NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA Efficacy Supplements
Application Number(s)	021977 / S-046 208510 / S-003
Priority or Standard	Priority
Submit Date(s)	NDA 021977 – 1/29/21 NDA 208510 – 5/28/21
Received Date(s)	NDA 021977 – 1/29/21 NDA 208510 – 5/28/21
PDUFA Goal Date	NDA 021977 – 7/29/21 NDA 208510 – 11/28/21
Division/Office	Division of Psychiatry / Office of Neuroscience
Review Completion Date	7/29/21
Established/Proper Name	Lisdexamfetamine dimesylate
Trade Name	Vyvanse
Pharmacologic Class	Stimulant
Code name	SPD489 or TAK-489
Applicant	Takeda Pharmaceuticals U.S.A., Inc.
Dosage form	Capsules 10, 20, 30, 40, 50, 60, and 70 mg Chewable tablets 10, 20, 30, 40, 50, and 60 mg
Applicant proposed Dosing Regimen	Not applicable because the Applicant did not propose specific dosing for (b) (4)
Applicant Proposed Indication(s)/Population(s)	Treatment of ADHD in (b) (4) children (ages (b) (4) years)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Stimulant drug therapy for attention deficit hyperactivity disorder
Recommendation on Regulatory Action	Approval with Limitation of Use
Recommended Indication(s)/Population(s)	LOU for patients ages (b) (4) years with ADHD
Recommended SNOMED CT Indication Disease Term for each Indication	N/A
Recommended Dosing Regimen	N/A

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

See respective disciplinary memos in DARRTS.

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Glossary

ADHD	Attention Deficit Hyperactivity Disorder
ADHD-RS-IV	ADHD Rating Scale, Preschool Version
ADaM	Analysis Data Model
AE	adverse event
BED	binge eating disorder
BMI	body mass index (kg/m^2)
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression- Improvement
CNS	central nervous system
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DPMH	Division of Pediatrics and Maternal Health
ECG	electrocardiogram
eCTD	electronic common technical document
ET	early termination
FAS	full analysis set
IND	Investigational New Drug
ITT	intent to treat
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
OCP	Office of Clinical Pharmacology
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PEB	Pediatric Exclusivity Board
PeRC	Pediatric Review Committee
PK	pharmacokinetic
PMR	postmarketing requirement
PPSR	proposed pediatric study request
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PWR	Pediatric Written Request
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SAS	safety analysis set
SEM	standard error of the mean

SDTM	Study Data Tabulation Model
TEAE	treatment emergent adverse event

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1 Executive Summary

1.1. Product Introduction

Vyvanse (lisdexamfetamine dimesylate) is a CNS stimulant approved on February 23, 2007, for the treatment of attention-deficit/hyperactivity disorder (ADHD) in patients aged 6 to 12 years-old. Further ADHD indications were approved on:

- April 23, 2008 - treatment of the adult population
- October 10, 2010 - treatment of adolescents aged 13 to 17-years-old
- January 31 2012 - maintenance treatment in adults
- April 26, 2013 - maintenance treatment in pediatric patients 6 to 17-years-old
- January 28, 2017 - chewable tablet approved under NDA 208510.

The Division issued a Pediatric Written Request (PWR) on June 3, 2014, to the Applicant requesting pharmacokinetic (PK) data, at least one adequate and well-controlled clinical trial with the goal of establishing safety and effectiveness of monotherapy, and long-term safety data, all in pediatric patients ages 4 to 5 years. Subsequently, at the time of approval of lisdexamfetamine chewable tablets, the Division required issued the same postmarketing requirements (PMRs) in the preschool ADHD population for that NDA as well.

The Applicant conducted three trials under IND 067482 using lisdexamfetamine 5, 10, 20, and 30-mg capsules or placebo in response to the PWR and the PMRs. Takeda submitted the same three study reports in the NDA 021977 (S-046) efficacy supplement on January 29, 2021, and in the NDA 208510 (S-003) efficacy supplement on May 28, 2021. The Applicant is seeking pediatric exclusivity and fulfillment of the two PREA PMRs, 3149-2 and 3149-3. The Division had previously determined that PMR 3149-1 for a preschool-age PK study was fulfilled and issued a letter to that effect on October 5, 2020. The aforementioned submitted studies are:

1. SPD489-211: PK Study in Patients 4 to 5 Years of Age with ADHD

2. TAK-489 (SPD489)-347: Phase 3, Randomized, Double-Blind, Multicenter, Parallel-Group, Placebo-Controlled, Fixed-Dose 6-Week Safety and Efficacy Study of Lisdexamfetamine Compared with Placebo in Preschool Children Aged 4 to 5 Years with ADHD

3. TAK-489 (SPD489)-348: Phase 3, Open-label, Multicenter, 12-Month Safety and Tolerability Study of Lisdexamfetamine in Preschool Children Aged 4 to 5 Years with ADHD.

On June 16, 2021, the FDA's Pediatric Exclusivity Board (PEB) agreed to grant exclusivity to Takeda for successfully conducting these trials. On June 22, 2021, the Pediatric Review

Committee (PeRC) and the Division concluded that Studies 2 and 3, above, also fulfilled the PMRs for NDA 208510 lisdexamfetamine chewable tablets, because the capsules and chewables are bioequivalent.

The Applicant's code names for lisdexamfetamine during development have been SPD489 (under Shire) or TAK-489 (under Takeda's sponsorship).

Lisdexamfetamine also is indicated to treat moderate to severe binge eating disorder (BED) and for maintenance therapy of BED; these indications were approved on January 30, 2015 and October, 14, 2016, respectively. These indications are not subject to the PWR.

The safety profile of lisdexamfetamine in 4- to 5-year-olds was reasonably acceptable for 6 weeks of treatment. However, ADHD is a chronic disease, and stimulant treatment may last for years in pediatric patients. The long-term 1-year safety study TAK-489 (SPD489)-348 (hereafter Study 348) showed patients experienced a mean decrease in body mass index (BMI), and 70% of patients had a loss of at least 10 percentiles on the CDC Growth Chart for all doses of lisdexamfetamine by the end of the study and 12% ended at the ≤3rd percentile. The Division of Pediatric and Maternal Health (DPMH) was consulted about the interpretation of open-label data on growth and has concluded, along with the Division, that the severity and frequency of the long-term decrease in weight in patients ages 4 to 5 years is an unacceptable risk for the use of lisdexamfetamine in this population.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Vyvanse (lisdexamfetamine dimesylate) is a central-nervous-system (CNS) stimulant-class drug originally FDA-approved on February 23, 2007 for the treatment of attention-deficit/hyperactivity disorder (ADHD) in patients ages 6 to 12 years-old, with subsequent supplements approved for the treatment of adolescents and adults with ADHD, maintenance treatment of ADHD, and binge-eating disorder in adults. As part of a Pediatric Written Request (PWR) issued for Vyvanse capsules on June 3, 2014, we requested that the Applicant conduct pharmacokinetic (PK), efficacy, and safety studies in the preschool age population (ages 4 to 5) with ADHD; when Vyvanse chewable tablets were subsequently approved, we issued PMR 3149-1, -2, and -3 for studies matching those requested in the earlier PWR. The Applicant conducted a PK study (Study 211), a 6-week placebo-controlled fixed-dose efficacy and safety study (Study 347), and a long-term 1-year open-label safety study (Study 348) in this population. The latter two studies were submitted for the current sNDA application. (Our OCP team previously reviewed Study 211; the study fulfilled PMR 3149-1 as of October 5, 2020.)

(b) (4)

For assessing risks (safety), the review team examined both Study 347 and Study 348 (the 1-year open-label study). The rates of adverse events (AEs) in Study 347 were generally comparable to rates observed in the approved pediatric population for this and other similar stimulant-class drugs, with the most common AEs greater than 5% (all doses combined) being decreased appetite, irritability, upper respiratory infections/ nasopharyngitis, and insomnia. There was some evidence of dose-response in terms of AE rates, particularly for the 30-mg dose with rates of decreased appetite at 21%, irritability at 11%, and insomnia at 13% (nearly all higher rates than the other dose arms). However, again, these AE rates were still generally comparable to those seen in children on other approved stimulant drugs. Of greater concern were results from the longer-term Study 348 related to weight loss and decreases in BMI. Mean values decreased for both, and the subject-level outliers in particular sometimes showed marked weight loss and decrease in BMI to the lowest percentiles (<5th) on CDC growth charts by the end of the study, and at overall rates of the study population much higher than observed in other stimulant-class drugs in approved age ranges. Of note, no other

stimulants have an indication based on clinical data for children with ADHD younger than 6 years of age. Immediate-release Adderall and 505(b)(2) products referencing Adderall are indicated for patients as young as 3 years of age, but that indication was based on extrapolation—an approach the Agency no longer accepts for this population and class of drugs. Two approved products—methylphenidate hydrochloride extended-release (Aptensio XR) and mixed salts of a single-entity amphetamine product extended-release capsules (Mydayis)—have Limitations of Use for pediatric patients ages 6 years or 12 years and younger, respectively. Overall, 12% of patients who completed Study 348 were at the ≤3rd percentile at study end, and 70% had a loss of at least 10 percentiles on the CDC Growth Chart for all doses of lisdexamfetamine. compared to 3% and 51% respectively with Aptensio XR; therefore, a Limitation of Use for this product is consistent with the precedent set by that label. Given the vulnerability of this very young and physically small population to potential failure-to-thrive, long-term growth suppression, malnutrition, and more, these findings render the risks of Vyvanse use unacceptable for preschool-aged children.

The Pediatric Review Committee (PeRC) and Pediatric Exclusivity Board (PEB) agreed that the PMRs for NDA 208510 (chewable tablets) and the PWR for NDA 021977 (oral capsules) and are now successfully fulfilled by the completion of Studies 211, 347, and 348, and pediatric exclusivity is now granted for an extra 6 months.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Attention Deficit/Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder of childhood, with a lifetime prevalence in the pediatric population of about 11%. • It typically presents in early school years and is characterized by difficulty paying attention, hyperactivity, and impulsive behavior. • These symptoms can cause significant impairment in academic and social functioning during critical years of development if left untreated.	ADHD is a prevalent condition in children and adolescents. In many cases, symptoms can continue into adulthood. ADHD symptoms can substantially compromise academic and work performance and can impair social development and relationships without treatment.
Current Treatment Options	• Behavioral therapies are considered first-line treatments for patients ages 4 to < 6 years with ADHD. • There are several products that have demonstrated safety and effectiveness in the treatment of ADHD, but there is little controlled data on stimulant treatment in patients 4 to < 6 years old. • Immediate-release Adderall and 505(b)(2) products referencing Adderall are	Due to ongoing common off-label use and the relative lack of approved treatment options for the preschool-aged population, these studies were requested via PWR for Vyvanse capsules and later required under PREA as PMRs for Vyvanse chewable tablets.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	indicated for patients as young as 3 years of age, but that indication was based on extrapolation—an approach the Agency no longer accepts for this population and class of drugs. • Stimulant products vary by time to therapeutic onset, duration of action, or both; these differences are tightly linked to differences in their PK profiles. Some products require more than one dose per day because of a short duration of action. • Non-stimulant products approved for ADHD contain atomoxetine, clonidine, or guanfacine.	
Benefit	(b) (4)	
Risk and Risk Management	• AEs of insomnia, irritability, upper respiratory infections/nasopharyngitis, and decreased appetite were reported the most (greater than 5%) in all the lisdexamfetamine treatment groups but particularly the 30-mg treatment group. The AE rates were generally comparable to those seen in other approved stimulants for children. • (b) (4)	Patients reported expected AEs with lisdexamfetamine, at rates comparable to other approved stimulants in children for short-term studies. However, there are long-term safety risks of severe

