CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208510Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA/eCTD #: 208,510/0003	**EDR Link:** \\CDSESUB1\evsprod\NDA208510\0003
Relevant IND: 67,482	**Indications:** Attention Deficit Hyperactive Disorder (ADHD) moderate to severe Binge Eating Disorder (BED)
Brand Name: Vyvanse	**Generic Name:** Lisdexamphetamine Dimesylate
Formulation: Immediate-Release Chewable Tablet	**Strength (mg):** 10, 20, 30, 40, 50, and 60
Submission Type: 505(b)(1)	**Submission Date:** March 31, 2016
Sponsor: Shire	**OCP Reviewers:** Huixia Zhang, PhD; Hao Zhu, PhD

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1. EXECUTIVE SUMMARY

Shire is seeking approval of lisdexamfetamine dimesylate in the form of a chewable tablet (Vyvanse chewable tablet) for the treatment of Attention Deficit Hyperactive Disorder (ADHD) in patients 6 years old and above, and Moderate to Severe Binge Eating Disorder (BED) in adult patients, via 505b (1) approach. The listed drug (LD) for this application is Vyvanse capsule (NDA 21,977), which was also developed by Shire. Vyvanse capsule was approved in the US in 2007 for the treatment of ADHD in children aged 6-12, in 2008 for the treatment of ADHD in adults, in 2010 for the treatment of ADHD in adolescents aged 13-17, in 2012 for the maintenance treatment of ADHD in adults, and in 2015 for the treatment of moderate to severe BED in adults.

The current development program is based on a single-dose, relative bioavailability study (Study SHP489-126) demonstrating similarity in pharmacokinetic (PK) profile and exposure of the active moiety dexamphetamine (d-AMP) between Vyvanse chewable tablet and Vyvanse capsule (LD). The effect of food on PK of the Vyvanse chewable tablet was also evaluated (Study SHP489-127). A pilot open-label study (SPD489-125) was conducted to compare prototype formulations and improve palatability of the chewable tablet dosage form. No clinical safety or efficacy studies were submitted in this application.

OCP's major findings are summarized as follows:

1. An adequate link has been established between Vyvanse chewable tablet and Vyvanse capsule (LD) through the relative bioavailability study. Even though additional partial AUCs have been investigated for scientific exploratory purpose, the determination was mainly based on Cmax and AUC.
2. The average exposure of the pharmacologically inactive prodrug, lisdexamfetamine (LDX), was not considered similar (i.e., slightly beyond the bioequivalence limits) between Vyvanse chewable tablet and Vyvanse capsule (LD). However, the average exposure of the active moiety, d-AMP, has been demonstrated to be similar (within bioequivalence limits for Cmax and AUC). In addition, the mean pharmacokinetic profiles of d-AMP between the two products are almost superimposable. Hence, the efficacy and safety profiles of the Vyvanse chewable tablet in general population are expected to be similar to those for the LD.
3. Based on the low variability of d-AMP while switching between Vyvanse capsule and Vyvanse chewable tablet, no large difference in clinical response is expected when patients switch between the two products at the same dose.
4. Vyvanse chewable tablet can be administered without regard to food.

1.1 Recommendation

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in the NDA to support a recommendation of approval of Vyvanse chewable tablet. Per the recommendation (Appendix) from the Office of Study Integrity and Surveillance (OSIS), the data from the pivotal relative bioavailability study is considered acceptable. No inspection of the clinical or analytical site for the pivotal study SHP489-126 was deemed necessary, because those sites were recently inspected and no issues were identified. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP?	Comment
Overall	☒ Yes ☐ No ☐ NA	Pending labeling agreements with the sponsor
Evidence of effectiveness	☒ Yes ☐ No ☐ NA	Clinical efficacy and safety information is extended from the LD based on PK similarity of the active moiety dexamphetamine.
Proposed dose for general patients	☒ Yes ☐ No ☐ NA	Same as for the LD
Labeling	☐ Yes ☒ No ☐ NA	Pending satisfactory agreement with the sponsor

1.2 Phase IV Commitments

Office of Clinical Pharmacology proposes the following post-marketing study.

PMC or PMR	Key Drug Development Question	Rationale	Design Summary (TBD)
☐ PMC ☒ PMR	What are the PK properties of Vyvanse chewable tablet in male or female children (4 to 5 years of age) with ADHD?	Concentration time profile of amphetamine determines the onset and duration of the clinical response. It is valuable to assess the PK profiles in patients 4-5 years old with ADHD and ensure its similarity to that in older patients. This information can help inform dose selection for the clinical efficacy and safety trial.	Study population: patients 4-5 years old with ADHD Study design: multiple dose, open label Sample size: prospectively powered to ensure a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution Dose(s): a relevant dose Endpoints: AUC, C_{max} Submit protocol by: June, 2017 Start study by: Dec, 2017

2. QUESTION BASED REVIEW

2.1 Specific Questions

2.1.1 Are similar average efficacy and safety profiles expected for Vyvanse chewable tablet and Vyvanse capsule?

Yes. Similar average efficacy and safety profiles are expected for Vyvanse chewable tablet and Vyvanse capsule.

