Pharmacokinetics and pharmacodynamics of an orally disintegrating tablet formulation of dexlansoprazole

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Abstract

Background: The pharmacokinetics and pharmacodynamics of a novel orally disintegrating tablet (ODT) formulation of delayed-release dexlansoprazole 30 mg was evaluated *versus* the dexlansoprazole 30 mg capsule in this phase I, open-label, multiple-dose, randomized, two-period crossover study.

Methods: Healthy adults received daily doses of 30 mg dexlansoprazole ODT or 30 mg dexlansoprazole delayed-release capsule for 5 days during two treatment periods, separated by a 7-day washout interval. Blood samples for dexlansoprazole plasma concentrations and intragastric pH measurements were collected through 24 hours postdose on days 1 and 5 of each period.

Results: Bioequivalence between the 30 mg ODT and 30 mg capsule dosage forms was demonstrated by the primary endpoints of dexlansoprazole peak concentration (C_{max}) and systemic exposure (AUC) values contained within the prespecified 90% confidence interval (CI) range of 0.80–1.25. Additional primary endpoints of intragastric mean pH values and percentage of time with pH > 4 over the 24-hour postdose interval were equivalent for dexlansoprazole ODT and dexlansoprazole capsule. Treatment-emergent adverse events were reported in 23% and 28% of participants receiving the ODT and capsule formulations, respectively. Headache was the most common adverse event in both treatment regimens (5.8% with ODT and 6.0% with capsule).

Conclusions: Administration of dexlansoprazole 30 mg ODT or 30 mg capsule provided equivalent plasma exposure when either was administered as a single dose or as once daily doses for 5 days. Pharmacodynamic equivalence between the two formulations was demonstrated by similar intragastric pH parameters on both day 1 and day 5. No effect of day on dexlansoprazole pharmacokinetics was observed. Dexlansoprazole ODT and dexlansoprazole capsule were both well tolerated.

Keywords: dexlansoprazole, gastroesophageal reflux disease, orally disintegrating tablet, pH, pharmacodynamics, pharmacokinetics, proton pump inhibitor

Introduction

Gastroesophageal reflux disease (GERD) is a prevalent gastrointestinal disorder that affects up to 20% of adults in North America [Dent *et al.* 2005; Katz *et al.* 2013]. National hospitalization estimates portray GERD as an increasingly common illness, citing a 216% rise in GERD diagnoses between 1998 and 2005 [Zhao and Encinosa, 2008]. GERD develops when the lower esophageal sphincter does not close properly, allowing stomach contents to return back up the esophagus, most prominently resulting in symptoms of heartburn, acid regurgitation and erosive esophagitis (EE) [Zhao and Encinosa, 2008; Katz *et al.* 2013]. Current therapies, such as antacids, histamine-2 receptor antagonists and proton-pump inhibitors (PPIs), aim to reduce acid in the stomach, though PPIs are the treatment of choice for relief of GERD symptoms, as well as for healing of EE [Katz *et al.* 2013]. PPIs inhibit the

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hydrogen–potassium adenosine triphosphatase enzyme (proton pump) at the final step of acid production, suppressing the secretion of proton ions in the stomach and increasing intragastric pH [Shin and Kim, 2013].

Unlike other PPIs, dexlansoprazole is formulated as a capsule with a dual delayed-release mechanism [Vakily *et al.* 2009; Takeda Pharmaceuticals America, Inc., 2016]. Dexlansoprazole is first released 1–2 hours following ingestion, followed by a second release within 4–5 hours postdose. This dual delayed release extends the duration of drug exposure and maintains pharmacologically active levels of drug over a longer period of time, resulting in prolonged elevation of intragastric pH [Vakily *et al.* 2009]. The prolonged acid suppression addresses potential breakthrough heartburn that might occur at night [Fass *et al.* 2009; Takeda Pharmaceuticals America, Inc., 2016]. The pharmacokinetic, pharmacodynamic, efficacy and safety profiles of dexlansoprazole capsule following administration of doses of 30 mg and 60 mg have been extensively studied in healthy adults and patients with GERD in randomized, double-blind, controlled clinical studies [Peura *et al.* 2009; Wittbrodt *et al.* 2009]. Both 30 mg and 60 mg strengths of dexlansoprazole capsule have been shown to be superior to placebo in maintaining heartburn-free periods in patients with healed EE or symptomatic nonerosive GERD [Fass *et al.* 2009; Metz *et al.* 2009].

