

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208056Orig1s000

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

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	208-056
IND	106,858
Submission Date(s)	03/26/2015, 5/15/2015, 5/21/2015, 9/25/2015, 11/23/2015
Brand Name	Dexilant SoluTab
Generic Name	Dexlansoprazole
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OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products
Sponsor	Takeda Development Center Americas, Inc
Submission Type	Original, 505(b)(1), Standard
Formulation, Strength	Delayed-Release Orally Disintegrating Tablets, 30 mg
Proposed indication	(b) (4) • Maintenance of healing of EE and relief of heartburn • Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD)

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1. Executive Summary

This original NDA is submitted in support of a new formulation of dexlansoprazole as delayed-release orally disintegrating tablet (Dexilant SoluTab®). Dexlansoprazole is currently available as a delayed-release capsule, (Dexilant®). Two doses are approved for Dexilant: 30 mg for the maintenance of healed Erosive Esophagitis (EE) and relief of heartburn as well as for symptomatic non-erosive Gastroesophageal reflux disease (GERD) and 60 mg for the healing of EE. Dexilant SoluTab is proposed for one strength, 30 mg, whereas the reference product Dexilant capsule has two strengths, 30 mg and 60 mg. (b) (4)

In support of this NDA, the sponsor has conducted 6 BA/BE studies and 1 in-vivo disintegration time study in healthy subjects. No additional clinical efficacy or safety trial employing the proposed ODT formulation was conducted.

In our review, we found that the bioequivalence was established between the proposed dexlansoprazole ODT 30 mg and Dexilant 30 mg capsule, but not between 2 dexlansoprazole ODT 30 mg and Dexilant 60 mg capsule.

Throughout the review, Dexilant SoluTab will also be referred as dexlansoprazole 30 mg OD tablet or dexlansoprazole delayed-release OD 30 mg tablet.

1.1 Recommendations

The Division of Clinical Pharmacology 3 has found the submission partially acceptable from a clinical pharmacology standpoint provided a mutual agreement on labeling languages is reached.

DCP3 recommends the approval of Dexilant SoluTab for the following two indications based on the established bioequivalence between Dexilant SoluTab 30 mg and Dexilant 30 mg Capsule.

- Maintaining healing of erosive esophagitis and relief of heartburn
- Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease.

(b) (4)

A required office level briefing for this NDA was held on December 21, 2015.

1.2 Recommended Post-Marketing Studies

None

1.3 Clinical Pharmacology Highlights

Bioequivalence at 30 mg Strength:

Dexilant SoluTab 30 mg tablet is bioequivalent to Dexilant 30 mg capsule, where 90% CIs for the dexlansoprazole C_{max}, AUC(0-t_{lq}c), and AUC(0-inf) were all within the 0.80 to 1.25 BE range following single dose and multiple dose administration for 5 days.

Bioequivalence at 60 mg Strength:

Two Dexilant SoluTab 30 mg tablets is not bioequivalent to one Dexilant 60 mg capsule. Two Dexilant SoluTab 30 mg tablets and one 60 mg Dexilant capsule provide equivalence for C_{max}; however, the AUC of two Dexilant SoluTab 30 mg tablets is approximately 25% and 22 % lower than that of Dexilant 60 mg capsule on Day 1 and Day 5, respectively. Lower 90% CI for AUC was also below 0.8 BE limit on both Day 1 and Day 5.

Implication of Lack of BE on Efficacy/Safety:

Intragastric pH profiles of two Dexilant SoluTab 30 mg tablets and one Dexilant 60 mg capsule are similar on both Day 1 and Day 5 despite that the AUC of dexlansoprazole from two Dexilant SoluTab 30 mg tablets is approximately 25% lower than that of one Dexilant 60 mg capsule on both Day 1 and Day 5. (b) (4)

 (b) (4)

Food Effect:

Administration of Dexilant SoluTab 30 mg tablet with high-fat breakfast reduced the C_{max} by 38%, delayed the t_{max} by 2 hours, but did not change the AUC significantly compared to the fasted state. As there is no available exposure-response data or efficacy data with lower than 30 mg dose for the reference product Dexilant Capsule to support that the reduction in C_{max} by 38% would not comprise the efficacy of dexlansoprazole, Dexilant SoluTab 30 mg tablet will be recommended to take at least 30 minutes before the meal in the label.

Water Effect:

When administration of Dexilant SoluTab 30 mg tablet was followed by rinsing the mouth with 240-mL water, the AUC was reduced by 20% and the C_{max} was reduced by 29% compared to when Dexilant SoluTab 30 mg tablet was administered without water. As there is no available exposure-response data or efficacy data with lower than 30 mg dose for the reference product Dexilant Capsule to support that reduction in the AUC by 20% and reduction in the C_{max} by 29% would not comprise the efficacy of dexlansoprazole, Dexilant SoluTab 30 mg tablet will be recommended to place on the tongue, allow it to disintegrate, and swallow the microgranules without water in the label.

Alternative Options for Dose Administration:

When a Dexilant SoluTab 30 mg tablet was mixed with water and administered via an oral syringe or via an NG tube, or swallowed as an intact OD tablet with water, each of them were bioequivalent to the oral administration of the intact OD tablet on the tongue allowed to disintegrate and swallowed without water. Therefore, in the label, we recommend that Dexilant SoluTab 30 mg can be administered with water via oral syringe or NG tube or may also be swallowed whole with water.

Disintegration Time:

In-vivo mean disintegration time for Dexilant SoluTab 30 mg tablet on tongue was 36 second (ranged 29-43 seconds). However, in the study that measured disintegration time, subjects sipped and swallowed 20 mL of spring water 30 seconds prior to the study drug administration which could shorten the true disintegration time. As the general definition of ODT is rapid oral disintegration in saliva without the need for chewing or drinking liquids to ingest these products, the reported in vivo disintegration time in this study with sipping 20 mL of water 30 seconds prior to the drug administration could be biased and unreliable. Therefore, the reported disintegration time in this study will not have a labeling implication. Nonetheless, the reported in-vivo disintegration time in this study is in a similar range as the reported in-vitro disintegration time of 32.9 second with 95% CI of 23.2-42.6 second.

Alcohol Dose Dumping:

Based on the in-vitro alcohol dose dumping study, there is a significant potential of alcohol dose-dumping at the acid stage in the presence of 40% alcohol. 90% of drug was released within 30 min in the presence of 40% alcohol, compared to 1-2% of drug release at the same time point in the presence of 0%, 5%, and 20% alcohol. This observed alcohol dose dumping may potentially shorten the t_{max} , reduce the AUC and C_{max} of dexlansoprazole by exposing this acid labile drug early in the acidic environment of the stomach, and thus, may reduce the efficacy. However, we do not anticipate the safety profile of the drug be affected by the alcohol dose dumping and a follow up in-vivo alcohol dose dumping study may not be needed. This observed alcohol dose dumping issue would be addressed in the product labeling by instructing patients to “avoid alcohol when taking Dexilant SoluTab”.

OSI Inspection:

An inspection was requested for two pivotal bioequivalence (BE) studies, study TAK-390MR(OD)_105 (BE study comparing 30 mg Dexilant capsule vs. 30 mg Dexilant ODT) and for study TAK-390MR(OD)_104 (BE study comparing 60 mg Dexilant capsule vs. 2 X 30 mg Dexilant ODT) for both clinical sites and bioanalytical sites on 04/20/2015. However, the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection on 06/12/2015 as OSIS recently inspected these sites that conducted the two studies and the inspectional outcome from the inspections was classified as No Action Indicated (NAI).

One of the formulation exploration study (TAK-390MR(OD)_101) was not reviewed in detail in this review since it was not conducted with the to-be-marketed formulation (TBM).

2 Question-Based Review

2.1 List of *In-vivo* and *In-vitro* Clinical Pharmacology Studies

The sponsor has conducted 7 phase I studies in development program of dexlansoprazole orally disintegration tablet formulation, Dexilant SoluTab.

Table 1: List of Submitted Clinical Pharmacology Studies

Study #	Objective(s)	Study Design	Treatment	Subjects
TAK-390MR(OD)_102	Bioequivalence	Phase 1, randomized, open-label, single-center, single-dose, 4-period, crossover study	A: Single oral dose of Dex 30 mg OD tablet Formulation X (Test) B: Single oral dose of Dex 30 mg OD tablet Formulation Y (Test) C: Single oral dose of Dex 30 mg OD tablet Formulation Z (Test) D: Single oral dose of Dex 30 mg capsule (Reference)	64 healthy adults
TAK-390MR(OD)_103	BA: Food effect study and effect of water rinse after administration	Phase 1, randomized, open-label, single-center, single-dose, 3-period crossover	A: Dex 30 mg OD tablet administered on the tongue on Day 1, allowed to disintegrate, and swallowed without water 30 minutes after starting to ingest a high-fat meal (Test) B: Dex 30 mg OD tablet administered on the tongue on Day 1 after a 10-hour fast, allowed to disintegrate, swallowed without water, and followed with a 240-mL water rinse (Test) C: Dex 30 mg OD tablet administered on the tongue on Day 1 after a 10-hour fast, allowed to disintegrate, and swallowed without water (Reference)	72 healthy adults
TAK-390MR(OD)_106	BA: OD tablet administered without water, swallowed intact with water, or mixed with water and administered orally via syringe or via nasogastric tube	Phase 1, randomized, open-label, single-center, single-dose, 4-period crossover study	A: Single oral dose of Dex 30 mg OD tablet mixed with water and administered orally via syringe (Test). B: Single oral dose of Dex 30 mg OD tablet mixed with water and administered via NG tube (Test). C: Single oral dose of Dex 30 mg OD tablet, swallowed intact with water (Test). D: Single oral dose of Dex 30 mg OD tablet, administered on the tongue, allowed to disintegrate, and swallowed without water (Reference).	77 healthy adults
TAK-390MR(OD)_101	BA, PD (intragastric pH response), and safety of OD tablet versus capsules	Phase 1, randomized, open-label, single-center, multiple-dose, 4-period, 3-way crossover study	A: Dex 30 mg OD tablet Formulation A for 5 days, fasted. B: Dex 30 mg OD tablet Formulation B for 5 days, fasted. C: Dex 30 mg capsule for 5 days, fasted. D: Dex 30 mg OD tablet Formulation A for 1 day, fed. E: Dex 30 mg OD tablet Formulation B for 1 day, fed.	48 healthy adults
TAK-390MR(OD)_104	BA	Phase 1, randomized, open-label, single-center, multiple-dose, 2-period crossover study	A: Dex 2×30 mg OD tablet QD administered on the tongue, allowed to disintegrate, and swallowed without water for 5 days (Test). B: Dex 1×60 mg capsule QD for 5 days (Reference).	52 healthy adults
TAK-390MR(OD)_105	PK, PD, and BA	Phase 1, randomized, open-label, single-center, multiple-dose, 2-period crossover study	A: Dex 30 mg OD tablet administered on the tongue, allowed to disintegrate, and swallowed without water for 5 days (Test). B: Dex 30 mg capsules for 5 days (Reference).	52 healthy adults

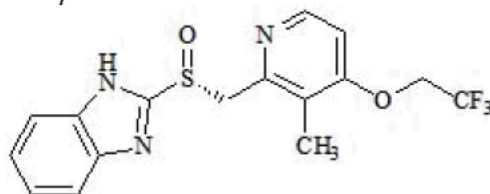
TAK-390MR(OD)_107	Sensory evaluation (In vivo disintegration time)	Phase 1/2 open-label sensory evaluation	Dex 30 mg OD tablet administered on the tongue, allowed to disintegrate, then expectorated	8 healthy adults
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2.2 General Attributes of the drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Drug Substance: Dexlansoprazole is the R-enantiomer of the racemate lansoprazole (a racemic mixture of the R- and S enantiomers), which has been approved in the United States (US) for use in adults since May 1995. Its empirical formula is: C₁₆H₁₄F₃N₃O₂S, with a molecular weight of 369.36.

Figure 1: Structure of Dexlansoprazole



Formulation: Dexilant SoluTab is being developed as delayed-release orally disintegrating (OD) tablet of dexlansoprazole at 30 mg strength only. It contains two types of enteric coated (EC) microgranules, (b) (4)

to achieve a prolonged release profile, similar to that of commercial Dexilant Capsules (reference product).

2.2.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

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

The proposed indications by the sponsor for Dexilant SoluTab are: (b) (4)

- Maintaining healing of EE and relief of heartburn
- Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD).

2.2.3 What are the proposed dosage(s) and route(s) of administration?

Dexilant SoluTab is formulated as delayed-release orally disintegrating tablet (ODT) at 30 mg strength for oral administration. The proposed indication and dosing regimens are (b) (4) as following:

Indication	Dosing regimens
	(b) (4)

Maintenance of Healed EE and Relief of Heartburn	30 mg ODT QD for up to 6 month
Symptomatic Non- Erosive GERD	30 mg ODT QD for 4 weeks

2.2.4 What is the regulatory background?

Dexlansoprazole is the R-enantiomer of the racemate lansoprazole (a racemic mixture of the R- and S enantiomers), which has been approved in the United States (US) for use in adults since May 1995. The first product of dexlansoprazole was delayed release capsule (also known as Dexilant) formulation and was approved in 2009. Dexlansoprazole delayed-release capsules are approved in the US for use in adults 18 years of age and older for treatment of healing all grades of erosive esophagitis (EE), maintenance of healed EE and relief of heartburn, and heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD).

In the current submission, the same sponsor, Takeda Development Center, has developed another oral formulation, a 30 mg dexlansoprazole delayed-release orally disintegrating (OD) tablet, Dexilant SoluTab, as an alternate dosage form for (b) (4) Dexilant capsule.

Formulation	Product Name	Strengths	Year of Approval
Lansoprazole, a racemic mixture of R and S enantiomers			
Delayed release capsule	Prevacid	15 mg, 30 mg	1995
Delayed-release ODT	Prevacid SoluTab	15 mg, 30 mg	2002
OTC capsule	Prevacid 24 Hr	15 mg	2009
Dexlansoprazole, R-enantiomer			
Delayed release capsule	Dexilant	30 mg, 60 mg	2009
Delayed release ODT	Dexilant SoluTab	30 mg	Current Submission

2.3 General Clinical Pharmacology

2.3.1 Is Dexilant SoluTab 30 mg bioequivalent to approved Dexilant 30 mg Capsule?

Yes, Dexilant SoluTab 30 mg is bioequivalent to Dexilant 30 mg capsule. Therefore, Dexilant SoluTab 30 mg can have the same indication as the Dexilant 30 mg capsule.

Study TAK-390MR(OD)-105 was an open-label, phase 1, randomized (1:1 ratio), single-center, multiple-dose, 2-period crossover study in 52 healthy subjects to evaluate the pharmacokinetic and pharmacodynamics of dexlansoprazole following the once daily administration of either dexlansoprazole delayed-release OD 30 mg tablets (formulation Z) or dexlansoprazole delayed-release 30 mg capsule for 5 days. In Regimen A, subjects were instructed to administer the dexlansoprazole delayed-release OD tablet directly on the tongue allow it to disintegrate on the tongue, and to swallow the granules without water and without chewing. In Regimen B, subjects were instructed to swallow the capsule with 240 mL of water. There was at least a 7-days of washout period between the last dose in the first period and the first dose of the second period. PK samples were collected for up to 24 hours post-dose on Day 1 and Day 5 following both treatments. Additionally, intragastric pH was recorded for 24 hours (sampled and recorded every 2 seconds) beginning immediately prior to study drug administration on Day 1 and Day 5 of Periods 1 and 2.

Following both single dose administration on day 1 and multiple dose administration on Day 5, although 30 mg dexlansoprazole delayed release OD 30 mg tablet and 30 mg capsules has similar C_{max} , T_{max} was reached earlier for ODT tablet compared the capsule (reference). In addition, ODT does not have a clear double peak profile as the capsule formulation. However, since the double peak feature of the Dexilant capsule is not considered to be relevant for its efficacy, the lack of double peak in ODT formulation does not raise a concern.

Figure 2: Mean (SD) Plasma Concentration-Time Profiles for Dexlansoprazole Following a Single and Multiple Dose of Dexlansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule in Healthy Subjects

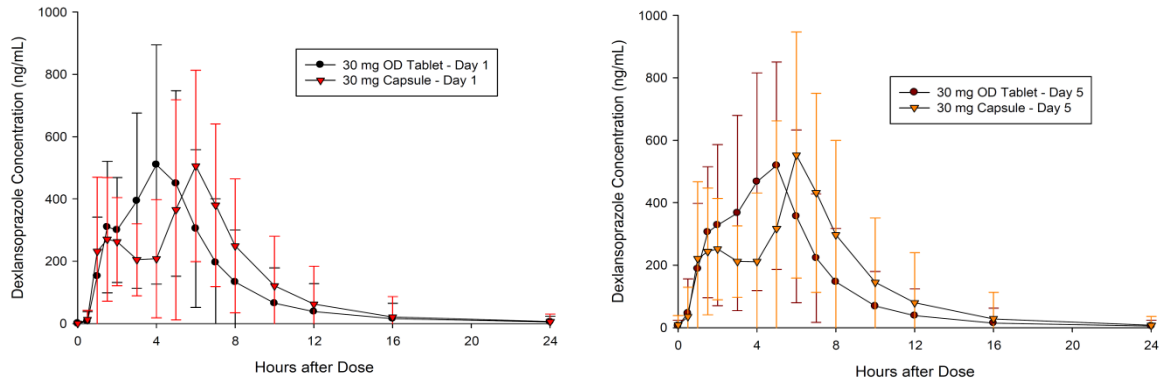


Table 2: PK Parameter Estimates of Dexlansoprazole on Day 1 and Day 5 Following Daily Administration of Dexlansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule for 5 Days in Healthy Subjects

	T_{max} (hr)*	C_{max} (ng/mL)	AUC(0-t_{lqc}) (ng·hr/mL)	AUC(0-inf) (ng·hr/mL)	T_{1/2} (hr)	CL/F (L/hr)	V_z/F (L)
Day 1 – Single Dose of Delayed-Release OD 30 mg Tablet (Regimen A) (a)							
N	50	50	50	46	46	46	46
Mean	4.0	688	2866	3048	2.10	14.24	41.33
SD	NR	337.2	2221.0	2376.8	1.186	8.237	38.649
CV%	NR	49	77	78	57	58	94
Day 1 – Single Dose of Delayed-Release 30 mg Capsule (Regimen B) (b)							
N	50	50	50	46	46	46	46
Mean	5.0	61	3049	3212	1.88	13.02	31.36
SD	NR	298.6	2515.6	2759.0	0.989	6.378	17.270
CV%	NR	48	83	86	53	49	55
Day 5 – Once-Daily Doses of Delayed-Release OD 30 mg Tablet (Regimen A) (a)							
N	50	50	50	50	49	50	49
Mean	4.0	752	3027	3036	2.09	14.22	44.16
SD	NR	358.7	2144.1	2143.9	1.167	8.526	48.780
CV%	NR	48	71	71	56	60	110
Day 5 – Once-Daily Doses of Delayed-Release 30 mg Capsule (Regimen B) (b)							
N	50	50	50	50	49	50	49
Mean	6.0	687	3330	3345	1.79	13.33	29.16
SD	NR	337.8	3130.3	3127.9	0.866	7.173	14.225
CV%	NR	49	94	94	48	54	49

*Median time

Table 3: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Daily Administration of the Dexlansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule for 1 or 5 Days in Healthy Subjects (Sponsor Provided)

Parameter (N) (a)	Point Estimate of the Relative BA	90% CIs for the Point Estimate
Day 1: Delayed-Release OD 30 mg Tablet (Regimen A) vs Delayed-Release 30 mg Capsule (Regimen B) (b)		
C _{max} (50/50)	1.0580	(0.9502 – 1.1781)
AUC(0-tlqc) (50/50)	0.9047	(0.8419 – 0.9721)
AUC(0-inf) (46/46)	0.9265	(0.8615 – 0.9964)
Day 5: Delayed-Release OD 30 mg Tablet (Regimen A) vs Delayed-Release 30 mg Capsule (Regimen B) (b)		
C _{max} (50/50)	1.0868	(0.9516 – 1.2411)
AUC(0-tlqc) (50/50)	0.9531	(0.8672 – 1.0476)
AUC(0-tau) (50/50)	0.9507	(0.8652 – 1.0445)

Source: Table 15.2.4.1.

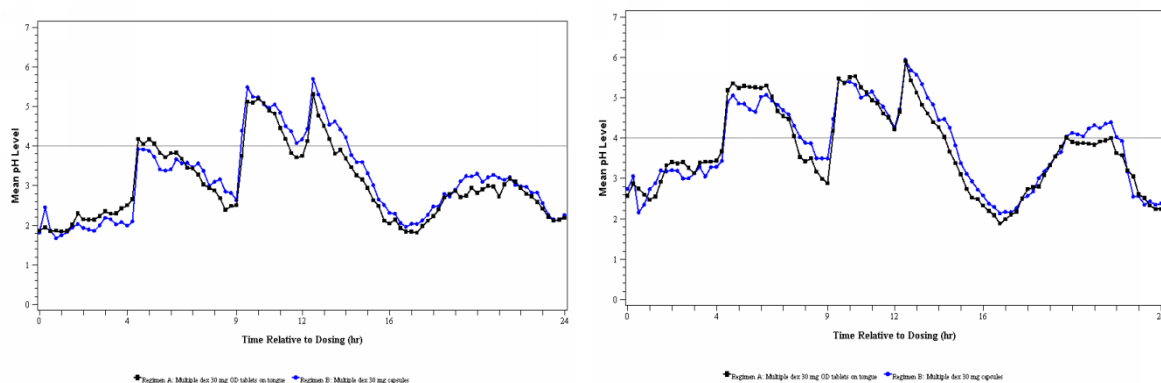
(a) N=(Test/Reference).

(b) Regimen A: Dexlansoprazole delayed-release OD 30 mg tablet, administered on the tongue, allowed to disintegrate, and swallowed without water (Test). Regimen B: Dexlansoprazole delayed-release 30 mg capsule swallowed with 240 mL of water (Reference).

Table 4: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Daily Administration of the Dexlansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule for 1 or 5 Days in Healthy Subjects (Reviewer's Analysis)

Parameter	Point Estimate of the Relative BA	Lower 90% CL	Upper 90% CIs
Day 1: Delayed-Release OD 30 mg Tablet vs. Delayed-Release 30 mg Capsule			
C _{max}	108.51	96.99	121.38
AUC(0-tlqc)	91.81	85.11	99.02
AUC(0-inf)	91.83	85.22	98.95
Day 5: Delayed-Release OD 30 mg Tablet vs. Delayed-Release 30 mg Capsule			
C _{max}	108.57	95.53	123.39
AUC(0-tlqc)	94.90	86.57	104.04
AUC(0-tau)	94.65	86.36	103.73

Figure 3: 24-Hour Mean pH Profiles on Day 1(left panel) and Day 5 (right panel) after Administration of Dexlansoprazole Delayed-Release OD 30 mg Tablet (black) or Delayed-Release 30 mg Capsule Formulations (blue) QD for 5 Days



Reviewer's Comment:

- Following a single dose and multiple doses administration for 5 days (QD), the 90% CIs for the dexlansoprazole C_{max}, AUC(0-tlqc), and AUC(0-inf) were within the 0.80 to 1.25 BE

range suggesting the dexlansoprazole delayed-release OD 30 mg tablet is bioequivalent to dexlansoprazole delayed-release 30 mg capsule following single dose and multiple dose.

- Following a single dose and multiples dose administration for 5 days (QD), dexlansoprazole delayed-release OD 30 mg tablets resulted in similar the intragastric pH profile as dexlansoprazole delayed-release 30 mg capsules.
- Sampling time for 24 hours and washout period of 7 days was appropriate as the half-life of dexlansoprazole was approximately 2 hour.
- PK analysis and BE analysis were repeated by the agency and, results were consistent with sponsor's result.

Study TAK-390MR(OD)-102: This study was another formulation exploration study (in addition to Study TAK-390MR(OD)-101 with formulation A and B) in which the sponsor compared the relative bioavailability of dexlansoprazole from three different formulations of dexlansoprazole delayed-release OD tablets 30 mg (formulation X, Y and Z) to dexlansoprazole delayed-release capsules 30 mg in a single dose, 4-period crossover study in 64 healthy subjects.

Figure 4: Mean Plasma Concentration Time Profiles of Dexlansoprazole Following Administration of a Single Dose of 3 Formulations of Dexlansoprazole Delayed-Release OD Tablets and Dexlansoprazole Delayed-Release Capsules in Healthy Subjects

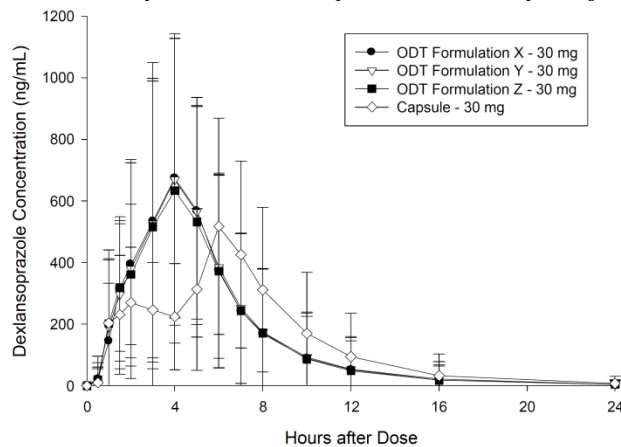


Table 5: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole from Delayed-Release OD Tablet Formulations X, Y, and Z, Relative to the Delayed-Release Capsule

Parameter	Point Estimate of the Relative Bioavailability	90% CIs for the Point Estimate
Dexlansoprazole Delayed-Release OD Tablet Formulation X vs Dexlansoprazole Delayed-Release Capsule		
C _{max}	1.4205	(1.2850 – 1.5703)
AUC(0-tl _{qc})	1.0914	(1.0129 – 1.1759)
AUC(0-inf)	1.0907	(1.0152 – 1.1718)
Dexlansoprazole Delayed-Release OD Tablet Formulation Y vs Dexlansoprazole Delayed-Release Capsule		
C _{max}	1.3753	(1.2441 – 1.5204)
AUC(0-tl _{qc})	1.0839	(1.0059 – 1.1679)
AUC(0-inf)	1.1213	(1.0425 – 1.2059)
Dexlansoprazole Delayed-Release OD Tablet Formulation Z vs Dexlansoprazole Delayed-Release Capsule		
C _{max}	1.2403	(1.1220 – 1.3711)
AUC(0-tl _{qc})	1.0047	(0.9325 – 1.0826)
AUC(0-inf)	1.0337	(0.9608 – 1.1122)

Dexlansoprazole AUC from each of these 3 delayed-release OD tablet formulations was equivalent to the AUC from the delayed-release capsule. However, the C_{max} of dexlansoprazole from Formulations X, Y, and Z were higher than that of dexlansoprazole delayed-release capsules and the upper bound of the 90% CIs was above 1.25 for all 3 formulations.

Since the C_{max} from Formulation Z of ODT was the closest to the C_{max} of delayed-release capsule, the sponsor had conducted a further relative BA study with two-way cross over study design to directly compare the relative bioavailability of dexlansoprazole delayed-release OD tablets 30 mg from Formulation Z to dexlansoprazole delayed-release 30 mg capsules in study TAK-390MR(OD)-105, and had demonstrated that these two products are bioequivalent (see above). Based on this bioequivalence, Formulation Z was chosen as the to-be-marketed formulation.

Failed BE in terms of C_{max} this study TAK-390MR(OD)-102 does not raise a major concern for the following reasons:

1. BE was established in a separated study 390MR(OD)-105 with two-way crossover study design to directly compare the relative bioavailability of dexlansoprazole delayed-release OD tablets 30 mg from Formulation Z to dexlansoprazole delayed-release 30 mg capsule.
2. Since the C_{max} of Formulation Z of dexlansoprazole delayed-release OD tablets 30 mg is about 24% higher than that of Dexilant 30 mg capsule, this difference in C_{max} would not compromise the efficacy of the drug. Additionally, the safety of this observed higher C_{max} from Formulation Z of dexlansoprazole delayed-release OD tablets 30 mg would be supported by the safety data from approved Dexilant 60 mg capsule.
3. PK parameters from studies that used Formulation Z of dexlansoprazole delayed-release OD tablets 30 mg is more consistent with the PK parameter from the BE study that passed BE criteria (study 390MR(OD)-105) than the PK parameters from the BE study that failed BE criteria (study TAK-390MR(OD)-102), as demonstrated in table 6.

