Applicant Presentation – Evan Scullin

Hello. My name is Evan Scullin. I am the Vice President of Medical Affairs at Arbor Pharmaceuticals. I'd like to thank the FDA and members of the Advisory Committees for the time that you've spent to prepare for today's meeting.

As you have seen, there were some substantial differences in the interpretation of data in Arbor's and the FDA's briefing documents. However, we do agree about the scope of the problem.

We agree that prescription stimulant nonmedical use is a serious public health concern. We agree that patients with ADHD are at greater risk for nonmedical use and the development of a substance use disorder. We agree that most nonmedical use of prescription stimulants is concentrated in adolescents and young adults. And finally, we agree that non-oral nonmedical use leads to more severe medical outcomes than oral nonmedical use.

We disagree in how formulations that resist manipulation can play a targeted and important role to address elements of this public health concern. Before we discuss any of the data, I think it is important to draw distinctions about what formulations like AR19 can do; and also, to be very clear about what they cannot do.

Manipulation-resistant formulations like AR19 are a harm reduction strategy to reduce their use by snorting, smoking, and injecting and their associated medical harms. As the FDA clearly articulated in its briefing document, this class of products cannot address oral misuse or abuse. It is important to recognize that no product can. To be an effective treatment for ADHD, it must work when taken by its intended route of administration.

A new formulation cannot address addiction because the potential of a drug to cause dependence is at the level of the active pharmaceutical ingredient itself. A new prescription stimulant cannot address polysubstance use because no formulation can prevent an individual from using other drugs or substances. What a manipulation-resistant formulation can do is impede the nonmedical use of that specific product by non-oral routes. And that is why we developed AR19 – to provide a

medication that not only effectively treats ADHD, but also impedes more dangerous drug taking behaviors.

AR19 is the first immediate release ADHD prescription stimulant formulated with physical and chemical barriers designed to resist manipulations required for snorting, smoking, and injecting. AR19 is a form of amphetamine sulfate, a central nervous system stimulant, which has been an FDA-approved ADHD treatment for decades. As such, AR19 could be used for any patient whose doctor feels would benefit from an immediate-release amphetamine medication. AR19 capsules contain pellets, that are about 1.2 millimeters in diameter. We have submitted the new drug application for AR19 under the 505(b)(2) pathway using Evekeo®, Arbor's currently approved amphetamine sulfate tablet, as the reference drug.

We originally formulated AR19 in 7 dose strengths, ranging from 2.5 to 40 milligrams, to provide clinicians flexible dosing options for both pediatric and adult patients. Based on the FDA's concern regarding the highest dose strength, Arbor agrees to eliminate the 40 milligrams dose. This would leave 30 milligrams as the highest-strength dose, which is a commonly prescribed dose of immediate-release amphetamine products today.

It is also important to clarify the target patient population that we think will benefit the most from AR19. Since older adolescents and young adults with ADHD have the highest prevalence of misuse and abuse, we see AR19 as a key part of a harm reduction strategy helping to protect this most vulnerable population. As you'll hear a little later in this presentation, nearly half of the patients with ADHD in this age group have snorted their medication. The manipulation-resistant formulation would make non-oral use difficult to do and less rewarding than what is available today.

Importantly, as the sponsor who would potentially be launching the first medication in this class, Arbor is committed to educating physicians, patients and families on the oral and non-oral misuse and abuse of ADHD prescription stimulants, and the specific benefits and risks of AR19.

Let me describe some of the attributes of AR19 that resist the manipulations that would be required for administration by non-oral routes.

AR19 is a pellets-in-capsule formulation. The active ingredient is distributed homogenously throughout each pellet. The fact that each capsule contains dozens of small pellets makes it difficult for someone to be able to handle them for physical manipulation. Relative to a tablet, our formulation increases the overall surface area, which maximizes its gelling properties. AR19 pellets are formulated to be hard and non-brittle. This provides resistance to particle size reduction so the pellets cannot be crushed into a fine powder. Finally, AR19 contains manipulation-resistant excipients that gel in small volumes of liquid to make injection difficult and to reduce intranasal bioavailability.

The AR19 development program consists of three biopharmaceutics studies, an efficacy and safety study, and a series of manipulation resistance studies. The biopharmaceutics studies demonstrated that AR19 is bioequivalent to Evekeo, that AR19 was bioequivalent under fed and fasted conditions as well as when sprinkled on food, and demonstrated the dose proportionality of AR19 capsules.