The LD, Vyvanse capsule, was shown to be safe and efficacious in the treatment of ADHD in patients 6 years and above, and for the treatment of moderate to severe BED in adults. For Vyvanse chewable tablet, there are no clinical trials conducted to evaluate its efficacy and

safety. However, the efficacy and safety data of Vyvanse chewable tablet can be extended from its LD, Vyvanse capsule, based on the following:

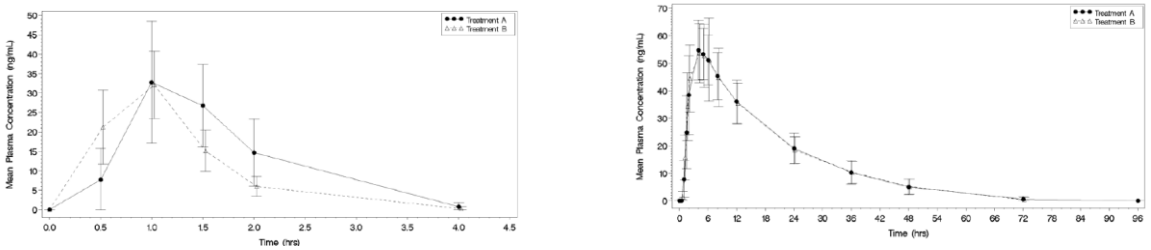
1) Exposure similarity (i.e., C_{max} and $AUCi_{nf}$) is demonstrated for d-AMP, the pharmacologically active moiety, between the two formulations (Table 1, and Figure 1). The mean pharmacokinetic profiles of d-AMP are almost superimposable (Figure 1).

Table 1: PK Parameters (Mean ± SD) of d-AMP After Administration Of 60mg Vyvanse Chewable Tablet Or Capsule Under Fasted Conditions			
Parameters	Capsule (R, n=36)	Chewable Tablet (T, n=36)	Geomean ratio (T/R, 90% CI)
C_{max} (ng/mL)	56.7±10.1	56.9 ±14.7	99.2 (93.1, 102.4)
AUC_{inf} (hr*ng/mL)	1161±272	1168±270	100.8 (97.4, 104.4)
-Source: -Table 10-13 of CSR			

2) It is also noted that there were differences in the PK profiles of the prodrug, LDX, between the two formulations (Table 2, Figure 1). Exposure to LDX (C_{max} and AUC_{last}) was about 15% less after chewable tablet administration. However, the observed difference is not considered clinically relevant, as LDX is deemed pharmacologically inactive.

Table 2: PK Parameters (Mean ± SD) of LDX After Administration Of 60mg Vyvanse Chewable Tablet Or Capsule Under Fasted Conditions			
Parameters	Capsule (R, n=36)	Chewable Tablet (T, n=36)	Geomean ratio (T/R, 90% CI)
C_{max} (ng/mL)	37.8±12.1	32.3 ±8.3	86.9 (78.0, 96.8)
AUC_{last} (hr*ng/mL)*	42.8±12.9	35.7±8.9	84.6 (77.5, 92.5)
*AUC_{last} was used because the concentrations of LDX were below lower limit of quantification at 5 hours post dose.			

Figure 1: Plasma Concentration vs. Time Profiles After Single Dose Administration of 60mg Vyvanse Capsule or Chewable Tablet: LDX (left panel); d-AMP (right panel)



Treatment A: SPD489 60 mg capsule - Fasting
Treatment B: SPD489 60 mg chewable tablet - Fasting
-Source: Figure 2 and Figure 5 of CSR

2.1.2 Is similar PK variability observed for Vyvanse capsule and Vyvanse chewable tablet?

Yes. Similar variability of the PK parameters for d-AMP is observed following Vyvanse capsule and Vyvanse chewable tablet administration.

Overall, inter-subject variability and intra-subject variability for d-AMP were low and similar after Vyvanse chewable tablet or Vyvanse capsule administration (Table 3). Following chewable tablet administration, inter-subject variability for d-AMP (C_{max} and $AUC_{0-\infty}$) was approximately 21% and 25%, respectively. Intra-subject variability was about 7-8%. Similar inter- and intra-subject variability was observed for capsule formulation (Table 3; Figure 2). The low inter-, and intra-patient variability suggested consistent drug delivery among and within patients.

In addition, subject-by-treatment variability (Table 4; Figure 2) also was low, which suggested that for individuals switching between capsule and chewable tablet, few are expected to experience large differences in the bioavailability of d-AMP. In general, similar clinical response is expected in patients switching between the two products with the same daily dose.

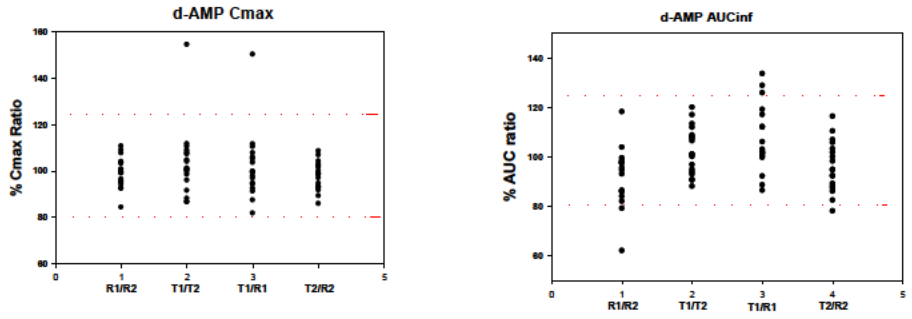
Table 3: Intra- and Inter-subject Variability (Estimate 95% CI) for d-AMP PK Parameters After Chewable Tablet and Capsule Administration (source: study 126)

	Chewable Tablet (n=18)		Capsule (n=18)	
Parameters	Inter-Subject	Intra-Subject	Inter-Subject	Intra-Subject
Log C_{max}	0.209 (0.149, 0.316)	0.084 (0.066, 0.114)	0.167 (0.120, 0.249)	0.046 (0.035, 0.066)
Log AUC_{inf}	0.250 (0.180, 0.371)	0.069 (0.051, 0.106)	0.246 (0.175, 0.374)	0.104 (0.081, 0.147)

Table 4: Summary of Subject-by-Treatment Interaction Variability Analysis for d-AMP (SD*)

Parameters	Estimate (95% CI)
C_{max}	0.041 (0.014, 0.073)
AUC_{inf}	0.004 (0.002, 0.086)
AUC_{last}	0.008 (0.001, 0.083)
*Expressed as standard deviation not variance.	

