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

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Running Title: Pharmacokinetics of Lisdexamfetamine Dimesylate in Adults

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**List of non-standard abbreviations**

$^{99m}$Tc-DTPA, technetium-99m-diethylenetriamine-pentaacetic acid

AC, ascending colon

ADHD, attention-deficit/hyperactivity disorder

AE, adverse event

ATC, postdose arrival time

AUC, area under the curve

AUC$_{0\text{-inf}}$, AUC from time zero to infinity

AUC$_{DSI}$, small intestine (distal only) GI transit curve

AUC$_{last}$, area under the plasma concentration-time curve to the last measurable time point

$C_{\text{max}}$, maximum observed plasma concentration

DSB, distal small bowel

ECG, electrocardiogram

FRMGRI, Fraction of Radioactive Marker in GI Region of Interest

GI, gastrointestinal

ICC, InteliSite Companion Capsules

IN, intranasal
IRB, institutional review board

LDX, lisdexamfetamine dimesylate

PEPT1, peptide cotransporter 1

PSB, proximal small bowel

QC, quality control

SITT, small intestine transit time

TEAE, treatment-emergent adverse event

T_{\text{max}}, \text{time to } C_{\text{max}}
ABSTRACT

Objective: To assess the pharmacokinetics and safety of lisdexamfetamine dimesylate (LDX) delivered and released regionally in the gastrointestinal (GI) tract. Methods: In this open-label, randomized, crossover study, oral (PO) 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. Results: Healthy males (N=18; 18-48 years) were enrolled. Mean (SD) maximum 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, respectively, for d-amphetamine after PO, PSB, DSB, and AC delivery of LDX. Median time to Cmax was 5, 4, 5, and 8 hours, respectively. Most TEAEs were mild to moderate. No clinically meaningful changes were observed (laboratory, physical examination, or electrocardiogram). Conclusions: 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 site(s) 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 vs highly polar compounds that are not absorbed as readily (Shargel, et al., 2005). Pharmacokinetic studies of different 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 (Spencer et al., 2006a; Volkow and Swanson, 2003). 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 (Shargel, et al., 2005; Staib et al., 1986). 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 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 impact 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 (Battelle-Institute V, Frankfurt am Main, Germany) (Harder et al., 1990; Staib et al., 1986), InteliSite Capsule (Casper Associates, Raleigh, NC, USA), and Enterion capsule (Phaeton Research, Nottingham, UK) (Prior, et al., 2004). Gamma scintigraphy (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). Nonbiodegradable, noninvasive InteliSite Companion Capsules (ICCs) with radiolabeled content are spring-loaded and 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. Scintigraphy and the remote-controlled capsules, when used together with conventional pharmacokinetic assessment, 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 classical pharmacokinetics to interpret the degree of drug absorption versus control.

Psychostimulants, 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, USA) is a long-acting prodrug stimulant indicated for the treatment of ADHD in children (6–12 y), adolescents (13–17 y), and in adults. LDX (therapeutically inactive molecule), after oral (PO) ingestion, is converted to l-lysine and active d-amphetamine (therapeutically active) (Figure 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 (Haffey et al., 2009; Krishnan and Zhang, 2008; Shojaei, et al., 2007). 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 to LDX pharmacokinetics with PO administration.
METHODS

Study Overview

This trial was a single-center (Scintipharma Inc., Lexington, KY, USA), open-label, 2-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 PO 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., 2010a).