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	based on short-term AE rates. However, results from the 1-year safety extension trial indicated that major weight and BMI decreases to the lowest percentiles (i.e., less than 5th) were also observed at higher than expected rates in patients taking 10-, 15-, 20-, and 30- mg. • Among patients in the long-term study, 12% of patients lost enough weight to shift into the underweight category (<5th percentile), and 70% experienced weight loss sufficient to drop at least 10 percentiles on the CDC growth chart.	loss of weight and the potential for growth suppression at a vulnerable age while taking lisdexamfetamine over time. A Limitation of Use for this population is consistent with the precedent set in the review and labeling of Aptensio XR.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	8.1.1 describes primary efficacy endpoint of ADHD-RS-IV Preschool Version
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

ADHD is a childhood-onset disease with core symptoms of inattentiveness and hyperactivity. The diagnosis is defined in the Diagnostic and Statistical Manual 5th edition (DSM-5) by the occurrence of six of nine symptoms of inattention and/or six of nine symptoms of hyperactivity and impulsivity. Treatment of ADHD may consist of pharmacotherapy (with stimulant medications typically being first-line), behavioral therapy, or their combination. Regardless of the approach used, treatment is recommended for all children, because early and effective treatment of ADHD has been reported to yield a better prognosis and fewer problems in adulthood (Sharma A, 2014). ADHD symptoms often manifest several years prior to entry into elementary school. The estimated prevalence of ADHD in the preschool population (ages 3 to 5 years) is 3 to 5%, which is similar to the prevalence of ADHD throughout childhood and adolescence (3 to 5%). If left untreated, symptoms of ADHD may lead to emotional dysregulation, impaired social development, and academic underachievement. Substance misuse is more common in those with ADHD than in the general population. The estimated prevalence of adult ADHD is 4.4% (Kessler & Adler L, 2006). Among patients with a substance-use disorder, 23% have comorbid ADHD. (Emmerik-van Oortmerssen K, 2012)

2.1. Analysis of Current Treatment Options

Psychostimulants, or central nervous system (CNS) stimulants, have been the mainstay of pharmacologic therapy for ADHD for over half of a century. Most approved stimulants are formulations of methylphenidate or amphetamine. Immediate-release (IR) formulations are typically dosed two to three times a day. Starting in the 1990's, manufacturers created extended-release (ER) formulations taken once daily to increase the duration of clinical effect to address ADHD symptoms during the school day as well as during evening activities. Some ER formulations have a duration of action up to 16 hours.

In the United States, ADHD-indicated stimulants (i.e., amphetamine and methylphenidate) are classified as Schedule II controlled substances, defined as drugs having a currently accepted medical use in the United States, but with a high potential for abuse, and with use potentially leading to severe psychological or physical dependence.

Non-stimulants, such as guanfacine or atomoxetine, are also approved for the treatment of ADHD. The currently marketed pharmacologic treatments for ADHD are listed in Table 1. Pharmacologic treatment of ADHD may include off-label usage of antidepressants, stimulants approved for treatment narcolepsy, and NMDA receptor antagonists, listed under Table 1.

Table 1: FDA-Approved Pharmacotherapy for Treatment of ADHD

Class	Active Moiety	Dosage Form	Strength
Stimulant	Methamphetamine	Tablet	5, 10 mg
		Tablet, extended release	5, 10 mg
	Methylphenidate	Tablet	2.5, 5, 10 mg
		Tablet, chewable	2.5, 5, 10 mg
		Tablet, extended release	10, 18, 20, 27, 36, 54 mg
		Tablet, extended release, chewable	20, 30, 40 mg
		Capsule, extended release	5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 85, 100 mg
		Transdermal	10, 15, 20, 30 mg/9hrs
		Suspension, extended release	5 mg/mL
		Solution	5, 10 mg/mL
	Dexmethylphenidate	Tablet	2.5, 5, 10 mg
		Capsule, extended release	5, 10, 15, 20, 25, 30, 35, 40 mg
	Amphetamine	Suspension, extended release	2.5 mg/mL
		Tablet	5, 10 mg
		Tablet, extended release, orally disintegrating	EQ 3.1, 6.3, 9.4, 12.5, 15.7, 18.8 mg base
	Dextroamphetamine	Tablet	2.5, 5, 7.5, 10, 15, 20, 30 mg
		Capsule, extended release	5, 10, 15 mg
		Solution	5 mg/mL
	Mixed Amphetamine Salts	Capsule, extended release	Total active ingredients: 5, 10, 12.5, 15, 25, 37.5, 50 mg
		Tablet	Total active ingredients: 5, 7.5, 10, 12.5, 15, 20, 30 mg
	Lisdexamfetamine	Tablet, chewable	10, 20, 30, 40, 50, 60 mg
		Capsule	10, 20, 30, 40, 50, 60, 70 mg
Non-stimulant	Atomoxetine	Capsule	10, 18, 25, 40, 60, 80, 100 mg
	Clonidine	Tablet	0.1, 0.2, 0.3 mg
		Tablet, extended release	0.1 mg
		Transdermal	0.1, 0.2, 0.3 mg/24 hrs
	Guanfacine	Tablet	EQ 1, 2, 3 mg base
		Tablet, extended release	EQ 1, 2, 3, 4 mg base

(Source: Reviewer created)

Drugs used off-label for treatment of ADHD:

- Antidepressants: bupropion, desipramine
- Narcolepsy drugs: modafinil, armodafinil
- Alzheimer's disease drug: memantine.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lisdexamfetamine is approved and marketed in the United States. The stimulant was developed under IND 067482.

Under NDA 021977, the capsule formulation was initially FDA-approved on February 23, 2007 for the treatment of ADHD in children 6 to 12 years of age with the following subsequent additional indications approved:

- Efficacy Supplement 1 – provides for the indication of ADHD to cover adults (new age group)
    - Approved April 23, 2008
- Efficacy Supplement 16 – provides for the indication of ADHD to cover adolescents aged 13 to 17 years (new age group)
    - Approved November 10, 2010
- Efficacy Supplement 22 – provides for the maintenance treatment of ADHD in adults
    - Approved January 31, 2012
- Efficacy Supplement 27 – provides for the maintenance treatment of ADHD in children and adolescents ages 6 to 17 years
    - Approved April 26, 2013
- Efficacy Supplement 37 – provides for data supporting the safety and effectiveness of lisdexamfetamine for the treatment of moderate to severe binge eating disorder
    - Approved January 30, 2015
- Efficacy Supplement 41 – provides for data supporting the safety and effectiveness for the maintenance treatment of moderate to severe binge eating disorder
    - Approved October 14, 2016.

Under NDA 208510, the Division approved lisdexamfetamine dimesylate chewable tablets on January 28, 2017, for the treatment of ADHD and the treatment of binge eating disorder.

3.2. Summary of Presubmission/Submission Regulatory Activity

The development of lisdexamfetamine occurred under IND 067482, originally owned by Shire. On July 1, 2020, the corporate name and sponsor designation for NDA 021977 (SDN 2548) and NDA 208510 (SDN 337) was changed to Takeda Pharmaceuticals.

Shire submitted their first proposed pediatric study request (PPSR) on February 20, 2013. The Agency issued an Inadequate Study Request Letter on May 8, 2013. Shire submitted a completed and accepted PPSR on October 11, 2013. The Agency issued a PWR on June 3, 2014, requesting three PMR studies per PREA for PK data, at least one adequate and well-controlled

clinical trial in the preschool population with the goal of establishing safety and effectiveness of monotherapy in 4 to 5-year-old children, and long-term safety data.

With the approval of Vyvanse chewable tablets (NDA 208510, January 28, 2017), the studies requested for Vyvanse capsules were required as PMRs:

1. 3149-1: Deferred pediatric study under PREA in children ages 4 to less than 6 years with a diagnosis of ADHD to obtain pharmacokinetic, safety, and tolerability data to inform dose selection for efficacy and safety studies in pediatric patients with ADHD.

2. 3149-2: A randomized, double-blind, placebo-controlled efficacy study of lisdexamfetamine dimesylate chewable tablets in children ages 4 to less than 6 years diagnosed with ADHD.

3. 3149-3: A 12-month open-label safety study of patients age 4 to less than 6 years (at the time of entry into PMR 3149-1 or PMR 3149-2, or at the time of enrollment if directly enrolled into PMR 3149-3) diagnosed with ADHD treated with lisdexamfetamine dimesylate chewable tablets.

The protocols for the three studies reviewed in this efficacy supplement were submitted for review under IND 067482. Protocol SPD489-211, the PK study, was most recently amended February 12, 2016 (SDN 496). The safety and efficacy trial, protocol SPD489-347, was amended three times, most recently submitted on August 8, 2017 (SDN 517). The long-term safety extension protocol (SPD489-348) was amended once and submitted July 13, 2017 (SDN 515).

The NDA 21977 (S-046) efficacy supplement submitted on January 29, 2021 is in response to the PWR. The Applicant is seeking pediatric exclusivity after completing the three studies.

The NDA 208510 (S-003) efficacy supplement submitted on May 28, 2021, contains the same three clinical studies conducted for the PWR and to fulfill the PREA PMR requirements above. On June 22, 2021, the PeRC agreed with the Division that the Applicant had fulfilled the PMRs for NDA 208510.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division and staff from the Office of Scientific Investigations met on February 19, 2021, to discuss if clinical site investigations were necessary for this efficacy supplemental application. We decided no inspection was necessary for the following reasons:

- No unexpected or serious safety signals exist;
- No data integrity issues exist; and
- Due to the COVID-19 pandemic, the inspection does not rise to the level of mission-critical for OSI.

4.2. Product Quality

There are no concerns with product quality for this application per OPQ/CMC. See their review for more details.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This supplement did not include any nonclinical information or nonclinical studies. This was acceptable, because the nonclinical studies previously conducted with the original NDA still covered the new age group (4 to 5 years) in this supplement. Minor changes were made to the nonclinical labeling language in Sections 8 and 13. Specifically and for the sake of consistency, the safety margins in Sections 8.1 and 13.1 are now calculated based on the body surface area of an adult. The safety margins in Section 8.4, which specifically relates to children, were calculated based on the body surface area of a child. Additionally, the dose comparison to amphetamine (d- to l- enantiomer ratio of 3:1) in Section 8.1 was removed, because it does not directly translate to this product (which is in the form of the d-only enantiomer).

6 Clinical Pharmacology

6.1. Executive Summary

The PK study SPD489-211 has been previously reviewed (DARRTS submission dated 12/07/2016) by OCP under NDA 208510. We agreed that the starting dose of 5 mg is reasonable and recommended a starting dose of 5 mg in the phase 3 Study 347 in children 4 to 5 years old with ADHD. There is no additional or new information related to OCP in this submission, and our assessment has not changed.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The clinical development program consisted of the three studies in Table 2 to establish the PK, safety, tolerability, and efficacy of monotherapy treatment with lisdexamfetamine on the core symptoms of ADHD in 4- and 5-year-old preschool children to fulfill a PWR.

