

CLINICAL REVIEW

Application Type 505(b)(2) NDA
Application Number(s) NDA 209905
Priority or Standard Standard

Submit Date(s) 3/30/2018
Received Date(s) 3/30/2018
PDUFA Goal Date 1/30/2019
Division / Office DPP/ODE I

Reviewer Name(s) John C. Umhau
Review Completion Date 01/28/2019

Established Name Racemic amphetamine sulfate
(Proposed) Trade Name Evekeo ODT
Therapeutic Class Stimulant
Applicant Arbor Pharmaceuticals

Formulation(s) Orally disintegrating tablets
Dosing Regimen 5, 10, 15, 20, (b) (4) mg
tablets, starting with 5 mg once
or twice daily: daily dosage may
be raised in increments of 5 mg
at weekly intervals until optimal
response is obtained. The first
dose should be taken upon
awakening and additional doses
(1-2) at intervals of 4 to 6 hours.

Indication(s) Attention Deficit Hyperactivity
Disorder
Intended Population(s) Children 6 years and older

Table of Contents

1. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	7
1.1 Recommendation on Regulatory Action	7
1.2 Risk-Benefit Assessment.....	7
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies	8
1.4 Recommendations for Postmarket Requirements and Commitments.....	8
2. INTRODUCTION AND REGULATORY BACKGROUND	8
2.1 Product Information	8
2.2 Table of Currently Available Treatments for Proposed Indication	8
2.3 Availability of Proposed Active Ingredient in the United States	10
2.4 Important Safety Issues with Consideration to Related Drugs	10
2.5 Summary of Presubmission Regulatory Activity	10
2.6 Other Relevant Background Information	11
3. ETHICS AND GOOD CLINICAL PRACTICES.....	12
3.1 Submission Quality and Integrity	12
3.2 Compliance with Good Clinical Practices	12
3.3 Financial Disclosures.....	12
4. SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES	13
4.1 Chemistry Manufacturing and Controls	13
4.2 Clinical Microbiology	13
4.3 Preclinical Pharmacology-Toxicology	13
4.4 Clinical Pharmacology	13
Mechanism of Action	13
Biopharmaceutics/Pharmacokinetics	13
4.5 Controlled Substances	15
4.6 Pediatric and Maternal Health	15
5. SOURCES OF CLINICAL DATA.....	15
5.1 Table of Clinical Trials	16
5.2 Review Strategy	16
6. REVIEW OF EFFICACY	16
7. REVIEW OF SAFETY	17
7.1 Methods	17
7.1.1 Studies Used to Evaluate Safety	17
7.1.2 Categorization of Adverse Events	17
7.1.3 Pooling of Data across Studies to Estimate and Compare Incidence	17
7.2 Adequacy of Safety Assessments	17

7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	17
7.2.2	Explorations for Dose Response.....	18
7.2.3	Special Animal and In Vitro Testing	18
7.2.4	Routine Clinical Testing.....	18
7.2.5	Metabolic, Clearance, and Interaction Workup	18
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class...	18
7.3	Major Safety Results.....	19
7.3.1	Deaths	19
7.3.2	Nonfatal Serious Adverse Events.....	19
7.3.3	Dropouts and Discontinuations	19
7.3.4	Significant Adverse Events.....	19
7.3.5	Submission-Specific Primary Safety Concerns	19
7.4	Supportive Safety Results	20
7.4.1	Common Adverse Events.....	20
7.4.2	Laboratory Findings.....	22
7.4.3	Vital Signs	23
7.4.4	Electrocardiograms (ECGs)	23
7.4.6	Immunogenicity	23
7.5	Other Safety Explorations.....	24
7.5.1	Dose Dependency for Adverse Events	24
7.5.2	Time Dependency for Adverse Events.....	24
7.5.3	Drug-Demographic Interactions	24
7.5.4	Drug-Disease Interactions.....	24
7.5.5	Drug-Drug Interactions	24
7.6	Additional Safety Evaluations	24
7.6.1	Human Carcinogenicity	24
7.6.2	Human Reproduction and Pregnancy Data.....	24
7.6.3	Pediatrics and Assessment of Effects on Growth	24
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound	24
7.7	Additional Safety Issue.....	24
8.	POSTMARKET EXPERIENCE.....	24
9.	APPENDICES.....	25
9.1	References	25
9.2	Labeling Recommendations	25
9.3	Advisory Committee Meeting.....	26
9.4	Review of Study AR11.001	26
9.4.1	Introduction	26
9.4.2	Review Strategy	26
9.4.3	Efficacy Summary	26
9.4.4	Methods.....	26
9.4.5	Patient Selection	28

9.4.6 Assessments	28
9.4.7 Analysis Plan.....	30
9.4.8 Demographics	31
9.4.9 Subject Disposition.....	31
9.4.10 Analysis of Endpoints	31
Primary Endpoint.....	31
Secondary Endpoints	33
9.4.11 Other Endpoints	34
9.4.12 Subpopulations	34
9.4.13 Analysis of Clinical Information Relevant to Dosing Recommendations	34
9.4.14 Discussion of Persistence of Efficacy and/or Tolerance Effects	34
9.4.15 Additional Efficacy Issues/Analyses	34
9.4.16 Safety Summary	35
9.4.17 Safety Monitoring	35
9.4.18 Categorization of Adverse Events	35
9.4.19 Overall Exposure at Appropriate Doses/Durations.....	35
9.4.20 Special Animal and/or In Vitro Testing	35
9.4.21 Routine Clinical Testing	36
9.4.22 Metabolic, Clearance, and Interaction Work	36
9.4.23 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.....	36
9.4.24 Major Safety Results	36
Deaths:	36
Nonfatal Serious Adverse Events:	36
Dropouts and/or Discontinuations:	36
Significant Adverse Events:	36
Submission Specific Primary Safety Concerns:	36
9.4.25 Common Adverse Events	37
9.4.26 Laboratory Findings	39
9.4.27 Vital Signs	39
9.4.28 Electrocardiograms (ECGs)	41
9.4.29 Special Safety Studies/Clinical Trials.....	41
9.4.30 Immunogenicity	41
9.4.31 Other Safety Explorations	41
Dose Dependency for Adverse Events:	41
Time Dependency for Adverse Events:.....	41
9.4.32 Drug-Demographic Interactions	41
9.4.33 Drug-Disease Interactions.....	41
9.4.34 Drug-Drug Interactions.....	41
9.4.35 Human Carcinogenicity	41
9.4.36 Human Reproduction and Pregnancy Data.....	41
9.4.37 Pediatrics and Assessment of Effects on Growth	41
9.4.38 Overdose, Drug Abuse, Withdrawal and Rebound	41
9.4.39 Conclusions	42

Table of Tables

Table 1. Currently Available ADHD Medications.	9
Table 2: Pharmacokinetic Parameters of d & l Amphetamine.	14
Table 3: Pharmacokinetic Parameters of <i>d</i> & <i>l</i> -Amphetamine under Fed and Fasted Conditions.	15
Table 4: Clinical Studies Supporting the NDA Application	16
Table 5: Subject Demographics.....	18
Table 6: Discontinuations during Studies AR17.001 and AR17.002	19
Table 7: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term—Study AR17.001.....	21
Table 8: Treatment-emergent Adverse Events by System Organ Class and Preferred Term—Study AR17.002.....	22
Table 11. AR11.001 Schedule of Assessments.	30
Table 12. Demographics and Baseline Characteristics, Study AR11.001.....	31
Table 13. Time Course of Effect on SKAMP-Combined Scores.	34
Table 14. Treatment-emergent Adverse Events during the Double-blind Phase, Study AR11.001.	38
Table 15. TEAEs Occurring in $\geq 2\%$ of Subjects During AR11.001 Open-label Phase..	39
Table 16. Out-of-Range Vital Signs During AR11.001.	40

Table of Figures

Figure 1. U.S. Medical Consumption of Amphetamine and Methylphenidate.	11
Figure 2. Change in Pulse, Study AR17.001 at 2 Hours Postdose.	23
Figure 3. AR11.001 Study Diagram.....	28
Figure 4. LS Mean SKAMP-combined Scores after 1 Week Double-blind Treatment. ..	33

1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Applicant has demonstrated bioequivalence to Evekeo immediate release (IR), the reference listed drug (RLD). No new safety findings were identified that would indicate a difference in the risk-benefit considerations for this form of amphetamine to treat attention deficit hyperactivity disorder at doses of 5, 10, and 20 mg. (b) (4)

Therefore, I recommend approval of the 5, 10, and 20 mg dose forms (b) (4)

The Applicant conducted a study in younger children to fulfill a post marketing requirement for Evekeo IR and the results of this clinical trial were included with this application for inclusion in section 14 of labeling. This study will be described an appendix to the Evekeo ODT review.

1.2 Risk-Benefit Assessment

There are a number of stimulant-based treatments for ADHD available at this time. However, the added benefit of another amphetamine dosing form option convenient for children, with no known increased risk, supports the approval of this application.

The Applicant has proposed dose forms of 5, 10, 20, (b) (4) mg compared to the RLD, which is only available in 5 and 10 mg tablets. The RLD labeling describes dosing for Evekeo IR as

The recommended starting dose of EVEKEO ODT for patients 6 to 17 years of age is 5 mg once or twice daily. If necessary, administer an additional dose after 4 to 6 hours. Titrate the dosage in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg daily.

In clinical practice, IR stimulants are usually administered twice per day. (b) (4)

(b) (4)

I recommend approval of only the 5, 10, 15, and 20 mg dose forms.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

The RLD is labeled down to 3 years old. However, the Applicant will be required to make a smaller dosage form (2.5 mg) as a PMR.

