

**FDA ADVISORY COMMITTEE BRIEFING DOCUMENT**

**AR19**  
**(amphetamine sulfate immediate-release capsules)**

**JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY  
COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT  
ADVISORY COMMITTEE**

**MEETING DATE: OCTOBER 8, 2020**

**ADVISORY COMMITTEE BRIEFING MATERIALS:  
AVAILABLE FOR PUBLIC RELEASE**

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## LIST OF ABBREVIATIONS

<b>Abbreviation</b>	<b>Definition</b>
AAPCC	American Association of Poison Control Centers
ADF	Abuse-deterrent formulation
ADHD	Attention-deficit/hyperactivity disorder
AE	Adverse event
API	Active pharmaceutical ingredient
AUC <sub>inf</sub>	Area under the curve extrapolated to infinity
AUC <sub>last</sub>	Area under the curve through the last observation
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
C <sub>max</sub>	Maximum plasma concentration
CNS	Central nervous system
E <sub>max</sub>	Peak score regardless of time
ER	Extended release
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
HAP	Human abuse potential
IR	Immediate release
IV	Intravenous
LS	Least squares
NDA	New Drug Application
NPDS	National Poison Data System
NSDUH	National Survey on Drug Use and Health
PD	Pharmacodynamic(s)
PEO	Polyethylene oxide
PSR	Particle size reduction
PK	Pharmacokinetic(s)
SAE	Serious adverse event
TMA	Thrombotic microangiopathy
TPP	Thrombotic thrombocytopenic purpura

## 1 INTRODUCTION

Since 2014, the Food and Drug Administration (FDA) has recognized the misuse and abuse of prescription stimulants as a serious public health concern and has called for sponsors to develop formulations to reduce that risk ([FDA, 2014](#)). In 2019, the FDA posted a notice in the Federal Register soliciting input on the potential role of abuse-deterrent formulations (ADFs) of prescription stimulants ([FDA, 2019](#)). The FDA has noted that prescription stimulants have a high potential for misuse and abuse, which can lead to serious health consequences. The FDA reported that most misuse and abuse of prescription stimulants is by the oral route; however, a sizable number of those misusing or abusing the medications do so by non-oral routes.

Arbor Pharmaceuticals, LLC (here-in-after Arbor) developed AR19, a pellets-in-capsule, immediate-release (IR) amphetamine sulfate formulation with physical and chemical barriers that resist manipulations required for snorting, smoking, and intravenous (IV) injection. In January 2020, Arbor submitted a New Drug Application (NDA) to the FDA requesting the approval of AR19 for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents (3 to 17 years of age) and adults 18 years and older. AR19 is produced in seven dose strengths of racemic amphetamine sulfate (i.e., 50% *d*-amphetamine and 50% *l*-amphetamine): 2.5, 5, 10, 15, 20, 30, and 40 mg. Amphetamine sulfate is a central nervous system (CNS) stimulant that has been FDA-approved for the treatment of ADHD for decades. The NDA for AR19 was submitted under the 505(b)(2) regulatory pathway using Evekeo<sup>®</sup>, a currently marketed amphetamine sulfate medication, as the reference drug.

AR19 capsules are filled with pellets that are approximately 1.2 mm in diameter ([Figure 1](#)). Amphetamine sulfate, the active pharmaceutical ingredient (API), is distributed homogeneously within each pellet.

**Figure 1: AR19 Pellets-in-Capsule Formulation**



AR19 is formulated with physical and chemical barriers to resist the manipulations required for non-oral routes of administration (i.e., snorting, smoking, and injecting). The following manipulation-resistant attributes of AR19 were incorporated:

- **Pellets-in-capsule formulation** – each AR19 capsule contains dozens of small pellets. The pellets are intended to be difficult to handle for physical manipulation. The pellet formulation also increases AR19's overall surface area relative to a tablet. When exposed to a small volume of liquid, this increased surface area maximizes AR19's gelling properties and resistance to injection.
- **Hard, non-brittle pellets** – AR19 pellets contain excipients that make them hard and non-brittle/pliable, which provides resistance to particle size reduction (e.g., crushing into a fine powder), the first step required for non-oral routes of administration.
- **Gelling agents** – AR19 pellets contain agents that (1) gel in small volumes of liquid to make injection difficult and (2) reduce intranasal bioavailability.

The ingredients that comprise AR19 pellets and the function of each ingredient are listed in **Table 1**. Each ingredient in AR19 plays a role in facilitating its intended immediate-release profile or manipulation-resistant properties. All excipients in AR19 have a well-established safety profile for all ages when taken orally as intended and are included in other FDA-approved oral medications.

**Table 1: AR19 Formulation Ingredients**

Ingredient	Function
d-, l-amphetamine sulfate	Active
Polyethylene oxide (PEO) 7M	Gelling/hardness
Polyethylene glycol 6000	Plasticizer
Pregelatinized starch	Gelling/disintegrant
Vitamin E/PEG 6000	Antioxidant
Citric acid anhydrous powder	Acidifier
Talc (pharma 700 grade)	Lubricant
Opadry II clear 85F190000	Coating

The composition of the pellets is similar, regardless of strength. The amounts of amphetamine sulfate and excipients are compositionally proportional within 3 subsets of the capsule strengths:

- Lower-strength subset: 2.5 and 5 mg capsules
- Mid-strength subset: 10, 15, and 20 mg capsules
- Higher-strength subset: 30 and 40 mg capsules

To ensure consistency of the manipulation-resistant properties across AR19 capsule strengths, the highest dosage strength within each subset (5, 20, and 40 mg) was evaluated in all key manipulation resistance studies.

Several broader public health issues warrant consideration for AR19:

- **Manipulation-resistant Terminology.** Arbor is seeking a label that accurately describes the physical and chemical properties of AR19 that make non-oral use of the product more difficult and less rewarding. Arbor has proposed using the term “manipulation resistant” to describe the AR19 formulation rather than “abuse deterrent.” The FDA and prior Advisory Committees have expressed concern that the term “abuse deterrent” may lead to false perceptions regarding safety because no formulation can prevent oral misuse or abuse, and no formulation can be abuse- or addiction-proof. While an ongoing FDA study will determine the final terminology for this class of products, Arbor will use “manipulation resistant” to appropriately reflect the properties of AR19 during the Advisory Committee meeting.
- **Affordability and Patient Access.** One practical concern about new medicines with manipulation-resistant properties is that they are priced higher than currently available products, limiting their uptake and potential public health benefit. In order to ensure that AR19 is accessible to patients and is able to achieve its intended public health impact, Arbor intends to price AR19 consistent with currently marketed ADHD prescription stimulants.
- **Nonclinical IV Safety.** AR19 pellets contain polyethylene oxide with a molecular weight of 7 million Dalton (PEO 7M). PEO is the primary excipient that prevents AR19 from being crushed into a fine powder for non-oral use and, along with another gelling excipient (pregelatinized starch), creates a highly viscous gel in small, injectable volumes of solvents. PEO 7M has also been used in other oral drug products such as Concerta®, which has been an FDA-approved prescription stimulant since 2000. PEO 7M was also an excipient used in Opana® ER, a potent oral opioid pain medication that was removed from the market due to rare, but serious, toxicities when it was extracted and repeatedly injected. There are important differences in both the pharmacology of the APIs of Opana ER (oxymorphone) and AR19 (amphetamine sulfate) as well as differences in the formulations that substantially reduce the likelihood of unintended consequences with IV misuse or abuse of AR19 (see [Section 6.3.4](#)). Furthermore, the IV toxicities associated with Opana ER have not been observed with other PEO 7M-containing products with IV abuse potential, including Concerta, which has been prescribed and dispensed more than 85 million times in the last 20 years. Arbor commissioned several nonclinical IV safety studies of AR19 to evaluate potential toxicities that could result from injection, which are discussed in [Section 7](#). Overall, the data suggest that IV misuse or abuse of AR19 would not lead to the adverse outcomes that were associated with injection of Opana ER.
- **Postmarketing Studies.** Arbor has proposed to conduct two postmarketing studies to evaluate the real-world public health impact of AR19. The first study will be conducted using the National Poison Data System, the electronic medical record and data system of human poisoning exposures that is used by all US poison information centers, to evaluate the frequency of adverse medical outcomes associated with AR19 exposures and to determine the prevalence of use by different routes of administration. The second study will include general population surveys to estimate the real-world rate of AR19 misuse and abuse relative to comparator products. Details of these studies are provided in [Section 8.1](#).
- **Enhanced Pharmacovigilance.** Arbor will use an enhanced pharmacovigilance program to evaluate potential signals of misuse, abuse, overdose, diversion, and any adverse safety signals. Arbor plans to explicitly extend the enhanced pharmacovigilance monitoring to include identification of events related to IV misuse or abuse of AR19. This enhanced pharmacovigilance plan will allow Arbor and the FDA to take prompt action, if necessary, to address any adverse safety signals. Details of this plan are provided in [Section 8.2](#).

## 2 BACKGROUND ON ADHD AND PRESCRIPTION STIMULANT MISUSE AND ABUSE

### 2.1 Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is the most common neurodevelopmental disorder and causes significant impairment in children, adolescents, and adults. ADHD is characterized by persistent and developmentally inappropriate hyperactivity, impulsivity, and inattention (APA, 2013). A meta-analysis on ADHD in children 18 and younger found an overall pooled prevalence estimate of 7.2% (Thomas et al., 2015).

Children with ADHD commonly experience academic underachievement, interpersonal relationship problems with family members and peers, and low self-esteem (Cuffe et al., 2015). Children with ADHD are at high risk of having co-occurring mental health and behavioral problems, including substance use disorders (Harstad & Levy, 2014). A meta-analysis of 27 longitudinal studies (1980-2009) found that individuals with a childhood ADHD diagnosis were 2.6 times more likely to develop illicit substance abuse or dependence in adolescence or adulthood than children without ADHD (Lee et al., 2011).

For approximately two-thirds of young patients with ADHD, the disorder persists into adulthood (Faraone et al., 2006). In adults, ADHD is associated with poor occupational adjustment, antisocial behavior, relationship difficulties, substance misuse, mood and affective problems, and personality disorder (Young et al., 2003).

### 2.2 Treatment of ADHD

The professional recommendations for the treatment of ADHD generally depend on the age of the individual. For preschool-aged children with ADHD, behavioral therapy is recommended as first-line treatment. However, among children 4 to 5 years of age with ADHD for whom behavioral intervention does not provide significant improvement, and for affected individuals aged 6 years and older, FDA-approved pharmacological treatment is recommended (Wolraich et al., 2019).

Prescription stimulants are the most common medications used to treat ADHD and are recommended as first-line therapy for school-aged children with ADHD along with the implementation of behavioral therapy (Harstad & Levy, 2014). Stimulants are generally subdivided into 2 classes: methylphenidates (e.g., Ritalin®, Concerta®) and amphetamines (e.g., Adderall®, Vyvanse®). While both classes are safe and effective when taken as intended for the treatment of ADHD in all age groups, a head-to-head comparison from a recent meta-analysis of 133 randomized controlled trials found that amphetamines were superior to methylphenidate with respect to ADHD core symptoms rated by clinicians in the treatment of ADHD in children, adolescents, and adults (Cortese et al., 2018). For patients who are intolerant or non-responsive to stimulants, some non-stimulant medications (e.g., atomoxetine, guanficine, and clonidine) are available, but the evidence for the efficacy of non-stimulant medications for the treatment of ADHD symptoms is not as robust as the evidence for stimulants (Wolraich et al., 2019).

Effective treatment with prescription stimulants reduces many of the poor outcomes associated with ADHD. A recent systematic review found that prescription stimulants not only reduce functional impairment and improve health-related quality of life, but also reduce the risk for accidents and trauma-related emergency department admissions and has protective effects for substance abuse, suicidal, and delinquent behavior (Faraone et al., 2015). Data also suggest that prescription stimulants may be protective against the risks for the development of

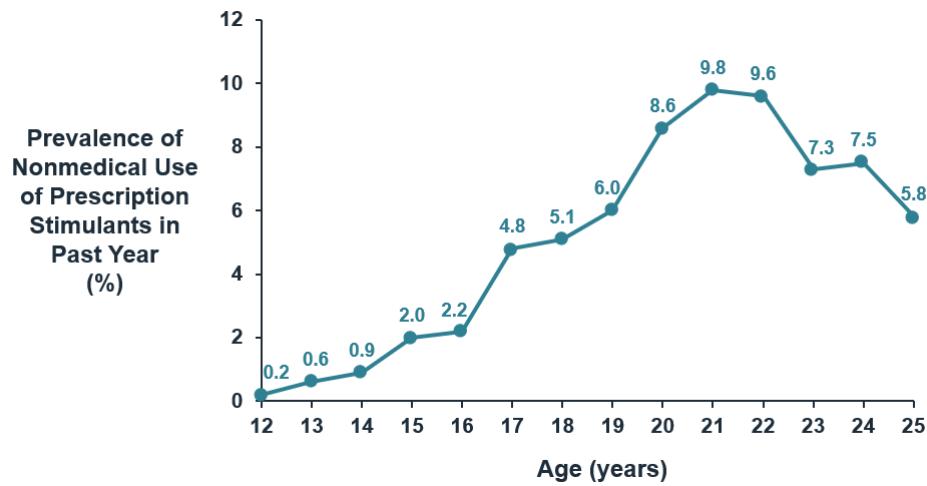
substance use disorders among individuals with ADHD (Chang et al., 2014; Groenman et al., 2013; Harstad & Levy, 2014; Katusic et al., 2005; McCabe et al., 2016; Wilens et al., 2003). For instance, the American Academy of Pediatrics suggests in its Guidance that treatment of youth with ADHD with a prescription stimulant may reduce the risk of developing substance use disorders by 85% (Harstad & Levy, 2014).

### 2.3 Misuse and Abuse of Prescription Stimulant Medications

Although effective in treating the symptoms of ADHD, prescription stimulants are associated with a high risk for misuse and abuse (Arria et al., 2008; Jasinski & Krishnan, 2009; Wilens et al., 2008). (“Misuse” is defined as using a medication in a way other than intended to achieve a therapeutic effect, and “abuse” is defined as using a medication for a nontherapeutic purpose such as to get high.) The National Survey on Drug Use and Health (NSDUH) estimated that 5.1 million individuals aged 12 years and older in the US misused or abused a prescription stimulant in 2018 (SAMHSA, 2018). Several studies have shown that misuse or abuse is more likely to occur with IR than extended-release (ER) prescription stimulants (Cassidy et al., 2015; Harstad & Levy, 2014; Weyandt et al., 2014; Wilens et al., 2016).

The peak incidence of nonmedical use (i.e., misuse or abuse) of prescription stimulants is approximately 16-19 years of age (Austic, 2015). The peak prevalence of misuse and abuse is approximately 21 years (Figure 2), suggesting that problematic drug-taking behaviors are typically initiated and take place in adolescence and early adulthood (SAMHSA, 2017).

**Figure 2: Prevalence of Past-year Prescription Stimulant Nonmedical Use by Age**



National Survey on Drug Use and Health (NSDUH), 2017.

While oral administration is the most common route of stimulant misuse and abuse, a considerable number of individuals use prescription stimulants by non-oral routes. A recent systematic review conservatively estimated that, on an annual basis, approximately 550,000 individuals in the US were using stimulants by snorting, approximately 50,000 people by smoking, and approximately 50,000 by injecting (Faraone et al., 2020).

The rationale for the non-oral use of a CNS-active drug is to achieve a greater and/or faster effect than taking the product orally. By circumventing the first-pass metabolism, the stimulant enters the brain more quickly than with oral use, which accelerates and/or intensifies the drug’s pharmacodynamic effects (Lile et al., 2011; Stahl, 2013). Desirable psychological or physiological experiences with non-oral use are thought to positively reinforce repeat use by these more dangerous non-oral routes of administration.

To provide greater insights into the prevalence of and motivations for misuse and abuse of prescription stimulants by route of administration, Arbor commissioned the Department of Epidemiology at the University of Florida and Inflexxion, Inc. (an independent healthcare research organization) to conduct several large epidemiologic surveys among adolescents, college students, and adults ([Table 2](#)). The prevalence of any use of prescription stimulants (i.e., for medical use, misuse, or abuse) was approximately 11% in adolescents, 35% in college students, and 11% among adults. Among these individuals, most misuse or abuse in all age groups was by the oral route, however, a sizable proportion reported non-oral misuse or abuse: 1 in 7 adolescents, 1 in 5 college students, and 1 in 6 adults.

Among those using prescription stimulants for any reason, the prevalence of snorting was approximately 10% in adolescents, 19% among college students, and 15% in adults. The prevalence of smoking tended to be higher among adolescents and college students (4-5%) than adults (2%). Injecting was most commonly reported by college students (3%).

**Table 2: Prevalence of Use and Misuse or Abuse of Prescription Stimulants by Route among Adolescents, College Students, and Adults**

Type of Prescription Stimulant Use	Prevalence, n (%)		
	Adolescents <sup>1</sup> (N=1,777)	College Students <sup>2</sup> (N=1,842)	Adults <sup>3</sup> (N=12,000)
<b>Any medical or nonmedical use</b>	<b>196 (11.0%)</b>	<b>641 (34.8%)</b>	<b>1,284 (10.7%)</b>
Any misuse or abuse	59 (30.1%)	583 (90.1%)	762 (59.3%)
Any non-oral misuse or abuse	27 (13.8%)	135 (21.1%)	207 (16.1%)
Snorting	19 (9.7%)	120 (18.7%)	188 (14.6%)
Smoking	8 (4.1%)	33 (5.1%)	29 (2.3%)
Injecting	2 (1.1%)	21 (3.3%)	27 (2.1%)

1. Study of Non-Oral Administration of Prescription Stimulants (SNAPS); Dept. of Epidemiology, University of Florida (2019).

2. Nonmedical Use of Prescription Medications in College Students; Inflexxion (2019).

3. Analysis of Survey of Nonmedical Use of Prescription Medications among the General Population; Inflexxion (2019).

The prevalence of non-oral use of prescription stimulants is higher among certain sub-populations of young individuals. For example, among college students diagnosed with ADHD who receive a prescription stimulant to treat their symptoms, 45% reported snorting their medication ([Inflexxion, 2019](#)). These findings are consistent with prior epidemiological studies in the peer-reviewed literature ([Arria et al., 2008](#); [DuPont et al., 2008](#); [Teter et al., 2006](#); [White et al., 2006](#)) as well as the FDA's literature review, which found rates of snorting as high as 50% in some populations ([FDA, 2019](#)). While IR prescription stimulants are more likely to be misused or abused than ER stimulants in general, studies also show that non-oral routes of administration are also more common with IR prescription stimulants ([Bright, 2008](#); [Cassidy et al., 2015](#); [Inflexxion, 2019](#)), none of which have any properties to resist manipulation.

The motivations for misuse and abuse of prescription stimulants is different from other CNS-active drugs. While the primary motivations for nonmedical use of opioid analgesics are to treat pain or to get high, the primary motivations for most prescription stimulant nonmedical users are to enhance performance at work or school, for energy, or to treat ADHD ([Table 3](#)). In a survey of college students with ADHD who report snorting prescription stimulants, more than half (52%) reported that the primary motivation for snorting was to achieve a faster effect on ADHD symptoms than the oral route ([Inflexxion, 2019](#)).

**Table 3: Primary Motivations for Misuse or Abuse of Prescription Stimulants by Route among College Students**

Primary reason for misuse or abuse	Oral (N=538)	Snorting (N=120)	Injecting (N=21)
To enhance performance at work/school	49%	41%	29%
For energy	23%	33%	48%
To treat ADHD	20%	16%	29%
To improve mood/elevate spirit	16%	25%	38%
To get high	10%	23%	43%
To control appetite or for weight loss	9%	19%	33%
To prevent or treat withdrawal	4%	8%	29%

Nonmedical Use of Prescription Medications in College Students; Inflexxion (2019).