- Study SPD489-211 was a phase 2 open-label PK study that established the starting dose of 5-mg lisdexamfetamine for the phase 3 studies.
- Study 347 was a phase 3, fixed-dose efficacy and safety study testing 10-mg, 20-mg, and 30-mg lisdexamfetamine doses versus placebo in preschool-aged children with ADHD.
- Study 348 was a phase 3, open-label, long-term safety and tolerability study in preschool-aged children with ADHD who were enrolled from an antecedent study (Study SPD489-211 or 347) or directly enrolled.

Table 2: List of Clinical Trials for NDA 021977/ S-046

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Route of Administration; Test Product(s); Dosage Regimen	Number of Patients	Healthy Patients or Diagnosis of Patients	Duration of Trial
PK and safety	SPD489-211	To evaluate the safety, tolerability, and PK of SPD489 in preschool children (4 to 5 years-old)	Phase 2, open-label, single-arm, dose-optimization	5, 10, 15, 20, or 30 mg capsules orally in the morning	24	ADHD	Up to 8 weeks
Efficacy	TAK-489 (SPD489)-347	To evaluate the safety, tolerability, and efficacy of TAK-489 in pediatric patients (4 to 5 years-old)	Phase 3, randomized, double-blind multicenter, parallel-group, placebo-controlled, fixed-dose	5, 10, 20, 30 mg or placebo once daily as a single capsule orally in the morning	199 TAK-489: 5 mg: 40; 10 mg: 37; 20 mg: 37; 30 mg: 39; (Total TAK-489: 153; placebo: 46)	ADHD	6 weeks
Long-term safety	TAK-489 (SPD489)-348	To evaluate the long-term safety and tolerability of TAK-489 in preschool children (4 to 5 years old).	Phase 3, multicenter, long-term, open-label extension of studies	5 mg, 10 mg, 15 mg, 20 mg, and 30 mg administered once daily as a single capsule	enrolled: 115 (Rollover from: SPD489-211: 17;	ADHD	52 weeks

			SPD489-211 and 347 or direct enrollment	orally in the morning	TAK-489 (SPD489)-347 placebo: 20; TAK-489 (SPD489)-347 TAK-489: 49; directly enrolled: 29)		

7.2. Review Strategy

The evaluation of efficacy is derived from the review of Study 347, the fixed-dose, placebo-controlled efficacy study. The safety evaluation also focuses on this efficacy study, as it includes a placebo comparator to lisdexamfetamine. The clinical reviewer has also assessed longer-term appetite and weight changes in 4 to 5-year-old patients over time from the year-long safety extension study (Study 348).

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study TAK-489 (SDP489)-347

Trial Design

Study 347 was a phase 3, randomized, double-blind, multicenter, parallel-group, placebo-controlled, fixed-dose safety and efficacy study of lisdexamfetamine compared with placebo in preschool children aged 4 to 5 years with ADHD. There were 44 clinical investigator sites, all located in the United States.

Study Endpoints

The primary endpoint was the change from baseline in the clinician-administered ADHD-Rating Scale-4th Edition (ADHD-RS-IV) Preschool Version Total Score at Visit 6 (Week 6).

The prespecified key secondary endpoint was the Clinical Global Impression-Improvement (CGI-I) score at Week 6.

Statistical Analysis Plan

The safety analysis set (SAS) consisted of all randomized patients who had taken at least one dose of investigational product. The Full Analysis Set (FAS) was used as the primary set for analysis of efficacy endpoints based on randomized treatment assignment. The FAS included all subjects in the Statistical Analysis System (SAS) who had at least one postdose ADHD-RS-IV Preschool Version Total Score assessment.

The study implemented a group sequential design with one interim analysis. The interim analysis was to be conducted after approximately 60% of planned subjects enrolled, who either completed or discontinued the study. If the study continued beyond the planned interim analysis, or if the interim analysis was waived, then the blinded sample size re-estimation was to be performed when approximately 75% of the 195 subjects had either completed or discontinued the study. The sample size would be recalculated based on whether the estimated pooled SD from all available subjects at sample size reassessment was considerably larger than the assumption (SD=14).

As the recruitment rate was higher than estimated, the planned unblinded interim analysis was waived, and the blind sample size re-estimation was performed. At the interim look documented in the study memo (dated July 24, 2018), 199 subjects had been randomized, and 148 subjects had data at both Baseline and Week 6. The estimated SD was 13.6457 based on 148 subjects with data at both Baseline and Week 6. Since the estimated pooled SD was smaller than the assumed SD=14, no increase in the planned sample size was required.

The Applicant analyzed the primary efficacy endpoint using the linear mixed-effects model for repeated measures (MMRM). The analysis included the fixed categorical effects of treatment (10, 20, 30 mg, and placebo), visit (Weeks 1, 2, 3, 4, 5, and 6), and treatment-by-visit interaction, the covariate of baseline ADHD-RS-IV Preschool Version Total Score, and the baseline ADHD-RS-IV Preschool Version Total Score-by-visit interaction adjusted in the model. The restricted maximum likelihood method was used, with an unstructured covariance structure shared across treatment groups used to model the within-patient errors. The Kenward-Roger method was used to estimate denominator degrees of freedom and adjust standard errors. The primary contrast of interest was at Visit 6 (Week 6) for the pooled SPD489 (10, 20, and 30 mg) dose group compared with placebo.

The following two sensitivity analysis models, which were within the pattern-mixture model framework, were used to examine the robustness of the primary efficacy analysis results for the missing not at random (MNAR) mechanisms:

- Model 1 (Placebo Multiple Imputation): The underlying assumption was that the missing data for a subject on the active treatment follow the distribution of the placebo responses (i.e., the mean values and intra-subject correlations based on the placebo responses were applied).

- Model 2 (Multiple Imputations with Penalties Applied to Dropouts): The underlying assumption was that subjects who dropped out performed worse than missing at random by a penalty.

The Applicant analyzed the CGI-I score at Week 6 (the prespecified secondary efficacy endpoint) in the same way as described for the primary endpoint, with the only difference being that MMRM used a Baseline value of Clinical Global Impression-Severity (CGI-S) as a covariate instead of the Baseline ADHD-RS-IV Preschool Version Total Score.

The Applicant also conducted exploratory subgroup analyses in primary and secondary endpoints on the FAS.

Dose response analyses:
Dose response relationship was evaluated using the MCP-Mod approach. The SAP pre-specified 4 candidate dose-response curves in the Linear, E_{max} or Logistic curve family.

Sample size calculation:
Approximately 245 subjects would be screened to randomize approximately 195 subjects in a 5:5:5:5:6 ratio to SPD489 5, 10, 20, 30 mg or placebo and to achieve 156 completers for the study (30 in each active treatment group and 36 in the placebo group) and 85% power for the primary efficacy analysis at a 2-sided 0.05 significance level.

The sample size planned at study initiation was estimated based on the primary comparison between SPD489 10, 20, and 30-mg arms pooled together (excluding the 5-mg group) compared with placebo on the primary efficacy endpoint, in a group sequential design with one interim analysis using the Lan-DeMets alpha spending function with O'Brien-Fleming boundary for the primary efficacy endpoint. Assumptions for the calculation included the true mean difference of 8.4 with the common standard deviation (SD) of 14 for the primary efficacy endpoint, for an effect size of 0.6, and a dropout rate of 20%.

During the protocol review stage under IND 678482 (SDN514) the Biometrics Team noted that:

[1] *The primary efficacy comparison was between the average effect of the three pooled doses with placebo. Since the primary goal of this study was on safety instead of efficacy, we had no objection to this proposed primary comparison. However, we informed the Applicant that if they intended to add an efficacy claim to the labeling, they would need to prespecify a multiple testing procedure to compare individual doses with placebo with the overall type I error rate controlled.*

[2] *Because the recruitment rate was higher than estimated, the Applicant waived the interim analysis per the criteria outlined in the SAP. The blinded sample size re-estimation led to a smaller estimate of the SD than the assumed, so the sample size was not increased.*

Protocol/SAP Amendments

The Applicant amended the protocol for Study 347 three times. The versions are dated:

- Amendment 3: August 4, 2017 (submitted August 8, 2017)
- Amendment 2: June 5, 2017
- Amendment 1: February 23, 2017
- Original Protocol: August 1, 2016

The original statistical plan (dated August 4, 2016) was amended once:

Amendment 1 (dated June 9, 2017) included the change of the protocol and SAP of Study 347 from a flexible-dose design to a fixed-dose design. There were also changes in the primary and key secondary endpoint analysis including their sensitivity analyses, which would compare placebo and pooled SPD489 10, 20, 30-mg dose strengths *together* instead of comparing individual arms. FDA conveyed the following statistical comment dated on July 5, 2017 to the Sponsor: "We have no objection to your plan of pooling all three SPD489 arms to fulfill the Written Request. However, if you intend to add a claim to the labeling, you would need to pre-specify a multiple testing procedure to compare individual arms with placebo with the overall type I error rate controlled."

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant performed this study according to the protocol and in compliance with Good Clinical Practices, including the archiving of essential documents.

Data Quality and Integrity

See Section 4.1 for information regarding the OSI inspection of this trial.

The Analysis Data Model (ADaM) and Study data Tabulation Model (SDTM) datasets were intact and evaluable using JMP programs for the clinical team and for evaluation by our Biometrics team.

Financial Disclosure

The Applicant submitted financial disclosures for Studies SPD489-221, 347, and 348. Although some investigators received "significant payments" from the Applicant, a greater number of investigators did not receive significant payments. The data did not appear biased by this issue. Refer to Appendix 15.2 for the Financial Disclosure form.

Patient Disposition

Of the 284 patients screened, 85 did not meet enrollment criteria and were not randomized to a treatment group. In total, 199 subjects were randomized (but 8 did not receive any study medication doses). The safety analysis set included 191 patients (45 in the placebo group; 146 treated with lisdexamfetamine 5, 10, 20, or 30 mg). The full analysis set (FAS) included 187 patients (45 in the placebo group; 142 treated with lisdexamfetamine).

There were 150 patients that completed the study (37 in the placebo group and 113 treated with lisdexamfetamine). The reasons for discontinuation during the trial included: adverse event (AE) (n=10, 5.2%), lost to follow up (n=11, 5.8%), protocol violation (n=3, 1.6%), withdrawal by parent (n=12, 6.3%), or other (n=5, 2.6%). Table 3 shows that the lisdexamfetamine 30-mg treatment group had the highest number of dropouts due to AEs. Refer to Section 8.2.4 Safety Results for these discontinuation reasons.

Table 3: Patient Discontinuation from AEs by Treatment Group (Randomized Set (N=199))

	Placebo (N=46)	SPD489 5 mg (N=40)	SPD489 10 mg (N=37)	SPD489 20 mg (N=37)	SPD489 30 mg (N=39)	All SPD489 (N=153)	Total (N=199)
AE as reason for D/C	2(4.4%)	0	2(5.7%)	2(5.9%)	4(10.5%)	8(7.5%)	10(5.2%)

Source: Reviewer adapted from Table 6 of CSR for Study 347

Protocol Violations/Deviations

Of the 199 patients randomized and enrolled in the study, 116 (58.3%) subjects had at least one protocol deviation. Table 4 describes the deviations by treatment group.