2. Introduction and Regulatory Background

Arbor Pharmaceuticals has submitted a 505(b)(2) application for an oral dissolving tablet (ODT) formulation referencing Evekeo IR.

2.1 Product Information

Racemic amphetamine sulfate formulated as immediate release (IR) tablets, (Evekeo (ANDA 200166 approved August 9, 2012)) is a stimulant indicated for treatment of ADHD, narcolepsy, and exogenous obesity. This 505(b)(2) NDA application is for an oral dissolving tablet (ODT) formulation referencing Evekeo as the RLD with a proposed indication for ADHD. The Applicant plans the following strengths for the ODTs: 5, 10, 15, 20, (b) (4) mg. The dosage and administration information for the ODTs will follow FDA-approved dosage and administration labeling for the RLD, Adderall IR mixed amphetamine salts tablets (NDA 11522), and dextroamphetamine sulfate IR tablets ((b) (4) ANDA 90533).

2.2 Table of Currently Available Treatments for Proposed Indication

A wide variety of interventions are used to treat ADHD including drug products, psychological interventions, complementary and alternative remedies, and dietary management.¹ Although these many modalities are all used for ADHD, the mainstay of treatment remains pharmacological. Most approved drugs are psychostimulants, although several antidepressants are used off-label (e.g., desipramine, nortriptyline, imipramine, and bupropion).

Methylphenidate and amphetamine are available in a multitude of drug delivery systems that extend the duration of action of these medications. Intermediate-acting formulations are designed to cover the school hours with a once daily dose preparation. Long-acting compounds are designed to cover both the school day and afterschool hours with a single dose given in the morning before school. Longer-acting formulations can then be complemented with immediate-release preparations for additional ADHD coverage as

needed. A methylphenidate-IR solution formulation and a long-acting methylphenidate extended release solution preparation are available for children who have difficulty swallowing pills and capsules. Although amphetamine is available as an extended release solution and an extended release orally disintegrating formulation, there is no immediate release amphetamine product available for children who have difficulty swallowing pills.

Table 1. Currently Available ADHD Medications.

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, 50, 60 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, 15, 20, 25, 30 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
		Tablet	0.1, 0.2, 0.3 mg
	Clonidine	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

Other Treatments used for ADHD

- Approved Pharmaceuticals used off label
 - Antidepressants: bupropion, desipramine, venlafaxine, reboxetine
 - Other Drugs: modafinil
- Complementary and alternative medicine interventions
 - Dietary therapy
 - Polyunsaturated fatty acids
 - Amino acids (L-carnitine)

- Minerals (zinc, iron)
 - Herbal therapy (St John's wort, Ginkgo biloba)
- Psychological interventions
 - Behavioral therapy: parent training; child, parent and/or teacher training
 - Cognitive training: working memory training; attention training
 - Other psychotherapies

2.3 Availability of Proposed Active Ingredient in the United States

Amphetamine is currently Schedule II in the United States. It is available by prescription as a brand-name product and generic in a variety of formulations (see Table 1).

2.4 Important Safety Issues with Consideration to Related Drugs

Amphetamines carry a boxed warning for abuse and dependence as well as sudden death and serious cardiovascular adverse reactions when misused. Other warnings and precautions include risk of increased blood pressure, psychosis or mania, long-term suppression of growth, seizure, peripheral vasculopathy (including Raynaud's phenomenon), serotonin syndrome (when combined with serotonergic agents or in an overdose setting), blurred vision, and exacerbation of tics. Other adverse reactions include loss of appetite, insomnia, abdominal pain, nausea and vomiting, nervousness, headache, dry mouth, and fever.

2.5 Summary of Presubmission Regulatory Activity

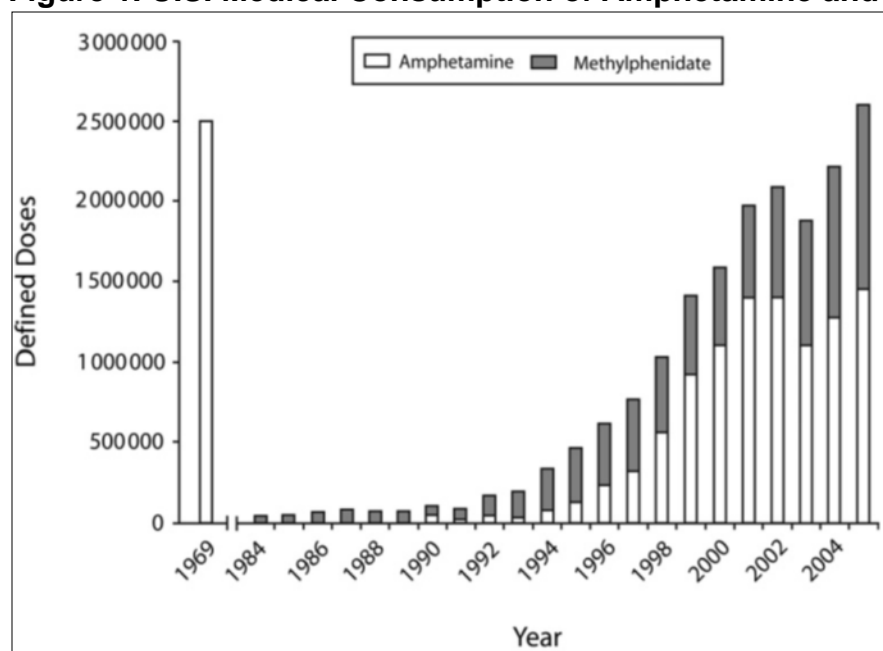
A Written-Response Only (WRO) meeting dated November 7, 2018 provided FDA feedback on the Applicant's clinical, pharmacokinetics, toxicology, CMC, and regulatory plan to develop an amphetamine sulfate ODT for purposes of an NDA submission. This plan included a pivotal comparative bioavailability study involving healthy adult volunteers to evaluate the rate and extent of oral absorption of amphetamine from an amphetamine sulfate ODT compared with Arbor's FDA-approved immediate release (IR) 10 mg amphetamine sulfate (Evekeo). FDA advised that the Applicant conduct a 3-way crossover study where the ODT is administered with water (i.e., swallowed intact) and without water (i.e., allowed to disintegrate in the mouth and then swallowed) and compared to the RLD conventional oral dosage form administered with water under fasting conditions. In the WRO, referring to Question 4, FDA noted that:

The CFR's Bioavailability or Bioequivalence (BA/BE) requirements for all strengths of your proposed ODT product not included in the pivotal BE study may be waived if the following requirements are met ...c) There are clinical safety and efficacy data on the proposed doses.

2.6 Other Relevant Background Information

Amphetamine was discovered by Gordon Alles in 1929 and was initially marketed for use and as a decongestant in 1929.² During World War II, amphetamine was used extensively for its stimulant and performance-enhancing effects and was issued to service members to use in combat. In 1945, over half a million civilians were using the drug for stimulant, anti-depressant, or weight loss properties—and the consumption rate in the United States was greater than two tablets per person per year. By 1962, the consumption rate was 65 doses per person per year. At this time, evidence emerged that amphetamine was addictive, leading to the passage of the 1970 Comprehensive Drug Abuse Prevention and Control Act. This act defines the modern set of controlled substance “schedules” and allowed authorities to establish production quotas for the most strictly controlled schedules, I and II. Under the supply controls, amphetamines became relatively minor drugs of abuse by the late 1970s. Amphetamine sulfate (Benzadrine) was initially approved in the United States in 1976. Amphetamine is currently Schedule II in the United States, and its use has increased as noted in Figure 1. As of 2002, there were approximately 303,000 individuals characterized as having physical dependency or addiction to amphetamine.

Figure 1. U.S. Medical Consumption of Amphetamine and Methylphenidate.



Defined dosages: 10 mg amphetamine and 30 mg methylphenidate, anhydrous base.

Source: *American Journal of Public Health* 98.6 (2008): 974-985.

3. Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The application was submitted via eCTD. All required datasets were included. The Applicant did not prospectively submit individual case report forms (CRFs) since there were no deaths or serious adverse events. On examination, preferred terms appeared to accurately reflect investigator verbatim terms.

3.2 Compliance with Good Clinical Practices

The Quality Assurance Unit from Worldwide Clinical Trials Early Phase Services, LLC, inspected and audited study sites to assure compliance with Good Clinical Practices. 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 as OSIS recently conducted an inspection.

3.3 Financial Disclosures

Was a list of clinical investigators provided: Yes ☒ No ☐

Total number of investigators identified: 7

Number of investigators who are Applicant employees (including both full-time and part-time employees): 0

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0

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:

Significant payments of other sorts:

Proprietary interest in the product tested held by investigator:

Significant equity interest held by investigator in sponsor of covered study:

Is an attachment provided with details of the disclosable financial interests/arrangements: Yes ☐ No ☐ N/A ☒

Is a description of the steps taken to minimize potential bias provided: Yes ☐ No ☐ N/A ☒

Number of investigators with certification of due diligence (FDA 3454, box 3) 0

Is an attachment provided with the reason: Yes ☐ No ☐ N/A ☒

4. Significant Issues from Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CMC was initially concerned with the size of the (b) (4)

4.2 Clinical Microbiology

Not Applicable.

4.3 Preclinical Pharmacology-Toxicology

Not Applicable.

4.4 Clinical Pharmacology

Mechanism of Action

Amphetamines increase extracellular dopamine via action on the dopamine active transporter and by triggering dopamine-containing vesicles to release. The pathological basis for ADHD is currently unknown—as is the reason for stimulant efficacy in the disorder.