Our efficacy and safety study found that AR19 is safe and effective for the treatment of ADHD in adults. AR19 would be safe and effective for both adult and pediatric patients. All excipients have a well-understood safety profile for all ages when taken orally as intended and are included in other FDA-approved oral medications.

Our manipulation resistance studies demonstrated that AR19 is difficult to manipulate, even by trained laboratory professionals. Even when optimally manipulated, our human abuse potential study showed that AR19 was associated with lower drug liking and willingness to take again. Therefore, AR19 can be expected to reduce non-oral use in the real world.

Because of concerns related to the intravenous safety of excipients that occurred with Opana ER, we formulated AR19 to prevent these issues. We studied the intravenous safety of AR19

in a series of nonclinical studies, which showed no evidence of toxicity of AR19 extracts in vitro or in vivo.

Next, I'd like to review a few broader public health issues that Arbor has carefully considered. First, Arbor proposes using the term "manipulation resistant" to best describe the AR19 formulation, rather than "abuse deterrent." As noted previously by the FDA and prior Advisory Committees, the term "abuse deterrent" may stigmatize patients and lead to the false perception that the medication is "abuse-proof."

"Manipulation-resistant," on the other hand, conveys the idea that the medication has barriers that would discourage someone from converting it into a form that could be used non-orally. Of course, the FDA will determine the final terminology, but we will be using this term for the rest of the presentation.

Another factor to consider is that much of the non-oral administration of stimulants is misuse, not abuse. By misuse, I mean using the medication in a way other than intended to get a therapeutic effect; and by abuse, I mean using the medication for a non-therapeutic purpose, like to get high.

Arbor will use an enhanced pharmacovigilance program to evaluate potential signals of misuse, abuse, overdose, diversion, and overall safety. Details were provided in our briefing document. Taken together, this plan will allow Arbor and FDA to take prompt action, if needed, to address any safety signals. Additionally, Arbor has submitted a post marketing study plan to the FDA to evaluate the real-world impact of AR19.

Finally, Arbor is also committed to ensuring patient access to AR19. One of the concerns often voiced about formulations with barriers to prevent non-oral use, and echoed in many of the public comments to the Federal Register, is that sponsors price them so high that access is very limited.

We recognize that AR19 must be accessible to patients in order to have its intended public health impact. Therefore, we intend to price AR19 consistent with currently marketed ADHD prescription stimulants.

Here is the agenda for the rest of our presentation. All external experts have been compensated for their time preparing

for the Advisory Committee meeting. None have an equity interest in the outcome. Before I turn over the presentation to Dr. Faraone, I'd like to discuss several topics to keep in mind over the rest of this presentation.

While there are opportunities to learn from opioid reformulations, it's important to recognize the many differences between stimulants and opioids. Not only is the pharmacology of the opioid class different from stimulants, so are the patterns of and motivations for nonmedical use. And the patient populations also have distinct characteristics.

Second, FDA's briefing document states that a single product would likely have little impact on the overall problem of prescription stimulant nonmedical use. We know from our own research with hundreds of physicians that they would like an option like AR19 that would provide protections for appropriate patients. And, many have said they would want to prescribe AR19 when an immediate-release amphetamine is indicated. The FDA acknowledges the increased harms associated with non-oral use. AR19 is designed to address these risks and is a step in the right direction that should be taken.

Third, the FDA's briefing document omits any information about the extensive equipment, time, and effort required to manipulate AR19 for non-oral use. We had proposed sharing these detailed methods with the Advisory Committee members in a confidential session to provide more context for AR19's physical and chemical barriers to non-oral use. Since we were not permitted that opportunity, we will try to provide as much detail as we can in this presentation.

Fourth, the FDA's review of our intranasal human abuse potential study was based on post-hoc analyses that removed outliers. All results we will show are pre-specified analyses with no outliers removed. Thank you. I'll now turn the presentation over to Dr. Faraone.

Applicant Presentation – Stephen Faraone

Thank you. I am Stephen Faraone, Vice Chair for Research and Professor in the department of psychiatry at SUNY Upstate Medical University.

Today, I speak not only as President of the World Federation of ADHD who has studied this disorder for over three decades, but also as the father of a young adult with ADHD.