Table 6: PK Parameters Comparison from Formulation Z of Dexlansoprazole Delayed-Release OD tablets 30 mg across Different Studies in Healthy Subjects

Parameters (unit)	103 (food and water effect)	Study 106 (Alternative Dose Administration)	Study 105 Passed BE	Study 102 Failed BE
C_{max} (ng/mL)	688 (48%)	744 (41%)	688 (49)	842 (60)
AUC_{0-t} (ng/mLh)	2789 (83%)	3011 (67%)	2866 (77%)	3558 (83)
$AUC_{0-\infty}$ (ng•h/mL)	2839 (86%)	3043 (69%)	3048 (78%)	4036 (79)
Median T_{max} (h) [min,max]	4.00 (1.5-6.00)	4.00 (1.50-6.03)	4.00 (1.00-6.00)	4.00 (1.0-7.00)
$T_{1/2}$ (hr)	2.07 (76%)	1.86 (51%)	2.10 (57)	2.01 (50)
CL/F (L/hr)	16.01 (60)	14.02 (63%)	14.24 (58)	11.90 (81%)
V_z/F (L)	47.35 (139)	36.13 (96%)	41.33 (94)	32.7 (121%)

Therefore, selection of Formulation Z as the to-be-marketed formulation is appropriate.

2.3.2 Is two Dexilant SoluTab 30 mg bioequivalent to approved Dexilant 60 mg Capsule?

No, two Dexilant SoluTab 30 mg tablet is not bioequivalent to one Dexilant 60 mg capsule. Two Dexilant SoluTab 30 mg tablets and one 60 mg Dexilant capsule provide equivalence C_{max} ; however, the AUC of two Dexilant SoluTab 30 mg tablets is approximately 25% and 22 % lower than that of Dexilant 60 mg capsule on Day 1 and Day 5, respectively. Lower 90% CI for AUC

was also below 0.8 BE limit both on Day 1 and Day 5. Nonetheless, these two formulations provided similar overall intragastric pH (PD) profiles in 0-24 hours on both Day 1 and Day 5.

Study TAK-390MR(OD)-104 was an open-label, phase 1, randomized (1:1 ratio), single-center, multiple-dose, 2-period crossover study in 52 healthy subjects to evaluate the pharmacokinetic and pharmacodynamics of dexlansoprazole following the once daily administration of either dexlansoprazole delayed-release ODT 2 x 30 mg tablets or dexlansoprazole delayed-release 60 mg capsule for 5 days. In Regimen A, subjects were administered the ODT tablet directly on the tongue, without water. One tablet was administered to each subject with instructions to allow the dexlansoprazole delayed release OD tablet to disintegrate on the tongue, and to swallow the granules without chewing. After the tablet had disintegrated and the subject had swallowed the granules, the administration of the second tablet proceeded in the same manner as the first tablet. In Regimen B, subjects were instructed to swallow the 60 mg capsule with 240 mL of water. There was at least a 7-days of washout period between the last dose in the first period and the first dose of the second period. PK samples were collected for up to 24 hours post-dose on Day 1 and Day 5 following both treatments. Additionally, intragastric pH was recorded for 24 hours (sampled and recorded every 5 seconds) beginning immediately prior to study drug administration on Day 1 and Day 5 of Periods 1 and 2.

Following both single dose administration on day 1 and multiple dose administration on Day 5, two 30 mg dexlansoprazole delayed release OD tablet has slight lower C_{max} and notable lower AUC compared to one 60 mg capsules. T_{max} was reached earlier for ODT tablet compared the capsule (reference). In addition, ODT does not have clear double peak profile as the capsule formulation on both Day 1 and Day 5. However, since the double peak feature of the Dexilant capsule is not considered to be relevant for its efficacy, the lack of double peak in ODT formulation does not raise a concern.

Figure 5: Mean (SD) Plasma Concentration-Time Profiles for Dexlansoprazole Following a Single Dose of Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule in Healthy Subjects

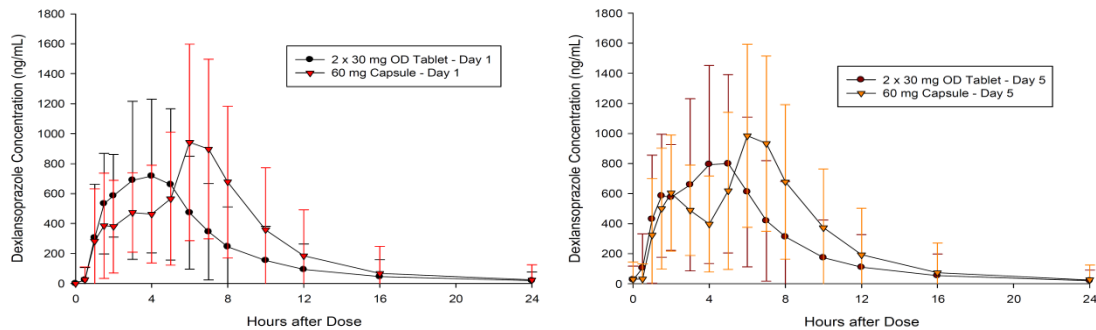


Table 7: Summary of the PK Parameter Estimates for Dexlansoprazole Following a Single Dose of the Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule in Healthy Subjects

	*t _{max} (hr)	C _{max} (ng/mL)	AUC _t (ng·hr/mL)	AUC _∞ (ng·hr/mL)	t _{1/2z} (hr)	CL/F (L/hr)	V _d /F (L)
Day 1 – Single Dose of Delayed-Release OD 2 x 30 mg Tablets (Regimen A) (a)							
N	52	52	52	50	50	50	50
Mean	3.00	1047	5060	5364	3.34	16.52	79.30

SD	NR	496.8	3689.9	4218.4	1.689	10.007	67.640
%CV	NR	47	73	79	51	61	85
Day 1 – Single Dose of Delayed-Release 1 x 60 mg Capsule (Regimen B) (b)							
N	52	52	52	50	50	50	50
Mean	6.00	1164	6747	7155	2.17	12.12	32.20
SD	NR	667.0	5489.7	6461.1	1.206	6.097	13.965
%CV	NR	57	81	90	56	50	43
Day 5 – Delayed-Release OD 2 x 30 mg Tablets QD (Regimen A) (a)							
N	52	52	52	52	51	52	51
Mean	4.00	1151	5819	5825	3.17	16.51	74.51
SD	NR	668.5	5105.6	5105.5	1.601	10.440	67.068
%CV	NR	58	88	88	51	63	90
Day 5 – Delayed-Release 1 x 60 mg Capsule QD (Regimen B) (b)							
N	52	52	52	52	51	52	51
Mean	6.00	1178	7184	7196	2.26	12.18	32.22
SD	NR	570.0	6314.0	6306.7	1.303	6.590	12.784
%CV	NR	48	88	88	58	54	40

*Median

Table 8: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Daily Administration of the Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule for 1 or 5 Days in Healthy Subjects (sponsor provided)

Parameter (N) (a)	Point Estimate of the Relative BA	90% CIs for the Point Estimate
Day 1: Delayed-Release OD 2 x 30 mg Tablets QD (Regimen A) vs Delayed-Release 1 x 60 mg Capsule QD (Regimen B) (b)		
C _{max} (52/52)	0.9186	(0.8371 – 1.0079)
AUC _t (52/52)	0.7463	(0.6979 – 0.7981)
AUC _∞ (50/50)	0.7458	(0.6973 – 0.7976)
Day 5: Delayed-Release OD 2 x 30 mg Tablets QD (Regimen A) vs Delayed-Release 1 x 60 mg Capsule QD (Regimen B) (b)		
C _{max} (52/52)	0.9352	(0.8466 – 1.0331)
AUC _t (52/52)	0.7773	(0.7189 – 0.8405)
AUC _τ (52/52)	0.7755	(0.7172 – 0.8385)

Source: Table 15.2.4.1.

(a) N=(Test/Reference).

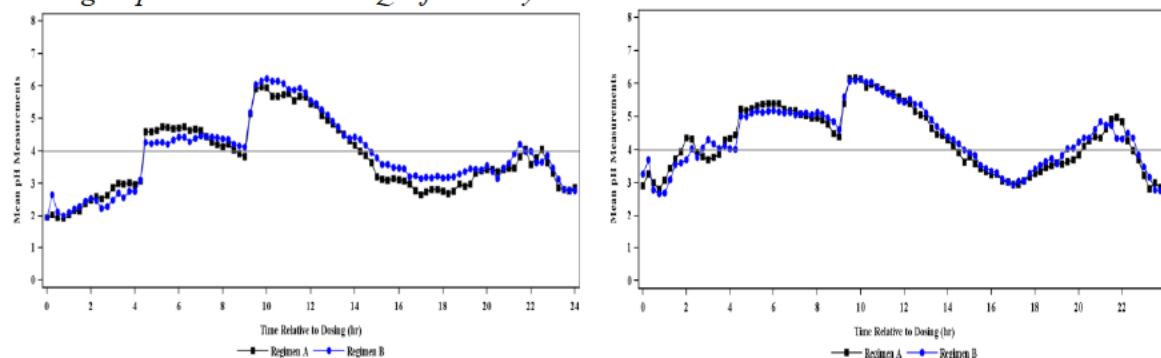
(b) Regimen A: Dexlansoprazole delayed-release OD 2 x 30 mg tablets QD, administered on the tongue, allowed to disintegrate, and swallowed without water (Test). Regimen B: Dexlansoprazole delayed-release 1 x 60 mg capsule QD swallowed with 240 mL of water (Reference).

Table 9: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Daily Administration of the Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule for 1 or 5 Days in Healthy Subjects (Reviewer's Analysis)

Parameter	Point Estimate of the Relative BA	Lower 90% CL	Upper 90% CIs
Day 1: Delayed-Release OD 2 X 30 mg Tablet (Regimen A) vs Delayed-Release 60 mg Capsule (Regimen B)			
C _{max}	92.94	84.41	102.32
AUC(0-tlqc)	75.22	70.15	80.64
AUC(0-inf)	75.71	72.10	84.13
Day 5: Delayed-Release OD 2 X 30 mg Tablet (Regimen A) vs Delayed-Release 60 mg Capsule (Regimen B)			

Cmax	93.61	84.93	103.18
AUC(0-tlqc)	77.88	70.71	81.1
AUC(0-tau)	78.23	72.55	84.37

Figure 6: 24-Hour Mean pH Profiles on Day 1 (left panel) and Day 5 (right panel) After Administration of Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule Formulations QD for 5 Days



Regimen A = Dexlansoprazole delayed-release OD 2 x 30 tablets QD administered on the tongue, allowed to disintegrate, and swallowed without water for 5 days.
Regimen B = Dexlansoprazole delayed-release 1 x 60 mg capsule for 5 days.

Reviewer's Comment:

- Administration of a single 60 mg dose of dexlansoprazole as two 30 mg OD tablets and as one 60 mg capsule provided equivalent Cmax, but failed the meet BE criteria for AUC where the AUC from the two 30 mg OD tablets was approximately 25% and 22 % lower than that of one 60 mg capsule on Day 1 and Day 5, respectively. Lower 90% CI for AUC was also below 0.8 BE limit both on Day 1 and Day 5.
- Although the two these formulations had similar overall intragastric pH profiles in 0-24 hours on both Day 1 and Day 5, it appears that compared to capsule formulation, ODT formulation was higher mean pH in 0-6 hours and lower mean pH in 12-18 hour, especially on Day 1. This difference on PD was not notable on Day 5. On Day 5, for the 0- to 24-hour interval and all subintervals, the % time pH>4 and mean pH were higher than the respective intervals on Day 1 for both regimens.
- Sampling time for 24 hours and washout period of 7 days was appropriate as the half-life of dexlansoprazole was approximately 2 hour.
- PK analysis, BE analysis, and PD plots were repeated and were consistent with sponsor's result.

2.3.2.1 What are the safety or efficacy implications, if any, for BE or bio-comparability studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Intragastric pH profiles of two Dexilant SoluTab 30 mg tablets and one Dexilant 60 mg capsule are similar on both Day 1 and Day 5 despite that the AUC for two Dexilant SoluTab 30 mg tablets is approximately 25% lower than the AUC for one Dexilant 60 mg capsule on both Day 1 and Day 5. (b) (4)

Figure 8: Mean Plasma PK Profiles and Mean pH Profiles of Dexlansoprazole after Administration of Exploratory Formulation A and B of Dexlansoprazole ODT or Dexlansoprazole Capsule from Study TAK-390MR (OD)_101

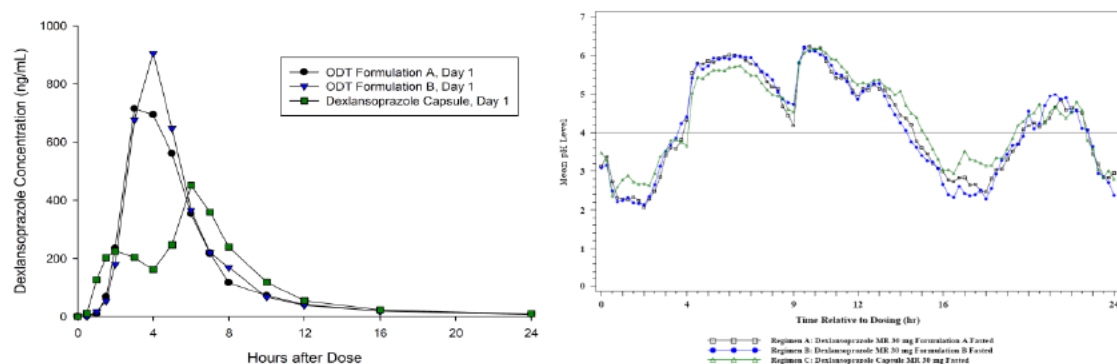


Table 10: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole from ODT Formulations A and B Relative to the Capsule from Study TAK-390MR (OD)_101

Parameter	Point Estimate of the Relative Bioavailability	90% CIs for the Point Estimate
	ODT Formulation A vs Dexlansoprazole Capsule	
Cmax	1.7962	1.6143 – 1.9986
AUC(0-inf)	1.2803	1.1816 – 1.3873
AUC(0-tlqc)	1.2781	1.1818 – 1.3821
Parameter	ODT Formulation B vs Dexlansoprazole Capsule	
Cmax	1.9745	1.7745 – 2.1970
AUC(0-inf)	1.3821	1.2763 – 1.4966
AUC(0-tlqc)	1.3870	1.2826 – 1.4999

Table 11: Intragastric pH Comparison Over the 24 Hours on Day 5 from Study TAK-390MR (OD)_101

Parameter	Regimen			90% CI		
	A (N=48)	B (N=48)	C (N=48)	A vs C	B vs C	A vs B
Mean pH	4.2	4.2	4.4	(-0.33, 0.07)	(-0.35, 0.05)	(-0.18, 0.22)
Percentage of Time pH >4	58	56	60	(-6.2, 1.4)	(-7.8, -0.1)	(-2.2, 5.4)

Source: [Table 15.2.10.1](#).

Note: Regimen A: Dexlansoprazole ODT Formulation A 30 mg QD for 5 days in the fasted state.

Regimen B = Dexlansoprazole ODT Formulation B 30 mg QD for 5 days in the fasted state.

Regimen C = Dexlansoprazole capsule 30 mg QD for 5 days in the fasted state.

Subjects with a pharmacodynamic parameter estimated for Regimen C and at least 1 of Regimens A or B were included in the analysis.

(b) (4)

(b) (4)

2.4 General Biopharmaceutics

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

Administration of Dexilant SoluTab 30 mg tablet with high-fat breakfast reduced the C_{max} by 38%, delayed T_{max} by 2 hours, but did not change the AUC compared to the fasted state. (b) (4)

However, as there is no exposure-response data or efficacy data with lower than 30 mg dose for the reference product Dexilant Capsule to support that the reduction in C_{max} by 38% would not comprise the efficacy of dexlansoprazole, the agency will recommend taking Dexilant SoluTab 30 mg tablet at least 30 minutes before the meal in the label.

Please note that during the drug development for the reference product Dexilant capsule, the efficacy of Dexilant capsule for maintenance of EE and treatment of GERD were only evaluated at 30 mg, 60 mg and 90 mg dose strengths, and no dose-response relationship was observed between these evaluated doses for both of these two indications. Any dose lower than 30 mg was not evaluated for both indications nor an exposure-response relationship was explored during the Dexilant capsule drug development program to support that the reduction in C_{max} by 38% would or would not compromise the efficacy of dexlansoprazole for of maintenance of EE and treatment of GERD.

This observed food effect on dexlansoprazole 30 mg ODT, reduction in C_{max} , is in opposite direction compared to the food effect in the reference product Dexilant capsule, in which coadministration of food with dexlansoprazole 90 mg capsule had increase the C_{max} by 12-55% and increased AUC by 9-37%. Although Dexilant capsule was administered before breakfast in all clinical efficacy and safety studies for Dexilant capsule approval, based on the result of this food effect study, Dexilant capsule is recommended to with without regard to food in the label.

Study TAK-390MR(OD)-103: The effect of food on Dexilant SoluTab 30 mg tablet was evaluated in an open-label, phase 1, randomized, single-center, single-dose, 3-period crossover study in 72 healthy subjects following a single dose administration of dexlansoprazole delayed-release OD 30 mg tablets under fed and fasted conditions. There was at least a 5-days of washout period between the treatments, and PK samplings were collected up to 24 hours post-dose. In the fasted regimen (Regimen C), following an overnight fasting of at least 10 hours, a single oral dose of dexlansoprazole 30 mg OD tablet was administered on the tongue and allowed to disintegrate, and swallowed without water. After the dose administration, subjects continued to fast additional 4 hours. In fed condition (Regimen A), following overnight fasting of at least 10-hours, a single oral dose of dexlansoprazole 30 mg OD tablet was administered on the tongue and allowed to disintegrate, and swallowed without water 30 minutes after starting to ingest a high-fat meal. The meal was consumed in its entirety within 25 minutes and no additional food was

allowed for 4 hours postdose. The standard high-fat breakfast contained approximately 800 to 1000 total calories, with 50% of calories being derived from fat content. An example of a standard high-fat breakfast was: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. This meal derived approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively. The content of the high-fat, high-caloric breakfast followed the recommendations given in the FDA guidance “Food Effect Bioavailability and Fed Bioequivalence Studies”.

When dexlansoprazole delayed release OD 30 mg tablet was administered under fed condition with high-fat meal, C_{max} was reduced by 38% compared fasted states where AUC remained similar. Time to maximum concentration (t_{max}) was delayed by 2 hrs in fed state compared to fasted state (4 hr vs. 6 hrs).

Figure 9: Mean (SD) Plasma Concentration-Time Profiles for Dexlansoprazole Following Administration of Dexlansoprazole Delayed-Release 30 mg OD Tablet in the Fed and Fasted State in Healthy Subjects

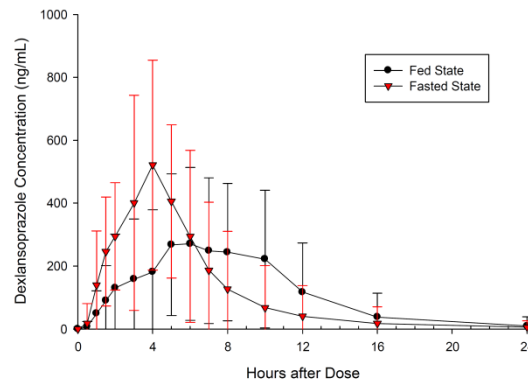


Table 12: Summary of the Dexlansoprazole PK Parameter (CV%) Estimates Following Administration of the Dexlansoprazole Delayed-Release 30 mg OD Tablet in the Fed and Fasted States in Healthy Subjects (n=65)

Parameters (unit)	Fasted	Fed
C_{max} (ng/mL)	688 (48%)	445 (57)
$AUC_{0-\infty}$ (ng/mLh)	2839 (86%)	2744 (93%)
AUC_{0-t} (ng•h/mL)	2789 (83%)	2683 (88%)
Median T_{max} (h) [min, max]	4.00 (1.5-6.00)	6.00 (1.5-10.08)
$T_{1/2}$ (hr)	2.07 (76%)	2.00 (51)
CL/F (L/hr)	16.01 (60%)	17.45 (65%)
V_z/F (L)	47.35 (139)	44.40 (73%)

Table 13: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Single Dose Oral Administration of the Dexlansoprazole 30 mg Orally Disintegrating Tablet in the Fed State and the Fasted State (sponsor provided):

Parameter (N) (a)	Point Estimate of the Relative BA	90% CIs for the Point Estimate
OD Tablet Administered in the Fed State (Regimen A) vs the Fasted State (Regimen C) (b)		
C_{max} (66/67)	0.6202	(0.5568 – 0.6908)
$AUC(0-t_{lqc})$ (66/67)	0.9364	(0.8664 – 1.0121)
$AUC(0-\infty)$ (65/67)	0.9481	(0.8776 – 1.0242)

(b) Regimen A: Dexlansoprazole 30 mg OD tablet, administered on the tongue, allowed to disintegrate, and swallowed without water after a high-fat meal (Test).

Regimen C: Dexlansoprazole 30 mg OD tablet, administered on the tongue after a fast, allowed to disintegrate, and swallowed without water (Reference).

The BE analysis was reanalyzed and results were consistent with sponsor's result.

Table 14: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Single Dose Oral Administration of the Dexlansoprazole 30 mg Orally Disintegrating Tablet in the Fed State and the Fasted State: (Reviewer's Analysis)

Delayed-Release OD 30 mg Tablet Fed (Regimen A) vs Fasted (Regimen C)			
Parameter (N)	Point Estimate of the Relative BA	Lower 90% CL	Upper 90% CIs
C _{max}	61.81	55.54	68.81
AUC(0-tl _{qc})	93.52	86.54	101.07
AUC(0-inf)	94.60	87.58	102.19

2.4.2 Can water be used to rinse mouth after administration of Dexilant SoluTab?

No, when administration of Dexilant SoluTab 30 mg tablet was followed by rinsing the mouth with 240-mL water, AUC was reduced by 20% and C_{max} was reduced by 29% compared to when Dexilant SoluTab 30 mg tablet was administered without water. (b) (4)

However, there is no exposure-response data or efficacy data with lower than 30 mg dose for the reference product Dexilant Capsule to support that reduction in AUC by 20% and reduction C_{max} by 29% would not comprise the efficacy of dexlansoprazole. (b) (4)

Therefore, the agency will recommend to place Dexilant SoluTab 30 mg tablet on the tongue, allow it to disintegrate, and swallow the microgranules without water in the label. Please see 2.4.1 for further discussion in similar matter.

Study TAK-390MR(OD)-103 also evaluated the effect of water on pharmacokinetic of dexlansoprazole following the single dose administration of dexlansoprazole delayed-release ODT 30 mg tablets. Please see section 2.4.1 for study design. In both treatments, subjects were fasted a minimum of 10 hour prior to dosing and remained fasted for 4 additional hours post-dose.

- **Treatment B:** A single oral dose of dexlansoprazole 30 mg OD tablet, administered on the tongue, allowed to disintegrate, swallowed without water, and followed with a 240-mL water rinse (Test).
- **Treatment C:** A single oral dose of dexlansoprazole 30 mg OD tablet, administered on the tongue, allowed to disintegrate, and swallowed without water (Reference).

Administering dexlansoprazole delayed release OD 30 mg tablet with water reduced the AUC and C_{max} by 20% and 29%, respectively, compared to when it was administered without water. The exposure difference appears to be mainly due to the concentration difference between 2 to 6 hours.

Figure 10: Mean (SD) Plasma Concentration-Time Profiles for Dexlansoprazole Following Administration of Dexlansoprazole Delayed-Release 30 mg OD Tablet in the Fasted State With or Without Water in Healthy Subjects

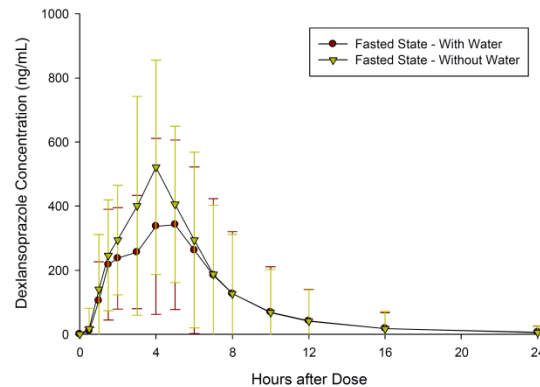


Table 15: Summary of the Dexlansoprazole PK Parameter (CV%) Estimates Following Administration of the Dexlansoprazole Delayed-Release 30 mg OD Tablet in the Fasted State With or Without Water in Healthy Subjects (n=64)

Parameters (unit)	With Water (Treatment B)	Without Water (Treatment C)
C _{max} (ng/mL)	508 (59%)	688 (48%)
AUC _{0-∞} (ng/mLh)	2402 (94%)	2839 (86%)
AUC _{0-t} (ng•h/mL)	2351 (91%)	2789 (83%)
Median T _{max} (h) [min, max]	4.00 (1.05-7.00)	4.00 (1.5-6.00)
T _{1/2} (hr)	2.59 (59%)	2.07 (76%)
CL/F (L/hr)	20.58 (66%)	16.01 (60%)
V _z /F (L)	71.98 (93%)	47.35 (139)

Table 16: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Single Dose Oral Administration of the Dexlansoprazole 30 mg Orally Disintegrating Tablet in the Fasted State With or Without Water in Healthy Subjects (sponsor provided):

OD Tablet Administered Fasted With Water (Regimen B) vs the Fasted State Without Water (Regimen C) (b)		
C _{max} (64/67)	0.7110	(0.6375 – 0.7930)
AUC(0-tlqc) (64/67)	0.7997	(0.7393 – 0.8652)
AUC(0-inf) (64/67)	0.8023	(0.7423 – 0.8672)

The BE analysis was reanalyzed and results were consistent with sponsor's result.

Table 17: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Single Dose Oral Administration of the Dexlansoprazole 30 mg Orally Disintegrating Tablet in the Fasted State With or Without Water in Healthy Subjects: (Reviewer's Analysis)

Delayed-Release OD 30 mg Tablet with water (Regimen B) vs without water (Regimen C)			
Parameter (N)	Point Estimate of the Relative BA	Lower 90% CL	Upper 90% CIs
C _{max}	70.65	63.44	78.69
AUC(0-tlqc)	79.69	73.69	86.19
AUC(0-inf)	79.97	74.00	86.41

2.4.3 What are the alternative options of administering Dexilant SoluTab?

When a single dose of Dexilant SoluTab 30 mg tablet was mixed with water and administered via an oral syringe or an NG tube, or swallowed as an intact OD tablet with water, were each bioequivalent to the oral administration of the intact OD tablet on the tongue allowed to disintegrate and swallowed without water. Therefore, in the label, we recommend that Dexilant SoluTab 30 mg can be administered with water via oral syringe or NG tube or may also be swallowed whole with water.

Study TAK-390MR(OD)-106 was an open-label, phase 1, randomized (1:1:1:1 ratio), single-center, single-dose, 4-period crossover study in 71 healthy subjects to evaluate the PK and assess the relative bioavailability of dexlansoprazole from the three alternative dose administration options of dexlansoprazole delayed-release OD 30 mg tablets compared to when dexlansoprazole delayed-release OD 30 mg tablet was administered in tongue and allowed to disintegrate on the tongue and swallowed without water. In all regimens, subjects fasted for a minimum of 10 hours prior to dosing on Day 1 and remained fasted for additional 4 hours post-dose. PK samples were collected for up to 24 hours post-dose and the washout interval between each period was at least 5 days.

- Regimen A: A single oral dose of dexlansoprazole delayed-release OD 30 mg tablet mixed with water and administered orally via syringe (Test).
- Regimen B: A single oral dose of dexlansoprazole delayed-release OD 30 mg tablet mixed with water and administered via NG tube (Test).
- Regimen C: A single oral dose of dexlansoprazole delayed-release OD 30 mg tablet, swallowed intact with water (Test).
- Regimen D: A single oral dose of dexlansoprazole delayed-release 30 mg OD tablet, administered on the tongue, allowed to disintegrate, and swallowed without water (Reference).

The mean dexlansoprazole plasma concentration-time profiles were similar under all four conditions of single-dose administration of dexlansoprazole delayed-release OD 30 mg tablets.

