24}$ . These results indicate that the exposure of TAK-390 on Day 5 was generally similar to that observed on Day 1 following oral administration of TAK-390MR 60 to 120 mg QD.

#### Pharmacodynamic Results:

The mean intragastric pH values and the percentages of time that the intragastric pH values exceeded 4 for 0 to 24 hours, 0 to 4 hours, >4 to 9 hours, >9 to 12 hours, >12 to 16 hours, and >16 to 24 hours relative to the time of dosing on Days 1 and 5 were evaluated. The mean intragastric pH results are summarized for each regimen in the following table, as are the differences between Regimens A, B, and C and Regimen D.

Analysis of Mean Intragastric pH Results							
Day Interval	Mean <sup>a</sup> Intragastric pH for Each Dosing Regimen				Differences <sup>b</sup> (Significance) Between Dosing Regimens		
	A	B	C	D	A versus D	B versus D	C versus D
<b>Day 1</b>							
Total 24 hours	4.27	4.25	4.47	4.12	0.15	0.13	0.35*
0-4 hours	3.44	3.85	4.42	3.88	-0.44	-0.02	0.55
>4-9 hours	4.34	4.34	4.64	4.34	0.00	-0.00	0.30
>9-12 hours	4.99	5.06	4.99	4.69	0.30*	0.38**	0.31*
>12-16 hours	4.94	4.86	4.98	4.19	0.75***	0.67***	0.80***
>16-24 hours	4.98	4.71	5.32	4.45	0.53	0.26	0.87*
<b>Day 5</b>							
Total 24 hours	4.55	4.51	4.57	4.13	0.43***	0.39**	0.44***
0-4 hours	4.71	4.86	4.93	4.78	-0.07	0.08	0.15
>4-9 hours	4.88	4.79	4.87	4.31	0.57***	0.49***	0.57***
>9-12 hours	5.26	5.04	5.24	4.60	0.66***	0.44**	0.63***
>12-16 hours	4.37	4.48	4.66	3.57	0.79***	0.90***	1.09***
>16-24 hours	4.79	4.06	4.79	3.85	0.94	0.22	0.94

Note: Regimen A = 60 mg of TAK-390MR, Regimen B = 90 mg of TAK-390MR, Regimen C = 120 mg of TAK-390MR, and Regimen D = 30 mg of lansoprazole

a The estimates of the mean are least squares means, which took into account the possibility of period effects.

b The differences presented are the differences in least squares means.

\*, \*\*, \*\*\* Indicate statistical significance at the  $p = 0.05$ ,  $0.01$ , or  $0.001$  level, respectively.

On Day 1, the mean intragastric pH during 0 to 24 hours, >9 to 12 hours, >12 to 16 hours, and >16 to 24 hours for each of the TAK-390MR regimens tended to be higher than the corresponding mean pH for the lansoprazole regimen. The mean intragastric pH for Regimens A (60 mg of TAK-390MR), B (90 mg of TAK-390MR), and C (120 mg of TAK-390MR) was statistically significantly higher than that for Regimen D (30 mg of lansoprazole) during the >9 to 12-hour and >12 to 16-hour intervals, but only Regimen C had a statistically significantly higher mean pH during the 0 to 24-hour and >16 to 24-hour intervals on Day 1. On Day 5, the mean intragastric pH for Regimens A, B, and C was similar across all the time intervals, and, with the exception of the 0 to 4-hour interval, mean intragastric pH tended to be higher for each of the TAK-390MR regimens than for the lansoprazole regimen. Regimens A, B, and C had a statistically significantly higher mean pH than did Regimen D during the

**Safety Results:**

Oral doses of 60 mg, 90 mg, or 120 mg of TAK-390MR or of 30 mg of lansoprazole administered daily for 5 consecutive days were safe and well tolerated in these healthy subjects. No deaths, other serious adverse events, or other significant adverse events occurred, and there were no consistent, clinically important changes in laboratory test results, vital signs, physical examinations, or ECGs. No trend toward increasing incidence of adverse events or increasing magnitude of effect on clinical laboratory results was noted with increasing doses of TAK-390MR. The mean plasma gastrin concentrations over 24 hours after administration of study drug were similar across the 4 regimens on both Day 1 and Day 5.

**Conclusion(s):**

Approximate dose proportionality was observed for mean  $C_{max}$  and AUC values following oral administration of 60 mg, 90 mg, or 120 mg of TAK-390MR QD for 1 or 5 days. The exposure of TAK-390MR on Day 5 was generally similar to that on Day 1 following oral administration of 60 mg, 90 mg, or 120 mg of TAK-390MR QD.