Although stimulant medications are highly effective in treating ADHD, a surprisingly high number of adolescents and young adults are misusing and abusing them through non-oral routes. So, I am here to describe the public health need for manipulation-resistant prescription stimulants to reduce use by dangerous routes of administration.

Treatment guidelines for ADHD recommend FDA-approved stimulants as first-line medical treatment, except for preschool children, for whom a trial of behavior therapy is indicated first.

A few years ago, several colleagues and I published a review showing how stimulants reduce many of the impairments associated with the disorder. These include real-world outcomes ranging from disruptive behavior and under-achievement in school and work, to very serious outcomes such as substance use disorders, accidents, suicide, and other causes of premature death. So clearly, inadequate treatment of ADHD has a serious public health impact.

As does nonmedical use of stimulant medications. Last year, 5.1 million people aged 12 and older misused or abused a prescription stimulant. This group includes 370,000 adolescents under the age of 17, two million young adults between the ages of 18 and 25, and two and a half million adults over the age of 26.

Non-oral use is a significant part of this problem. In a recent systematic review in the Journal of the American Academy of Child and Adolescent Psychiatry, my colleagues and I estimated that more than half a million people snort stimulants and 50,000 smoke or inject them.

And while oral use is the most common route for misuse and abuse, FDA seems to minimize the prevalence of snorting, smoking, and injecting. These numbers demonstrate a real problem. We should welcome methods that mitigate non-oral use

and not wait for the problem to reach epidemic proportions before implementing preventive interventions.

Snorting, smoking, and injecting CNS-active drugs leads to faster or greater effects than taking them orally. By circumventing first-pass metabolism, the drug enters the brain more quickly, which accelerates and intensifies its effects. As a result, non-oral routes put users at higher risk for compulsive use and addiction. This is not a "theoretical pathway" as characterized by FDA. This pathway to addiction has been so well documented in the scientific literature, that it is described in professional guidelines and psychopharmacology textbooks.

Next, let's review the epidemiology. National surveys show that most people start misusing and abusing prescription stimulants in their late teens, with a peak prevalence at 21 years old. This means that young people who are leading up to and attending college are the most vulnerable to initiating this behavior.

And the numbers show a high rate of non-oral use. Among those who have ever used a prescription stimulant, about 1 in 7 adolescents, 1 in 5 college students and 1 in 6 adults have taken them non-orally.

Across all age groups, snorting was the most common route by far, followed by smoking and injecting. The FDA has suggested that smoking is not a relevant route of abuse. However, these data suggest that it is just as, if not more common, than injecting in all populations.

What we've learned about the epidemiology of non-oral use improved our understanding of both the target populations, and which medications are most attractive for abuse. The prevalence of non-oral use is highest among college students with ADHD. 45% of those prescribed a stimulant had snorted it and half of those patients did so to achieve a faster effect on their ADHD symptoms. The American Academy of Pediatrics and supportive literature have identified immediate-release medications as more likely to be misused or abused than extended-release products, and that amphetamine is more frequently misused or abused than methylphenidate.

FDA's briefing document notes that the prevalence of nonmedical use of prescription stimulants is lower than prescription opioids in the general population. I'd suggest that the more relevant comparison is the population of college students. As you can see, the rate of snorting for prescription stimulants is nearly 2 times greater than prescription opioids, and the rate of injecting is similar. Many young people just don't fully appreciate the risks of non-oral use because the drugs were prescribed by a doctor. But those risks are real.

While studies of illicit behaviors are imperfect, the preponderance of evidence shows that snorting and injecting pose increased risks for severe clinical outcomes compared with oral use. These include cardiovascular effects, neuropsychiatric effects, pulmonary complications, psychological dependence, and impairment of family social and occupational function.

I recently analyzed data from the National Poison Data System to assess the health consequences of prescription amphetamine medication use by various routes of administration. My colleagues and I found that the risks for major medical effects and death were substantially higher for non-oral compared with oral use. The relative risk for life-threatening events was nearly three times greater for snorting and more than 7 times greater for injecting. The risk of death was 10 times higher for snorting and 24 times higher for injecting.

In conclusion, there is a serious public health need to reduce the harms associated with non-oral routes of administration. Today, no immediate-release ADHD stimulant is formulated to resist manipulation for non-oral use.

While oral misuse or abuse is most common, we must not minimize the prevalence of snorting, smoking, and injecting, or the very real and serious health outcomes from these more dangerous routes.