One example of a protocol violation leading to discontinuation involved Patient ID SPD489-(b) (6) The patient did not return the sleep diary (minor violation), nor the study drug (major violation twice), so the clinical site removed the patient from the study.

Table 4: Protocol Deviations by Treatment Group (Randomized Set (N=199))

	Placebo	SPD489 5 mg	SPD489 10 mg	SPD489 20 mg	SPD489 30 mg	All SPD489	Total
Characteristic	(N=46) Count(%)	(N=40) Count(%)	(N=37) Count(%)	(N=37) Count(%)	(N=39) Count(%)	(N=153) Count(%)	(N=199) Count(%)
Any deviation	25 (54.3)	24 (60.0)	22 (59.5)	23 (62.2)	22 (56.4)	91 (59.5)	116
Accidental unblinding	0	0	2 (5.4)	0	0	2 (1.3)	2 (1.0)
Concomitant medication	0	2 (5.0)	0	2 (5.4)	2 (5.1)	6 (3.9)	6 (3.0)
Exclusion criteria	0	1 (2.5)	3 (8.1)	1 (2.7)	2 (5.1)	7 (4.6)	7 (3.5)
Informed consent	1 (2.2)	1 (2.5)	1 (2.7)	1 (2.7)	1 (2.6)	4 (2.6)	5 (2.5)
Missing endpoint assessments	1 (2.2)	2 (5.0)	1 (2.7)	2 (5.4)	0	5 (3.3)	6 (3.0)
Missing	3 (6.5)	2 (5.0)	0	0	2 (5.1)	4 (2.6)	7 (3.5)
Other protocol deviation	3 (6.5)	0	1 (2.7)	3 (8.1)	6 (15.4)	10 (6.5)	13 (6.5)
Study procedures/assessments	8 (17.4)	11 (27.5)	9 (24.3)	8 (21.6)	9 (23.1)	37 (24.2)	45 (22.6)
Study treatment admin/dispense	2 (4.3)	2 (5.0)	4 (10.8)	3 (8.1)	3 (7.7)	12 (7.8)	14 (7.0)
Study treatment compliance	12 (26.1)	13 (32.5)	10 (27.0)	10 (27.0)	11 (28.2)	44 (28.8)	56 (28.1)
Visit scheduling	8 (17.4)	11 (27.5)	6 (16.2)	9 (24.3)	4 (10.3)	30 (19.6)	38 (19.1)

Source: Reviewer adapted from Table 7 of CSR for Study 347

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There were no substantial differences in treatment compliance protocol deviations among treatment groups as seen in Table 4; the compliance deviations at 28.1% overall is less than the rates seen in other stimulant trials, likely due to caregiver involvement. There was minimal concomitant medication usage (3.0% overall).

Demographic Characteristics (Full Analysis Set (FAS) N=187)

The demographic characteristics in Table 5 were similar among the treatment groups. As also seen in the general U.S. pediatric population with ADHD, there were about twice as many males (n=126) as females (n=61) in the study. Table 5 depicts the ages by treatment group. The groups were well-matched with respect to age. The overall mean (SD) age of subjects enrolled in the study was 61.2 (6.54) months. The overall median age of patients was 5.1 years-old. Most patients' race were either white or black/African American (n=89, 46.6% each). The majority (n=159, 83.2%) of patients' ethnicity was not Hispanic or Latino.

Table 5: Demographic Characteristics in Study 347, Full Analysis Set N=187

	SPD489 5mg		SPD489 10mg		SPD489 20mg		SPD489 30mg		Placebo			
Sex	Count	Column %	Count	Column %	Count	Column %	Count	Column %	Count	Column %	Count	% of Total
F	12	31%	12	36%	10	30%	11	30%	16	36%	61	33%
M	27	69%	21	64%	23	70%	26	70%	29	64%	126	67%
All	39	100%	33	100%	33	100%	37	100%	45	100%	187	100%

	SPD489 5mg		SPD489 10mg		SPD489 20mg		SPD489 30mg		Placebo			
Age Group	Count	Column %	Count	Column %	Count	Column %	Count	Column %	Count	Column %	Count	% of Total
Age 4	17	44%	15	45%	13	39%	14	38%	20	44%	79	42%
Age 5	22	56%	18	55%	20	61%	23	62%	25	56%	108	58%
All	39	100%	33	100%	33	100%	37	100%	45	100%	187	100%

	SPD489 5mg		SPD489 10mg		SPD489 20mg		SPD489 30mg		Placebo			
Race	Count	Column %	Count	Column %	Count	Column %	Count	Column %	Count	Column %	Count	% of Total
Missing	0	0%	0	0%	0	0%	0	0%	1	2.2%	1	0.5%
AMERICAN INDIAN OR ALASKA NATIVE	0	0%	0	0%	0	0%	1	2.7%	0	0.0%	1	0.5%
BLACK OR AFRICAN AMERICAN	20	51.3%	15	45.5%	14	42.4%	15	40.5%	23	51.1%	87	46.5%
MULTIPLE	1	2.6%	0	0%	1	3.0%	3	8.1%	1	2.2%	6	3.2%
OTHER	1	2.6%	2	6.1%	0	0%	1	2.7%	1	2.2%	5	2.7%
WHITE	17	43.6%	16	48.5%	18	54.5%	17	45.9%	19	42.2%	87	46.5%
All	39	100%	33	100%	33	100%	37	100%	45	100%	187	100%

	SPD489 5mg		SPD489 10mg		SPD489 20mg		SPD489 30mg		Placebo			
Ethnicity	Count	Column %	Count	Column %	Count	Column %	Count	Column %	Count	Column %	Count	% of Total
HISPANIC OR LATINO	6	15.4%	10	30.3%	2	6.1%	5	13.5%	8	17.8%	31	16.6%
NOT HISPANIC OR LATINO	33	84.6%	23	69.7%	31	93.9%	32	86.5%	37	82.2%	156	83.4%
All	39	100%	33	100%	33	100%	37	100%	45	100%	187	100%

Source: Reviewer created using JMP Clinical 7.0

Other Baseline Characteristics (e.g., Disease Characteristics)

The majority of patients in Study 347 were diagnosed with ADHD, combined subtype, as seen in Table 6.

Table 6: Number of ADHD Patients by Subtype

ADHDSUB	N
Combined Subtype	183
Predominately Hyperactive-Impulsive	12
Predominately Inattentive	4

Source: Clinical Reviewer created using JMP from ADSL dataset, Study 347

(b) (4)

(b) (4)

[redacted]

8.2. Review of Safety

8.2.1. Safety Review Approach

(b) (4)

[redacted] The reviewer also evaluated growth over time as reported in the CSR and datasets of the open-label safety extension study.

8.2.2. Review of the Safety Database

Overall Exposure

Lisdexamfetamine is a marketed drug with years of exposure in pediatric patients aged 6 to 17 and in adults.

During the 6-week Study 347 (titration and fixed-dose periods), the median average daily doses (range) for each lisdexamfetamine dose group were as follows:

- 5.0 mg (range: 3-6 mg) for the SPD489 5-mg group
- 9.0 mg (range: 2-10 mg) for the SPD489 10-mg group
- 15.8 mg (range: 5-18 mg) for the SPD489 20-mg group
- 20.4 mg (range: 3-25 mg) for the SPD489 30-mg group

The Applicant defined total days of dosing as (date of last dose - date of first dose + 1). The median total days was 40 to 42 days for all treatment groups. Per the Applicant, person-time was derived as the total number of days in which the investigational product (lisdexamfetamine or placebo) was taken for each patient and then summed over all patients for the whole

duration of the study. The resulting total exposure in person-years was the same number as patients per treatment group. For example, placebo= 45, 5 mg= 39, etc. See Table 13. The Applicant's CSR described that seven patients lacked complete datasets.

Table 13: Exposure to Investigational Product by Group and Person-Year

	Placebo (N=45)	5 mg (N=39)	10 mg (N=35)	20 mg (N=34)	30 mg (N=38)	All SPD489 (N=146)
Total exposure (Person-years)	45	39	35	34	38	146

Source: Reviewer adapted from Table 20 of CSR for Study 347

Longer-term exposure took place during the Study 348, the 1-year open-label study. The mean (SD) duration of exposure for all patients (i.e., antecedent trials or direct enroll) was 255 (113) days. The median days of exposure was 321. The mean and median daily dose after titration was 22 mg/day.

Adequacy of the Safety Database

The number of patients aged 4 to 5 in the safety set was 191. Within that set, 146 received lisdexamfetamine, and 45 were in the placebo group. The size of the safety database was acceptable for placebo-controlled comparison.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

The Applicant's safety assessments were acceptable. The safety assessments included reporting of treatment-emergent AEs, vital signs, weight and body mass index (BMI), clinical laboratory tests, ECG, sleep assessments with the Children's Sleep Habits Questionaire, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

Issues Regarding Data Integrity and Submission Quality

No issues were identified with the datasets or quality of the NDA submission. The dictionary terms, or preferred terms, appeared to accurately reflect investigator verbatim terms.

Categorization of Adverse Events

The Applicant used MedDRA 18.0 to categorize AEs which is acceptable. The dictionary-derived terms applied by the Applicant were adequate to characterize the safety profile of lisdexamfetamine. The clinical reviewer grouped the terms initial insomnia and insomnia together when comparing the rate of insomnia in the placebo group and to other approved stimulants.

Routine Clinical Tests

Investigators conducted questionaires and clinical test at each weekly visit, Baseline to Week 6.

8.2.4. Safety Results

Deaths

No deaths occurred.

Serious Adverse Events

No serious adverse events occurred.

Dropouts and/or Discontinuations Due to Adverse Effects

Table 3: Patient Discontinuation from AEs by Treatment Group (Randomized Set (N=199))in Section 8.1.2 of this review shows that the lisdexamfetamine 30-mg treatment group had the highest number of dropouts (n=4) due to AEs. There were two patients each who dropped out from the placebo, 10-mg, and 20-mg lisdexamfetamine treatment groups--a total of 10 patients. The reasons for discontinuation are expected based on known AEs with stimulants as shown in Table 14. Lack of efficacy appeared to be the main cause of dropouts in the placebo group. Some patients had more than one reason for discontinuation. For example, Subject ID (b) (6) listed three reasons (i.e., abdominal pain upper, diarrhea, irritability) for discontinuation from the 30-mg group.

Table 14: Reasons for Discontinuation (Study 347)

		Treatment Group			
AEBODSYS	AEDECOD	Placebo	SPD489 10mg	SPD489 20mg	SPD489 30mg
Gastrointestinal disorders	Abdominal pain upper	0	0	0	1
	Diarrhea	0	0	0	1
Investigations	Blood pressure increased	0	0	0	1
Metabolism and nutrition disorders	Decreased appetite	0	0	1	1
Psychiatric disorders	Abnormal behavior	1	0	0	0
	Affect lability	0	1	1	0
	Anger	0	0	0	1
	Attention deficit/hyperactivity disorder	1	0	0	0
	Initial insomnia	0	1	0	0
	Irritability	0	1	0	1
	Tic	0	0	1	0
		2 D/C	2 D/C	2 D/C	4 D/C

Source: Reviewer created using JMP 14.0

Significant Adverse Events

No significant adverse events were identified in the safety evaluation of Study 347.

Treatment Emergent Adverse Events and Adverse Reactions

In the placebo-controlled Study 347, similar rates of TEAEs were reported in either sex. The clinical safety analysis found reported TEAEs as expected from a stimulant and are consistent with the known safety profile of lisdexamfetamine.