The currently available delayed-release PPIs are formulated as capsules or tablets that are meant to be swallowed whole, which may cause problems for patients with difficulty swallowing. Difficulty swallowing, or dysphagia, is a common comorbidity in many disease states and is highly prevalent among patients with stroke, dementia, Parkinson's disease, Huntington's disease and multiple sclerosis [Daniels, 2006]. In the general population, heartburn and/or acid regurgitation were significantly associated with comorbid dysphagia [odds ratio (OR), 4.7; 95% confidence interval (CI), 2.9–7.4] [Locke *et al.* 1997]. GERD was the most common diagnosis in a population-based survey evaluating prevalence and risk factors for dysphagia, and in another study of dysphagic patients, PPI use was significantly associated with frequent (OR, 3.1; 95% CI, 2.2–4.4) and infrequent (OR, 1.5; 95% CI, 1.3–1.8) dysphagia [Cho *et al.* 2015].

Dexlansoprazole 30 mg delayed-release capsules are approved for use in adults for relief of heartburn and maintenance of healed EE for up to 6 months, as well as 4-week therapy for heartburn associated with symptomatic nonerosive GERD [Takeda Pharmaceuticals America, Inc., 2016]. Dexlansoprazole 60 mg delayed-release capsules are approved for use in adults for healing of all grades of EE for up to 8 weeks [Takeda Pharmaceuticals America, Inc., 2016]. As a follow-on to the dexlansoprazole capsule formulation, a 30 mg orally disintegrating tablet (ODT) formulation of dexlansoprazole was developed and has recently been approved in the United States for the same indications, that is, relief of heartburn, maintenance of healed EE and treatment of heartburn associated with GERD, as the 30 mg dexlansoprazole capsule [Takeda Pharmaceuticals America, Inc., 2016]. The dexlansoprazole ODT consists of dexlansoprazole dual delayed-release microgranules in an inert, highly water-soluble base. The tablet formulation was designed to disintegrate in the mouth without chewing or swallowing with water as an alternative to the dexlansoprazole capsule. An ODT formulation may be a desirable option for those unable or unwilling to take oral capsules [Carnaby-Mann and Crary, 2005; Pahwa, 2010]. The ODT formulation also provides flexibility in dosing by providing the option of mixing the tablet in water and administering the granules orally *via* syringe or *via* nasogastric tube [Kukulka *et al.*, manuscript in preparation]. Herein, we report the findings from a phase I study that evaluated the pharmacokinetics and pharmacodynamics of the 30 mg dexlansoprazole ODT relative to the 30 mg dexlansoprazole capsule.

Methods

The pharmacokinetic and pharmacodynamic properties of the dexlansoprazole ODT were investigated in a phase I, randomized, open-label, single-center, two-period crossover study conducted in healthy adults at Celerion (Tempe, AZ, USA) between August 2012 and October 2012. The study was designed in accordance with the US Food and Drug Administration (FDA) Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations [US Food and Drug Administration and Center for Drug Evaluation and Research, 2003], approved by the Independent Investigational Review Board, and conducted in accordance with the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice [International Conference on

	Screening		Treatment period 1					Washout period (≥7 days)		Treatment period 2					Follow up	
Day	−28	−1	1	2	3	4	5	6	−1	1	2	3	4	5	6	+ 5–10
Sequence 1	n = 26	Check in	30 mg ODT, once daily					Discharge	Check in	30 mg capsule, once daily					Discharge	Phone call
Sequence 2	n = 26	Check in	30 mg capsule, once daily					Discharge	Check in	30 mg ODT, once daily					Discharge	Phone call

Figure 1. Schematic of study design. Participants were confined to the clinic from day −1 to day 6. During each 5-day treatment period, participants received daily doses of 30-mg dexlansoprazole capsule or ODT. There was a minimum 7-day washout period between the last dose in the first treatment period and the first dose of the second treatment period. A follow-up phone call was made 5 to 10 days after the last dose of study drug to inquire of any ongoing adverse events, new adverse events, and concomitant medications taken since final dose. ODT, orally disintegrating tablet.

Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2001; World Medical Association, 2013]. Written informed consent was obtained from each enrollee prior to the initiation of any study procedure.