Figure 2: Distribution of d-AMP PK Parameter Ratios Between Treatments (study 126)



2.2 Standard Questions

2.2.1 What are the PK properties of lisdexamphetamine and d-amphetamine after single dose administration of Vyvanse chewable tablet?

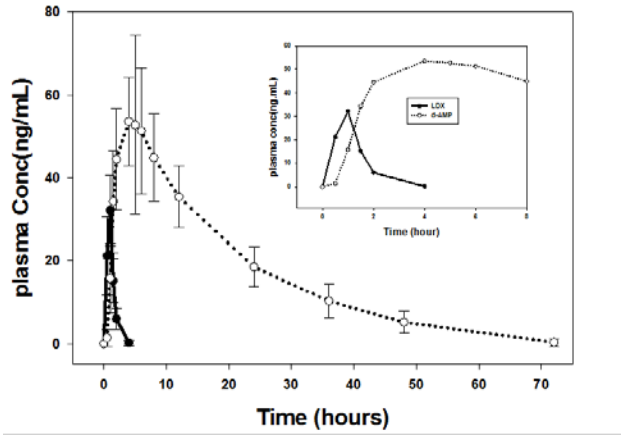
Following a single dose administration of 60mg Vyvanse chewable tablet to healthy volunteers under fasting conditions, LDX, the pharmacologically inactive prodrug, reached C_{max} in about 1 hour (Table 5, Figure 3). After that, LDX concentration quickly declined in the circulation. LDX plasma concentration at 5 hrs post dose was below lower limit of quantification. D-AMP, the pharmacologically active moiety, reached C_{max} in about 4.4 hours post dose (Table 5, Figure 3), with an estimated half life of about 12.7 hours. With a once daily dosing regimen for Vyvanse chewable tablet, no accumulation of LDX, but about 30% accumulation of d-AMP is expected after multiple dosing. The overall exposure to d-AMP was about 36.5-fold of that to the parent after single dose administration of Vyvanse chewable tablet.

Table 5: PK Parameters (Mean ± SD) Of LDX And d-AMP After 60 mg Vyvanse Chewable Tablet Administration Under Fasting Conditions

Parameters	LDX	d-AMP
C_{max} (ng/mL)	32.3 ±8.3	56.9 ±14.7
T_{max} (hr)	1.0±0.2	4.4±1.2
AUC_{inf} (hr*ng/mL)	35.7±8.9*	1168±270
$T_{1/2}$ (hr)	-	12.7±2.3

*$AUC_{last:}$ area under the curve from the time of dosing to the last measurable concentration

Figure 3: Plasma Concentration Time Profiles Of LDX And d-AMP After A Single Dose Administration of 60mg Vyvanse Chewable Tablet To Healthy Volunteers Under Fasting Conditions



2.2.2 Does food affect the bioavailability of Vyvanse chewable tablet?

High-fat, high-calorie meal decreased C_{max} of LDX by ~ 26%, and increased LDX exposure (AUC_{last}) by ~ 37% (Table 6), while decreased the exposure (C_{max} and AUC_{inf}) of d-AMP by ~ 5-7% (Table 7). The magnitude of change in exposure is not expected to have a significant

effect on the efficacy or safety of the product. Vyvanse chewable tablet can be administered without regard to food.

Table 6: PK Parameters (Mean ± SD) of LDX After Administration of 60mg Vyvanse Chewable Tablet Under Fasting or Fed Conditions			
Parameters	Fasting (R, n=35)	Fed (T, n=35)	Geomean ratio (T/R, 90% CI)
C_{max} (ng/mL)	32.3±30.2	20.7 ±8.4	74.3 (63.6, 86.7)
T_{max} (hr)	0.97±0.17	1.36±0.36	-
AUC_{last} (hr*ng/mL)	33.9±29.3	39.9±11.1	137.4 (121.7, 155.3)
-Source: -Table 6-9 of Study 127 CSR AUC_{last}: area under the curve from the time of dosing to the last measurable concentration			

Table 7: PK Parameters (Mean ± SD) of d-AMP After Administration of 60mg Vyvanse Chewable Tablet Under Fasting or Fed Conditions			
Parameters	Fasting (R, n=35)	Fed (T, n=35)	Geomean ratio (T/R, 90% CI)
C_{max} (ng/mL)	54.9±11.7	52.5 ±10.3	95.2 (88.8, 102.2)
T_{max} (hr)	3.9±1.0	4.9±0.8	-
AUC_{inf} (hr*ng/mL)	1073±201	1025±199	93.0 (86.8, 99.6)
-Source: -Table 10-13 of Study 127 CSR			

3. INDIVIDUAL STUDY REVIEW

Analytical Methods: wherever it is mentioned throughout the document that the performance of the analytical method is acceptable, it implies that the method used met the following requirements:

• Quality control sample range is acceptable	☑ Yes ☐ No
• Internal standard was used	☑ Yes ☐ No
• Method was validated prior to use	☑ Yes ☐ No
• Sample chromatograms were provided	☑ Yes ☐ No
• Calibration range samples accuracy and precision are acceptable	☑ Yes ☐ No
• Quality control samples accuracy and precision are acceptable	☑ Yes ☐ No
Method overall performance is acceptable	☑ Yes ☐ No

Acronym used for Vyvanse in the review: SPD489

3.1 Bioequivalence

Report # SHP489-126 **Study Period:** 3/9/2015-4/21/2015
Title: A Phase 1, Randomized, Open-Label, 2-Sequence, 4-Period Crossover Study Evaluating the Bioavailability of SPD489 60 mg Capsule Formulation Compared to SPD489 60 mg Chewable Tablet Formulation in Healthy Adults.

- **Objectives:** 1) To compare the pharmacokinetics of SPD489 60 mg in its capsule formulation and SPD489 60 mg in chewable tablet formulation as assessed by estimates of relative bioavailability; 2) to assess the safety and tolerability of SPD489 in both capsule and chewable tablet formulations in healthy adults.
- **Study Design:** This was a Phase 1, randomized, open-label, 2-sequence, 4-period replicated crossover study in 18 healthy adults. The study consisted of a screening period and 4 treatment periods separated by a washout of 7 days between doses administered orally in a fasting state. On Day 1 of Treatment Period 1, eligible subjects were randomized to 1 of the 2 treatment sequences in a 1:1 ratio as follows:
  Treatment Sequence ABAB (n=9): Treatment (Trt) Period 1: A single dose of SPD489 60 mg in capsule form was administered orally in a fasting state. In Trt Period 2, a single dose of SPD489 60 mg in chewable tablet form was administered in a fasting state. Subjects then repeated the sequence in Trt Period 3 (SPD489 60 mg capsule) and in Trt Period 4 (SPD489 60 mg chewable tablet).
  Treatment Sequence BABA (n=9): Treatment Period 1: A single dose of SPD489 60 mg in chewable tablet form was administered orally in a fasting state. In Treatment Period 2, a single dose of SPD489 60 mg in capsule form was administered orally in a fasting state.
  Subjects then repeated the sequence in Treatment Period 3 (SPD489 60 mg chewable tablet) and in Treatment Period 4 (SPD489 60 mg capsule).
  Following an overnight fast of at least 10 hours, subjects received 240 mL of water, either with the capsule formulation (Treatment A) or once the tablet had been thoroughly chewed and swallowed (Treatment B). Subjects refrained from fluids for at least 2 hours after dosing and continued to fast for at least 4 hours after administration of investigational product. Subjects were not permitted to lie down within the first 4 hours following administration of investigational product.
- **Blood Sampling Times (PK):** Predose, 0.5, 1, 1.5, 2, 4, 5, 6, 8, 12, 24, 36, 48, 72, and 96 hours post dose at each dosing period.
- **Analytical Method:**

Analyte	lisdexamfetamine	*d*-amphetamine
Method	LC-MS/MS	LC-MS/MS
Matrix	plasma	plasma
Linear range (ng/mL)	1-100	2-200
Performance	acceptable	acceptable

- **Results:**

Formulations

Table 1. Products used in Study 126			
SPD489 60 mg	**Manufacturer**	**Formulation**	**Batch #**
capsules	Shire	Immediate-Release capsule	3128367
chewable tablet	Shire	Immediate-Release chewable tablet	P140030-0001L

Study Population

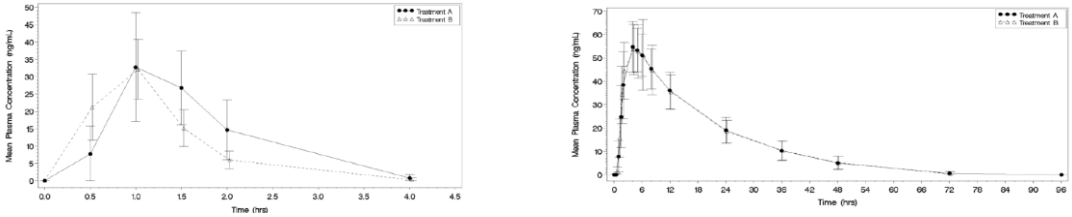
Table 2: Demographic Properties of Study Subjects (# subjects)	
Treated/Completed/Withdrawn Due To AE/Other Reasons	18/18/0/0
Age (mean±SD)	37.7±10.8
Male/Female	12/6
BMI (mean±SD)	26.5±2.7
Race (Caucasian/Black/Asian/Hispanic)	16/2/0/0

Pharmacokinetics

Table 3: Lisdexamphetamine (LDX) PK Parameters (Mean ± SD) After Vyvanse Chewable Tablet Or Capsule Administration Under Fasted Conditions			
Parameters	Treatment A (R, n=36)	Treatment B (T, n=36)	Geomean ratio (T/R, 90% CI)
C_{max} (ng/mL)	37.8±12.1	32.3 ±8.3	86.9 (78.0, 96.8)
T_{max} (hr)	1.3±0.3	1.0±0.2	-
AUC_{0-1h} (hr*ng/mL)	12.0±7.3	18.6±6.3	186.3 (150.2, 231.1)
$AUC_{1h-last}$(hr*ng/mL)	30.8±13.0	17.1±4.8	58.1 (52.0, 64.9)
AUC_{0-2h} (hr*ng/mL)	36.5±11.8	34.7±8.7	96.7 (87.4, 107.0)
$AUC_{2h-last}$(hr*ng/mL)	6.3±8.6	1.0±2.6	53.2 (37.1, 76.3)
AUC_{last} (hr*ng/mL)	42.8±12.9	35.7±8.9	84.6 (77.5, 92.5)
Treatment A: SPD489 60 mg capsule, Fasting –Reference (R; Treatment B: SPD489 60 mg chewable tablet, Fasting-Test (T) -Source: -Table 6-9 of CSR			