Figure 11: Mean (SD) Plasma Concentration-Time Profiles for Dexlansoprazole Following a Single Dose administration of Dexlansoprazole Delayed-Release OD 30 mg Tablet in Healthy Subjects under Various Dose Administration Conditions (Sponsor provided)

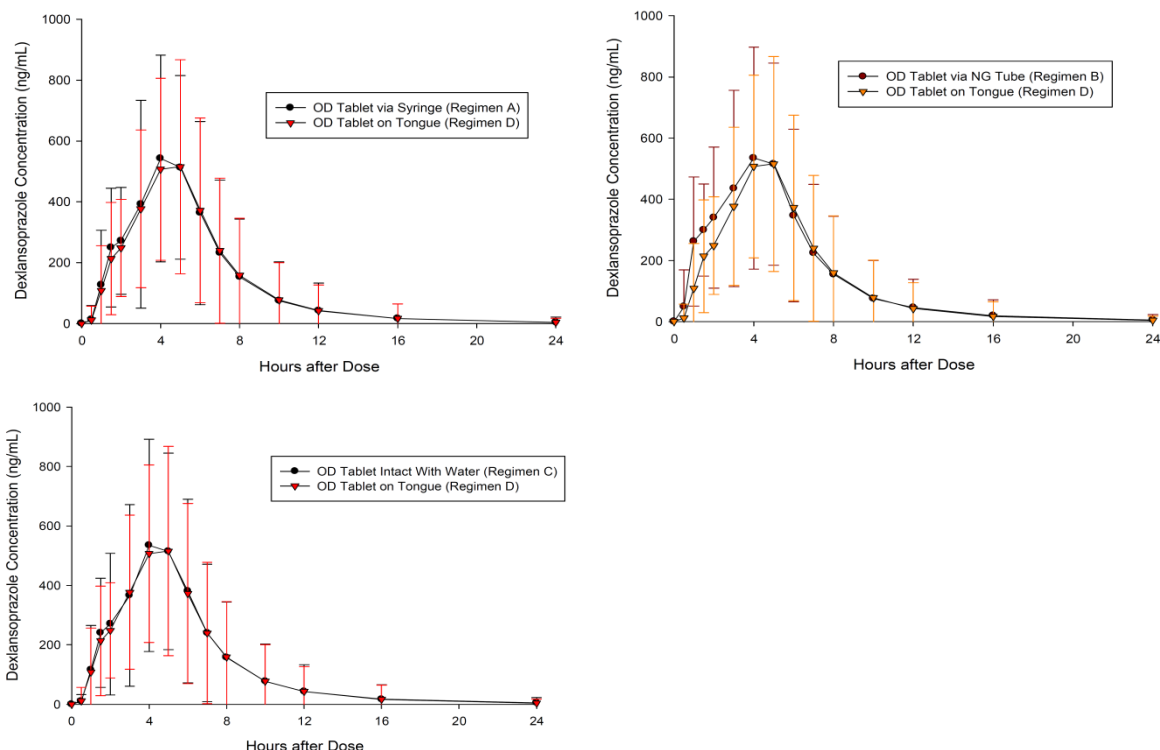


Table 18: Summary of the Plasma PK Parameter Estimates for Dexlansoprazole Following Administration of Dexlansoprazole Delayed- Release OD 30 mg Tablet under Various Conditions in Healthy Subjects

Parameters (unit)	OD Tablet via Syringe (Regimen A)	OD Tablet via NG Tube (Regimen B)	OD Tablet Intact With Water (Regimen C)	OD Tablet on Tongue (Regimen D)
C_{max} (ng/mL)	760 (44%)	786 (41%)	775 (47%)	744 (41%)
AUC_{0-t} (ng/mLh)	3080 (76%)	3276 (68%)	3058 (71%)	3011 (67%)
$AUC_{0-\infty}$ (ng•h/mL)	3120 (78%)	3340 (70%)	3121 (73%)	3043 (69%)
Median T_{max} (h) [min, max]	4.00 (1.00-6.02)	4.00 (1.00-12.00)	4.00 (1.50 -6.02)	4.00 (1.50-6.03)
$T_{1/2}$ (hr)	1.85 (56%)	1.89 (59%)	1.98 (60%)	1.86 (51%)
CL/F (L/hr)	13.52 (52%)	12.70 (58%)	13.38 (55%)	14.02 (63%)
V_z/F (L)	32.97 (72%)	31.66 (86%)	37.52 (98%)	36.13 (96%)

Table 19: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Administration of Dexlansoprazole Delayed- Release OD 30 mg Tablet as an Aqueous Mixture via an Oral Syringe or NG Tube, as the Intact Tablet Swallowed With Water, or as the Intact Tablet on the Tongue Without Water in Healthy Subjects (Sponsor Provided)

Parameter	Point Estimate of the Relative BA	90% CIs for the Point Estimate
Oral Syringe Administration (Regimen A [Test]) vs Intact Tablet on the Tongue (Regimen D [Reference])		
C _{max} (N=72/74)	1.0218	(0.9318-1.1205)
AUC(0-tl _{qc}) (N=72/74)	1.0069	(0.9405-1.0780)
AUC(0-inf) (N=72/74)	1.0070	(0.9411-1.0776)
NG Tube Administration (Regimen B [Test]) vs Intact Tablet on the Tongue (Regimen D [Reference])		
C _{max} (N=71/74)	1.0613	(0.9674-1.1644)
AUC(0-tl _{qc}) (N=71/74)	1.0831	(1.0113-1.1600)
AUC(0-inf) (N=70/74)	1.0814	(1.0100-1.1579)
Intact Tablet Swallowed With Water (Regimen C [Test]) vs Intact Tablet on the Tongue (Regimen D [Reference])		
C _{max} (N=74/74)	1.0040	(0.9164-1.1000)
AUC(0-tl _{qc}) (N=74/74)	1.0154	(0.9491-1.0864)
AUC(0-inf) (N=73/74)	1.0191	(0.9527-1.0901)

The BE analysis was reanalyzed and results were consistent with sponsor's result.

Table 20: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Administration of Dexlansoprazole Delayed- Release OD 30 mg Tablet as an Aqueous Mixture via an Oral Syringe or NG Tube, as the Intact Tablet Swallowed with Water, or as the Intact Tablet on the Tongue without Water in Healthy Subjects (Reviewer's analysis):

Parameter (N)	Point Estimate of the Relative BA	Lower 90% CL	Upper 90% CIs
Oral Syringe Administration (Regimen A) vs Intact Tablet on the Tongue (Regimen D)			
C _{max}	101.92	93.02	111.67
AUC(0-tl _{qc})	100.71	94.12	107.76
AUC(0-inf)	100.72	94.18	107.71
NG Tube Administration (Regimen B) vs Intact Tablet on the Tongue (Regimen D)			
C _{max}	106.61	97.25	116.88
AUC(0-tl _{qc})	108.46	101.32	116.09
AUC(0-inf)	108.34	101.24	115.95
Intact Tablet Swallowed With Water (Regimen C) vs Intact Tablet on the Tongue (Regimen D)			
C _{max}	101.099	92.33	110.70
AUC(0-tl _{qc})	101.892	95.28	108.96
AUC(0-inf)	102.29	95.68	109.37

2.4.4 What is the disintegration time for the proposed orally disintegrating tablet (ODT)?

Both mean and median disintegration time for Dexilant SoluTab 30 mg tablet on tongue was 36 second (ranged 29-43 seconds). However, in this study that measured disintegration time, subjects sipped and swallowed 20 mL of spring water 30 seconds prior to study drug administration which could shorten the true disintegration time. As the general definition of ODT is rapid oral disintegration in saliva without the need for chewing or drinking liquids to ingest these products, the reported in vivo disintegration time in this study with sipping 20 mL of was 30 seconds prior to study drug administration could be biased and unreliable. Therefore, the reported disintegration time in this study will not have labeling implication. Nonetheless, the reported in-vivo disintegration time in this study is in similar range as the reported in-vitro disintegration time of 32.9 second with 95% CI of 23.2~42.6 second (according to the Biopharm reviewer Dr. Peng Duan in OB/ONDP).

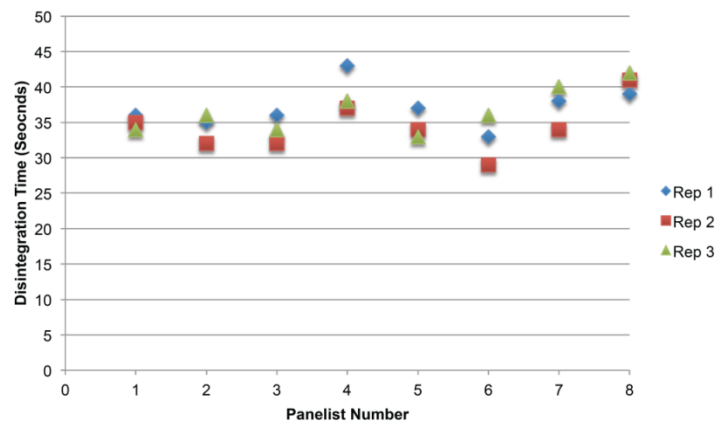
TAK-390MR(OD)-107 was an open-label, single –center study in 8 healthy subjects to evaluate the in vivo disintegration time of a single dexamethasone delayed-release OD 30 mg tablet. Each subject evaluated the disintegration time of 3 separate single doses of the OD 30 mg tablet; on a given testing day, subjects may have received up to 2 doses of study drug (maximum dose of 60 mg/day), and the entire 3 doses may have been administered over several days. For each disintegration time assessment, subjects sipped and swallowed 20 mL of spring water 30 seconds prior to study drug administration. Thirty seconds after the water was consumed, the OD tablet was placed on the tongue and gently rolled against the roof of the mouth with the tongue until the tablet disintegrated into small granules. At the point at which the subject would normally swallow the granules, they recorded the elapsed time and expectorated the disintegrated tablet mass and not swallowed.

Individual disintegration times in each trial ranged from 29 seconds to 43 seconds, with an overall mean of 36 seconds.

Table 21: In Vivo Disintegration Times of a Single Dose of a Dexamethasone Delayed- Release OD 30 mg Tablet

Subject	Disintegration Time (sec)			Mean	Median
	1	2	3		
1	36	35	34	35.0	35
2	35	32	36	34.3	35
3	36	32	34	34.0	34
4	43	37	38	39.3	38
5	37	34	33	34.7	34
6	33	29	36	32.7	33
7	38	34	40	37.3	38
8	39	41	42	30.7	41
Mean				36.0	36
Range of individual trials				29, 43	N/A
1 st quartile				N/A	34
3 rd quartile				N/A	38

Figure 12: Individual Disintegration Time



2.4.5 Does ethanol *in vitro* have a dose-dumping effect on the MR product? If so, whether an *in vivo* study with ethanol has been conducted? What is the clinical relevance of the findings?

In this submission, only *in-vitro*, but not *in-vivo*, alcohol dose dumping study was conducted. According to the Biopharm reviewer Dr. Peng Duan in OB/ONDP, based on the *in-vitro* alcohol dose dumping study, there is significant potential of alcohol dose-dumping for drug release at the acid stage in the presence of 40% alcohol. 90% of drug was released within 30 min in the presence of 40% alcohol, compared to 1-2% of drug release at the same time point in the presence of 0%, 5%, and 20% alcohol. Please refer to Biopharm review by Dr. Peng Duan for further details.

This observed early release of dexlansoprazole from Dexilant SoluTab in presence of 40% alcohol will expose dexlansoprazole early in the acidic environment of the stomach. As dexlansoprazole is an acid-labile drug, the acidic environment of stomach will potentially degrade dexlansoprazole and thus, will potentially shorten the t_{max} , reduce the AUC and the C_{max} and therefore, may compromise the efficacy of the drug, but less likely the safety of the drug. As we do not anticipate this alcohol induced dose dumping of dexlansoprazole from Dexilant SoluTab will affect the safety profile of the drug, a follow-up *in-vivo* alcohol dose dumping study may not be necessary. This observed alcohol dose dumping issue would be addressed by the product labeling by instructing the patients to avoid alcohol when taking Dexilant SoluTab in the label.

2.4.6 Were there any major changes to the drug substance and/or drug product during the development process? Are there *in vivo* bioequivalence (BE) or comparability studies to compare PK or PD of various formulations?

During the drug development, the sponsor explored several different formulations of dexlansoprazole delayed release OD tablets. In study TAK-390MR(OD)_101, the sponsor explored formulation A and B and both of these formulations failed to meet the BE criteria to Dexilant capsule. Since these two formulations were not developed any further due to failed BE, this study was not reviewed in detail in this review.

The sponsor conducted further formulation exploration study TAK-390MR(OD)_102 where sponsor compared the relative bioavailability dexlansoprazole from three formulations of dexlansoprazole delayed-release OD tablets 30 mg (formulation X, Y and Z) relative to dexlansoprazole delayed-release capsules 30 mg in a single-dose, 4-period crossover study. In this study, dexlansoprazole AUC from each of the 3 delayed-release OD tablet formulations was equivalent to the AUC from the delayed-release capsule. However, C_{max} of dexlansoprazole from Formulations X, Y, and Z were all higher than that of dexlansoprazole delayed-release capsules, and the upper bound of 90% CIs was above 1.25 for all 3 formulations. Since the C_{max} from Formulation Z was the closest to the C_{max} from the delayed-release capsule, the sponsor had conducted further relative BA study with two-way cross over study design to directly compare the relative bioavailability of dexlansoprazole delayed-release OD tablets 30 mg from Formulation Z to dexlansoprazole delayed-release capsules 30 mg in study TAK-390MR(OD)-105 and had demonstrated Formulation Z of dexlansoprazole delayed-release OD tablets 30 mg is bioequivalent to dexlansoprazole delayed-release capsules 30 mg. Please see section 2.3.1 for further details of the study result. Based on this established bioequivalence, Formulation Z was chosen as the to-be-marketed formulation and conducted further studies such as bioequivalence study with two 30 mg ODT (TAK-390MR(OD)_104), food and water effect study (TAK-390MR(OD)_103), alternative dose administration study (TAK-390MR(OD)_106), and *in-vivo* disintegration time study (TAK-390MR(OD)_107) with this formulation Z.

2.5 Analytical Section

2.5.1 How are the active moieties identified and measured in the plasma/urine in the clinical pharmacology and biopharmaceutics studies?

Concentration of dexlansoprazole in human plasma samples were identified and measured with validated HPLC-MS/MS bioanalytical methods.

2.5.2 Which metabolites have been selected for analysis and why?

No metabolites were selected for analysis as the parent drug dexlansoprazole account for the major component in the plasma.

2.5.3 For all moieties measured, is free, bound, or total measured?

Total drug concentration was measured.

2.5.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

The concentrations of dexlansoprazole in human plasma were determined using validated liquid chromatography mass spectrometry (HPLC/MS/MS) methods developed by (b) (4) in all studies (method validation report P896, Project AEMS).

2.5.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used? What are the lower and upper limits of quantification (LLOQ/ULOQ)?

Calibration standard curve consisted of 8 levels ranged from 2.00 to 2000 ng/mL in human plasma, with an LLOQ of 2.00 ng/mL, and was calculated using a linear (1/concentration squared weighted) least-squares regression algorithm. Average back calculated values and reproducibility from each level of the calibration curve met the acceptance criteria of being <15% (<20% at LLOQ). % CV ranged between 1.03% to 7.04% and % difference from theoretical ranged from -1.84% to 1.33%.

2.5.6 What are the accuracy, precision and selectivity at these limits?

The accuracy and precisions of all QC samples were within the acceptable range (<20% for LLOQ QC and <15% for all other QC).

Matrix		Intra-assay	Inter-Assay
Plasma	Precision (CV%)	0.732% to 13.7% (<16.1% for LLOQ QC)	3.75% to 8.01%, (12.8 % for LLOQ QC)
	Accuracy	-0.357% to 12% (<14.4% for LLOQ QC)	4.92% to 7.76%. (12.9% for LLOQ QC)

The ability to analyze samples with an insufficient volume for a full aliquot was validated by analyzing six replicate, diluted, medium-level QC 60.00 ng/mL in plasma sample. The ability to dilute samples originally above the upper limit of the calibration range was validated by analyzing six replicate 4000 ng/mL QCs in plasma samples. The both QCs had acceptable level of precision and accuracy (< 15%), where %CV was 3.62% and 1.89%, and the % difference from theoretical was 3.17% and -0.779%.

The bioanalytical methods were specific and selective. When blank human plasma samples from six individuals, containing EDTA, were extracted and analyzed for lansoprazole and its internal standard, there were no significant chromatographic peaks detected at the mass transitions and expected retention times of the analyte or internal standard which would interfere with quantitation. When aliquots of blank human plasma were fortified with only the analyte or internal standard and analyzed in triplicate, there were no significant chromatographic peaks detected at the mass transition and expected retention time of the unfortified components which would interfere with quantitation.

There was no significant matrix suppression effects that could compromise the sensitivity or accuracy of the assay. Human plasma samples from six individuals were fortified with lansoprazole at a low QC level (nominally 6.00 ng/mL), and analyzed in triplicate to evaluate potential matrix suppression effects. %CV ranged 1.75% to 5.51% and % difference from theoretical was -5.47% to 3.80%.

No apparent abnormalities associated with reinjection of sample extracts were observed.

2.5.7 What is the sample stability under the conditions used in the study?

Dexlansoprazole in plasma samples were stored at frozen at -20°C until analysis and analyzed within the stability limit in all studies.

freeze-thaw	room temperature	at -20°C
5 cycles	24.75 hr	232 Days

No apparent abnormalities associated with post-preparative storage for up to 74.5 hours at room temperature were observed. Post-preparative extract stability was demonstrated by analyzing quality controls which were extracted and stored at room temperature for approximately 74.5 hours prior to analysis versus freshly-prepared calibration curves and quality controls

2.5.8 What is the plan for the QC samples and for the reanalysis of the incurred samples?

QC samples at 5 different concentrations of lansoprazole in human plasma were at 6.0, 15.0, 60.0, 250, and 1500 ng/mL.

At least 5% of the study samples were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification in all studies. The incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20% in all studies.

3 Appendix

3.1 Individual Study Reports

Study: TAK-390MR(OD)_102

Title: A Phase 1, Randomized, Open-Label, Single Center, Single Dose, Four Period, Crossover Study to Assess the Bioavailability of Three 30 mg Dexlansoprazole Delayed Release Orally Disintegrating Tablet Formulations Relative to Dexlansoprazole Delayed Release Capsule (30 mg) in Healthy Subjects

Sponsor: Takeda Global Research & Development Center, Inc.
Clinical Site: Celerion, Inc., Tempe, AZ
Bioanalytical Site: (b) (4)
Pharmacogenomic:
Study Date: 08/09/2011 – 09/11/2011

OBJECTIVE:

The primary objective of this study was to determine the BA of dexlansoprazole from a single dose of 3 formulations of dexlansoprazole delayed-release OD tablets 30 mg relative to dexlansoprazole delayed-release capsules 30 mg.

STUDY DESIGN:

- Regimen A: A single oral dose of dexlansoprazole delayed-release OD 30 mg tablet, Formulation X.
- Regimen B: A single oral dose of dexlansoprazole delayed-release OD 30 mg tablet, Formulation Y.
- Regimen C: A single oral dose of dexlansoprazole delayed-release OD 30 mg tablet, Formulation Z.
- Regimen D: A single oral dose of dexlansoprazole 30 mg delayed-release capsule (Reference).

This study was an open-label, phase 1, randomized, single-center, single-dose, 4-period crossover study in 64 healthy subjects to evaluate the pharmacokinetic of dexlansoprazole following the single dose administration of either different formulations of dexlansoprazole delayed-release ODT 30 mg tablets (formulation X, Y and Z) or dexlansoprazole delayed-release 30 mg capsule. Subjects fasted for a minimum of 10 hours prior to dosing and 4 hours postdosing and breakfast was not served on the day of dosing during each period. Subjects who received the dexlansoprazole delayed-release OD tablet formulations were administered the tablet directly on the tongue, without water. Subjects were instructed to allow the dexlansoprazole delayed-release OD tablet to disintegrate on the tongue and to swallow the granules without chewing. Subjects who received the dexlansoprazole delayed-release capsule were instructed to swallow the intact capsule with 240 mL of water. There was at least a 5-day of washout period between each period. Pharmacokinetic blood samples were collected for up to 24 hours post-dose to determine the plasma concentrations of dexlansoprazole.

Excluded Medications and Dietary Products

28 Days Prior to Check-in (Day -1 of Period 1)	14 Days Prior to Check-in (Day -1 of Period 1)	72 Hours Prior to Check-in (Day -1 of Period 1)
Prescription medications (a)	OTC medications (b)	Alcohol-containing products
Nutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Vitamin supplements	Products containing caffeine
Nicotine-containing products	Foods or beverages containing grapefruit or Seville-type (sour) oranges	
Hepatic or renal clearance altering agents		
Intake of known OTC inhibitors/inducers of CYPs 3A4/5 and 2C19	Immunization/Vaccines	

(a) Hormonal contraception and hormone replacement therapy (HRT) were allowed as long as a subject had been on a stable dose for a minimum of 90 days prior to Day 1 of Period 1.

(b) Occasional use of acetaminophen (≤ 2 g/day) was allowed or other medication as approved by Takeda on a case-by-case basis. Acetaminophen was not allowed on Day 1 of any study period.

Study Population: The study included healthy males and non-pregnant, non-lactating females ages between 18-55 with good health with a BMI between 18-30 kg/m². This study had 64 healthy volunteers enrolled and 62 of them completed the study as planned by completing all four treatments. Two subjects discontinued prematurely, one subject due to adverse event and one subject with voluntary withdrawal.

Pharmacogenomic: genotyping for CYP2C19 was conducted on Day 1 of period 1 for all subjects since dexlansoprazole is metabolized by the polymorphic isozyme CYP2C19.

Pharmacokinetic Measurements:

PK blood samples were collected at 0 hour (within 30 minutes before dosing) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours after dosing to determine the plasma concentration of dexlansoprazole on each period.

PK Parameters Analysis:

Pharmacokinetic parameter estimates for dexlansoprazole were calculated using WinNonlin version 5.2 or higher with non-compartmental methods. Statistical analysis was performed using ANOVA to compare the natural logarithmic (ln)-transformed PK parameters AUCs and Cmax of dexlansoprazole. The ANOVA model included sequence, period, and treatment as fixed effects, and subject within sequence as a random effect. Pairwise comparisons of each dexlansoprazole delayed-release OD tablet formulation to the dexlansoprazole delayed-release capsule were conducted and 90% CI for dexlansoprazole Cmax and AUCs central value ratios were computed. Bioequivalence (BE) between the regimens was concluded if the 90% CIs were completely contained within the equivalence range of 0.80 and 1.25 for dexlansoprazole Cmax and AUCs.

Actual sampling times, rather than scheduled sampling times, were used in all relevant computations. Concentrations below the lower limit of quantitation were set to zero for PK analysis.

Bioanalytical Method:

- Concentrations of dexlansoprazole in human plasma were measured by a validated LC/MS/MS at (b) (4)
 - Project samples were analyzed according to (b) (4), entitled "Determination of Lansoprazole in Human Plasma by LC/MS/MS," which was validated under Project Code "AEMS." This method is applicable to the quantitation of lansoprazole within a nominal range of 2.00 to 2000 ng/mL.
- Plasma samples were stored frozen at -20°C or colder until analysis

- Calibration standard curve consisted of 8 level ranged from 2 to 2000 ng/mL in human plasma, and was calculated using a linear (1/concentration squared weighted) least-squares regression algorithm. The R^2 ranges between 0.9975- 0.9995.
- QC samples at 5 different concentrations (6.00, 15.0, 60.0, 250, and 1500 ng/mL) of dexlansoprazole were prepared
- The inter-assay coefficients of variation of the QCs run ranged from 2.39% to 8.16%, with mean percent differences from theoretical ranging from -3.10% to 3.86%.
- The differences of back-calculated calibration curve values from nominal values ranged from -2.87 to 2.50%.
- At least 10% of the study samples were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification. The incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20%.
- Plasma samples, stored at approximately -20°C, were analyzed within the time period for which the long-term stability of plasma dexlansoprazole has been established.
 - Plasma samples were collected between 08/09/2011 through 09/11/2011.
 - Plasma samples were analyzed between 09/15/2011 through 10/25/2011.
 - The maximum storage period from collection through analysis was 76 days.
 - The long term storage stability of omeprazole in human plasma at -20 °C was established for at least for 232 days.

RESULTS:

Figure 1: Mean Plasma Concentration Versus Time Curves of Dexlansoprazole Following Administration of a Single Dose of 3 Formulations of Dexlansoprazole Delayed-Release OD Tablets and Dexlansoprazole Delayed-Release Capsules to Healthy Subjects

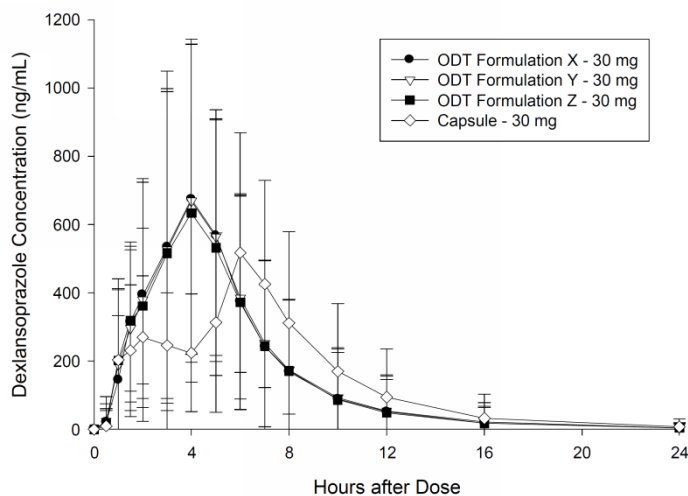


Table 1: Summary of Pharmacokinetic Parameter Estimates of Dexlansoprazole Following Administration of a Single Dose of Dexlansoprazole 30 mg Delayed-Release OD Tablet Formulations X, Y, and Z and Dexlansoprazole Delayed-release 30 mg Capsules to Healthy Subjects

	Tmax (a) (hr)	Cmax (ng/mL)	AUC(0-t _{lqc}) (ng·hr/mL)	AUC(0-inf) (ng·hr/mL)	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)
Dexlansoprazole Delayed-Release OD Tablet Formulation X							
N	62	62	62	50	50	50	50
Mean	NR	910	3657	4026	1.90	10.46	25.19
SD	NR	461.2	2758.6	3009.0	0.986	5.338	15.170
Min	1.00	185	978	1140	0.74	1.93	9.24
Median	4.00	890	2730	2985	1.59	10.05	19.22
Max	12.02	2230	15103	15575	4.43	26.33	87.01
%CV	NR	51	75	75	52	51	60
Dexlansoprazole Delayed-Release OD Tablet Formulation Y							
N	62	62	62	50	50	50	50
Mean	NR	890	3700	4161	1.93	10.56	25.86
SD	NR	463.0	2812.8	3046.7	1.034	6.441	21.482
Min	1.50	202	551	1072	0.77	1.90	10.24
Median	4.00	854	2961	3635	1.59	8.26	20.39
Max	9.98	2120	15292	15767	4.74	27.98	148.14
%CV	NR	52	76	73	54	61	83
Dexlansoprazole Delayed-Release OD Tablet Formulation Z							
N	62	62	62	50	50	50	50
Mean	NR	842	3558	4036	2.01	11.90	32.71
SD	NR	507.4	2966.9	3192.8	1.004	9.642	39.620
Min	1.00	84	506	517	0.86	1.99	10.70
Median	4.00	736	2825	3134	1.56	9.57	20.32
Max	7.00	2370	14801	15094	4.56	58.05	276.37
%CV	NR	60	83	79	50	81	121
Dexlansoprazole Delayed-Release Capsule							
N	62	62	62	50	50	50	50
Mean	NR	627	3452	3925	2.12	11.73	30.45
SD	NR	311.3	2644.4	2924.0	1.036	7.336	18.935
Min	0.98	204	746	942	0.81	2.10	11.82
Median	5.99	566	2530	2786	1.73	10.77	24.32
Max	12.00	1670	13583	14298	5.11	31.86	115.11
%CV	NR	50	77	75	49	63	62

Figure 2: Box Plots for Dexlansoprazole C_{max} and AUC Values Following Oral Administration of Dexlansoprazole Delayed-Release 30 mg OD Tablet Formulations X, Y, and Z, and 30 mg Dexlansoprazole Delayed-Release Capsule to Healthy Subjects

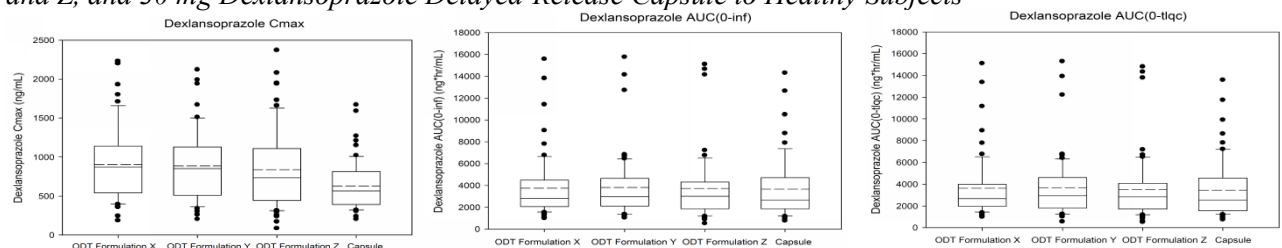


Table 2: Statistical Comparisons of Pharmacokinetic Parameter Estimates for Dexlansoprazole From Delayed-Release OD Tablet Formulations X, Y, and Z, Relative to the Delayed-Release Capsule

Parameter	Point Estimate of the Relative Bioavailability	90% CIs for the Point Estimate
Dexlansoprazole Delayed-Release OD Tablet Formulation X vs Dexlansoprazole Delayed-Release Capsule		
C _{max}	1.4205	(1.2850 – 1.5703)
AUC(0-tl _{qc})	1.0914	(1.0129 – 1.1759)
AUC(0-inf)	1.0907	(1.0152 – 1.1718)
Dexlansoprazole Delayed-Release OD Tablet Formulation Y vs Dexlansoprazole Delayed-Release Capsule		
C _{max}	1.3753	(1.2441 – 1.5204)
AUC(0-tl _{qc})	1.0839	(1.0059 – 1.1679)
AUC(0-inf)	1.1213	(1.0425 – 1.2059)
Dexlansoprazole Delayed-Release OD Tablet Formulation Z vs Dexlansoprazole Delayed-Release Capsule		
C _{max}	1.2403	(1.1220 – 1.3711)
AUC(0-tl _{qc})	1.0047	(0.9325 – 1.0826)
AUC(0-inf)	1.0337	(0.9608 – 1.1122)

Effect of Genotype on Dexlansoprazole Pharmacokinetics

Evaluation of CYP2C19 genotype indicated that 32 subjects were homozygous extensive metabolizers (EMs) (*1/*1), 7 subjects were heterozygous EMs (*1/*2 or *1/*4), 3 subjects were CYP2C19 homozygous (*17/*17) ultrarapid metabolizers (UMs), 14 subjects were CYP2C19 heterozygous (*1/*17 and *2/*17) UMs, and 3 subjects were homozygous poor metabolizer (*2/*2). No samples for genotype analysis were available for 4 subjects (Subjects 7001/015, 7001/018, 7001/036, and 7001/085). One additional sample was obtained, but was never received by the lab (Subject 7001/074); No formal statistical analyses on dexlansoprazole PK were conducted based on CYP2C19 genotype. Metabolizer status was not expected to have an effect on the PD assessments or the determination of BA as this was a crossover study design and each subject acted as his or her own control.