Next, it is a known and well-accepted pathway that non-orally using CNS active drugs puts users at higher risk for compulsive use and addiction. Anything we can do to prevent someone from using amphetamines non-orally would help to disrupt this progression.

Finally, the literature guides us on several targets for our efforts. We know the age group that is at highest risk – adolescents and young adults. And we know amphetamines in general, and immediate-release amphetamines in particular, are the most sought-after ADHD medication for non-oral use.

Since I think we can all agree that we don't want our children manipulating and abusing prescription drugs, anything we can do to reduce nonoral use – including the development of manipulation resistant formulations – would be a public health benefit. Thank you, I'll now turn over the presentation to Dr. Kinzler.

Applicant Presentation – Eric Kinzler

Thank you. My name is Eric Kinzler. I am an independent consultant and the study director for in vitro testing at DRUGSCAN. DRUGSCAN is an independent laboratory that is solely focused on testing formulations of prescription medications that are designed to resist physical manipulation and chemical extraction for unintended routes of administration. To date, we have evaluated nearly every product that has labeling for resistance to non-oral use.

We conducted extensive studies to evaluate the physical and chemical properties of AR19 that are designed to resist manipulation for snorting, smoking and injecting. In some studies, we used common household tools and methods. In others, we employed sophisticated laboratory tools and methods that would not be feasible in the real world, to test the product to the extreme. Since there is currently no guidance for the evaluation of manipulation-resistant stimulants, AR19 studies were informed by the principles outlined in the FDA guidance for evaluating abuse-deterrent opioids. Arbor also conducted additional experiments and conditions that were requested by the FDA. We used Evekeo, Adderall, or amphetamine sulfate API, or combinations of these as comparators.

The first non-oral route we'll discuss is snorting. At-risk individuals who snort prescription stimulants do so because they can achieve faster effects than if they simply took the drug orally. These faster effects provide positive reinforcement and increase the likelihood of repeat use. Currently, no immediate-

release prescription stimulants offer any barriers to snorting; so, faster effects are achieved simply by crushing and then snorting the product.

Manipulation-resistant formulations may include two different types of barriers to prevent someone from snorting. First are the physical barriers to manipulation, which can make it difficult to crush into a powder, time-consuming, requiring specialized or modified tools, or all of them. Second, a product can be formulated to make less drug bioavailable when snorted, thereby reducing its likeability and abuse potential. In other words, even if the person is able to make the product snortable, they won't enjoy the experience as much. With both of these barriers in place, an at-risk individual will be less likely to snort the drug.

Let's start with the first barrier – difficulty of manipulation. We evaluated how difficult it was to manipulate AR19 in a series of particle size reduction studies.

Particle size reduction is the first step in transforming a drug into an abusable form for snorting, smoking, or injecting. At DRUGSCAN, we test a full range of common household tools that are routinely used to manipulate a drug for this purpose. The specific tools are chosen to evaluate all potential mechanisms of physical manipulation for a particular product. All in vitro testing was performed three times per condition to ensure reproducibility of the result.

The mechanisms used to physically manipulate oral medications for non-oral use include cutting, crushing, grating, and grinding. To evaluate the feasibility of particle size reduction 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, we tested multiple makes and models.

DRUGSCAN selected 7 tools for the primary study to represent the different ways someone might attempt to manipulate AR19 or Evekeo. FDA guidance defines particles smaller than 500 microns as amenable for snorting. This chart will show the percentage of particles that we were able to reduce below that threshold for each of the tools.

For Evekeo, which is a non-manipulation resistant formulation, all of the tools successfully reduced most of the tablet into a suitable form for snorting quickly and without any modification to the tools themselves.

For AR19, most tools were completely ineffective. Although Tools 4 and 6 were relatively effective, neither reduced the majority of pellets into small particles. DRUGSCAN scientists had to modify a tool to get the majority of AR19 pellets under 500 microns. After several weeks of experimentation, we developed an optimized procedure that required modifying Tool 7 and applying select accessories. This was a 20-minute, multi-step procedure that required additional equipment.

But even with all this time and effort, AR19 could not be reduced to a fine powder. In contrast, we achieved a fine powder with the non-manipulation resistant comparator, Evekeo, using Tool 3 for just 30 seconds. The inability to reduce AR19 to a fine powder reduced intranasal absorption, as will be discussed now by Dr. Setnik.