This study was conducted in accordance with the principles of the 18th World Medical Assembly (Helsinki, 1964) and amendments of the 29th (Tokyo, 1975), 35th (Venice, 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 (IRB; Chesapeake Research Review, Inc. Columbia, MD, USA). Prior to screening, written informed consent using an IRB-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 the human immunodeficiency virus and the hepatitis B surface antigen and hepatitis C antibody screen as well as 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 prior to receiving the first dose of study drug, and inclusion/exclusion criteria were reviewed again upon admission to determine eligibility. Participants were randomized to a treatment sequence and were required to fast overnight (≥8 hours) prior to LDX administration. Nonbiodegradable and noninvasive ICCs were designed to actively deliver drugs with spring-loaded action to various areas of the GI tract upon radiofrequency signal (Parr et al., 1999; Pithavala et al., 1998). The ICC has been used to determine regional drug absorption and bioavailability, with its radiolabeled content visualized via gamma scintigraphy. Indium-111 chloride (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 5 dosing periods of the study were made up of 2 administrations, PO and IN regimens during phase 1, as previously reported (Ermer et al., 2010a), and 3 administrations, PSB, DSB, and AC regimens during phase 2. The PO regimen consisted of a 50-mg LDX capsule that was not radiolabeled and was delivered PO 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 \(^{99m}\text{Tc-DTPA}\), which has been previously reported (Ermer et al., 2010a) and is not presented here. Each ICC delivery regimen (PSB, DSB, and AC) was prepared as a single preparation (the equivalent of 50 mg LDX was dissolved in water and filled into an ICC, containing up to 25 µCi \(^{111}\text{In chloride}\)). The ICCs were administered orally with 120 to 240 mL of water followed by 240 mL of a radiolabeled drink (\(^{99m}\text{Tc-DTPA}, \leq 50 \mu\text{Ci}\)). The 50-mg/d dose strength of LDX used in this study is equivalent to an amphetamine base dose of 14.8 mg/d (Findling et al., 2009).

The 2-way crossover (2 dosing periods conducted during phase 1 as a 2-sequence treatment regimen: PO vs IN) has been previously reported (Ermer et al., 2010a). The 3-way crossover (3 dosing periods) was performed in phase 2, and the treatment regimen included 6 sequences (Figure 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 7 administrations could be received (2 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 prior to the dosing period, and participants remained in the unit and were not discharged until approximately 48 hours after drug release from the ICC. After taking the ICC, the participant continued fasting for an additional 4 hours (beyond the 8 hours prior to dose administration) as long as the ICC had emptied from the stomach. If the ICC had not emptied from the stomach, then the fast was continued until gastric emptying was confirmed. Water was permitted ad libitum until 2 hours predose and after 2 hours postdose. Participants were asked to return to the unit 72 hours post-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 PO and GI delivery. The safety population consisted of enrolled participants who took ≥1 dose of LDX and had completed ≥1 follow-up safety assessment. 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 prerelease of ICC), 15, 30, and 45 minutes and at 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose for the PO regimen or after drug release from the ICC for the PSB, DSB, and AC regimens. Blood samples were collected in K₃EDTA tubes placed on ice and then centrifuged at approximately 4°C. The plasma from the sample
for each participant was collected in 2 polypropylene tubes. One tube was shipped on dry ice to a laboratory for analysis and the other was stored at -75°C as backup.

Plasma d-amphetamine from LDX and intact LDX concentrations were measured using a validated liquid chromatography with tandem mass spectrometry method. The method utilized liquid-liquid extraction followed by analysis on a Sciex API 3000 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 ng/mL and 100.00 ng/mL for intact LDX and 2.00 ng/mL and 200.00 ng/mL for amphetamine using a 200-µl plasma aliquot. Quality-control (QC) samples were prepared in control human plasma at 3 concentration levels and 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 US Food and Drug Administration Guidance for Industry on Bioanalytical Method Validation (US Food and Drug Administration, 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 Sandefer, 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 $^{99m}$Tc and $^{111}$In were monitored simultaneously due to their different energies of gamma ray emission and that they are not absorbed in the GI tract. To monitor GI transit of the ICC, the $^{111}$In chloride was included with LDX in the capsule, and to delineate the target sites, the water used to swallow the ICC contained $^{99m}$Tc-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 minute each, were taken from participants in the supine position. For the PSB and DSB delivery regimens, the images were conducted at about 15- to 30-minute 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-minute 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 maximum amount of radioactivity to be administered including the potential for up to 2 additional repeat administrations was 250 µCi of $^{99m}$Tc-DPTA (50 µCi per
administration of ICC) and 125 µCi of $^{111}$In chloride (25 µCi per administration of ICC).
The maximum 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 Measurements, 2003). 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 following termination of treatment. Clinical laboratory tests, electrocardiogram (ECG), and physical examinations were conducted at screening, predose, discharge or 48 hours 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 prior to allowing participants to proceed to the next dosing period of the study.