Safety:

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory test (haematology, clinical chemistry, urinalysis,) 12-lead electrocardiogram (ECG), and adverse event (AE) monitoring. According to the sponsor, there was no death or serious adverse event (SAE) during the study. One subject (7001/045) experienced an adverse event of decreased neutrophils, absolute, on Study Day 7 that led to discontinuation of study drug. The investigator considered the event to be mild in severity and not related to study drug.

Of the 64 enrolled subjects, 10 (15.6%) experienced a TEAE during the study. The adverse events were primarily mild in intensity. The most common adverse event was vessel puncture site pain, which was experienced by 3 (4.7%) subjects.

Reviewer's Comment:

- *Dexlansoprazole AUC from each of the 3 delayed-release OD tablet formulations was equivalent to the AUC from the delayed-release capsule.*
- *The C_{max} of dexlansoprazole from Formulations X, Y, and Z were higher than that of dexlansoprazole delayed-release capsules and the upper bound of the 90% CIs was above 1.25 for all 3 formulations.*
- *The C_{max} from Formulation Z was closest to the C_{max} from the delayed-release capsule and thus was chosen for further evaluation.*
- *Sampling time for 24 hours and washout period of 5 days was appropriate as the half-life of dexlansoprazole was approximately 2 hour.*

Study: TAK-390MR(OD)_103, Food Effect Study

Title: A Phase 1, Randomized, Open-Label, Single-Center, Single-Dose, 3-Period, Crossover Study to Assess the Effect of Food on the Bioavailability of Dexlansoprazole 30 mg Delayed-Release Orally Disintegrating Tablets Administered on the Tongue, and to Assess the Bioavailability of Dexlansoprazole 30 mg Delayed-Release Orally Disintegrating Tablets When Administered on the Tongue With Water Relative to Administration on the Tongue Without Water in Healthy Subjects

Sponsor: Takeda Global Research & Development Center, Inc., Deerfield, IL
Clinical Site: Covance Madison Clinical Research Unit, Madison, WI
Bioanalytical Site: (b) (4)
Pharmacogenomic: (b) (4)
Study Date: 04/03/2012 – 07/28/2012

OBJECTIVE:

- To determine the effect of food on the BA of dexlansoprazole from a single dose of dexlansoprazole 30 mg OD tablet administered on the tongue, allowed to disintegrate, and swallowed without water.
- To determine the BA of dexlansoprazole from dexlansoprazole 30 mg OD tablet administered on the tongue, allowed to disintegrate, and swallowed, followed by a water rinse relative to dexlansoprazole 30 mg OD tablet administered on the tongue, allowed to disintegrate, and swallowed without water.

Test Product: Dexlansoprazole delayed-release 30 mg OD tablets, Formulation Z

STUDY DESIGN:

- Treatment A: A single oral dose of dexlansoprazole 30 mg OD tablet, administered on the tongue on Day 1, allowed to disintegrate, and swallowed without water 30 minutes after starting to ingest a high-fat meal (Test).
- Treatment B: A single oral dose of dexlansoprazole 30 mg OD tablet, administered on the tongue on Day 1 after a 10-hour fast, allowed to disintegrate, swallowed without water, and followed with a 240-mL water rinse (Test).
- Treatment C: A single oral dose of dexlansoprazole 30 mg OD tablet, administered on the tongue on Day 1 after a 10-hour fast, allowed to disintegrate, and swallowed without water (Reference).

This study was an open-label, phase 1, randomized (1:1:1 ratio), single-center, single-dose, 3-period crossover study in 72 healthy subjects to evaluate the effect of food and water on pharmacokinetic of dexlansoprazole following the single dose administration of dexlansoprazole delayed-release ODT 30 mg tablets. In Regimen A, subjects fasted overnight (at least 10 hours) and began to consume the high-fat breakfast 30 minutes prior to administration of the study drug. The meal was consumed in its entirety within 25 minutes and no additional food was allowed for 4 hours postdose. In the fasted regimens (Regimens B and C), subjects fasted for a minimum of 10 hours prior to dosing on Day 1 and remained fasted for 4 hours postdose. There was at least a 5-day of washout period between the periods. Pharmacokinetic blood samples were collected for up to 24 hours post-dose on Day 1 and Day 2 to determine the plasma concentrations of dexlansoprazole.

The standard high-fat breakfast contained approximately 800 to 1000 total calories, with 50% of calories being derived from fat content. An example of a standard high-fat breakfast was: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. This meal derived approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively. The content of the high-fat, high-caloric breakfast followed the recommendations given in the FDA guidance “Food Effect Bioavailability and Fed Bioequivalence Studies”.

Excluded Medications and Dietary Products

28 Days Prior to Check-in (Day -1 of Period 1)	14 Days Prior to Check-in (Day -1 of Period 1)	72 Hours Prior to Check-in (Day -1 of Period 1)
Prescription medications (a)	OTC medications (a)	Alcohol-containing products
Nutraceuticals (eg, St. John’s wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Vitamin supplements	Products containing caffeine and/or xanthine
Nicotine-containing products	Foods or beverages containing grapefruit or Seville-type (sour) oranges and marmalade	
Hepatic or renal clearance altering agents	Immunization/vaccines (b)	
Intake of known OTC inhibitors/inducers of CYPs 3A4/5 and 2C19(c)		

OTC=over-the-counter.

(a) Occasional use of acetaminophen (≤ 1 g/day) or other medication (as approved by Takeda on a case-by-case basis) was allowed except on Day 1 of each treatment period.

(b) Inclusive of, but not limited to, Swine flu (H1N1) vaccinations.

(c) Examples include: omeprazole, lansoprazole, cimetidine, and ranitidine.

Note: Hormonal contraception and hormone replacement therapy were allowed, as long as a subject had been on a stable dose for a minimum of 60 days prior to Day 1 of Period 1.

Study Population: The study included healthy males and non-pregnant, non-lactating females ages between 18-55 with good health with a BMI between 18-30 kg/m². This study had 72 healthy volunteers enrolled and 63 of them completed the study as planned by completing all three treatments.

- Three subjects voluntarily withdrew from the study:
 - 2 subjects withdrew after receiving dextansoprazole under fasting conditions with water in the first treatment period (Subjects 8001-052 and 8001-069)
 - 1 subject withdrew after receiving dextansoprazole following a high-fat meal in the second treatment period (Subject 8001-074).
- Three subjects (8001-011, 8001-040, and 8001-097) had positive drug screens (classified as “other”) at Baseline of Periods 2 or 3.
- 3 subjects discontinued study drug due to adverse events.
 - Subject 8001-003 (Sequence CAB) experienced pressured speech and agitation after dosing in the first treatment period (fasting conditions without water) that were attributed to a history of psychiatric illness that had not been disclosed at Screening.
 - Subject 8001-021 (Sequence CAB) experienced a worsening of anemia after completion of the second treatment period (high-fat meal administration).
 - Subject 8001-084 (Sequence BCA) had an episode of anxiety-related symptoms after dosing in the first treatment period (fasting conditions with water) that were attributed to concurrent medical conditions of leukodystrophy, supraventricular

tachycardia (treated with metoprolol), tricuspid valve insufficiency and migraines that had not been disclosed at Screening.

Pharmacogenomic: genotyping for CYP2C19 was conducted on Day 1 of period 1 for all subjects since dextansoprazole is metabolized by the polymorphic isozyme CYP2C19. As this is a crossover study, and each subject served as his/her own control and received all regimens, inclusion of CYP2C19 poor metabolizers (PMs) was not expected to affect the overall results of the study.

Pharmacokinetic Measurements:

PK blood samples were collected at 0 hour (within 30 minutes before dosing) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours after dosing to determine the plasma concentration of dextansoprazole on Day 1 of each period.

PK Parameters Analysis:

Pharmacokinetic parameter estimates for dextansoprazole were calculated using Phoenix WinNonlin version 6.2.1. Statistical analysis was performed using ANOVA to compare the natural logarithmic (ln)-transformed PK parameters AUCs and C_{max} of dextansoprazole. The ANOVA model included sequence, period, and treatment as fixed effects, and subject within sequence as a random effect. Pairwise comparisons between each of the test regimens (Regimens A and B) and the reference regimen (Regimen C) were made and the 90% CIs for the ratio of central values for C_{max} and AUCs were constructed for comparisons.

A lack of food effect on the BA of dextansoprazole from the dextansoprazole delayed-release 30 mg OD tablet was concluded if the 90% CIs for the comparison between Regimen A and C were within the range of 0.80 and 1.25 for both C_{max} and AUCs.

Bioequivalence between the tablet administered on the tongue with water and the tablet administered on the tongue without water was concluded if the 90% CIs for the comparison between Regimen B and C were completely contained within the equivalence range of 0.80 and 1.25.

Actual sampling times, rather than scheduled sampling times, were used in all relevant computations. Concentrations below the lower limit of quantitation were set to zero for PK analysis.

Bioanalytical Method:

- Concentrations of dextansoprazole in human plasma were measured by a validated LC/MS/MS at (b) (4)
 - Project samples were analyzed according to (b) (4) entitled “Determination of Lansoprazole in Human Plasma by LC/MS/MS,” which was validated under Project Code “AEMS.” This method is applicable to the quantitation of lansoprazole within a nominal range of 2.00 to 2000 ng/mL.
- Plasma samples were stored frozen at -20°C or colder until analysis
- Calibration standard curve consisted of 8 level ranged from 2 to 2000 ng/mL in human plasma, and was calculated using a linear (1/concentration squared weighted) least-squares regression algorithm. The R² ranges between 0.9977- 0.9995.
- QC samples at 5 different concentrations (6.00, 15.0, 60.0, 250, and 1500 ng/mL) of dextansoprazole were prepared
- The inter-assay coefficients of variation of the QCs run ranged from 2.86% to 5.15%, with mean percent differences from theoretical ranging from -0.605% to 1.25%.
- The differences of back-calculated calibration curve values from nominal values ranged from -2.31 to 1.76%.

- Approximately 10% of the study samples were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification. The incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20%.
- Plasma samples, stored at approximately -20°C, were analyzed within the time period for which the long-term stability of plasma dexlansoprazole has been established.
 - Plasma samples were collected between 04/03/2012 through 07/28/2012.
 - Plasma samples were analyzed between 05/17/2012 through 08/03/2012.
 - The maximum storage period from collection through analysis was 120 days.
 - The long term storage stability of omeprazole in human plasma at -20 °C was established for at least for 232 days.

RESULTS:

Pharmacokinetics:

When dexlansoprazole delayed release OD 30 mg tablet was administered under fed condition with high-fat meal, C_{max} was reduced by 38% compared fasted states where AUC remained similar. Time to maximum concentration (t_{max}) was delayed by 2 hrs in fed state compared to fasted state (4 hr vs. 6 hrs).

Figure 1: Mean (SD) Plasma Concentration-Time Plots for Dexlansoprazole Following Administration of Dexlansoprazole Delayed-Release 30 mg OD Tablet in the Fed and Fasted State in Healthy Subjects

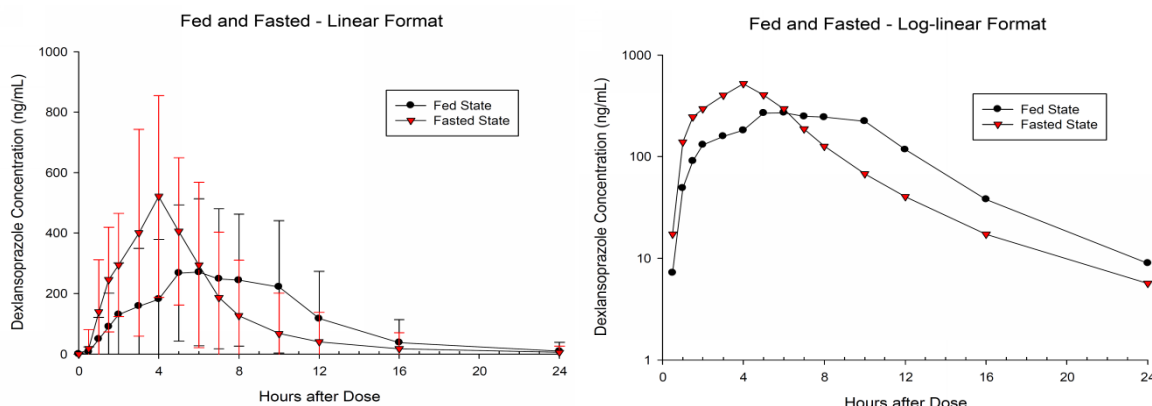
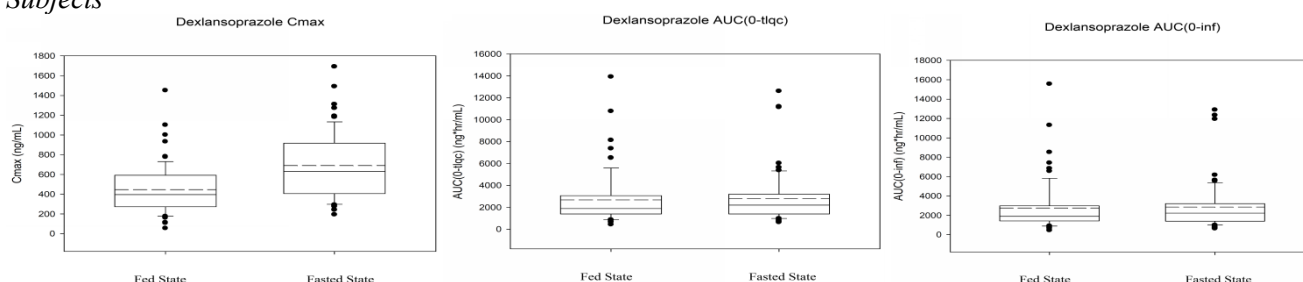


Table 1: Summary of the Pharmacokinetic Parameter Estimates for Dexlansoprazole Following Administration of the Dexlansoprazole Delayed-Release 30 mg OD Tablet in the Fed and Fasted States to Healthy Subjects

	Tmax (hr)	Cmax (ng/mL)	AUC(0-tlqc) (ng-hr/mL)	AUC(0-inf) (ng-hr/mL)	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)
Fed State (Regimen A) (a)							
N	66	66	66	65	65	65	65
Mean	NR	445	2683	2744	2.00	17.45	44.40
SD	NR	252.3	2367.0	2554.8	1.024	11.331	32.563
Min	1.50	53.7	427	435	0.77	1.93	15.81
Median	6.00	397	1887	1896	1.68	15.82	35.21
Max	10.08	1450	13924	15558	5.81	68.91	171.50
CV%	NR	57	88	93	51	65	73
Fasted State (Regimen C) (b)							
N	67	67	67	67	67	67	67
Mean	NR	688	2789	2839	2.07	16.01	47.35
SD	NR	327.7	2307.1	2437.7	1.566	9.663	65.981
Min	1.50	193	629	634	0.70	2.33	12.26
Median	4.00	630	2201	2216	1.51	13.54	29.29
Max	6.00	1690	12607	12882	8.53	47.30	424.26
CV%	NR	48	83	86	76	60	139

Figure 2: Box Plots for Dexlansoprazole Cmax and AUC Values Following a Single Dose of Dexlansoprazole Delayed-Release OD 30 mg Tablet in the Fed and Fasted States in Healthy Subjects



Administering dexlansoprazole delayed release OD 30 mg tablet with water reduced the AUC and Cmax by 20% and 29%, respectively, compared to when it was administered without water. The exposure difference appears to be mainly due to the concentration difference between 2 to 6 hours. The concentration profiles under two conditions are superimposable between 6 to 24 hours. Tmax remained the same (4 hr) in both conditions.

Figure 3: Mean (SD) Plasma Concentration-Time Plots for Dexlansoprazole Following Administration of Dexlansoprazole Delayed-Release 30 mg OD Tablet in the Fasted State With or Without Water in Healthy Subjects

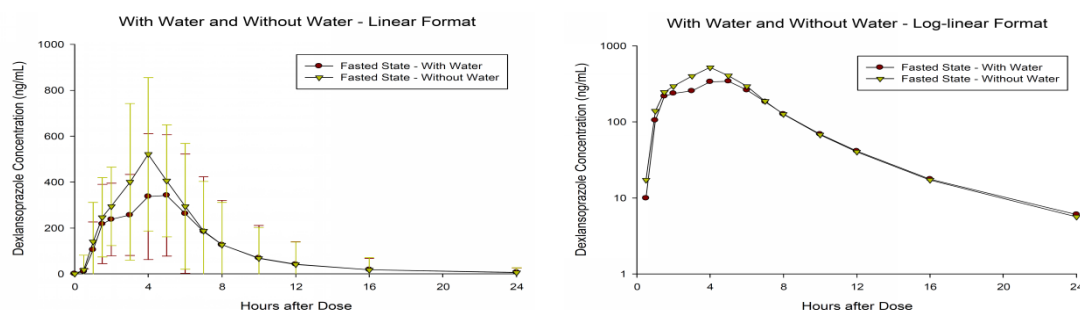


Table 2: Summary of the Pharmacokinetic Parameter Estimates of Dexlansoprazole Following Administration of the Dexlansoprazole Delayed-Release 30 mg OD Tablet in the Fasted State With or Without Water in Healthy Subjects

	Tmax (hr)	Cmax (ng/mL)	AUC(0-tlqc) (ng-hr/mL)	AUC(0-inf) (ng-hr/mL)	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)
Fasted State, With Water (Regimen B) (a)							
N	64	64	64	64	64	64	64
Mean	NR	508	2351	2402	2.59	20.58	71.98
SD	NR	297.9	2142.1	2251.3	1.533	13.540	67.224
Min	1.05	83.6	384	394	0.71	2.31	12.83
Median	4.00	448	1656	1664	1.90	18.03	48.90
Max	7.00	1580	12146	12984	7.57	76.20	424.98
CV%	NR	59	91	94	59	66	93
Fasted State, Without Water (Regimen C) (b)							
N	67	67	67	67	67	67	67
Mean	NR	688	2789	2839	2.07	16.01	47.35
SD	NR	327.7	2307.1	2437.7	1.566	9.663	65.981
Min	1.50	193	629	634	0.70	2.33	12.26
Median	4.00	630	2201	2216	1.51	13.54	29.29
Max	6.00	1690	12607	12882	8.53	47.30	424.26
CV%	NR	48	83	86	76	60	139

Figure 4: Box Plots for Dexlansoprazole Cmax and AUC Values Following a Single Dose of Dexlansoprazole Delayed-Release OD 30 mg Tablet in the Fasted States With or Without Water in Healthy Subjects

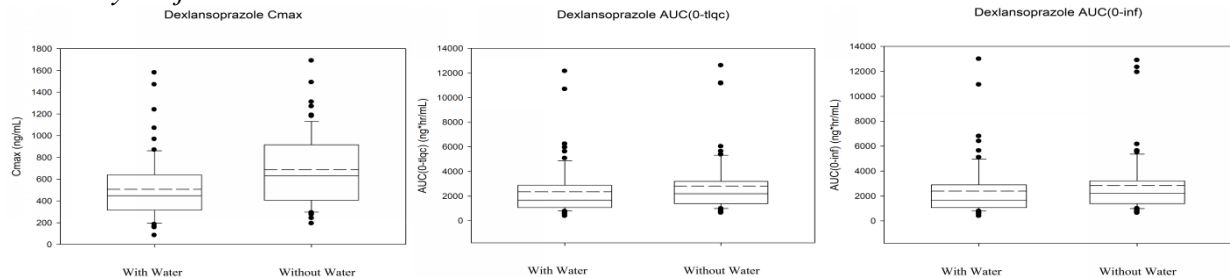


Table 3: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Administration of the Dexlansoprazole 30 mg Orally Disintegrating Tablet in the Fed State and the Fasted State With or Without Water in Healthy Subjects (Sponsor Provided)

Parameter (N) (a)	Point Estimate of the Relative BA	90% CIs for the Point Estimate
OD Tablet Administered in the Fed State (Regimen A) vs the Fasted State (Regimen C) (b)		
Cmax (66/67)	0.6202	(0.5568 – 0.6908)
AUC(0-tlqc) (66/67)	0.9364	(0.8664 – 1.0121)
AUC(0-inf) (65/67)	0.9481	(0.8776 – 1.0242)
OD Tablet Administered Fasted With Water (Regimen B) vs the Fasted State Without Water (Regimen C) (b)		
Cmax (64/67)	0.7110	(0.6375 – 0.7930)
AUC(0-tlqc) (64/67)	0.7997	(0.7393 – 0.8652)
AUC(0-inf) (64/67)	0.8023	(0.7423 – 0.8672)

The BE analysis was reanalyzed and results were consistent with sponsor's result.

Table 4: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following single Dose Administration of the Dexlansoprazole 30 mg Orally Disintegrating Tablet in the Fed State and the Fasted State and the Fasted State With or Without Water: (Reviewer's Analysis)

Parameter	Point Estimate of the Relative BA	Lower 90% CL	Upper 90% CIs
Delayed-Release OD 30 mg Tablet Fed (Regimen A) vs Fasted (Regimen C)			
C _{max}	61.81	55.54	68.81
AUC(0-tl _{qc})	93.52	86.54	101.07
AUC(0-inf)	94.60	87.58	102.19
Delayed-Release OD 30 mg Tablet with water (Regimen B) vs without water (Regimen C)			
C _{max}	70.65	63.44	78.69
AUC(0-tl _{qc})	79.69	73.69	86.19
AUC(0-inf)	79.97	74.00	86.41

Effect of Genotype on Dexlansoprazole Pharmacokinetics

The CYP2C19 genotype was determined for 72 subjects. Of these, 35 subjects were homozygous extensive metabolizers (EMs, *1/*1), 10 subjects were heterozygous EMs (*1/*2), 4 subjects were CYP2C19 homozygous ultrarapid metabolizers (UMs,*17/*17), 20 subjects were CYP2C19 heterozygous (*1/*17 or *2/*17) UMs, and 3 subjects were CYP2C19 homozygous PMs (*2/*2) (Appendix 16.2.8.6.2). No formal statistical analyses were conducted based on CYP2C19 genotype. Metabolizer status was not expected to have an effect on the determination of BA as this was a crossover study design and each subject acted as his or her own control.

Safety:

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory test (haematology, clinical chemistry, urinalysis,) 12-lead electrocardiogram (ECG), and adverse event (AE) monitoring. According to the sponsor, there was no death or serious adverse event (SAE) during the study. Three subjects discontinued study drug due to adverse events; 2 of these subjects experienced events related to pre-existing conditions, and the third subject experienced anemia due to the phlebotomy procedure.

Overall, the only adverse events reported for 2 or more subjects during any treatment were headache (3 subjects), arthropod bite (3 subjects), and vessel puncture site pain (2 subjects) in the high-fat meal treatment regimen. Overall, the majority of the adverse events were mild in intensity and were not considered to be related to study drug. There were no clinically important findings noted in the physical examination, safety clinical laboratory, vital sign, or ECG data.

Reviewer's Comment:

- Administration of dexlansoprazole delayed-release OD 30 mg tablets with high-fat meal reduced the C_{max} by 38% and did not impact AUC compared to fasted state.
- Administration of the dexlansoprazole delayed-release 30 mg OD tablet on the tongue followed by a rinse with 240 mL of water reduced dexlansoprazole C_{max} by approximately 29% and AUCs by 20% as compared to the administration of the OD tablet without water
- Sampling time for 24 hours and washout period of 5 days was appropriate as the half-life of dexlansoprazole was approximately 2 hour.
- BE analysis were repeated and were consistent with sponsor's result.
- For Dexilant capsule, food had increased C_{max} by 12-55% and AUC by 9-37%, but no significant difference in intragastric pH between fed and fasted condition were observed. Although Dexilant capsule was administered before breakfast in all clinical phase 3 efficacy/safety studies for Dexilant capsule approval, based on the result of this food effect study, Dexilant capsule is instructed to be taken without regard to food in its label.

Study **TAK-390MR(OD)_104**

Title: **A Phase 1, Randomized, Open-Label, Single-Center, Multiple-Dose, Two-Period, Crossover Study to Assess the Bioavailability, Safety, and Pharmacodynamics of Two 30 mg Dexlansoprazole Delayed-Release Orally Disintegrating Tablets Administered on the Tongue Relative to Oral Administration of One 60 mg Dexlansoprazole Delayed-Release Capsule in Healthy Subjects**

Sponsor: Takeda Global Research & Development Center, Inc.
Clinical Site: Celerion, Inc., Tempe, AZ
Bioanalytical Site: (b) (4)
Pharmacogenomic:
Study Date: 01/31/2014 – 04/24/2014

Objectives:

- Primary: To assess the PK of dexlansoprazole on Day 1 and Day 5 following oral doses of dexlansoprazole delayed-release OD 2 x 30 mg tablets QD administered on the tongue, allowed to disintegrate, and swallowed without water relative to dexlansoprazole 1 x 60 mg capsule QD for 5 days.
- Secondary: To evaluate the safety profile of dexlansoprazole delayed-release OD 2 x 30 mg tablets and dexlansoprazole delayed-release 1 x 60 mg capsule following daily oral doses for 5 days.
- Additional : To assess the intragastric pH profile of dexlansoprazole on Day 1 and Day 5 following daily oral doses of dexlansoprazole delayed-release OD 2 x 30 mg tablets administered on the tongue, allowed to disintegrate, and swallowed without water and dexlansoprazole 1 x 60 mg capsule for 5 days.