Biopharmaceutics/Pharmacokinetics

The Applicant submitted two studies in support of this NDA.

- Comparative Bioavailability Study AR17.001, entitled, “Comparative Bioavailability Study of Single-Dose Amphetamine Sulfate Oral Disintegrating Immediate Release Tablets (ODT-IR) Swallowed Intact with Water, versus Single-Dose ODT-IR Tablets Disintegrated/Dissolved in the Oral Cavity Swallowed without Water, versus Amphetamine Sulfate Immediate Release (IR) Reference Tablets (Evekeo) Administered to Fasting, Healthy Adult Volunteers.”
- Food-Effect Bioavailability Study AR17.002, entitled, “A Single-Dose, Two-Period, Two-Way Crossover Bioavailability Study of Amphetamine Sulfate Oral Disintegrating Immediate Release Tablets (ODT-IR) 20 mg Administered to Healthy Adult Volunteers under Fed and Fasted Conditions.”

Pharmacokinetic parameters were within acceptable limits to establish bioequivalence between the Evekeo ODT clinical trial formulation and the RLD:

- d,l-amphetamine concentrations after administration of Evekeo ODT with or without water is equivalent to that of the RLD, (Table 2)
- Food does not have significant effect on the exposures (C_{max} , AUC) to d,-amphetamine after administration of Evekeo ODT under fed and fasting conditions. Evekeo ODT can be administered with or without food, (Table 3)
- The dosing regimen of the RLD is acceptable for Evekeo ODT

Table 2: Pharmacokinetic Parameters of d & l Amphetamine.

Drug	Population	AUC _{last} ng·hr/mL (SD)	C _{max} ng/mL (SD)	T _{max} hour (SD)	t _{1/2} hour (SD)
d-Amphetamine					
Treatment A: Amphetamine ODT-IR 20 mg with Water	Child, ADHD	494 (96.1)	29.9 (5.28)	2.74 (0.909)	10.0 (1.38)
Treatment B: Amphetamine ODT-IR 20 mg without Water	Healthy Adult	493 (105)	29.4 (5.94)	3.28 (0.698)	10.0 (1.41)
Treatment C: Evekeo (RLD) 2 x 10 mg with Water	Healthy Adult	479 (86.3)	29.4 (4.93)	2.51 (0.936)	10.1 (1.55)
l-Amphetamine					
Treatment A: Amphetamine ODT-IR 20 mg with Water	Child, ADHD	485 (96.1)	25.1 (4.29)	3.03 (1.14)	11.6 (1.80)
Treatment B: Amphetamine ODT-IR 20 mg without Water	Healthy Adult	486 (105)	24.8 (4.92)	3.45 (1.02)	11.8 (2.25)
Treatment C: Evekeo (RLD) 2 x 10 mg Tablets with Water	Healthy Adult	471 (79.4)	24.8 (4.28)	2.72 (1.13)	11.6 (2.04)

Table 3: Pharmacokinetic Parameters of *d* & *l*-Amphetamine under Fed and Fasted Conditions.

Parameter	<u>Treatment A:</u> Amphetamine Sulfate ODT-IR 20 mg, Fed		<u>Treatment B:</u> Amphetamine Sulfate ODT-IR 20 mg, Fasted	
	Mean	SD	Mean	SD
<i>d</i>-Amphetamine				
T _{max} (h)	4.47	1.2	3.05	1.1
C _{max} (ng/mL)	26.7	4.6	28.0	6.0
AUC _{last} (h*ng/mL)	457	98.5	483	103.0
T _{1/2} (h)	10.1	1.5	10.8	2.0
<i>l</i>-Amphetamine				
T _{max} (h)	4.82	1.3	3.00	1.1
C _{max} (ng/mL)	23.1	4.1	24.1	5.1
AUC _{last} (h*ng/mL)	443	95.5	476	98.1
T _{1/2} (h)	12.0	1.9	13.4	3.4

4.5 Controlled Substances

Amphetamine is currently DEA schedule II and is a known drug of abuse. In a recent national survey, of the approximately 16.0 million U.S. adults who reported prescription stimulant use in the preceding year, 5.0 million reported misuse, and 0.4 million had use disorders.² One household survey of stimulant abuse found that approximately half of the 3.2 million individuals who reported non-medical stimulant use in the last year used only pharmaceutical stimulants and a quarter had only ever used pharmaceuticals. The same survey estimated that of the 300,000 Americans addicted to amphetamine, a third had only ever used prescription stimulants.

The Controlled Substances Staff (CSS) was consulted as part of the November 7, 2014 WRO. They noted that pharmacokinetic (PK) properties are important for determining the abuse potential of a drug. CSS described the importance of determining the early time points after ODT administration because of concern that an ODT might release drug faster than a conventional immediate release tablet. However, there were no significant differences at early time points noted in absorption noted in study AR17.001.

4.6 Pediatric and Maternal Health

There is no pertinent new data in this application.

5. Sources of Clinical Data

The clinical material in support of this NDA application includes one clinical comparative bioavailability study (AR17.001) and one clinical food effect bioavailability study (AR17.002). No other in-vivo or in-vitro biopharmaceutic, clinical pharmacology or

pharmacokinetic studies were performed in the Evekeo ODT development program.

5.1 Table of Clinical Trials

Table 4: Clinical Studies Supporting the NDA Application

Study	Study Objective	Study Design	Subjects	Treatment
AR17.001 Comparative Bioavailability Study	To compare the bioavailability of amphetamine from (1) Evekeo ODT swallowed with water, (2) Evekeo ODT dissolved in the oral cavity and then swallowed without water, and (3) the RLD swallowed with water, all under fasting condition.	Single-dose open-label, randomized, 3- period, 3- treatment, 6- sequence, crossover study design.	Healthy adult volunteers N=42 enrolled and N=37 completed M/F: 20/22 enrolled 18 to 45 years of age	Test Product: Treatment A , Evekeo ODT 1 x 20 mg tablet swallowed intact with water. Treatment B , Evekeo ODT 1 x 20 mg tablet dissolved in oral cavity then swallowed without water. Reference Product: Treatment C , RLD 2 x 10 mg tablets swallowed intact with water.
AR17.002 Food Effect Bioavailability Study	To compare the rate of absorption and oral bioavailability of Evekeo ODT 20 mg when administered under fed and fasted conditions.	Single-dose, open-label, randomized, 2- period, 2- treatment crossover study design.	Healthy adults N=32 enrolled and N=31 completed [M/F: 23/9 enrolled] 18-45 years of age	Evekeo ODT 1 x 20 mg tablet was administered in Treatment A (fed condition, i.e., Test) and Treatment B (fasted condition, i.e., Ref).

5.2 Review Strategy

Considering that there are no efficacy studies, this review focuses on the safety record of the bioequivalence (BE) and food effect studies in Table 4.

6. Review of Efficacy

The Applicant did not conduct any clinical efficacy studies; this application relies on the findings of efficacy and safety from the RLD. Study AR17.001 demonstrates the bioequivalence of Evekeo ODT to Evekeo IR (the RLD; ANDA 200166); ANDA 200166 refers to NDA 83901 (Amphetamine Sulfate tablets, approved August 31, 1984) held by Lannett. Therefore, this study provides a bridge to safety and efficacy data from Lannett's NDA for Amphetamine Sulfate tablets.

Study AR11.001, entitled "A Multicenter, Dose-Optimized, Double-Blind, Randomized, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of AR11 in Pediatric Patients (Ages 6-12) with Attention Deficit Hyperactivity Disorder (ADHD) in a Laboratory Classroom" was submitted for inclusion in section 14 of the Evekeo ODT label. It is a study of the RLD, Evekeo IR, and is reviewed in the Appendix.

7. Review of Safety

Safety Summary

No new, unlabeled safety signals were identified in the Evekeo ODT development program. Given the extensive safety experience to date with amphetamine, the relatively brief duration of the bioequivalence and food effect studies (single dose studies), and the subject population (mostly healthy adult volunteers), these two PK studies are not expected to produce meaningful new safety data that could be extrapolated to the clinical use of Evekeo ODT.

7.1 Methods

7.1.1 Studies Used to Evaluate Safety

Two biopharmaceutical clinical studies were performed in the Evekeo ODT development program: AR17.001 and AR17.002. Safety parameters included clinical laboratory evaluations, physical and oral cavity examinations, vital signs, ECGs, and AE documentation and follow-up.

7.1.2 Categorization of Adverse Events

Adverse Events were coded by system organ class and preferred term based on the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary version 19.0

7.1.3 Pooling of Data across Studies to Estimate and Compare Incidence

Not Applicable

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A 20-mg form of the ODT was evaluated in Study AR17.001. There was no data presented on the (b) (4). In the November 7, 2014 WRO, Question 4, the FDA commented on the acceptability of a BA waiver for all proposed doses. We noted, among other factors, the need for clinical safety and efficacy data on the proposed doses. (b) (4)

(b) (4)

Table 5: Subject Demographics.

		Study	
		AR17.001 N=42	AR17.002 N=32
Age, years	M (SD)	31.6 (6.9)	30.9 (5.0)
	Range	19 to 41	22 to 40
Female Sex, % (n)		52 (22)	28 (9)
Race, % (n)	Asian	5 (2)	3 (1)
	Black/African-American	19 (8)	31 (10)
	White	76 (32)	65 (20)
	Other	0	3 (1)
Hispanic, % (n)		33 (14)	53 (17)

Reviewer note: Based on [2015 U.S. Census Department data](#), African-Americans (13 percent of the U.S. Population) were slightly over-represented in these studies. However, these differences are relatively small, and unlikely to be important in pharmacokinetic cross-over studies where each subject acts as his or her own control. I do not expect that the subjects' demographics had an impact on these bioequivalence studies.