**Pharmacokinetic Analysis**

The pharmacokinetic parameters computed included maximum 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$_{0-\infty}$), 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 aforementioned 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 (eg, mean, SD, n, 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 maximum likelihood estimates of variance components. Estimates and 90% CI for the regimen ratios of PSB, DSB, and AC versus PO for d-amphetamine $C_{\text{max}}$ and $\text{AUC}_{\text{last}}$ were calculated using PO values within the mixed model framework.
RESULTS

Participant Disposition and Demographics

Eighteen healthy men (18 to 48 years; mean [SD] age, 25.1 [8.35] years) were enrolled and randomized, 17 completed the study, and 1 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 (SD) body mass index of 25.1 (2.58) kg/m² and were predominantly white (83.3%) and of non-Hispanic or non-Latino ethnicity.

Pharmacokinetics and Scintigraphy

Pharmacokinetic results for IN LDX administration have been previously reported (Ermer et al., 2010a). In that particular analysis, results indicated that the pharmacokinetic parameters of d-amphetamine from LDX were similar for both PO and IN administration. The plasma concentration-time courses of d-amphetamine from LDX, up to 48 hours postdose, for both modes of administration were similar. IN delivery of intact LDX was achieved with no swallowing for up to 5 minutes postdose and was consistent with rapid absorption that is characteristic of that method of administration (Ermer et al., 2010a; Shargel, et al., 2005).

Plasma pharmacokinetic parameters of intact LDX for the pharmacokinetic population by PO and ICC GI delivery are summarized in Table 1 and illustrated in Figure 3. For intact LDX, a comparison of pharmacokinetic parameters (\(AUC_{0-\text{inf}}\), \(AUC_{0-\text{last}}\), and \(C_{\text{max}}\)) for the ICC delivery regimens (PSB, DSB, and AC) to those of PO is presented in Table...
2. At 1 hour postdose, the intact LDX plasma concentration profiles varied, with mean (SD) values ranging from 2.1 (3.40) to 30.0 (12.93) ng/mL across regimens. After 1.5 hours, the LDX plasma concentrations for PO, PSB, and DSB were similar, whereas 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 about the same time and followed later by PO administration. PSB and DSB delivery resulted in the largest $C_{\text{max}}$; AC delivery resulted in the smallest $C_{\text{max}}$. $T_{\text{max}}$ and median $t_{1/2}$ values were similar with all regimens. Systemic exposure to intact LDX by the $\text{AUC}_{0-\text{last}}$ parameter was similar after PSB and DSB delivery and was the least with AC delivery. Likewise, based on $\text{AUC}_{0-\text{inf}}$, the systemic exposure to LDX was similar after PSB and DSB delivery and was less with AC delivery.

