Pharmacokinetics of Lisdexamfetamine Dimesylate after Targeted Gastrointestinal Release or Oral Administration in Healthy Adults

James C. Ermer, Mary B. Haffey, Walter J. Doll, Patrick Martin, Erik P. Sandefer, Kerry Dennis, Mary Corcoran, Laura Trespidi, and Richard C. Page


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ABSTRACT:
The purpose of this work was to assess the pharmacokinetics and safety of lisdexamfetamine dimesylate (LDX) delivered and released regionally in the gastrointestinal (GI) tract. In this open-label, randomized, crossover study, oral capsules and InteliSite delivery capsules containing LDX (50 mg) with radioactive marker were delivered to the proximal small bowel (PSB), distal SB (DSB), and ascending colon (AC) during separate periods. Gamma scintigraphy evaluated regional delivery and GI transit. LDX and d-amphetamine in blood were measured postdose (<72 h). Treatment-emergent adverse events (TEAEs) were assessed. Healthy males (n = 18; 18-48 years) were enrolled. Mean (S.D.) maximal plasma concentration (Cmax) was 37.6 (4.54), 40.5 (4.95), 38.7 (6.46), and 25.7 (9.07) ng/ml; area under the concentration-time curve to the last measurable time point was 719.1 (157.05), 771.2 (152.88), 752.4 (163.38), and 574.3 (220.65) ng · h · ml-1, respectively, for d-amphetamine after oral, PSB, DSB, and AC delivery of LDX. Median time to Cmax was 5, 4, 5, and 8 h, respectively. Most TEAEs were mild to moderate. No clinically meaningful changes were observed (laboratory, physical examination, or electrocardiogram). LDX oral administration or targeted delivery to small intestine had similar d-amphetamine systemic exposure, indicating good absorption, and had reduced absorption after colonic delivery. The safety profile was consistent with other LDX studies.

Introduction

Drug delivery to sites of action is affected by physiochemical and physiologic variables (Farré and Camí, 1991). Physiochemical factors can affect absorption (lipid solubility, molecular size, and pKa). Greater lipophilicity tends to increase transfer across membranes compared with highly polar compounds that are not absorbed as readily (Shargel et al., 2005). Pharmacokinetic studies of different drug delivery to sites of action is affected by physiochemical and physiologic variables (Farré and Camí, 1991). Physiochemical factors can affect absorption (lipid solubility, molecular size, and pKa). Greater lipophilicity tends to increase transfer across membranes compared with highly polar compounds that are not absorbed as readily (Shargel et al., 2005). Pharmacokinetic studies of different drug delivery to sites of action is affected by physiochemical and physiologic variables (Farré and Camí, 1991). Physiochemical factors can affect absorption (lipid solubility, molecular size, and pKa). Greater lipophilicity tends to increase transfer across membranes compared with highly polar compounds that are not absorbed as readily (Shargel et al., 2005). Pharmacokinetic studies of different dosage forms of a drug can also affect absorption. For example, sustained-release formulations may release the drug slowly over time, allowing for a more consistent blood concentration. On the other hand, immediate-release dosage forms may result in a rapid rise in blood concentration followed by a more rapid decline. The choice of dosage form can depend on the desired effects of the drug (Spencer et al., 2006a).

Some factors that affect absorption and bioavailability are dosage form, administration route, first-pass effect, and prodrug design (Farré and Camí, 1991). Physiochemical and pharmacologic properties, including the degree of aqueous and lipid solubility, extent of ionization, pKa, affinity for a tissue component, and formulation size, are not sufficient to fully characterize the extent of absorption from different GI segments. Thus, supplemental novel methods have been developed (Shargel et al., 2005).

Traditionally, in vitro dissolution tests followed by conventional pharmacokinetic studies, coupled with intubation and fluoroscopy methods, have been performed (Staib et al., 1986; Shargel et al., 2005). Although designed to assess drug absorption, these methods are not useful in establishing drug-release mechanisms (Davis et al., 1992). The intubation method involves the use of long feeding tubes that are usually introduced through the nasal passages, travel down the esophagus, and then enter the selected GI tract regions, typically including the early small intestine, the distal small intestine, and then administration routes provide data on feasible delivery methods for enhanced gastrointestinal (GI) absorption, as indicated by relative rate and extent of absorption from optimal immediate- and/or sustained-release formulations (Volkow and Swanson, 2003; Spencer et al., 2006a).