Table 4: D-amphetamine (d-AMP) PK Parameters (Mean ± SD) After Vyvanse Chewable Tablet Or Capsule Administration Under Fasted Conditions			
Parameters	Treatment A (R, n=36)	Treatment B (T, n=36)	Geomean ratio (T/R, 90% CI)
C_{max} (ng/mL)	56.7±10.1	56.9 ±14.7	99.2 (93.1, 102.4)
T_{max} (hr)	4.3±0.81	4.4±1.2	-
AUC_{0-4h} (hr*ng/mL)	119±35.1	135±33.2	114.5 (107.9, 121.5)
$AUC_{4h-last}$(hr*ng/mL)	967±251	944±240	98.0 (93.9, 102.3)
AUC_{0-5h} (hr*ng/mL)	173±42.6	188±42.2	108.9 (104.2, 113.8)
$AUC_{5h-last}$(hr*ng/mL)	913±246	891±232	98.1 (93.7, 102.6)
AUC_{last} (hr*ng/mL)	1086±261	1079±260	99.5 (95.7, 103.4)
AUC_{inf} (hr*ng/mL)	1161±272	1168±270	100.8 (97.4, 104.4)
$T_{1/2}$ (hr)	12.3±2.4	12.7±2.3	-
Treatment A: SPD489 60 mg capsule, Fasting –Reference (R); Treatment B: SPD489 60 mg chewable tablet, Fasting-Test (T)-Source: -Table 10-13 of CSR			

Figure 1: Mean Plasma Concentration vs. Time Profiles: LDX (left); d-AMP (right)



Treatment A: SPD489 60 mg capsule - Fasting
Treatment B: SPD489 60 mg chewable tablet - Fasting
-Source: Figure 2 and Figure 5 of CSR

Variability Results:

Table 5: Inter- and Intra-Subject Variability (Estimate (95% CI)) for d-AMP PK Parameters (-Source: Table 14 of CSR)				
Parameters	Inter-Subject		Intra-Subject	
	Capsule	Tablet	Capsule	Tablet
$LogAUC_{inf}$	0.24 (0.17,0.37)	0.25(0.18,0.37)	0.10 (0.08,0.15)	0.07(0.05,0.11)
$LogC_{max}$	0.17 (0.12,0.25)	0.21(0.15,0.32)	0.05(0.04, 0.07)	0.08(0.07,0.11)

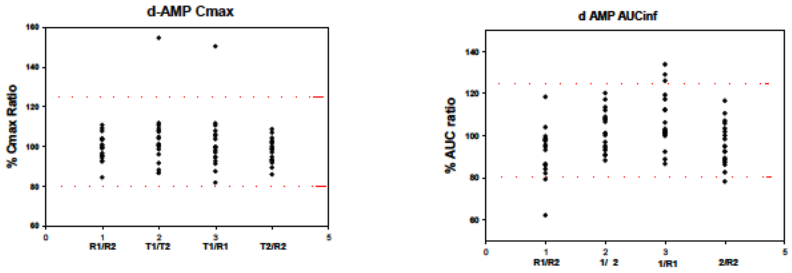
Table 6: Subject-by-Treatment Interaction Variability Analysis for d-AMP	
Parameters	Estimate (95% CI)
C_{max}	0.042 (0.014, 0.073)
AUC_{inf}	0.004 (0.002, 0.086)
AUC_{last}	0.008 (0.001, 0.083)

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Sponsor's Summary & Conclusions:**
  - ✓ Differences in the pharmacokinetic profiles of LDX were seen among the 2 treatments. Partial AUC analysis indicated that compared to capsule formulation, more LDX is absorbed in the first hour after dosing, and less in the systemic circulation at the later phase when Vyvanse was administered as chewable tablet. Overall, exposure (C_{max} and AUC_{last}) to LDX is ~ 15% less following 60mg Vyvanse chewable tablet administration compared to 60mg Vyvanse capsule administration. However, the observed difference is not considered clinically relevant, as LDX is an inactive prodrug.
  - ✓ The PK profiles of *d*-AMP almost overlaid to each other after a single dose administration of 60 mg Vyvanse capsule or chewable tablet. Both conventional BE metrics (i.e., C_{max} and AUC_{inf}) and partial AUC analysis passed the BE criteria, and only minimal difference was observed in C_{max} and AUC_{inf} (<1%) between the two formulations. Vyvanse capsule and chewable tablet are considered BE for d-AMP.
  - ✓ Intra-subject and inter-subject for d-AMP $AUC_{0-\infty}$ and C_{max} were low after Vyvanse administration (either formulation): <25% for inter-subject variability, and ≤10% for intra-subject variability. Subject-by-treatment variability is also small: 4.2% for C_{max} and 0.4% for AUC_{inf}. The low Subject-by-treatment variability suggests that for individuals switching between capsule and chewable tablet, few will experience large differences in responses to Vyvanse.
- **Reviewer's Comments:**