Another public health challenge posed by prescription stimulants is the high rate of diversion in the community. Among young people aged 10-17 years taking prescription stimulants, more than one-third (35%) reported having sold, given, or traded away their medication ([SNAPS, 2019](#)). Among college students who had been prescribed a stimulant to treat their ADHD, 65% reported being asked to divert their medication and nearly two-thirds of these individuals did so ([Inflexxion, 2019](#)). Congruent with the high rate of diversion in the college population, 57% of college students who misuse or abuse prescription stimulants do not have ADHD, and 78% of college students who snort prescription stimulants used a diverted medication ([Inflexxion, 2019](#)).

Intranasal and IV routes of prescription amphetamine misuse and abuse are associated with the greatest risk of major adverse medical outcomes ([Faraone et al., 2019](#)). These adverse effects may include cardiovascular effects, neuropsychiatric effects, pulmonary complications, physical and psychological dependence, and transmission of infectious diseases ([FDA, 2007](#); [Teva Pharmaceuticals USA, 2017](#); [Tseng et al., 2014](#)). As shown in [Table 4](#), a recent analysis of data from the National Poison Data System found that the likelihood of experiencing a major (life-threatening) medical effect or death was substantially higher for non-oral exposures to prescription amphetamines than unintentional oral exposures ([Faraone et al., 2019](#)).

**Table 4: Likelihood of Adverse Outcomes for Non-oral Exposures to Prescription Amphetamines Relative to Unintentional Oral Exposures**

Adverse Outcome of Use	Odds Ratio (95% CI) vs Unintentional Oral Use of Prescription Amphetamines (N=3,953)	
	Snorting (N=598)	Injecting (N=164)
Major effect (life-threatening)	2.9 (1.9, 4.4)	7.5 (4.7, 12.8)
Death	9.9 (2.3, 105.1)	24.2 (5.3, 308.8)

Based on data from Faraone et al (2019).

Furthermore, nonmedical users of prescription stimulants who administer the drug by snorting, smoking, and injecting – in addition to other risk factors such as psychiatric comorbidity – are at greater risk for polysubstance/illicit drug use ([Allain et al., 2015](#); [Heal et al., 2013](#); [Lile et al., 2011](#); [Teter et al., 2006](#)). Therefore, non-oral use of prescription stimulants may serve as an important juncture in the initiation and development of more dangerous drug-taking behaviors ([Stahl, 2013](#)).

Currently, there are no approved IR ADHD stimulant medications available that are formulated to resist manipulation by those who seek to misuse or abuse them by a non-oral route. There is an unmet public health need for manipulation-resistant stimulant medications for treating ADHD to reduce the adverse health effects that are associated with non-oral use by inhibiting the initiation of more dangerous routes of administration and progression to riskier drug-taking behaviors.

### 3 OVERVIEW OF AR19 DEVELOPMENT PROGRAM

Arbor developed AR19 to provide physicians, parents, and patients with an effective treatment option for ADHD that also has meaningful barriers to non-oral routes of administration. All excipients present in AR19 are safe for oral use in both children and adults. The AR19 development program consists of three biopharmaceutics studies, one clinical efficacy and safety study in adults, one intranasal human abuse potential (HAP) study, a comprehensive series of in vitro manipulation studies, and several in vitro and in vivo nonclinical IV safety studies ([Figure 3](#)).

**Figure 3: Overview of AR19 Development Program**

Biopharmaceutics	Efficacy and Safety	Manipulation Resistance
<b>AR19-002</b> Comparative bioavailability study of AR19 and Evekeo	<b>AR19-004</b> Randomized, double-blind, placebo-controlled study of AR19 in adults	<b>AR19-001</b> Randomized, double-blind, active- and placebo-controlled intranasal HAP study
<b>AR19-003</b> Food-effect bioavailability study of AR19		<b>In Vitro</b> Manipulation studies for snorting, smoking and injection
<b>AR19-005</b> PK dose proportionality study of AR19		<b>Nonclinical IV Safety</b> In vitro hemolytic potential and In vivo nonclinical IV safety studies

#### Studies Supporting Approval of AR19 for the Treatment of ADHD

The approval of AR19 for the treatment of ADHD in the pediatric population is supported by the bioequivalence of AR19 to Evekeo, an FDA-approved racemic amphetamine sulfate medication for use in children (see [Section 4.1](#)). A prior clinical efficacy and safety study demonstrated that Evekeo is safe and effective for the treatment of ADHD in children ([Childress et al., 2015](#)). The approval of AR19 in the adult population is supported by a clinical efficacy and safety study in adults (see [Section 5](#)).

#### Studies Supporting Manipulation-Resistant Labeling for Non-oral Routes of Administration

To support the labeling of AR19 with properties that can be expected to reduce snorting, smoking, and injecting, Arbor undertook a systematic approach to assess the physical and chemical properties of AR19 that are intended to resist manipulation and discourage administration by non-oral routes. Because there is no FDA Guidance document for the evaluation of manipulation-resistant stimulants ([FDA, 2019](#)), these study designs and methodologies were informed by the principles outlined in the FDA Guidance document on the evaluation of abuse-deterrent opioid formulations ([FDA, 2015](#)), real-world techniques cited on drug abuse forums, and consultations with the FDA and other experts. The studies used

Evekeo, Adderall, amphetamine sulfate API, or multiple products as non-manipulation-resistant comparators.

Across the entire development program, more than 2800 experiments were conducted across the following in vitro studies:

- **Particle size reduction (PSR) studies** evaluated a full range of common household tools, assessing the ability to reduce particle size for snorting, smoking, or injecting.
- **Simulated smoking studies** evaluated whether the products could be smoked or volatilized.
- **Large volume extraction studies** evaluated the drug release profile in large volumes of a variety of common household and advanced solvents under various conditions.
- **Small volume extraction and syringeability studies** evaluated the feasibility of extracting amphetamine sulfate in small volumes of solution and syringing the extract.

All in vitro manipulation resistance testing was performed independently by DRUGSCAN, a College of American Pathologists-accredited and Substance Abuse and Mental Health Services Administration-certified laboratory with extensive expertise in the evaluation of products designed to resist non-oral misuse and abuse.

#### Studies Evaluating Toxicity by Unintended Routes of Administration

Arbor conducted several in vitro and in vivo studies to thoroughly evaluate the potential toxicity of IV AR19 extracts. These included:

- Characterization of the PEO content of syringeable AR19 extracts;
- An in vitro hemolytic potential study of representative AR19 extracts; and
- Single- and 7-day repeat-dose in vivo IV safety studies in rabbits.

## 4 BIOPHARMACEUTICS STUDIES OF AR19

Three clinical biopharmaceutics studies were performed to; (1) demonstrate bioequivalence of AR19 to Evekeo, an FDA-approved IR amphetamine sulfate prescription stimulant, to provide the scientific bridge to safety and efficacy for the pediatric population, (2) evaluate the effect of food on AR19 bioavailability, and (3) determine dose proportionality.

### 4.1 Comparative Bioavailability Study – AR19.002

AR19.002 was a pivotal, open-label, randomized, two-period, two-treatment, two-sequence crossover study in which 36 healthy adult subjects received a single dose of AR19 20 mg in one period, and a single dose of Evekeo 2 x 10 mg in another period, both under fasting conditions.

The 90% confidence intervals (CI) for the geometric least squares (LS) mean ratios of the maximum plasma concentration ( $C_{max}$ ), exposure through the end of the study ( $AUC_{last}$ ), and exposure extrapolated to infinity ( $AUC_{inf}$ ) were within the pre-specified bioequivalence bounds of 80% to 125% for both *d*-amphetamine and *l*-amphetamine (Table 5). The study demonstrated that AR19 20 mg was bioequivalent to two Evekeo 10 mg tablets.

**Table 5: Bioequivalence Evaluation of AR19 20 mg and Evekeo 2 x 10 mg (AR19.002)**

PK Parameter	Geometric Mean		Geometric LS Mean Ratio (%)	90% CI	
	AR19	Evekeo		Lower	Upper
<i>d</i> -amphetamine					
$C_{max}$	26.6	27.0	98.4	96.1	100.6
$AUC_{last}$	427.0	429.3	99.5	96.9	102.1
$AUC_{inf}$	449.0	451.3	99.5	96.8	102.3
<i>l</i> -amphetamine					
$C_{max}$	23.8	24.1	98.8	96.4	101.3
$AUC_{last}$	436.9	440.1	99.3	96.6	102.1
$AUC_{inf}$	476.2	479.9	99.2	96.1	102.5

### 4.2 Food-Effect Bioavailability Study – AR19.003

AR19.003 was an open-label, randomized, four-period, four-treatment, four-sequence crossover study in which 36 healthy adult subjects were scheduled to receive a single oral dose of each of AR19 20 mg under four conditions: fasted, fed (with a standard high-fat, high-calorie breakfast), sprinkled on applesauce, and sprinkled on yogurt. The study demonstrated that the presence of food did not alter the  $C_{max}$  or AUC exposure parameters for AR19 and that AR19 could be sprinkled on food with bioequivalent exposures in each condition (Table 6). Because there is no food effect, AR19 capsules can be taken with or without meals and the pellets can be sprinkled on applesauce or yogurt for oral administration.

**Table 6: Food Effect Evaluation of AR19 20 mg under Various Conditions (AR19.003)**

Comparison (Test vs Ref)	PK Parameter	Geometric Mean		Geometric LS Mean Ratio (%)	90% CI	
		Fed	Fasted		Lower	Upper
<i>d</i> -amphetamine						
<i>d</i> -amphetamine vs Fasted	$C_{max}$	24.9	26.8	92.9	90.2	95.7
	$AUC_{last}$	408.3	421.8	96.8	93.5	100.2
	$AUC_{inf}$	429.3	443.9	96.7	93.3	100.2
<i>d</i> -amphetamine vs Fed	$C_{max}$	27.2	26.8	101.4	98.4	104.4
	$AUC_{last}$	443.1	421.8	105.1	101.5	108.8
	$AUC_{inf}$	464.5	443.9	104.7	101.0	108.5
<i>l</i> -amphetamine vs Fasted	$C_{max}$	26.9	26.8	100.6	97.7	103.6
	$AUC_{last}$	430.4	421.8	102.0	98.6	105.6
	$AUC_{inf}$	454.4	443.9	102.4	98.8	106.1
<i>l</i> -amphetamine						
<i>l</i> -amphetamine vs Fed	$C_{max}$	23.0	24.5	93.6	91.1	96.2
	$AUC_{last}$	425.5	446.8	95.2	91.9	98.7
	$AUC_{inf}$	463.3	486.4	95.2	91.5	99.1
<i>l</i> -amphetamine vs Applesauce	$C_{max}$	24.8	24.5	101.2	98.4	104.0
	$AUC_{last}$	468.9	446.8	104.9	101.2	108.8
	$AUC_{inf}$	509.4	486.4	104.7	100.6	109.0
<i>l</i> -amphetamine vs Yogurt	$C_{max}$	24.6	24.5	100.4	97.7	103.1
	$AUC_{last}$	457.8	446.8	102.4	98.9	106.2
	$AUC_{inf}$	500.7	486.4	102.9	99.0	107.0

#### 4.3 PK Dose Proportionality Study – AR19.005

AR19.005 was an open-label, randomized, two-period, two-treatment, two-sequence, crossover study in which 24 healthy adult subjects received a single dose of AR19 2 x 2.5 mg capsules in one period and a single dose of AR19 30 mg in another period, under fasting conditions.

Pharmacokinetic (PK) parameters for *d*- and *l*-amphetamine were calculated including dose-normalized  $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$  (Table 7). The dose-normalized parameters were bioequivalent. Therefore, it can be concluded that the AR19 formulation did not alter the known linear pharmacokinetics of amphetamine.

**Table 7: Dose-Normalized PK Parameters for AR19 2 x 2.5 mg and 30 mg (AR19.005)**

PK Parameter	Geometric Mean		Geometric LS Mean Ratio (%)	90% CI	
	AR19 2 x 2.5 mg	AR19 30 mg		Lower	Upper
<b>d-amphetamine</b>					
Dose-normalized C <sub>max</sub>	1.42	1.46	97.2	94.3	100.2
Dose-normalized AUC <sub>last</sub>	21.7	23.0	94.0	90.4	97.7
Dose-normalized AUC <sub>inf</sub>	22.7	24.5	92.7	89.1	96.5
<b>l-amphetamine</b>					
Dose-normalized C <sub>max</sub>	1.38	1.43	96.7	94.1	99.3
Dose-normalized AUC <sub>last</sub>	24.5	26.2	93.6	89.7	97.5
Dose-normalized AUC <sub>inf</sub>	26.6	29.1	91.2	87.0	95.5

#### 4.4 Conclusions from the Biopharmaceutics Studies

- AR19 is bioequivalent to Evekeo, establishing the scientific bridge to efficacy and safety as the basis for approval for the proposed indication in the pediatric population.
- AR19 may be taken without regard to meals and sprinkled on food.
- Exposure to amphetamine with AR19 is linearly related to dose.

### 5 CLINICAL EFFICACY AND SAFETY STUDY OF AR19 IN ADULTS – AR19.004

AR19.004 was a randomized, fixed-dose, double-blind, multicenter study that investigated the safety and efficacy of AR19 for the treatment of ADHD in adults aged 18 to 55 years. Patients were randomized to 20 mg or 40 mg AR19 daily or placebo in a 1:1:1 ratio. After randomization, treatment with AR19 or placebo was initiated at 10 mg/day and was titrated in weekly intervals in 10-mg increments to 20 or 40 mg/day in accordance with the randomization assignment. Patients received study drug twice daily, once in the morning and again 4 to 6 hours later, for approximately 5 weeks for each treatment. The primary efficacy endpoint was met, and the secondary efficacy endpoint results provide additional support for the efficacy of AR19 for the treatment of ADHD. No serious adverse events (SAEs) occurred and the safety and tolerability profile was consistent with the known profile of amphetamine sulfate.

This study is considered pivotal for the approval of AR19 in the adult population. However, because the efficacy and safety profile of amphetamine sulfate is well understood and the focus of this Advisory Committee meeting is the manipulation-resistant properties of AR19, the detailed results from the study are provided in the [Appendix](#).

## 6 MANIPULATION RESISTANCE STUDIES

Across the entire development program, more than 2800 combinations of conditions were evaluated, ranging from simple methods with household tools that are commonly used by individuals who use prescription stimulants by non-oral routes, to sophisticated methods with laboratory equipment that are beyond the capacity of most individuals in the real world. The rationale for the testing of modified tools and advanced, laboratory conditions is to assess the robustness of the formulation to manipulation and challenge the limits of the physical and chemical barriers ([Altomare et al., 2017](#)). Because no formulation can be “abuse-proof,” the manipulation resistance studies sought to determine whether the time, effort, and materials necessary to prepare AR19 for a non-oral route, along with the limited reward from those efforts (e.g., lower drug liking, lower dose possible for injection), can be expected to reduce misuse and abuse by those routes of administration.

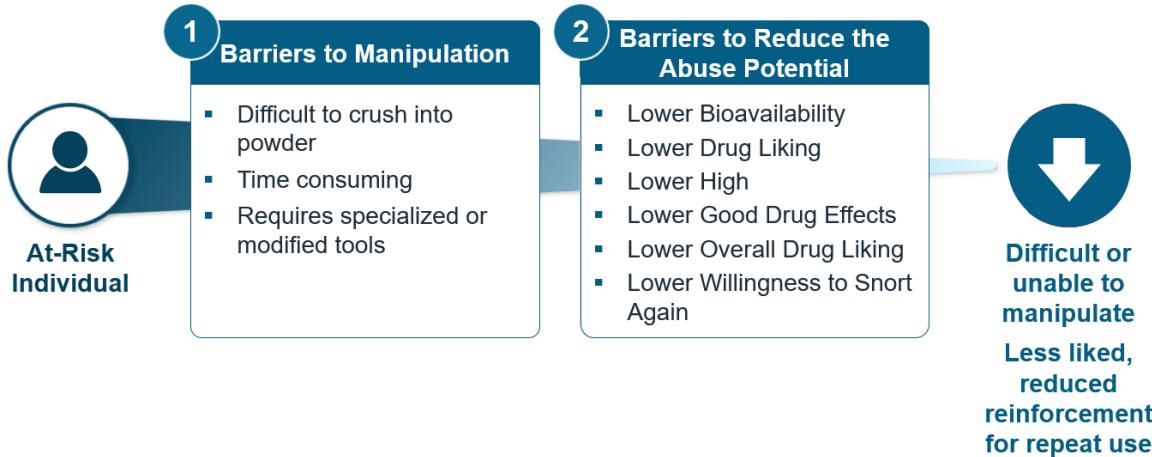
### 6.1 Snorting

Snorting is the most common non-oral route of misuse or abuse of prescription stimulant medications, with the highest prevalence among older adolescents and young adults. As described in [Section 2.3](#), intranasal administration provides a more rapid rise in plasma concentrations over time than the oral route by bypassing the first-pass metabolism, which produces correspondingly faster pharmacodynamic effects than oral use ([Allain et al., 2015](#); [Lile et al., 2011](#); [Stahl, 2013](#)).

In general, there are two types of formulation barriers that might impede an at-risk individual from snorting a prescription stimulant ([Figure 4](#)):

1. **Barriers to manipulation**, whereby the time, effort, and materials necessary to convert the medication into a snortable form make it difficult to perform. Intranasal users seek to manipulate prescription stimulants into a fine powder to enhance absorption via the nasal mucosa. The resistance of AR19 to physical manipulation was evaluated in a series of particle size reduction studies (see [Section 6.1.1](#)).
2. **Barriers to reduce the abuse potential** of a product if it is snorted. To assess the impact of these barriers, an intranasal HAP study evaluated the pharmacokinetics and pharmacodynamics of intranasal AR19 after optimized physical manipulation, which was performed in advance for subjects by certified pharmacy staff (see [Section 6.1.2](#)).

**Figure 4: Potential Barriers to Snorting a Prescription Stimulant**



### 6.1.1 Particle Size Reduction Studies

Particle size reduction (PSR) is usually the first step required to prepare a prescription stimulant for a non-oral route of administration. For a non-oral user, the ideal form of a manipulated prescription stimulant is a fine powder that can be snorted, smoked, or dissolved in a small volume for injection. DRUGSCAN iteratively determined the methods, tools, and testing conditions for PSR to ensure maximal reduction for AR19 and Evekeo. The goals of the PSR studies were to:

1. Evaluate the feasibility of different types of tools for physically manipulating AR19 5, 20, and 40 mg (the highest dosage strengths within each compositionally proportional subset) to particle sizes that are amenable for non-oral routes of administration relative to the non-manipulation-resistant comparator, Evekeo 10 mg.
2. Quantify the time, effort, and materials required to reduce the particle size of the products using each tool.
3. Identify the optimal methods of PSR that produced the smallest particle sizes in a consistent and reproducible manner for AR19 and Evekeo, respectively.

The mechanisms used to physically manipulate solid oral dosage forms for non-oral use include cutting, crushing, grating, and grinding ([Table 8](#)). To evaluate the feasibility of PSR for AR19 and Evekeo, DRUGSCAN conducted an extensive evaluation of a large battery of household tools; several tools were tested for each mechanism of manipulation. For many tools, multiple makes and models were tested.