ABBREVIATIONS: GI, gastrointestinal; ICC, InteliSite Companion Capsules; ADHD, attention-deficit/hyperactivity disorder; LDX, lisdexamfetamine dimesylate; PEPT1, peptide cotransporter 1; PSB, proximal small bowel; DSB, distal small bowel; AC, ascending colon; IN, intranasal; 111In, Indium-111; 99mTc-DTPA, technetium-99m-diethylenetriamine-pentaacetic acid; QC, quality control; AE, adverse event; TEAE, treatment-emergent adverse event; Cmax, maximal observed plasma concentration; Tmax, time to Cmax; T1/2, apparent terminal half-life; ATC, postdose arrival time; AUC, area under the curve; AUC0-inf, AUC from time zero to infinity; AUC0-Distal, small intestine (distal only) gastrointestinal transit curve; AUClast, area under the plasma concentration-time curve to the last measurable time point; AUC0-1, AUC of small intestine gastrointestinal transit curve; CI, confidence interval; SITT, small intestine transit time.
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the colon. A drug is then delivered to these segments over the course of a multiple-treatment study. This technique is uncomfortable for the participants and requires prolonged residence in the clinical facility, necessitating multiple fluoroscopies. The intubation tubes have an impact on GI motility (Read et al., 1983). A less invasive and more pharmaceutically relevant technique is the use of remote-controlled drug-release systems, which include the high-frequency capsule (Batelle-Institute V, Frankfurt am Main, Germany) (Staib et al., 1986; Harder et al., 1990), IntelliSite capsule (Casper Associates, Raleigh, NC), and Enterion capsule (Phaeton Research, Nottingham, UK) (Prior et al., 2004). Gamma scintigraphy (a well established radionuclide imaging technique) provides information on regional drug absorption and is a useful tool to evaluate various drug-delivery methods (Davis et al., 1992; Meseguer et al., 1994). Non-biodegradable, non-invasive IntelliSite Companion Capsules (ICCs) with radiolabeled content are spring-loaded and are designed to actively deliver drug in selected regional segments of the GI tract. The capsule is opened after a radiofrequency signal is sent from the amplifier, resulting in release and dispersion of the drug and the surrogate radioactive marker, which is visualized via gamma scintigraphy. When used with conventional pharmacokinetic assessment, scintigraphy and the remote-controlled capsules can be used to determine regional drug absorption and evaluate comparative relative bioavailability (Connor et al., 2001). Although this technology allows visualization of the radioactive component rather than the drug, the drug’s dispersion at the site of absorption can be monitored (Davis et al., 1992). The timing and extent of formulation dispersion, coupled with knowledge of GI transit values after drug release and of the drug’s solubility, can be correlated with classic pharmacokinetics to interpret the degree of drug absorption versus control.

Phystimulants, amphetamines, and methylphenidate are first-choice treatments for attention-deficit/hyperactivity disorder (ADHD) symptom management (Pliszka et al., 2006). Lisdexamfetamine dimesylate (LDX) Vyvanse; Shire US Inc., Wayne, PA) is a long-acting prodrug stimulant indicated for the treatment of ADHD in children (6–12 years), adolescents (13–17 years), and in adults. After oral ingestion, LDX (therapeutically inactive molecule) is converted to d-lysine and active d-amphetamine (therapeutically active) (Fig. 1) (Pennick, 2010). The conversion of LDX to d-amphetamine is unlikely to be affected by GI pH and variations in normal GI transit times (Shojaei et al., 2007; Krishnan and Zhang, 2008; Haffey et al., 2009). Although a small amount of LDX is hydrolyzed to d-amphetamine in the GI tract, the conversion of LDX into active d-amphetamine occurs primarily in the blood (Pennick, 2010). LDX absorption likely occurs via a high-capacity carrier-mediated transport system involving peptide cotransporter 1 (PEPT1) in the small intestine, although the involvement of other peptide and amino acid transporters cannot be ruled out (Pennick, 2010). More detailed knowledge of LDX absorption throughout the GI tract may provide useful information to substantiate and extend our understanding of the mechanisms responsible for its absorption. Hence, the study objective was to assess the pharmacokinetics of LDX when released into targeted GI tract regions compared with LDX pharmacokinetics with oral administration.

Materials and Methods

Study Overview. This trial was a single-center (Scintimpharma Inc., Lexington, KY), open-label, two-phase, randomized crossover study designed to investigate the pharmacokinetics and safety of LDX in healthy adults. It was designed to compare the pharmacokinetic parameters of LDX administration, when delivered by a single oral dose, with those of regional delivery in the GI tract to the proximal small bowel (PSB), distal SB (DSB), and ascending colon (AC). Results from the intranasal (IN) delivery portion of this study have been separately reported (Ermer et al., 2011).