Study participants

Healthy male and female adults aged 18–55 years, weighing at least 50 kg, with a body mass index ⩾ 18 and ⩽ 30 kg/m² were eligible for inclusion in the study. Eligible participants were to be in good health, without evidence of any hematologic, neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine, or psychiatric disorder and no history of malignant disease. Participants were considered ineligible if they had recently received agents that could alter hepatic or renal clearance or that contained caffeine, xanthine or grapefruit products, or if they had evidence of drug or alcohol abuse. Routine use of over-the-counter drugs or nicotine products, or prior use of any investigational drug was not allowed. Female participants who were pregnant, lactating, or intending to either become pregnant or donate ova before, or 30 days after the study, were also excluded from the study. Other exclusion criteria included prior use of dexlansoprazole or lansoprazole and a known hypersensitivity to any component of the dexlansoprazole ODT, dexlansoprazole capsule, or other PPIs. If any participant violated the exclusion criteria after randomization, he or she was removed from the study.

Approximately 52 male and female adults (26 per treatment sequence) were to be selected for participation in the study. This sample size allowed for up to 6 dropouts (an approximate 12% dropout rate) and provided at least 90% probability of concluding equivalence for dexlansoprazole area under the plasma-concentration curve (AUC) between the two treatment regimens if the true difference between central AUC values was no more than 5%. The power for concluding equivalence on dexlansoprazole maximum observed plasma concentration (C_{max}) between the two regimens was expected to be 76%. The sample size was based on the intrasubject variance of 0.063 for log (AUC), derived from a previous study assessing the bioavailability of dexlansoprazole between the 30 mg ODT and the 30 mg capsule [Takeda Clinical Trial ID: TAK-390MR(OD)_102].

The sample size ($n = 52$) also provided at least 90% power for determining pharmacodynamic equivalence between the two treatment regimens regarding the percentage of time with pH > 4 over 24 hours if the true difference between central values was no more than 5%. This power calculation was based on the intrasubject variance of 126 in the percentage of time with pH > 4 over 24 hours. These variances for pH were observed in another prior study assessing the pharmacodynamic response to the 30 mg dexlansoprazole ODT [Takeda Clinical Trial ID: TAK-390MR(OD)_101].

Study design

Each treatment period in the two-period crossover design consisted of a 6-day confinement period with the last dose in period 1 and the first dose in period 2 separated by a 7-day washout interval (Figure 1). Adverse events were monitored through both treatment periods; ongoing or emerging adverse events were further evaluated 5–10 days after the last dose of study drug with a follow-up phone call.

Participants were randomized to one of two sequence groups, alternating the order in which

they received either the dexlansoprazole 30 mg ODT or dexlansoprazole 30 mg capsule once daily for 5 days. Dexlansoprazole ODT was administered on the tongue and participants were instructed to allow the tablet to completely disintegrate before swallowing the granules without chewing. No water was allowed with administration of the ODT. Dexlansoprazole capsules were swallowed intact with water (240 ml) and participants were allowed to drink at any time except for 1 hour prior to and 1 hour after dosing. FDA guidance recommends assessment of bioavailability to be conducted under fasting conditions [US Food and Drug Administration and Center for Drug Evaluation and Research, 2003]. Therefore, both ODT and capsule were administered following an overnight fast of ≥10 hours, and no food was allowed for 4 hours postdose on days 1 and 5 when pharmacokinetic and pharmacodynamic assessments were performed. No food was allowed overnight and for 1 hour postdose on days 2 through 4, when no pharmacokinetic and pharmacodynamic assessments were performed.

The FDA guidance also recommends conducting the bioequivalence study with the highest marketed dosage strength [US Food and Drug Administration and Center for Drug Evaluation and Research, 2003]. The current study compared the bioavailability of the 30 mg ODT with the 30 mg capsule since the dexlansoprazole ODT product is only manufactured in the 30 mg dosage strength [Takeda Pharmaceuticals America, Inc., 2016].

Sample collection

Blood samples (3 ml each) for determination of plasma dexlansoprazole concentrations were drawn into evacuated collection tubes containing potassium ethylenediaminetetraacetic acid on days 1 and 5 of each treatment period. Sample collection times relative to time of dosing were within 30 minutes predose, and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24 hours postdose, and were completed before any other assessments were performed, if scheduled at the same time. Dexlansoprazole is metabolized in part *via* the polymorphic cytochrome P450 (CYP) 2C19 enzyme system. Higher dexlansoprazole plasma concentrations may be observed in participants who are deficient in the CYP2C19 enzyme [Takeda Pharmaceuticals America, Inc., 2016]. Therefore, one 10 ml whole-blood sample for CYP2C19 genotyping was collected before dosing on day 1 of treatment period 1 from each participant.