7.2.2 Explorations for Dose Response

Not provided.

7.2.3 Special Animal and In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

The studies conducted were bioequivalence studies. No new information was presented on amphetamine metabolism, clearance, or drug interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

To assess for ECG changes, increased blood pressure and pulse, investigators measured these at screening and 2 and 4 hours after dosing in Study AR17.001 and AR17.002. Subjects received study drug in an inpatient setting to monitor closely for AEs. Laboratory tests, physical exams, and electrocardiograms (ECGs) were also collected pre- and post-study.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during the studies.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events (SAEs) during either study AR17.001 or AR17.002.

7.3.3 Dropouts and Discontinuations

There were no dropouts due to adverse events in any study.

Table 6: Discontinuations during Studies AR17.001 and AR17.002

Study	Subject ID	Discontinuation Reason
AR17.001	(b) (6)	Discontinued at the Period 2 check-in due to protocol deviation/ non-compliance.
		Discontinued at the Period 3 check-in due to protocol deviation/ non-compliance
		Discontinued at the Period 3 check-in due to protocol deviation/ non-compliance
		Discontinued at the Period 3 check-in due to protocol deviation/ non-compliance
AR17.002		Positive urine drug and cotinine test at the Period 2 check-in

7.3.4 Significant Adverse Events

There were no significant adverse events during either study AR17.001 or AR17.002.

7.3.5 Submission-Specific Primary Safety Concerns

There were no submission-specific primary safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

There was no placebo administered during the submitted studies and so AEs can only be compared to the RLD. There were no signals for unusual or increased rates of AEs with the ODT formulation compared to the RLD (see Tables 7 and 8).

Study AR17.001

In study AR17.001, a total of 15 treatment-emergent adverse events (TEAEs) were reported by eight subjects over the course of the study, all following dose administration. Five TEAEs were reported by four subjects (9.5%) after each of the study treatments. One TEAE was moderate in severity (dermatitis contact following Treatment B) and the rest were mild. All TEAEs during study AR17.001 are shown in Table 7. The most common TEAE was headache, reported three times by two different subjects (one subject (2.4%) following Treatment B and two subjects (4.8%) following Treatment C). None of the TEAEs were related to abnormal laboratory evaluations, vital signs, or ECGs.

Table 7: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term—Study AR17.001

	Treatment A Evekeo ODT with Water (n=)	Treatment B Evekeo ODT without Water (n=)	Treatment C Evekeo IR (n=)	Overall
System Organ Class Preferred Term	Subjects n (%)	Subjects n (%)	Subjects n (%)	Subjects n (%)
Any TEAE	4 (9.5)	4 (9.5)	4 (9.5)	8 (19.0)
Gastrointestinal disorders	2 (4.8)	2 (4.8)	1 (2.4)	4 (9.5)
Abdominal pain	0	1 (2.4)	0	1 (2.4)
Aphthous ulcer	1 (2.4)	0	0	1 (2.4)
Dry mouth	0	0	1 (2.4)	1 (2.4)
Dyspepsia	0	1 (2.4)	0	1 (2.4)
Nausea	1 (2.4)	0	0	1 (2.4)
Injury, poisoning, and procedural complications	0	0	1 (2.4)	1 (2.4)
Laceration	0	0	1 (2.4)	1 (2.4)
Musculoskeletal and connective tissue disorders	0	1 (2.4)	0	1 (2.4)
Back pain	0	1 (2.4)	0	1 (2.4)
Nervous system disorders	1 (2.4)	1 (2.4)	2 (4.8)	3 (7.1)
Dizziness	1 (2.4)	0	0	1 (2.4)
Headache	0	1 (2.4)	2 (4.8)	2 (4.8)
Respiratory, thoracic, and mediastinal disorders	1 (2.4)	0	1 (2.4)	2 (4.8)
Nasal congestion	1 (2.4)	0	1 (2.4)	2 (4.8)
Skin and subcutaneous tissue disorders	1 (2.4)	1 (2.4)	0	2 (4.8)
Dermatitis contact	1 (2.4)	1 (2.4)	0	2 (4.8)

Treatment A = 1 x 20 mg Evekeo ODT swallowed intact with water.

Treatment B = 1 x 20 mg Evekeo ODT disintegrated in the oral cavity, then swallowed without water.

Treatment C = 2 x 10 mg Evekeo IR (RLD) swallowed intact with water.

Study AR17.002

Of the 32 subjects who participated in the study, 31 completed both study periods. One randomized subject, Subject (b) (6) was terminated at the Period 2 check-in due to protocol deviation/non-compliance (positive urine drug and cotinine testing). No AEs were serious or led to subject discontinuation. A total of 11 AEs were reported by six subjects over the course of the study, all following dose administration. Four AEs were reported by three subjects (3/31, 9.7%) following Treatment A (fed), and seven AEs were reported by five subjects (5/32, 15.6%) following Treatment B (fasted). All 11 AEs during the study were mild in severity and resolved by the end of the study without intervention. The most common TEAEs were palpitations (reported by two subjects following Treatment B) and change in sustained attention (reported once after Treatment A and once following Treatment B by the same subject). No AEs were related to clinically

significant abnormalities in laboratory evaluations, physical or oral cavity examinations, vital signs, or ECGs.

Table 8: Treatment-emergent Adverse Events by System Organ Class and Preferred Term—Study AR17.002.

	Treatment A Evekeo ODT Fed (n=32)	Treatment B Evekeo ODT Fasted (n=31)	Overall
Organ Class Preferred Term	Subjects n (%)	Subjects n (%)	Subjects n (%)
Any AE	3 (9.7)	5 (15.6)	6 (18.8)
Cardiac Disorders	0	2 (6.3)	2 (6.3)
Palpitations	0	2 (6.3)	2 (6.3)
Gastrointestinal Disorders	1 (3.2)	1 (3.1)	2 (6.3)
Constipation	1 (3.2)	0	1 (3.1)
Dry mouth	0	1 (3.1)	1 (3.1)
General Disorders	1 (3.2)	0	1 (3.1)
Fatigue	1 (3.2)	0	1 (3.1)
Nervous System Disorders	1 (3.2)	2 (6.3)	2 (6.3)
Hyperaesthesia	1 (3.2)	0	1 (3.1)
Paraesthesia	0	1 (3.1)	1 (3.1)
Tension headache	0	1 (3.1)	1 (3.1)
Psychiatric Disorders	1 (3.2)	2 (6.3)	2 (6.3)
Anxiety	0	1 (3.1)	1 (3.1)
Change in sustained attention	1 (3.2)	1 (3.1)	1 (3.1)

Treatment A=Amphetamine Sulfate ODT, 20mg Fed
Treatment B=Amphetamine Sulfate ODT, 20mg Fasted

Reviewer note: The adverse reactions reported are expected for this class of drugs. There is no indication that the ODT formulation has any risks (e.g., oral AEs) that are different from the RLD.

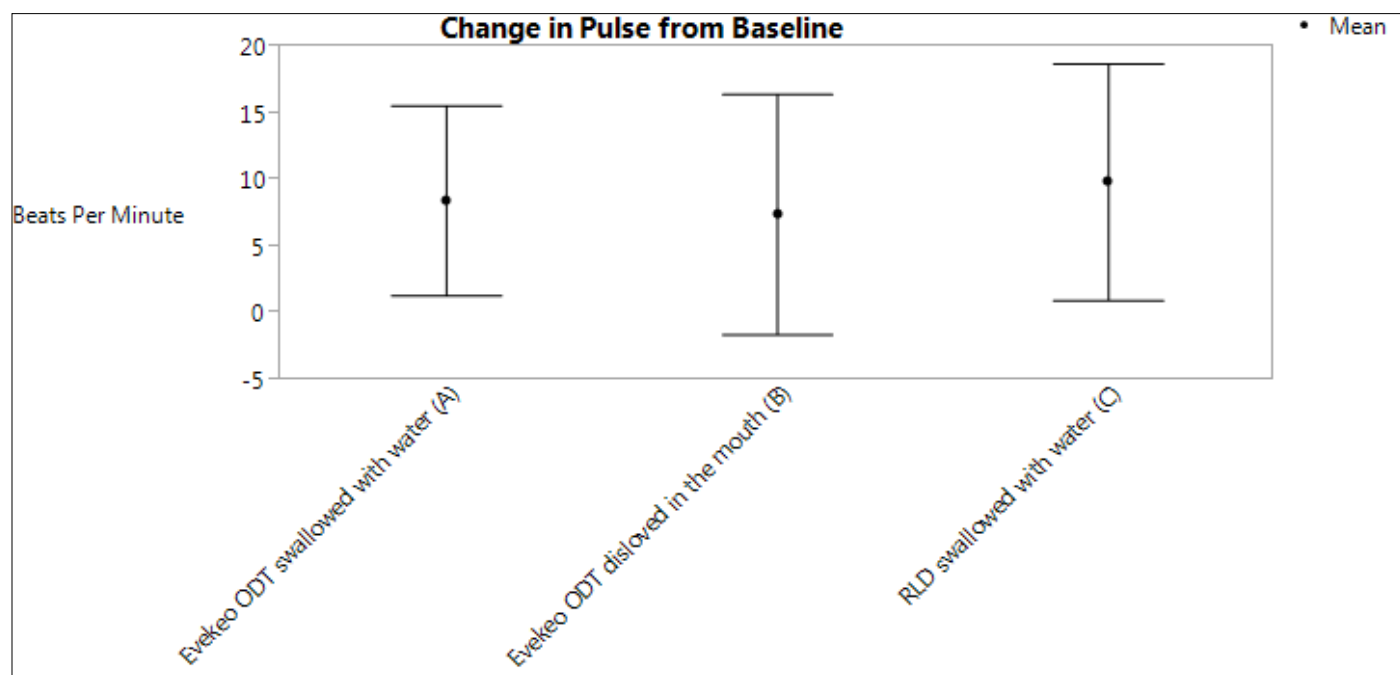
7.4.2 Laboratory Findings

For Study AR17.001 and Study AR17.002, hematology, serum chemistry, and urinalysis tests were performed at Screening, at admission to the first study period, and at study discharge. Therefore, values provide limited information regarding the relative effect of the test drugs. There was no AR17-related signal based on any out-of-range laboratory value.