STUDY DESIGN:

- Treatment A: Once-daily oral doses of dexlansoprazole delayed-release OD 2 x 30 mg tablets (formulation Z) administered on the tongue, allowed to disintegrate, and swallowed without water for 5 days (Test).
- Treatment B: Once-daily oral doses of dexlansoprazole delayed-release 1 x 60 mg capsules for 5 days (Reference).

This study was an open-label, phase 1, randomized (1:1 ratio), single-center, multiple-dose, 2-period crossover study in 52 healthy subjects to evaluate the pharmacokinetic and pharmacodynamics of dexlansoprazole following the once daily administration of either dexlansoprazole delayed-release ODT 2 x 30 mg tablets or dexlansoprazole delayed-release 60 mg capsule for 5 days. In Regimen A, subjects were administered the ODT tablet directly on the tongue, without water. One tablet was administered to each subject with instructions to allow the dexlansoprazole delayed release OD tablet to disintegrate on the tongue, and to swallow the granules without chewing. After the tablet had disintegrated and the subject had swallowed the granules, the administration of the second tablet proceeded in the same manner as the first tablet. In Regimen B, subjects were instructed to swallow the 60 mg capsule with 240 mL of water. There was at least a 7-day of washout period between the last dose in the first period and the first dose of the second period. PK samples were collected for up to 24 hours post-dose to determine the plasma concentrations of dexlansoprazole on Day 1 and Day 5 following both treatments. Additionally, intragastric pH recording was performed for 24 hours (sampled and recorded every 5 seconds) beginning immediately prior to study drug administration on Day 1 and Day 5 of Periods 1 and 2.

On Days 1 and 5 of each period, subjects fasted for a minimum of 10 hours prior to dosing and continued to fast for 4 hours post-dose. On Day 2 of each period, subjects fasted overnight for a minimum of 10 hours and were dosed 1 hour before breakfast and after the 24-hour blood collection for dexlansoprazole plasma concentrations. On Days 3 and 4 of each period, subjects fasted overnight for a minimum of 10 hours and were dosed 1 hour before breakfast.

On Days 1 and 5 of each period, breakfast was not served. Lunch was served approximately 4 hours

postdose, dinner was served approximately 9 hours postdose, and a snack was served approximately 12 hours postdose. No additional meals were served on Days 1 or 5. On Days 2, 3, and 4 of each period, breakfast was served approximately 1 hour postdose, lunch was served approximately 4 hours postdose, dinner was served approximately 9 hours postdose, and a snack was served approximately 12 hours postdose.

Excluded Medications and Dietary Products

28 Days Prior to Check-in (Day -1 of Period 1)	7 Days Prior to Check-in (Day -1 of Period 1)	72 Hours Prior to Check-in (Day -1 of Period 1)
Prescription medications (including oral contraceptives) (a)	OTC medications (b)	Products containing caffeine and/or xanthine
Nutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Vitamin supplements	Poppy seeds
Nicotine-containing products	Foods or beverages containing grapefruit or grapefruit juice, star fruit or star fruit juice, Seville-type (sour) oranges and marmalade, apple, orange, or pineapple juice, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussel's sprouts, mustard), and charbroiled meats	
Immunization/vaccines (c)	Alcohol-containing products	
Intake of known OTC inhibitors/inducers of CYPs 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1, and 2A6 (d)		

OTC=over-the-counter.

(a) Hormonal contraception and hormone replacement therapy were allowed, as long as a subject has been on a stable dose for a minimum of 60 days prior to Day 1 of Period 1.

(b) Occasional use of acetaminophen (≤ 1 g/day) or other medication as approved by TDC Americas on a case-by-case basis was allowed except on Day 1 and Day 5 of each treatment period.

(c) Inclusive of but not limited to swine flu (H1N1) and flu vaccinations.

(d) Omeprazole, lansoprazole, cimetidine, chlorpheniramine, and ranitidine.

Note: Topical lidocaine to assist in the placement of the pH probe was allowed.

Study Population: The study included healthy males and non-pregnant, non-lactating females ages between 18-55 with good health with a BMI between 18-30 kg/m². This study had 52 healthy volunteers enrolled and all of them completed the study as planned by completing both treatments.

Pharmacogenomic: genotyping for CYP2C19 was conducted on Day 1 of period 1 for all subjects since dexlansoprazole is metabolized by the polymorphic isozyme CYP2C19.

Pharmacokinetic Measurements:

PK blood samples were collected at 0 hour (within 30 minutes before dosing,) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours after dosing to determine the plasma concentration of dexlansoprazole on Day 1 and Day 5 on each period.

PK Parameters Analysis:

Pharmacokinetic parameter estimates for dexlansoprazole were calculated using Phoenix WinNonlin version 6.3 with non-compartmental methods. Statistical analysis was performed using ANOVA to compare the natural logarithmic (ln)-transformed PK parameters AUCs and Cmax of dexlansoprazole. The ANOVA model included sequence, period, and treatment as fixed effects, and subject within sequence as a random effect. Bioequivalence (BE) between the regimens was concluded if the 90% CIs were completely contained within the equivalence range of 0.80 and 1.25 for dexlansoprazole Cmax and AUCs.

For each regimen, the effect of Day (or multiple dose vs single dose) was evaluated using paired t-test on Tmax and natural log of Cmax, and AUC(0-tlqc). “No effect” was concluded if the 90% CIs for the ratio of Cmax and AUCs central values were within the (0.80-1.25) interval.

Actual sampling times, rather than scheduled sampling times, were used in all relevant computations. Concentrations below the lower limit of quantitation were set to zero for PK analysis.

Bioanalytical Method:

- Concentrations of dexlansoprazole in human plasma were measured by a validated LC/MS/MS at (b) (4)
 - Project samples were analyzed according to (b) (4) entitled “Determination of Lansoprazole in Human Plasma by LC/MS/MS,” which was validated under Project Code “AEMS.” This method is applicable to the quantitation of lansoprazole within a nominal range of 2.00 to 2000 ng/mL.
- Plasma samples were stored frozen at -20°C or colder until analysis
- Calibration standard curve consisted of 8 level ranged from 2 to 2000 ng/mL in human plasma, and was calculated using a linear (1/concentration squared weighted) least-squares regression algorithm. The R² ranges between 0.9956- 0.9990.
- QC samples at 5 different concentrations (6.00, 15.0, 60.0, 250, and 1500 ng/mL) of dexlansoprazole were prepared.
- The inter-assay coefficients of variation of the QCs run ranged from 2.85% to 3.71%, with mean percent differences from theoretical ranging from -7.92% to 4.49%.
- The differences of back-calculated calibration curve values from nominal values ranged from -8.36 to 6.30%.
- Approximately 10% of the first 1000 study samples and 5% of remaining samples were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification. The incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20%.
- Plasma samples, stored at approximately -20°C, were analyzed within the time period for which the long-term stability of plasma dexlansoprazole has been established.
 - Plasma samples were collected between 01/31/2014 through 03/29/2014.
 - Plasma samples were analyzed between 04/08/2014 through 05/06/2014.
 - The maximum storage period from collection through analysis was 98 days.
 - The long term storage stability of omeprazole in human plasma at -20 °C was established for at least for 232 days.

Pharmacodynamics:

Intragastric pH recording every 5 seconds was performed for 24 hours beginning immediately prior to study drug administration on Day 1 and Day 5 of Periods 1 and 2. Median intragastric pH values over 15-minute intervals was determined and used for estimating the PD parameters for Days 1 and 5 of each period. Mean 24-hour pH and % of time pH>4 over 24 hours were determined as the PD parameters.

The PD parameters were also calculated for the following intervals: 0 - 6, 6 -12, 12 - 18, and 18- 24 hours postdose. The PD parameters were also calculated for the interval of 6 to 24 hours postdose.

ANOVA models were fitted to the above PD parameters on Day 1 and Day 5. The model included fixed effects of sequence, period, and regimen as well as a random effect of subject nested within sequence. The cohort effect was tested in the ANOVA model along with the cohort and period interaction. The cohort and cohort/period interaction factors were not statistically significant, so these terms were excluded from the final model. Pairwise comparisons between regimens were conducted. Ninety percent CIs for the difference in the least squares means of the 2 regimens were computed. Pharmacodynamic equivalence between the 2 regimens was concluded if the 90% CIs were completely contained within the equivalence range of (-12%, 12%) for % time pH>4 over the 0 to 24-hour interval.

RESULTS:

Pharmacokinetics:

Following both single dose administration on day 1 and multiple dose administration on Day 5, 2 x 30 mg dexlansoprazole delayed release OD 30 mg tablet has slight lower C_{max} and notable lower AUC compared to 1 x 60 mg capsules. T_{max} was reached earlier for ODT tablet compared the capsule (reference). In addition, ODT does not have clear double peak profile as the capsule formulation on both Day 1 and Day 5.

Figure 1: Mean (SD) Plasma Concentration-Time Plots for Dexlansoprazole Following a Single Dose of Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule to Healthy Subjects

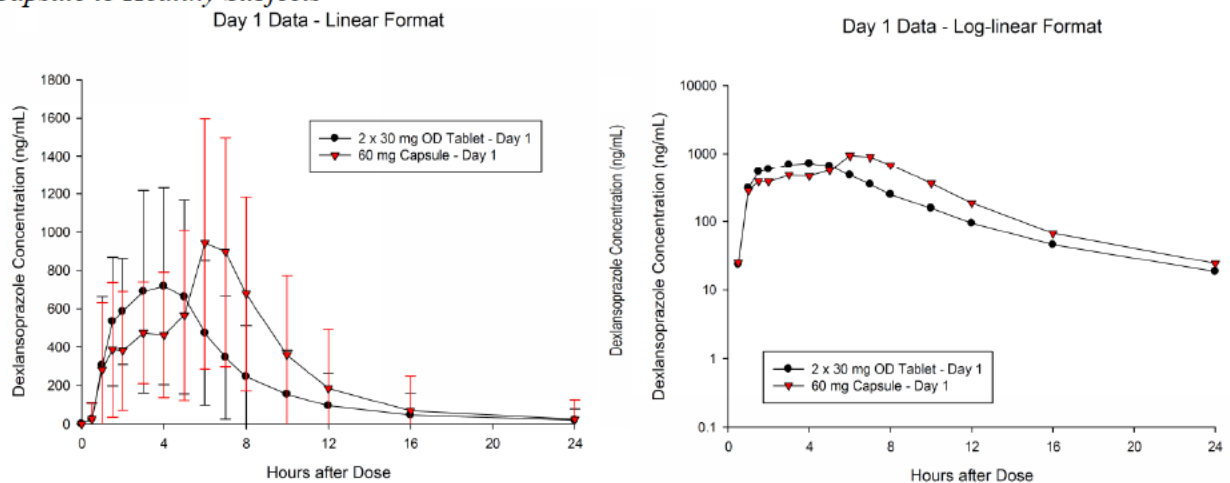
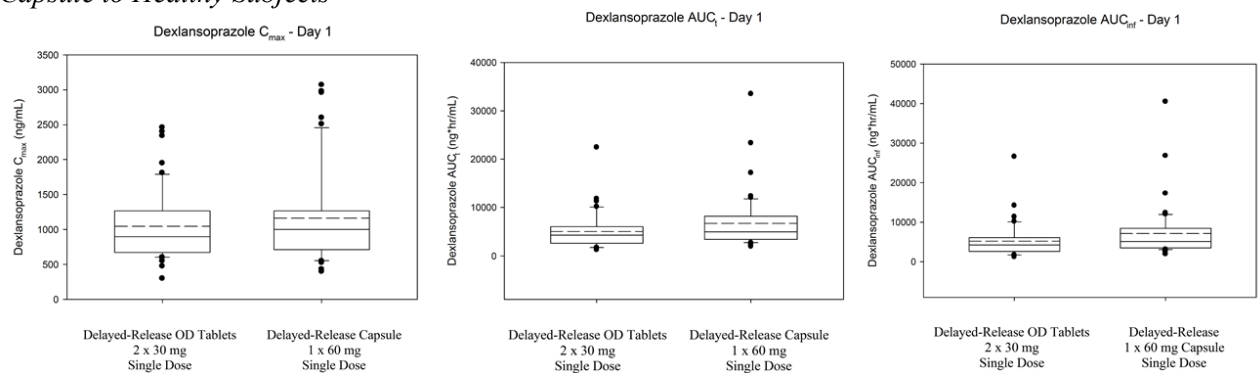


Table 1: Summary of the Pharmacokinetic Parameter Estimates for Dexlansoprazole Following a Single Dose of the Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 60 mg Capsule to Healthy Subjects

	$t_{\max}$ (hr)	$C_{\max}$ (ng/mL)	AUC_t (ng·hr/mL)	AUC_{∞} (ng·hr/mL)	$t_{1/2z}$ (hr)	CL/F (L/hr)	V_z/F (L)
Day 1 – Single Dose of Delayed-Release OD 2 x 30 mg Tablets (Regimen A) (a)							
N	52	52	52	50	50	50	50
Mean	NR	1047	5060	5364	3.34	16.52	79.30
SD	NR	496.8	3689.9	4218.4	1.689	10.007	67.640
Min	1.00	298	1208	1221	0.97	2.26	14.80
Median	3.00	898	4262	4362	2.99	13.76	59.46
Max	10.00	2460	22455	26585	7.93	49.14	280.91
%CV	NR	47	73	79	51	61	85
Day 1 – Single Dose of Delayed-Release 1 x 60 mg Capsule (Regimen B) (b)							
N	52	52	52	50	50	50	50
Mean	NR	1164	6747	7155	2.17	12.12	32.20
SD	NR	667.0	5489.7	6461.1	1.206	6.097	13.965
Min	1.00	398	1938	1945	0.96	1.48	13.31
Median	6.00	1000	4968	5102	1.99	11.76	27.70
Max	8.02	3070	33507	40499	7.55	30.85	67.61
%CV	NR	57	81	90	56	50	43

Figure 2: Box Plots for Dexlansoprazole $C_{\max}$ and AUC Values Following a Single Dose of Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule to Healthy Subjects



The boundary of the box closest to zero indicates the 25th percentile, the dashed line within the box marks the mean, the solid line marks the median, and the boundary of the box farthest from zero indicates the 75th percentile. Error bars above and below the box indicate the 90th and 10th percentiles, respectively. Solid circles indicate all data points outside the 90th and 10th percentiles.

These box plots confirmed that the mean $C_{\max}$ values were similar for both regimens while mean AUC values were lower for the ODT tablets compared to capsule regimen, and overall variability was not substantially different.

Figure 3: Mean (SD) Plasma Concentration-Time Plots for Dexlansoprazole on Day 5 Following Once-Daily Administration of Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule for 5 Days in Healthy Subjects

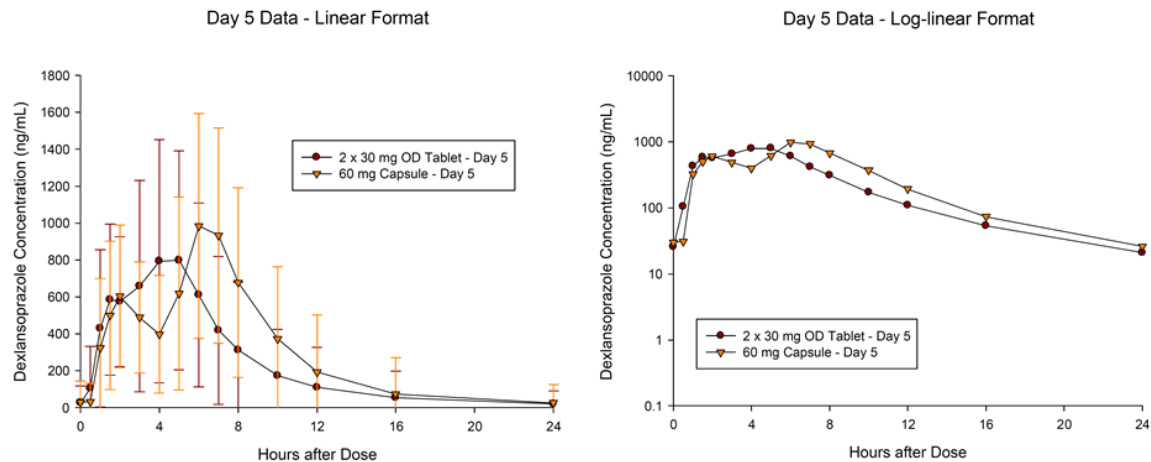
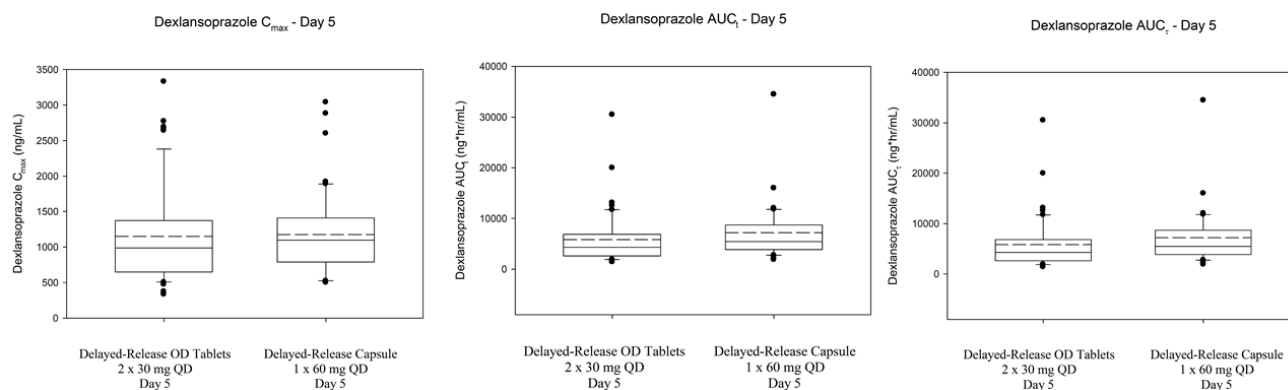


Table 2: Summary of the Pharmacokinetic Parameter Estimates of Dexlansoprazole on Day 5 Following Daily Administration of Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule for 5 Days to Healthy Subjects

	t_{max} (hr)	C_{max} (ng/mL)	AUC_t (ng·hr/mL)	AUC_{∞} (ng·hr/mL)	$t_{1/2z}$ (hr)	CL/F (L/hr)	V_z/F (L)
Day 5 – Delayed-Release OD 2 x 30 mg Tablets QD (Regimen A) (a)							
N	52	52	52	52	51	52	51
Mean	NR	1151	5819	5825	3.17	16.51	74.51
SD	NR	668.5	5105.6	5105.5	1.601	10.440	67.068
Min	0.50	338	1423	1428	0.90	1.97	15.07
Median	4.00	991	4291	4301	3.00	13.96	47.28
Max	6.00	3330	30470	30479	7.78	42.01	262.82
%CV	NR	58	88	88	51	63	90
Day 5 – Delayed-Release 1 x 60 mg Capsule QD (Regimen B) (b)							
N	52	52	52	52	51	52	51
Mean	NR	1178	7184	7196	2.26	12.18	32.22
SD	NR	570.0	6314.0	6306.7	1.303	6.590	12.784
Min	1.00	504	1888	1917	0.91	1.74	15.64
Median	6.00	1100	5460	5460	2.14	11.02	29.37
Max	8.00	3040	34473	34473	8.02	31.30	84.98
%CV	NR	48	88	88	58	54	40

Figure 4: Box Plots for Dexlansoprazole C_{max} and AUC Values on Day 5 Following Daily Administration of Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule for 5 Days to Healthy Subjects



The boundary of the box closest to zero indicates the 25th percentile, the dashed line within the box marks the mean, the solid line marks the median, and the boundary of the box farthest from zero indicates the 75th percentile. Error bars above and below the box indicate the 90th and 10th percentiles, respectively. Solid circles indicate all data points outside the 90th and 10th percentiles

As observed on Day 1 following a single dose, these box plots confirmed that the mean Cmax values are similar for both regimens, while the mean AUCs from the from OTD tablets were lower than that of capsule, and overall variability is not substantially different on Day 5.

Table 3: Statistical Comparisons of Pharmacokinetic Parameter Estimates for Dexlansoprazole Following Daily Administration of the Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule for 1 or 5 Days to Healthy Subjects (Sponsor Provided)

Parameter (N) (a)	Point Estimate of the Relative BA	90% CIs for the Point Estimate
Day 1: Delayed-Release OD 2 x 30 mg Tablets QD (Regimen A) vs Delayed-Release 1 x 60 mg Capsule QD (Regimen B) (b)		
C _{max} (52/52)	0.9186	(0.8371 – 1.0079)
AUC _t (52/52)	0.7463	(0.6979 – 0.7981)
AUC _∞ (50/50)	0.7458	(0.6973 – 0.7976)
Day 5: Delayed-Release OD 2 x 30 mg Tablets QD (Regimen A) vs Delayed-Release 1 x 60 mg Capsule QD (Regimen B) (b)		
C _{max} (52/52)	0.9352	(0.8466 – 1.0331)
AUC _t (52/52)	0.7773	(0.7189 – 0.8405)
AUC _τ (52/52)	0.7755	(0.7172 – 0.8385)

Table 4: Statistical Comparisons of Pharmacokinetic Parameter Estimates for Dexlansoprazole Following Daily Administration of the Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule for 1 or 5 Days to Healthy Subjects (Reviewer's Analysis)

Parameter	Point Estimate of the Relative BA	Lower 90% CL	Upper 90% CIs
Day 1: Delayed-Release OD 2 X 30 mg Table vs. Delayed-Release 60 mg Capsule			
C _{max}	92.94	84.41	102.32
AUC(0-tlqc)	75.22	70.15	80.64
AUC(0-inf)	75.71	72.10	84.13
Day 5: Delayed-Release OD 2 X 30 mg Tablet vs. Delayed-Release 60 mg Capsule			
C _{max}	93.61	84.93	103.18
AUC(0-tlqc)	77.88	70.71	81.1
AUC(0-tau)	78.23	72.55	84.37

The ANOVA analysis on the relative BA indicated that the 90% CIs for dexlansoprazole Cmax central value ratios between a single dose of dexlansoprazole delayed-release OD 2 x 30 mg

tablets and delayed-release 1 x 60 mg capsule were contained within the 0.80 to 1.25 BE limits. However, The 90% CIs for dexlansoprazole AUC central value ratios were below 0.80. The point estimates of the relative BA indicated that the AUCs from the OD tablets were approximately 25% and 22% lower than those from the capsule on Day 1 and Day 5, respectively. Lower 90% CI for AUC was also below 0.8 BE limit both on Day 1 and Day 5.

Both dexlansoprazole capsule and ODT formulations had similar the mean plasma profiles on Day 1 vs. Day 5 suggesting that PK of dexlansoprazole did not change following multiple dosing for 5 days regardless of the formulation.

Figure 5: Mean (SD) Plasma Concentration-Time Plots for Dexlansoprazole on Day 1 and Day 5 Following Once-Daily Administration of Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet for 5 Days in Healthy Subjects

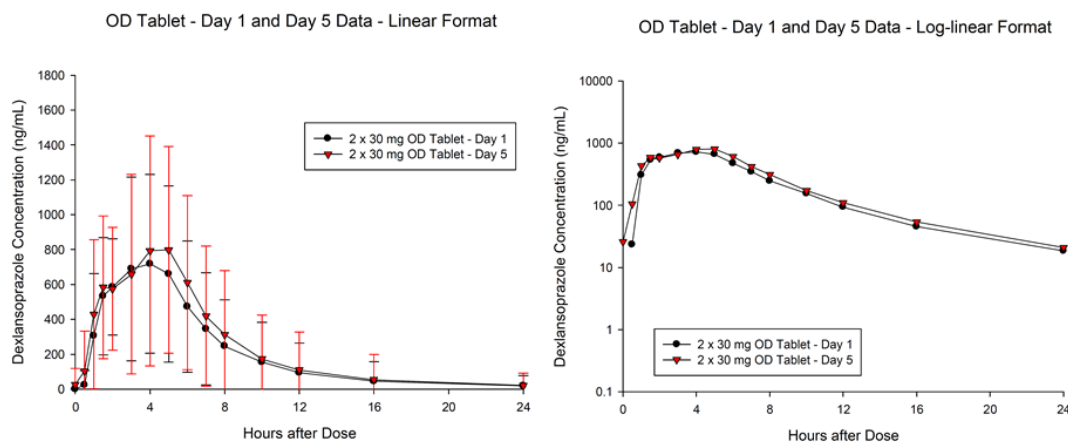


Figure 6: Mean (SD) Plasma Concentration-Time Plots for Dexlansoprazole on Day 1 and Day 5 Following Once-Daily Administration of Dexlansoprazole Delayed-Release 1 x 60 mg Capsule for 5 Days in Healthy Subjects

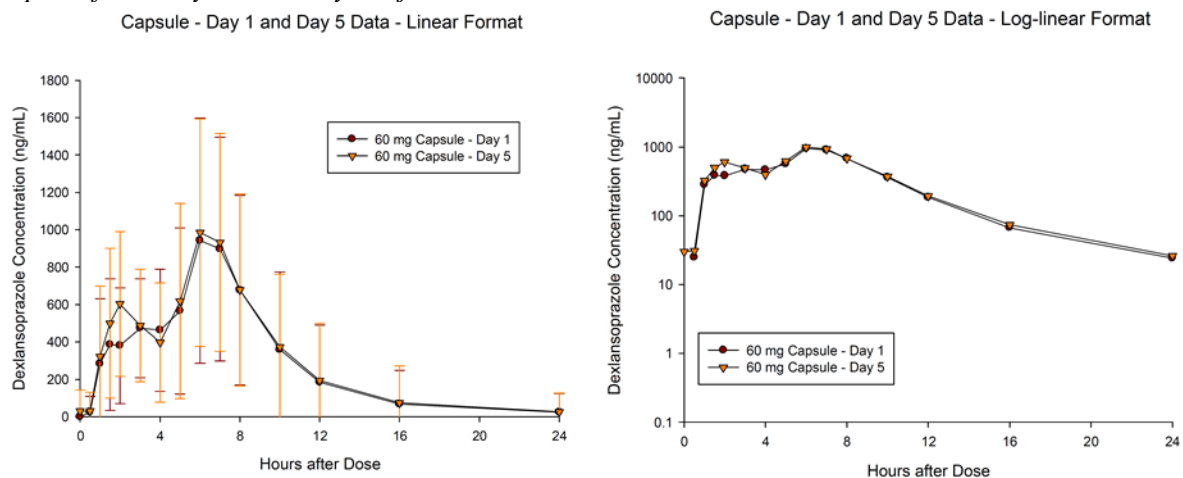
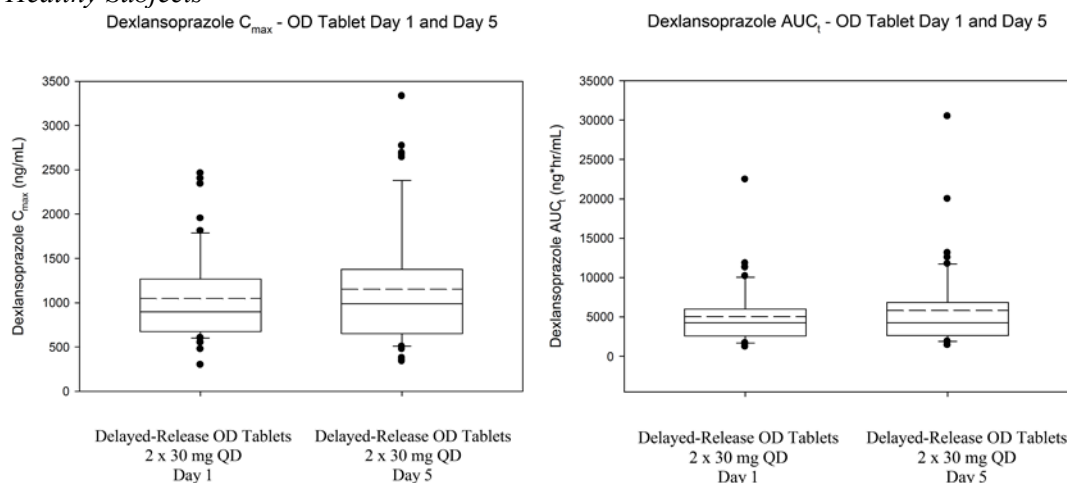


Table 5: Summary of the Pharmacokinetic Parameter Estimates of Dexlansoprazole Following Daily Administration of the Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule for 5 Days to Healthy Subjects

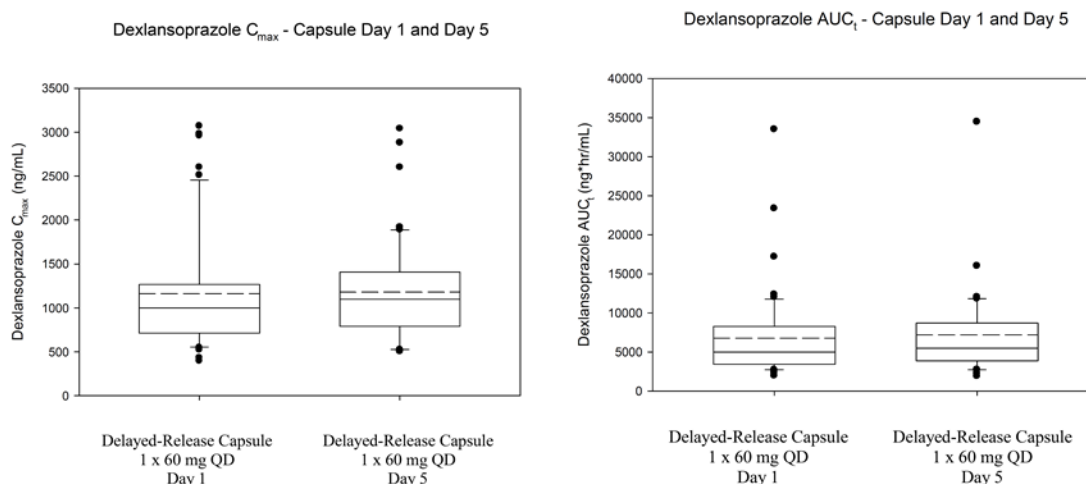
	C_{max} (ng/mL)	AUC_t (ng·hr/mL)	$AUC(a)$ (ng·hr/mL)	$t_{1/2z}$ (hr)
Day 1 – Single Dose of Delayed-Release OD 2 x 30 mg Tablets (Regimen A) (b)				
N	52	52	50	50
Mean	1047	5060	5364	3.34
SD	496.8	3689.9	4218.4	1.689
%CV	47	73	79	51
Day 5 – Delayed-Release OD 2 x 30 mg Tablets QD (Regimen A) (b)				
N	52	52	52	51
Mean	1151	5819	5825	3.17
SD	668.5	5105.6	5105.5	1.601
%CV	58	88	88	51
Day 1 – Delayed-Release 1 x 60 mg Capsule Single Dose (Regimen B) (c)				
N	52	52	50	50
Mean	1164	6747	7155	2.17
SD	667.0	5489.7	6461.1	1.206
%CV	57	81	90	56
Day 5 – Delayed-Release 1 x 60 mg Capsule QD (Regimen B) (c)				
N	52	52	52	51
Mean	1178	7184	7196	2.26
SD	570.0	6314.0	6306.7	1.303
%CV	48	88	88	58

Figure 7: Box Plots for Dexlansoprazole C_{max} and AUC Values on Days 1 and Day 5 Following Daily Administration of the Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet for 5 Days to Healthy Subjects



The boundary of the box closest to zero indicates the 25th percentile, the dashed line within the box marks the mean, the solid line marks the median, and the boundary of the box farthest from zero indicates the 75th percentile. Error bars above and below the box indicate the 90th and 10th percentiles, respectively. Solid circles indicate all data points outside the 90th and 10th percentiles

Figure 8: Box Plots for Dexlansoprazole C_{max} and AUC Values Following Daily Administration of the Dexlansoprazole Delayed-Release 1 x 60 mg Capsule for 5 Days to Healthy Subjects



The boundary of the box closest to zero indicates the 25th percentile, the dashed line within the box marks the mean, the solid line marks the median, and the boundary of the box farthest from zero indicates the 75th percentile. Error bars above and below the box indicate the 90th and 10th percentiles, respectively. Solid circles indicate all data points outside the 90th and 10th percentiles

There was “no effect” of Day on dexlansoprazole PK as the 90% CIs for the ratios of C_{max} and AUC_t central values were within the 0.80 to 1.25 interval for both the OD tablets and the capsule formulation.