**Table 8: Battery of Representative Tools for Particle Size Reduction**

Mechanism of Manipulation	Representative Tools
Cutting	<ul style="list-style-type: none"> <li>• Razor blade without handle</li> <li>• Razor blade with handle</li> <li>• Knife</li> </ul>
Crushing	<ul style="list-style-type: none"> <li>• Spoon</li> <li>• Hammer</li> <li>• Pill crusher</li> <li>• Mortars and pestles</li> </ul>
Grating	<ul style="list-style-type: none"> <li>• Cheese grater</li> <li>• Electric pet grooming device</li> </ul>
Grinding	<ul style="list-style-type: none"> <li>• Spice grinders</li> <li>• Salt/pepper grinders</li> <li>• Coffee grinders</li> </ul>

Following the extensive initial evaluation, DRUGSCAN selected 7 tools for the primary particle size reduction study to be representative of the different ways someone might attempt to physically manipulate AR19 or Evekeo. [Figure 5](#) illustrates the mean percentage of small particles that could be achieved with each tool. The FDA has identified particles <500 µm as a meaningful threshold for particles available for insufflation ([FDA, 2017](#)).

For Evekeo, all household tools successfully reduced nearly the entire tablet into a fine powder in less than 1 minute. For AR19, none of the household tools were able to reduce the majority of the pellets to particle sizes suitable for snorting – despite applying much more time and effort than was needed to manipulate Evekeo.

Due to the inability of any household tool to reliably and consistently cut, crush, grate, or grind the majority of AR19 pellets into particles <500 µm, experienced DRUGSCAN scientists undertook a systematic, iterative development process to modify a tool that could further reduce the particle size of AR19. Extensive exploratory investigations were conducted using a variety of accessories to identify incremental enhancements. After several weeks of experimentation, DRUGSCAN developed an optimized procedure that required modifying Tool 7 and applying select accessories. This optimized procedure to manipulate AR19 required a multi-step, 20-minute process that involved the following steps:

**Step 1: Modifying Tool 7** with a device, which costs around \$150 and takes approximately 7 minutes.

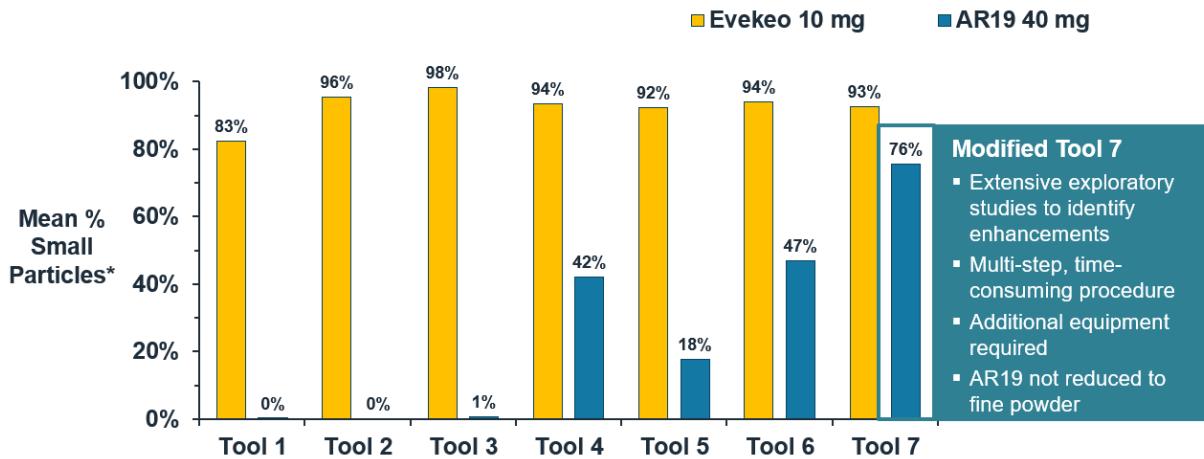
**Step 2: Enhancing Modified Tool 7** by applying a second modification with the device, which takes approximately 2 minutes.

**Step 3: Setting workspace with specific accessories**, which takes approximately 2 minutes. Failure to use these specific accessories led to an inability to reduce AR19, degradation of Modified Tool 7, or loss of AR19 pellets from the workspace.

**Step 4: Manipulating AR19 pellets with Modified Tool 7**, a laborious physical process that took approximately 7 minutes. Applying Modified Tool 7 for longer than 7 minutes did not further reduce the particle size of pellets.

**Step 5: Collecting manipulated AR19 particles**. After the manipulation process, the particles tended to stick to Modified Tool 7 and the accessories. An additional accessory was needed to recover all the material, which took approximately 2 minutes.

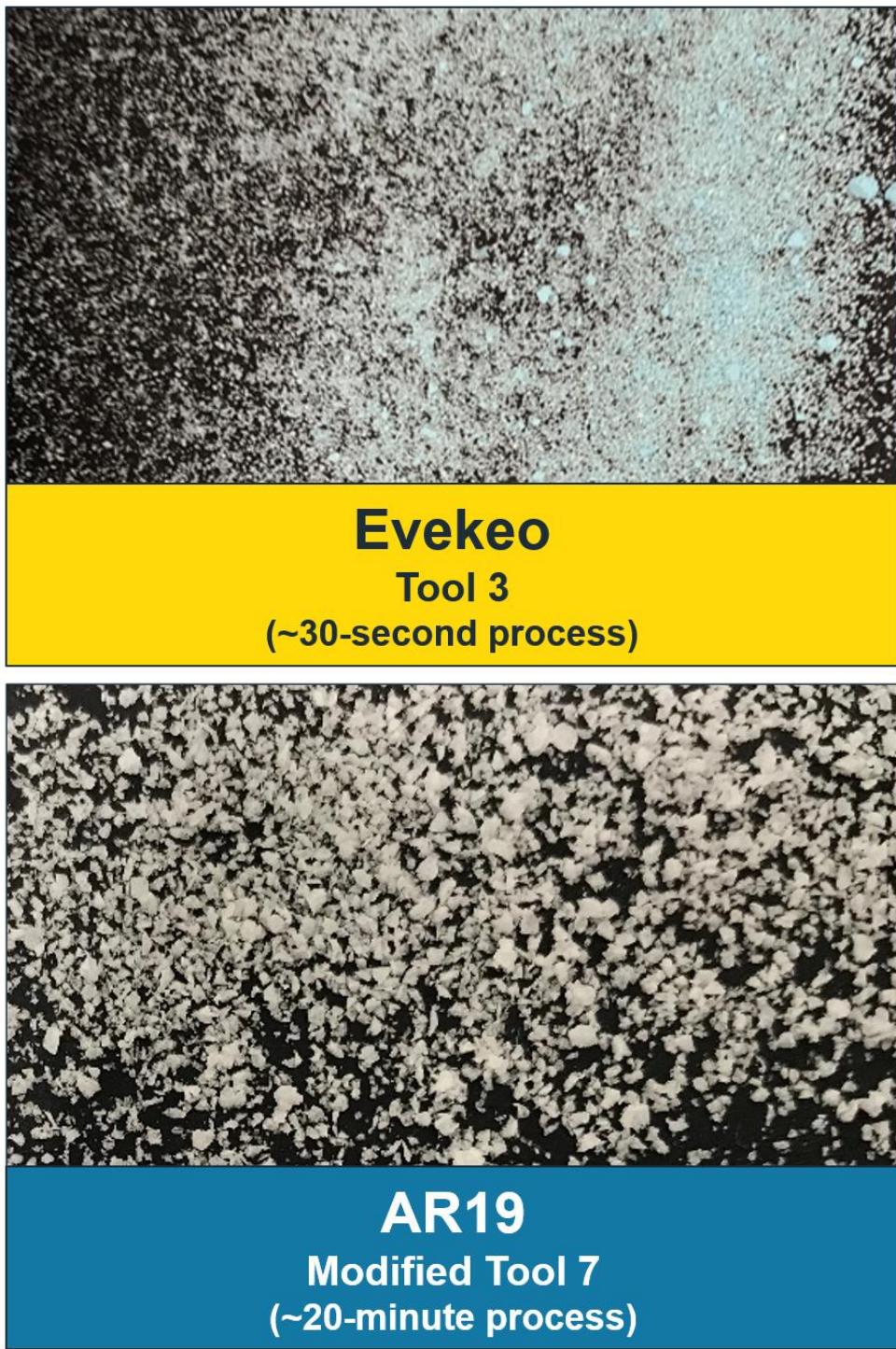
**Figure 5: Mean Percentage of Particles <500 µm after Particle Size Reduction with Maximum Manipulation Using Representative Tools from Full Battery**



\* Small particles defined by FDA guidance as <500 microns (FDA, 2017)

Although optimized manipulation of AR19 and Evekeo both provided particles small enough for snorting, the manipulated AR19 particles were much larger than the Evekeo particles (Figure 6). Despite optimization, Modified Tool 7 was not able to reduce AR19 into a fine powder regardless of the amount of time that the Modified Tool 7 was applied. No other method was found that could further reduce the particle size of AR19, including the application of 20 different varieties of thermal pretreatments (e.g., microwaving, baking, and freezing at different temperatures for various amounts of time).

**Figure 6: Particle Size Reduction of Evekeo and AR19**



Note: Photographs taken at the same magnification.

The time and effort required to prepare AR19 for snorting were considerably longer and greater than that for Evekeo. It was hypothesized that the manipulation-resistant excipients (with amphetamine embedded in the PEO matrix) and the inability to produce a fine powder would impair nasal absorption of AR19 and provide reduced drug liking and willingness to take the drug again relative to currently available amphetamine products. This hypothesis was evaluated in an intranasal HAP study.

### 6.1.2 *Intranasal Human Abuse Potential Study*

Intranasal HAP studies evaluate a product's pharmacokinetics (PK) and pharmacodynamics (PD) after being optimally manipulated for snorting. The study drugs are prepared by trained pharmacy staff at the clinical site under laboratory conditions using the optimized method of particle size reduction for each respective product.

Due to the difficulty of the optimized manipulation method for AR19, DRUGSCAN provided a laboratory scientist to the clinical site to teach the pharmacists how to perform the manipulation procedure with Modified Tool 7 and select accessories. Pharmacists were required to demonstrate their ability to manipulate AR19 reliably and consistently prior to being certified to manipulate AR19 for the HAP study.

Importantly, subjects in an intranasal HAP study do not manipulate the products themselves and, therefore, do not incorporate the time and effort required to manipulate the respective products into their pharmacodynamic assessments (e.g., willingness to take drug again).

#### 6.1.2.1 Study Design

AR19.001 was a placebo- and active-controlled, double-blind, double-dummy, three-way crossover HAP study that evaluated the abuse potential of optimally manipulated AR19 40 mg capsule pellets in comparison with the amphetamine sulfate API 40 mg and placebo when administered intranasally to non-dependent, recreational stimulant users.

The study enrolled subjects aged 18 to 55 years who had used stimulants for recreational purposes at least 10 times in their lifetime and at least 1 time in the last 12 weeks and snorted a drug for recreational purposes on at least 3 occasions in the year prior to the screening. Prior to enrollment in the treatment phase, all subjects had to be able to discriminate intranasal amphetamine sulfate API 40 mg from placebo in a randomized, double-blind Qualification Phase according to prespecified criteria. The primary analysis population consisted of 37 subjects, which is considered an adequate sample size for studies of this type and is consistent with the sample size of intranasal HAP studies of opioid products with abuse-deterring labeling.

Because the optimized particle size reduction procedure for AR19 (Modified Tool 7 with select accessories) could only produce a relatively coarse material that could easily be distinguished from amphetamine sulfate API, which was a fine powder, subjects snorted two products sequentially in a random order in each treatment period to maintain the study's double-blind: a fine powder (amphetamine sulfate API or placebo powder) and a coarse material (manipulated AR19 or manipulated AR19 placebo) with a 5-day washout period between treatment periods (primary treatment in **bold**):

- **Amphetamine sulfate API 40 mg** powder and optimally manipulated AR19 placebo
- **Optimally manipulated AR19 40 mg** and placebo powder
- **Placebo powder** and optimally manipulated AR19 placebo

PK and PD measurements were taken through 36 hours following study drug administration. As mentioned above, all study drugs were prepared in advance for the subjects, so they did not experience the time and effort of the multi-step procedure with Modified Tool 7 and select accessories, which was required to get AR19 into a snortable form.

### 6.1.2.2 Primary and Secondary Endpoints

The primary and key secondary endpoints are outlined in [Table 9](#). The primary endpoint, maximum ( $E_{max}$ ) Drug Liking, was the highest Drug Liking score for each subject observed at any time from 15 minutes through 36 hours post-dose. The key secondary endpoints included other aspects of the drug-taking experience over time (e.g., Drug High and Good Drug Effects), as well as global assessment measures after the PD effects of amphetamine sulfate had dissipated (12, 24, and 36 hours post-dose). These global assessments included Overall Drug Liking, which measured how much subjects liked the drug effects overall, and Take Drug Again, which measured how likely subjects would be to snort the drug again if given the opportunity. The  $E_{max}$  score for each respective endpoint reflects the highest score reported for each subject regardless of time.

**Table 9: Primary and Key Secondary Pharmacodynamic Endpoints of HAP Study**

Endpoint	Timing of Assessments
Drug Liking	15 minutes through 36 hours
Drug High	15 minutes through 36 hours
Good Drug Effects	15 minutes through 36 hours
Overall Drug Liking	12, 24, and 36 hours
Take Drug Again	12, 24, and 36 hours

Currently, there is no FDA guidance on the development and evaluation of manipulation-resistant stimulant formulations ([FDA, 2019](#)). At the request of the FDA, the statistical analysis of study validity and the primary endpoint were based on the principles outlined in the FDA guidance for the evaluation of abuse-deterrent opioids ([FDA, 2015](#)). This guidance notes that “the science of abuse deterrence is relatively new,” and “FDA intends to take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products.” Furthermore, the guidance notes that “no absolute magnitude of effect can be set for establishing abuse-deterrent characteristics” and “FDA intends to consider the *totality of the evidence* when reviewing the results of studies evaluating the abuse-deterrent properties of a product.” (Note: Arbor seeks to refer to AR19 as “manipulation resistant” rather than “abuse deterrent” for reasons cited in [Section 1](#)).

The abuse-deterrent opioid guidance outlines two statistical tests for Drug Liking  $E_{max}$ , which were utilized in this study, both tested at the one-sided 0.025 significance level:

- **Statistical testing with a validation margin.** For this test, the lower bound of the 95% CI for the difference between the positive control (amphetamine sulfate API) and placebo on Drug Liking  $E_{max}$  is tested against a specific value (i.e., the validation margin). The abuse-deterrent opioid guidance specifies a validation margin of at least 15, which was the value used in this study.
- **Statistical testing with an “abuse deterrence” margin.** For this test, the lower bound of the 95% CI for the difference between the positive control (amphetamine sulfate API) and the test drug (AR19) on Drug Liking  $E_{max}$  must exceed a specific margin,  $\delta_1$ . (Note: a standard statistical test for superiority is equivalent to setting a margin of 0.) The value of  $\delta_1$  is calculated as  $\delta^* \times (\mu_c - 50)$ , where  $\delta^*$  is a percentage,  $\mu_c$  is the mean Drug Liking  $E_{max}$  of the positive control, and 50 represents a neutral score on the bipolar Drug Liking

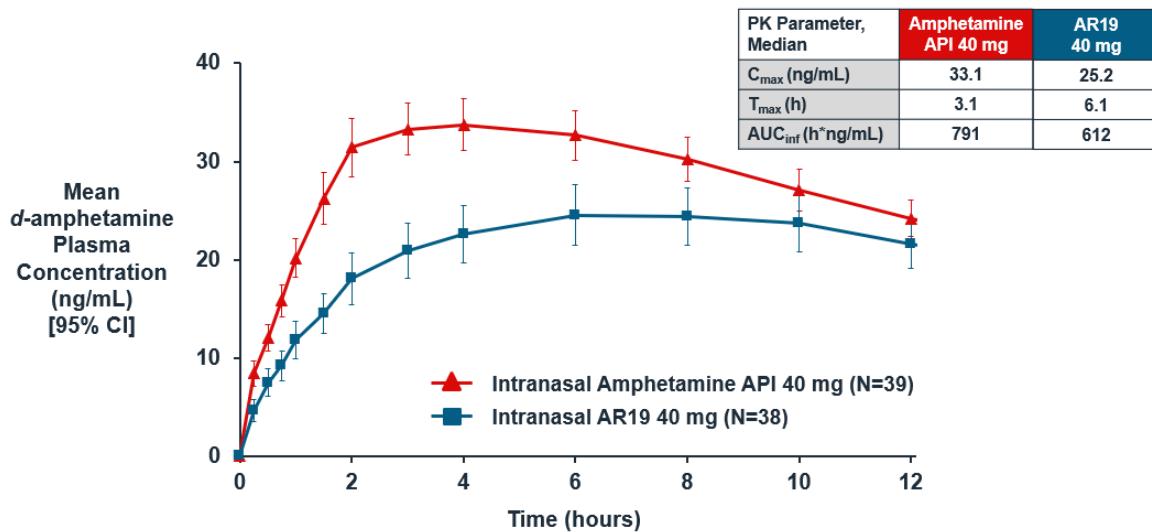
scale. Therefore,  $\delta_1$  represents a certain percentage of the maximum liking of the positive control. Because AR19 is the first prescription stimulant to be evaluated with manipulation-resistant properties, there was no precedent for an appropriate margin. The FDA instructed Arbor to set  $\delta^*$  as 10% for the primary analysis in this study.

All other statistical tests were performed using two-sided hypothesis tests at the 0.05 significance level without any statistical margins.

#### 6.1.2.3 Pharmacokinetic Results

Intranasal administration of amphetamine sulfate API 40 mg was associated with a rapid increase in plasma *d*-amphetamine concentrations (Figure 7). Intranasal administration of optimally manipulated AR19 40 mg was associated with statistically significantly lower maximum plasma amphetamine concentrations ( $C_{max}$ ) and exposures ( $AUC_{inf}$ ) than intranasal API (all  $p<0.0001$ ). Compared to API, the median  $C_{max}$  and  $AUC_{inf}$  were 25% lower and  $T_{max}$  was 3 hours longer with AR19. (Similar PK findings were observed with *l*-amphetamine.) These results confirmed the hypothesis that the inability to reduce AR19 to a fine powder and its manipulation-resistant excipients would significantly reduce its intranasal bioavailability.

**Figure 7: Mean *d*-amphetamine Plasma Concentrations through 12 Hours (AR19.001)**



#### 6.1.2.4 Pharmacodynamic Results

##### Test of Study Validity

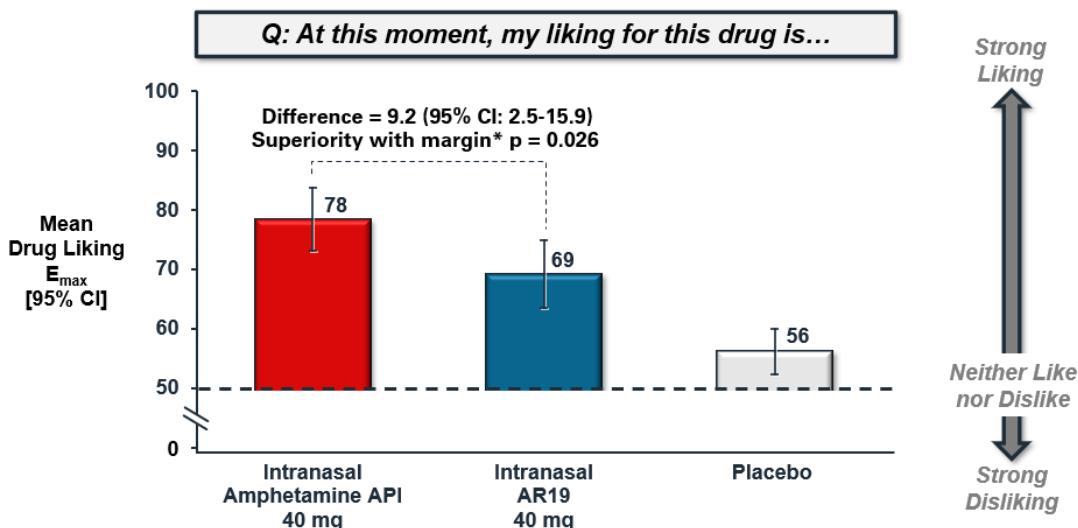
Drug Liking is measured over time on a 100-point, bipolar scale where 0 indicates *strong disliking*, 50 indicates *neither like nor dislike*, and 100 indicates *strong liking*. Drug Liking  $E_{max}$  is the greatest score observed for each subject in the study, regardless of the measurement time point.