7.4.3 Vital Signs

For Study AR17.001 and Study AR17.002, vital signs (blood pressure and pulse rate) were evaluated at screening, predose, 2 and 4 hours postdose, and discharge. Of particular interest was the possibility that there might be significant differences in pulse and blood pressure due to a more rapid absorption of the ODT formulation (which did not prove to be the case based on pharmacokinetic analysis). Comparing the three dose groups (RLD, ODT with water, ODT dissolved in the mouth), there were no apparent differences in the change from baseline in systolic blood pressure, diastolic blood pressure, or pulse. For a representative depiction of these comparisons, see Figure 1.

Figure 2. Change in Pulse, Study AR17.001 at 2 Hours Postdose.



Source: Applicant submission.

7.4.4 Electrocardiograms (ECGs)

For both PK studies, electrocardiograms were performed at Screening, study discharge, and at 2 and 4 hours post dose. There were no significant changes.

7.4.5 Special Safety Studies/Clinical Trials

Not Applicable

7.4.6 Immunogenicity

Not Applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There were no clinical data presented regarding the safety of the (b) (4) dose forms.

7.5.2 Time Dependency for Adverse Events

Not Applicable.

7.5.3 Drug-Demographic Interactions

Not Applicable.

7.5.4 Drug-Disease Interactions

Not Applicable.

7.5.5 Drug-Drug Interactions

Not Applicable; data as per RLD.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not Applicable; data as per RLD.

7.6.2 Human Reproduction and Pregnancy Data

Not Applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not Applicable; data as per RLD.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

See comments under section 4.5.

7.7 Additional Safety Issue

Not applicable.

8. Postmarket Experience

Not applicable.

9. Appendices

9.1 References

- 1) Catala-Lopez, Ferran, et al. "The pharmacological and non-pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents: a systematic review with network meta-analyses of randomized trials." *PLoS one* 12.7 (2017): e0180355.
- 2) Rasmussen, Nicolas. "America's first amphetamine epidemic 1929–1971: a quantitative and qualitative retrospective with implications for the present." *American Journal of Public Health* 98.6 (2008): 974-985.
- 3) Compton, Wilson M., et al. "Prevalence and correlates of prescription stimulant use, misuse, use disorders, and motivations for misuse among adults in the United States." *American Journal of Psychiatry* (2018): appi-ajp.

9.2 Labeling Recommendations

Clinically, no labeling changes are recommended to the RLD's boxed warning, warnings and precautions, or adverse reactions specific to this formulation.

The Division, in consultation with the Controlled Substance Staff and the 505(b)(2) Committee, has decided the benefits of the convenience of a (b) (4)

According to the Division of Medication Error Prevention and Analysis (DMEPA), the proposed packaging is label is confusing. The blister card configurations do not correspond with the medication contained within, and this could lead to medication errors. For example, the 5 mg strength blister card (b) (4) because of the layout of the label. However, the blister card contains 30 tablets.

The Applicant proposes that study AR11.001 (using the RLD) be summarized in section 14 of the proposed Evekeo ODT labeling (see Appendix 9.4 for review of this study).

Reviewer Comment: The packaging label as initially designed is confusing and could lead to medication errors. This is addressed by the DMEPA review.

Considering that the dependence section in the label (section 9, (b) (4), has not been updated to include rebound symptoms (especially in children) and a better description of stimulant withdrawal syndrome for amphetamine, the CSS is considering new recommendations for a class label change for amphetamines.

This effort would consider the current status of stimulant abuse rates and involve other labels for stimulant drugs and is beyond the scope of this review.

9.3 Advisory Committee Meeting

This 505(b)(2) application relies on the findings of safety and efficacy of Evekeo IR and there were no questions for an Advisory Committee.

9.4 Review of Study AR11.001

9.4.1 Introduction

AR11.001 was a postmarketing ADHD pediatric efficacy and safety study utilizing Arbor's IR amphetamine sulfate tablets (Evekeo IR; AR11) in pediatric patients (ages 6 to 12 years) with ADHD. This study was a randomized, double-blind, placebo-controlled, crossover laboratory classroom study that included an 8-week, open-label dose optimization phase followed by randomization to 1 week of active drug or placebo followed by a crossover to the opposite treatment for 1 week.

9.4.2 Review Strategy

The overall clinical review strategy included the following:

- Examination of the efficacy results from AR11.001
- Evaluation of deaths, serious adverse events, adverse events that led to dropouts, and other significant adverse events among AR11-treated patients
- Review of common adverse events and changes in vital sign and suicidality measures

9.4.3 Efficacy Summary

From the Biometrics review:

The study results support the efficacy of AR11 (Evekeo) on the reduction of signs and symptoms of ADHD evaluated by Swanson, Kotkin, Agler, M-Flynn, Pelham Rating Scale (SKAMP) scores. The primary efficacy endpoint of the SKAMP-Combined scores at 2 hours post-dose is statistically significantly lower (i.e., better) in the AR11 treatment compared to the placebo ($p < 0.0001$). SKAMP-Combined scores were statistically significantly better for patients in the AR11 treatment group compared to patients in the placebo treatment group beginning at 0.75 hours post-dose and at each assessment through 10 hours post-dose.

9.4.4 Methods

Objectives:

Primary Objective

The primary objective of this study was to establish that an optimal dose of AR11 results in a significant reduction in signs and symptoms of ADHD compared with placebo treatment in pediatric patients 6 to 12 years old with ADHD.

Secondary Objectives

- To determine the onset of clinical effect (SKAMP-Combined score)
- To determine the duration of clinical effect (SKAMP-Combined score)
- To investigate the safety and tolerability of AR11 compared with placebo in pediatric patients 6 to 12 years old with ADHD

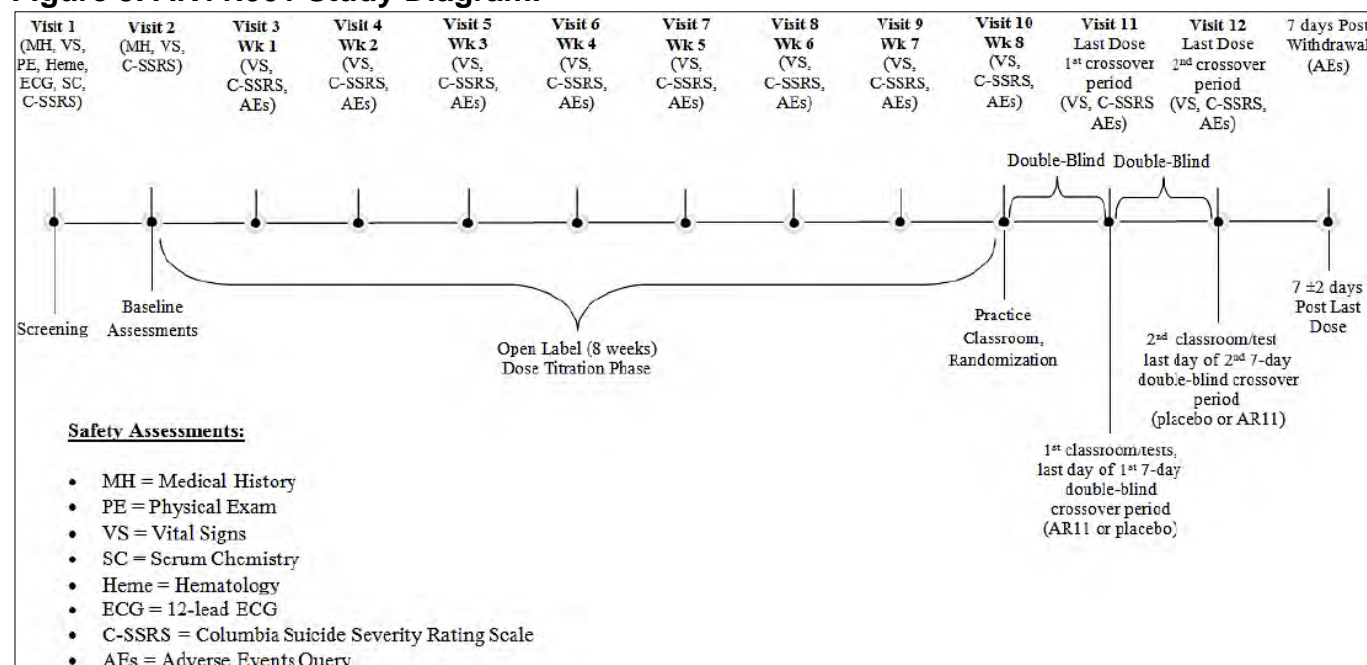
Study Design:

Following an 8-week open-label dose optimization phase, patients entered a double-blind phase and were randomly assigned to either their optimized dose of AR11 or to placebo for 1 week. After 1 week, subjects participated in a Laboratory Classroom evaluation. Subjects were then crossed-over to a week of the alternative treatment followed by a second Laboratory Classroom evaluation. The primary efficacy outcome was the SKAMP-Combined score at 2 hours post-dose during the two Laboratory Classroom days (see Figure 3).