Plasma dexlansoprazole concentrations were measured by a validated liquid chromatography tandem mass spectrometry assay at PPD, Inc. (Middleton, WI, USA). The validated detection limits for dexlansoprazole were from 2.00 ng/ml to 2000 ng/ml, and values below this range were considered to be zero for pharmacokinetic analyses.

Intragastric pH recording for pharmacodynamic analysis of dexlansoprazole was performed for 24 hours beginning immediately prior to study drug administration on day 1 and day 5 of treatment periods 1 and 2. A single-channel antimony probe attached to a data recorder unit manufactured by Sandhill Scientific, Inc. (Highlands Ranch, CO, USA) was used for pH recording. The unit was calibrated with standard buffers (pH approximately 1 and 7) before each use. On day −1 of period 1, the probe was inserted into the stomach *via* the nares to a distance of approximately 10 cm past the lower esophageal sphincter. This preparatory insertion was to verify that insertion of the probe could be tolerated and to obtain the length of the probe insertion to be used on day 1 and day 5 of both treatment periods. On days 1 and 5 of each treatment period, the probe was inserted into the stomach *via* the nares to the predetermined length identified on day −1. To minimize the discomfort of probe insertion, administration of a topical anesthetic was permitted. Standard clinical procedures were employed for this procedure, including permitting consumption of water during the procedure. The continuous pH recording session commenced immediately prior to study drug administration. Intragastric pH was sampled and recorded every 2 seconds through the time of dosing until 24 hours postdose on days 1 and 5 of each period.

Endpoints

The primary endpoints in this study included the pharmacokinetic parameters C_{max} and AUC, and pharmacodynamic parameters describing intragastric pH during the 24-hour period postdose (Table 1). Secondary endpoints included pharmacokinetic parameters used to measure the extent to which a drug is active within systemic circulation and pharmacodynamic parameters describing the intragastric pH in 6-hour intervals (Table 1).

Table 1. Definition of study endpoints.

Parameter	Definition
Primary endpoints	
C_{max}	Maximum observed plasma concentration
AUC_{last}	Area under the plasma concentration-time curve, which quantifies the amount of systemic drug exposure from time 0 to the time of the last quantifiable concentration
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity; calculated only on day 1 of each period
AUC_{tau}	Area under the plasma concentration-time curve from time 0 to time tau, where tau is the duration of a specific dosing interval; calculated only for day 5 of each period
Mean pH (24 hours)	Average intragastric pH over the 24 hour-period postdose
Percentage of time with intragastric pH > 4 (24 hours)	Percentage of time that median intragastric pH values > 4 for the 24-hour period postdosing
Secondary endpoints	
T_{max}	Time to reach C_{max}
$T_{1/2}$	Terminal elimination half-life, or the time required for drug concentration to decrease by 50%
CL/F	Apparent clearance after extravascular administration
Vz/F	Apparent volume of distribution after extravascular administration
Mean pH (>6 to 24 hours)	Mean intragastric pH for >6 to 24 hours postdose interval
Percentage of time with intragastric pH > 4 (>6 to 24 hours)	Percentage of time with intragastric pH > 4 for >6 to 24 hours postdose interval

The time to reach C_{max} (T_{max}), terminal elimination half-life ($T_{1/2}$), apparent clearance after extravascular administration (CL/F) and apparent volume of distribution after extravascular administration (Vz/F) were secondary pharmacokinetic endpoints; secondary pharmacodynamic endpoints consisted of the mean pH and percentage of time with pH > 4 during the 6- to 24-hour period following dose.

Treatment-emergent adverse events and overall safety profiles of once daily doses of dexlansoprazole ODT and capsule were assessed using safety variables that included physical examination findings, clinical laboratory testing, vital sign measurements, and 12-lead electrocardiogram. Treatment-emergent adverse events were defined as adverse events that began or worsened during the period between receiving the first dose of study drug and 30 days following the last dose. Adverse events were classified as serious if they were life-threatening, resulted in death, required hospitalization or extension of pre-existing hospitalization, led to incapacitation, or necessitated intervention to prevent any of the aforementioned situations.