1) Study Design: The study design is consistent with the bioequivalence/bioavailability guidance. Hence, it is acceptable. Specifically, the design elements are discussed in details below.
    - Dose: relative BA/BE is compared at the highest strength of 60mg for chewable tablet against the 60mg capsule. Per the orange book, the 70mg Vyvanse capsule is listed as the RLD. Considering the unavailability of the new formulation at 70mg strength (according to the sponsor, 70 mg is not developed for the chewable tablet formulation (b) (4)), and the dose proportionality shown for Vyvaynse capsule in the therapeutic dose range, the comparison at 60mg is considered acceptable.
    - Study design: the study deployed a replicate study design, which is not the standard two-formulation, two-period, two-sequence crossover design. Per guidance on "statistical approaches to establishing bioequivalence", the replicate design allows comparisons of not only population averages but also variances of a BE measure, which assesses within-subject variability for the T and R products, as well as the subject-by-formulation interaction. We acknowledge the sponsor's effort.
    - Washout period: the washout period between treatments is 7 days. It is considered adequate to avoid any potential carryover effect, considering the half- life of LDX and d-AMP is about 1hr and 12 hr, respectively.
    - Subjects: healthy subjects were enrolled in the study, and prior or concomitant medication use was not reported. This avoided potential confounding effects from extrinsic or intrinsic factors that might affect the PK of LDX and d-AMP.
    - PK Sampling Schedule: blood samples were collected 96 hours post dose and the sampling frequency was considered reasonable. It is adequate to capture the PK profiles of LDX and d-AMP, and for accurate PK parameter estimation, considering the half- life of LDX and d-AMP is about 1hr and 12 hr, respectively.
2) Study conduct (Protocol deviation): Per the protocol, subjects were to refrain from drinking water until 2 hours post dose. Subject 1001 had drink of water 2 minutes prior to the 2 hour post dose restriction. This is considered to bear minimal effect on the study results.
3) Data analysis (Treatment compliance): All the subjects enrolled completed the study and no subjects were excluded from the analysis. This ensured unbiased analysis of the study results.
4) PK results:
    - For LDX, differences in the pharmacokinetic profiles were seen between the 2 treatments; about 15% lower mean exposure (C_{max} and AUC) was observed after 60mg Vyvanse chewable tablet administration as compared to 60mg Vyvanse capsule administration. However, these differences are not considered clinically relevant. For efficacy, LDX is a pharmacologically inactive prodrug. It is not considered to contribute to efficacy after Vyvanse administration. In addition, the decreased exposure of LDX after chewable tablet administration is not considered to lead to additional safety concern.
    - For d-AMP, the major moiety related to the effectiveness and safety, the mean PK profiles almost completely superimposable to each other and average PK parameters (C_{max} and AUC) meet bioequivalence criteria, suggesting similar average pharmacological effects after administration of both capsule and chewable tablet formulations.

- Variability: Inter-subject, intra-subject, , and subject-by-treatment variability for d-AMP (Table 5, Table 6, Figure 2) $AUC_{0-\infty}$ and C_{max} were low and similar after the administration of the capsule or the chewable tablet. The low and similar Subject-by-treatment variability (as compared to the intra-subject variability for the capsule alone) suggests that for individuals switching between capsule and chewable tablet, it is unlikely that patients will experience large differences in clinical responses.

Figure 2: Distribution of d-AMP PK Parameter Ratios Between Treatments



- **Overall Comments:** Though LDX, a pharmacologically inactive prodrug, is not found to be bioequivalent after Vyvanse capsule and chewable tablet administration, the pharmacologically active moiety, d-AMP, however, is bioequivalent. An adequate link between Vyvanse capsule and chewable tablet has been established through the bioequivalence study.

3.2 Food Effect

Report # SHP489-127 **Study Period:** 4/10/2015-5/19/2015
Title: A Phase 1, Randomized, Open-label, 2-Sequence, 3-Period Crossover Study in Healthy Adult Subjects to Compare the Relative Bioavailability of SPD489 60 mg Chewable Tablet Formulation in a Fasting and Fed State

- **Objective:** 1) to compare the pharmacokinetics of a single dose of SPD489 60 mg as a chewable tablet in both a fasting and fed state as assessed by estimate of relative bioavailability; 2) To assess the safety and tolerability of SPD489 60 mg in chewable tablet formulation in healthy adults.
- **Study Design:** This was a Phase 1, randomized, open-label, 2-sequence, 3-period replicated crossover study that consisted of a screening period and 3 treatment periods; each 6-day treatment period was separated by a 7-day washout between doses.
  Eligible subjects were admitted to the clinical research center (CRC) on Day -1 of the first treatment period and were randomized (1:1) the following day (Day 1) to either treatment sequence ABA(n=12) or treatment sequence BAB (n=12), where:
  Treatment A: SPD489 (60 mg in a chewable tablet) was administered orally in a fasting state. Subjects were fasted overnight for at least 10 hours prior to and for at least 4 hours after administration of investigational product. Subjects were then given the SPD489 tablet, followed by 240 mL of water. The tablet was to be thoroughly chewed before swallowing. Subjects subsequently continued to fast for 4 hours and continued to refrain from fluids for 2 hours.
- Treatment B: SPD489 (60 mg in a chewable tablet) was administered orally in a fed state. Subjects were given a high-fat breakfast 30 minutes prior to administration of investigational

product. Subjects were then given the SPD489 tablet, followed by 240 mL of water. The tablet was to be thoroughly chewed before swallowing. Subjects subsequently continued to fast for 4 hours and continued to refrain from fluids for 2 hours.