Study Features:

- 30-day screening period and baseline evaluation.
- Dose optimization during the open-label phase to AR11 (10 to 15 mg/d, 20 to 25 mg/d, 30 to 35 mg/d, or 40 mg/d).
- Dosing was twice daily except on the classroom study day when only the established morning dose was given.
- An abbreviated, practice Laboratory Classroom day was held during Visit 10.
- Randomization to an assigned treatment sequence, A or B (AR11/placebo or placebo/AR11, respectively) occurred at Visit 10.
- Double-blind treatment occurred over 2 weeks: 1 week of AR11 with no dose adjustments and 1 week of placebo.
- Each double-blind study drug week culminated with a test Laboratory Classroom day, occurring at Visits 11 and 12.
- Efficacy assessments were conducted at 0.75, 2, 4, 6, 8, and 10 hours post-dose on the Laboratory Classroom day.
- The final safety assessments were completed during the post-withdrawal follow-up phone call approximately 1 week after Visit 12.

Figure 3. AR11.001 Study Diagram.



Source: Applicant submission.

9.4.5 Patient Selection

For inclusion into the trial, male or females between 6 and 12 years of age were required to meet DSM-IV-TR criteria for ADHD, have a clinician-administered Clinical Global Impression of Severity (CGI-S) score of > 3, an Attention Deficit Hyperactivity Disorder-Rating Scale (ADHD-RS) score \geq the 90th percentile in at least 1 of the following categories: hyperactive-impulsive subscale, inattentive subscale, or total score. In the clinical judgment of the investigator, the subject must have been in need of pharmacological treatment for ADHD. Performance at the basic level of the Permanent Product Measure of Performance (PERMP) at baseline was also an inclusion criterion.

Subjects were excluded who had a primary psychiatric diagnosis other than ADHD or secondary or comorbid diagnoses other than ADHD (with the exception of simple phobias). These included oppositional defiant disorder, elimination disorders, motor skills disorders, communication disorders, learning disorders, adjustment disorders, and sleep disorders. Subjects were excluded who had significant cognitive impairment, seizure disorder, cardiac or ECG abnormalities, hypertension, untreated thyroid disease, glaucoma, Tourette's disorder, chronic tics, or a history of infection with human immunodeficiency virus, hepatitis B, or hepatitis C. Subjects with drug or alcohol abuse within the past 12 months or current psychotropic medication use were excluded.

9.4.6 Assessments

The primary efficacy endpoint was the SKAMP-Combined score at 2 hours post-dose as measured during the Laboratory Classroom days (Visit 11 and Visit 12). The SKAMP is a 13-item, independent-observer rating of subject impairment of classroom observed

behaviors. Each item is rated on a 7-point impairment scale (0 = normal to 6 = maximal impairment). Items are specific to place (classroom setting) and time (during a typical classroom period), and the scale can be used to assess multiple ratings taken within a day. During the practice Laboratory Classroom session at Visit 10, the SKAMP scale was assessed pre-dose and at 0.75, 2, and 4 hours post-dose. During the Laboratory Classroom session at Study Visits 11 and 12, the SKAMP scale was assessed pre-dose and at 0.75, 2, 4, 6, 8, and 10 hours post-dose. The following composite scores were assessed:

- SKAMP-Combined scores (items 1-13),
- SKAMP-Attention subscale scores (items 1-4)
- SKAMP-Depotment subscale scores (items 5-8)

The combined scores and subscale scores for the SKAMP were obtained by summing the values of corresponding items in the assessment.

Other assessments:

- The Permanent Product Measurement of Performance (PERMP) is a 10-minute written test performed as seatwork in the classroom. Subjects were given 5 pages of 80 math problems and instructed to work independently at their assigned table to complete as many problems as possible in 10 minutes. The number of problems correct, and the number of problems attempted, were used to measure a subject's performance. During the Laboratory Classroom session at Visits 11 and 12, the PERMP was assessed pre-dose and at 0.75, 2, 4, 6, 8, and 10 hours post-dose.
- The ADHD-Rating Scale (ADHD-RS) is an 18-item scale based on DSM-IV criteria of ADHD that rates symptoms on a 4-point scale. Each item was scored using a combination of severity and frequency ratings from a range of 0 (reflecting no symptoms or a frequency of never or rarely) to 3 (reflecting severe symptoms or a frequency of almost always), with total scores ranging from 0 to 54. The ADHD-RS was used to determine trial eligibility and to compare scores during the open-label period. The following ADHD-RS scores were assessed at each visit:
 - ADHD-RS Total score,
 - ADHD-RS Hyperactivity/Impulsivity subscale score, and
 - ADHD-RS Inattentiveness subscale score (odd items).
- The Conners' Parent Rating Scale (CPRS) was used to measure features associated with ADHD and to compare scores during the open-label period. The parent/guardian performed the assessment. The subject received normalized t-scores on the following scales: oppositional, cognitive problems/inattention, hyperactivity, anxious, perfectionism, social problems, and psychosomatic.
- The Clinical Global Impression Scale (CGI) was used to measure features associated with ADHD. Improvement relative to Baseline was assessed by the Clinical Global Impression of Improvement (CGI-I; see Table 9).

Table 9. AR11.001 Schedule of Assessments.

Study Visit Number	+	1	2	3	4	5	6	7	8	9	10	11	12
			Open Label									Double Blind	
Visit Name	SCR	BL	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8 Practice CR		LD 1stCR	LD 2ndCR
Study Day Assessment	-30 to -1	1	8 ±2d	15 ±2d	22 ±2d	29 ±2d	36 ±2d	43 ±2d	50 ±2d	57		7d post V10	7d post V11
ADHD-RS	X	X	X	X	X	X	X	X	X	X	X		
CPRS		X				X				X			
CGI-S	X	X	X	X	X	X	X	X	X	X	X		
CGI-I			X	X	X	X	X	X	X	X	X		
Vital signs	X ^a	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X												
Physical examination	X												
Height/weight	X	X											
Hematology	X												
Serum chemistry	X												
Pregnancy	X	X										X	X
C-SSRS		X	X	X	X	X	X	X	X	X	X	X	X
PERMP		X									X ^b	X ^c	X ^c
SKAMP											X ^b	X ^c	X ^c
IWRS entry		X	X	X	X	X	X	X	X	X	X	X	X
Dispense OL AR11		X	X	X	X	X	X	X	X				
Dose titration allowed			X	X	X	X	X	X	X				
Last OL dose										X ^d			
Dispense DB Drug												X	X

Abbreviations: ADHD-RS = Attention Deficit Hyperactivity Disorder-Rating Scale; BL = Baseline; CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; CPRS = Conner's Parent Rating Scale; CR = classroom; C-SSRS = Columbia Suicide Severity Rating Scale; DB = double-blind; ECG = electrocardiogram; LD = laboratory day; MINI-KID = Mini International Neuropsychiatric Inventory for Children and Adolescents; OL = open-label; PERMP = Permanent Product Measure of Performance; SCR = screening; V = visit number; SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale; Wk = week.

^aAt all visits, vital signs included blood pressure and pulse assessments. At Screening, vital signs also included respiratory rate and temperature.

^bAssessments occurred before dosing and at 0.75, 2, and 4 hours after dosing.

^cAssessments occurred before dosing and at 0.75, 2, 4, 6, 8, and 10 hours after dosing.

^dDosed in clinic.

9.4.7 Analysis Plan

All continuous study assessments were to be summarized by treatment and time point using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical study assessments were to be summarized by treatment and time point using frequency counts and percentages. Hypothesis testing, unless otherwise indicated, was to be two-sided and performed at the 5% significance level. Primary and

secondary variables/endpoints were to be assessed using a mixed model repeated measures analysis.

9.4.8 Demographics

Table 10. Demographics and Baseline Characteristics, Study AR11.001.

Characteristics		Placebo/AR11 N=50	AR11/Placebo N=47	Total N=97
Age, years	Mean	9.6	9.6	9.6
	SD	1.78	1.97	1.86
Female Sex, n (%)		20 (40)	18 (38)	38 (39)
Age Categories n (%)	6 – 7 Years	9 (18)	7 (15)	16 (17)
	8 – 10 Years	22 (44)	22 (47)	44 (45)
	11 – 12 Years	19 (39)	18 (38)	37 (38)
Race n (%)	White	28 (56)	30 (64)	58 (60)
	Black/ African American	20 (40)	13 (28)	33 (34)
	Asian	0	1 (2)	1 (1)
	Native Hawaiian/ Pacific Islander	0	1 (2)	1 (1)
	Other	2 (4)	2 (4)	4 (4)

9.4.9 Subject Disposition

Of the 107 subjects enrolled, 97 were randomized to receive either placebo/AR11 (50) or AR11/placebo (47). Ninety-five (89%) subjects completed the study and 12 (11%) subjects prematurely discontinued from the study. The mostly frequently reported reasons for premature discontinuation included AE (n=6, 50% subjects; see section 9.4.24) and withdrawal of consent (n=4; 33%).