Statistical analysis
All data analyses were generated using Statistical Analysis System (SAS) Version 9.2 (SAS Institute, Cary, NC, USA). Pharmacokinetic parameters were derived from plasma concentrations measured on days 1 and 5 of each treatment period and were estimated using Phoenix WinNonlin Version 6.3 software (Certara, Princeton, NJ, USA). For each treatment regimen, descriptive statistics for pharmacokinetic parameters were generated for all evaluable participants. Actual sampling times were used over scheduled sampling times in all relevant computations. Individual ratios of the two regimens for dexlansoprazole C_{max} and AUCs on the original scale and the difference on the natural log scale were summarized; geometric means were calculated for dexlansoprazole C_{max} and AUCs. AUC_{last} (AUC from time 0 to the time of last quantifiable concentration) was used to measure systemic exposure after a single dose on day 1 and after multiple doses on day 5 of each treatment period. AUC_{∞} (AUC from time 0 to infinity) was used to quantify the systemic exposure after a single dose on day 1 of each treatment period only, whereas AUC_{tau} (AUC from time 0 to end of the dosing

interval) was only used to quantify exposure on day 5 of each treatment period.

Using analysis of variance (ANOVA) models on days 1 and 5, both pharmacokinetic and pharmacodynamic parameters were analyzed with sequence, treatment period, treatment regimen, cohort and the interaction between period and cohort as fixed factors, and the study participants nested within sequence and cohort as a random factor. The cohort effect was included in the ANOVA models since participants were enrolled in multiple cohorts for the crossover study. Cohort effect and the interaction between cohort and period were to be excluded from the final model if they were found not to be statistically significant. The effect of single or multiple doses for each regimen was evaluated using a paired *t*-test on T_{max} and natural log-transformed C_{max} and AUCs performed within the ANOVA framework described. The two treatment regimens were considered bioequivalent if the 90% CIs for C_{max} and AUC central value ratios were within the bioequivalence range of 0.80–1.25 [US Food and Drug Administration and Center for Drug Evaluation and Research, 2003].

Pharmacokinetic parameters from participants who had data for both regimens were included in the statistical analyses. Because of the crossover study design, each participant received both regimens and served as his or her own control; CYP2C19 genotype was not expected to affect pharmacodynamic assessment or determination of bioavailability. No formal statistical analyses were conducted, based on CYP2C19 genotype.

After dosing, pharmacodynamic parameters were calculated for each formulation. The median intragastric pH was determined over 15-minute intervals from pH values collected every 2 seconds. The 15-minute medians were used to reduce the variability in pH measurements. The mean pH was then calculated as the average of these 15 minute-interval medians over the 24-hour period (primary endpoint) or over the >6-hour to 24-hour interval (secondary endpoint) postdose. A second parameter measured during these intervals was the percentage of time with intragastric pH > 4 (defined as the percentage of the 15-minute median pH values that were greater than 4). With consideration of relevant measures of variance in the literature, pharmacodynamic equivalence between the ODT and capsule was declared if the 90% CIs for the difference

in percentage of time with pH > 4 between regimens were contained within the prespecified range of −12% to 12% [Hartmann *et al.* 1998; Simon *et al.* 2003; Armstrong *et al.* 2007].

Results

Study population

There were 26 healthy adults in each treatment arm enrolled in the study (Figure 1). Demographic characteristics for those enrolled in each treatment sequence were similar. There was an equal distribution of men and women; most of the participants were White (92%), and about half were of Hispanic ethnicity (52%). None of the participants was a current smoker, and 23% of participants identified as current alcohol drinkers. The mean age ± standard deviation was 40.1 ± 10.2 years for all participants. CYP2C19 genotyping revealed that the majority of study participants were homozygous extensive metabolizers ($n = 27$); the remainders were heterozygous extensive metabolizers ($n = 6$), ultra-rapid metabolizers ($n = 18$), or a poor metabolizer ($n = 1$).

Pharmacokinetics

The pharmacokinetic parameter estimates following a single administration of ODT or capsule formulation of 30 mg dexlansoprazole are summarized in Table 2. Values for C_{max}, $T_{1/2}$ and CL/F on day 1 for the ODT and capsule formulations were similar. The extent of drug exposure in the body, measured by the AUC_∞, was also similar between the two formulations, with mean day 1 AUC_∞ values of 3048 ng·hr/ml and 3212 ng·hr/ml for the ODT and capsule, respectively (Table 2). Bioequivalence between the ODT and capsule was demonstrated as the 90% CIs for C_{max} and AUC_∞ fell within the 0.80–1.25 range (Table 3). The absorption of dexlansoprazole occurred slightly faster with the ODT than with the capsule, reaching a maximum concentration in a median time of 4 hours and 5 hours, respectively. The mean Vz/F for the ODT was greater than that observed for the 30 mg capsule (Table 2). Similar results were observed for pharmacokinetic parameter estimates and their corresponding statistical analyses after 5 daily doses of either ODT or capsule formulation (data not shown). When day 1 and day 5 data were compared, the 90% CIs for the pharmacokinetic parameter estimates indicated no difference in plasma exposure for single or daily dose

Table 2. Pharmacokinetic parameters for dexlansoprazole following single administration of orally disintegrating tablet or capsule (day 1).