In general, the mean intragastric pH was higher and the mean percent of time intragastric pH exceeded 4 was greater during the TAK-390MR regimens (Regimens A, B, and C) than during the lansoprazole regimen (Regimen D) on both Day 1 and Day 5. During the >9 to 12-hour interval and the >12 to 16-hour interval on both Day 1 and Day 5 and the >4 to 9-hour interval on Day 5, all pairwise comparisons of Regimens A, B, and C with Regimen D were statistically significant for both the mean intragastric pH and the mean percent of time intragastric pH exceeded 4. The intragastric pH results on Day 5 were similar across the TAK-390MR regimens.

Overall, oral administration of 60 mg, 90 mg, or 120 mg of TAK-390MR once daily for 5 consecutive days was safe and well tolerated in these healthy adult subjects. Results were similar across the various dosing regimens, and there was no consistent indication that the higher doses of TAK-390MR were associated with a higher incidence of adverse events or a greater magnitude of change in clinical laboratory test results.

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## Study T-P105-129 PK in subjects with symptomatic GERD

<b>Name of Company:</b> TAP Pharmaceutical Products Inc <b>Name of Finished Product:</b> Dexlansoprazole MR Capsules <b>Name of Active Ingredient:</b> (+)-2-[(R)-{[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1H-benzimidazole		
<b>Title of Study:</b> A Phase 1, Single-Center, Randomized, Open-Label, Parallel-Group, Multiple-Dose Study to Evaluate the Pharmacokinetics and Safety of Dexlansoprazole MR (30 mg, 60 mg, and 90 mg) in Subjects with Symptomatic, Nonerosive Gastroesophageal Reflux Disease (GERD)		
<b>Investigator:</b> 1 investigator		
<b>Study Center:</b> Single investigative site in the United States of America		
<b>Publication (Reference):</b> None		
<b>Study Period:</b> Date of First Dose: 20 June 2006 Date of Last Procedure: 28 July 2006		<b>Phase of Development:</b> 1
<b>Objective:</b> The objective of this study was to evaluate in subjects with symptomatic, nonerosive gastroesophageal reflux disease (GERD) the pharmacokinetic characteristics and safety of multiple, oral doses of 30 mg, 60 mg, or 90 mg of dexlansoprazole modified release (MR [TAK-390MR]) administered once daily (QD) for 8 consecutive days.		
<b>Methodology:</b> This was a Phase 1, single-center, randomized, open-label, parallel-group, multiple-dose study. The study consisted of a Screening Period, which lasted a minimum of 8 days and a maximum of 21 days, and a Treatment Period, which had a duration of 8 days. Thirty-six male and female subjects were enrolled and were randomly assigned in equal numbers to one of the 3 treatment groups, as summarized in the following table.		
<b>Treatment Groups and Dose Assignments</b>		
<b>Treatment Group</b>	<b>Number of Subjects</b>	<b>Dose of Dexlansoprazole MR</b>
1	12	30 mg QD for 8 consecutive days
2	12	60 mg QD for 8 consecutive days
3	12	90 mg QD for 8 consecutive days
<p>During the Screening Period, subjects documented in their subject diary the presence of heartburn symptoms (including daytime and nighttime symptoms) each day from Day -8 through Day -2. Those who had at least 4 days of heartburn during this interval, did not have erosive esophagitis on endoscopy, and met the other admission criteria at screening and Day -1 qualified for the study.</p> <p>On Day -1, subjects were randomly assigned to one of the 3 treatment groups and entered the Treatment Period. During the Treatment Period, study drug was administered orally QD on Day 1 through Day 8. On Day 1 through Day 4, subjects were instructed to take a single dose orally each day before breakfast at home and to record the date and time of dosing with study drug in their diary. In the afternoon on Day 4, subjects returned to the investigative site for confinement, which continued until all study procedures had been completed on Day 9. During confinement, subjects were administered study drug under the supervision of site personnel at approximately 0800 hours on Day 5 through Day 8. Gelusil was provided as a rescue medication during the study, except during the interval from 4 hours before dosing through 4 hours after dosing on Day 5 and Day 8 (the days of blood sampling for pharmacokinetic assessment).</p>		
<b>Number of Subjects (Planned and Analyzed):</b> Thirty-six subjects were planned and enrolled. Thirty-four subjects were included in the pharmacokinetic analyses of dexlansoprazole, and 36 subjects were included in the safety analyses.		
<b>Diagnosis and Main Criteria for Inclusion:</b> Male and female subjects at least 18 years of age with symptomatic, nonerosive GERD.		

**Duration of Treatment:** During the Treatment Period, each subject was randomly assigned to one of the 3 treatment groups and received single, daily doses of 30 mg, 60 mg, or 90 mg of dexlansoprazole MR for 8 consecutive days. During both the Screening Period and the Treatment Period, subjects could take Gelusil tablets (Pfizer Inc, New York, New York) as a rescue medication for relief of symptoms of heartburn.