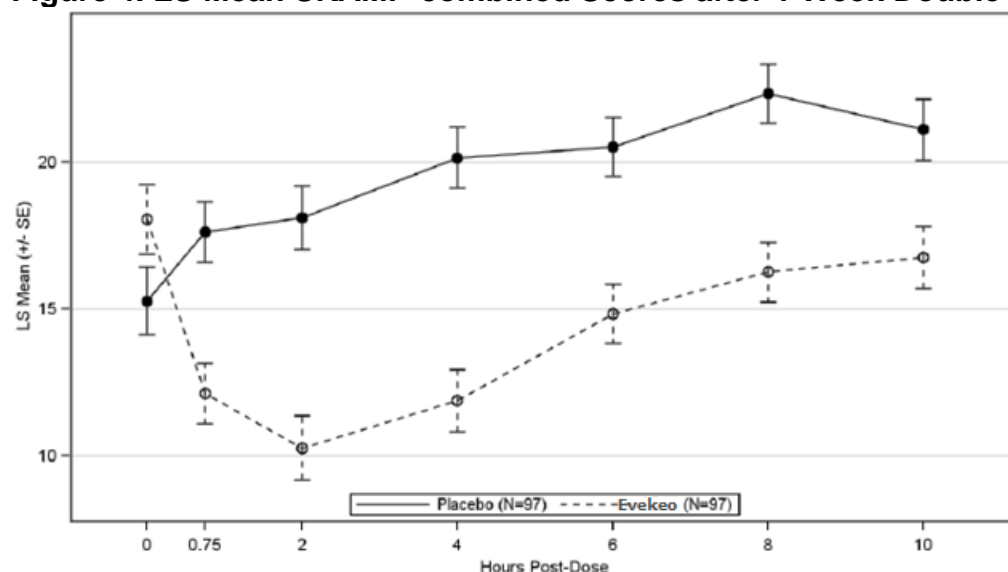
9.4.10 Analysis of Endpoints

Primary Endpoint

The efficacy analysis is summarized from the Biometrics review. A mixed-model, repeated-measures analyses was performed on the ITT population (defined as all randomized subjects who received at least one dose of double-blind study drug and had at least one post-dose assessment of the primary efficacy variable), with study center, period (1 and 2), sequence (AR11/placebo and placebo/AR11), and time point (0.75, 2, 4, 6, 8, and 10 hours post-dose)-by-treatment (AR11 and placebo) interaction as fixed effects and subject's intercept as a random effect. An unstructured covariance matrix was used to model within subject/within-treatment variability. The treatment difference was estimated using least-squares (LS) means from the mixed-effects repeated-measures model. The treatment comparison was conducted as a 2-sided test at the 0.05 level of significance.

The primary analysis result shows that SKAMP-Combined Scores at 2 hours post-dose was statistically significantly lower (i.e., better) in the AR11 treatment compared to the placebo (a LS mean difference of -7.9, 95% CI (-10.1, -5.6), $p < 0.0001$). The mean change from pre-dose at 2 hours post-dose in SKAMP-Combined scores was also numerically lower in the AR11 treatment compared to the placebo (a LS mean difference of -10.5, 95% CI (-13.2, -7.8); see Figure 4).

Figure 4. LS Mean SKAMP-combined Scores after 1 Week Double-blind Treatment.



Source: Applicant submission.

Secondary Endpoints

Prespecified secondary efficacy outcomes as determined by SKAMP-Combined scores at 0.75, 4, 6, 8, and 10 hours post-dose on each Laboratory Classroom Day (Visits 11 and 12) were the onset of clinical effect and the duration of clinical effect.

The Applicant's prespecified secondary efficacy results ("onset" and "duration"):

- The "onset" of AR11 effect (first statistically significant separation from placebo) was seen at 0.75 hours post-dose (a LS mean difference of -5.5, 95% CI (-7.5, -3.5), $p < 0.0001$).
- The "duration" of AR11 effect (last measurement where AR11 statistically separated from placebo) was the final measurement at 10 hours post-dose (a LS mean difference of -4.3, 95% CI (-6.4, -2.3), $p < 0.0001$). The treatment differences are statistically significant at all post-dose timepoints.

Team Leader Comment: Statistical separation from placebo does not equate to clinical effect. To determine clinical effect, one must consider the absolute difference from placebo as well as the raw measured scores. It would be surprising if an IR formulation had a duration of 10 hours. Indeed, when the scores are plotted (see Figure 4), the AR11 group returns to baseline scores approximately 6 hours after dosing. The reason for the statistical difference from placebo is that the placebo group continues to worsen throughout the day. Therefore, separation from placebo at 10 hours post-dose does not reflect continued clinical efficacy at 10 hours post-dose.

Table 11. Time Course of Effect on SKAMP-Combined Scores.

Time point	AR11 LS Mean (SE) N=97	Placebo LS Mean (SE) N=97	LS Mean (SE) N=97	p-value	95% CI
0.75 hours postdose	12.1 (1.03)	17.6 (1.02)	-5.5 (1.01)	<0.0001	-7.5, -3.5
2 hours postdose	10.3 (1.09)	18.1 (1.09)	-7.9 (1.14)	<0.0001	-10.1, -5.6
4 hours postdose	11.9 (1.05)	20.2 (1.05)	-8.3 (1.06)	<0.0001	-10.4, -6.2
6 hours postdose	14.8 (1.00)	20.5 (1.00)	-5.7 (0.96)	<0.0001	-7.6, -3.8
8 hours postdose	16.3 (1.01)	22.3 (1.00)	-6.1 (0.96)	<0.0001	-8.0, -4.2
10 hours postdose	16.8 (1.05)	21.1 (1.04)	-4.3 (1.05)	<0.0001	-6.4, -2.3

Abbreviations: CI = confidence interval; LS = least-squares; SE = standard error; SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale. Source: Statistical Tables [14.2.4](#) and [14.2.5](#)

9.4.11 Other Endpoints

Efficacy was also assessed by the following measures during the Laboratory Classroom days (Visits 11 and 12): Model-adjusted average of SKAMP-Combined scores over the entire Laboratory Classroom day, SKAMP-Combined scores at 0.75, 4, 6, 8, and 10 hours post-dose, model-adjusted average of SKAMP-Attention and -Depotment scores over the entire Laboratory Classroom Day, SKAMP-Attention and -Depotment scores at 0.75, 2, 4, 6, 8, and 10 hours post-dose, and PERMP scores at 0.75, 2, 4, 6, 8, and 10 hours post-dose. Additional efficacy outcomes included the CGI-S, CGI-I, ADHD-RS,15 and CPRS. Analyses of these endpoints were consistent with the primary endpoint analysis (see biostatistics review for more details).

9.4.12 Subpopulations

No statistically significant differences were found between the treatment effect of subgroups based on race, gender or age (see biostatistics review for more details).

9.4.13 Analysis of Clinical Information Relevant to Dosing Recommendations

There were no findings that would change the standing dose recommendations for an immediate-release amphetamine product.

9.4.14 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable to this application.

9.4.15 Additional Efficacy Issues/Analyses

This clinical study includes a randomized, double-blind, placebo-controlled, two-arm two-period, crossover design trial with no wash-out period between the two treatment

periods, creating the possibility of a differential carryover effect or treatment by period interaction. The statistical reviewer did not find that this was a significant source of bias in the study.

9.4.16 Safety Summary

There were no new safety issues noted from the evaluation of vital sign or adverse event (AE) data. During the double-blind phase, there were no SAEs, and no subjects withdrew from the Study.

9.4.17 Safety Monitoring

Safety was monitored by adverse events (AEs) and vital signs (blood pressure and pulse) assessed at each visit. In addition, the Columbia Suicide Severity Rating Scale (C-SSRS) was administered at Baseline and all subsequent scheduled visits to assess emergent suicidal thoughts or behaviors. Medical history captured all medical conditions at Visit 1 (Screening Visit) and Visit 2 (Baseline Visit). Physical examinations, ECGs, and clinical laboratory tests were conducted at Screening and at any subsequent visit as deemed necessary.

9.4.18 Categorization of Adverse Events

Adverse event verbatim terms were coded to preferred terms using MedDRA Version xx. Mapping of verbatim to preferred terms was appropriate.

9.4.19 Overall Exposure at Appropriate Doses/Durations

The study enrolled children ages 6 to 12 years (N=107) with ADHD; 61% male, 60% white, and 81% with combined inattentive and hyperactive/impulsive ADHD. The mean age was 9.6 years; 17% were between 6 and 7 years, 45% between 8 and 10 years, and 38% between 11 and 12 years. See section 9.4.8 for more information on Study demographics.

Dosing was flexible and began with 10 mg daily with increases of 5 mg at weekly intervals until "optimal response" was obtained. The maximum dose was 40 mg/day in divided doses. Mean (SD) length of exposure was 60.2 (11.73) days, with 53.9 (10.03) days during open-label treatment and 7.0 (0.23) days during double-blind treatment. The mean (SD) length of exposure by daily dose during double-blind treatment was 5.0 (2.68) days for 32 subjects who received a daily dose of 10 to 15 mg at any time during double-blind treatment, 6.5 (1.35) days for 48 subjects who received a daily dose of 20- to 25 mg, 6.5 (1.38) days for 23 subjects who received a daily dose of 30 to 35 mg, and 6.8 (0.41) days for the 6 subjects who received a daily dose of 40 mg.

9.4.20 Special Animal and/or In Vitro Testing

None.

9.4.21 Routine Clinical Testing

Adverse events (AEs)/serious AEs (SAEs) were evaluated throughout the Study. Vital signs were evaluated at the screening, baseline and each clinic visit. Suicidal thoughts and behavior was evaluated with the C-SSRS at screening, baseline, and each clinic visit. There were three instances of suicidal ideation and one instance of suicidal behavior during the open-label phase of the study, but none during the double-blind phase. Hematology, blood chemistry evaluations, ECG, and physical examination were conducted at screening and (if needed) during the study.

9.4.22 Metabolic, Clearance, and Interaction Work

No new information.