This study was conducted in accordance with the principles of the 18th World Medical Assembly (Helsinki, Finland, 1964) and amendments of the 29th (Tokyo, Japan, 1975), 35th (Venice, Italy, 1983), 41st (Hong Kong, 1989), and 48th (South Africa, 1996) World Medical Assemblies, Declaration of Helsinki, and Good Clinical Practice according to the International Conference on Harmonisation guidelines. The study protocol was approved by an independent institutional review board (Chesapeake Research Review, Inc., Columbia, MD). Before screening, written informed consent using an institutional review board-approved consent form was obtained.

Participants. Normal, healthy adult male participants between ages 18 and 65 years who agreed to use an acceptable method of contraception during the study and for 1 week after the last evaluation were eligible for inclusion in the study. To be included, participants also needed to test negative for HIV and the hepatitis B surface antigen and hepatitis C antibody screen. Participants also had to have a satisfactory medical assessment with no clinically significant and relevant abnormalities. Other criteria included a body mass index of 20 to 29 kg/m² inclusive and the ability to swallow capsules and comply with study procedures.

Study Design. Screening was performed between 28 and 3 days before receiving the first dose of study drug, and inclusion and exclusion criteria were reviewed again upon admission to determine eligibility. Participants were randomized to a treatment sequence and were required to fast overnight (≥8 h) before LDX administration. Non-biodegradable and noninvasive ICCs were designed to actively deliver drugs with spring-loaded action to various areas of the GI tract upon radiofrequency signal (Pithaval et al., 1998; Parr et al., 1999). The ICC has been used to determine regional drug absorption and bioavailability, with its radiolabeled content visualized via gamma scintigraphy. Indium-111 (111In) chloride (25 μCi) was the surrogate radioactive marker used to track the capsule throughout the GI tract to the targeted site of delivery, as well as to confirm and monitor the dispersion of the released drug formulation after capsule opening; technetium-99m-diethylenetriamine-pentaacetic acid (99mTc-DTPA; 50 μCi) was coadministered with the drink when the capsule was swallowed and was used for GI anatomy visual confirmation by scintigraphy.

The five dosing periods of the study were made up of two administrations, oral and IN regimens during phase 1, as previously reported (Ermer et al., 2011), and three administrations, PSB, DSB, and AC regimens during phase 2. The oral regimen consisted of a 50-mg LDX capsule that was not radiolabeled.

**Fig. 1.** Chemical structure of lisdexamfetamine dimesylate and d-amphetamine.
and was delivered orally with 240 ml of water. The IN delivery regimen was a single 100-μl preparation (50 mg of LDX in 0.9% saline) that also contained up to 100 μCi [99mTc]-DTPA, which has been previously reported (Ermer et al., 2011) and is not presented here. Each ICC delivery regimen (PSB, DSB, and AC) was prepared as a single preparation (the equivalent of 50 mg of LDX was dissolved in water and filled into an ICC, containing up to 25 μCi of 111In chloride). The ICCs were administered orally with 120 to 240 ml of water, followed by 240 ml of a radiolabeled drink ([99mTc]-DTPA, 50 μCi). The 50 mg/day dose strength of LDX used in this study is equivalent to an amphetamine base dose of 14.8 mg/day (Findling et al., 2009).

The two-way crossover (two dosing periods conducted during phase 1 as a two-sequence treatment regimen: oral versus IN) has been previously reported (Ermer et al., 2011). The three-way crossover (three dosing periods) was performed in phase 2, and the treatment regimen included six sequences (Fig. 2). Participants received PSB, DSB, and AC regimens by ICC delivery, as indicated in the randomization schedule. The dosing day for each dosing period was separated from the next by at least 7 days. If necessary, a maximum of seven administrations could be received (two additional ICCs in phase 2). Each participant was assigned to a specific treatment regimen sequence that could be adjusted in certain circumstances (e.g., GI transit time). Confinement began 1 day before the dosing period, and participants remained in the unit and were not discharged until approximately 48 h after drug release from the ICC. After taking the ICC, the participant continued fasting for an additional 4 h (beyond the 8 h before dose administration) as long as the ICC had emptied from the stomach. If the ICC had not emptied from the stomach, the fast was continued until gastric emptying was confirmed. Water was permitted ad libitum until 2 h before the dose and after 2 h postdose. Participants were asked to return to the unit 72 h after ICC opening for pharmacokinetic blood sampling and 7 to 14 days after the completion of the final study phase or withdrawal for follow-up examination.