Table 6: Statistical Comparisons of Pharmacokinetic Parameter Estimates for Dexlansoprazole Following Daily Administration of the Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule for 1 or 5 Days to Healthy Subjects

Parameter (N)	Point Estimate of the Relative BA	90% CIs for the Point Estimate
Regimen A: Delayed-Release OD 2 x 30 mg Tablets QD Day 5 vs Day 1 (a)		
C_{max} (N=52)	1.0482	(0.9618 – 1.1425)
AUC_t (N=52)	1.0840	(1.0060 – 1.1681)
Regimen B: Delayed-Release 1 x 60 mg Capsule QD Day 5 vs Day 1 (a)		
C_{max} (N=52)	1.0407	(0.9575 – 1.1312)
AUC_t (N=52)	1.0468	(1.0015 – 1.0942)

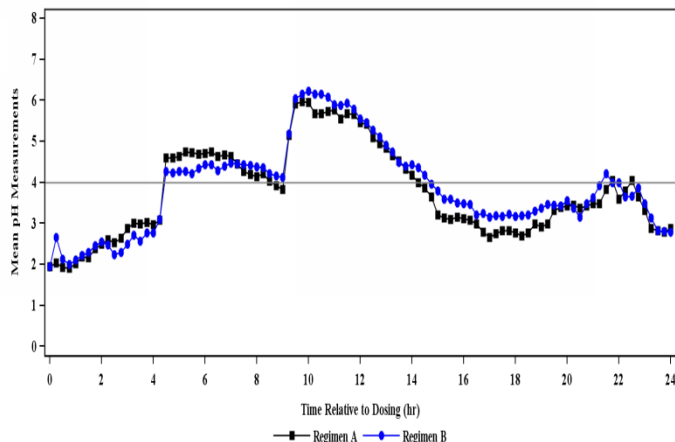
Effect of Genotype on Dexlansoprazole Pharmacokinetics

The CYP2C19 genotype was determined for all 52 subjects. Of these, 27 subjects were homozygous extensive metabolizers (EMs, *1/*1), 10 subjects were heterozygous EMs (*1/*2), 14 subjects were CYP2C19 heterozygous (*1/*17, *2/*17 or *4/*17) ultra-rapid metabolizers (UMs), and 1 subject was a CYP2C19 homozygous PM (*2/*2). No formal statistical analyses on dexlansoprazole PK were conducted based on CYP2C19 genotype. However, the PM subject (Subject 5002-102) had the second highest plasma dexlansoprazole AUC values on Days 1 and 5 in each regimen. Subject 5002-057 (*1/*2 extensive metabolizer) had the highest AUC values on Days 1 and 5 in each regimen. The subjects with the lowest AUC_{∞} (Day 1) or AUC_t (Day 5) values in each regimen were Subjects 5002-118 (heterozygous UM) in Regimen A Day 1, Regimen B Day 1, and Regimen B Day 5, and 5002-189 (homozygous EM) in Regimen A Day 5).

Metabolizer status was not expected to have an effect on the PD assessments or the determination of BA as this was a crossover study design and each subject acted as his or her own control.

Analysis of Pharmacodynamics

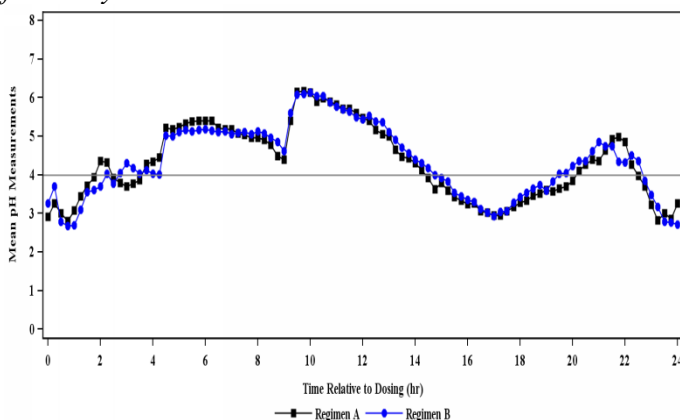
Figure 9: 24-Hour Mean pH Profiles on Day 1 after a Single Dose of Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule Formulations



Regimen A = Dexlansoprazole delayed-release OD 2 x 30 tablets QD administered on the tongue, allowed to disintegrate, and swallowed without water for 5 days.

Regimen B = Dexlansoprazole delayed-release 1 x 60 mg capsule for 5 days.

Figure 10: 24-Hour Mean pH Profiles on Day 5 After Administration of Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet or Delayed-Release 1 x 60 mg Capsule Formulations QD for 5 Days



Regimen A = Dexlansoprazole delayed-release OD 2 x 30 tablets QD administered on the tongue, allowed to disintegrate, and swallowed without water for 5 days.

Regimen B = Dexlansoprazole delayed-release 1 x 60 mg capsule for 5 days.

Table 7: Comparison of Percentage of Time Intra-gastric pH >4 Over 24 Hours and by Interval Following Administration of Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet and Delayed-Release 1 x 60 mg Capsule

Interval	Mean (SD) for Percentage of Time pH >4		P-value (a)	90% CIs (a)
	Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablets	Dexlansoprazole Delayed-Release 1 x 60 mg Capsule		
Day 1				
0 to 24 hours postdose (N=51)	46.9 (19.72)	49.3 (19.25)	0.241	(-6.0, 1.0)
>6 to 24 hours postdose (N=51)	51.1 (21.33)	56.3 (21.29)	0.032*	(-9.0, -1.2)
0 to 6 hours postdose (N=51)	34.2 (22.89)	28.3 (21.67)	0.110	(-0.2, 11.2)
>6 to 12 hours postdose (N=51)	78.0 (27.18)	80.1 (24.55)	0.556	(-8.7, 4.2)
>12 to 18 hours postdose (N=51)	43.9 (28.71)	54.6 (27.02)	0.002*	(-15.9, -5.0)
>18 to 24 hours postdose (N=51)	31.5 (30.26)	34.2 (30.96)	0.337	(-7.4, 2.0)
Day 5				
0 to 24 hours postdose (N=52)	60.0 (18.40)	59.9 (18.21)	0.979	(-2.6, 2.5)
>6 to 24 hours postdose (N=52)	61.3 (18.51)	62.1 (17.73)	0.542	(-4.0, 1.8)
0 to 6 hours postdose (N=52)	56.2 (23.68)	53.3 (24.59)	0.242	(-1.3, 7.3)
>6 to 12 hours postdose (N=52)	90.0 (14.88)	90.0 (15.55)	0.876	(-3.4, 2.8)
>12 to 18 hours postdose (N=52)	50.1 (27.16)	52.6 (26.61)	0.364	(-8.1, 2.4)
>18 to 24 hours postdose (N=52)	43.8 (30.32)	43.8 (28.83)	0.996	(-5.9, 5.9)

Source: Table 15.2.6.1.

*Indicates $p \leq 0.05$

(a) P-values, and 90% CIs from ANOVA with sequence, period, and regimen as fixed effects and subjects nested within each cohort and within each sequence as a random effect.

Note: Subjects with a PD parameter estimated for both regimens were included in the analyses.

Table 8: Comparison of Mean pH Over 24 Hours and by Interval Following Administration of Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablet and Delayed-Release 1 x 60 mg Capsule

Interval	Mean (SD) for Mean pH		P-value (a)
	Dexlansoprazole Delayed-Release OD 2 x 30 mg Tablets	Dexlansoprazole Delayed-Release 1 x 60 mg Capsule	
Day 1			
0 to 24 hours postdose (N=51)	3.76 (0.956)	3.89 (0.887)	0.122
>6 to 24 hours postdose (N=51)	3.97 (0.999)	4.19 (0.957)	0.015*
0 to 6 hours postdose (N=51)	3.14 (1.107)	2.99 (1.091)	0.428
>6 to 12 hours postdose (N=51)	4.99 (1.108)	5.13 (0.934)	0.301
>12 to 18 hours postdose (N=51)	3.64 (1.136)	3.96 (1.038)	0.005*
>18 to 24 hours postdose (N=51)	3.29 (1.524)	3.48 (1.583)	0.153
Day 5			
0 to 24 hours postdose (N=52)	4.33 (0.919)	4.36 (0.913)	0.577
>6 to 24 hours postdose (N=52)	4.36 (0.903)	4.45 (0.895)	0.229
0 to 6 hours postdose (N=52)	4.22 (1.160)	4.09 (1.143)	0.268
>6 to 12 hours postdose (N=52)	5.40 (0.744)	5.43 (0.722)	0.585
>12 to 18 hours postdose (N=52)	3.85 (1.145)	3.99 (1.125)	0.201
>18 to 24 hours postdose (N=52)	3.85 (1.460)	3.94 (1.409)	0.538

Source: Table 15.2.6.1.

*Indicates $p \leq 0.05$.

(a) P-values, and 90% CIs from ANOVA with sequence, period, and regimen as fixed effects and subjects nested within each cohort and within each sequence as a random effect.

Note: Subjects with a PD parameter estimated for both regimens were included in the analyses.

Although the two formulations had similar overall PD profiles 0-24 hours on both Day 1 and Day 5, it appears that compared to capsule formulation, ODT formulation was higher mean pH in 0-6

hours and lower mean pH in 12-18 hour, especially on Day 1. This difference on PD was not notable on Day 5. On Day 5, for the 0- to 24-hour interval and all subintervals, the % time pH>4 and mean pH were higher than the respective intervals on Day 1 for both regimens.

Safety:

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory test (haematology, clinical chemistry, urinalysis,) 12-lead electrocardiogram (ECG), and adverse event (AE) monitoring. According to the sponsor, there was no death or serious adverse event (SAE) or adverse events resulting in the study drug discontinuation.

Incidences of adverse events were comparable in both treatment groups (33% for the OD tablet and 35% for the capsule). During both treatments, adverse events were primarily mild in intensity, and were not considered to be related to study drug. Adverse events reported for 2 or more subjects during a particular treatment regimen were headache (5 subjects), nausea (3 subjects), and dizziness (2 subjects) for the OD tablet formulation, and headache (6 subjects), decubitus ulcer (3 subjects), and oropharyngeal pain and flatulence (2 subjects each) for the capsule formulation.

There were no clinically important findings noted in the physical examination, safety clinical laboratory, vital sign, or ECG data.

Reviewer's Comment:

- *Administration of a single 60 mg dose of dextansoprazole as two 30 mg OD tablets and as one 60 mg capsule provided equivalent C_{max}, but failed the BE for AUC where the AUC from the 2 OD tablets was approximately 25% and 22 % lower than from the capsule on Day 1 and Day 5, respectively. Lower 90% CI for AUC was also below 0.8 BE limit both on Day 1 and Day 5.*
- *There was no effect of Day on dextansoprazole PK for both regimen since 90% CIs for the ratio of C_{max} and AUC(0-tlq) central values were within the 0.80 to 1.25 interval.*
- *Although the two formulations had similar overall PD profiles in 0-24 hours on both Day 1 and Day 5, it appears that compared to capsule formulation, ODT formulation was higher mean pH in 0-6 hours and lower mean pH in 12-18 hour, especially on Day 1. This difference on PD was not notable on Day 5. On Day 5, for the 0- to 24-hour interval and all subintervals, the % time pH>4 and mean pH were higher than the respective intervals on Day 1 for both regimens.*
- *Sampling time for 24 hours and washout period of 7 days was appropriate as the half-life of dextansoprazole was approximately 2 hour.*
- *PK analysis and PK BE analysis, PD plots were repeated and were consistent with sponsor's result.*

Study: TAK-390MR(OD)_105

Title: A Phase 1, Randomized, Open-Label, Single-Center, Multiple-Dose, Two-Period, Crossover Study to Assess the Pharmacodynamics and Bioavailability of 30 mg Dexlansoprazole Delayed-Release Orally Disintegrating Tablets Administered on the Tongue Relative to Oral Administration of 30 mg Dexlansoprazole Delayed-Release Capsules in Healthy Subjects

Sponsor: Takeda Global Research & Development Center, Inc.
Clinical Site: Celerion, Inc., Tempe, AZ
Bioanalytical Site: (b) (4)
Pharmacogenomic:
Study Date: 08/08/2012 – 10/26/2012

OBJECTIVE:

- To assess the intragastric pH profile (PD) of dexlansoprazole on Day 1 and Day 5 following daily oral doses of dexlansoprazole delayed-release OD 30 mg tablets administered on the tongue, allowed to disintegrate, and swallowed without water relative to dexlansoprazole delayed release 30 mg capsules for 5 days.
- To assess the Pharmacokinetic (PK) of dexlansoprazole on Day 1 and Day 5 following daily oral doses of dexlansoprazole delayed-release OD 30 mg tablets administered on the tongue, allowed to disintegrate, and swallowed without water relative to dexlansoprazole delayed-release 30 mg capsules for 5 days.

STUDY DESIGN:

- Treatment A: Once-daily oral doses of dexlansoprazole delayed-release OD 30 mg tablets (formulation Z) administered on the tongue, allowed to disintegrate, and swallowed without water for 5 days (Test).
- Treatment B: Once-daily oral doses of dexlansoprazole delayed-release 30 mg capsules for 5 days (Reference).

This study was an open-label, phase 1, randomized (1:1 ratio), single-center, multiple-dose, 2-period crossover study in 52 healthy subjects to evaluate the pharmacokinetic and pharmacodynamics of dexlansoprazole following the once daily administration of either dexlansoprazole delayed-release ODT 30 mg tablets or dexlansoprazole delayed-release 30 mg capsule for 5 days. In Regimen A, subjects were administered the tablet directly on the tongue, without water. Subjects were instructed to allow the dexlansoprazole delayed-release OD tablet to disintegrate on the tongue, and to swallow the granules without chewing. In Regimen B, subjects were instructed to swallow the capsule with 240 mL of water. There was at least a 7-day of washout period between the last dose in the first period and the first dose of the second period. Pharmacokinetic blood samples were collected for up to 24 hours post-dose to determine the plasma concentrations of dexlansoprazole on Day 1 and Day 5 following both treatments. Additionally, intragastric pH recording was performed for 24 hours (sampled and recorded every 2 seconds) beginning immediately prior to study drug administration on Day 1 and Day 5 of Periods 1 and 2.

On Days 1 and 5 of each period, subjects fasted for a minimum of 10 hours prior to dosing and continued to fast for 4 hours post-dose. On Day 2 of each period, subjects fasted overnight for a minimum of 10 hours and were dosed 1 hour before breakfast and after the 24-hour blood

collection for dexlansoprazole plasma concentrations. On Days 3 and 4 of each period, subjects fasted overnight for a minimum of 10 hours and were dosed 1 hour before breakfast.

On Days 1 and 5 of each period, breakfast was not served. Lunch was served approximately 4 hours postdose, dinner was served approximately 9 hours postdose, and a snack was served approximately 12 hours postdose. No additional meals were served on Days 1 or 5. On Days 2, 3, and 4 of each period, breakfast was served approximately 1 hour after dose, lunch was served approximately 4 hours postdose, dinner was served approximately 9 hours postdose, and a snack was served approximately 12 hours postdose.

Excluded Medications and Dietary Products

28 Days Prior to Check-in (Day -1 of Period 1)	14 Days Prior to Check-in (Day -1 of Period 1)	72 Hours Prior to Check-in (Day -1 of Period 1)
Prescription medications (a)	OTC medications (a)	Alcohol-containing products
Nutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Vitamin supplements	Products containing caffeine and/or xanthine
Nicotine-containing products	Foods or beverages containing grapefruit or Seville-type (sour) oranges and marmalade	
Hepatic or renal clearance altering agents	Immunization/vaccines (b)	
Intake of known OTC inhibitors/inducers of CYPs 2D6, 3A4/5, and 2C19(c)		

(a) Occasional use of acetaminophen (≤ 1 g/day) or other medication (as approved by Takeda on a case-by-case basis) was allowed except on Days 1 and 5 of each treatment period.

(b) Inclusive of, but not limited to, Swine flu (H1N1) vaccinations.

(c) Omeprazole, lansoprazole, cimetidine, chlorpheniramine, and ranitidine.

Note: Topical use of lidocaine for placement of the pH probe was allowed.

Study Population: The study included healthy males and non-pregnant, non-lactating females ages between 18-55 with good health with a BMI between 18-30 kg/m². This study had 52 healthy volunteers enrolled and 50 of them completed the study as planned by completing both treatments. Subject 6001-165 (Sequence AB) did not return for the second treatment period, and Subject 6001-201 (Sequence AB) was discontinued from study drug at the Check-in visit of Period 2 due to an adverse event (elevated CK).

Pharmacogenomic: genotyping for CYP2C19 was conducted on Day 1 of period 1 for all subjects since dexlansoprazole is metabolized by the polymorphic isozyme CYP2C19.

Pharmacokinetic Measurements:

PK blood samples were collected at 0 hour (within 30 minutes before dosing) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours after dosing to determine the plasma concentration of dexlansoprazole on Day 1 and Day 5 on each period.

PK Parameters Analysis:

Pharmacokinetic parameter estimates for dexlansoprazole were calculated using Phoenix WinNonlin version 6.2.1. Statistical analysis was performed using ANOVA to compare the natural logarithmic (ln)-transformed PK parameters AUCs and C_{max} of dexlansoprazole. The ANOVA model included sequence, period, and treatment as fixed effects, and subject within sequence as a random effect. Bioequivalence (BE) between the regimens was concluded if the

90% CIs were completely contained within the equivalence range of 0.80 and 1.25 for dextansoprazole Cmax and AUCs.

For each regimen, the effect of Day (or multiple dose vs single dose) was evaluated using paired t-test on Tmax and natural log of Cmax, and AUC(0-tlqc). “No effect” was concluded if the 90% CIs for the ratio of Cmax and AUCs central values were within the (0.80-1.25) interval.

Actual sampling times, rather than scheduled sampling times, were used in all relevant computations. Concentrations below the lower limit of quantitation were set to zero for PK analysis.

- AUC(0-tau) : Area under the plasma concentration-time curve from time 0 to time tau over a dosing interval, where tau is the length of the dosing interval, calculated using the linear trapezoidal rule. Calculated for Day 5 of each period only.
- AUC(0-tlqc) Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (tlqc), calculated using the linear trapezoidal rule.
- AUC(0-inf) Area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC(0-inf) = AUC(0-tlqc) + lqc/\lambda_z$, where tlqc is the time of last quantifiable concentration and lqc is the last quantifiable concentration. Calculated on Day 1 of each period only.

Bioanalytical Method:

- Concentrations of dextansoprazole in human plasma were measured by a validated LC/MS/MS at (b) (4)
 - Project samples were analyzed according to (b) (4) entitled “Determination of Lansoprazole in Human Plasma by LC/MS/MS,” which was validated under Project Code “AEMS.” This method is applicable to the quantitation of lansoprazole within a nominal range of 2.00 to 2000 ng/mL.
- Plasma samples were stored frozen at -20°C or colder until analysis
- Calibration standard curve consisted of 8 level ranged from 2 to 2000 ng/mL in human plasma, and was calculated using a linear (1/concentration squared weighted) least-squares regression algorithm. The R² ranges between 0.9947- 0.9996.
- QC samples at 5 different concentrations (6.00, 15.0, 60.0, 250, and 1500 ng/mL) of dextansoprazole were prepared
- The inter-assay coefficients of variation of the QCs run ranged from 2.56% to 5.78%, with mean percent differences from theoretical ranging from -2.32% to 2.68%.
- The differences of back-calculated calibration curve values from nominal values ranged from -2.98 to 2.17%.
- At least 5% of the study samples were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification. The incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20%.
- Plasma samples, stored at approximately -20°C, were analyzed within the time period for which the long-term stability of plasma dextansoprazole has been established.
 - Plasma samples were collected between 08/08/2012 through 10/09/2012.
 - Plasma samples were analyzed between 10/24/2012 through 11/14/2012.
 - The maximum storage period from collection through analysis was 98 days.
 - The long term storage stability of omeprazole in human plasma at -20 °C was established for at least for 232 days.

Pharmacodynamics:

Intragastric pH recording every 2 seconds was performed for 24 hours beginning immediately prior to study drug administration on Day 1 and Day 5 of Periods 1 and 2. Median intragastric pH values over 15-minute intervals was determined and used for estimating the PD parameters for Days 1 and 5 of each period. Mean 24-hour pH and % of time pH>4 over 24 hours were determined as the PD parameters.

The PD parameters were also calculated for the following intervals: 0 to 6, >6 to 12, >12 to 18, and >18 to 24 hours postdose. The PD parameters were also calculated for the interval of >6 to 24 hours postdose.

ANOVA models were fitted to the above PD parameters on Day 1 and Day 5. The model included fixed effects of sequence, period, and regimen as well as a random effect of subject nested within sequence. The cohort effect was tested in the ANOVA model along with the cohort and period interaction. The cohort and cohort/period interaction factors were not statistically significant, so these terms were excluded from the final model. Pairwise comparisons between regimens were conducted. Ninety percent CIs for the difference in the least squares means of the 2 regimens were computed. Pharmacodynamic equivalence between the 2 regimens was concluded if the 90% CIs were completely contained within the equivalence range of (-12%, 12%) for % time pH>4 over the 0 to 24-hour interval.

RESULTS:

Pharmacokinetics:

Following both single dose administration on day 1 and multiple dose administration on Day 5, although 30 mg dexlansoprazole delayed release OD 30 mg tablet and 30 mg capsules has similar C_{max}, T_{max} was reached earlier for ODT tablet compared the capsule (reference). In addition, ODT does not have clear double peak profile as the capsule formulation.