Applicant Presentation – Beatrice Setnik

Thank you Dr. Kinzler. I am Beatrice Setnik, the Chief Scientific Officer at Altasciences. I am pleased to report on the intranasal human abuse potential study, which I will refer to as the HAP study.

Returning to the diagram Dr. Kinzler just showed, it’s important to understand that HAP studies are only designed to evaluate the second type of barrier – the pharmacological effects of a product. In these studies, trained pharmacy staff prepare the drugs for abuse, using the already-identified optimized method of producing the smallest particle sizes. Since subjects don’t experience the time and effort required to get the drug into a snortable form or the process to identify the manipulation technique, HAP studies only measure the pharmacokinetics and pharmacodynamics of a drug when snorted.

Consistent with FDA guidance, the intranasal HAP study for AR19 enrolled recreational stimulant users with recent intranasal experience, who were not physically dependent on

drugs or alcohol. Other inclusion criteria are listed on this slide and were provided in our briefing document.

It is important to underscore that AR19 was not manipulated by subjects in the study. Instead, trained pharmacists manipulated AR19 at the clinical site. Since the optimal manipulation method, using Modified Tool 7, was so difficult to perform, Dr. Kinzler's lab actually had to send a laboratory scientist to our clinical site to teach our pharmacists how to do it. Just reading the instructions wasn't enough to learn how to do the procedure. Our pharmacists then had to demonstrate their ability to reliably and consistently manipulate AR19 to the expected particle size prior to being certified to manipulate AR19 for subjects in the HAP study.

I'll move now to study results beginning with pharmacokinetics. Intranasal amphetamine API, indicated by the red line, was associated with a rapid increase in plasma concentrations. In contrast, intranasal AR19 led to a more gradual rise, as shown by the blue line, that did not reach the levels associated with the control.

As shown in the table on the top right, the maximum plasma concentration, or Cmax, was 25% lower with AR19; the median time to peak concentration, or Tmax, was 3 hours longer; and, the median exposure was about 25% lower. These results confirmed that the inability to reduce AR19 to a fine powder reduces intranasal absorption. This is important for the reasons mentioned earlier by Dr. Faraone. He noted that greater rates of rise in drug concentration are associated with greater abuse potential. AR19 substantially reduces that rate of rise relative to the comparator, so we would expect it to have a lower abuse potential.

As described in the FDA Guidance document, "the overall assessment of abuse potential in abuse-potential studies should be based on the pattern of findings across all of the measures." Therefore, I will review the key pharmacodynamic endpoints.

Before presenting the study results, I want to acknowledge the difference between our analyses and FDA's analyses of the pharmacodynamic endpoints. The FDA's review of this study was based primarily on post-hoc analyses in a modified population

that excluded data from 4 subjects, which was not prespecified. Additionally, the FDA applied statistical margins to endpoints that were not prespecified. All analyses I will be showing today were prespecified in the study protocol. These results are based on all completers in the study accounting for the totality of the data. No outliers are removed from any of the analyses that I will present today.

This slide will show the results for the primary endpoint of Drug Liking Emax, or the maximum drug liking score observed from the time of drug administration until 36 hours post dose. On the y-axis, the mean Drug Liking Emax scores range from 0 to 100. 100 represents strong liking, 50 represents neither like nor dislike, and a score of 0 represents strong disliking.

As expected, placebo was not associated with substantial drug liking and is close to neutral. Amphetamine 40 milligrams was associated with a maximum average Drug Liking score of 78. AR19 40 milligrams was nine points lower on Drug Liking Emax compared to amphetamine API. This is consistent with the PK results I just reviewed, in which AR19 showed lower plasma concentrations. When contrasting AR19 versus amphetamine, the p-value with a superiority margin of 10 percent, narrowly missed the threshold for significance of 0.025, with a p-value of 0.026.

Because the rationale for snorting a stimulant is to achieve a quick effect, it is important to look at Drug Liking over time to provide clinical context for the Emax results. In the first 15 minutes, the critical time when individuals would be expecting to have achieved a quick effect after snorting amphetamine, AR19 was indistinguishable from placebo. At all subsequent timepoints the Drug Liking for AR19 remained well below amphetamine API. This pattern of reduced Drug Liking with AR19 is consistent with its reduced intranasal bioavailability.