9.4.23 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The C- SSRS was used to detect suicidal ideation and suicidal behavior; pulse and blood pressure were monitored.

9.4.24 Major Safety Results

Deaths:

There were no deaths during the Study.

Nonfatal Serious Adverse Events:

There were no SAEs during the Study.

Dropouts and/or Discontinuations:

During open-label treatment, six subjects prematurely withdrew from study drug due to an AE. Three subjects withdrew due to irritability (Subjects (b) (6)), one subject each withdrew due to affect lability (Subject (b) (6)), initial insomnia (Subject (b) (6)), and acrodermatitis/rash (Subject (b) (6)). The initial insomnia was coded as severe, but all other AEs were moderate in severity. No subjects prematurely withdrew from study drug due to an AE during the double-blind treatment.

Significant Adverse Events:

During open-label treatment, three subjects reported at least one occurrence of suicidal ideation and one subject reported at least one occurrence of suicidal behavior. One additional subject demonstrated nonsuicidal self-injurious behavior.

Submission Specific Primary Safety Concerns:

None.

9.4.25 Common Adverse Events

During double-blind treatment for the Randomized Safety population, all AEs occurred at frequencies of $\leq 4.1\%$ within each treatment group. Events are summarized in Table 12 below. Adverse events within the system organ class (SOC) of Psychiatric Disorders; Gastrointestinal Disorders; Metabolism and Nutrition Disorders; Eye Disorders; and Respiratory, Thoracic, and Mediastinal Disorders were reported for subjects on AR11 and not for subjects on placebo. The most frequently reported AEs were similar to those observed during open-label treatment and included decreased appetite in four (4%) of subjects while on AR11.

When AEs were summarized across the entire study, the following AEs occurred at a higher frequency in the placebo/AR11 group versus the AR11/placebo group:

- Decreased appetite: n=17 (34%) versus n=11 (23%)
- Abdominal pain, upper: n=11 (22%) versus n=5 (11%)
- Nausea: n=5 (10%) versus n=1 (2%)
- Fatigue: n=7 (14%) versus n=3 (6%)
- Irritability: n=8 (16%) versus n=5 (11%)
- Affect lability: n=4 (8%) versus n=1 (2%)

Conversely, the following AE occurred at a higher frequency in the AR11/placebo group versus the placebo/AR11 group: dry mouth n=5 (11%) versus n=1 (2%). All other AEs occurred at differences of < 3 subjects between the treatment groups.

Reviewer note: During the double-blind phase, the subjects who received the placebo first and then were restarted on the AR11 experienced twice as many adverse events. These AEs are commonly associated with amphetamine. For those in the group who received the drug first and then the placebo, there were equal numbers of adverse effects in the two periods. These findings suggest that AEs commonly occur with starting the drug, but subjects may develop tolerance over 8 weeks of treatment.

During double-blind treatment, ten (10%) subjects on AR11 treatment had 20 treatment-related AEs and six (6%) subjects on placebo treatment had 6 treatment-related AEs. Ten (20%) subjects who received placebo/AR11 experienced 20 treatment-related AEs, whereas six (13%) subjects who received AR11/placebo experienced 6 treatment-related AEs.

Table 12. Treatment-emergent Adverse Events during the Double-blind Phase, Study AR11.001.

System Organ Class Preferred Term	Double Blind Period 1		Double Blind Period 2	
	AR11 N=47	Placebo N=50	AR11 N=50	Placebo N=47
Subjects with at least one TEAE	8	5	13	11
Metabolism and Nutrition Disorders				
Decreased appetite/weight loss			5	1
Gastrointestinal Disorders				
Abdominal pain upper ^a			3	
Vomiting	1			
Psychiatric Disorders				
Insomnia			4	
Affect lability ^b			4	
Infections and Infestations				
Upper respiratory tract infection ^c	3	1		4
Viral gastroenteritis				1
Nervous System Disorders				
Headache		1	1	
Lightheadedness			1	
Cardiac Disorders				
Tachycardia			2	3
Skin and Subcutaneous Tissue Disorders				
Rash	2	1		
Injury, poisoning and procedural complications				
Injury	1	1	2	1
Renal and urinary disorders		1		
Eye Disorders			1	
General disorders and administration site conditions			1	
Respiratory, thoracic and mediastinal disorders	1			

^aIncludes stomach ache.

^bIncludes anxiety, mood swings, and irritability.

^cIncludes pharyngitis, streptococcal.

Table 13. TEAEs Occurring in $\geq 2\%$ of Subjects During AR11.001 Open-label Phase.

System Organ Class Preferred Term	Total (N=105) n (%)
Subjects with at least one TEAE	69 (65.7)
Metabolism and Nutrition Disorders	29 (27.6)
Decreased appetite	29 (27.6)
Gastrointestinal Disorders	27 (25.7)
Abdominal pain upper	15 (14.3)
Dry mouth	6 (5.7)
Nausea	6 (5.7)
Vomiting	6 (5.7)
Psychiatric Disorders	24 (22.9)
Insomnia	7 (6.7)
Affect lability	6 (5.7)
Mood swings	3 (2.9)
Infections and Infestations	23 (21.9)
Upper respiratory tract infection	11 (10.5)
Pharyngitis streptococcal	3 (2.9)
General Disorders and Administration Site Conditions	22 (21.0)
Irritability	15 (14.3)
Fatigue	10 (9.5)
Pyrexia	3 (2.9)
Nervous System Disorders	16 (15.2)
Headache	14 (13.3)
Cardiac Disorders	10 (9.5%)
Tachycardia	9 (8.6)
Investigations	8 (7.6)
Weight decreased	4 (3.8)
Skin and Subcutaneous Tissue Disorders	5 (4.9)
Rash	3 (2.9)

9.4.26 Laboratory Findings

Laboratory evaluations were not conducted when subjects were on study drug.

9.4.27 Vital Signs

For 6- to 12-year-olds, normal heart rate ranges from 75 to 118 bpm, normal systolic blood pressure ranges from 97 to 120 mmHg, and normal diastolic blood pressure ranges from 57 to 80 (based on <http://www.pedscases.com/pediatric-vital-signs-reference-chart>; accessed 01/29/2019). Table 14 presents abnormal vital signs recorded during Study AR11.001.

Table 14. Out-of-Range Vital Signs During AR11.001.

	Open-label Phase n=105	Double-blind Phase AR11.001 n=97	Double-blind Phase Placebo n=97
Heart rate <75 n range	42 59 - 74	10 63 - 69	19 56 - 74
Heart rate >120 n range	7 118 - 138	0	1 121
Systolic blood Pressure <97 n range	55 75 - 96	22 80 - 96	22 82 - 96
Systolic blood Pressure >120 n range	10 121 - 132	5 122 - 130	6 121 - 126
Diastolic blood Pressure <57 n range	45 41 - 56	14 46 - 56	14 49 - 56
Diastolic blood Pressure >80 n range	7 81 - 91	1 86	2 81

Team Leader Comment: There is no pattern of vital sign abnormalities consistent with a drug-placebo difference. However, subjects randomized to placebo had been on AR11 prior to randomization and there may have been some tolerance to the potential effects of AR11. In the open-label phase, there is no pattern of AR11 consistently raising or lowering pulse or blood pressure.

During both open-label and double-blind treatment, the most prevalent potentially clinically significant vital signs event was an increase in blood pressure from Baseline of ≥ 10 mmHg in diastolic blood pressure, which occurred in 41 (39%) subjects during open-label treatment and, during the double-blind phase, in 19 (20%) subjects on AR11 and 23 (24%) subjects on placebo. Event frequencies were comparable between double-blind treatment groups, except with regard to post-Baseline systolic blood pressure values above the 95th percentile. Eight (8.2%) subjects on AR11 compared with 3 (3.1%) subjects on placebo had post-Baseline systolic blood pressure values above the 95th percentile.

9.4.28 Electrocardiograms (ECGs)

ECGs were only recorded at the screening visit, and 14 (13.3%) subjects had abnormal findings. None of the abnormal findings were clinically significant.

9.4.29 Special Safety Studies/Clinical Trials

None.

9.4.30 Immunogenicity

None.

9.4.31 Other Safety Explorations

Dose Dependency for Adverse Events:

No new information was provided.

Time Dependency for Adverse Events:

No new information was provided.

9.4.32 Drug-Demographic Interactions

There were too few AEs reported to conduct an analysis of AEs by sex, age, or race. On superficial examination, no AEs occurred exclusively in one demographic group.

9.4.33 Drug-Disease Interactions

No new information was provided.

9.4.34 Drug-Drug Interactions

None.

9.4.35 Human Carcinogenicity

No new information was provided.

9.4.36 Human Reproduction and Pregnancy Data

No new information was provided.

9.4.37 Pediatrics and Assessment of Effects on Growth

No new information was provided that would indicate the effect of AR11 on Growth.

9.4.38 Overdose, Drug Abuse, Withdrawal and Rebound

No new information was identified with respect to overdose, drug abuse, withdrawal, or rebound effects.

9.4.39 Conclusions

Study AR11.001 is appropriate for inclusion in labeling for the ODT formulation. Section 6 will describe the most common AEs seen during the open-label dose optimization phase as well as include a 2% Table for the randomized, cross-over phase. Section 14 will describe the study, [REDACTED] (b) (4)

[REDACTED] Instead, the language will accurately describe that AR11 was statistically significantly different from placebo at the measured time points.

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/

BERNARD A FISCHER on behalf of JOHN C UMHAU
01/30/2019 02:44:54 PM
Signed on behalf of John Umhau

BERNARD A FISCHER
01/30/2019 02:46:42 PM
Acting Team Leader