	T_{max} (hr)	C_{max} (ng/ml)	AUC_∞ (ng·hr/ml)	$T_{1/2}$ (hr)	CL/F (l/hr)	Vz/F (l)
Single 30 mg dose of ODT						
Participants, *n*	50	50	46	46	46	46
Mean ± SD	NR	688 ± 337.2	3048 ± 2376.8	2.10 ± 1.186	14.24 ± 8.237	41.33 ± 38.649
Median	4.00	590	2437	1.56	12.32	27.99
(min, max)	(1.00, 6.00)	(164, 1730)	(693, 12026)	(0.73, 5.77)	(2.49, 43.30)	(11.65, 205.59)
% CV	NR	49	78	57	58	94
Single 30 mg dose of capsule						
Participants, *n*	50	50	46	46	46	46
Mean ± SD	NR	618 ± 298.6	3212 ± 2759.0	1.88 ± 0.989	13.02 ± 6.378	31.36 ± 17.270
Median	5.00	537	2294	1.52	13.08	27.90
(min, max)	(1.00, 7.02)	(279, 1780)	(948, 18275)	(0.89, 5.73)	(1.64, 31.64)	(12.42, 100.35)
% CV	NR	48	86	53	49	55

Note: Because of variability in the terminal phase of the plasma concentration-time curve, the terminal elimination rate constant could not be determined for some participants, and therefore the PK parameters that use this constant in their calculations (i.e. $T_{1/2}$, AUC_∞, CL/F and Vz/F) could not be estimated. AUC_∞, area under the plasma concentration-time curve from time 0 to infinity; CL/F, apparent clearance after extravascular administration; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; max, maximum; min, minimum; NR, not reported; ODT, orally disintegrating tablet; PK, pharmacokinetics; $T_{1/2}$, terminal elimination half-life; T_{max}, time to reach maximum observed plasma concentration; SD, standard deviation; Vz/F, apparent volume of distribution after extravascular administration.

Table 3. Statistical comparison of pharmacokinetic parameters for dexlansoprazole following administration of orally disintegrating tablet or capsule.

Parameter	Participants, *n*		Relative bioavailability, point estimate (90% CI)
	ODT	Capsule	
Single dose of ODT versus capsule (day 1)			
C_{max}	50	50	1.0580 (0.9502–1.1781)
AUC_∞	46	46	0.9265 (0.8615–0.9964)
Single versus daily doses of ODT (day 5 versus day 1)			
C_{max}	52	n/a	1.0778 (0.9657–1.2029)
AUC_{last}	52	n/a	1.0693 (0.9811–1.1654)
Single versus daily doses of capsule (day 5 versus day 1)			
C_{max}	n/a	50	1.0827 (0.9739–1.2037)
AUC_{last}	n/a	50	1.0362 (0.9794–1.0962)

AUC_∞, area under the plasma concentration-time curve from time 0 to infinity; AUC_{last}, area under the plasma concentration-time curve from 0 to time of last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration; n/a, not applicable; ODT, orally disintegrating tablet.

administrations of either the ODT or capsule. For both formulations, peak concentration and systemic exposure achieved after a single-dose administration on day 1 did not differ from those achieved after 5 daily doses (Table 3).

Pharmacodynamics

The pH profile over a 24-hour time period after participants had received daily doses of either dexlansoprazole ODT or capsule for 5 days was similar (Figure 2). The mean intragastric pH after 5 daily doses of the dexlansoprazole ODT was 3.7; the corresponding pH for the capsule was 3.8 (Figure 3 and Supplementary Table S1). The percentage of time with intragastric pH > 4 was 45.8% for the 24-hour postdose time interval after 5 daily administrations of the ODT, and 47.3% after the capsule (90% CI for the difference: –4.9, 2.2) (Figure 3 and Supplementary Table S1). Similarly, the ODT and capsule maintained intragastric pH > 4 for

45.9% and 49.5% of the time, respectively, during the >6-hour to 24-hour postdose interval, which included overnight hours (90% CI for the difference: −7.4, 0.4) (Supplementary Table S1).