We observed the same profile of results over time for Drug High and Good Drug Effects, as well. The left graph shows that AR19 was associated with lower mean High values than amphetamine API over the first 3 hours. The right graph shows a very similar profile for Good Drug Effects.

Probably the most important endpoint for a drug that is intended to prevent repeated use is Take Drug Again. We asked the participants whether they would take the drug again if given the opportunity. A score of 50 means neutral, 100 means definitely so, and 0 means definitely not. This is measured at 12, 24, and 36 hours; in other words, subjects are asked to reflect on their entire drug taking experience, after its effects have worn off. Emax is the greatest score at any of those timepoints. As would be expected, placebo showed a low score that was close to neutral. Amphetamine was the highest. AR19 was 11 points lower than amphetamine, demonstrating a statistically significant decrease in willingness to snort AR19 again.

The FDA suggested that there was a lack of a consistent pattern of results on the secondary endpoints. However, the totality of the data on the pre-specified analyses for the secondary endpoints show a very consistent pattern. This forest plot illustrates the mean difference between amphetamine and AR19. Scores to the left of 0 indicate less liking for AR19. As you can see, these important pharmacodynamic endpoints all showed that AR19 has a lower abuse potential than amphetamine API.

To summarize, the manipulation-resistant studies demonstrate that AR19 is difficult to manipulate and less rewarding and less attractive to snort. AR19 could not be prepared for snorting with common household tools. Achieving a snortable form of AR19 required a modified tool, specific equipment, and considerable time and effort. Even with that, AR19 still could not be reduced to a fine powder. Based on this alone, it is unlikely that a typical individual could or would perform the necessary manipulation required to prepare AR19 for snorting.

Even when optimally manipulated, AR19 was placebo-like for Drug Liking at 15 minutes post dose, a timepoint that drug users are looking for an intense effect. AR19 was also associated with lower Drug Liking and High over time, as well as a lower willingness to take again, consistent with its pharmacokinetic profile. Because subjects did not have to manipulate AR19, it is likely that the willingness to Take Drug Again scores are

conservative. Taken together, the data support that the multiple barriers in AR19 can be expected to reduce the likelihood of snorting. Dr. Kinzler will now return to continue his review of the manipulation resistance studies.

Applicant Presentation – Eric Kinzler

Thank you, Dr. Setnik. I will now briefly review the studies related to simulated smoking.

Utilizing a simulated smoking apparatus with optimized times and temperatures, we determined that smoking is not a feasible route of administration for AR19. With a laboratory heating block, we were able to volatilize up to 58% of amphetamine API, showing that smoking of pure amphetamine was possible. However, when we tried to volatilize the amphetamine from Evekeo and AR19, we could not get more than 11% of amphetamine volatilized from either product at any temperature. Furthermore, experiments with an open flame, which is more representative of real-world methods, resulted in less than 5% of API volatilized from AR19. Therefore, smoking is not a feasible route of administration for AR19.

The next set of experiments were small volume extraction and syringeability studies to evaluate the feasibility of injection. First, let me provide some background on the interpretation of these studies. We know that all prescription ADHD formulations must be bioavailable and release the product when taken via the intended oral route. As such, no product is abuse-proof.

The ability of a product to reduce the incentive for injection depends on two factors, which have to be considered together. The first factor is the input, which is the amount of time, effort, and materials that are required to prepare a product for injection. The second factor is the output, which is the API recovery from those conditions. The FDA’s review of these studies focuses only on the output, without the context of the time and effort required.

We assessed both factors by testing real-world techniques used by people who inject drugs, as well as advanced methods that require laboratory tools and techniques that are beyond the

capacity and willingness of most people in the real world. Another thing to consider is that intravenous users are looking to inject a dose that will achieve a desired effect. So, the dose in milligrams is a more important consideration than the percent extracted.

FDA found a reference that 10 milligrams of intravenous dextroamphetamine is a reasonable minimum reinforcing dose, meaning the lowest dose that could be differentiated from placebo. But what is more clinically relevant is a dose that provides a profound effect that is often sought by IV amphetamine users. Based on our literature review, we found that initially, a typical IV user seeks doses in the range of 20 to 40 milligrams. When they become experienced, their dose requirement escalates dramatically up to 100 to 300 milligrams per injection; and, they may inject multiple times per day. For context, we will show results both in terms of percentage and milligram recovery.