**Test Product, Dose and Mode of Administration, and Lot Numbers:**

Test Product	Product Dosage Strength	Study Dose	Mode of Administration	Manufacturer	Drug Product Lot Number
Dexlansoprazole MR	One 30-mg capsule	30 mg QD	Oral	Takeda Pharmaceutical Company Limited	Z540G011
Dexlansoprazole MR	One 60-mg capsule	60 mg QD	Oral	Takeda Pharmaceutical Company Limited	Z540R024
Dexlansoprazole MR	One 90-mg capsule	90 mg QD	Oral	Takeda Pharmaceutical Company Limited	Z540S042

**Reference Therapy, Dose and Mode of Administration, and Lot Numbers:** No reference therapy was utilized in this study.

**Criteria for Evaluation:**

**Pharmacokinetics:**

The pharmacokinetic profile of dexlansoprazole was assessed through blood sampling on Day 5 and Day 8, and dexlansoprazole plasma concentrations were determined using a validated assay of liquid chromatography tandem mass spectrometry with a lower limit of quantitation of 5 ng/mL. Pharmacokinetic parameters for dexlansoprazole in plasma were estimated using standard noncompartmental methods. The pharmacokinetic parameters estimated for dexlansoprazole included: the maximum (peak) plasma drug concentration ( $C_{max}$ ), the time to maximum (peak) drug concentration ( $t_{max}$ ), the apparent terminal elimination rate constant ( $\lambda_z$ ), the apparent terminal elimination-phase half-life ( $t_{1/2z}$ ), and the area under the plasma concentration-time curve (AUC) from time zero to the time of the last measurable concentration ( $AUC_t$ ) and to 24 hours ( $AUC_{24}$ ).

**Safety:**

Safety was monitored by assessing adverse events (AEs), concomitant medication usage, clinical laboratory variables, and vital signs.

**Statistical Methods:**

**Pharmacokinetics:**

Descriptive statistics for the plasma concentrations and for each of the pharmacokinetic parameters for dexlansoprazole were computed for Day 5 and Day 8 for each treatment group. To estimate the intersubject and intrasubject variability of dexlansoprazole  $C_{max}$  and AUCs, mixed linear models were used on the natural logarithms of dose-normalized  $C_{max}$ ,  $AUC_t$ , and  $AUC_{24}$ . The models had fixed factors of treatment, day, and treatment-by-day interaction, as well as a random factor of subject-within-treatment.

The dose proportionality of pharmacokinetic parameters for 30 mg, 60 mg, and 90 mg of dexlansoprazole MR was assessed based on an overall comparison of the 3 treatment groups and the individual, pairwise comparisons. The comparisons were performed via 90% confidence intervals for the central values ratios of dose-normalized  $C_{max}$  and AUCs obtained within the framework of the mixed linear model.

The effect of treatment day was assessed based on comparison of the pharmacokinetic parameters obtained on Day 5 versus those obtained on Day 8. The comparisons were performed via 90% confidence intervals for the central values ratios obtained within the framework of the mixed linear model.

**Statistical Methods (Cont):**

**Safety:**

All subjects who received at least 1 dose of study drug were included in the analyses of safety. Treatment-emergent AEs were summarized for each treatment group and overall. Baseline and postdose values and mean change from baseline to postdose were summarized by treatment group for clinical laboratory variables and for vital signs.

Subjects with laboratory or vital sign results that met predefined criteria for potentially clinically important values were identified.

**Summary and Conclusions:**

**Baseline Demographics:**

Ten (28%) subjects were male, and 26 (72%) were female. Twenty-eight (78%) subjects were white, 6 (17%) were black, and 2 (6%) were American Indian or Alaska native. Twenty-four (67%) subjects were Hispanic or Latino. The mean age of the subjects was 42.5 years (standard deviation: ± 12.30 years).

**Pharmacokinetic Results:**

Noncompartmental pharmacokinetic parameter estimates for dexlansoprazole on Day 5 and Day 8 for subjects receiving oral doses of 30 mg, 60 mg, or 90 mg of dexlansoprazole MR QD for 8 consecutive days are summarized in the following table.