Table 3 summarizes and Figure 4 and inset illustrate mean plasma pharmacokinetic parameters of d-amphetamine from LDX for the pharmacokinetic population by PO and ICC GI delivery. For d-amphetamine, a comparison of the geometric ratios ($\text{AUC}_{0-\text{inf}}$, $\text{AUC}_{0-\text{last}}$, and $C_{\text{max}}$) of the ICC delivery regimens (PSB, DSB, and AC) to those of the PO delivery regimen is presented in Table 2. The d-amphetamine plasma concentrations for the PO, PSB, and DSB regimens were similar at all time points sampled. AC delivery resulted in lower d-amphetamine plasma concentrations at $\leq 16$ hours 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-fold and ~1.0-fold relative to the PO 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 PO regimen) with a later $T_{\text{max}}$. Systemic exposure to d-amphetamine, as indicated by the geometric mean (SD) AUC$_{0-\text{last}}$ and AUC$_{0-\text{inf}}$, was similar after PSB and DSB delivery (~1.0-fold to ~1.1-fold each, respectively, relative to PO absorption); exposure was less with AC delivery (~0.7-fold each relative to PO absorption) but was still a considerable amount of relative absorption. All regimens had essentially identical median $t_{1/2}$ values (11.1 to 11.9 hours) for d-amphetamine. For intact LDX and d-amphetamine, a comparison of the geometric means of the pharmacokinetic parameters (AUC$_{0-\text{inf}}$, AUC$_{0-\text{last}}$, and $C_{\text{max}}$) 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 (SD) gastric emptying time was 2.7 (5.38) hours. The participants were then removed from the camera, and the signal was sent to the ICC at a mean (SD) time of 3.3 (5.59) hours postdose to open the capsule. The mean (SD) 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) hours. The mean (SD) 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) hours. The mean (SD) 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 [FRMGRI] × h). The mean (SD) evacuation time postdose of the opened ICC in all participants in the feces was 28.9 (11.22) hours.

For DSB delivery, scintigraphic imaging indicated that the mean (SD) gastric emptying time was 1.5 (2.06) hours and that the capsule was opened at a mean (SD) of 3.6 (1.88) hours postdose. The mean (SD) ATC\textsubscript{50\%} and SITT\textsubscript{50\%} were 7.8 (3.34) and 4.3 (3.01) hours, respectively. The mean AUC (SD) of small intestine (distal only) GI transit curve (AUC\textsubscript{DSI}) after the radioactive marker release was 4.3 (3.08) units (FRMGRI × h). The mean (SD) evacuation time postdose of the opened ICC for DSB delivery in the feces was 29.3 (12.87) hours.

Scintigraphic imaging data for AC delivery indicated that the mean (SD) gastric emptying time was 2.6 (4.47) hours and the opening of the capsule for AC delivery was at a mean (SD) of 10.1 (5.41) hours after the ICC was visualized in the cecum. The mean (SD) ATC for the unopened ICC in the colon was 8.3 (5.56) hours, and the mean (SD) SITT calculated as the ATC minus gastric emptying was 5.7 (2.24) hours. The mean (SD) evacuation time postdose of the opened ICC in the feces was 30.0 (20.41) hours.

**Safety**

On day 1 of a dosing period, 18 participants received PO LDX 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 5 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: PO (5 of 18 participants [27.8%]), PSB (5 of 17 participants [29.4%]), DSB (3 of 17 participants [17.6%]), and AC (4 of 16 participants [25.0%]).

The TEAEs (n [%]) among participants treated with PO LDX administration were anorexia (4 [22.2%]) and pain (1 [5.6%]). With PSB LDX delivery, the TEAEs reported were anorexia (2 [11.8%]), headache (2 [11.8%]), diarrhea (1 [5.9%]), dry mouth (1 [5.9%]), insomnia (1 [5.9%]), nausea (1 [5.9%]), and vomiting (1 [5.9%]). Reports of TEAEs with the DSB delivery regimen of LDX were abdominal pain (1 [5.9%]), anorexia (1 [5.9%]), and headache (1 [5.9%]), whereas with AC delivery, they were insomnia (2 [12.5%]), abdominal pain upper (1 [6.3%]), diarrhea (1 [6.3%]), hypervigilance (1 [6.3%]), and logorrhea (1 [6.3%]). The majority of TEAEs related to treatment administration were mild or moderate in severity. There was 1 severe TEAE due to severe nausea upon administration of the PSB ICC, but it was considered not related to the treatment and resolved within 4.5 hours. There were no serious TEAEs, participant withdrawal or discontinuation, or deaths. Moreover, no clinically meaningful changes in mean laboratory parameters, physical examination findings, or ECG occurred during the study.
DISCUSSION

Absorption (systemic exposure) of LDX was comparable after PO or small bowel delivery (i.e., PSB and DSB), but LDX was not as well absorbed after AC delivery. LDX administration by PO or small bowel delivery resulted in predictable and similar d-amphetamine plasma concentration profiles and pharmacokinetics. LDX delivery to the AC produced less LDX and d-amphetamine exposure vs the other regimens. These data suggest that LDX can be effectively and readily absorbed when delivered to various segments of the GI. Scintigraphy data in this study confirmed that targeted LDX delivery to the PSB, DSB, and AC with the ICC was achieved. Overall, these data also suggest that the absorption windows for LDX release in the small intestine were similar to those achieved with PO administration; drug delivery and absorption in the AC, although less, was effective.