**Pharmacokinetics.** The primary study outcome was to determine the pharmacokinetic parameters of intact LDX and d-amphetamine from LDX after oral and GI delivery. The safety population consisted of enrolled participants who took one or more doses of LDX and had completed one or more follow-up safety assessments. The pharmacokinetic population was defined as all participants in the safety population who had evaluable concentration-time profiles for LDX or d-amphetamine from LDX. Blood samples (3 ml) were collected at 0 (predose or before release of ICC), 15, 30, and 45 min and at 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 h postdose for the oral regimen or after drug release from the ICC for the PSB, DSB, and AC regimens. Blood samples were collected in K<sub>3</sub>EDTA tubes placed on ice and then centrifuged at approximately 4°C. The plasma from the sample for each participant was collected in two polypropylene tubes. One tube was shipped on dry ice to a laboratory for analysis, and the other was stored at approximately 4°C. The plasma from d-amphetamine from LDX and intact LDX concentrations were measured using a validated liquid chromatography with tandem mass spectrometry method. The method used liquid-liquid extraction, followed by analysis on a Sciex API 3000 (PerkinElmer Life and Analytical Sciences, Waltham, MA) tandem mass spectrometric detection in a heated nebulizer positive ionization mode equipped with liquid chromatography. The lower and upper limits of quantification, respectively, were 1.00 and 100.00 ng/ml for intact LDX and 2.00 and 200.00 ng/ml for amphetamine using a 200-μl plasma aliquot. Quality-control (QC) samples were prepared in control human plasma at three concentration levels and were assayed with each set of samples against freshly prepared calibration standards. The QC sample concentrations of LDX and amphetamine were 3, 20, and 80 ng/ml, and 6, 40, and 160 ng/ml, respectively. Concentrations below the lower limit of quantification were reported as nonquantifiable.

In this study, QC samples and calibration standards were found to be within acceptable limits based on the U.S. Food and Drug Administration Guidance for Industry; Bioanalytical Method Validation (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf, 2010). For LDX, the mean concentrations were 2.91, 19.53, and 78.23 ng/ml for low-QC (3 ng/ml), mid-QC (20 ng/ml), and high-QC (80 ng/ml) standards, respectively. For d-amphetamine, the mean concentrations were 5.76, 39.50, and 150.83 ng/ml for low-QC (6 ng/ml), mid-QC (40 ng/ml), and high-QC (160 ng/ml) standards, respectively.

**Gamma Scintigraphy.** Gamma scintigraphy was used to monitor ICC integrity, drug release, and transit after drug release (Digenis and Sanderfer, 1991; Davis et al., 1992) to examine the absorption of LDX released in the GI tract after ICC delivery regimens (PSB, DSB, and AC). The radioactive isotopes 99mTc and 111In were monitored simultaneously because of their different energies of gamma-ray emission and because they are not absorbed in the GI tract. To monitor GI transit of the ICC, the 111In chloride was included with LDX in the capsule, and to delineate the target sites, the water used to swallow the ICC contained [99mTc]-DTPA. The remote-controlled ICC was opened with an external signal for release once it reached the appropriate anatomic region. Subsequently, blood samples were collected to assess absorption.

A series of images, 1 min each, were taken from participants in the supine position. For the PSB and DSB delivery regimens, the images were conducted at approximately 15- to 30-min intervals until ICC drug release and, at a minimum, to coincide with blood-sampling times. For the AC delivery regimen, the images were recorded at approximately 30-min intervals until gastric emptying had occurred and for the same amount of time until capsule drug release. Subsequently, images were collected at a minimum to coincide with blood-sampling times.

**Safety.** The maximal amount of radioactivity to be administered including the potential for up to two additional repeat administrations was 250 μCi of [99mTc]-DTPA (50 μCi per administration of ICC) and 125 μCi of 111In chloride (25 μCi per administration of ICC). The maximal radiation dose for the study was 1,849 mSv and was within limits of the recommended permissible standard allowable radiation for individuals with infrequent annual exposure, which is 5 mSv (National Council on Radiation Protection and Mea-
measurements, 1993). All adverse events (AEs) and serious AEs were collected from informed consent until the follow-up visit. The intensity of an AE was recorded as mild, moderate, or severe. Treatment-emergent AEs (TEAEs) referred to events with onset after the first date of treatment and no later than 3 days after termination of treatment. Clinical laboratory tests, electrocardiogram, and physical examinations were conducted at screening, predose, discharge, or 48 h postdose (all except physical examination) and at the 7- to 14-day follow-up visit. Assessments administered at screening and during the postdosing period were performed before allowing participants to proceed to the next dosing period of the study.

Pharmacokinetic Analysis. The pharmacokinetic parameters computed included maximal observed plasma concentration ($C_{\text{max}}$), time to $C_{\text{max}}$ ($T_{\text{max}}$), area under the plasma concentration-time curve to the last measurable time point (AUC$_{\text{last}}$), AUC from time zero to infinity (AUC$_{\text{inf}}$), and apparent terminal half-life ($t_{1/2}$). AUC$_{\text{last}}$ was calculated by the linear trapezoidal method for increasing plasma concentrations and the log-trapezoidal method for decreasing plasma concentrations. These pharmacokinetic parameters were determined using the plasma concentration-time data for LDX and d-amphetamine by noncompartmental analysis and by the computation of actual blood-sampling times.