In Table 15, the most common (>5%) TEAEs were decreased appetite (particularly in the 20- and 30-mg groups), insomnia (particularly in the 30-mg group), irritability, and upper respiratory viral-type infections in the combined-dose lisdexamfetamine group.

Table 15: TEAEs by Treatment Group, Study 347

	Treatment Group (Safety dataset)					
	SPD489 5mg	SPD489 10mg	SPD489 20mg	SPD489 30mg	Placebo	Total
	Count (%)	Count (%)	Count (%)	Count (%)	Count (%)	Count (%)
Total	N=39	N=35	N=34	N=38	N=45	N=191
Gastrointestinal disorders	1 (2.6)	1 (2.9)		1 (2.6)	1 (2.2)	4 (2.1)
Abdominal pain upper	1 (2.6)	1 (2.9)		1 (2.6)	1 (2.2)	4 (2.1)
Infections and infestations	3 (7.7)	2 (5.7)	2 (5.9)	2 (5.3)	1 (2.2)	10 (5.2)
Upper respiratory tract infection	2 (5.1)	2 (5.7)			1 (2.2)	5 (2.6)
Nasopharyngitis	1 (2.6)		2 (5.9)	2 (5.3)		5 (2.6)
Metabolism and nutrition disorders	3 (7.7)	3 (8.6)	6 (18)	8 (21)	4 (8.9)	24 (13)
Decreased appetite	3 (7.7)	3 (8.6)	6 (18)	8 (21)	4 (8.9)	24 (13)
Nervous system disorders				2 (5.3)	2 (4.4)	4 (2.1)
Somnolence				2 (5.3)	2 (4.4)	4 (2.1)
Psychiatric disorders	6 (15)	7 (20)	4 (12)	10 (26)	3 (6.7)	30 (16)
Insomnia	1 (2.6)	2 (5.7)		5 (13)	3 (6.7)	11 (5.8)
Affect lability	2 (5.1)	3 (8.6)	1 (2.9)	1 (2.6)		7 (3.7)
Irritability	3 (7.7)	4 (11)	3 (8.8)	4 (11)		14 (7.3)
Respiratory, thoracic and mediastinal disorders	1 (2.6)	2 (5.7)	2 (5.9)	2 (5.3)	1 (2.2)	8 (4.2)
Cough	1 (2.6)	2 (5.7)	2 (5.9)	2 (5.3)	1 (2.2)	8 (4.2)

Source: Reviewer created using JMP Clinical 8.0

Rates of Decreased Appetite from Safety and Efficacy Trials of Other Stimulants

There are no stimulants approved for the preschool population based on clinical trial data; for general reference on AE rates, the clinical reviewer compared the rate of decreased appetite from lisdexamfetamine (20-mg: 18%, 30-mg: 21%) to other approved stimulants indicated for pediatric patients aged 6 to 12 years, the nearest age range.

From the Adhansia XR (methylphenidate) label, during the 6-week open-label Adhansia XR treatment phase of the efficacy and safety trial, adverse reactions reported in >5% of patients included decreased appetite (35%) and weight decreased (12%). However, during the 1-week placebo-controlled treatment phase, no difference occurred in the incidence of adverse reactions between Adhansia XR and placebo.

From the Jornay PM (methylphenidate) label, patients aged 6 to 12 years reported more decreased appetite (19%) in the Jornay PM group compared to placebo group (4%).

Safety data in patients aged 4 to 5 years is also obtained from the limited data submitted to the Division as required by previous PREA PMRs. For Mydayis (mixed salts of single-entity amphetamine), patients aged 4 to 5 years took Mydayis 6.25 mg compared to placebo in a safety and efficacy trial. Patients in the Mydayis group reported decreased appetite at 2.2% vs. 4.7% in the placebo group. The tested Mydayis 6.25 mg dose was not effective and likely accounts for the low rates of AEs in the preschool-aged patients.

Double-blind data from Aptensio XR (methylphenidate) in patients 4 to 5 years-old showed that patients taking Aptensio XR reported decreased appetite at 1% compared to zero percent in the placebo group.

The rate of decreased appetite from the lisdexamfetamine doses (especially 20 to 30 mg) in patients aged 4 to 5 were relatively higher than the rates seen with other stimulants described above (and seen in Table 16), although direct comparison may be faulty/limited due to different study designs and dosing. Therefore, the clinical reviewer further evaluated weight-related parameters from the lisdexamfetamine safety extension study. Refer to Section 8.2.7 of this review for more details.

Table 16: Other Stimulants' Rates of Decreased Appetite or Weight Decreased AEs vs. Vyvanse

	Adhansia XR (6 to 12 yr)	PBO	Jornay PM (6 to 12 yr)	PBO	Mydayis (4 to 5 yr)	PBO	Aptensio XR (4 to 5 yr)	PBO	Vyvanse (4 to 5 yr)*	PBO
Dose optimization phase			Study 1							
Decreased appetite	35%	-	27%	-			20%	-		
Weight decreased	12%	-	-	-			18%	-		
Placebo-controlled phase										
Decreased appetite	0.4%	0%	<5%	<5%	2.2%	4.7%	1%	0%	13%	9%
Weight decreased	0.4%	0%	-	-						
Placebo-controlled phase			Study 2 (parallel design)							
Decreased appetite			19%	4%						

Source: Approved labels and clinical reviews
PBO- placebo
*Vyvanse combined doses of 10 to 30 mg

Laboratory Findings

The laboratory tests did not indicate abnormalities induced by lisdexamfetamine. There were no notable changes from baseline or apparent differences between the treatment groups in routine clinical laboratory values (hematology, chemistry, and urinalysis). The JMP Clinical 8.0 analysis of liver function enzymes did not indicate any cases of Hy's Law.

Some patients (range 16 to 25%) had "high" counts on various parameters (e.g., eosinophils, lymphocytes) on their CBC panels during different visits over the 6-week trial. Table 15 indicates that 5 to 6% of patients assigned to lisdexamfetamine reported symptoms of colds (cough, nasopharyngitis) compared to about 2% in the placebo group. This issue is likely the reason for increases on the CBC panel and is common in 4 to 5-year-olds. Eight (5+3) patients of the 18 reporting cough or nasopharyngitis were taking lisdexamfetamine and had high eosinophil counts at baseline or Week 6, respectively.

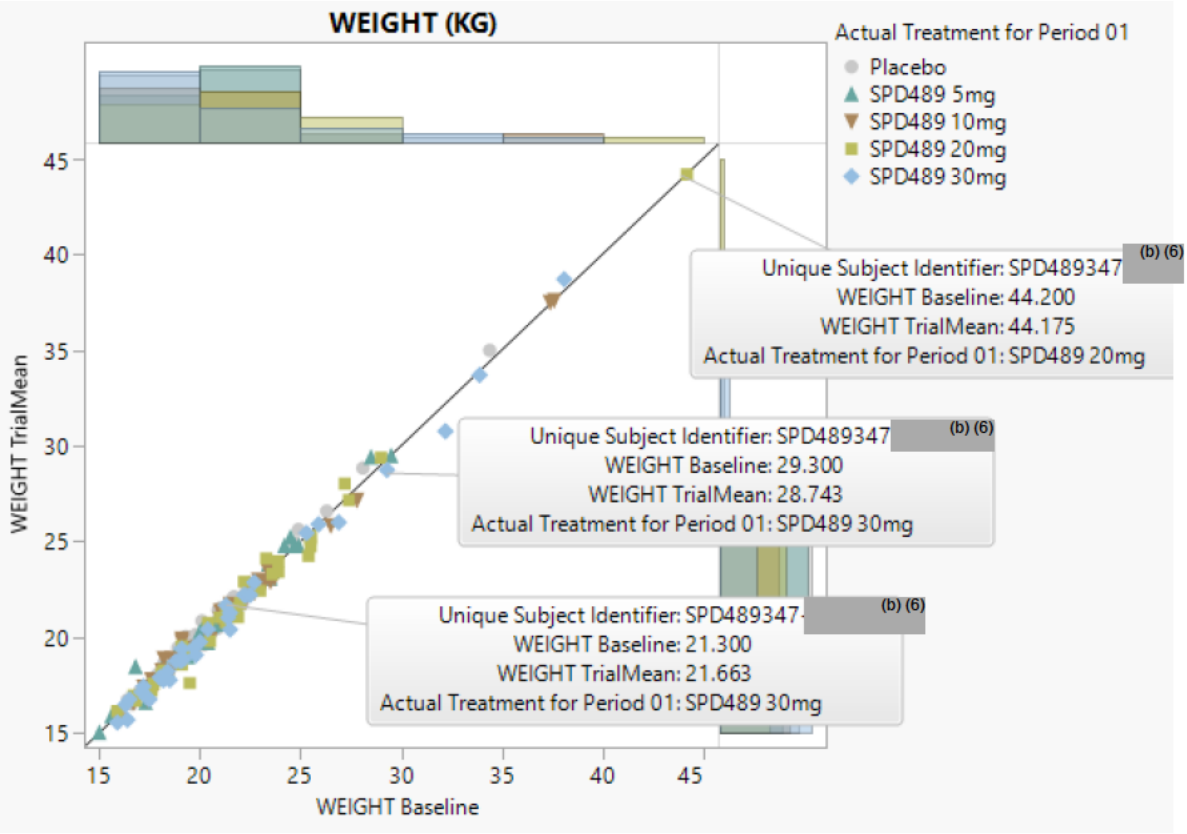
Vital Signs

Vital sign assessments included weight, height, BMI, pulse, and blood pressure. There were no clinically meaningful differences between the treatment groups over the 6-week trial.

Weight

The shift plot in Figure 4 indicates that the majority of patients experienced little difference between their baseline weight (kg) and mean weight over the duration of the 6-week trial, regardless of randomized treatment. Sample patients are marked on the shift plot, with outliers weighing more than most patients at baseline. Likewise, there was no apparent difference in patients' BMIs between those taking placebo or lisdexamfetamine.

Figure 4: Shift Plot of Patients Baseline and Mean Trial Weights (Study 347)



Source: Reviewer created using JMP Clinical 8.0

Blood Pressure

Based on AE reporting in the pooled lisdexamfetamine group compared to the placebo group, investigators reported that 2% of patients in the lisdexamfetamine arms experienced increased blood pressure versus 0% in the placebo arm. The clinical reviewer's safety analysis did not reveal significantly different rates of increased mean blood pressure in the individual dose arms for lisdexamfetamine or placebo, although the mean blood pressures in the lisdexamfetamine

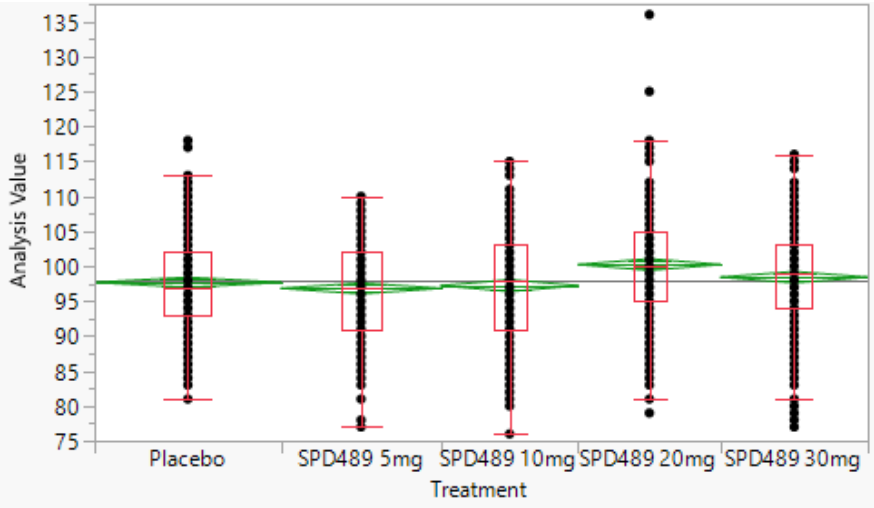
arms trended towards slight elevation compared to the placebo arm as seen in Table 16. Analysis of average systolic (SBP) and diastolic blood pressure (DBP) yielded similar results in Figures 6 and 7, with the lisdexamfetamine 20 and 30 mg arms being slightly elevated. In the lisdexamfetamine 20 mg group, Subject ID (b) (6) experienced SBP of 136 mmHg (highest outlier on Figure 6); The subject's average DBP was 66 mmHg. No interventions were made. Overall, the mild elevations in blood pressure in the lisdexamfetamine treatment groups are not clinically concerning in the preschool population.