The mean Drug Liking  $E_{max}$  values were 78.4 for amphetamine sulfate API 40 mg and 56.2 for placebo (median of the difference, 24.0; lower 95% CI, 15.0). This difference did not achieve statistical significance at a prespecified alpha level of 0.025 with a validation margin of 15 based on the abuse-deterrent opioid guidance ( $p=0.04$ ). However, in light of the known intranasal abuse potential of amphetamine from epidemiological data, the absence of formal guidance for stimulants, and the fact that amphetamine sulfate API was well-liked in the study (with a mean score of 78.4), further analyses considering the totality of the data were deemed appropriate.

### Primary Endpoint – Drug Liking E<sub>max</sub>

Consistent with the PK results, the mean Drug Liking E<sub>max</sub> was lower with AR19 than amphetamine sulfate API (difference 9.2; 95% CI: 2.5 to 15.9) ([Figure 8](#)). The 95% CI for the difference between treatments excluded 0 (i.e., the mean Drug Liking E<sub>max</sub> of AR19 was significantly lower than amphetamine sulfate API), however the difference did not achieve the target 10% margin at the 0.025 alpha level ( $p=0.026$ ). The observed treatment effect is consistent with achieving a 9% margin ( $p=0.022$ ).

**Figure 8: Primary Endpoint – Drug Liking E<sub>max</sub> (AR19.001)**

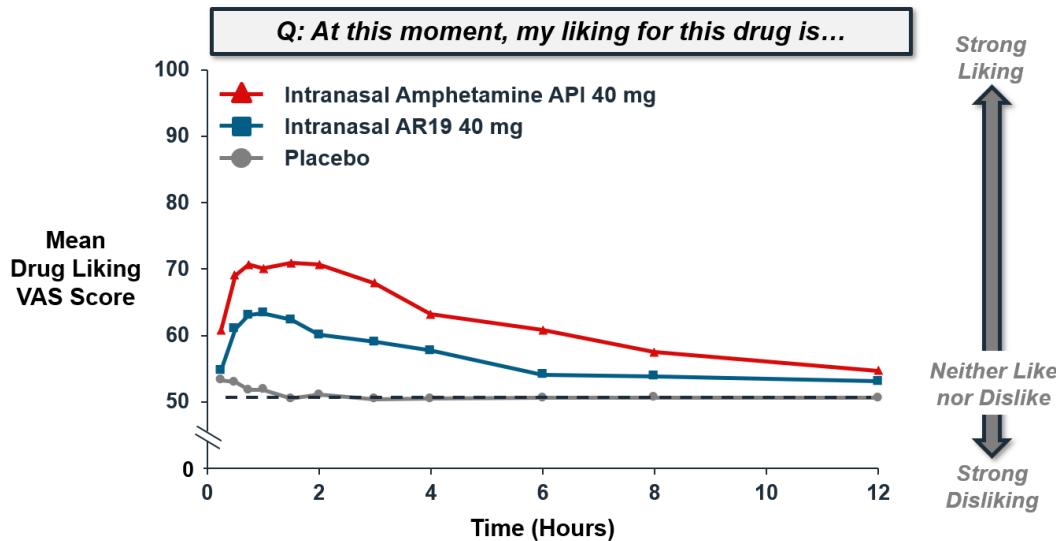


\* Margin = 10%  $\times$  ( $\mu_{\text{API}} - 50$ ).

### Drug Liking Over Time

Consistent with the PK results, the mean Drug Liking score for AR19 was numerically lower than amphetamine sulfate API at every time point through 12 hours. [Figure 9](#) illustrates that the greatest reductions in mean Drug Liking with AR19 occurred in the first few hours, which is the time frame that intranasal users of stimulants would be expecting the greatest effects.

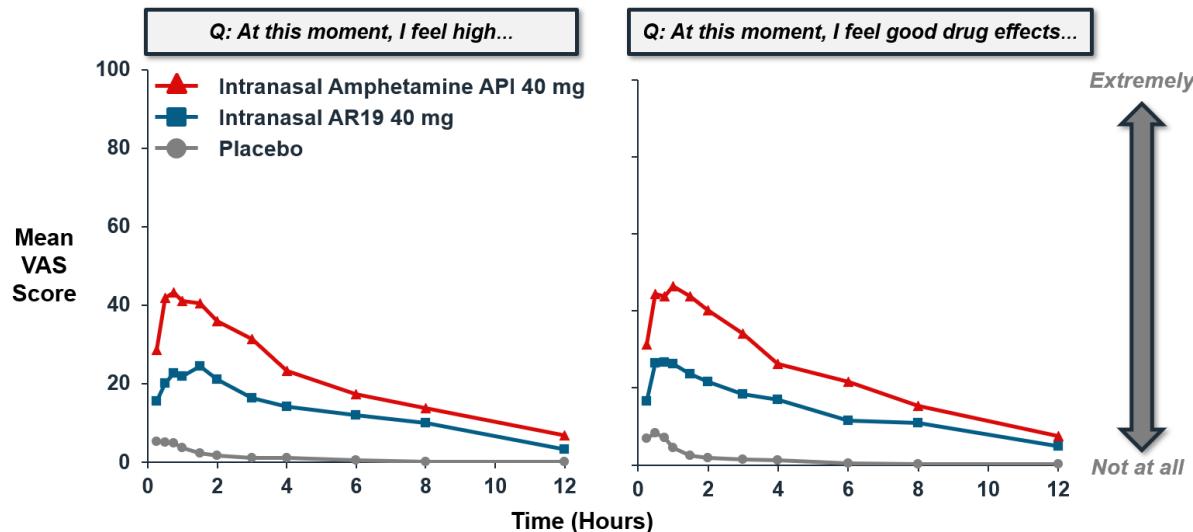
**Figure 9: Drug Liking Over Time (AR19.001)**



### Drug High and Good Drug Effects

Drug High and Good Drug Effects are measured over time on a unipolar scale where 0 indicates *not at all* and 100 indicates *extremely*. Consistent with the PK results and Drug Liking over time, subjects reported lower scores for Drug High and Good Drug Effects over time with AR19 than with amphetamine sulfate API (Figure 10). The  $E_{max}$  values for both these measures were statistically significantly lower for AR19 than amphetamine sulfate API (see Figure 13).

**Figure 10: Drug High and Good Drug Effects Over Time (AR19.001)**

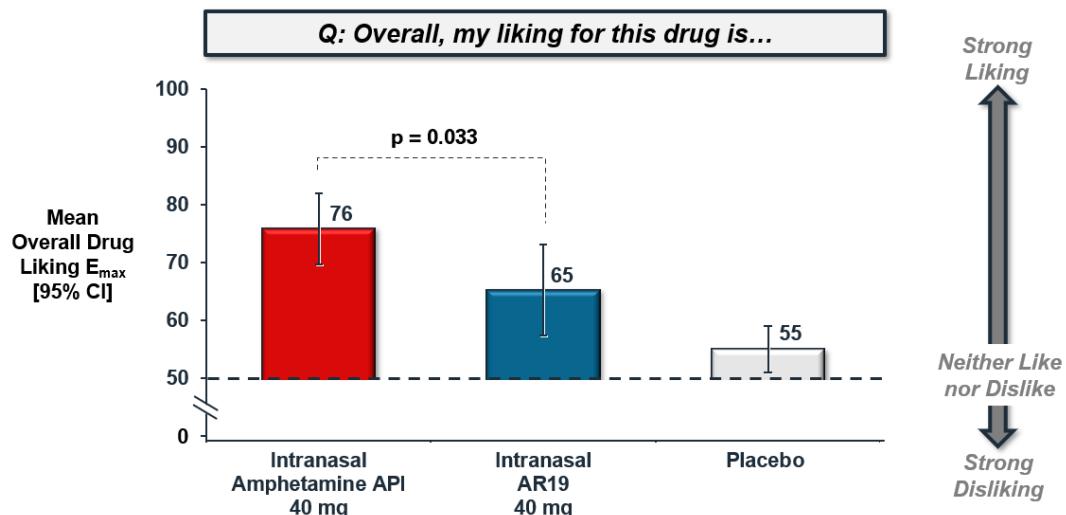


### Global Assessment Measures of Abuse Potential

To assess the overall drug-taking experience after the effects of the study drugs had worn off and to predict future behavior, participants were asked 12, 24, and 36 hours after administration how much they liked the drug overall and about their willingness to take the drug again if given the opportunity. The  $E_{max}$  score for each measure reflects the highest score reported by each subject at any of those late time points.

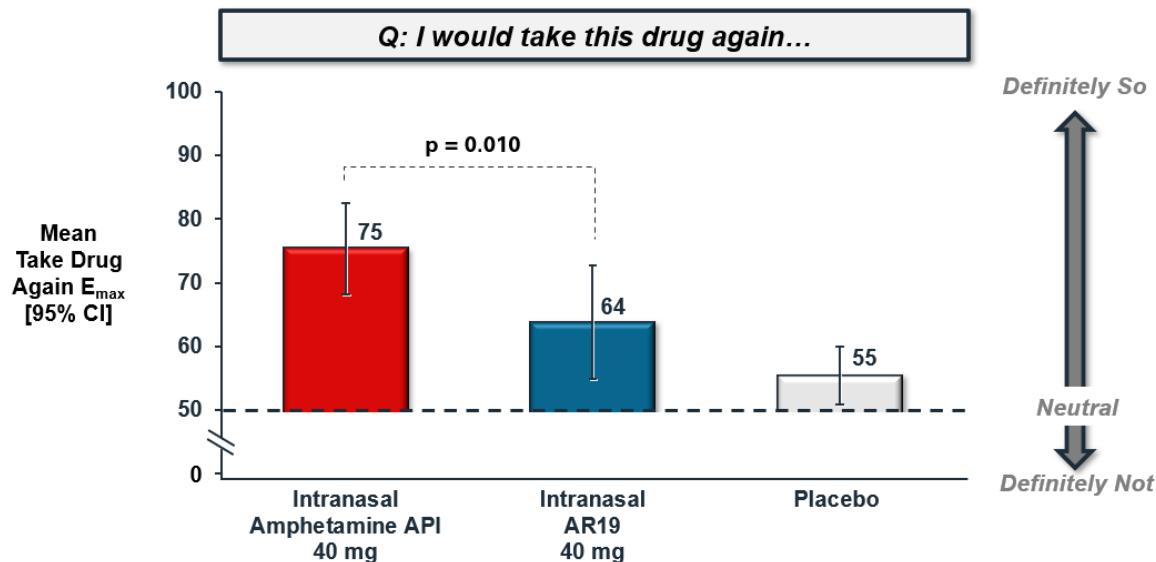
AR19 was associated with a statistically significantly lower Overall Drug Liking  $E_{max}$  than amphetamine sulfate API (Figure 11).

**Figure 11: Overall Drug Liking  $E_{max}$  (AR19.001)**



Subjects in the study expressed statistically significantly less willingness to snort AR19 again than API, even without experiencing the substantial time, effort, and materials required to get AR19 into a snortable form (Figure 12).

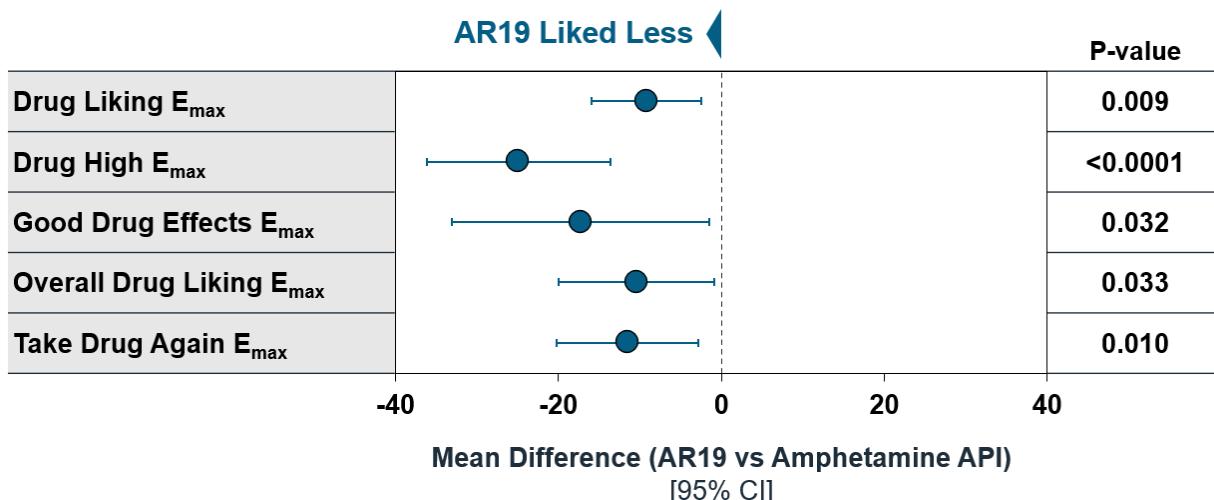
**Figure 12: Take Drug Again E<sub>max</sub> (AR19.001)**



#### Summary of Findings Across Key Pharmacodynamic Endpoints

The treatment differences between AR19 and amphetamine sulfate API showed a consistent reduction in at-the-moment measures (Drug Liking, Drug High and Good Drug Effects) as well as global measures of future drug-taking behavior (Overall Drug Liking and Take Drug Again) for AR19 (Figure 13). Overall, the results on the abuse liability endpoints were congruent with the reduced intranasal bioavailability with AR19, showing that AR19 – even when optimally manipulated using a laboratory procedure – has a lower intranasal abuse liability than amphetamine sulfate API.

**Figure 13: Treatment Differences Between AR19 and Amphetamine Sulfate API on Key Pharmacodynamic Endpoints**



Note: all p-values are two-sided.

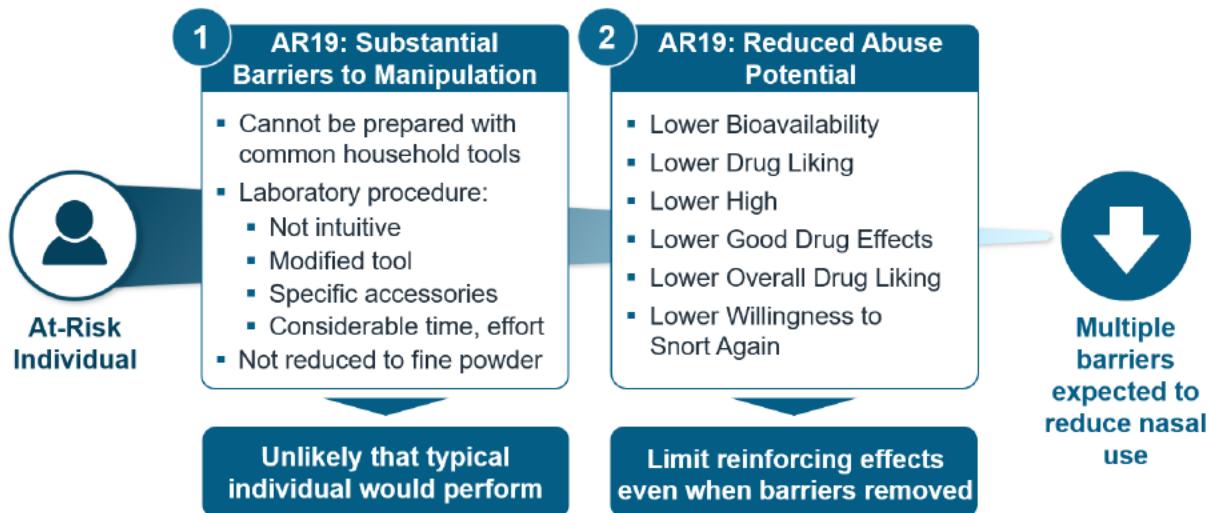
### 6.1.3 Conclusions for the Intranasal Route

The totality of in vitro and clinical data demonstrated that AR19 can be expected to reduce misuse and abuse by the intranasal route (Figure 14).

In terms of the **barriers to manipulation**, all common household tools failed to reduce the majority of AR19 pellets to small particles. DRUGSCAN scientists spent several weeks developing a multi-step procedure with a modified tool (Modified Tool 7) and specific accessories that could reliably and consistently reduce the majority of AR19 pellets into small particles. Despite the much greater time and effort required for this optimized procedure, AR19 pellets could not be reduced to fine powder preferred by intranasal drug users. In light of the arduous nature of the preparation process and specialized accessories required, it is unlikely that a typical at-risk individual would be willing or able to manipulate AR19 into a snortable form.

In terms of the **barriers to reducing abuse potential**, the intranasal HAP study demonstrated that the inability to reduce AR19 into a fine powder and the manipulation-resistant excipients translated into statistically significantly lower bioavailability after snorting optimally manipulated AR19 than after snorting amphetamine sulfate API. Furthermore, subjects expressed significantly lower drug liking, lower high, and lower willingness to snort AR19 again than API, even *without* taking into account the substantial time, effort, and materials required for the optimized manipulation procedure with Modified Tool 7 and select accessories.

**Figure 14: Summary of Barriers to Snorting with AR19**



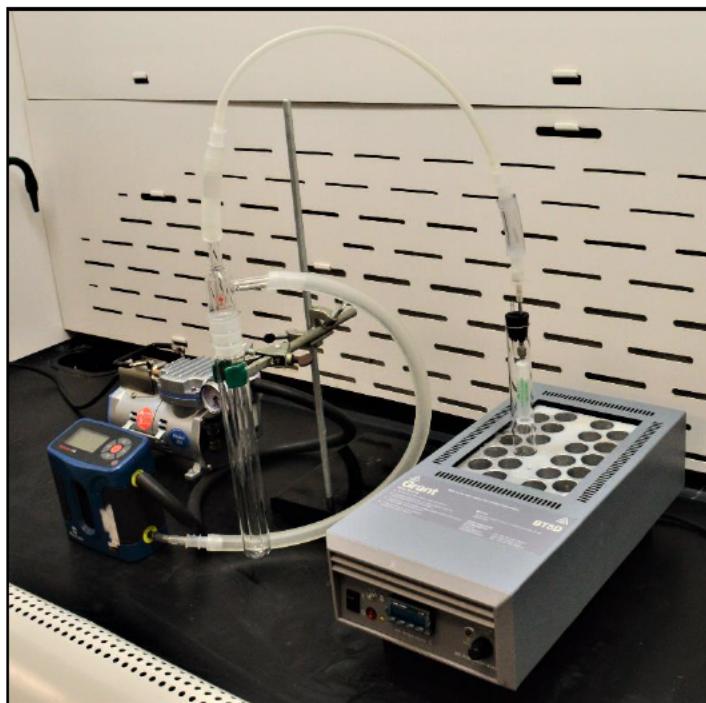
**The totality of data demonstrates that AR19 can be expected to reduce misuse and abuse by snorting:**

- Evekeo could be reduced to a fine powder quickly with any household tool. AR19 was considerably more difficult to manipulate and required a time-consuming, multi-step procedure with a modified tool and specific accessories to reduce the majority of pellets into small particles in a reliable and consistent manner.
- Insufflation of optimally manipulated AR19 was less rewarding than insufflation of amphetamine sulfate API. The intranasal HAP study participants had significantly lower amphetamine concentrations with AR19 and reported lower drug liking, high, and willingness to snort AR19 again.