Statistical Analysis. Summary statistics (e.g., mean, S.D., n, and geometric means) were determined for all pharmacokinetic parameters by regimen; descriptive statistics were used to summarize plasma concentrations by regimen. A linear mixed-analysis effects model was used to compare log-transformed pharmacokinetic parameters among regimens. Fixed terms were used for sequence and regimen; random terms were used for participant within sequence, fit by generalized least squares with restricted maximal likelihood estimates of variance components. Estimates and 90% confidence interval (CI) for the regimen ratios of PSB, DSB, and AC versus oral for d-amphetamine $C_{\text{max}}$ and AUC$_{\text{last}}$ were calculated using oral values within the mixed model framework.

### Results

**Participant Disposition and Demographics.** Eighteen healthy men [18–48 years; mean (S.D.) age, 25.1 (8.35) years] were enrolled and randomized, 17 completed the study, and one did not complete because of refusal to swallow the ICC even though prestudy screening showed this participant was able to swallow large oral dosage forms. Participants had a mean (S.D.) body mass index of 25.1 (2.58) kg/m$^2$ and were predominantly white (83.3%) and of non-Hispanic or non-Latino ethnicity.

**Pharmacokinetics and Scintigraphy.** Pharmacokinetic results for IN administration of LDX have been reported previously (Ermer et al., 2011). In that particular analysis, results indicated that the pharmacokinetic parameters of d-amphetamine from LDX were similar for both oral and IN administration. The plasma concentration-time courses of d-amphetamine from LDX, up to 48 h postdose, for both modes of administration were similar. IN delivery of intact LDX was achieved with no swallowing for up to 5 min postdose and was consistent with rapid absorption that is characteristic of that method of administration (Shargel et al., 2005; Ermer et al., 2011).

Plasma pharmacokinetic parameters of intact LDX for the pharmacokinetic population by oral and ICC GI delivery are summarized in Table 1 and are illustrated in Fig. 3. For intact LDX, a comparison of pharmacokinetic parameters (AUC$_{0-\text{inf}}$, AUC$_{0-\text{last}}$, and $C_{\text{max}}$) for the IN delivery regimens (PSB, DSB, and AC) to those of oral regimens is presented in Table 2. At 1 h postdose, the intact LDX plasma concentration profiles varied, with mean (S.D.) values ranging from 2.1 (3.40) to 30.0 (12.93) ng/ml across regimens. After 1.5 h, the LDX plasma concentrations for oral, PSB, and DSB were similar, whereas

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**Table 1**

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Statistic</th>
<th>Oral n = 18</th>
<th>ICC to PSB n = 17</th>
<th>ICC to DSB n = 17</th>
<th>ICC to AC n = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$, ng/ml</td>
<td>Mean (S.D.)</td>
<td>19.8 (5.60)</td>
<td>28.2 (10.55)</td>
<td>36.6 (12.03)</td>
<td>2.8 (4.76)</td>
</tr>
<tr>
<td>$T_{\text{max}}$, h</td>
<td>Median</td>
<td>1</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8$^c$</td>
</tr>
<tr>
<td>$t_{1/2}$, h</td>
<td>Mean (S.D.)</td>
<td>0.5 (0.10)$^a$</td>
<td>0.5 (0.10)</td>
<td>0.5 (0.10)</td>
<td>0.7 (0.60)$^c$</td>
</tr>
<tr>
<td>AUC$_{\text{last}}$, ng·h·ml$^{-1}$</td>
<td>Mean (S.D.)</td>
<td>23.4 (7.46)</td>
<td>33.4 (12.74)</td>
<td>45.9 (17.26)</td>
<td>3.0 (5.39)</td>
</tr>
<tr>
<td>AUC$_{\text{inf}}$, ng·h·ml$^{-1}$</td>
<td>Mean (S.D.)</td>
<td>25.2 (7.21)$^a$</td>
<td>35.1 (12.50)</td>
<td>47.1 (17.26)</td>
<td>12.7 (5.03)$^a$</td>
</tr>
</tbody>
</table>

$^a$ n = 7; $^b$ n = 17; $^c$ n = 4.

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**Fig. 3.** Mean plasma concentration of intact LDX after oral or GI ICC delivery of LDX.