The pH profiles were similar between formulations after a single dose of either dexlansoprazole ODT or capsule on day 1 (data not shown). Both ODT and capsule formulations showed better pH control on day 5 *versus* day 1 with greater mean pH and percentage of time with pH > 4 after 5

Figure 2. Mean pH profile for the 24-hour time interval postdose (day 5). Dexlansoprazole 30-mg ODT (black) or 30-mg capsule (blue) was administered daily for 5 days. Intragastric pH was recorded every 2 seconds. Mean values for 15-minute intervals are shown.
hr, hours; ODT, orally disintegrating tablet.

days of dosing. Acid control for both dosage forms was similar on day 1 (data not shown).

Summary of adverse events

The majority of adverse events were classified as mild in intensity (42 of 44 adverse events) and considered unrelated to the study drug (31 of 44 adverse events). Treatment-emergent adverse events were reported for 23% and 28% of study participants receiving the 30 mg ODT and capsule formulations, respectively. Of a total 23 adverse events, headache, constipation, erythema and pruritus were the only events to occur in two or more participants receiving the ODT formulation. Headache and abdominal pain occurred in two or more participants receiving the dexlansoprazole capsule. Headache was the most common adverse event in both treatment regimens, occurring in 5.8% and 6.0% of participants receiving dexlansoprazole ODT and capsule, respectively. Both erythema and pruritus occurred in 3.8% and 2.0% of participants receiving the ODT and capsule formulations, respectively. Events that were deemed related to the study drug included constipation, headache and pollakiuria, which occurred in participants receiving the ODT, and palpitations, constipation, abdominal pain, flatulence, headache and dysgeusia, which were observed among those receiving the dexlansoprazole capsule. One patient receiving the 30 mg ODT during treatment period 1 discontinued
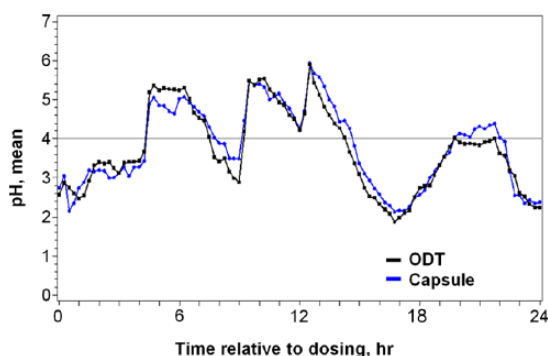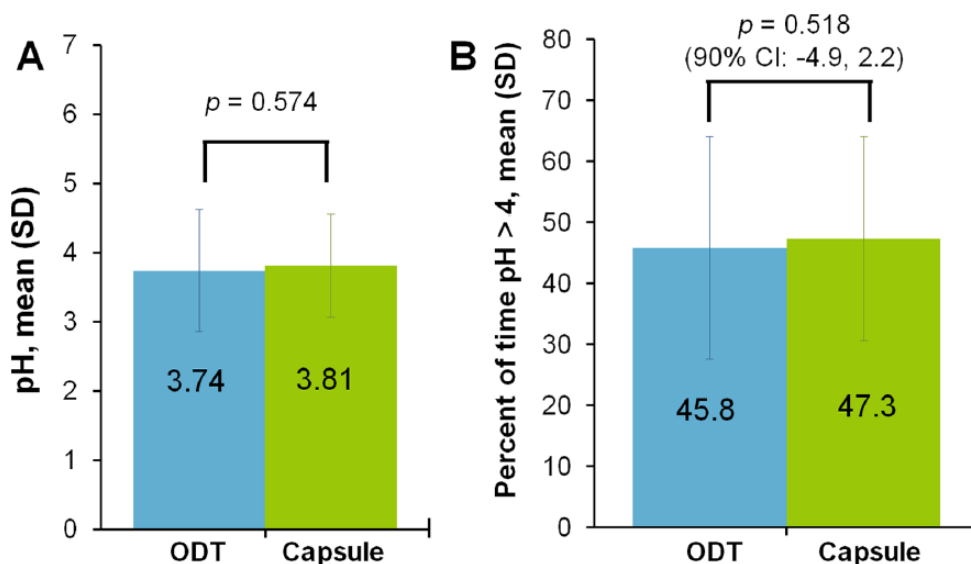

Figure 3. Pharmacodynamic evaluation of dexlansoprazole orally disintegrating tablet and capsule (day 5). (A) Mean pH and (B) percentage of time with intragastric pH >4 over 24 hours on day 5 following daily administration of dexlansoprazole 30-mg ODT or 30-mg capsule.
CI, confidence interval; ODT, orally disintegrating tablet; SD, standard deviation.

because of elevated creatine kinase levels observed prior to receiving the 30 mg capsule at check-in of treatment period 2. This patient's creatine kinase levels subsequently resolved at time of discharge from the study. No serious adverse events or deaths were reported.