## 6.2 Smoking Route

Some individuals who misuse or abuse a prescription stimulant heat a dosage form to volatilize and inhale the API. To evaluate the smokeability of drug products in a controlled fashion, DRUGSCAN used a simulated smoking apparatus with a heating block (Figure 15), which allows for rigorous control of temperature. The smoking process was simulated with an apparatus that applies heat and a partial vacuum. Smoking was also simulated by direct heating with a butane torch, which is more representative of real-world methods for smoking.

**Figure 15: Simulated Smoking Apparatus**



Amphetamine is particularly susceptible to degradation when heated, so it was important to determine the optimal heating time and temperature prior to formal testing. An exploratory study was conducted to identify the optimal smoking temperature and time with pure amphetamine sulfate API. Flanking temperatures (above and below the optimal temperature) were also tested in the formal study.

Under conditions optimal for the volatilization of amphetamine, up to 58% of amphetamine sulfate could be volatilized when using the pure (non-formulated) API. When the same experiment was attempted with Evekeo and AR19, no more than 11% of amphetamine sulfate could be volatilized at any temperature for either product. Furthermore, experiments with an open flame, which is more representative of real-world methods, resulted in less than 5% volatilized amphetamine sulfate from AR19. Therefore, smoking does not appear to be a feasible route of administration for AR19.

**Smoking is not a feasible route of administration for AR19 based on the very low (<11%) volatilization of amphetamine sulfate from the formulation.**

### 6.3 Intravenous Route

Preparing a syringeable extract of a prescription stimulant would typically involve (1) crushing the tablet, (2) dissolving it in a small, injectable amount of water (0.5-1.0 mL), (3) drawing the extract into an insulin syringe through a filter to avoid injecting particulates and clogging the needle, and (4) injecting.

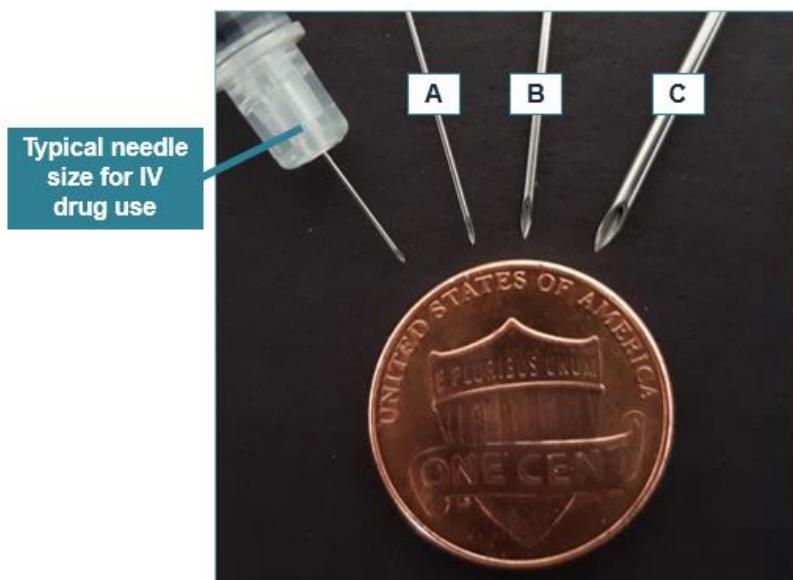
Since no formulation can be abuse-*proof*, the physical and chemical barriers to extraction can be partially overcome with sufficient time, effort, knowledge of chemistry, and laboratory materials. The goal of small volume extraction and syringeability testing, therefore, is not to demonstrate that the formulation cannot be injected, but rather, whether the extent of time, effort, materials, and knowledge (i.e., the input) and the reduced yield of syringeable API obtained (i.e., the output) can be expected to impede a substantial proportion of individuals from injecting the product. To answer these questions, the approach of the small volume extraction and syringeability studies is to test real-world techniques used by people who inject drugs as well as advanced methods that require laboratory tools and techniques that are beyond the capability of most individuals in the real world.

Another relevant consideration for the interpretation of these studies is that the goal of an IV user is to inject a dose of API that will provide the desired effect. Therefore, the actual dose (in mg) is a more relevant consideration than the percent of the total tablet or capsule extracted. Individuals initiating IV amphetamine use typically inject doses in the range of 20-40 mg ([Barceloux, 2012](#)). Upon becoming experienced, the IV dose individuals require escalates dramatically up to 100-300 mg per injection and may involve multiple injections per day ([Barceloux, 2012](#)). Therefore, a formulation that would be expected to reduce IV use would be difficult and time-consuming to prepare a desirable IV dose of amphetamine.

#### 6.3.1 Needle Gauges and Filter Assessment

In light of the anticipated gelling properties of AR19, the typical needle size that IV drug users prefer was not evaluated in the DRUGSCAN studies ([Figure 16](#)). Needle gauges A, B, and C were utilized for the syringeability assessment. Notably, Needle Gauge C is commonly used for blood transfusions and was tested as an extreme case.

**Figure 16: Needle Gauge Sizes**



Exploratory studies determined that it was not possible to syringe AR19 with simple filters that are commonly used by IV drug users, so a laboratory filter was used to prepare AR19 extracts.

### 6.3.2 Small Volume Extraction and Syringeability with a Small Needle

Forty-eight (48) sets of conditions were used to attempt to prepare Evekeo 10 mg and AR19 5, 20, and 40 mg for IV use in a small volume of solution with a small needle. This series of testing evaluated intact or optimally manipulated tablets/capsule pellets extracted in a small volume at various temperatures for a range of times, with or without agitation, followed by attempts at syringing with Needle Gauge A. As shown in [Table 10](#), 77% of conditions achieved greater than 60% syringeable amphetamine yield from Evekeo. In contrast, none of these methods were successful in extracting any appreciable amount of syringeable amphetamine from AR19; most conditions yielded a viscous, non-syringeable gel ([Figure 17](#)).

**Table 10: Yield of Syringeable Amphetamine from Conditions Evaluating Small Volume Extraction with a Small Needle**

Yield of syringeable amphetamine	% of Conditions Evaluating Small Volume Extraction with Small Needle (N=48)			
	Evekeo 10 mg	AR19 5 mg	AR19 20 mg	AR19 40 mg
>60% to 100%	77%	0%	0%	0%
>45% to 60%	8%	0%	0%	0%
>30% to 45%	8%	0%	0%	0%
>15% to 30%	6%	8%	2%	0%
0 to 15%	0%	92%	98%	100%

**Figure 17: Non-syringeable Gel Produced by AR19 after Small Volume Extraction**



### 6.3.3 Advanced Conditions for IV Misuse or Abuse

Because a high syringeable yield could be achieved with Evekeo in the smallest extraction volume using the smallest gauge needle, it was not necessary to continue testing it in more advanced conditions. Advanced testing of AR19 evaluated higher extraction volumes, larger needles, and/or applications of pretreatment. To allow for the presentation of all results, testing was grouped into 4 Levels, where higher levels reflect more extreme conditions (i.e., larger solvent volumes, larger needles, and/or with pretreatment).

The median yield of syringeable amphetamine recovered from all Levels was less than 10% (4 mg) ([Table 11](#)). A small number of extreme conditions yielded up to approximately 50% (20 mg) syringeable yield. The sets of conditions that achieved the highest syringeable yield from AR19 required optimal physical manipulation, pretreatment, extraction for an extended time at elevated temperatures, and large gauge needles not typically used for IV drug use. The complete procedure that achieved the highest syringeable amphetamine from AR19 40 mg capsule (50.2% or 20.1 mg) took approximately 60 minutes to complete with laboratory equipment. Several representative extracts from [Table 11](#), including the conditions with the greatest syringeable yields from Levels 2, 3, and 4, were evaluated in the nonclinical IV safety studies described in [Section 7](#).

**Table 11: Yield of Syringeable Amphetamine from Advanced Conditions**

Advanced Conditions	No. Combinations of Conditions	Yield of Syringeable Amphetamine from AR19 40 mg	
		Median (Range), %	Median (Range), mg
Level 1	96	0% (0-29.6)	0 mg (0-11.8)
Level 2	96	0% (0-42.0)	0 mg (0-16.8)
Level 3	96	8.7% (0-43.3)	3.5 mg (0-17.3)
Level 4	106	9.5% (0-50.2)	3.8 mg (0-20.1)

#### **6.3.4 Differences in IV Abuse Potential Between AR19 and Opana® ER**

One of the key excipients that impart the manipulation-resistance to AR19 is PEO 7M. This excipient was also used in Opana® ER, an oxymorphone tablet formulated to deter snorting, that was found to be associated with IV safety issues, which are described in detail in [Section 7](#). These safety events were attributable to the unique incentives for IV use, needle-sharing behaviors, and how the product was prepared for injection. This section describes the key differences between Opana ER and AR19 in both pharmacology and formulation, which impact their relative IV abuse liability and potential for unintended consequences of IV administration.

#### Relative Bioavailability by the Oral and IV Routes

The oral bioavailability of amphetamine sulfate (the API in AR19) is high and is estimated to be approximately 75% or more ([Markowitz & Patrick, 2017](#); [Teva Pharmaceuticals USA, 2017](#)) which means that 75% of an orally-administered dose reaches systemic circulation. For an AR19 40 mg capsule, this means that upon oral administration, 30 mg of amphetamine sulfate reaches systemic circulation. When a medication is administered intravenously, the bioavailability is 100%. Therefore, the relative IV: oral amphetamine sulfate dose is 1.33-fold greater ( $100\% \div 75\% = 1.33$ ) with IV use.

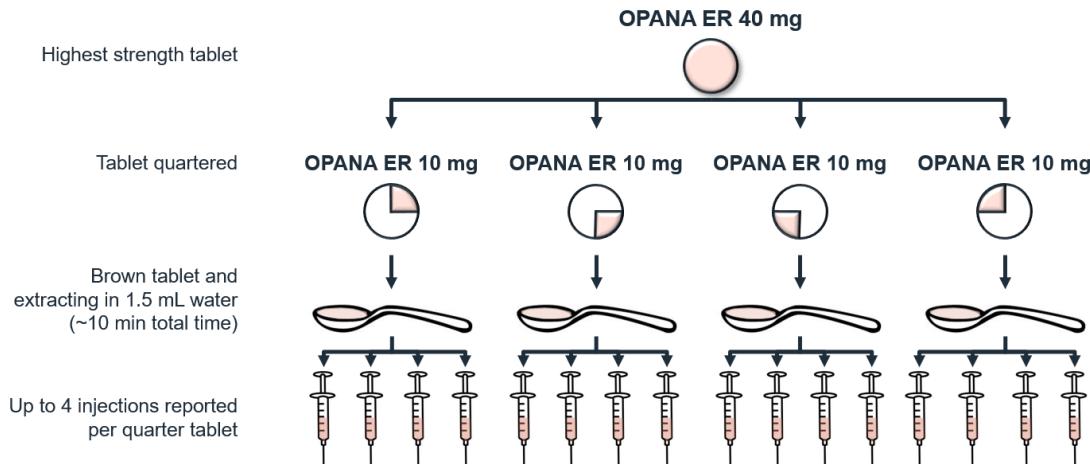
In contrast, oxymorphone (the API in Opana ER) is only 10% bioavailable when taken orally ([Sloan et al., 2005](#)). Therefore, the relative IV: oral oxymorphone dose is 10-fold greater ( $100\% \div 10\% = 10$ ) when injected compared to when taken orally. In light of a 10-fold greater systemic concentration when injected than when taken orally, there was substantial inherent motivation to use Opana ER by the IV route. Additionally, the fact that oxymorphone is so potent intravenously, explains why a single Opana ER tablet – or even parts of one tablet – could be used to prepare several IV doses and shared among multiple injectors.

#### Preparation for Injection and IV Use Behaviors with Opana ER

A thorough, qualitative study evaluated the injecting-drug behaviors with Opana ER in Scott County, Indiana to understand the methods for IV abuse of Opana ER ([Broz et al., 2018](#)). As

illustrated in [Figure 18](#), the typical method used to prepare Opana ER for injection involved quartering a 40 mg tablet, heating with a lighter to make the pill crushable, adding approximately 1.5 mL of water, and sharing 2-4 injections per quarter tablet with the resulting extract for an overall process that took about 10 minutes. Therefore, a single Opana ER 40 mg tablet could be used to prepare up to 16 potent IV doses for injection.

**Figure 18: Method Used to Prepare Opana ER for Injection**

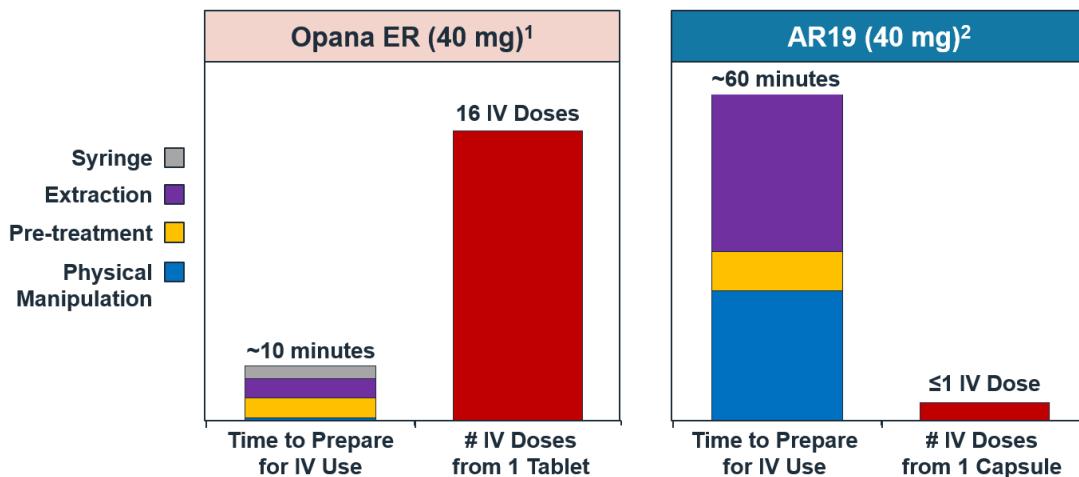


Importantly, when the procedure that successfully defeated Opana ER was applied to AR19, no syringeable extract could be drawn up due to the gelling properties.

#### Incentive for IV Use Based on Input and Output

Another important consideration is the relative incentive of the time and effort necessary (i.e., input) to get a particular syringeable yield (i.e., output). For Opana ER 40 mg, a 10-minute preparation process allowed for up to 16 potent IV oxymorphone doses from a single tablet; so, a relatively minimal effort was rewarded by a substantial output ([Figure 19](#)). The fact that so many injections could be achieved from a single tablet also explains the needle-sharing behaviors and resulting infectious disease outbreaks associated with Opana ER. In contrast, for AR19 40 mg, it would take approximately 60 minutes to achieve about one relatively low IV amphetamine dose.

**Figure 19: Time and Effort Required for IV Use of Opana ER and AR19 and Resulting Number of IV Doses**



1. Data adapted from Broz et al (2018). 2. Method providing the highest yield of syringeable amphetamine from AR19.

### 6.3.5 Large Volume Extraction and Syringeability

There is a minimal incentive for an individual to attempt large volume extraction of an IR amphetamine product for oral use since medications are rapidly bioavailable by design when taken orally as intended. In addition, the large volumes of solvents used in these studies substantially exceed what is feasible for direct injection.

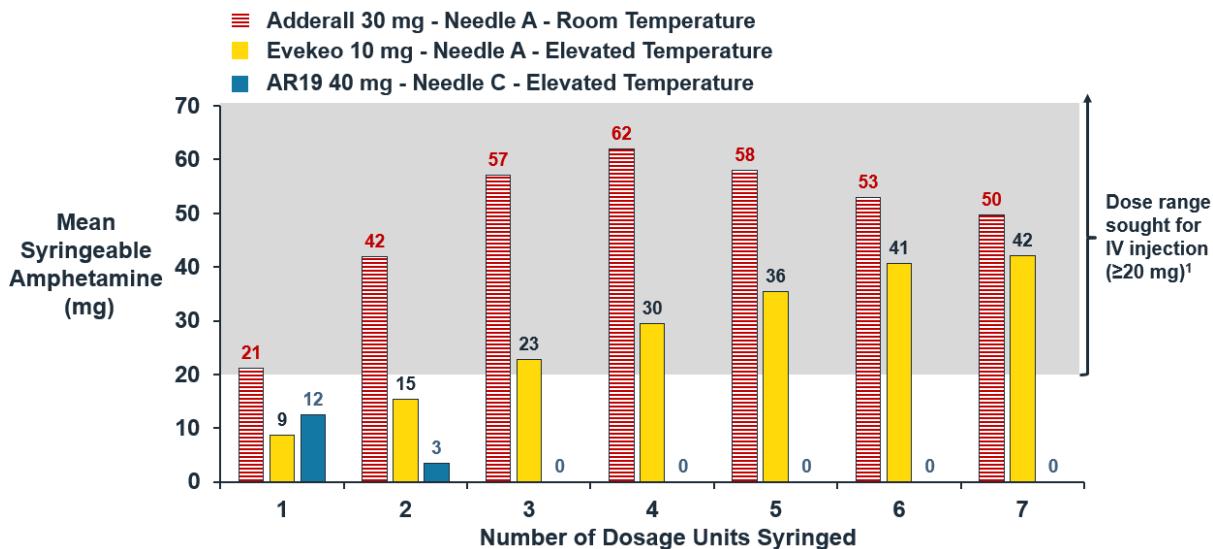
Nonetheless, to further investigate the manipulation-resistant properties of AR19 formulation for IV administration, DRUGSCAN conducted extraction and syringeability experiments with larger solvent volumes than those used in the small volume extraction and syringeability tests described in [Section 6.3.2](#) and [Section 6.3.3](#). However, syringeable amphetamine recoveries with large volumes were similar to or lower than those using small volumes, showing that large volume extraction is not a feasible method for overcoming AR19's injection-resistant barriers.

### 6.3.6 Multiple Tablet/Capsule Extraction and Syringeability Testing

Since the yield of syringeable amphetamine from a single AR19 40 mg capsule was low, DRUGSCAN evaluated whether an IV user might be able to achieve a suitable IV dose by using multiple capsules. Multiple-tablet/capsule extractions were performed using up to 7 dosage units of AR19 40 mg, Evekeo 10 mg, and Adderall 30 mg. Adderall 30 mg was considered a more relevant comparator since it represents a high-dose strength that would be attractive for IV use. All products were manipulated using their respective optimized physical manipulation procedures and extracted in a small volume. Adderall 30 mg was syringed with the smallest gauge needle (Needle A) following extraction at room temperature, Evekeo 10 mg was syringed with the Needle A following extraction at elevated temperature, and AR19 was syringed with the largest gauge needle (Needle C) following extraction at elevated temperature.

The addition of multiple tablets substantially increased the syringeable amphetamine yields for both Adderall and Evekeo ([Figure 20](#)). In contrast, adding more pellets from additional capsules of AR19 actually *reduced* the syringeable amphetamine yield below what could be achieved from a single capsule due to AR19's gelling properties. Similar results were observed with multi-dose extraction of pre-treated AR19 pellets. Therefore, the results from the in vitro testing demonstrate that multiple-dose extraction is not a feasible route of IV misuse or abuse with AR19.

**Figure 20: Syringeable Amphetamine Recovery from Multiple-Dose Extractions**



1. Amphetamine IV dose range based on Barceloux (2012).

### 6.3.7 Conclusions for the Intravenous Route

**The totality of data demonstrates that AR19 can be expected to reduce misuse and abuse by the IV route:**

- AR19 could not be prepared for injection using methods typically used by IV drug users.
- Multiple steps, laboratory equipment, and extensive time, effort, and knowledge were required for maximal recovery with small volume extraction. The maximum syringeable amphetamine sulfate recovery from AR19 (20.1 mg) would be considered a low dose for IV users of amphetamine.
- AR19 has a substantially lower IV abuse potential than Opana ER because of differences in the pharmacology of the APIs and differences in the formulations.
- Multiple-dose extraction to increase the syringeable yield was not possible with AR19.