For context, intravenous users typically use 0.5 to 1 mL for injection with 1 cc insulin syringes, which you can see on the far left in this picture. The testing for AR19 included solvent volumes and needles several times larger than those commonly used. For example, Needle Gauge C on the right is extreme, as it is typically used for blood transfusions. We found that commonly available filters like cigarette filters were not effective, so we had to use a laboratory filter.

Let me show you a video of how IV users of prescription stimulants typically prepare a tablet for injection. After crushing, the user would dissolve the crushed tablet in a small volume of water. Then, they would draw up the liquid with an insulin syringe through a filter, like the cigarette filter used here. This is done to avoid injecting particulate and clogging the needle. From this, the user would achieve a small, injectable extract. This simple method is how one would be able to prepare an injection of all immediate-release amphetamine products, which offer no barriers to manipulation.

Applying the same conditions to AR19 are unsuccessful. AR19 rapidly formed a viscous gel that was completely non-syringeable through the cigarette filter. All that could be pulled up was air because there is no liquid. It is all a gel. As you can see,

when the laboratory technician pulls out the syringe, AR19 turned into a sticky, viscous substance that is completely non-syringeable. With this example in mind, let me turn to the results across all of our experiments.

Let me start with the conditions involving extractions in a small volume and syringing with Needle Gauge A. Looking first at Evekeo, all of the conditions evaluated were successful in getting more than 15 percent yield of syringeable amphetamine. In contrast, the majority of methods tested for AR19 yielded less than 15 percent of syringeable amphetamine and most conditions yielded no syringeable material at all, which is consistent with the video I just showed.

Because standard IV conditions were ineffective, we also tested four different levels of advanced, laboratory conditions. Hundreds of combinations were tested. Higher levels listed here reflect more extreme conditions, like larger solvent volumes, larger needles, and with pretreatment. The median extraction of syringeable amphetamine recovered from these experiments was less than 4 milligrams or 10 percent. The highest recovery yielded up to 20 milligrams or 50%.

The condition that achieved the highest syringeable yield required optimal physical manipulation, pretreatment, extraction for extended periods of time at elevated temperatures, and large gauge needles not typically used by IV drug users. While we were able to achieve this in the laboratory, the extreme nature of these conditions makes it unlikely that this method could be reproduced in the real world.

We evaluated several representative extracts from this table in our nonclinical safety studies. The non-clinical safety studies of AR19 are important in light of the rare cases of thrombotic microangiopathy or “TMA” observed with IV injection of Opana ER, an opioid product that contained PEO 7 million, an excipient also used in AR19. It is important to note that Opana ER was a tablet formulated primarily to prevent snorting. In contrast, Arbor formulated AR19 to provide robust resistance to snorting, smoking, and injecting; and, Arbor designed the development program to specifically assess the benefits and potential risks by each of these non-oral routes.

There are important differences between AR19 and Opana ER in both pharmacology and formulation that distinguish them from one another, especially in terms of intravenous abuse liability and the risks of unintended consequences.

In terms of formulation, Opana ER was a tablet and AR19 is a pellets-in-capsule formulation. Relative to a tablet, pellets increase the surface area of the product when exposed to a small volume of injectable solvent. This increases the gelling of the product. Furthermore, AR19 contains an additional gelling agent that was not present in Opana ER. This additional agent increases AR19's resistance to injection.

With respect to pharmacology, the IV abuse liability of amphetamine, the active ingredient in AR19, and oxymorphone, the opioid active ingredient in Opana ER, are quite different due to their relative bioavailabilities by different routes of administration. Let me explain.

The oral bioavailability of amphetamine is 75%, meaning that 75% of the drug reaches systemic circulation when taken orally. When any drug is administered intravenously, its bioavailability is 100%. Therefore, the amount of amphetamine that reaches systemic circulation with injection is 1.3 times greater than with oral administration.

In contrast, oxymorphone has a very low oral bioavailability of 10%. This means that the amount of oxymorphone that reaches systemic circulation when injected is 10 times greater than when taken orally. This substantially greater effect made injecting Opana ER extremely desirable for IV users. And because the drug was so potent intravenously, this also explains how a single Opana ER tablet, or even a piece of tablet, could yield multiple IV doses. In fact, a single Opana ER tablet could provide up to 16 injections.