Figure 1: Mean (SD) Plasma Concentration-Time Plots for Dexlansoprazole Following a Single Dose of Dexlansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule to Healthy Subjects

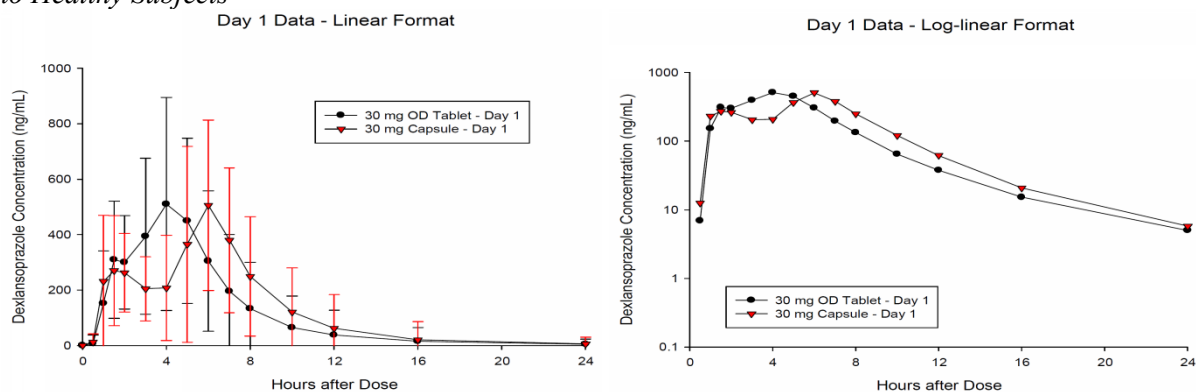


Table 1: Summary of the Pharmacokinetic Parameter Estimates for Dexlansoprazole Following a Single Dose of the Dexlansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule to Healthy Subjects

T _{max} (hr)	C _{max} (ng/mL)	AUC(0-t _{lqc}) (ng·hr/mL)	AUC(0-inf) (ng·hr/mL)	T _{1/2} (hr)	CL/F (L/hr)	V _z /F (L)
Day 1 – Single Dose of Delayed-Release OD 30 mg Tablet (Regimen A) (a)						

N	50	50	50	46	46	46	46
Mean	NR	688	2866	3048	2.10	14.24	41.33
SD	NR	337.2	2221.0	2376.8	1.186	8.237	38.649
Min	1.00	164	681	693	0.73	2.49	11.65
Median	4.00	590	2197	2437	1.56	12.32	27.99
Max	6.00	1730	11110	12026	5.77	43.30	205.59
CV%	NR	49	77	78	57	58	94

Day 1 – Single Dose of Delayed-Release 30 mg Capsule (Regimen B) (b)							
N	50	50	50	46	46	46	46
Mean	NR	618	3049	3212	1.88	13.02	31.36
SD	NR	298.6	2515.6	2759.0	0.989	6.378	17.270
Min	1.00	279	937	948	0.89	1.64	12.42
Median	5.00	537	2179	2294	1.52	13.08	27.90
Max	7.02	1780	17049	18275	5.73	31.64	100.35
CV%	NR	48	83	86	53	49	55

Figure 2: Box Plots for Dexlansoprazole C_{max} and AUC Values Following a Single Dose of Dexlansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule to Healthy Subjects

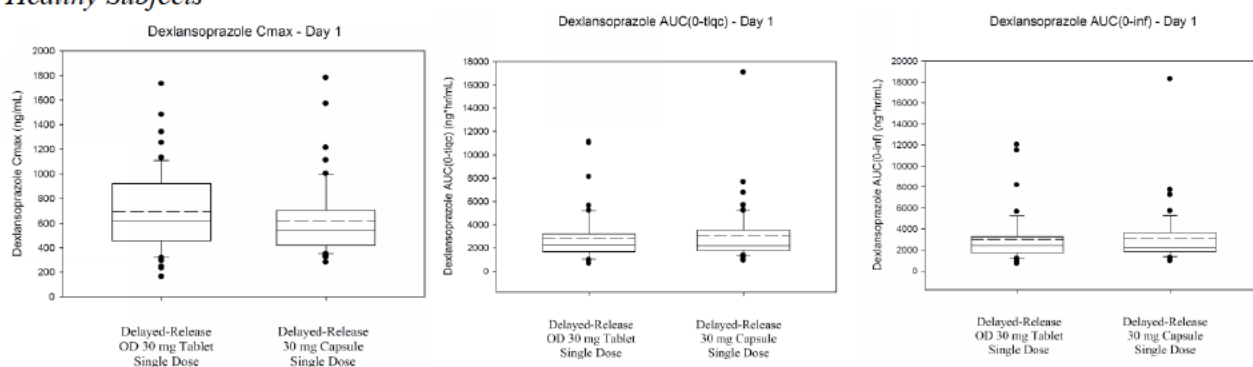


Figure 3: Mean (SD) Plasma Concentration-Time Plots for Dexlansoprazole on Day 5 Following Once-Daily Administration of Dexlansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule for 5 Days in Healthy Subjects

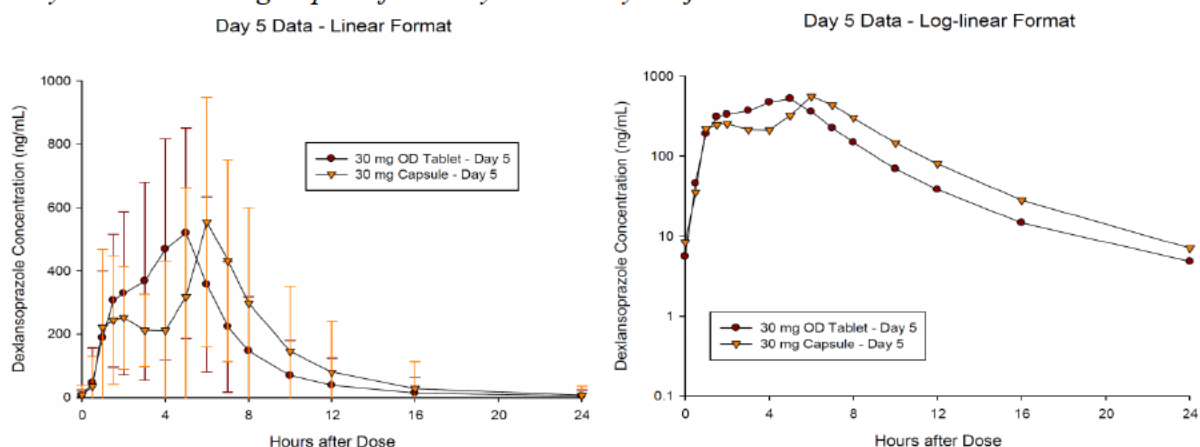


Table 2: Summary of the Pharmacokinetic Parameter Estimates of Dexlansoprazole on Day 5 Following Daily Administration of Dexlansoprazole Delayed- Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule for 5 Days to Healthy Subjects

	Tmax (hr)	Cmax (ng/mL)	AUC(0-tlqc) (ng hr/mL)	AUC(0-tau) (ng hr/mL)	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)
Day 5 – Once-Daily Doses of Delayed-Release OD 30 mg Tablet (Regimen A) (a)							
N	50	50	50	50	49	50	49
Mean	NR	752	3027	3036	2.09	14.22	44.16
SD	NR	358.7	2144.1	2143.9	1.167	8.526	48.780
Min	1.00	169	644	644	0.93	2.70	12.03
Median	4.00	654	2240	2251	1.68	13.33	24.53
Max	6.02	1550	11100	11100	5.96	46.62	260.35
CV%	NR	48	71	71	56	60	110
Day 5 – Once-Daily Doses of Delayed-Release 30 mg Capsule (Regimen B) (b)							
N	50	50	50	50	49	50	49
Mean	NR	687	3330	3345	1.79	13.33	29.16
SD	NR	337.8	3130.3	3127.9	0.866	7.173	14.225
Min	1.00	182	835	851	0.89	1.62	12.24
Median	6.00	604	2361	2371	1.48	12.67	24.84
Max	8.00	1910	18504	18504	5.23	35.26	86.22
CV%	NR	49	94	94	48	54	49

Figure 4: Box Plots for Dexlansoprazole Cmax and AUC Values on Day 5 Following Daily Administration of Dexlansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule for 5 Days to Healthy Subjects

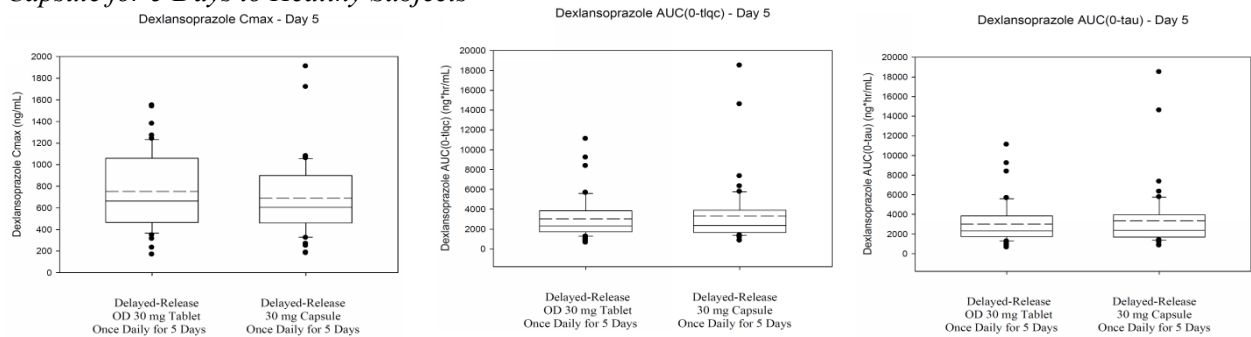


Table 3: Statistical Comparisons of Pharmacokinetic Parameter Estimates for Dexlansoprazole Following Daily Administration of the Dexlansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule for 1 or 5 Days to Healthy Subjects

Parameter (N) (a)	Point Estimate of the Relative BA	90% CIs for the Point Estimate
Day 1: Delayed-Release OD 30 mg Tablet (Regimen A) vs Delayed-Release 30 mg Capsule (Regimen B) (b)		
C _{max} (50/50)	1.0580	(0.9502 – 1.1781)
AUC(0-tl _q c) (50/50)	0.9047	(0.8419 – 0.9721)
AUC(0-inf) (46/46)	0.9265	(0.8615 – 0.9964)
Day 5: Delayed-Release OD 30 mg Tablet (Regimen A) vs Delayed-Release 30 mg Capsule (Regimen B) (b)		
C _{max} (50/50)	1.0868	(0.9516 – 1.2411)
AUC(0-tl _q c) (50/50)	0.9531	(0.8672 – 1.0476)
AUC(0-tau) (50/50)	0.9507	(0.8652 – 1.0445)

Table 4: Statistical Comparisons of Pharmacokinetic Parameter Estimates for Dexlansoprazole Following Daily Administration of the Dexlansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule for 1 or 5 Days to Healthy Subjects (Reviewer's Analysis)

Parameter	Point Estimate of the Relative BA	Lower 90% CL	Upper 90% CIs
Day 1: Delayed-Release OD 30 mg Tablet (Regimen A) vs Delayed-Release 30 mg Capsule (Regimen B)			
C _{max}	108.50585	96.997296	121.37987
AUC(0-tl _q c)	91.804743	85.112662	99.022997
AUC(0-inf)	91.827915	85.219452	98.948841
Day 5: Delayed-Release OD 30 mg Tablet (Regimen A) vs Delayed-Release 30 mg Capsule (Regimen B)			
C _{max}	108.56849	95.525894	123.39186
AUC(0-tl _q c)	94.902732	86.567007	104.04112
AUC(0-tau)	94.646748	86.360668	103.72786

Both dexlansoprazole capsule and ODT formulations had similar the mean plasma profiles on Day 1 vs. Day 5.

Figure 5: Mean (SD) Plasma Concentration-Time Plots for Dexlansoprazole on Day 1 and Day 5 Following Once-Daily Administration of Dexlansoprazole Delayed-Release OD 30 mg Tablet for 5 Days in Healthy Subjects

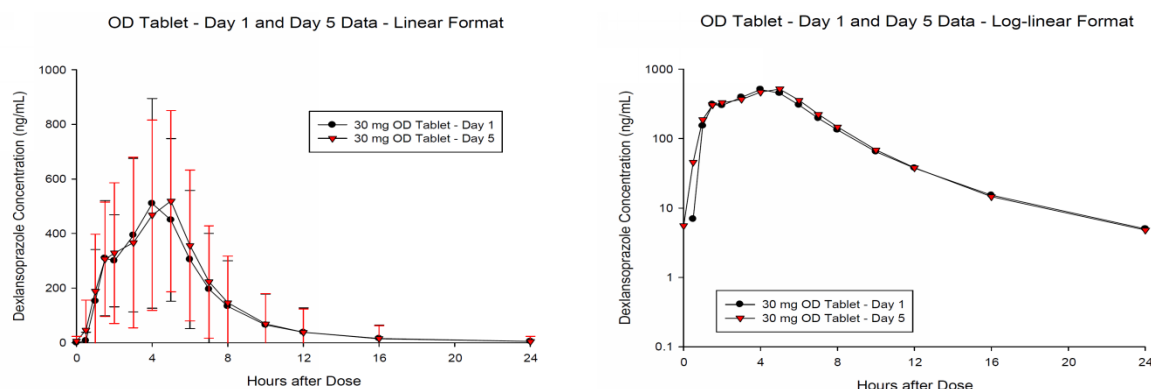


Figure 6: Mean (SD) Plasma Concentration-Time Plots for Dexlansoprazole on Day 1 and Day 5 Following Once-Daily Administration of Dexlansoprazole Delayed-Release 30 mg Capsule for 5 Days in Healthy Subjects

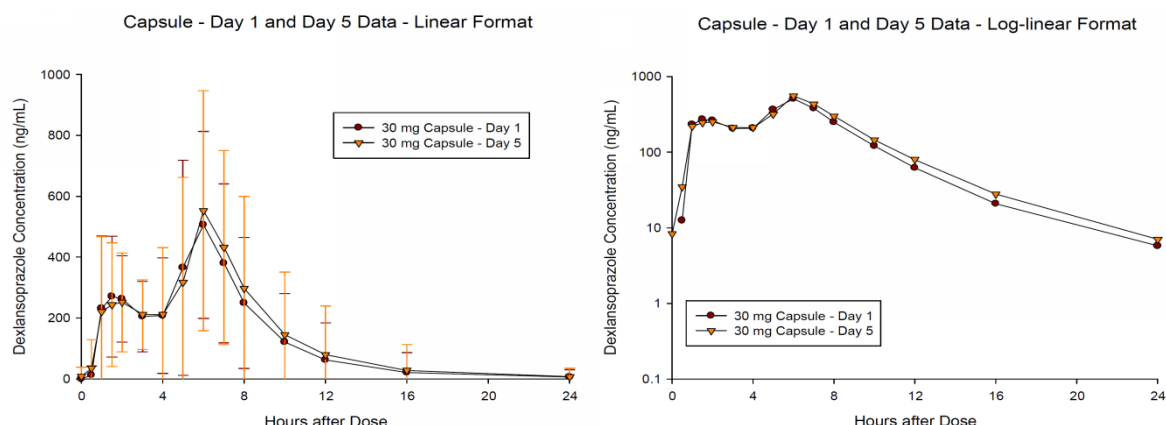


Table 5: Summary of the Pharmacokinetic Parameter Estimates of Dexlansoprazole Following Daily Administration of the Dexlansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule for 5 Days to Healthy Subjects

	C _{max} (ng/mL)	AUC(0-t _{lqc}) (ng·hr/mL)	AUC(a) (ng·hr/mL)	T _{1/2} (hr)
Day 1 – Single Dose of Delayed-Release OD 30 mg Tablet (Regimen A) (b)				
N	50	50	46	46
Mean	688	2866	3048	2.10
SD	337.2	2221.0	2376.8	1.186
CV%	49	77	78	57
Day 5 – Once-Daily Doses of Delayed-Release OD 30 mg Tablet (Regimen A) (b)				
N	50	50	50	49
Mean	752	3027	3036	2.09
SD	358.7	2144.1	2143.9	1.167
CV%	48	71	71	56
Day 1 – Single Dose of Delayed-Release 30 mg Capsule (Regimen B) (c)				
N	50	50	46	46
Mean	618	3049	3212	1.88
SD	298.6	2515.6	2759.0	0.989
CV%	48	83	86	53
Day 5 – Once-Daily Doses of Delayed-Release 30 mg Capsule (Regimen B) (c)				
N	50	50	50	49
Mean	687	3330	3345	1.79
SD	337.8	3130.3	3127.9	0.866
CV%	49	94	94	48

Figure 7: Box Plots for Dexlansoprazole C_{max} and AUC Values on Days 1 and Day 5 Following Daily Administration of the Dexlansoprazole Delayed-Release OD 30 mg Tablet for 5 Days to Healthy Subjects

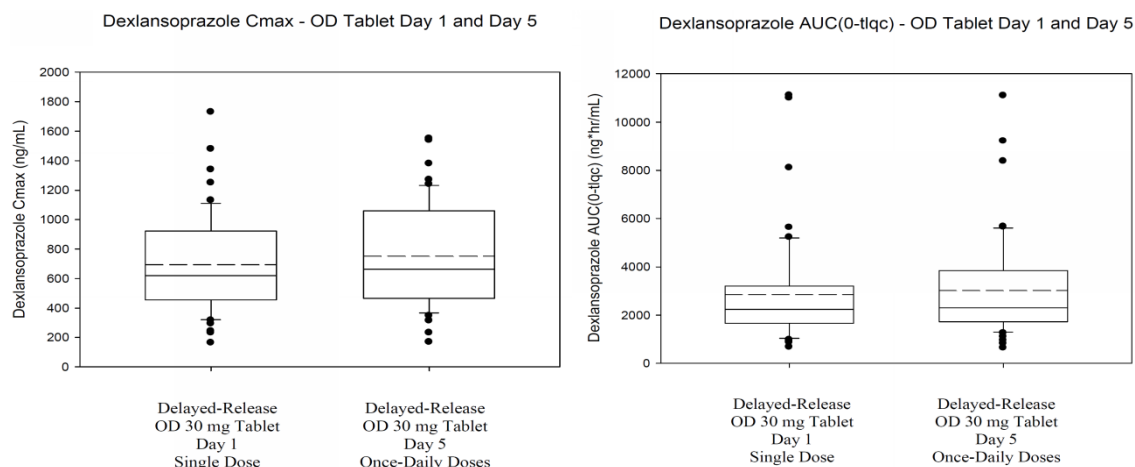


Figure 8: Box Plots for Dexlansoprazole Cmax and AUC Values Following Daily Administration of the Dexlansoprazole Delayed-Release 30 mg Capsule for 5 Days to Healthy Subjects

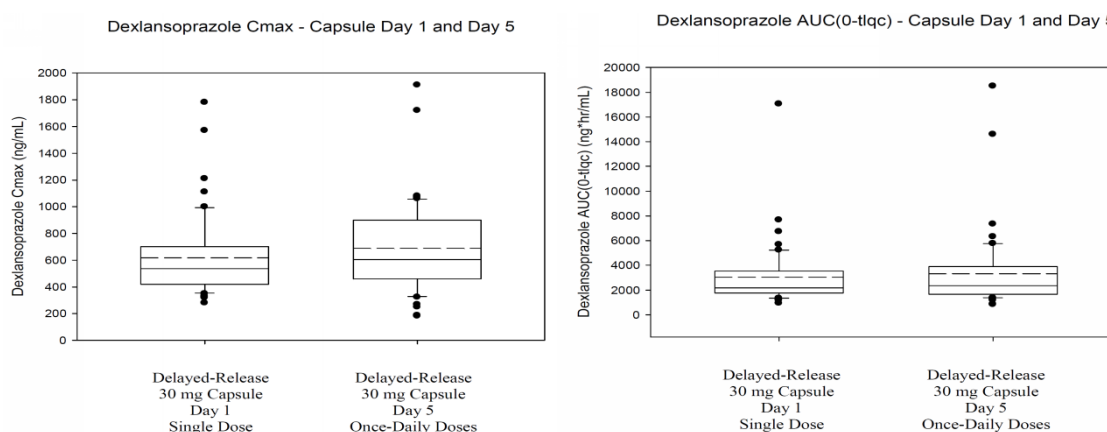


Table 6: Statistical Comparisons of Pharmacokinetic Parameter Estimates for Dexlansoprazole Following Daily Administration of the Dexlansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule for 1 or 5 Days to Healthy Subjects

Parameter (N)	Point Estimate of the Relative BA	90% CIs for the Point Estimate
Regimen A: Once-Daily Dosing of Delayed-Release OD 30 mg Tablet Day 5 vs Day 1 (a)		
Cmax (N=52)	1.0778	(0.9657 – 1.2029)
AUC(0-t1qc) (N=52)	1.0693	(0.9811 – 1.1654)
Regimen B: Once-Daily Dosing of Delayed-Release 30 mg Capsule Day 5 vs Day 1 (a)		
Cmax (N=50)	1.0827	(0.9739 – 1.2037)
AUC(0-t1qc) (N=50)	1.0362	(0.9794 – 1.0962)

Effect of Genotype on Dexlansoprazole Pharmacokinetics

The CYP2C19 genotype was determined for 52 subjects. Of these, 27 subjects were homozygous extensive metabolizers (EMs, *1/*1), 6 subjects were heterozygous EMs (*1/*2), 18 subjects were CYP2C19 heterozygous (*1/*17 or *2/*17) ultra-rapid metabolizers (UMs), and 1 subject was a CYP2C19 homozygous PM (*2/*2). No formal statistical analyses on dexlansoprazole PK were conducted based on CYP2C19 genotype.

However, the PM subject (Subject 6001-075) had the highest plasma dextansoprazole AUC values on Days 1 and 5 in each regimen. The subjects with the lowest AUC values in each regimen were homozygous EM (Subjects 6001-108) and heterozygous UMs (6001-192 and 6011-526). Metabolizer status was not expected to have an effect on the PD assessments or the determination of BA as this was a crossover study design and each subject acted as his or her own control.

Analysis of Pharmacodynamics

Figure 9: 24-Hour Mean pH Profiles on Day 1 after a Single Dose of Dextansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule Formulations

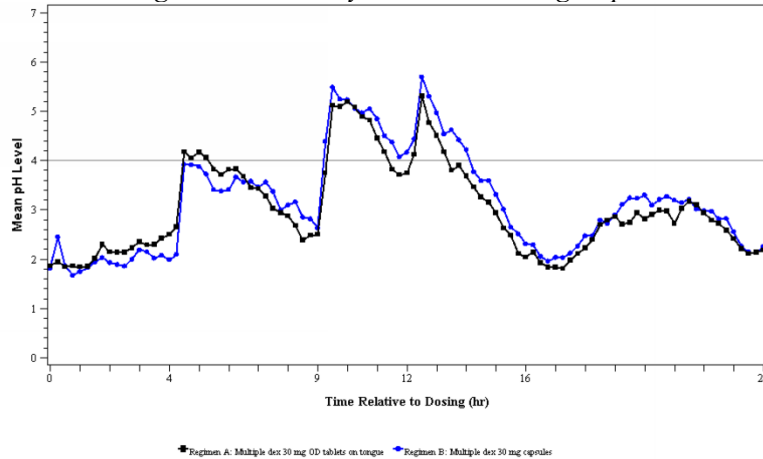


Figure 10: 24-Hour Mean pH Profiles on Day 5 After Administration of Dextansoprazole Delayed-Release OD 30 mg Tablet or Delayed-Release 30 mg Capsule Formulations QD for 5 Days

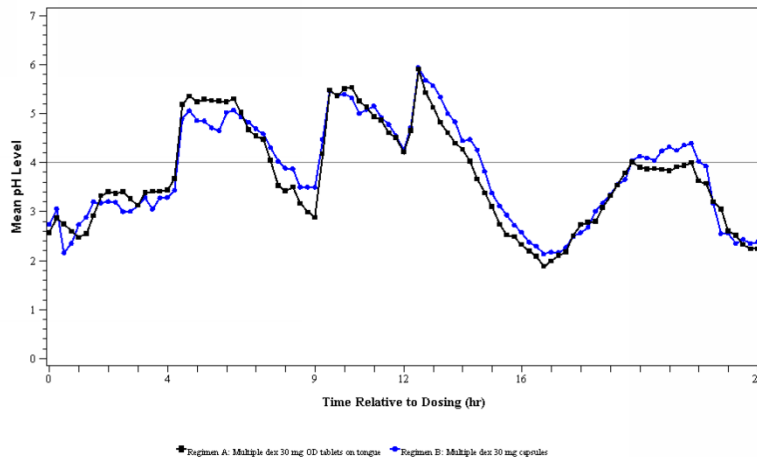


Table 7: Comparison of Percentage of Time Intra-gastric pH >4 Over 24 Hours and by Interval Following Administration of Dextansoprazole Delayed-Release OD 30 mg Tablet and Delayed-Release 30 mg Capsule

Interval	Mean (SD) for Percentage of Time pH>4		P-value (a)	90% CIs (a)
	Dexlansoprazole Delayed-Release OD 30 mg Tablet	Dexlansoprazole Delayed-Release 30 mg Capsule		
Day 1				
0 to 24 hours postdose (N=50)	32.4 (17.87)	32.4 (17.12)	0.988	(-4.1, 4.1)
>6 to 24 hours postdose (N=49)	35.4 (19.13)	38.1 (18.65)	0.309	(-7.2, 1.7)
0 to 6 hours postdose (N=50)	24.5 (22.59)	17.4 (18.98)	0.055	(1.0, 13.2)
>6 to 12 hours postdose (N=49)	50.7 (27.79)	52.9 (26.08)	0.638	(-9.5, 5.3)
>12 to 18 hours postdose (N=49)	33.3 (21.55)	39.4 (23.68)	0.056	(-11.4, -0.9)
>18 to 24 hours postdose (N=49)	22.1 (24.34)	21.9 (27.28)	0.974	(-5.8, 6.1)
Day 5				
0 to 24 hours postdose (N=50)	45.8 (18.19)	47.3 (16.69)	0.518	(-4.9, 2.2)
>6 to 24 hours postdose (N=50)	45.9 (18.47)	49.5 (16.86)	0.134	(-7.4, 0.4)
0 to 6 hours postdose (N=50)	45.6 (22.23)	40.9 (22.74)	0.086	(0.2, 9.5)
>6 to 12 hours postdose (N=50)	65.3 (20.87)	70.3 (21.06)	0.104	(-9.9, 0.1)
>12 to 18 hours postdose (N=49)	39.2 (21.77)	44.4 (19.27)	0.080	(-9.9, -0.3)
>18 to 24 hours postdose (N=50)	33.0 (27.70)	33.1 (27.94)	0.990	(-5.2, 5.1)

Table 8: Comparison of Mean pH Over 24 Hours and by Interval Following Administration of Dexlansoprazole Delayed-Release OD 30 mg Tablet and Delayed-Release 30 mg Capsule

Interval	Mean (SD) for Mean pH		
	Dexlansoprazole Delayed-Release OD 30 mg Tablet	Dexlansoprazole Delayed-Release 30 mg Capsule	P-value (a)
	Day 1		
0 to 24 hours postdose (N=50)	3.05 (0.889)	3.14 (0.813)	0.420
>6 to 24 hours postdose (N=49)	3.18 (0.925)	3.40 (0.856)	0.069
0 to 6 hours postdose (N=50)	2.72 (1.184)	2.46 (0.959)	0.169
>6 to 12 hours postdose (N=49)	3.80 (1.161)	4.00 (0.953)	0.281
>12 to 18 hours postdose (N=49)	3.02 (0.987)	3.34 (1.032)	0.020*
>18 to 24 hours postdose (N=49)	2.71 (1.296)	2.86 (1.400)	0.334
Day 5			
0 to 24 hours postdose (N=50)	3.74 (0.878)	3.81 (0.744)	0.574
>6 to 24 hours postdose (N=50)	3.73 (0.893)	3.89 (0.764)	0.180
0 to 6 hours postdose (N=50)	3.78 (1.034)	3.57 (0.956)	0.106
>6 to 12 hours postdose (N=50)	4.44 (0.802)	4.59 (0.683)	0.222
>12 to 18 hours postdose (N=49)	3.40 (1.034)	3.59 (0.853)	0.158
>18 to 24 hours postdose (N=50)	3.35 (1.432)	3.45 (1.446)	0.522

Although the two formulations had similar over all PD profiles 0-24 hours on both Day 1 and Day 5, it appears that mean pH for ODT was slightly higher from 0-6 hours and slightly lower between 12-18 hour compared to capsule on both Day 1 and Day 5.

In addition, on Day 5, for the 0 to 24-hour interval and all sub-intervals, the % time pH>4 and mean pH were higher than the respective intervals on Day 1.

Safety:

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory test (haematology, clinical chemistry, urinalysis,) 12-lead electrocardiogram (ECG), and adverse event (AE) monitoring. According to the sponsor, there was no death or serious adverse event (SAE) during the study. One subject (6001-201) was discontinued from the study due to elevated CK noted at the Check-in visit for Period 2; this event was captured for the last treatment administered (OD tablet formulation) but was not considered to be related to study drug.

Incidences of adverse events were comparable in both treatment groups (<28%). The adverse events were primarily mild in intensity and considered unrelated to study drug. The most frequent adverse event during both treatments was headache (3 subjects in each group). There were no clinically important findings noted in the physical examination, safety clinical laboratory, vital sign, or ECG data.

Reviewer's Comment:

- *Following a single dose and multiple doses for 5 days, the 90% CIs for the dextansoprazole C_{max}, AUC(0-t_{lq}c), and AUC(0-inf) were within the 0.80 to 1.25 BE range suggesting the dextansoprazole delayed-release OD 30 mg tablet is bioequivalent to dextansoprazole delayed-release 30 mg capsule following single dose and multiple dose.*
- *There was no effect of Day on dextansoprazole PK for both regimen since 90% CIs for the ratio of C_{max} and AUC(0-t_{lq}c) central values were within the 0.80 to 1.25 interval.*
- *Following single dose and multiples dose administration for 5 days (QD), dextansoprazole delayed-release OD 30 mg tablets resulted in similar the intragastric pH parameters to that of dextansoprazole delayed-release 30 mg capsules.*
- *Sampling time for 24 hours and washout period of 7 days was appropriate as the half-life of dextansoprazole was approximately 2 hour.*
- *PK analysis and BE analysis were repeated and were consistent with sponsor's result.*

Study: TAK-390MR(OD)_106

Title: A Phase 1, Randomized, Open-Label, Single Center, Single-Dose, 4-Period, Crossover Study to Assess the Bioavailability of 30 mg Dexamisoprazole Delayed-Release Orally Disintegrating Tablets Mixed With Water and Administered Orally Via Syringe or Via Nasogastric Tube, or Swallowed Intact With Water, Relative to Administration on the Tongue Without Water in Healthy Subjects

Sponsor: Takeda Global Research & Development Center, Inc.
Clinical Site: Celerion, Inc., Neptune, NJ
Bioanalytical Site: (b) (4)
Pharmacogenomic: (b) (4)
Study Date: 08/10/2012 – 12/04/2012

OBJECTIVE:

- Primary: To determine the BA of dexamisoprazole from a single-dose of 3 alternative administration options of dexamisoprazole delayed-release OD 30 mg tablet relative to dexamisoprazole delayed-release OD 30 mg tablet administered on the tongue, allowed to disintegrate, and swallowed without water.
- Secondary: To evaluate the safety profile of the dexamisoprazole delayed-release OD 30 mg tablet following a single dose in each of the 4 regimens.