In relation to LDX absorption in the AC, it is intriguing that low levels of LDX absorption relative to those achieved with the other routes of administration (Figure 3) resulted in disproportionately higher d-amphetamine plasma concentrations (Figure 4), again, relative to those achieved with the other routes. Although no definitive assessment can be made, this dichotomy may be attributable to the intrinsically slower 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 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 (Figure 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, PO absorption is often affected by gastric emptying time and low intestinal motility (Lin, 2007). 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 affecting 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 SW et al., 2010). Plasma concentrations of d-amphetamine measured over time increased linearly in a dose-dependent manner after PO doses of LDX, with no indication of enzyme saturation in healthy adults, and exhibited low intersubject and intrasubject variability (Ermer et al., 2010b). 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 formulation 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). Specifically, 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 hour in healthy participants with a high-fat meal (Krishnan and Zhang, 2008; Shojaei, et al., 2007). Therefore, LDX may be taken with or without food or dissolved in water without affecting absorption (Goodman, 2007). Because it is a prodrug (not a controlled-release vehicle), it is absorbed rapidly from the GI tract and converted to d-amphetamine, and thus it is not affected by changes in transit times (Goodman, 2007). Results from the present and other LDX studies suggest that food and other agents may not affect the pharmacokinetics of oral and targeted LDX delivery to the small intestine, based on their similar pharmacokinetic profile, but that it may be different in the colon. An in vitro study of LDX demonstrated neither concentration-dependent nor mechanism-based inhibition by time-dependent inactivation of cytochrome P-450 isoforms, indicating low potential for initiation of drug-drug
interactions (Krishnan and Moncrief, 2006). Because LDX is slowly converted into d-amphetamine, the capacity for its clearance is not saturated (Moncrief, et al., 2006).

The safety data in this study suggest that there were no safety findings of clinical concern and were consistent with previous published safety data in children, adolescents, and adults for LDX (Adler et al., 2008; Findling et al., 2008; Findling et al., 2009; Findling et al., 2011; Weisler et al., 2009; Wigal et al., 2010). TEAEs were predominantly mild to moderate in intensity. Overall, regardless of regimen, the most common TEAEs with a ≥5% incidence were abdominal pain, abdominal pain upper, anorexia, diarrhea, dry mouth, headache, hypervigilance, insomnia, logorrhea, nausea, pain, and vomiting. The majority of the reported TEAEs were similar to those commonly associated with amphetamine use, such as abdominal pain, anorexia, dry mouth, headache, and insomnia (Horrigan and Barnhill, 2000; Spencer et al., 2006b). There were no serious TEAEs or discontinuations. Moreover, TEAE incidence rates and severity were similar between LDX regimens and suggest that there are no differences in safety with the various delivery methods.

The small sample population of healthy adults and exclusion/inclusion criteria for participants may not be representative of the whole population or the clinical setting. Although this study consisted of a male adult population, potential for sex difference is not likely pertinent to this study, because the study focused on absorption windows and not factors of GI motility. Also, this study was not designed for comprehensive assessment of safety. Nonetheless, the safety profile of LDX has been described in
randomized controlled trials of adult participants with ADHD (Adler et al., 2008; Wigal et al., 2010). Previously, in a study in healthy adults, food was shown not to affect the observed AUC and $C_{\text{max}}$ of d-amphetamine after a 70-mg/d dose of LDX; however, $T_{\text{max}}$ was prolonged by approximately 1 hour after a high-fat meal.