Note: Time zero for PO regimen is time of dosing. Time zero for PSB, DSB, and AC regimens is time of ICC opening.
the LDX plasma concentration for AC delivery was lower at all the time points sampled. Time to peak plasma concentrations of intact LDX with ICC delivery were at approximately the same time and were followed later by oral administration. PSB and DSB delivery resulted in the largest $C_{\text{max}}$; AC delivery resulted in the smallest $C_{\text{max}}$. Values of $T_{\text{max}}$ and median $t_{1/2}$ were similar with all regimens. Systemic exposure to intact LDX by the AUC$_{0-\text{last}}$ parameter was similar after PSB and DSB delivery and was the least with AC delivery. Likewise, based on AUC$_{0-\text{inf}}$, the systemic exposure to LDX was similar after PSB and DSB delivery and was less with AC delivery.

Table 3 summarizes and Fig. 4 and inset illustrate mean plasma pharmacokinetic parameters of $d$-amphetamine from LDX for the pharmacokinetic population by oral and ICC GI delivery. For $d$-amphetamine, a comparison of the geometric ratios (AUC$_{0-\text{inf}}$/AUC$_{0-\text{last}}$ and $C_{\text{max}}$) of the ICC delivery regimens (PSB, DSB, and AC) to those of the oral delivery regimen is presented in Table 2. The $d$-amphetamine plasma concentrations for the oral, PSB, and DSB regimens were similar at all sampled time points. AC delivery resulted in lower $d$-amphetamine plasma concentrations at $\leq 16$ h postdose, and then $d$-amphetamine was eliminated with an almost identical profile to the other regimens. The PSB and DSB regimens produced essentially identical $C_{\text{max}}$ results (1.1- and 1.0-fold relative to the oral regimen) at approximately the same time ($T_{\text{max}}$), whereas delivery to the AC resulted in a lower $C_{\text{max}}$ (0.6-fold relative to the oral regimen) with a later $T_{\text{max}}$. Systemic exposure to $d$-amphetamine, as indicated by the geometric mean (S.D.) AUC$_{0-\text{inf}}$ and AUC$_{0-\text{last}}$ was similar after PSB and DSB delivery (1.0- to 1.1-fold each, respectively, relative to oral absorption); exposure was less with AC delivery (0.7-fold each relative to oral absorption) but was still a considerable amount of relative absorption. All regimens had essentially identical median $t_{1/2}$ values (11.1–11.9 h) for $d$-amphetamine. For intact LDX and $d$-amphetamine, a comparison of the geometric means of the pharmacokinetic parameters (AUC$_{0-\text{inf}}$/AUC$_{0-\text{last}}$, $C_{\text{max}}$) for all regimens is presented in Table 2.

Gamma-scintigraphic imaging confirmed that PSB, DSB, and AC delivery of solubilized LDX (50 mg) was target-delivered to the appropriate GI location. Imaging for the site-specific release to the PSB indicated that the ICC was emptied from the stomach, and a mean (S.D.) gastric emptying time was 2.7 (5.38) h. The participants were then removed from the camera, and the signal was sent to the ICC at a mean (S.D.) time of 3.3 (5.59) h postdose to open the capsule. The mean (S.D.) time after opening of the ICC for 50% of the radioactive marker released from the ICC to arrive at the colon (postdose arrival time$_{50\%}$; ATC$_{50\%}$) was 9.6 (5.65) h. The mean (S.D.) time for 50% of the marker to move through the small intestine and arrive at the colon after release of the marker from the ICC (small intestine transit time$_{50\%}$; SITT$_{50\%}$) was 6.4 (4.09) h. The mean (S.D.) AUC of small intestine (proximal and distal) GI transit curve (AUC$_{\text{SI}}$) after the radioactive marker release was 6.4 (3.89) units (fraction of radioactive marker in GI region of interest $\times$ hour). The mean (S.D.) evacuation time postdose of the opened ICC in all participants in the feaces was 28.9 (11.22) h.

For DSB delivery, scintigraphic imaging indicated that the mean (S.D.) gastric emptying time was 1.5 (2.06) h and that the capsule was opened at a mean (S.D.) of 3.6 (1.88) h postdose. The mean (S.D.) ATC$_{50\%}$ and SITT$_{50\%}$ were 7.8 (3.34) and 4.3 (3.01) h, respectively. The mean AUC (S.D.) of small intestine (distal only) GI transit curve (AUC$_{\text{SI}}$) after the radioactive marker release was 4.3 (3.08) units (fraction of radioactive marker in GI region of interest $\times$ hour). The mean (S.D.) evacuation time postdose of the opened ICC for DSB delivery in the feaces was 29.3 (12.87) h.