Table 17: Baseline and Week 6 Mean (SD) Sitting Systolic and Diastolic Blood Pressure (mmHg) by Arm (Study 347)

	Placebo N=45	SPD489 5 mg N=39	SPD489 10 mg N=35	SPD489 20 mg N=34	SPD489 30 mg N=38
SBP Baseline mean (SD) mmHg	98 (6.8)	98 (8.1)	96 (9.1)	100 (7.2)	98 (8.0)
DBP Baseline mean (SD) mmHg	61 (7.1)	62 (8.2)	60 (6.7)	63 (4.9)	61 (6.7)
SBP Week 6/ET mean (SD) mmHg	98 (6.3)	97 (7.2)	98 (7.3)	102 (9.4)	100 (7.4)
DBP Week 6/ET mean (SD) mmHg	62 (5.5)	64 (5.0)	62 (6.6)	64 (5.0)	65 (5.6)

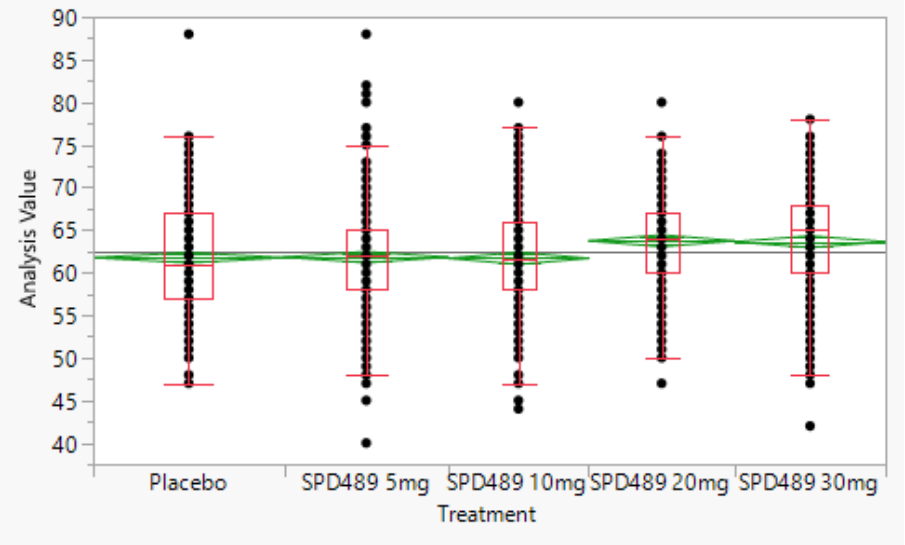
Source: Reviewer created using JMP Clinical 8.0 from Study Dataset

Figure 5: Average Systolic Blood Pressure (mmHg) by Treatment (Study 347)



Source: Reviewer created using JMP Clinical 8.0

Figure 6: Average Diastolic Blood Pressure (mmHg) by Treatment (Study 347)



Source: Reviewer created using JMP Clinical 8.0

Electrocardiograms (ECGs)

ECG changes from baseline were variable (e.g., increase, decrease, different visits) between treatment groups, with no notable overall trends. The Applicant's CSR indicated that no interventions were made for patients with potentially clinically important changes in ECG. One patient (2.5%) in the placebo group had an ECG change to abnormal. In the lisdexamfetamine 10 mg group, three patients (8.6%) had ECG changes. In the lisdexamfetamine 30-mg group, three patients (7.9%) had changes from baseline. None were clinically significant.

QT

In Study 347, the QTc interval was calculated using both Bazett (QTcB = QT/(RR)1/2) and Fridericia (QTcF = QT/(RR)1/3) corrections. There were no clinically meaningful findings during the trial.

Immunogenicity

Lisdexamfetamine is a small molecule and not a biopharmaceutical; therefore, there is a low probability of it causing immunogenicity reactions. No immunogenicity reactions were reported from Study 347, nor during the development program for lisdexamfetamine.

Columbia Suicide Severity Rating Scale (C-SSRS)

During the Study 347, three patients answered positively on the question, "Wish to be dead?" The C-SSRS was clinician-administered at weekly visits. None of the positive answers appeared directly related to lisdexamfetamine use.

- Week 2- One subject in the 5-mg SPD489 group (Subject ID (b) (6)) responded "Yes" to the C-SSRS question "Wish to be dead?" (described as "just want to kill myself; subject was reported to have said this statement when angry because he didn't get gummy bears").

- Week 1- One subject in the 10-mg SPD489 group (Subject ID (b) (6)) responded "Yes" to the C-SSRS question "Wish to be dead?" (described as "I want to die when I get very angry").

- Week 3- One subject in the 20-mg SPD489 group (Subject ID (b) (6)) responded "Yes" to the C-SSRS questions "Wish to be dead?" and "Nonspecific Active Suicidal Thoughts?" (described as "patient told teacher he wanted to kill himself"). This was recorded as a TEAE of mild suicidal ideation which resolved and the dose of lisdexamfetamine was unchanged.

Analysis of Submission-Specific Safety Issues

Patients in the lisdexamfetamine 30-mg treatment group reported higher rates of insomnia and initial insomnia combined (5/38=13.2%), decreased appetite (8/38= 21.1%), and irritability (4/38=10.5%) compared to all other treatment arms during Study 347, as seen in Table 18. (The lisdexamfetamine 5 and 10-mg groups (lower doses) reported the highest rates of affect lability, for unclear reasons.)

Table 18: Dose-Related AEs from Study 347

	Placebo	SPD489 5 mg	SPD489 10 mg	SPD489 20 mg	SPD489 30 mg
Insomnia	6.7%	2.6%	5.7%	-	13%
Decreased appetite	8.9%	7.7%	8.6%	18%	21%
Irritability	-	7.7%	11%	8.8%	11%
Affect lability	-	5.1%	8.6%	2.9%	2.6%

Source: Reviewer Analysis from AE Dataset

The review team reviewed the labels for other approved stimulants with an indication for 6 years and above. Refer to Section 8.2.4 for the discussion of decreased appetite with other stimulants. Rates of insomnia in other stimulants were varied. For example, patients (6 to 12

years-old) taking Jornay PM (methylphenidate) reported 33% insomnia compared to 9% in the placebo group, as in Table 19. Due to the dose-optimization design of the Adhansia XR (methylphenidate) study in pediatric patients 6 to 12 years, less insomnia (10%) and irritability (10%) were reported during the open-label treatment phase, and no difference was seen between treatment and placebo during the placebo-controlled, double-blind phase. Although these comparisons are limited due to different study designs, populations, and dosing, the rates of the same AEs appear generally lower than those seen in the higher dose arms for lisdexamfetamine (except for insomnia rates for Jornay PM).

Table 19: Other Stimulants' Rates of Selected AEs Compared to Vyvanse

	Adhansia XR (6 to 12 yr)	PBO	Jornay PM (6 to 12 yr)	PBO	Mydayis (4 to 5 yr)	PBO	Aptensio XR (4 to 5 yr)	PBO	Vyvanse (4 to 5 yr)*	PBO
Dose optimization phase			Study 1							
Insomnia	10%	-	41%	-			23%	-		
Irritabililty	10%	-	6%	-			18%	-		
Affect lability	9%	-	22%	-			10%	-		
Placebo-controlled phase										
Insomnia	0%	0%	<5%	<5%	-	-	-	-	6%	7%
Irritibililty	0.4%	0%	<5%	<5%	-	-	-	-	4%	0%
Affect lability	0%	0%	<5%	<5%	-	-	-	-	7%	0%
			Study 2 (parallel design)							
Insomnia			33%	9%						
Irritability			-	-						
Affect lability			6%	1%						

Source: Approved labels and clinical reviews
*Vyvanse combined doses of 10 to 30 mg
PBO- placebo
Dash- insomnia, irritability, or affect lability was not reported

Accordingly, during this NDA review for lisdexamfetamine (b) (4)

After discussion of the safety of the lisdexamfetamine 30-mg dose in patients ages 4 to 5, the clinical reviewer also closely analyzed the long-term effects of decreased appetite from the open-label Study 348. We determined that there was a major safety signal in *all* the pooled treatment doses that precluded the possibility of approval. This information is presented in Section 8.2.9 Additional Safety Explorations, Pediatrics and Assessment of Effects on Growth.

8.2.5. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.6. Safety Analyses by Demographic Subgroups

White patients reported higher rates of TEAEs than other races/ethnicities. No other differences between subgroups were noted. However, the results of safety analyses by demographic subgroup are not interpretable to the general preschool ADHD population, because the study was not powered or sized to detect differences conclusively.

Specific Safety Studies/Clinical Trials

Refer to Section 8.2.7, Pediatrics and Assessment of Effects on Growth for more details on the open-label 1-year safety study results for Study 348.

8.2.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

Human Reproduction and Pregnancy

Not applicable to the preschool population.

Pediatrics and Assessment of Effects on Growth

Study 348 was a 1-year, open-label, safety extension trial enrolling patients from the PK study, efficacy and safety trial, or by direct enrollment. Using the Applicant's datasets, the safety set was 115 patients, with 69 completers at Week 52 or Early Termination (ET). Of the completers, there were 46 male and 23 female patients. The patients were titrated to an optimal dose of lisdexamfetamine 5, 10, 15, 20, or 30 mg/day. Of the 69 completers, 19 patients were taking lisdexamfetamine 5, 10, or 15 mg/day. There were 20 patients taking 20 mg and 30 taking 30 mg. The male patients were taking the highest doses of either lisdexamfetamine 20 or 30

mg/day. The females took lisdexamfetamine 5, 10, or 15 mg/day; only four females took 20-mg doses. The mean and median daily dose after titration for both sexes was lisdexamfetamine 22 mg/day. There were no deaths or SAEs reported.