## 7 NONCLINICAL IV SAFETY STUDIES

In 2013, the US Centers for Disease Control and Prevention (CDC) published a report that identified an association between IV administration of an extract of manipulated Opana ER and thrombotic thrombocytopenic purpura (TTP)-like illness ([Marder et al., 2013](#)). In response to these epidemiological findings, the FDA conducted a nonclinical IV toxicity study with Opana ER excipients, which identified a dose-dependent relationship between IV injection of Opana ER extracts (which consisted mostly of PEO 7M) and a syndrome that resembled thrombotic microangiopathy (TMA) ([Hunt et al., 2017](#)). The TMA-like syndrome was also produced by IV injection of high molecular weight PEO alone, which was attributed to changes in blood flow dynamics in small blood vessels ([Hunt et al., 2017](#)).

High molecular weight PEO changes the way red blood cells travel through small blood vessels by reducing the thickness of the relatively cell-free plasma layer adjacent to the vessel wall ([Marhefka et al., 2009](#)), which results in more frequent damaging impacts between endothelial and blood cells. The resulting hemolysis and release of free hemoglobin can overwhelm scavenger mechanisms and lead to systemic inflammation and iron deposition in tissues. The resulting endothelial cell damage can produce thrombosis and compromise blood flow to tissues.

As has been described by the FDA at prior Advisory Committee meetings ([FDA, 2020](#)), not all PEO-based formulations have been associated with IV toxicity risks. PEO-based products are expected to exhibit different risk profiles based on the following factors:

- Differences in manufacturing processes, curing methods, heat, additives, etc.
- Differences in molecular weight of PEO used
- Differences in methods used to prepare these products for IV abuse
- Differential patterns of abuse of the drug substances and/or drug products

These statements are substantiated by the observation that injection-related toxicities have not been observed with other PEO-containing oral drug products with IV abuse liability. For example, PEO 7M is also used as a primary excipient in Concerta, which has been FDA-approved for the treatment of ADHD since 2000 with no reports of TMA, TTP, or microangiopathic hemolytic anemia in the FDA Adverse Event Reporting System (FAERS) despite more than 85 million prescriptions dispensed.

AR19 contains PEO 7M and an additional gelling agent to resist extraction in small volumes and impede IV injection. However, in light of the unique risks observed with Opana ER, Arbor conducted several in vitro and in vivo studies to thoroughly evaluate the potential toxicity risks of manipulated AR19 extracts. These included:

- an in vitro hemolytic potential study of representative AR19 extracts;
- characterization of the PEO content of syringeable AR19 extracts; and
- single- and 7-day, repeat-dose IV safety studies in rabbits with injectable AR19 extracts and 7M PEO.

## 7.1 In Vitro Hemolytic Potential Study

An in vitro hemolytic potential model was developed to evaluate the risk of drug products inducing hemolysis when administered intravenously. The in vitro system utilized a syringe pump to pass human blood samples through a 30G needle at 1.152 mL/min to simulate blood flow through arterioles. The degree of hemolysis is assessed by centrifuging the expelled blood at 10,000 g for 1 minute and then measuring free hemoglobin concentration in the supernatant. With a positive control known to induce hemolysis in vivo, this model was designed to provide a relevant in vitro framework for assessing the risk of potential adverse effects following IV administration of drug products ([Persich et al., 2020](#)).

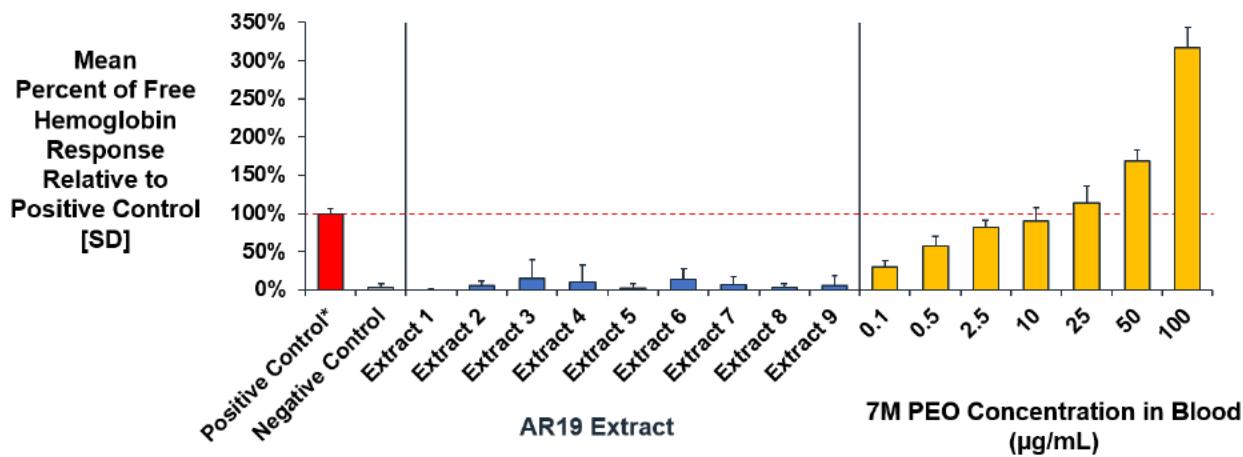
The study evaluated 4 types of test samples diluted and mixed with human blood to simulate IV injection followed by mixing with the blood volume of an average adult (5 L):

- a negative control (water);
- a positive control (8M PEO) at a blood concentration of 40 µg/mL;
- fixed concentrations of 7M PEO at blood concentrations ranging from 0.1-100 µg/mL; and
- 9 different extracts of manipulated AR19.

For each type of sample, 10 replicates were tested. Nine AR19 extracts were chosen to be representative of the different methods an individual might use to attempt to prepare AR19 for injection. These extracts were representative of the following factors and included the extract with the highest yield of syringeable amphetamine from the entire development program (Extract 8):

- with and without optimal physical manipulation
- with and without optimal pretreatment
- different solvents
- different extraction volumes
- different extraction temperatures
- a range of extraction times
- with and without agitation

[Figure 21](#) shows percentage of the degree of hemolysis caused by each test sample relative to the positive control of PEO 8M, noted by the red bar and the red dotted line. There was no evidence of in vitro hemolysis with any of the AR19 extracts, as evidenced by the relatively low percentages relative to the positive control and the lack of deviation from the negative control. In contrast, PEO 7M produced hemolysis in a concentration-related manner. These results confirmed that the in vitro test system could detect and measure hemolysis caused by high molecular weight PEO and that none of the AR19 extracts caused hemolysis.

**Figure 21: Results of In Vitro Hemolytic Potential Study**


\* Positive control: 8M PEO at blood concentration of 40 µg/mL

## 7.2 Characterization Injectability, PEO Content, and Amphetamine Content of AR19 Extracts

During the course of the small volume extraction and syringeability testing, DRUGSCAN scientists performed syringeability assessments immediately following extraction without regard to whether the extract was injectable (i.e., at a temperature suitable for injection into a blood vessel).

As shown in [Table 12](#), all nine 40 mg AR19 extracts were **syringeable** because they could be drawn into a syringe immediately following extraction (including at near-boiling temperatures that are too high for injection). Five extracts were **injectable** because they could be expelled from a syringe at a physiological temperature suitable for IV injection. Of the 5 extracts that were also injectable, Extract 8 had the highest total PEO content as well as the highest yield of syringeable amphetamine from the entire program. Therefore, AR19 Extract 8 was selected for evaluation in the *in vivo* IV safety study.

**Table 12: Syringeability, Injectability, and Composition of AR19 Extracts**

Extract Code	Syringeable (any temperature)	Injectable (temperature suitable for injection)	Amount of Material in Syringeable Extract		
			Total PEO (mg)	PEO >1M Da (mg)	Amphetamine (mg)
1	Yes	Yes	1.7	1.3	4.9
2	Yes	Yes	6.6	BLQ	11.2
3	Yes	No	21.8	13.5	16.8
4	Yes	No	BLQ	BLQ	1.2
5	Yes	No	NA	NA	17.3
6	Yes	Yes	BLQ	BLQ	5.0
7	Yes	No	2.4	1.6	12.1
8	Yes	Yes	20.6	BLQ	20.1
9	Yes	Yes	9.1	BLQ	11.1

NA= Mass of extract too small to be analyzed; BLQ= Below the limit of quantification.

The PEO content of Extract 8 was further evaluated to characterize the distribution of the molecular weight of the PEO in the extract (Table 13). Due to the pretreatment that was required as one of the steps to prepare AR19 for injection, the PEO in AR19 had been degraded to an extent to where *no* high molecular weight PEO (>1M Da) was present. To our knowledge, low molecular weight PEO <1M has not been found to be associated with IV safety issues in any other product and did not cause appreciable hemolysis in our in vitro study. While PEO-related safety issues would not be expected with an IV extract with this PEO molecular weight profile, Arbor conducted a series of nonclinical IV safety studies to confirm this expectation.

**Table 13: PEO Content in AR19 Extract 8**

PEO Molecular Weight (Dalton)	PEO Content in Extract 8
≥ 7,000,000	0%
< 7,000,000 – 5,000,000	0%
< 5,000,000 – 2,000,000	0%
< 2,000,000 – 1,000,000	0%
< 1,000,000 – 80,045	16.3%
< 80,045 – 37,189	19.4%
< 37,189 – 18,062	13.2%
< 18,062 – 7,020	31.0%
< 7,020 – 1,406	20.2%
Total	100%

### 7.3 In Vivo IV Safety Studies

To assess the risk of IV administration of AR19, Arbor commissioned Covance Laboratories (Somerset, NJ), to perform a series of in vivo IV safety studies in rabbits with AR19 Extract 8 and PEO 7M.

#### 7.3.1 *Dose-range-finding Studies*

Several studies were performed to identify the appropriate doses for AR19 and the positive control, PEO 7M, for the pivotal in vivo IV safety study:

- A pilot single-dose study with PEO 7M in which 4 rabbits were given single doses at 0.35 mg/kg (Study MV26MB).
- A pilot maximum tolerated single-dose and 7-day range-finding study in rabbits with PEO 7M (Study WC93QV). In the single-dose phase, pairs of rabbits were given single doses at 0.2, 0.3, or 0.4 mg/kg. In the 7-day phase, groups of 4 rabbits were given daily doses of the vehicle or PEO 7M at 0.04, 0.1, or 0.3 mg/kg.
- A pilot maximum tolerated single-dose and 7-day range-finding study in rabbits with AR19 Extract 8 (Study WY18BQ). In the single-dose phase, pairs of rabbits were given single doses at 28.3 or 84.9 mg/kg. In the 7-day phase, groups of 4 rabbits were given daily doses of the vehicle or AR19 Extract 8 at 28.3, 56.6, or 84.9 mg/kg (i.e., the human equivalent of 1, 2, or 3 IV doses per day based on body weight).

### 7.3.2 Pivotal In Vivo IV Safety Study

#### 7.3.2.1 Study Design and Conduct

The pivotal in vivo IV safety study was a Good Laboratory Practice (GLP)-compliant, 7-day study with AR19 Extract 8 (Study LT30TD). The study included five treatment groups: saline for injection (negative control), PEO 7M at 0.35 mg/kg (positive control), and AR19 Extract 8 at the human equivalent of injecting 1, 2, or 3 IV doses based on the rabbit's body weight.

The rationale for the PEO 7M and AR19 dosing groups are provided below:

- For PEO 7M, the dose was selected based on previous maximum tolerated dose and 7-day range-finding studies.
- For the AR19 dosing groups, doses were selected based on the theoretical human dose from 1, 2, or 3 AR19 40 mg capsule contents being prepared for IV injection using the procedure from the in vitro manipulation studies that produced the highest yield of syringeable amphetamine sulfate (Extract 8). Assuming a 60 kg human body weight and scaling to a rabbit dose on an mg/kg basis, this results in a 28.3 mg/kg total extract weight (per human equivalent dose) for a rabbit.

Each dosing group included 14 New Zealand White rabbits (7/sex) that were dosed once daily for 7 days via a 2.0-minute IV infusion. In each group, 8 rabbits (4/sex) were euthanized and necropsied the day after the last dose and the remaining 6 rabbits (3/sex) were euthanized and necropsied after a 14-day recovery period. The sample size for this study (14 per group) was considered adequate because TMA-related effects were observed with PEO 7M in Arbor's dose-range-finding studies and in previously conducted animal studies with as few as 4 animals per group ([Hunt et al., 2017](#)).

Animals were monitored throughout the study and underwent scheduled observations and evaluations as summarized in [Table 14](#).

**Table 14: Observations and Evaluations for the Pivotal In Vivo IV Safety Study**

Observation	Description
<b>Cage-side observations</b>	
Viability checks and clinical signs	All animals were observed for mortality and general condition at least twice daily.
Dose observations	On treatment days, all animals were observed by group/sex for signs of toxic or pharmacologic effects once prior to and 30-60 minutes after test/control item administration.
<b>Physical examinations</b>	
Physical examinations	Each animal was removed from its cage and examined at least once during pretest and weekly during the treatment and recovery periods for general condition, skin, nose, oral cavity, abdomen, and external genitalia as well as an evaluation of respiration.
Body weight	Non-fasted body weights recorded pretest and weekly during the treatment and recovery periods and on the day of scheduled necropsy.
Food consumption	Food consumption was measured/weighed for each animal daily, during the week prior to treatment initiation and, during the treatment and recovery periods.
Ophthalmoscopy	Gross examinations of eyelids, lacrimal apparatus, and conjunctiva; cornea, anterior chamber, iris, lens, vitreous humor, retina, and optic disc examined by indirect ophthalmoscopy. Evaluations were performed pretest, at the end of dosing, and at the end of recovery by a veterinary ophthalmologist.

Observation	Description
<b>In-life sampling</b>	
Toxicokinetics	Blood samples were obtained for the determination of plasma concentrations of PEO and AR19 extract at regular intervals post-dose.
Free hemoglobin	Free hemoglobin concentrations (a measure of hemolysis) were obtained pre-dose and at regular intervals post-dose and at necropsy.
Hematology	Red blood cell count, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, white blood cell count, platelet count, and reticulocyte count were obtained pre-dose and at regular intervals post-dose and at necropsy.
Clinical chemistry	Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, urea nitrogen, creatinine, glucose, total cholesterol, triglycerides, total protein, albumin, globulin, albumin/globulin ratio, total bilirubin, sodium, potassium, chloride, calcium, and phosphorus levels were obtained pre-dose, at Day 6, and at necropsy.
<b>Terminal investigations</b>	
Macroscopic pathology	A complete microscopic examination was performed on all animals; all abnormal observations were recorded.
Organ weights	Adrenal glands, brain, epididymides, heart, kidneys, liver, lungs and bronchi, ovaries, pituitary, prostate, seminal vesicles, spleen, testes, thymus, thyroids, uterus, and cervix were weighed following necropsy.
Histopathology	All relevant tissues were processed, sectioned at approximately 5 microns, and examined microscopically for all animals.

### 7.3.2.2 Results

After the first dose of PEO 7M 0.35 mg/kg, all rabbits died or were euthanized due to moribund condition. Postmortem evaluation showed evidence of clotted blood in the atria and ventricles of the hearts of the rabbits. As a result of this finding, no further dosing of PEO 7M was performed.

In contrast, all animals tolerated daily IV doses of AR19 Extract 8 without adverse effects. Specifically, there were no clinical signs of toxicity, ophthalmic findings detectable by eye examination, or changes in food consumption, body weight, or organ weights. All hematology, coagulation parameters, and clinical chemistry parameters were within normal ranges throughout the study and at necropsy. All macroscopic and microscopic pathologic findings were also normal ([Table 15](#)).

**Table 15: Summary of Findings from the Pivotal In Vivo IV Safety Study**

Evaluations	Human equivalent (dose/day)		
	1x IV AR19 Extract 8	2x IV AR19 Extract 8	3x IV AR19 Extract 8
Clinical observations	No adverse findings	No adverse findings	No adverse findings
Ophthalmic findings	No adverse findings	No adverse findings	No adverse findings
Food consumption	No adverse findings	No adverse findings	No adverse findings
Body weight	No adverse findings	No adverse findings	No adverse findings
Hematology	No adverse findings	No adverse findings	No adverse findings
Coagulation	No adverse findings	No adverse findings	No adverse findings
Clinical chemistry	No adverse findings	No adverse findings	No adverse findings
Urinalysis	No adverse findings	No adverse findings	No adverse findings
Macroscopic pathology	No adverse findings	No adverse findings	No adverse findings
Microscopic pathology	No adverse findings	No adverse findings	No adverse findings

## 7.4 Conclusions from Nonclinical IV Safety Studies

- In *in vitro* studies, there was no evidence of hemolysis with any AR19 extract, while PEO 7M produced hemolysis in a concentration-dependent manner.
- The extract with the highest amount of injectable PEO and amphetamine content (Extract 8) was evaluated in a repeat-dose, *in vivo* IV safety study.
- In rabbits, daily IV injection of AR19 Extract 8 for 7 days at the human equivalent of 3 AR19 40-mg capsules per day was well tolerated, but a single injection of PEO 7M 0.35 mg/kg resulted in death.
- Intravenous injection of AR19 Extract 8 at the human equivalent of 3 capsules/day was well tolerated likely because the pretreatment degraded all PEO to molecular weights <1M Da.

## 8 POSTMARKETING STUDY PLAN AND ENHANCED PHARMACOVIGILANCE

### 8.1 Proposed Postmarketing Studies

In order to evaluate the real-world effects of the manipulation-resistant properties of AR19, Arbor is proposing to conduct two postmarketing studies:

- AR19.MA016: "*Evaluation of AR19 Exposures in the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS)*." This study will evaluate medical outcomes of oral and non-oral misuse and abuse of prescription stimulants, including AR19, compared to prescription stimulant oral medical users. The objectives of the study will be to:
  - Evaluate the frequency of and medical outcomes associated with AR19 exposures.
  - Determine the duration of exposure, route of administration, and clinical effects for AR19 cases.
  - Assess patient demographics and exposure characteristics for AR19 exposures compared to other prescription stimulant exposures.
- AR19.MA017: "*NAVIPPRO Periodic Survey of AR19 and Other Prescription Stimulant Medications Nonmedical Use Among the General Population Using an Online Survey Panel (YouGov, General Population)*." The objectives of the study will be to:
  - Estimate the real-world rate of misuse and abuse of AR19.
  - Estimate the real-world rate of misuse and abuse of comparator prescription stimulant products.
  - Describe the use of AR19 via alternative routes of administration (i.e., route other than specified on the approved product label).
  - Describe the use of comparator prescription stimulant products via alternative routes of administration (i.e., route other than specified on the approved product label).

## 8.2 Enhanced Pharmacovigilance

Arbor will use an enhanced pharmacovigilance program to monitor, detect, and evaluate potential signals of misuse, abuse, overdose, diversion, and potential safety signals of AR19. Explicit in this program is the goal to monitor for, detect, and evaluate any potential postmarketing safety signals associated with potential misuse or abuse of AR19 by the IV route.

The program intends to utilize databases that collect brand-specific data to allow Arbor to proactively track national and regional trends in misuse, abuse, and diversion of prescription stimulants including for AR19. Arbor will also conduct Proactive Signal Trending detection activities specifically for AR19.

### Pharmacovigilance Monitoring of AR19

Arbor will conduct pharmacovigilance including signal detection and management on a monthly basis and timely review of all cases. These will include spontaneous cases from any source that will be reviewed for trends in increased frequencies, increased severities, trends in reporting, and rare events. Individual case reviews will be conducted for serious/fatal cases and events of special interest (misuse, abuse, overdose, hypersensitivity, etc.) to identify any potential unknown issue or change in known issue for the product.