Scintigraphic imaging data for AC delivery indicated that the mean (S.D.) gastric emptying time was 2.6 (4.47) h and the opening of the capsule for AC delivery was at a mean (S.D.) of 10.1 (5.41) h after the ICC was visualized in the cecum. The mean (S.D.) ATC for the unopened ICC in the colon was 8.3 (5.56) h, and the mean (S.D.) SITT$_{50\%}$ calculated as the ATC minus gastric emptying was 5.7 (2.24) h. The mean (S.D.) evacuation time postdose of the opened ICC in the feaces was 30.0 (20.41) h.

Safety. On day 1 of a dosing period, 18 participants received LDX orally in phase 1; in phase 2, LDX was administered using an ICC in 17 participants to target the PSB, in 17 participants to target the DSB, and in 16 participants to target the AC. Sixteen participants received all five regimens and completed the study. There were no serious TEAEs and no treatment-related withdrawals. One participant refused to swallow the ICC capsule and was discontinued. The number of participants reporting any TEAEs and the incidence of any TEAEs reported were similar for all regimens: oral [5 of 18 participants

### TABLE 2

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Geometric Mean</th>
<th>Ratio PSB/Oral (90% CI)</th>
<th>Ratio DSB/Oral (90% CI)</th>
<th>Ratio AC/Oral (90% CI)</th>
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<tr>
<td>LDX AUC$_{0-\text{inf}}$ ng · h · ml$^{-1}$</td>
<td>Mean (S.D.)</td>
<td>23.98 (3.12)</td>
<td>43.97 (10.45)</td>
<td>1.4 (1.20, 1.59)</td>
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<td>$C_{\text{max}}$ ng/ml</td>
<td>Mean (S.D.)</td>
<td>22.49 (3.18)</td>
<td>43.23 (3.98)</td>
<td>1.4 (1.14, 1.75)</td>
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<td>$d$-Amphetamine AUC$_{0-\text{last}}$ ng · h · ml$^{-1}$</td>
<td>Mean (S.D.)</td>
<td>19.34 (2.78)</td>
<td>34.69 (4.06)</td>
<td>1.4 (1.09, 1.76)</td>
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<tr>
<td>$C_{\text{max}}$ ng/ml</td>
<td>Mean (S.D.)</td>
<td>761.3 (824.3)</td>
<td>791.3 (564.9)</td>
<td>1.1 (0.92, 1.27)</td>
</tr>
</tbody>
</table>

### TABLE 3

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Statistic</th>
<th>Oral n = 18</th>
<th>ICC to PSB n = 17</th>
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<th>ICC to AC n = 16</th>
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<td>40.5 (4.95)</td>
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<td>25.7 (9.07)</td>
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<td>$T_{\text{max}}$ h</td>
<td>Median</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>$t_{1/2}$ h</td>
<td>Mean (S.D.)</td>
<td>11.6 (2.80)</td>
<td>11.8 (2.60)</td>
<td>11.2 (2.00)</td>
<td>11.5 (1.90)</td>
</tr>
<tr>
<td>AUC$_{0-\text{inf}}$ ng · h · ml$^{-1}$</td>
<td>Mean (S.D.)</td>
<td>719.1 (157.05)</td>
<td>771.2 (152.88)</td>
<td>752.4 (163.38)</td>
<td>574.3 (220.65)</td>
</tr>
<tr>
<td>AUC$_{0-\text{last}}$ ng · h · ml$^{-1}$</td>
<td>Mean (S.D.)</td>
<td>776.9 (167.69)</td>
<td>839.8 (166.89)</td>
<td>811.9 (185.58)</td>
<td>635.3 (224.48)</td>
</tr>
</tbody>
</table>
Absorption (systemic exposure) of LDX was comparable after oral or small bowel delivery (i.e., PSB and DSB), but LDX was not as well absorbed after AC delivery. LDX administration by oral or small bowel delivery (i.e., PSB and DSB), but LDX was not as well absorbed after AC delivery. LDX absorption, based on the nature of the slower movement and permeability in the colon, most likely due to the limited motility, decreased fluid content, and increased viscosity of this segment, coupled with the relatively rapid conversion of LDX upon absorption and minimal LDX accumulation. By this paradigm, LDX accumulation in the blood would be lower after colonic absorption, and the LDX being absorbed would be converted rapidly, resulting in the disproportionately higher plasma levels of d-amphetamine relative to those of LDX.