Discussion

This crossover study was designed to compare the pharmacokinetic and pharmacodynamic profiles of dexlansoprazole ODT with those of the dexlansoprazole capsule formulation. Both products are formulated with a dual delayed-release mechanism; they contain two types of enteric-coated granules designed to release drug in a pH-dependent manner. The dual delayed-release technology is designed to provide an initial release of drug 1–2 hours following dosing, and a subsequent release 4–5 hours after administration. The capsule should be swallowed whole, which may prove difficult for some patients.

Difficulty with swallowing has been reported in almost 20% of patients in one survey, with 3% of patients citing frequent difficulty with swallowing [Cho *et al.* 2015]. Patients with frequent difficulty swallowing were also significantly associated with frequent heartburn and acid regurgitation [Cho *et al.* 2015]. In general, patients who have difficulty swallowing have been found to be less compliant with their treatment regimens, and this lack of adherence can potentially adversely affect patient morbidity [Carnaby-Mann and Crary, 2005]. An ODT formulation represents a more convenient mode of delivery to patients with difficulty swallowing, with improved ease of administration, reduced physiological stress, better compliance and no increased risk of airway compromise [Carnaby-Mann and Crary, 2005; Maalouf, 2013]. A study of the pill-swallowing experience in adults found that 76% of participants preferred ODT delivery to a conventional tablet, which some find difficult to swallow [Carnaby-Mann and Crary, 2005].

Quantification of systemic drug exposure by C_{max} and AUC values is used to determine the relative bioavailability of different formulations. Prior investigation of the pharmacokinetics and pharmacodynamics of the delayed-release dexlansoprazole capsule have indicated that pharmacodynamic effects, such as change in pH, are related to AUC levels [Vakily *et al.* 2009]. Similar AUC levels and comparable pharmacodynamic parameters

observed in this study indicate similar acid suppression activity between the ODT and capsule forms. The results presented here demonstrate pharmacokinetic and pharmacodynamic equivalence for the 30 mg dexlansoprazole ODT and 30 mg dexlansoprazole capsule. The determination of bioequivalence allows the 30 mg ODT to be prescribed for the same indications for which the 30 mg dexlansoprazole capsule is approved [Takeda Pharmaceuticals America, Inc., 2016]. Importantly, no difference in systemic exposure between the two dosage forms was observed after a single dose or after daily doses for 5 days. The 24-hour pH control was equivalent between each formulation after a single dose or after daily doses for 5 days. In addition, percentage of time with intragastric pH > 4 was similar over the 24-hour period following administration of either the ODT or capsule, including during the >6-hour to 24-hour interval, a timespan covering nighttime acid production over to the next morning. For both ODT and capsule formulations, greater pH control was observed on day 5 than on day 1; the difference may be partly attributed to lower intragastric pH values prior to the beginning of the 24-hour pH-monitoring period on day 1. The cumulative inhibitory effect following multiple daily dosing is anticipated due to the prolonged binding of the active form of PPIs (sulfenamide) [Vakily *et al.* 2009]. The majority of adverse events were mild and considered unrelated to the study drug; no serious adverse events were reported.

Both dexlansoprazole 30 mg capsule and 30 mg ODT are approved for use in adults as a treatment for heartburn associated with symptomatic nonerosive GERD for 4 weeks, maintenance of healed EE for up to 6 months and relief of heartburn [Takeda Pharmaceuticals America, Inc., 2016]. The ODT formulation of dexlansoprazole was developed as a more convenient method of delivery than those traditionally reserved for patients with difficulty swallowing. Further options that add to the dosing flexibility of the ODT formulation include administering dexlansoprazole ODT granules orally *via* syringe or *via* nasogastric tube after disintegration in water (Kukulka *et al.*, manuscript in preparation). Evaluation of the pharmacokinetic and pharmacodynamic profiles of dexlansoprazole 30 mg ODT reported herein suggests that this novel formulation may be used as a substitute for the 30 mg capsule, with added benefits of simpler administration for patients who may have difficulty swallowing.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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