- **Blood Sampling Schedule (PK):** Predose, 0.5, 1, 1.5, 2, 4, 5, 6, 8, 12, 24, 36, 48, 72, and 96 hours post dose at each dosing period.
- **Analytical Method:**

Analyte	**lisdexamfetamine**	***d*-amphetamine**
Method	LC-MS/MS	LC-MS/MS
Matrix	plasma	plasma
Linear range (ng/mL)	1-100	2-200
Performance	acceptable	acceptable

- **Results:**

Formulations

Table 1. Products used in Study 127			
SPD489 60 mg	**Manufacturer**	**Formulation**	**Batch #**
capsules	Shire	Immediate-Release	3128367
chewable tablet	Shire	Immediate-Release	P140030-0001L

Study Population

Table 2: Demographic Properties of Study Subjects (# subjects)	
Treated/Completed/Withdrawn Due To AE/Other Reasons	24/23/0/1
Age (mean±SD)	42±9.5
Male/Female	14/10
BMI (mean±SD)	28.0±2.2
Race (Caucasian/Black/Asian/Hispanic)	17/7/0/0

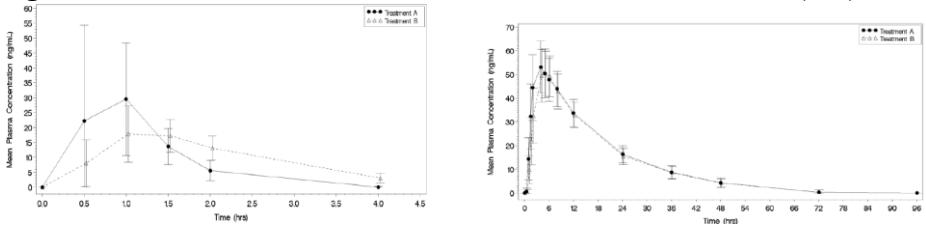
Pharmacokinetics

Table 3: LDX PK Parameters (Mean ± SD) After Vyvanse Chewable Tablet Administration Under Fasted or Fed Conditions			
Parameters	Treatment A (R, n=35)	Treatment B (T, n=35)	Geomean ratio (T/R, 90% CI)
C_{max} (ng/mL)	32.3±30.2	20.7 ±8.4	74.3 (63.6, 86.7)
T_{max} (hr)	0.97±0.17	1.36±0.36	-
$AUC_{0\text{-}1h}$ (hr*ng/mL)	18.5±20.3	8.5±6.0	49.2 (40.2, 60.2)
$AUC_{1h\text{-}last}$(hr*ng/mL)	15.5±9.7	31.4±7.6	229.7 (206, 256)
$AUC_{0\text{-}2h}$ (hr*ng/mL)	33.2±27.0	24.8±10.3	83.9 (73.4, 96.0)
$AUC_{2h\text{-}last}$(hr*ng/mL)	0.72±2.96	15.1±4.9	-
AUC_{last} (hr*ng/mL)	33.9±29.3	39.9±11.1	137.4 (121.7, 155.3)
Treatment A: Fasting –Reference (R); Treatment B: Fed-Test (T) -Source: Table 6-9 of CSR			

Table 4: PK Parameters of d-AMP (Mean ± SD) After Vyvanse Chewable Tablet Administration Under Fasted or Fed Conditions			
Parameters	Treatment A (n=35)	Treatment B (n=35)	Geomean ratio (T/R, 90% CI)

C_{max} (ng/mL)	54.9±11.7	52.5 ±10.3	95.2 (88.8, 102.2)
T_{max} (hr)	3.9±1.0	4.9±0.8	-
AUC_{0-4h} (hr*ng/mL)	132±36.3	106±32.0	79.4 (73.2, 86.0)
$AUC_{4h-last}$(hr*ng/mL)	871±173	848±165	94.9 (88.6, 101.6)
AUC_{0-5h} (hr*ng/mL)	184±45.1	157±41.0	84.1 (78.3, 90.3)
$AUC_{5h-last}$(hr*ng/mL)	820±166	798±159	94.8 (88.5, 101.6)
AUC_{last} (hr*ng/mL)	1003±191	954±182	92.9 (87.0, 99.2)
AUC_{inf} (hr*ng/mL)	1073±201	1025±199	93.0 (86.8, 99.6)
$T_{1/2}$ (hr)	12.3±2.1	12.5±2.9	-
Treatment A: Fasting –Reference (R); Treatment B: Fed-Test (T);-Source: Table 10-13 of CSR			

Figure 1: Mean Plasma Concentration vs. Time Profiles: LDX(left); d-AMP (right)



Treatment A: fasting; Treatment B: fed

-source: Figure 2 and Figure 5 of Study Report

Variability Results:

Table 5: Intra- and Inter-Subject Variability (Estimate (95% CI)) for PK Parameters for d-AMP in SD Scale(*-Source: Table 14 of CSR*)

Parameters	Inter-Subject		Intra-Subject	
	Fasting	Fed	Fasting	Fed
$LogC_{max}$	0.20(0.14, 0.29)	0.21(0.16, 0.30)	0.09(0.07, 0.14)	0.06(0.04, 0.11)
$LogAUC_{inf}$	0.16(0.12, 0.25)	0.19(0.14, 0.31)	0.11(0.08, 0.17)	0.10(0.07, 0.21)