### Medical Literature Monitoring

Medical databases such as Medline, Embase, and Northern Lights will be monitored for clinical reports of AR19 toxicity that might be attributable to PEO.

### Web Monitoring

The Internet has emerged as an important means to track and monitor illicit trends in drug use, misuse, and abuse, including information regarding the manipulation of prescription drugs. Internet monitoring in the AR19 postmarketing surveillance program will identify potential occurrences of misuse, abuse, diversion, or manipulation of AR19. In addition, internet monitoring will encompass events among those who may attempt to intravenously administer AR19 as reported on drug abuse websites such as Bluelight, Reddit, Drugs-Forum, Shroomery, and Zoklet. Postings will be monitored for content related to diversion, route of administration, and manipulation. Web monitoring will provide, to the extent available, current qualitative information to help illuminate the extent and nature of AR19 misuse and abuse.

### News Media Monitoring

Media monitoring of news outlets serves as a source for detecting potential signals involving misuse, abuse and overdose, diversion, and manipulation for abuse on a real-time basis. Arbor will contract with a vendor to monitor local news media utilizing a keyword search strategy. News outlets may include television/radio transcripts, local and national newspapers, and magazines.

### Proactive Signal Trending Reports

Proactive signal detection and management for AR19 will occur on a monthly basis and will include a review of all cases cumulatively and for the month. These data include cases from any source (e.g., spontaneous, literature, clinical trials), and are reviewed for increased frequencies, increased severities, trends in reporting, and rare events. Individual case reviews will be completed for serious/fatal cases and identify events of special interest (misuse, abuse, overdose, hypersensitivity, etc.) to define any potential unknown issue or change in a known

issue for the product. Events to be monitored and reported to FDA as part of this enhanced pharmacovigilance program will include TTP, microangiopathic hemolytic anemia, TMA, and reports of hypersensitivity/allergic reactions. In conducting proactive signal trending, if any new information is identified during the review, a complete investigation of that information (e.g., full analysis of all cases, Safety Evaluation Report) will be completed and a recommendation will be made to FDA if appropriate. Recommendations may include proposed changes to labeling, healthcare professional letters, or further enhanced monitoring to continue to assess that new information.

#### American Association of Poison Control Centers' National Poison Data System

The American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS) is a case data warehouse for the nation's 55 poison control centers. Each poison control center submits de-identified case data to the NPDS case warehouse after providing necessary poison exposure management and information services to callers. Longitudinal monitoring of NPDS case data will allow evaluation of changes in the percentage of exposures due to stimulants and street drugs before and after the introduction of AR19 to the market.

#### Reporting to FDA

Arbor will implement the approved surveillance plan and submit reports annually, or as requested by the FDA.

### **8.3 Educational Plans**

#### **8.3.1 *Prescriber Education***

Arbor has prepared a comprehensive plan to inform and educate potential AR19 prescribers and dispensers about the following:

- The prevalence of prescription stimulant misuse and abuse among patients and other individuals
- Characteristics of those who misuse or abuse prescription stimulants
- Populations at risk for prescription stimulant misuse and abuse
- Pathways of prescription stimulant misuse and abuse
- Adverse medical and nonmedical outcomes
- AR19 attributes to resist manipulation for misuse and abuse by snorting, smoking, and injecting

#### **8.3.2 *Targeted Educational Plan***

Arbor has analyzed the current literature to identify educational needs and potential challenges for healthcare providers pertaining to the anticipated use of AR19 for the treatment of ADHD. In this regard, Arbor will develop suitable informational and educational modules for psychiatrists, pediatricians, neurologists, primary care physicians, general practitioners, nurse practitioners, physician assistants, and pharmacists about the importance of appropriate prescribing of Schedule II drugs like AR19. The goals of the education plan are as follows:

- Provide an overview of the pharmacologic management of ADHD with prescription stimulant medications
- Inform on the epidemiology, pathways, and medical and nonmedical adverse outcomes of oral and non-oral nonmedical use of prescription stimulants and their diversion

- Characterize patient risk factors and motivations associated with nonmedical use and diversion of prescription stimulants, included by non-oral (intranasal, IV, and smoking) routes of administration, to help clinicians identify high-risk patients
- Advise on screening and risk-reduction tactics when prescribing prescription stimulants

## 9 BENEFIT-RISK ASSESSMENT

The benefit-risk profile of AR19 formulation is predicated on its usefulness in the treatment of patients with ADHD and its potential benefits for public health, due to its resistance to manipulation for the purpose of snorting, smoking, and injecting.

### 9.1 Benefit-Risk Assessment of AR19 for Patients with ADHD

AR19 immediate-release amphetamine sulfate capsules are proposed for the treatment of ADHD in children 3 to 17 years old and adults 18 years and older. All excipients in AR19 have a well-established safety profile when taken orally as intended and are included in other FDA-approved oral medications.

In terms of benefits for patients, clinical bioavailability studies have demonstrated AR19 is bioequivalent to the reference drug, Evekeo, which is approved for the treatment of ADHD in pediatric patients; and, a Phase 3 study has demonstrated the efficacy and safety of AR19 for the treatment of ADHD in adults. Therefore, AR19 would be therapeutically equivalent to currently marketed IR amphetamine products and can be expected to provide the same therapeutic benefit in pediatric and adult patients with ADHD. Arbor is proposing 7 capsule strengths for AR19 (2.5, 5, 10, 15, 20, 30, and 40 mg) to provide physicians with the flexibility to initiate and titrate patients to a dose that provides an optimal response, consistent with the clinical goals of patient-centered care for the management of ADHD. Additionally, AR19 capsule pellets may be sprinkled on food, which would provide a benefit to any patient who has difficulty swallowing capsules or tablets. The manipulation-resistant properties of AR19 would also provide the added benefit of rendering the product less attractive for non-oral use, which carries a higher risk of patient harm.

In terms of risks for patients, amphetamine is a Schedule II substance under the Controlled Substances Act. The safety profile of amphetamine is well established in the literature and in its decades of clinical use, which is captured in current labeling. The development program has not identified any novel or additional safety concerns for AR19 relative to currently marketed IR amphetamine products when taken by the intended oral route of administration.

Taken together, AR19 has demonstrated a positive benefit-risk profile for its proposed indication for the treatment of ADHD.

### 9.2 Benefit-Risk Assessment of AR19 for Public Health

Most misuse and abuse of prescription stimulant medications is by the oral route of administration. However, an appreciable proportion of individuals misuse or abuse prescription stimulants by non-oral routes of administration such as snorting, smoking, and injecting. By using a prescription stimulant non-orally, the individual bypasses the first-pass metabolism and achieves more rapid and profound effects. Survey data have found that the motivations for non-oral use of prescription stimulants are multifactorial, but most frequently include (1) treating ADHD when the regular dose was not working orally, (2) to enhance performance at work or

school, (3) for energy, and (4) to get high. Regardless of the motivation for non-oral use, the prevalence of these routes of administration are concerning across all age groups, but particularly among older adolescents and young adults.

As detailed earlier in this document, non-oral routes of administration are associated with more frequent and more severe adverse health outcomes (e.g., hospitalization, overdose, death). Furthermore, initiation of non-oral use of prescription stimulants appears to be a key juncture in the progression of substance use, including experimentation with increasingly dangerous routes of administration and illicit drugs.

AR19 has been formulated with physical and chemical barriers to provide meaningful resistance to manipulations necessary for preparing the product for snorting, smoking, or injecting. The benefits of the AR19 formulation include the following:

- Particle size reduction studies have demonstrated that AR19 provides substantial resistance to physical manipulation, which is usually the first step in preparing a prescription stimulant for snorting, smoking, or injecting. While Evekeo (and all other IR amphetamine products) can be crushed quickly and easily into a fine powder with household tools, no tool or method – despite weeks of extensive laboratory testing – was able to effectively reduce AR19 to a fine powder regardless of the amount of time and effort spent manipulating the formulation. Even with the most effective physical manipulation procedure identified by experienced scientists using a modified tool with select accessories, only a relatively coarse material could be produced, which resulted in lower intranasal bioavailability than the comparator.
- An intranasal human abuse potential study demonstrated that optimally manipulated and insufflated AR19 40 mg pellets produced significantly lower amphetamine concentrations than amphetamine sulfate API. Even though subjects did not experience the extensive, multi-step procedure to prepare AR19 for insufflation, they nonetheless reported significantly lower drug liking, lower drug high, lower good drug effects, lower overall drug liking, and lower willingness to snort again than amphetamine sulfate API.
- Simulated smoking studies demonstrated that almost no amphetamine is produced upon heat volatilization of AR19, so smoking or inhaling is not a feasible route for misuse or abuse of AR19.
- Small volume extraction and syringeability studies have demonstrated that AR19, even with rigorous time- and labor-intensive procedures using laboratory equipment, provides substantially less syringeable amphetamine than its non-manipulation-resistant comparators, which released API quickly and almost completely under conditions that required minimal effort. Furthermore, since most individuals who inject amphetamine require multiple tablets or capsules to achieve their desired dose, it was a particularly important finding that that the extraction of pellets from multiple AR19 capsules actually decreased the amount of syringeable amphetamine that could be recovered.

Overall, the studies in the development program have demonstrated that the AR19 formulation makes snorting, smoking, and injecting more difficult and less rewarding than currently available IR amphetamine medications. By imposing meaningful barriers to non-oral misuse and abuse, AR19 can be expected to reduce the harms associated with these more dangerous routes of administration.

In terms of risks, several theoretical concerns regarding manipulation-resistant formulations of prescription stimulants can be assessed:

- One theoretical concern is that a manipulation-resistant formulation may prompt a shift from snorting or smoking prescription stimulants to IV use. In the small volume extraction and syringeability testing, the maximum amount of syringeable amphetamine that could be obtained from AR19 from the several hundred combinations of experimental conditions tested was 50.2% (20.1 mg) from a 40 mg capsule following an extensive, 60-minute, multi-step procedure with laboratory methods. Given that 20 mg is a low IV dose for amphetamine, the procedure required to prepare a single IV dose with AR19 was extensive in nature and would require laboratory equipment, and multiple AR19 capsules cannot be extracted to increase the dose, there is no incentive for such a shift.
- Another theoretical concern is that making prescription stimulants difficult to misuse or abuse non-orally might drive individuals to illicit drugs. Due to the widespread availability of alternative prescription stimulants that are easy to manipulate, it is likely that non-oral users of prescription stimulants who have not previously abused an illicit stimulant would obtain an alternative prescription stimulant to AR19 rather than initiate non-oral use with an illicit stimulant.
- Another concern is with regard to the toxicity of excipients that impart manipulation-resistant properties if injected. All excipients in AR19 have a well-established safety profile for all ages when taken orally as intended and are included in other FDA-approved oral medications. Nonclinical IV safety studies found no evidence of adverse effects associated with IV administration of AR19 extracts.

Overall, the development program demonstrated that the manipulation-resistant attributes of AR19 can be expected to impart meaningful barriers to snorting, smoking, and injecting the product and reduce their associated medical and nonmedical risks. Thus, AR19 has demonstrated a favorable benefit-risk profile for public health on account of its manipulation-resistant properties to reduce misuse and abuse by the inherently more dangerous non-oral routes of administration.

### **9.3 Integrated Benefit-Risk Assessment of AR19**

AR19 addresses an unmet public health need by reducing the harms associated with non-oral use of an IR amphetamine medication without compromising patient access to appropriate medical treatment for ADHD.

AR19 would provide a therapeutically equivalent medication for patients with ADHD with no additional safety risks beyond what is known with currently marketed IR amphetamine products when taken as prescribed.

AR19 has also been shown to make manipulation more difficult and less rewarding, reducing the positive reinforcement that exists with currently marketed IR amphetamine products that can be easily prepared for non-oral administration to achieve faster or greater effects. AR19 can be expected to interdict at multiple points on identified progression pathways of nonmedical use of prescription stimulants by impeding efforts to manipulate and prepare capsules for non-oral routes of administration, discouraging impulsive non-oral use, and diminishing euphoric effects from non-oral administration. Considering the high rate of diversion of prescription stimulants, AR19 would provide protections against non-oral use not only among patients, but also among individuals other than the intended patient who have not been properly evaluated, screened, and prescribed the medication by a qualified health professional.

## 10 REFERENCES

- Allain, F., Minogianis, E.-A., Roberts, D. C., & Samaha, A.-N. (2015). How fast and how often: The pharmacokinetics of drug use are decisive in addiction. *Neuroscience and Biobehavioral Reviews*, 56, 166-179.
- Altomare, C., Kinzler, E. R., Buchhalter, A. R., Cone, E. J., & Costantino, A. (2017). Laboratory-based testing to evaluate abuse-deterrent formulations and satisfy the Food and Drug Administration's recommendation for category 1 testing. *Journal of Opioid Management*, 13(6), 441-448.
- APA. (2013). American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th Edn. Washington, DC.
- Arria, A. M., Caldeira, K. M., O'Grady, K. E., Vincent, K. B., Johnson, E. P., & Wish, E. D. (2008). Nonmedical use of prescription stimulants among college students: associations with attention-deficit-hyperactivity disorder and polydrug use. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 28(2), 156-169.
- Austic, E. (2015). Peak ages of risk for starting nonmedical use of prescription stimulants. *Drug and Alcohol Dependence*, 152, 224-229.
- Barceloux, D. G. (2012). *Medical Toxicology of Drug Abuse: Synthesized Chemicals and Psychoactive Plants*: John Wiley & Sons.
- Bright, G. M. (2008). Abuse of medications employed for the treatment of ADHD: results from a large-scale community survey. *The Medscape Journal of Medicine*, 10(5), 111.
- Broz, D., Zibbell, J., Foote, C., Roseberry, J. C., Patel, M. R., Conrad, C., McAlister, C. (2018). Multiple injections per injection episode: High-risk injection practice among people who injected pills during the 2015 HIV outbreak in Indiana. *International Journal of Drug Policy*, 52, 97-101.
- Cassidy, T. A., Varughese, S., Russo, L., Budman, S. H., Eaton, T. A., & Butler, S. F. (2015). Nonmedical use and diversion of ADHD stimulants among US adults ages 18-49: A national internet survey. *Journal of Attention Disorders*, 19(7), 630-640.
- Chang, Z., Lichtenstein, P., Halldner, L., D'Onofrio, B., Serlachius, E., Fazel, S., Larsson, H. (2014). Stimulant ADHD medication and risk for substance abuse. *Journal of Child Psychology and Psychiatry*, 55(8), 878-885.
- Childress, A. C., Brams, M., Cutler, A. J., Kollins, S. H., Northcutt, J., Padilla, A., & Turnbow, J. M. (2015). The efficacy and safety of evekeo, racemic amphetamine sulfate, for treatment of attention-deficit/hyperactivity disorder symptoms: A multicenter, dose-optimized, double-blind, randomized, placebo-controlled crossover laboratory classroom study. *Journal of Child and Adolescent Psychopharmacology*, 25(5), 402-414.
- Cortese, S., Adamo, N., Del Giovane, C., Mohr-Jensen, C., Hayes, A. J., Carucci, S., Coghill, D. (2018). Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *The Lancet Psychiatry*, 5(9), 727-738.
- Cuffe, S. P., Visser, S. N., Holbrook, J. R., Danielson, M. L., Geryk, L. L., Wolraich, M. L., & McKeown, R. E. (2015). ADHD and psychiatric comorbidity: Functional outcomes in a school-based sample of children. *Journal of Attention Disorders*, 1087054715613437.
- DuPont, R. L., Coleman, J. J., Bucher, R. H., & Wilford, B. B. (2008). Characteristics and motives of college students who engage in nonmedical use of methylphenidate. *American Journal on Addictions*, 17(3), 167-171.

- Faraone, S. V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J., Ramos-Quiroga, J., & Franke, B. (2015). Attention-deficit/hyperactivity disorder. *Nature Reviews Disease Primers*, 1, 15020.
- Faraone, S. V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological Medicine*, 36(2), 159-165.
- Faraone, S. V., Hess, J., & Wilens, T. (2019). Prevalence and consequences of the nonmedical use of amphetamine among persons calling poison control centers. *Journal of Attention Disorders*, 23(11), 1219-1228.
- Faraone, S. V., Rostain, A. L., Montano, C. B., Mason, O., Antshel, K. M., & Newcorn, J. H. (2020). Systematic review: nonmedical use of prescription stimulants: risk factors, outcomes, and risk reduction strategies. *Journal of the American Academy of Child & Adolescent Psychiatry*, 59(1), 100-112.
- FDA. (2007). FDA directs ADHD drug manufacturers to notify patients about cardiovascular adverse events and psychiatric adverse events. Retrieved from <https://www.fda.gov/science-research/pediatrics/safety-report-updates>
- FDA. (2014). Janet Woodcock response to citizen petition, Docket No. FDA-2006-P-0453. September 18, 2014. Retrieved from <https://www.regulations.gov/document?D=FDA-2006-P-0453-0005>
- FDA. (2015). Abuse-deterrent opioids—evaluation and labeling: Guidance for industry. Retrieved from <https://www.fda.gov/media/84819/download>
- FDA. (2017). General principles for evaluating the abuse deterrence of generic solid oral opioid drug products: Guidance for industry. Retrieved from <https://www.fda.gov/media/96643/download>
- FDA. (2019). FDA in Brief: FDA seeks input on development and evaluation of abuse-deterrent formulations of central nervous system stimulants. Retrieved from <https://www.fda.gov/news-events/fda-brief/fda-brief-fda-seeks-input-development-and-evaluation-abuse-deterrent-formulations-central-nervous>
- FDA. (2020). Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting. January 15, 2020 (PM Session). Retrieved from <https://www.fda.gov/media/134715/download>
- Groenman, A. P., Oosterlaan, J., Rommelse, N. N., Franke, B., Greven, C. U., Hoekstra, P. J., Oades, R. D. (2013). Stimulant treatment for attention-deficit hyperactivity disorder and risk of developing substance use disorder. *The British Journal of Psychiatry*, 203(2), 112-119.
- Harstad, E., & Levy, S. (2014). Attention-deficit/hyperactivity disorder and substance abuse. *Pediatrics*, 134(1), e293-e301.
- Heal, D. J., Smith, S. L., Gosden, J., & Nutt, D. J. (2013). Amphetamine, past and present—a pharmacological and clinical perspective. *Journal of Psychopharmacology*, 27(6), 479-496.
- Hunt, R., Yalamanoglu, A., Tumlin, J., Schiller, T., Baek, J. H., Wu, A., Miller, P. (2017). A mechanistic investigation of thrombotic microangiopathy associated with IV abuse of Opana ER. *Blood, The Journal of the American Society of Hematology*, 129(7), 896-905.
- Inflexxion. (2019). National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®). Nonmedical Use of Prescription Medications in College Students. Prepared for Arbor Pharmaceuticals by Inflexxion, an IBH Company, Costa Mesa, CA, 08 September 2019.