Results from this study and other LDX studies suggest that its solubility profile is not affected by pH within the biological range, whether delivered with an ICC or orally (Shojaei et al., 2007). Moreover, increasing the pH above this range resulted in only slight reductions in LDX solubility. Supportive of these data is an in vitro assay, in which LDX was not converted by enzymes that simulated the conditions of the GI tract, inclusive of gastric and intestinal fluids; this is consistent with intact LDX absorption in the body (Pennick, 2010). LDX is composed of the amino acid L-lysine covalently linked to d-amphetamine by a dipeptide-like linkage (Fig. 1) (Pennick, 2010). Although a small amount of LDX is hydrolyzed to d-amphetamine in the GI tract, the conversion of LDX into active d-amphetamine occurs primarily in the blood (Pennick, 2010). GI absorption of drugs may be affected by saturation of a carrier-mediated absorption pathway, drug instability with pH, metabolism (e.g., GI mucosa), protein binding, and other factors (Ratain, 1992). As reviewed by Lin (2007), oral absorption is often affected by gastric-emptying time and low intestinal motility. Long-term alterations in GI physiology such as aging, inflammatory bowel disease or other GI diseases, surgical removal of the GI tract, cystic fibrosis, and AIDS affect pH, transport, absorption area, and acid secretion (Fleisher et al., 1999). The ICC noninvasive delivery method to the small intestine and colon used in this study provided information on absorption in these regions under physiologic conditions. This method may prove useful in probing characteristics of targeted GI absorption to elucidate factors that affect regional absorption of drugs.

Various pharmacokinetic studies of psychostimulants have indicated consistency in terms of bioavailability with various formulations of mixed amphetamine salts extended release or methylphenidate (Ermer et al., 2007a; Tuerck et al., 2007), but the prodrug mechanism of LDX suggests more-consistent pharmacokinetics. A study in children with ADHD demonstrated that d-amphetamine from LDX is
dose-proportional and exhibited low intersubject variability after single-dose administration (Boellner et al., 2010). Plasma concentrations of d-amphetamine measured over time increased linearly in a dose-dependent manner after oral doses of LDX, with no indication of enzyme saturation in healthy adults, and exhibited low intersubject and intrasubject variability (Ermer et al., 2010). These data indicate reliable delivery of the active drug over a wide dose range upon prodrug administration. These effects may likely be attributed to the prodrug mechanism of LDX, which requires intrinsic enzymatic cleavage of intact LDX to active d-amphetamine and is not dependent on typical exogenous formulations or drug-release delivery systems such as are characteristic of other stimulants (Ermer et al., 2007b).

Physical and chemical interactions may occur between drugs and food, other drugs, or formulation components (Fleisher et al., 1999). Physiochemical and biological characteristics of LDX (e.g., high water solubility, lack of effect on absorption or conversion by changes in gastric environment and pH, and gradual conversion to active d-amphetamine) may contribute to the consistent delivery of d-amphetamine and low variability among participants [Vyvanse (package insert), 2011]. There are several factors that may affect absorption in general that should be considered for LDX. For example, absorption rate of a drug may be increased with increases in dissolution rate. On the other hand, increases in the degradation rate of drugs may decrease luminal concentration and limit the extent of absorption (Fleisher et al., 1999). Another factor that may delay or decrease drug absorption is reduction in the rate of radial diffusion in the intestinal lumen (Fleisher et al., 1999). An example of an interaction that has been shown to have significant effects on absorption is food intake. It is primarily dependent on meal size and the physiochemical properties of the actual drug, which may reduce, delay, increase, accelerate, or have no effect on absorption (Fleisher et al., 1999; Lin, 2007). In particular, in the case of LDX, food had no effect on the systemic exposure of d-amphetamine; however, it delayed \( T_{\text{max}} \) of d-amphetamine and intact LDX by approximately 1 h in healthy participants with a high-fat meal (Shojaei et al., 2007; Krishnan and Zhang, 2008). Therefore, LDX may be taken with or without food or may be dissolved in water without affecting absorption (Goodman, 2007).

Because LDX is a prodrug (not a controlled-release vehicle), it is dissolved in water without affecting absorption (Goodman, 2007). Therefore, LDX may be taken with or without food. As with other small bowel delivery regimens and identical d-amphetamine plasma concentration profiles and results. AC delivery produced less exposure to LDX and d-amphetamine compared with other regimens. Overall, LDX treatment regimens demonstrated a safety profile consistent with that demonstrated in other LDX clinical studies, with no unexpected safety findings or results of clinical concern.

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**Authorship Contributions**

**Performed data analysis:** Ermer, Haffey, Doll, Martin, Sandefer, Dennis, Corcoran, Trespidi, and Page.

**Conducted experiments:** Doll, Sandefer, and Page.

**Wrote or contributed to the writing of the manuscript:** Ermer, Haffey, Doll, Martin, Sandefer, Dennis, Corcoran, Trespidi, and Page.

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Address correspondence to: James Ermer, Shire Development Inc., Clinical Pharmacology and Pharmacokinetics, 725 Chesterbrook Blvd., Wayne, PA 19087. E-mail: jaermer@shire.com