**Summary of Pharmacokinetic Parameter Estimates of Dexlansoprazole on Day 5 and Day 8 of Once-Daily Administration of 30 mg, 60 mg, and 90 mg of Dexlansoprazole MR**

Dose (mg)	Measure	$t_{max}$ (h)	$C_{max}$ (ng/mL)	$C_{max}/Dose$ (ng/mL/mg)	$AUC_t$ (ng·h/mL)	$AUC_M$ (ng·h/mL)	$AUC_M/Dose$ (ng·h/mL/mg)	$t_{1/2}^a$ (h)
<b>Day 5</b>								
30	N	10	10	10	10	10	10	9
	Mean	3.65	796.40	26.6	4702.41	4732.42	158	2.52 (1.67)
	%CV	63	70	70	109	108	108	69
60	N	12	12	12	12	12	12	12
	Mean	5.13	1466.25	24.4	11398.01	11428.46	190	2.86 (2.04)
	%CV	41	42	42	94	93	93	76
90	N	12	12	12	12	12	12	12
	Mean	3.33	1971.00	21.9	12783.04	12798.74	142	2.86 (2.12)
	%CV	68	62	62	96	96	96	51
<b>Day 8</b>								
30	N	10	10	10	10	10	10	9
	Mean	3.95	661.90	22.1	4890.20	4913.34	164	2.40 (1.68)
	%CV	57	68	68	114	113	113	74
60	N	12	12	12	12	12	12	12
	Mean	4.63	1550.17	25.8	12044.56	12097.18	202	3.28 (2.13)
	%CV	43	41	41	98	97	97	79
90	N	12	12	12	12	12	12	12
	Mean	3.21	2232.75	24.8	13670.43	13687.18	152	2.48 (2.04)
	%CV	55	64	64	100	100	100	47

Note: %CV = percent coefficient of variation.

a Arithmetic mean (harmonic mean).

**Summary and Conclusions (Cont):**

The initiation of absorption of dexlansoprazole was rapid following oral administration of 30 mg, 60 mg, or 90 mg of dexlansoprazole MR; mean plasma dexlansoprazole concentrations ranged from 273 ng/mL for the 30-mg dose to 1205 ng/mL for the 90-mg dose at approximately 1.5 hours after dosing on both Day 5 and Day 8. After the initial increase in the mean plasma dexlansoprazole concentrations, mean concentrations declined until again increasing to reach a maximum value ( $C_{max}$ ) at approximately 3 to 5 hours ( $t_{max}$ ) after dosing. Higher  $C_{max}$  and AUC values were observed as the dose of dexlansoprazole MR increased. The estimated intrasubject variability for dexlansoprazole dose-normalized  $C_{max}$  and AUCs was 31% and 22%, respectively, and the estimated intersubject variability for dexlansoprazole dose-normalized  $C_{max}$  and AUCs was 49% and 105%, respectively. The systemic exposure of dexlansoprazole on Day 8 was generally similar to that observed on Day 5, indicating that steady-state had been achieved by Day 5.

**Safety Results:**

In this study, oral doses of 30 mg, 60 mg, and 90 mg of dexlansoprazole MR administered once daily for 8 consecutive days were well tolerated by subjects with symptomatic, nonerosive GERD. Safety results were similar among the 3 dexlansoprazole MR treatment groups, except that the number of subjects experiencing at least 1 AE was higher in the group receiving 90 mg of dexlansoprazole MR (8 subjects, 67%) than in the group receiving 30 mg of dexlansoprazole MR (3 subjects, 25%) or the group receiving 60 mg of dexlansoprazole MR (4 subjects, 33%). The AEs experienced by  $\geq 2$  subjects in any treatment group, based on the Medical Dictionary for Regulatory Activities High Level Term, were Headaches Not Elsewhere Classified (1 subject in the 30-mg, 3 subjects in the 60-mg, and 7 subjects in the 90-mg dexlansoprazole MR treatment groups) and Nausea and Vomiting Symptoms (0 subjects in the 30-mg, 0 subjects in the 60-mg, and 2 subjects in the 90-mg dexlansoprazole MR treatment groups). No deaths or serious adverse events occurred, and no subject prematurely discontinued from the study due to an AE. No consistent, clinically important changes in laboratory test results, vital signs, or physical examinations were observed.

**Conclusions:**

The plasma dexlansoprazole concentration-time profiles following once-daily, oral administration of 30 mg, 60 mg, or 90 mg of dexlansoprazole MR for 5 or 8 days in subjects with symptomatic, nonerosive GERD displayed modified-release characteristics in this study, similar to those previously observed in healthy subjects. Higher  $C_{max}$  and AUC values were observed as the dose of dexlansoprazole MR increased. The estimated intrasubject variability for dexlansoprazole dose-normalized  $C_{max}$  and AUCs was 31% and 22%, respectively, and the estimated intersubject variability for dexlansoprazole dose-normalized  $C_{max}$  and AUCs was 49% and 105%, respectively. The systemic exposure of dexlansoprazole on Day 8 was generally similar to that observed on Day 5, indicating that steady-state had been achieved by Day 5.

In this study, no safety concerns were associated with administration of 8 consecutive once-daily doses of 30 mg, 60 mg, or 90 mg of dexlansoprazole MR in subjects with symptomatic, nonerosive GERD.

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