In conclusion, LDX was well absorbed (systemic exposure) after PO or small-bowel delivery regimens and demonstrated identical d-amphetamine plasma concentration profiles and results. AC delivery produced less exposure to LDX and d-amphetamine vs 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

Participated in research design: Ermer, Haffey, Doll, Martin, Sandefer, Dennis, Corcoran, Trespidi, and Page.

Conducted experiments: Doll, Sandefer, and Page.

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

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

Contributed new reagents or analytic tools: Doll, Sandefer, and Page.
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Spencer TJ, Wilens TE, Biederman J, Weisler RH, Read SC, and Pratt R (2006b) Efficacy and safety of mixed amphetamine salts extended release (Adderall XR) in the management of


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b) Previous Presentation: This data has been presented at the U.S. Psychiatric & Mental Health Congress (USPMH), November 18-21, 2010, Kissimmee, FL.

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Ermer, Haffey, Doll, Martin, Sandefer, Dennis, Corcoran, Trespidi, and Page have given final approval of this version.
**Figure Legends**

Figure 1. Chemical structure of lisdexamfetamine dimesylate and d-amphetamine.

Figure 2. Flow diagram for dosing schedule. LDX, lisdexamfetamine dimesylate; PO, oral; IN, intranasal; PSB, proximal small bowel; DSB, distal small bowel; AC, ascending colon.

Figure 3. Mean plasma concentration of intact LDX following PO or GI ICC delivery of LDX. LDX, lisdexamfetamine dimesylate; PO, oral; GI, gastrointestinal; ICC, InteliSite Companion Capsules; PSB, proximal small bowel; DSB, distal small bowel; AC, ascending colon.

Figure 4. Mean plasma concentration of d-amphetamine from LDX following PO or GI ICC delivery of LDX. LDX, lisdexamfetamine dimesylate; PO, oral; GI, gastrointestinal; ICC, InteliSite Companion Capsules; PSB, proximal small bowel; DSB, distal small bowel; AC, ascending colon.
Table 1. Plasma Pharmacokinetic Parameters of Intact LDX With Various LDX Regimens (Pharmacokinetic Population)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Statistic</th>
<th>LDX Regimen (50 mg LDX)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n=18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PO</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>Mean (SD)</td>
<td>19.8 (5.60)</td>
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<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>Median</td>
<td>1</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>Mean (SD)</td>
<td>0.5 (0.10)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;last&lt;/sub&gt; (ng·h/mL)</td>
<td>Mean (SD)</td>
<td>23.4 (7.46)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng·h/mL)</td>
<td>Mean (SD)</td>
<td>25.2 (7.21)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>n=7; <sup>b</sup>n=17; <sup>c</sup>n=4.

Abbreviations: AC, ascending colon; AUC<sub>last</sub>, area under the plasma concentration-time curve to the last measurable time point; AUC<sub>0-inf</sub>, area under the plasma concentration-time curve from time zero to infinity; C<sub>max</sub>, maximum observed plasma concentration; DSB, distal small bowel; ICC, InteliSite Companion Capsules; LDX, lisdexamfetamine dimesylate; PO, oral; PSB, proximal small bowel; T<sub>max</sub>, time to maximum observed plasma concentration; t<sub>1/2</sub>, apparent terminal half-life.
Table 2. Geometric Means and Mean Ratios of AUC_{0-inf}, AUC_{last}, and C_{max}, for Intact LDX and d-Amphetamine After PO, PSB, DSB, and AC Delivery