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- **Sponsor's Summary & Conclusion:**
  - ✓ Food decreased the rate of absorption of the prodrug LDX, delaying the time to C_{max} by about 0.4hr (from ~1hr to ~1.4 hr), and increased the extent of absorption of LDX by about 37% after oral administration of Vyvanse chewable tablet when compared to a fasting condition. However, the observed differences in pharmacokinetic parameters are not relevant as LDX is the pharmacologically inactive prodrug of d-AMP.
  - ✓ Food delayed T_{max} of d-AMP by approximate one hour, from 3.9hr when administered under fasted conditions to 4.9 hr when administered under fed conditions. Partial AUC analysis (ie., AUC_{0-4}, AUC_{0-5}) also indicated that food delayed the systemic availability of d-AMP. However, food had no clinically significant effect on the extent of availability of d-AMP (C_{max} and AUC_{inf} were decreased by 5-7%, with 90% CI fell within 80-125% range). Vyvanse chewable tablet can be taken regardless of food.
- **Reviewers Comments:**
  1) Study Design: The study design is consistent with the food effect guidance. Hence, it is acceptable. Specifically, the design elements are discussed in details below.
     a. Dose: the dose studied for food effect is the highest available strength (60mg) for chewable tablet, which met Guidance recommendation.

b. Food: high fat, high calorie breakfast provided in the study met Guidance recommendation.
c. Water: the Guidance recommends "Water can be allowed as desired except for one hour before and after drug administration". Per study report, subjects were refrained from water for 2 hours after drug administration, but it is not clear if water was also restrained 1 hour before. A significant effect on the PK of d-AMP is not expected by the reviewer even if there water was allowed one hour before.
d. Washout period: the washout period between treatments is 7 days. It is considered adequate to avoid any potential carryover effect, considering the half- lives of LDX and d-AMP is about 1hr and 12 hr, respectively.
e. Study design: The study deployed a replicated design. This design allows us to assess the variability of food effect on Vyvanse and the chewable tablet.
a. Subjects: healthy subjects were enrolled in the study. This avoided potential confounding effects from intrinsic factors that might affect the PK of LDX and d-AMP. None of the studied subjects reported prior or concomitant medication use, except that one subject reported the ongoing use (since 2012) of medroxyprogesterone acetate for contraception. Medroxyprogesterone acetate is not considered to affect the PK of LDX or d-AMP, so data from the subject was included in the analysis.
b. PK Sampling Schedule: blood samples were collected 96 hours post dose and the sampling frequency was considered reasonable. It is adequate to capture the PK profiles of LDX and d-AMP, and for accurate PK parameter estimation, considering the half- life of LDX and d-AMP is about 1hr and 12 hr, respectively.

2) Study Conduct (Protocol deviation): Per the sponsor, no protocol deviations were reported for this study.
3) Data Analysis (Treatment compliance and Outliers): 24 subjects were enrolled in the study, and 23 of them had completed the study. The one subject (subject ID: 001-1018) received one dose of chewable tablet, and then "lost to follow-up" afterwards. The subject was then not included in the data analysis. Data from the rest of the test subjects are all included in data analysis. Nobody has been considered as outliers and excluded from the analysis.
4) PK results: No clinically meaningful food effect is identified for the chewable tablet. Vyvanse chewable tablet can be administered without regard to food.
   a. For LDX, food decreased LDX mean C_{max} about 25%, and increased mean AUC_{last} about 37%. AUC_{last} was defined as area under the curve from the time of dosing to the last measurable concentration. Considering the very short half-life of LDX (< 1hr), no significant difference in the values of AUC_{last} and AUC_{inf} is expected. It is acceptable to report AUC_{last} instead of AUC_{inf}.
   For efficacy, LDX is not considered as a pharmacologically active moiety. The changes in C_{max} and AUC after the chewable tablet is given with food are not considered to contribute meaningfully to the efficacy. Because food decreased the C_{max} of LDX for the chewable tablet, so the C_{max} related safety profile should not be worsened when the chewable tablet is given with food. It is noted that the mean AUC of LDX increased about 37%. The safety profiles up to 70mg of Vyvanse capsule have been evaluated in clinical trials and are considered acceptable. The highest recommended dose of Vyvanse capsule (70mg) is about

17% higher than the tested dose 60mg in the study. The extra 20% higher exposure (AUC) is not very likely to cause a significant safety concern. Therefore, the ~37% increase in LDX AUC of after food administration is not considered clinically significant.

b. For *d*-AMP, the active moiety after Vyvanse administration, food decreased 5-7% in C_{max} and AUC_{inf}, with no apparent change in variability (Table 5). Both parameters passed BE criteria.

c. Some partial AUCs for both LDX and d-amphetamine are investigated as part of the exploratory analysis. Partial AUC analysis (AUC_{0-5}) for d-AMP missed lower BE limit by 1.2%. These changes are not considered clinically significant.

- **Overall Comments:** Food is not considered to have a clinically significant effect. Vyvanse chewable tablet can be administered with or without food.

4. OFFICE OF STUDY INTEGRITY AND SURVEILLANCE MEMO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 7/1/2016

TO: Division of Psychiatry Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208510

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Clinical Pharmacology of Miami, Inc.	550 West 84th Street, Miami, FL

Reference ID: 3954142

Office of Study Integrity and Surveillance

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208510

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

Although the last inspection was classified as a VAI, baased on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

Reference ID: 3954142

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/S/

SHILA S NKAH
07/01/2016

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/s/

HUIXIA ZHANG
12/07/2016

HAO ZHU
12/07/2016

MEHUL U MEHTA
12/07/2016