- Jasinski, D., & Krishnan, S. (2009). Human pharmacology of intravenous lisdexamfetamine dimesylate: abuse liability in adult stimulant abusers. *Journal of Psychopharmacology*, 23(4), 410-418.
- Katusic, S. K., Barbaresi, W. J., Colligan, R. C., Weaver, A. L., Leibson, C. L., & Jacobsen, S. J. (2005). Psychostimulant treatment and risk for substance abuse among young adults with a history of attention-deficit/hyperactivity disorder: A population-based, birth cohort study. *Journal of Child and Adolescent Psychopharmacology*, 15(5), 764-776.
- Lee, S. S., Humphreys, K. L., Flory, K., Liu, R., & Glass, K. (2011). Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. *Clinical Psychology Review*, 31(3), 328-341.
- Lile, J. A., Babalonis, S., Emurian, C., Martin, C. A., Wermeling, D. P., & Kelly, T. H. (2011). Comparison of the behavioral and cardiovascular effects of intranasal and oral d-amphetamine in healthy human subjects. *The Journal of Clinical Pharmacology*, 51(6), 888-898.
- Marder, E., Kirschke, D., Robbins, D., Dunn, J., Jones, T. F., Racoosin, J., Chang, A. (2013). Thrombotic thrombocytopenic purpura (TTP)-like illness associated with intravenous Opana ER abuse—Tennessee, 2012. *MMWR. Morbidity and Mortality Weekly Report*, 62(1), 1.
- Marhefka, J., Zhao, R., Wu, Z., Velankar, S., Antaki, J., & Kameneva, M. (2009). Drag reducing polymers improve tissue perfusion via modification of the RBC traffic in microvessels. *Biorheology*, 46(4), 281-292.
- Markowitz, J. S., & Patrick, K. S. (2017). The clinical pharmacokinetics of amphetamines utilized in the treatment of attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*, 27(8), 678-689.
- McCabe, S. E., Dickinson, K., West, B. T., & Wilens, T. E. (2016). Age of onset, duration, and type of medication therapy for attention-deficit/hyperactivity disorder and substance use during adolescence: a multi-cohort national study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 55(6), 479-486.
- Persich, P., Engels, G. E., van Oeveren, W., Galia, E., Benay, S., & Thun, S. (2020). Development of an in vitro system and model-based translational framework to assess haemolysis risk following intravenous abuse of medications containing polyethylene oxide. *Toxicology in Vitro*, 65, 104776.
- SAMHSA. (2017). NSDUH Detailed Tables: National Survey on Drug Use and Health. Retrieved from <https://www.samhsa.gov/data/report/2017-nsduh-detailed-tables>
- SAMHSA. (2018). NSDUH Detailed Tables: National Survey on Drug Use and Health. Retrieved from <https://www.samhsa.gov/data/report/2018-nsduh-detailed-tables>
- Sloan, P., Slatkin, N., & Ahdieh, H. (2005). Effectiveness and safety of oral extended-release oxymorphone for the treatment of cancer pain: a pilot study. *Supportive Care in Cancer*, 13(1), 57-65.
- SNAPS. (2019). The Study of Non-Oral Administration of Prescription Stimulants (SNAPS).
- Stahl, S. M. (2013). *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications, 4th edition*. Cambridge: Cambridge University Press.
- Teter, C. J., McCabe, S. E., LaGrange, K., Cranford, J. A., & Boyd, C. J. (2006). Illicit use of specific prescription stimulants among college students: prevalence, motives, and routes of administration. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 26(10), 1501-1510.

- Teva Pharmaceuticals USA. (2017). Adderall Prescribing Information. Retrieved from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/011522s043lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/011522s043lbl.pdf)
- Thomas, R., Sanders, S., Doust, J., Beller, E., & Glasziou, P. (2015). Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics*, 135(4), e994-e1001.
- Tseng, W., Sutter, M. E., & Albertson, T. E. (2014). Stimulants and the lung. *Clinical Reviews in Allergy & Immunology*, 46(1), 82-100.
- Weyandt, L. L., Oster, D. R., Marraccini, M. E., Gudmundsdottir, B. G., Munro, B. A., Zavras, B. M., & Kuhar, B. (2014). Pharmacological interventions for adolescents and adults with ADHD: stimulant and nonstimulant medications and misuse of prescription stimulants. *Psychology Research and Behavior Management*.
- White, B. P., Becker-Blease, K. A., & Grace-Bishop, K. (2006). Stimulant medication use, misuse, and abuse in an undergraduate and graduate student sample. *Journal of American College Health*, 54(5), 261-268.
- Wilens, T. E., Adler, L. A., Adams, J., Sgambati, S., Rotrosen, J., Sawtelle, R., Fusillo, S. (2008). Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. *Journal of the American Academy of Child and Adolescent Psychiatry*, 47(1), 21-31.
- Wilens, T. E., Faraone, S. V., Biederman, J., & Gunawardene, S. (2003). Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. *Pediatrics*, 111(1), 179-185.
- Wilens, T. E., Zulauf, C., Martelon, M., Morrison, N. R., Yule, A., & Anselmo, R. (2016). Nonmedical stimulant use in college students: association with attention-deficit/hyperactivity disorder and other disorders. *Journal of Clinical Psychiatry*, 77(7), 940.
- Wolraich, M. L., Hagan, J. F., Allan, C., Chan, E., Davison, D., Earls, M., Frost, J. (2019). Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*, 144(4), e20192528.
- Young, S., Toone, B., & Tyson, C. (2003). Comorbidity and psychosocial profile of adults with attention deficit hyperactivity disorder. *Personality and Individual Differences*, 35(4), 743-755.

## 11 APPENDIX: METHODS AND RESULTS OF STUDY AR19.004

### 11.1 Study Design

AR19.004 was designed in consultation with the FDA to support an indication for the adult population. This was a randomized, fixed-dose, double-blind, multicenter trial that investigated the safety and efficacy of AR19 in the treatment of ADHD in adults from 18 through 55 years of age. Subjects were randomized to 20 mg or 40 mg AR19 daily or placebo in a 1:1:1 ratio. The study consisted of:

1. a 30-day screening period and baseline evaluation;
2. titration with AR19 for 4 weeks to 20 mg or 40 mg daily dose or with placebo;
3. at least two weeks at a stable dose of AR19 or placebo; and
4. post-withdrawal follow-up phone call one week after the final dose.

After randomization, AR19 or placebo was initiated at 10 mg/day and was titrated in weekly intervals in 10-mg increments to 20 or 40 mg/day, depending on randomization. Subjects received study drug twice daily, once in the morning and again 4 to 6 hours later. The study duration from the first dose of study drug to the follow-up visit was approximately 6 weeks. The duration of dosing was approximately 5 weeks for each treatment.

Participants were male or female between 18 and 55 years of age who met criteria for the diagnosis of ADHD using Conners' Adult ADHD Diagnostic Interview, including the onset of ADHD symptoms before the age of 12, had an Adult ADHD Investigator Symptom Rating Scale (AISRS) total score of  $\geq 26$  at baseline, had a clinician-administered Clinical Global Impression - Severity score of 4 or greater at baseline, and in the clinical judgment of the Investigator, the subject needed pharmacological treatment for ADHD.

**Primary Efficacy Endpoint:** The primary efficacy endpoint was the change from baseline in AISRS total score at Week 5 in AR19 (20 and 40 mg/day) versus placebo.

**Secondary Efficacy Endpoints:** Secondary efficacy endpoints included the following:

- Changes from baseline of AISRS hyperactivity/impulsivity and inattentive subscale scores compared to Week 5.
- Clinical Global Impression of Severity (CGI-S) at Week 5 compared with baseline.
- Clinical Global Impression of Improvement (CGI-I) at Week 5.
- Changes from baseline of the Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A), subscales, indices, and composites compared with Week 5.

**Efficacy Analysis:** The primary efficacy analysis was performed on the Full Analysis Set (FAS) population. The primary analyses were originally performed on the basis of case report forms, however the FDA requested that analyses be performed on the basis of windows  $\pm 3$  days around the target visit date; these window-based analyses are provided in this document. The change from baseline in AISRS at Week 5 was compared between each of the two different AR19 dose groups and the placebo group. To account for these comparisons, a Bonferroni multiple comparison adjustment was utilized. Both comparisons were conducted at the 0.025 (0.05/2) alpha level. No other adjustments for multiplicity were applied to any other endpoints or comparisons.

Continuous variables were analyzed using mixed-model repeated measures (MMRM) analysis. For the CGI-S and CGI-I assessments, Cochran-Mantel-Haenszel (CMH) row mean score tests were used to compare the treatment groups.

## 11.2 Disposition and Baseline Characteristics

**Table 16** summarizes the disposition for all screened subjects. A total of 320 subjects were randomized and received at least 1 dose of study medication (the Safety population). Among the 54 subjects who discontinued early from the study, the most common reasons were lost to follow-up (4.1% of randomized subjects), withdrawal by subject (3.8%), other (3.4%), and AE(s) (3.1%).

**Table 16: Summary of Subject Disposition (Randomized Population, AR19.004)**

	Placebo (N=106)	AR19 20 mg (N=107)	AR19 40 mg (N=107)	Total (N=320)
<b>Analysis Populations<sup>1</sup> – n (%)</b>				
Safety	106 (100.0)	107 (100.0)	107 (100.0)	320 (100.0)
Full Analysis Set	103 (97.2)	106 (99.1)	105 (98.1)	314 (98.1)
<b>Study Completion – n (%)</b>				
Completed	92 (86.8)	87 (81.3)	87 (81.3)	266 (83.1)
Discontinued	14 (13.2)	20 (18.7)	20 (18.7)	54 (16.9)
<b>Reason for Premature Discontinuation – n (%)</b>				
Adverse Event	3 (2.8)	2 (1.9)	5 (4.7)	10 (3.1)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-up	4 (3.8)	5 (4.7)	4 (3.7)	13 (4.1)
Non-compliance with study drug	1 (0.9)	0 (0.0)	3 (2.8)	4 (1.3)
Physician Decision	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.3)
Pregnancy	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.3)
Protocol Violation	0 (0.0)	2 (1.9)	0 (0.0)	2 (0.6)
Study Terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject Unable to Tolerate 20 or 40 mg Daily Dose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by subject	3 (2.8)	4 (3.7)	5 (4.7)	12 (3.8)
Other	3 (2.8)	6 (5.6)	2 (1.9)	11 (3.4)

1. Safety = subjects who were randomized and received at least one dose of study medication. Full Analysis Set = safety subject who had one or more post-baseline on-treatment primary efficacy assessments.

Demographic and baseline characteristics for the Safety population are summarized in **Table 17**. The majority of subjects were male (54.4%); the mean age was 34.4 years (range 18 to 55 years). Of the ADHD types (inattentive, hyperactive/impulsive, and combined), the majority were characterized as having the combined type ADHD (83.1%), and nearly all the remainder of subjects with the inattentive ADHD type (16.6%). Demographics and baseline characteristics were similar across placebo, AR19 20 mg, and AR19 40 mg groups.

**Table 17: Demographic and Baseline Characteristics (Safety Population, AR19.004)**

Characteristics	Placebo (N=106)	AR19 20 mg (N=107)	AR19 40 mg (N=107)	Total (N=320)
<b>Age (years)</b>				
Mean (SD)	34.2 (10.75)	35.6 (10.28)	33.5 (9.35)	34.4 (10.15)
Range (Min, Max)	(18, 55)	(18, 54)	(19, 55)	(18, 55)
<b>Sex - n (%)</b>				
Male	54 (50.9)	57 (53.3)	63 (58.9)	174 (54.4)
Female	52 (49.1)	50 (46.7)	44 (41.1)	146 (45.6)
<b>Race - n (%)</b>				
White	80 (75.5)	89 (83.2)	88 (82.2)	257 (80.3)
Black or African American	13 (12.3)	13 (12.1)	15 (14.0)	41 (12.8)
Asian	6 (5.7)	1 (0.9)	2 (1.9)	9 (2.8)
Native Hawaiian or Pacific Islander	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.3)
American Indian or Alaska Native	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.3)
Other	6 (5.7)	4 (3.7)	1 (0.9)	11 (3.4)
<b>Body Mass Index (kg/m<sup>2</sup>)</b>				
Mean (SD)	27.3 (4.6)	27.6 (4.9)	27.8 (5.0)	27.6 (4.8)
Range (Min, Max)	(17.0, 38.7)	(17.3, 38.5)	(17.6, 38.6)	(17.0, 38.7)
<b>Ethnicity - n (%)</b>				
Hispanic or Latino	14 (13.2)	13 (12.1)	14 (13.1)	41 (12.8)
Not Hispanic or Latino	92 (86.8)	94 (87.9)	93 (86.9)	279 (87.2)
<b>ADHD Type - n (%)</b>				
Inattentive	14 (13.2)	19 (17.8)	20 (18.7)	53 (16.6)
Hyperactive/Impulsive	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.3)
Combined	91 (85.8)	88 (82.2)	87 (81.3)	266 (83.1)

## 11.3 Efficacy

### 11.3.1 Primary Efficacy Endpoint Results

The primary efficacy measure was the total score on the AISRS. This 18-item scale directly corresponds to the 18 ADHD items in the Diagnostic and Statistical Manual of Mental Disorders where 9 inattentive items alternate with 9 hyperactive-impulsive items. Each item is scored as follows: 0 (none), 1 (mild), 2 (moderate), 3 (severe); the maximum total score for the scale is 54 points, with 27 points for each subscale.

Both AR19 20 mg and 40 mg dose groups achieved a statistically significant greater change from baseline in AISRS total score than placebo (Table 18), so the primary efficacy endpoint was met.

**Table 18: AISRS Total Score Change from Baseline at Week 5 (FAS, AR19.004)**

Treatment	Change from Baseline LS Mean (SE)	LS Mean Treatment Difference vs Placebo (97.5% CI)	P-value
Placebo	-11.2 (1.29)		
AR19 20 mg	-18.4 (1.29)	-7.2 (-11.3, -3.1)	<0.001
AR19 40 mg	-18.5 (1.30)	-7.3 (-11.4, -3.2)	<0.001

Note: To account for multiple comparisons, a Bonferroni adjustment was utilized. CIs are 97.5% and alpha is 0.025.

### 11.3.2 Secondary Efficacy Endpoint Results

#### AISRS Hyperactivity/Impulsivity and Inattentive Subscale Scores

The change from Baseline at Week 5 in AISRS subscales is presented in [Table 19](#). The first subscale, which measured hyperactivity/impulsivity, demonstrated improvement ( $p<0.001$ ) for both the AR19 20 mg and 40 mg dose groups relative to the placebo group. The second subscale, which measured inattentiveness, similarly demonstrated improvement ( $p<0.001$ ) for both the AR19 20 mg and 40 mg dose groups relative to the placebo group.

**Table 19: AISRS Subscales Change from Baseline at Week 5 (FAS, AR19.004)**

AISRS Subscale	Treatment	Change from Baseline LS Mean (SE)	LS Mean Treatment Difference vs Placebo (97.5% CI)	P-value
Hyperactivity/Impulsivity	Placebo	-5.3 (0.62)		
	AR19 20 mg	-8.4 (0.62)	-3.1 (-5.1, -1.1)	<0.001
	AR19 40 mg	-8.2 (0.62)	-2.9 (-4.9, -1.0)	<0.001
Inattentive Subscale	Placebo	-6.0 (0.75)		
	AR19 20 mg	-10.1 (0.75)	-4.1 (-6.4, -1.7)	<0.001
	AR19 40 mg	-10.3 (0.75)	-4.3 (-6.7, -2.0)	<0.001

#### Clinical Global Impression of Severity (CGI-S) at Week 5 Compared to Baseline

The CGI-S scale is scored from 1 to 7 where 1 is *normal*, and 7 is *among the most extremely ill patients*. At Week 5, the mean CGI-S score for the placebo, AR19 20 mg, and AR19 40 mg dose groups were 3.6, 3.0, and 3.0, respectively. This resulted in a LS mean change from baseline of -0.9, -1.5, and -1.6, for the placebo, AR19 20 mg, and AR19 40 mg dose groups. The LS mean treatment differences versus placebo were -0.6 for the AR19 20 mg group and -0.7 for the AR19 40 mg group (both  $p<0.001$ ).

#### Clinical Global Impression of Improvement (CGI-I) at Week 5 lower scores better

The CGI-I scale ranges from 1 (very much improved) to 7 (very much worse). At Week 5, the LS mean CGI-I score for placebo, AR19 20 mg, and AR19 40 groups were 3.1, 2.4, and 2.4 on the CGI-I assessment, respectively. The LS mean treatment differences versus placebo were -0.7 for both the AR19 20 mg and the AR19 40 mg groups (both  $p<0.001$ ).

#### Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A) at Week 5 Compared to Baseline

Both AR19 20 mg and AR19 40 mg groups demonstrated statistically significant differences from placebo on the LS mean change from baseline on the global BRIEF-A score and all 10 sub-indices with the exception of the 20 mg dose, which did not reach statistical significance for the Emotional Control and Inhibit sub-indices.

### 11.3.3 Efficacy Conclusions

In the primary endpoint efficacy analysis, both the 20 mg and 40 mg AR19 dose groups achieved statistically significant AISRS total score changes from baseline in the FAS compared to placebo. The secondary endpoints also provided evidence of a meaningful effect of AR19 on ADHD in adults. These data support the efficacy of the 20 mg and 40 mg AR19 dosage regimens evaluated in adults with ADHD. (Note: in clinical practice, the dose of a prescription stimulant is titrated to effect.)

## 11.4 Safety

**Table 20** provides an overview of safety in Study AR19.004. Approximately half (50%) of subjects from all treatment groups reported at least 1 treatment-emergent adverse event (TEAE). No Serious TEAEs were reported and few subjects discontinued for a TEAE.

**Table 20: Overview of Adverse Events (Safety Population, AR19.004)**

Event Type	Placebo (N=106) n (%) [events]	AR19 20 mg (N=107) n (%) [events]	AR19 40 mg (N=107) n (%) [events]
TEAEs	53 (50.0) [109]	74 (69.2) [155]	58 (54.2) [165]
Treatment-Related TEAEs	38 (35.8) [72]	57 (53.3) [98]	50 (46.7) [117]
Severe TEAEs	5 (4.7) [8]	5 (4.7) [7]	3 (2.8) [3]
Serious TEAEs	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Treatment-Related Serious TEAEs	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Deaths	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
TEAEs Resulting in Study Drug Discontinuation	3 (2.8) [9]	2 (1.9) [3]	5 (4.7) [11]

### 11.4.1 Treatment-Emergent Adverse Events Related to Study Drug

**Table 21** summarizes the TEAEs related to the study drug that occurred at  $\geq 3\%$  incidence and  $\geq 1.5$  times the rate for placebo in one of the AR19 groups. The events of insomnia, dry mouth, decreased appetite, palpitations and tachycardia are consistent with the known safety profile of amphetamine sulfate.

**Table 21: Treatment-Emergent Adverse Events Related to Study Drug Occurring in  $\geq 3\%$  in Subjects and  $\geq 1.5$  Times Placebo (Safety Population, AR19.004)**

System Organ Class Preferred Term	Placebo (N=106) n (%)	AR19 20 mg (N=107) n (%)	AR19 40 mg (N=107) n (%)
<b>Psychiatric disorders</b>			
Insomnia	4 (3.8%)	9 (8.4%)	8 (7.5%)
Initial insomnia	3 (2.8%)	2 (1.9%)	5 (4.7%)
<b>Gastrointestinal disorders</b>			
Dry mouth	4 (3.8%)	6 (5.6%)	12 (11.2%)
<b>Metabolism and nutrition disorders</b>			
Decreased appetite	5 (4.7%)	10 (9.3%)	14 (13.1%)
<b>Cardiac disorders</b>			
Palpitations	2 (1.9%)	2 (1.9%)	6 (5.6%)
Tachycardia	0	6 (5.6%)	4 (3.7%)
<b>Skin and Subcutaneous Tissue Disorders</b>			
Hyperhidrosis	1 (0.9%)	2 (1.9%)	5 (4.7%)

### 11.4.2 Serious Adverse Events and Deaths

No SAEs or deaths were reported during this study

### 11.4.3 Serious Adverse Events Leading to Discontinuation

Subjects in all treatment groups experienced adverse events leading to study discontinuation; 3 (2.8%) subjects from placebo, 2 (1.9%) from AR19 20 mg, and 5 (4.7%) from the AR19 40 mg groups withdrew from the study.

#### 11.4.4 ***Safety Conclusions***

Overall, AR19 was generally well tolerated. Safety events experienced by subjects in this study were consistent with the known safety profile of amphetamine sulfate in the adult ADHD population.