Investigational Product: Dexamisoprazole delayed-release OD 30 mg tablets, Formulation Z

STUDY DESIGN:

- Regimen A: A single oral dose of dexamisoprazole delayed-release OD 30 mg tablet mixed with water and administered orally via syringe (Test).
- Regimen B: A single oral dose of dexamisoprazole delayed-release OD 30 mg tablet mixed with water and administered via NG tube (Test).
- Regimen C: A single oral dose of dexamisoprazole delayed-release OD 30 mg tablet, swallowed intact with water (Test).
- Regimen D: A single oral dose of dexamisoprazole delayed-release 30 mg OD tablet, administered on the tongue, allowed to disintegrate, and swallowed without water (Reference).

This study was an open-label, phase 1, randomized (1:1:1:1 ratio), single-center, single-dose, 4-period crossover study in healthy subjects to evaluate the PK and assess the BA of dexamisoprazole from the 3 alternative administration options of dexamisoprazole delayed-release OD 30 mg tablets relative to dexamisoprazole delayed-release OD 30 mg tablet allowed to disintegrate on the tongue and swallowed without water. Pharmacokinetic blood samples were collected for up to 24 hours post-dose to determine the plasma concentrations of dexamisoprazole. The washout interval between each period was at least 5 days.

Treatment Sequences

Sequences	Number of Subjects Planned	Number of Subjects Enrolled	Period 1	Period 2	Period 3	Period 4
1	20	18	A	B	D	C
2	20	19	B	C	A	D
3	20	20	C	D	B	A

In all regimens, subjects fasted for a minimum of 10 hours prior to dosing on Day 1 and remained fasted for 4 hours postdose.

In Regimen A, the intact tablet was placed in a slip-tip syringe, and water was drawn into the syringe to achieve a final volume of 15 mL to 20 mL. Once the tablet had completely disintegrated, the contents of the syringe were mixed and the entire mixture was then delivered into the subject's mouth. As a rinse, an additional 10 mL of water was drawn into the syringe used for dosing and delivered through the syringe into the subject's mouth. The rinse was performed twice for a total volume (initial dose and 2 rinses) of approximately 40 mL.

In Regimen B, the intact tablet was placed in a slip-tip syringe, and water was drawn into the syringe to achieve a final volume of 15 mL to 20 mL. Once the tablet had completely disintegrated, the contents of the syringe were mixed and the entire mixture was then delivered through an 8 French NG tube for direct delivery into the subject's stomach. Topical lidocaine and up to 120 mL of water were allowed per site procedures to aid placement of the NG tube in Regimen B. As a rinse, an additional 10 mL of water was drawn into the syringe used for dosing and delivered through the NG tube. The rinse was performed twice for a total volume (initial dose and 2 rinses) of approximately 40 mL.

In Regimen C, subjects were instructed to swallow the intact tablet with 240 mL of water.

In Regimen D, subjects had the tablet administered directly on the tongue, without water. The subjects were instructed to allow the dexlansoprazole delayed-release OD tablet to disintegrate on the tongue, and to swallow the granules without chewing.

Excluded Medications and Dietary Products

28 Days Prior to Check-in (Day -1 of Period 1)	14 Days Prior to Check-in (Day -1 of Period 1)	72 Hours Prior to Check-in (Day -1 of Period 1)
Prescription medications (a)	OTC medications (a)	Alcohol-containing products
Nutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Vitamin supplements	Products containing caffeine and/or xanthine
Nicotine-containing products	Foods or beverages containing grapefruit or Seville-type (sour) oranges and marmalade	
Hepatic or renal clearance altering agents	Immunization/vaccines (b)	
Intake of known OTC inhibitors/inducers of CYPs 2D6, 3A4/5, and 2C19 (c)		

OTC=over-the-counter.

(a) Occasional use of acetaminophen (≤ 1 g/day) or other medication (as approved by Takeda on a case-by-case basis) was allowed except on Day 1 of each treatment period. Topical use of lidocaine was allowed for placement of NG tube on Day 1 of Regimen B.

(b) Inclusive of, but not limited to, H1N1 and flu vaccinations.

(c) Examples include: omeprazole, lansoprazole, cimetidine, chlorpheniramine, and ranitidine.

Note: Hormonal contraception and hormone replacement therapy were allowed, as long as a subject had been on a stable dose for a minimum of 60 days prior to Day 1 of Period 1.

Study Population: The study included healthy males and non-pregnant, non-lactating females ages between 18-55 with good health with a BMI between 18-30 kg/m². This study had 77 healthy volunteers enrolled and 71 of them completed the study as planned by completing all 4 treatments period.

- Three subjects voluntarily discontinued from the study:
 - 1 subjects withdrew prior to Period 2,

- Subject 7001-226 is missing treatment B, C, D
- 2 subjects discontinued prior to Period 4,
 - Subject 7001-117 missing treatment D.
 - Subject 7001-175 is missing treatment A
- One subject (7001-015) was discontinued at the Check-in visit of Period 2 for a positive drug screen (missing treatments A, B, and C).
- Two subjects discontinued study drug due to adverse events.
 - Subject 7001-086 completed the first 2 treatment periods, but was unable to tolerate placement of the NG tube, and was not dosed in Period 3 (missing treatments A and B).
 - Subject 7001-095 completed the first 3 treatment periods, but was discontinued from the study due to elevated CK at the Check-in visit of Period 4 (missing treatment B).

Pharmacogenomic: genotyping for CYP2C19 was conducted on Day 1 of period 1 for all subjects since dexlansoprazole is metabolized by the polymorphic isozyme CYP2C19.

Pharmacokinetic Measurements:

PK blood samples were collected at 0 hour (within 30 minutes before dosing) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours after dosing to determine the plasma concentration of dexlansoprazole on Day 1 of each period.

PK Parameters Analysis:

Pharmacokinetic parameter estimates for dexlansoprazole were calculated using Phoenix WinNonlin version 6.3. Statistical analysis was performed using ANOVA to compare the natural logarithmic (ln)-transformed PK parameters AUCs and Cmax of dexlansoprazole. The ANOVA model included sequence, period, and treatment as fixed effects, and subject within sequence as a random effect. Bioequivalence (BE) between the regimens was concluded if the 90% CIs were completely contained within the equivalence range of 0.80 and 1.25 for dexlansoprazole Cmax and AUCs.

Actual sampling times, rather than scheduled sampling times, were used in all relevant computations. Concentrations below the lower limit of quantitation were set to zero for PK analysis.

Bioanalytical Method:

- Concentrations of dexlansoprazole in human plasma were measured by a validated LC/MS/MS at (b) (4)
 - Project samples were analyzed according to (b) (4) entitled “Determination of Lansoprazole in Human Plasma by LC/MS/MS,” which was validated under Project Code “AEMS.” This method is applicable to the quantitation of lansoprazole within a nominal range of 2.00 to 2000 ng/mL.
- Plasma samples were stored frozen at -20°C or colder until analysis
- Calibration standard curve consisted of 8 level ranged from 2 to 2000 ng/mL in human plasma, and was calculated using a linear (1/concentration squared weighted) least-squares regression algorithm. The R² ranges between 0.9959- 0.9997.
- QC samples at 5 different concentrations (6.00, 15.0, 60.0, 250, and 1500 ng/mL) of dexlansoprazole were prepared
- The inter-assay coefficients of variation of the QCs run ranged from 2.52% to 9.12%, with mean percent differences from theoretical ranging from -4.15% to 6.01%.

- The differences of back-calculated calibration curve values from nominal values ranged from -6.25 to 5.36%.
- At least 5% of the study samples were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification. The incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20%.
 - Plasma samples, stored at approximately -20°C, were analyzed within the time period for which the long-term stability of plasma dexlansoprazole has been established.
 - Plasma samples were collected between 08/10/2012 through 12/04/2012.
 - Plasma samples were analyzed between 11/09/2012 through 1/15/2013.
 - The maximum storage period from collection through analysis was 158 days.
 - The long term storage stability of omeprazole in human plasma at -20 °C was established for at least for 232 days.

RESULTS:

Pharmacokinetics:

As demonstrated in figure 1, the mean dexlansoprazole plasma concentration-time profiles were similar under all 4 conditions of single-dose administration of dexlansoprazole delayed-release OD 30 mg tablets either as intact tablet on the tongue without water, as an intact tablet swallowed with water, an aqueous mixture via a syringe or as an aqueous mixture via an NG tube.

Figure 1: Mean (SD) Plasma Concentration-Time Plots for Dexlansoprazole Following a Single Dose administration of Dexlansoprazole Delayed-Release OD 30 mg Tablet in Healthy Subjects under various dose administration conditions (Sponsor provided)

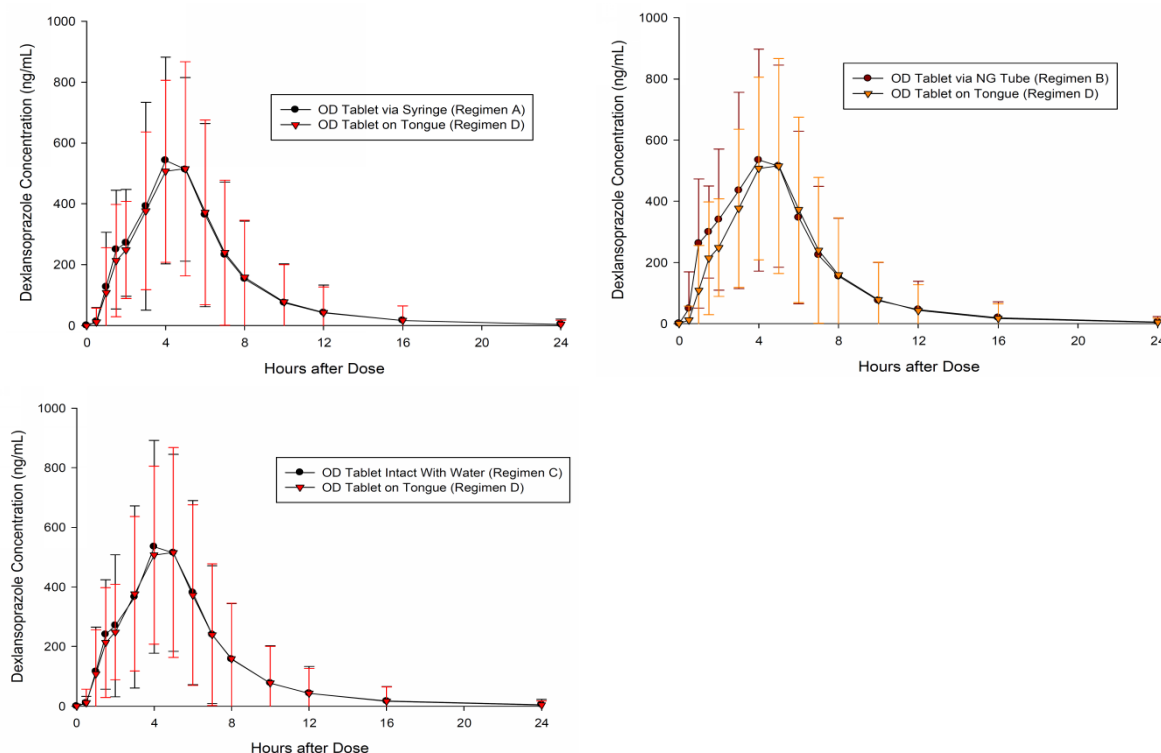
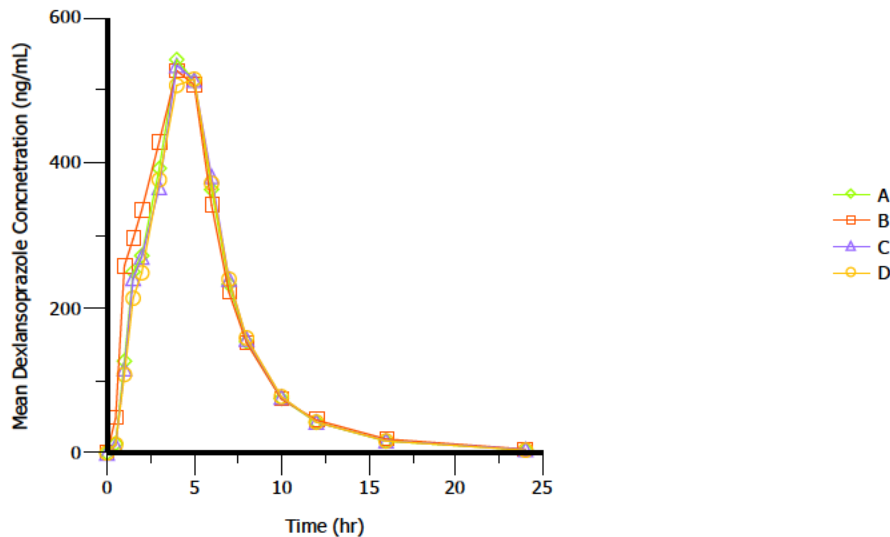


Figure 2: Mean (SD) Plasma Concentration-Time Plots for Dexlansoprazole Following a Single Dose administration of Dexlansoprazole Delayed-Release OD 30 mg Tablet in Healthy Subjects under various dose administration conditions (Reviewer's Analysis)



Subject 7001-028 (Sequence BCAD) was dosed in all 4 treatment periods, but his NG tube was clogged in Period 1, and all of his Period 1 plasma concentration data were BLOQ.

Among the 77 enrolled subjects, 74 subjects received a single dose of study drug (dexlansoprazole delayed-release OD 30 mg tablet) mixed with water and administered via oral syringe (Regimen A), 73 subjects received study drug mixed with water and administered via an NG tube (Regimen B), 75 subjects swallowed the study drug intact with water (Regiment C), and 75 subjects allowed the study drug to disintegrate on the tongue without water (Regiment D).

Table 1: Summary of the Plasma Pharmacokinetic Parameter Estimates for Dexlansoprazole Following Administration of Dexlansoprazole Delayed-Release OD 30 mg Tablet under various conditions in Healthy Subjects

	Tmax (hr)	Cmax (ng/mL)	AUC(0-tlqc) (ng·hr/mL)	AUC(0-inf) (ng·hr/mL)	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)
Oral Syringe Administration (Regimen A)							
N	72	72	72	72	72	72	72
Mean	NR	760	3080	3120	1.85	13.52	32.97
SD	NR	331.3	2326.3	2431.3	1.032	7.066	23.751
Minimum	1.00	218	852	858	0.71	1.75	10.83
Median	4.00	709	2513	2521	1.45	11.90	23.57
Maximum	6.02	1870	16231	17102	6.13	34.96	120.49
%CV	NR	44	76	78	56	52	72

NG Tube Administration (Regimen B)							
N	71	71	71	70	70	70	70
Mean	NR	786	3276	3340	1.89	12.70	31.66
SD	NR	320.4	2222.9	2338.0	1.115	7.377	27.239
Minimum	1.00	146	825	831	0.71	2.18	11.40
Median	4.00	742	2717	2741	1.52	10.95	21.97
Maximum	12.00	1610	12850	13734	6.32	36.11	181.30
%CV	NR	41	68	70	59	58	86
Administration of the Intact Tablet Swallowed With Water (Regimen C)							
N	74	74	74	73	73	73	73
Mean	NR	775	3058	3121	1.98	13.38	37.52
SD	NR	361.3	2170.6	2276.4	1.189	7.303	36.641
Minimum	1.50	116	769	814	0.71	1.94	12.86
Median	4.00	732	2490	2524	1.48	11.89	22.81
Maximum	6.02	1810	14606	15454	6.74	36.84	237.01
%CV	NR	47	71	73	60	55	98
Administration of the Intact Tablet on the Tongue (Regimen D)							
N	74	74	74	74	74	74	74
Mean	NR	744	3011	3043	1.86	14.02	36.13
SD	NR	306.5	2017.5	2087.3	0.950	8.824	34.724
Minimum	1.50	161	593	607	0.77	2.17	12.32
Median	4.00	703	2403	2414	1.50	12.43	24.35
Maximum	6.03	1630	13150	13793	5.02	49.43	208.28
%CV	NR	41	67	69	51	63	96

Table 2: Statistical Comparisons of Pharmacokinetic Parameter Estimates for Dexlansoprazole Following Administration of Dexlansoprazole Delayed-Release OD 30 mg Tablet as an Aqueous Mixture via an Oral Syringe or NG Tube, as the Intact Tablet Swallowed With Water, or as the Intact Tablet on the Tongue Without Water to Healthy Subjects

Parameter	Point Estimate of the Relative BA	90% CIs for the Point Estimate
Oral Syringe Administration (Regimen A [Test]) vs Intact Tablet on the Tongue (Regimen D [Reference])		
C _{max} (N=72/74)	1.0218	(0.9318-1.1205)
AUC(0-tl _q c) (N=72/74)	1.0069	(0.9405-1.0780)
AUC(0-inf) (N=72/74)	1.0070	(0.9411-1.0776)
NG Tube Administration (Regimen B [Test]) vs Intact Tablet on the Tongue (Regimen D [Reference])		
C _{max} (N=71/74)	1.0613	(0.9674-1.1644)
AUC(0-tl _q c) (N=71/74)	1.0831	(1.0113-1.1600)
AUC(0-inf) (N=70/74)	1.0814	(1.0100-1.1579)
Intact Tablet Swallowed With Water (Regimen C [Test]) vs Intact Tablet on the Tongue (Regimen D [Reference])		
C _{max} (N=74/74)	1.0040	(0.9164-1.1000)
AUC(0-tl _q c) (N=74/74)	1.0154	(0.9491-1.0864)
AUC(0-inf) (N=73/74)	1.0191	(0.9527-1.0901)

Table 3: Statistical Comparisons of PK Parameter Estimates for Dexlansoprazole Following Administration of Dexlansoprazole Delayed- Release OD 30 mg Tablet as an Aqueous Mixture via an Oral Syringe or NG Tube, as the Intact Tablet Swallowed With Water, or as the Intact Tablet on the Tongue Without Water to Healthy Subjects (Reviewer's analysis)

Parameter (N)	Point Estimate of the Relative BA	Lower 90% CL	Upper 90% CIs
Oral Syringe Administration (Regimen A) vs Intact Tablet on the Tongue (Regimen D)			
C _{max}	101.92	93.02	111.67
AUC(0-tl _q c)	100.71	94.12	107.76
AUC(0-inf)	100.72	94.18	107.71
NG Tube Administration (Regimen B) vs Intact Tablet on the Tongue (Regimen D)			
C _{max}	106.61	97.25	116.88
AUC(0-tl _q c)	108.46	101.32	116.09
AUC(0-inf)	108.34	101.24	115.95
Intact Tablet Swallowed With Water (Regimen C) vs Intact Tablet on the Tongue (Regimen D)			
C _{max}	101.099	92.33	110.70
AUC(0-tl _q c)	101.892	95.28	108.96
AUC(0-inf)	102.29	95.68	109.37

Effect of Genotype on Dexlansoprazole Pharmacokinetics

The CYP2C19 genotype was determined for 76 subjects (the analytical laboratory was unable to extract DNA from the blood sample for 1 subject 7001-120/1037). Of these, 28 subjects were homozygous extensive metabolizers (EMs, *1/*1), 14 subjects were heterozygous EMs (*1/*2 or *1/*9), 3 subjects were CYP2C19 homozygous ultrarapid metabolizers (UMs,*17/*17), 29 subjects were CYP2C19 heterozygous (*1/*17 or *2/*17) UMs, and 2 subjects were CYP2C19 homozygous PMs (*2/*2 or *3/*3). No formal statistical analyses on dexlansoprazole PK were conducted based on CYP2C19 genotype. Metabolizer status was not expected to have an effect on the PD assessments or the determination of BA as this was a crossover study design and each subject acted as his or her own control.

Safety:

The safety endpoints evaluated in this study included physical examinations, vital signs, clinical laboratory test (haematology, clinical chemistry, urinalysis,) 12-lead electrocardiogram (ECG), and adverse event (AE) monitoring. According to the sponsor, there was no death or serious adverse event (SAE) during the study. Two subjects discontinued study drug due to adverse events (inability to tolerate NG tube or elevated CK). Neither of these events were considered to be related to study drug,

Incidences of adverse events were comparable in all 4 treatment groups (5-7 subjects per treatment). The only adverse event reported for 2 or more subjects during any regimen was Headache. The adverse events were primarily mild in intensity and considered unrelated to study drug. There were no clinically important findings noted in the physical examination, vital sign, or ECG data. There were no remarkable findings in the clinical laboratory safety data; the occurrence of markedly abnormal laboratory values or changes in laboratory values reported as adverse events was low, and all of these values resolved without intervention.

Reviewer's Comment:

- *Single doses of dexlansoprazole delayed-release OD 30 mg tablets administered as an aqueous mixture via an oral syringe or an NG tube, or as an intact OD tablet swallowed with*

water, were each bioequivalent to the oral administration of the intact OD tablet on the tongue without water in terms of dexlansoprazole C_{max} and AUCs.

- *Sampling time for 24 hours and washout period of 5 days was appropriate as the half-life of dexlansoprazole was approximately 2 hour.*
- *PK profile plot, PK analysis and BE analysis were repeated and were consistent with sponsor's result.*

TAK-390MR(OD)_107

Title: An Open-Label Sensory Evaluation of Dexlansoprazole Delayed-Release Orally Disintegrating Tablets in Healthy Subjects:

Sponsor: Takeda Global Research & Development Center, Inc., Deerfield, IL

Clinical Site: Senopsys LLC, Woburn, MA,

Objective: The objective of this program was to measure the in vivo disintegration time of a single dexlansoprazole delayed-release orally disintegrating tablet (ODT).

Study Drug: Dexlansoprazole delayed-release orally disintegrating tablet (ODT) 30 mg

Study Design: This was an open-label, single –center study in 8 healthy subjects to evaluate the in vivo disintegration time of a single dexlansoprazole delayed-release OD 30 mg tablet. Each subject evaluated the disintegration time of 3 separate single doses of the OD 30 mg tablet; on a given testing day, subjects may have received up to 2 doses of study drug (maximum dose of 60 mg/day), and the entire 3 doses may have been administered over several days. Disintegration time testing was performed on 3 testing dates, with at least 4 subjects participating on each date. For each disintegration time assessment, subjects sipped and swallowed 20 mL of spring water 30 seconds prior to study drug administration. Thirty seconds after the water was consumed, the OD tablet was placed on the tongue and gently rolled against the roof of the mouth with the tongue until the tablet disintegrated into small granules. At the point at which the subject would normally swallow the granules, they recorded the elapsed time and expectorated the disintegrated tablet mass and not swallowed. There were no dietary restrictions for this study.

Study Population: 8 subjects were enrolled and completed the study.

Four women and 4 men were enrolled. All of the female subjects were postmenopausal. All of the subjects were White and of non-Hispanic ethnicity. Subjects ranged in age from 35 to 67 years.

Characteristic	Subject							
	001	002	003	004	005	006	007	008
Age (yr)	65	67	57	62	58	51	57	35
Sex	Female	Male	Female	Female	Female	Male	Male	Male
Race	White	White	White	White	White	White	White	White
Hispanic/Latino	No	No	No	No	No	No	No	No

Pharmacokinetic Measurements: Drug concentrations were not measured in this study.

Endpoint: Disintegration time of the OD tablet

RESULTS:

Individual disintegration times in each trial ranged from 29 seconds to 43 seconds, with an overall mean of 36 seconds.

Table 1: In Vivo Disintegration Times of a Single Dose of a Dexlansoprazole Delayed- Release OD 30 mg Tablet

Subject	Disintegration Time (sec)			Mean	Median
	1	2	3		
1	36	35	34	35.0	35
2	35	32	36	34.3	35
3	36	32	34	34.0	34
4	43	37	38	39.3	38
5	37	34	33	34.7	34
6	33	29	36	32.7	33
7	38	34	40	37.3	38
8	39	41	42	30.7	41
Mean				36.0	36
Range of individual trials				29, 43	N/A
1 st quartile				N/A	34
3 rd quartile				N/A	38

Figure 1: Individual Disintegration Time

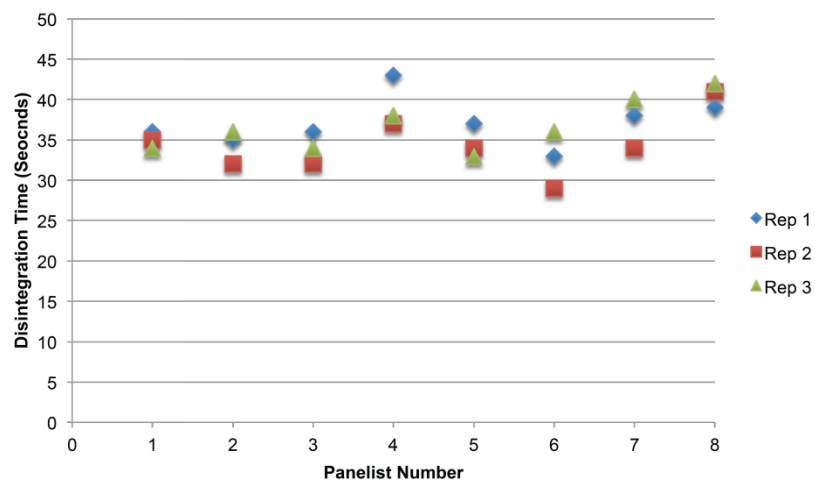
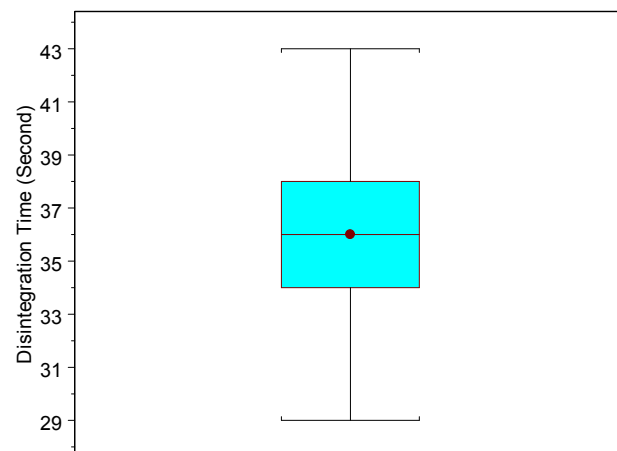


Figure 2: Median and Interquartile Range of Disintegration Times



SAFETY:

The safety endpoints evaluated in this study included adverse event monitoring, medical history, concomitant medications, and pregnancy tests, if applicable. All of the female subjects were postmenopausal, and pregnancy tests were not necessary. No clinical laboratory evaluations were performed.

According to the sponsor, there was no death or serious adverse event (SAE) other significant adverse events occurred during the study. None of the subjects reported any adverse events.

Reviewer's Comment:

- *Both mean and median disintegration time for dextansoprazole delayed-release OD 30 mg on tongue was 36 second (ranged 29-43 seconds) in this study. However, in this protocol, subjects sipped and swallowed 20 mL of spring water 30 seconds prior to study drug administration which could shorten the true disintegration time. As the general definition of ODT is rapid oral disintegration in saliva without the need for chewing or drinking liquids to ingest these products, the reported in vivo disintegration time in this study with sipping 20 mL of was 30 seconds prior to study drug administration is biased and unreliable.*
- *The current ODT guidance recommends the definition of ODT having in-vitro disintegration time of approximately 30 seconds or less when based on USP disintegration test method. However, this study only focused on in vivo disintegration time.*
- *In the BE study with dextansoprazole capsule, dextansoprazole delayed-release OD 30 mg tablets was administered on the tongue, allowed to disintegrate, and swallowed without water and without chewing. This in study, dextansoprazole 30 mg ODT was demonstrated to be bioequivalent to dextansoprazole capsule 30 mg.*

Internal note:

- Prevacid (lansoprazole) Solutable: Oral disintegration time (on the tongue) were (mean $\pm$ SD) 48.4 ± 19.4 seconds for 15 mg tablet and 53.14 ± 21.5 second for 30 mg tablet. 15 mg and 30 mg Prevacid Solutab tablet were bioequivalent to the Prevacid capsule. Solutable 30 mg tablet when given with water and without water were bioequivalent.
- Ondansetron ODT: Oral disintegration time (on the tongue) for ondansetron ODT (Zofran) was (mean $\pm$ SD) 7.93 ± 3.46 seconds and for ondansetron soluble film (Zuplenze) was (mean $\pm$ SD) 10.94 ± 3.47 seconds.

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/s/

DILARA JAPPAR
12/23/2015

HAE YOUNG AHN
12/23/2015