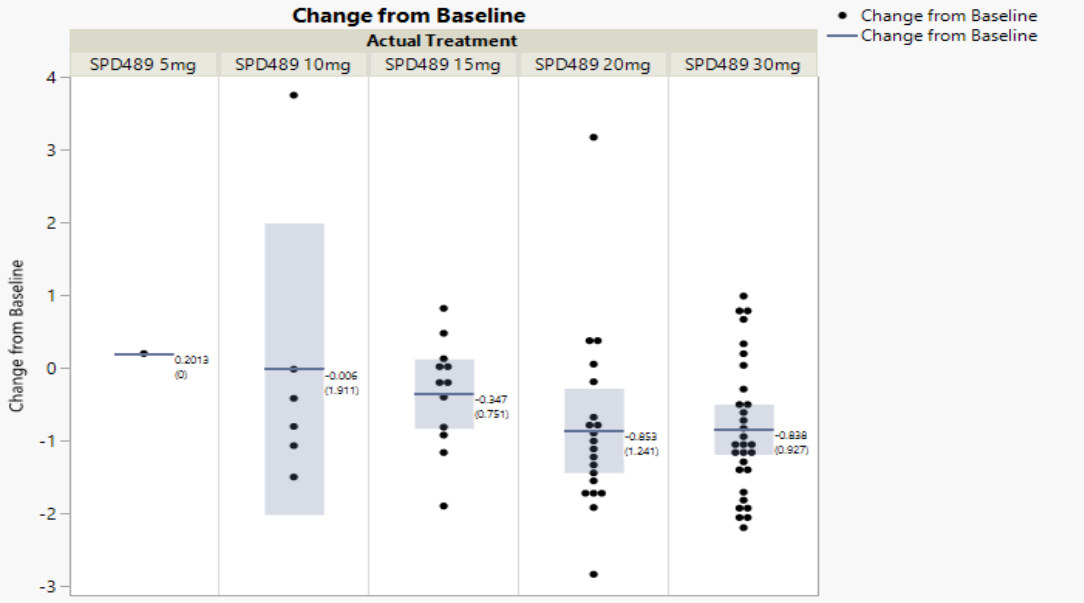
Long-term growth suppression is a known adverse reaction associated with stimulant use in pediatric patients. During the 6-week efficacy and safety trial (Study 347), no clinically meaningful difference in weight or BMI was noted between the lisdexamfetamine and placebo arms. However, by the end of Study 348, many patients appeared to fall off their anticipated growth curves on the Centers for Disease Control and Prevention's (CDC) Growth Chart.

According to Takeda's CSR for this study, there were eight patients (8/115 (7.0%)) at Week 52 or Early Termination (ET) in the underweight category (<5th percentile on the CDC Growth Chart). One patient (0.9%) started the trial underweight, and seven patients (4.5%) had shifts from other weight categories to underweight by the end of the trial.

For the 69 completers of Study 348, the clinical reviewer analyzed certain parameter (BMI, height, weight, weight percentile on the CDC Growth Chart) changes from baseline to 52 weeks/end-of-treatment (ET), because the team was concerned about the 21.1% decreased appetite AE rate in the 6-week efficacy trial. BMI is a measure of weight (kg)/ height (m^2). The clinical reviewer's assessments were discussed with DPMH who advised that the interpretation of growth parameters using open-label data is acceptable overall, with some remaining limitations in interpretability (being open-label, number of dropouts, etc.) to also consider.

The mean (SD) BMI (kg/m^2) change from baseline to Week 52/ET by treatment group is shown in Figure 7. The greatest mean (SD) BMI loss occurred in the 20-mg and 30-mg groups respectively, at -0.85 (1.2) and -0.84 (0.93). These losses in BMI over time appear dose-dependent, because the means trend lower than the mean change from baseline in the lisdexamfetamine 5 and 10-mg treatment arms in Figure 7.

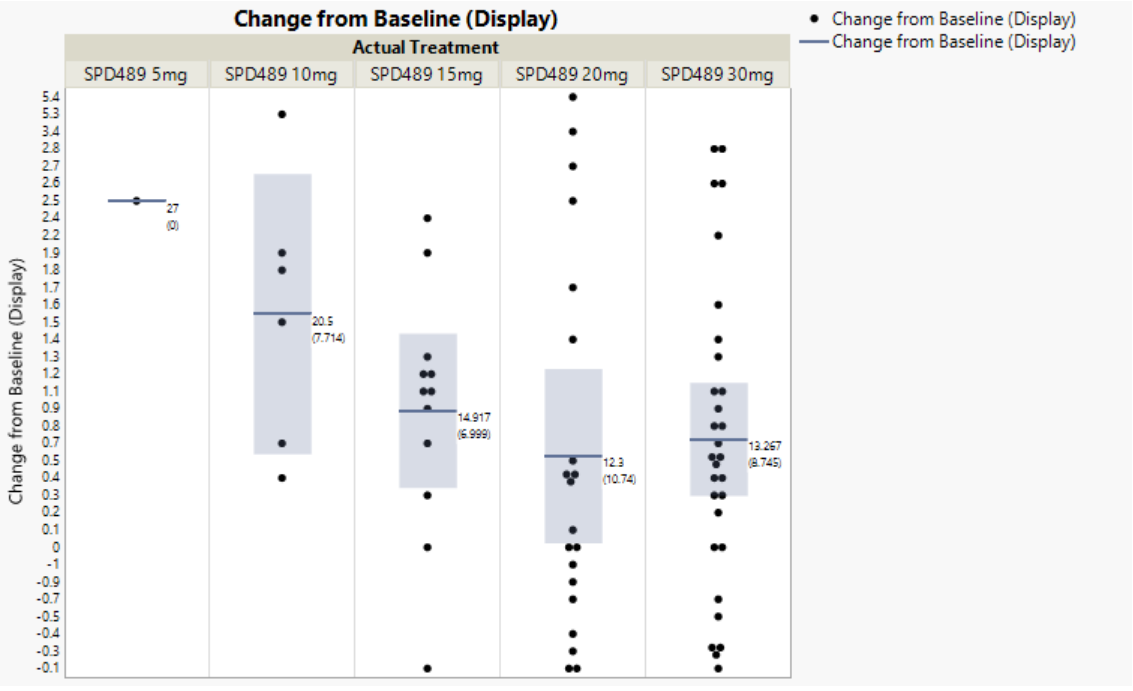
Figure 7: Mean (SD) Change in BMI from Baseline to Week 52/ET (Study 348)



Source: Reviewer created using JMP Clinical 8.0.

The least amount of weight gain (mean (SD) kilograms per treatment arm) over 1 year occurred in the 20-mg and 30-mg groups, respectively: 12.3(10.7)kg and 13.3(8.7) kg shown in Figure 8. For context, the mean weight gain in the 10- mg group was 20.5(7.7) kg.

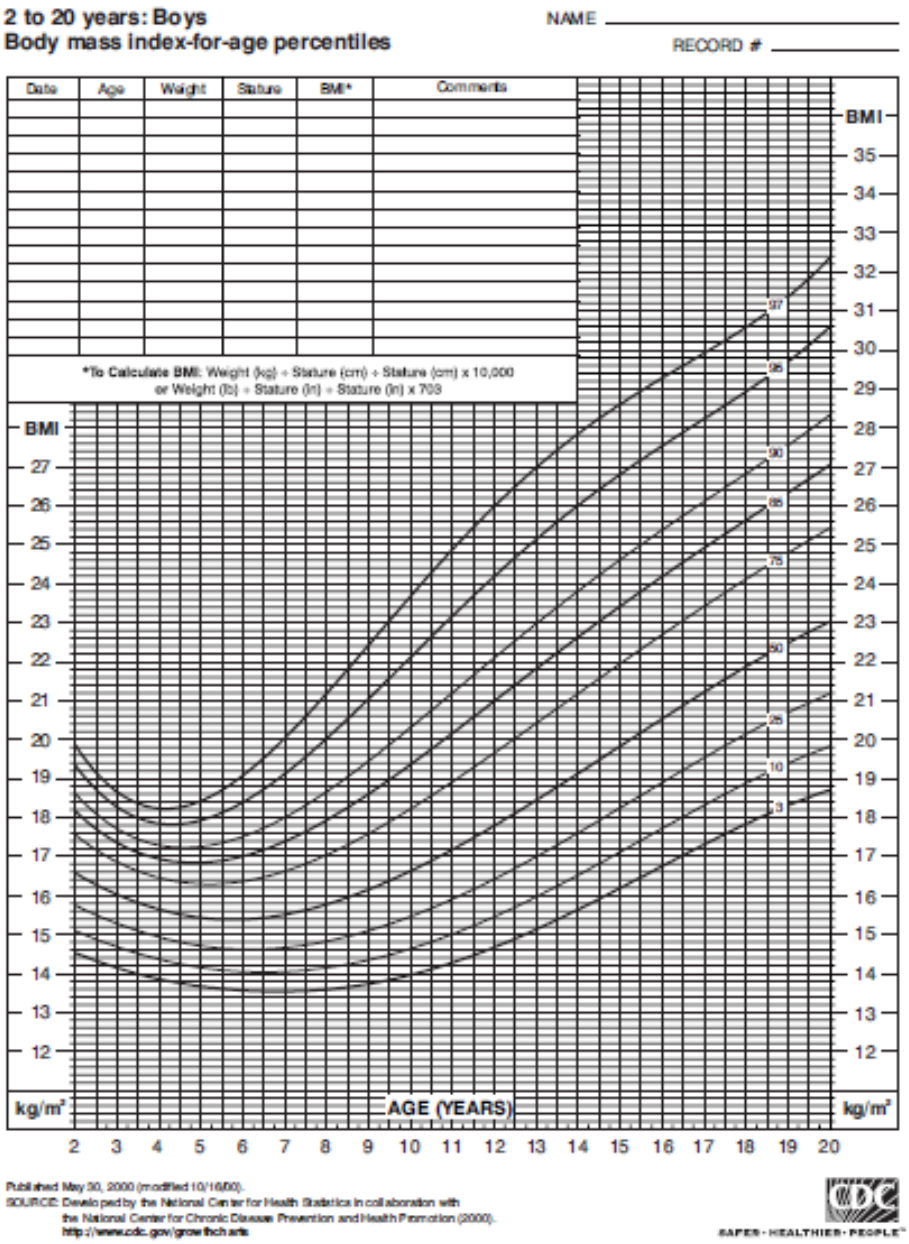
Figure 8: Mean (SD) Change is Weight (kg) from Baseline to Week 52/ET (Study 348)



Source: Reviewer created using JMP Clinical 8.0.

Using the data from the 69 completers, the clinical reviewer analyzed (using Microsoft Excel) baseline BMI and change in BMI after Week 52/ET in individual outlier patients instead of only examining the mean group BMI change; these values were plotted relative to standard percentiles for age on CDC Growth Curve Charts. For context, Figure 9 is the chart for males.

Figure 9: CDC BMI Index for Age Percentiles for Males



Source: https://www.cdc.gov/growthcharts/data/set2clinical/cj41l073.pdf

Of the 45 male patients who completed the trial, 26 of them had baseline BMIs on the 50th percentile curve or above on the Growth Chart. Most of those patients' change from baseline was not further evaluated, as their weight loss was less likely to be of clinical concern. However, three males who were at the 50th or greater percentile ended the 1-year trial in the ≤15th percentile, which is a marked and concerning drop.

Also concerning, there were 14 patients who were at <50th percentile at baseline who further declined in BMI by Week 52/ET. Of these, two ended the trial in the 15th percentile, three in the 10th percentile; two in the 5th percentile, and seven in the *3rd percentile or lower* on the Growth Chart. Underweight is defined as <5th percentile by the Applicant.