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Geometric Mean (ng·h/mL)</th>
<th>Ratio PSB/PO (90% CI)</th>
<th>Ratio DSB/PO (90% CI)</th>
<th>Ratio AC/PO (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDX</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{0-inf}</td>
<td>23.98</td>
<td>1.4 (1.20, 1.59)</td>
<td>1.8 (1.59, 2.11)</td>
<td>0.4 (0.34, 0.56)</td>
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<tr>
<td>AUC_{last}</td>
<td>22.49</td>
<td>1.4 (1.14, 1.75)</td>
<td>1.9 (1.55, 2.39)</td>
<td>0.2 (0.13, 0.24)</td>
</tr>
<tr>
<td>C_{max}</td>
<td>19.34</td>
<td>1.4 (1.09, 1.76)</td>
<td>1.8 (1.41, 2.28)</td>
<td>0.2 (0.15, 0.29)</td>
</tr>
<tr>
<td><strong>d-Amphetamine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{0-inf}</td>
<td>761.3</td>
<td>1.1 (0.92, 1.27)</td>
<td>1.0 (0.89, 1.22)</td>
<td>0.7 (0.63, 0.87)</td>
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<td>AUC_{last}</td>
<td>702.0</td>
<td>1.1 (0.89, 1.30)</td>
<td>1.0 (0.86, 1.26)</td>
<td>0.7 (0.58, 0.84)</td>
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<tr>
<td>C_{max}</td>
<td>37.51</td>
<td>1.1 (0.94, 1.23)</td>
<td>1.0 (0.89, 1.17)</td>
<td>0.6 (0.53, 0.71)</td>
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</table>

Abbreviations: AC, ascending colon; AUC_{last}, area under the plasma concentration-time curve to the last measurable time point; AUC_{0-inf}, area under the plasma concentration-time curve from time zero to infinity; C_{max}, maximum observed plasma concentration; CI, confidence interval; DSB, distal small bowel; ICC, InteliSite Companion Capsules; LDX, lisdexamfetamine dimesylate; PO, oral; PSB, proximal small bowel.
Table 3. Plasma Pharmacokinetic Parameters for d-Amphetamine With Various LDX Regimens (Pharmacokinetic Population)

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<tr>
<th>Pharmacokinetic Parameter</th>
<th>Statistic</th>
<th>LDX Regimen (50 mg LDX)</th>
<th>n=18</th>
<th>n=17</th>
<th>n=17</th>
<th>n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PO</td>
<td>ICC to PSB</td>
<td>ICC to DSB</td>
<td>ICC to AC</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>Mean (SD)</td>
<td>37.6 (4.54)</td>
<td>40.5 (4.95)</td>
<td>38.7 (6.46)</td>
<td>25.7 (9.07)</td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>Median</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>Mean (SD)</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>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;last&lt;/sub&gt; (ng·h/mL)</td>
<td>Mean (SD)</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>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng·h/mL)</td>
<td>Mean (SD)</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>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AC, ascending colon; AUC<sub>last</sub>, area under the plasma concentration-time curve to the last measurable time point; AUC<sub>0-inf</sub>, area under the plasma concentration-time curve from time zero to infinity; C<sub>max</sub>, maximum observed plasma concentration; DSB, distal small bowel; ICC, InteliSite Companion Capsules; LDX, lisdexamfetamine dimesylate; PO, oral; PSB, proximal small bowel; T<sub>max</sub>, time to maximum observed plasma concentration; t<sub>1/2</sub>, apparent terminal half-life.
Figure 1

Lisdexamfetamine dimesylate (prodrug) → I-Lysine + d-Amphetamine (active)

Site of cleavage
LDX (50 mg) Regimens:
A=PO (LDX 50-mg capsule)
B=IN (LDX 50-mg solution)
C=PSB (LDX 50-mg solution delivered in ICC)
D=DSB (LDX 50-mg solution delivered in ICC)
E=AC (LDX 50-mg solution delivered in ICC)
Figure 3

Intact LDX Plasma Concentration (ng/mL) (Mean)

Time (h)

Note: Time zero for PO regimen is time of dosing. Time zero for PSB, DSB, and AC regimens is time of ICC opening.
Figure 4

- PO (LDX 50-mg capsule)
- PSB (LDX 50-mg solution delivered in ICC)
- DSB (LDX 50-mg solution delivered in ICC)
- AC (LDX 50-mg solution delivered in ICC)

Note: Time zero for PO regimen is time of dosing. Time zero for PSB, DSB, and AC regimens is time of ICC opening.