The same analysis of change in BMI from baseline was conducted for the 23 female completers from Study 347. Of the 23 female patients who completed the trial, 17 of them had baseline BMI's on the 50th percentile curve or above on the female Growth Chart. Most of those patients' change from baseline was not further evaluated due to less significant clinical concern. Yet, there were two of these females that weighed at ≤30th percentile on the Growth Chart at the end of the trial.

Six female patients who were at <50th percentile at baseline had a lower percentile BMI by Week 52/ET. Of these, one ended the trial in the 40th percentile, one in the 25th percentile; one in the 15th percentile, two in the 10th percentile, and *one in the 3rd percentile or lower* on the Growth Chart. Reasons for these outlier females experiencing less drastic decrease in BMI compared to the males may be:

- Only four female patients were taking lisdexamfetamine 20 mg, the rest of the 23 were taking 5-, 10-, or 15- mg/day.
- There were twice as many males in the trial as females.

Table 20 compiles the male and female BMI loss over time and where the resulting BMI puts the patients on their respective sex Growth Chart.

Overall, 11.6% of completer patients ended Study 348 at the ≤3rd percentile and 69.5% had a loss of at least 10 percentiles on the CDC Growth Chart for all doses of lisdexamfetamine.

Table 20: Percent of Patients at **≤3rd** percentile on Growth Chart after 1 year (Study 348)

7/14 (50 %) of male patients that started the trial at < 50th percentile ended at the ≤3rd percentile.	1/6 (17%) female patients that started the trial at <50th percentile ended at the ≤3rd percentile.
7/45 (16%) males aged 4 to 5 who completed the trial ended at ≤3rd percentile.	1/23 (4.3%) females aged 4 to 5 who completed the trial ended at ≤3rd percentile.
7+1= 8/69 (12%) completers ended the 52-week trial underweight based on loss of BMI.	

Source: Reviewer Analysis plotting Applicant BMI data onto CDC Growth Charts

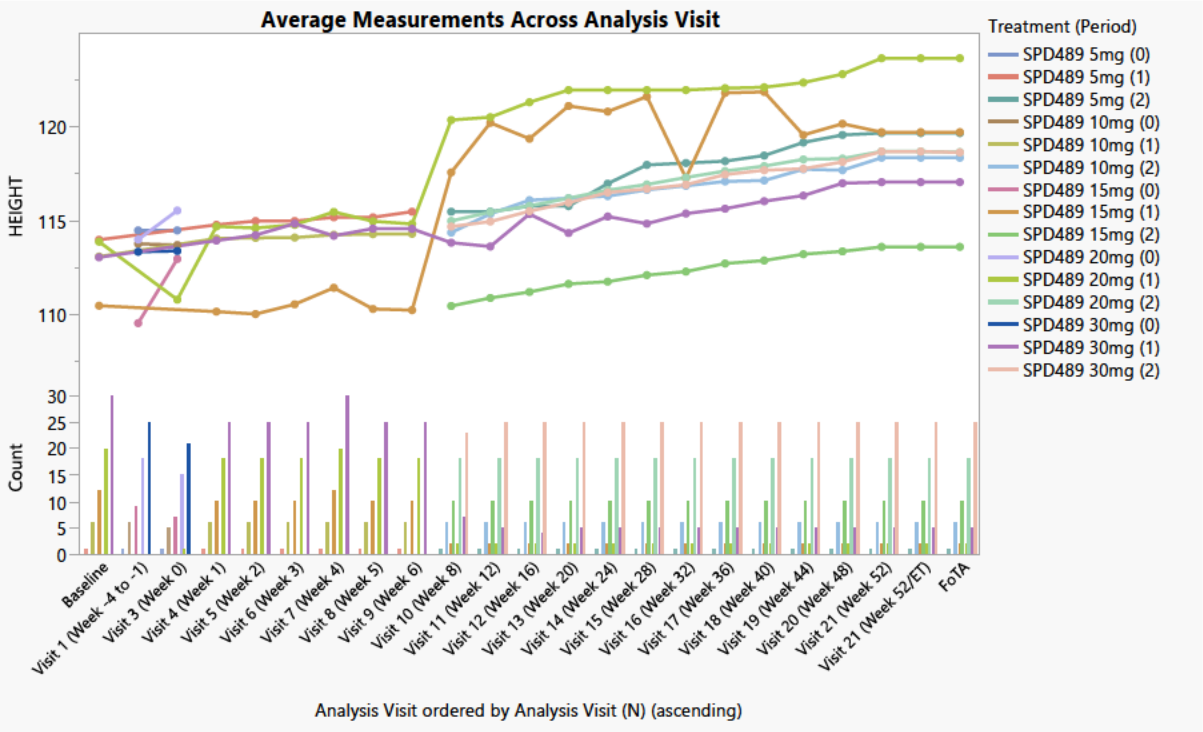
Rates of Decreased Appetite or Weight Loss from Open-label Long-term Safety Trials of Other Stimulants in the Preschool Population

The Division has open-label long-term safety data in the preschool population for two stimulants, Mydayis (mixed salts of single-entity amphetamine) and Aptensio XR (methylphenidate) for comparison to the safety results of lisdexamfetamine after 1 year. After 6 months taking open-label Mydayis 6.25 mg/day, patients reported decreased appetite 7/140 (5%) and weight decreased 9/140 (6.4%). After 1 year of taking Aptensio XR, 20 of 39 (51%) patients' weight percentiles decreased by at least 10 percentiles on the CDC Growth Chart for weight. The range of decreased percentiles was -10 to -42. Only one patient ended the trial in the 5th percentile.

Long-term lisdexamfetamine use was associated with greater loss of BMI and decreased weight percentiles (12% patients ended at ≤3rd weight percentile, and 70% dropped at least 10 percentiles) for lisdexamfetamine than that seen in Mydayis and Aptensio XR for the same age group. Of interest, Mydayis already received a limitation of use for younger children below age 13 (due partly to increased rates of decreased appetite), and Aptensio XR received a limitation of use for preschool-aged children in part due to this long-term weight loss signal. (See their respective clinical reviews for more details.)

Regarding height, during Study 348, the 4 to 5 year-old patients taking any dose of lisdexamfetamine did not appear to demonstrate slowed height velocity based on the overall trend of average height increased over 1 year, as in Figure 10. So we could not conclude that growth suppression occurred during this study (only weight loss which also likely drove the decrease in BMI values). However, longer-term consequences of ongoing drastic weight loss with chronic dosing could still hypothetically affect growth during the crucial developmental period of childhood.

Figure 10: Average Height (cm) from Baseline to Week 52/ET (Study 347)



Source: Reviewer created using JMP Clinical 8.0

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Although lisdexamfetamine is categorized as Schedule II due to risk of abuse, the preschool population is monitored and administered lisdexamfetamine by caregivers. Rates of overdose and abuse are minimally expected in this population.

8.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The postmarketing experience of lisdexamfetamine does not change the safety profile, and no unexpected or novel safety signals were identified.

Expectations on Safety in the Postmarket Setting

Based upon the LOU for patients aged 4 to 5, we expect to see a decrease in drug use data for children less than 6-years-old being prescribed lisdexamfetamine.

8.2.9. Integrated Assessment of Safety

The safety issues of insomnia/initial insomnia and decreased appetite in the safety and efficacy trial of lisdexamfetamine in patients aged 4 to 5 (Study 347) were the most

common and appeared to be dose-dependent, with AE rates generally the highest in the 30-mg treatment arm in Study 347. This finding led to further investigation of long-term loss of weight/BMI percentiles on the CDC Growth Chart for all doses of lisdexamfetamine in patients aged 4 to 5 in the year-long safety extension trial, Study 348. Of the 69 completers from the 1 year study, rates of patients whose percentiles dropped into the underweight category (<5th percentile) on the CDC Growth Chart were higher (12%) than those seen in Aptensio XR (3%), which has a Limitation of Use in its product labeling for the preschool-aged population for the same safety concern. Additionally, 70% (49/69) of patients taking lisdexamfetamine 5, 10, 15, 20 or 30 mg/day for 1 year, compared to 51% (20/39) of those taking Aptensio XR for 1 year, had a loss of at least 10 percentiles on the CDC Growth Chart. Therefore, (b) (4) lisdexamfetamine for treatment of ADHD (b) (4) and a limitation of use is recommended.

8.3. Statistical Issues

See the efficacy review for more details.

8.4. Conclusions and Recommendations

The Applicant, Takeda, conducted three trials in patients with ADHD aged 4 to 5. These trials serve to meet requirements for the PWR to grant pediatric exclusitivity and fulfillment of the PMRs from the lisdexamfetamine chewable tablet approval letter.

Based on one 6-week efficacy and safety trial and evaluation of the 1-year safety study, the benefits of lisdexamfetamine do not outweigh the risks in the preschool population. The risks will be discussed as a limitation of use (LOU) in labeling for this population. (b) (4)

9 Advisory Committee Meeting and Other External Consultations

None.

10 Pediatrics

The Division of Psychiatry (DP) consulted the Division of Pediatrics and Maternal Health (DPMH) to perform a labeling review and for participation in review related meetings including the Pediatric Review Committee (PeRC) and the Pediatric Exclusivity Board (PEB). Refer to the DPMH review dated April 5, 2021, for further information on labeling recommendations. Initial labeling recommendations from DPMH were predicated on the presumptive approval of the submission based on early discussions with DP and other consultants. Upon further review of the adverse event profile, particularly regarding weight and body mass index (BMI), DP and DPMH agreed that frequency and magnitude of these adverse effects (b) (4). Refer to DPMH addendum to review dated July 15, 2021.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

A Limitation of Use will be included in the Dosage and Administration section of labeling for patients with ADHD less than 6-years-old due to potentially severe long-term weight/BMI loss. Section 8.4 of the label was updated to describe that patients ages 4 to 5 were studied, and use of lisdexamfetamine for these patients is not recommended.

12 Risk Evaluation and Mitigation Strategies (REMS)

None.

13 Postmarketing Requirements and Commitment

None.

14 Division Director (Clinical) Comments

I have personally reviewed and edited the information above and agree with the conclusions of the review team.

15 Appendices

15.1. References

Emmerik-van Oortmerssen K, v. d. (2012). Prevalence of attention-deficit hyperactivity disorder in substance use disorder patients: A meta-analysis and meta-regression analysis. *Drug and Alcohol Dependence*, 11-19.

Kessler, R., & Adler L, B. R. (2006). The Prevalence and Correlates of Adult ADHD in the United States: Results from the National Comorbidity Survey Replication. *Am J Psychiatry*, 716-723.

Sharma A, C. J. (2014). A review of the pathophysiology, etiology and treatment of Attention-Deficit Hyperactivity Disorder (ADHD). In *Annals of Pharmacotherapy* (pp. 209-225).

15.2. Financial Disclosure

The Applicant provided financial disclosure for the PK study, the efficacy and safety trial, and the long-term safety trial. The form below is for the efficacy and safety trial, Study 347. See 8.1.2 Study Results for more information.

Covered Clinical Study (Name and/or Number): Study 347

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 53 total; The number of investigators without any significant payment is 45.		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 8		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 8 Proprietary interest in the product tested held by investigator: 0		

Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 8		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTOPHER E LEE
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BERNARD A FISCHER on behalf of TIFFANY R FARCHIONE
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