Here is how it works. The highest strength tablet of Opana ER contained 40 milligrams of oxymorphone. From the literature, we know that individuals who abused Opana ER commonly quartered the tablet into four, 10 milligram pieces and shared them with multiple users. Preparing a quartered tablet for injection involved browning and extracting it in a small volume of 1 to 2 milliliters of water. From that 10-minute preparation,

individuals could prepare up to four injections per quarter tablet. Simple math tells us that one 40 milligram tablet of Opana ER could produce up to 16 injections of oxymorphone.

The very high intravenous potency of oxymorphone also explains the needle sharing behavior and HIV outbreak associated with Opana ER. When we tried this same method on AR19, no syringeable extract could be drawn up due to the gelling properties. This substantiates that the additional gelling excipient in AR19 and its pellet formulation provides robust resistance to injection, unlike Opana ER.

It is also important to consider the time and effort necessary to get a particular yield or output. Again, for Opana ER, it took just 10 minutes to physically manipulate, pretreat, extract, and syringe a 40-milligram tablet. And from one tablet, one could extract up to 16 injectable doses. A very minimal effort for a substantial return. The opposite is true with AR19. It took us about an hour of complex laboratory techniques to achieve about one relatively low IV dose from the highest-strength 40 milligrams capsule.

We also looked at the potential for extracting multiple capsules at once, since we know intravenous amphetamine users seek doses above 20 milligrams to achieve a desired effect. So, we evaluated between two and seven dosage units for Adderall 30 milligram, Evekeo 10 milligram, and AR19 40 milligram capsules. We evaluated Adderall and Evekeo using the smallest needle gauge and AR19 using the blood transfusion size needle.

For Adderall, the additional tablets increased the yield of syringeable amphetamine up to a maximum of 62 milligrams. For Evekeo, additional tablets also increased the syringeable yield of amphetamine. For AR19 40 milligrams, however, adding additional capsules actually reduced the amount of syringeable amphetamine recovered. We repeated this experiment with multiple pre-treated capsules, with essentially the same results. We agree with the FDA’s conclusion that it is not feasible to extract multiple capsules of AR19 simultaneously.

To summarize, AR19 has demonstrated resistance to manipulation for snorting, smoking, and injecting.

AR19 could not be prepared for snorting with common household tools. Optimal manipulation required a modified tool, additional equipment and accessories, and extensive time and effort. Even with the optimized techniques, AR19 still could not be reduced to a fine powder. The intranasal human abuse potential study demonstrated that AR19, even when optimally manipulated, has a lower abuse potential than amphetamine sulfate API.

Smoking was also not a feasible route of administration for AR19, with low recoveries.

Our extensive in vitro testing found that it is not possible to prepare a suitable extract from AR19 using common methods of IV drug users. A time-consuming, multi-step process using laboratory equipment was needed to achieve even a relatively low dose for injection.

Therefore, the data demonstrate that AR19 can be expected to reduce snorting, smoking, and injecting, and therefore reduce their associated harms. Thank you. I'll now turn the presentation to Dr. Dillberger.

Applicant Presentation – John Dillberger

Thank you. I'm John Dillberger. I am pathologist and toxicologist with more than 30 years of experience in evaluating the nonclinical safety of new drug products. I am certified in veterinary pathology since 1987 and toxicology since 1991. I will review the results from the nonclinical safety studies.

As Dr. Kinzler mentioned, thrombotic microangiopathy, or TMA, was observed in humans with repeated intravenous use of manipulated Opana ER. TMA was attributed to the high-molecular weight PEO excipient in that product. High-molecular weight PEO alters blood flow in small blood vessels, increasing collisions between red blood cells and the blood vessel lining. Such collisions can damage both red blood cells, causing hemolysis, and the blood vessel lining, leading to thrombosis. Because AR19 also contains high-molecular weight PEO, we wanted to investigate two questions with respect to manipulated AR19 injected intravenously: might manipulated AR19 cause TMA and might manipulated AR19 cause any other sort of adverse effect.

As has been described by the FDA at prior Advisory Committee meetings, multiple marketed PEO-containing products have not been associated with TMA. The differences in TMA risk among PEO-containing products might be based on differences in manufacturing processes, curing methods, heat, additives and other related factors; the molecular weight range of the PEO in the product; the manipulations and extraction methods used to prepare an injectable solution; and, differential patterns of abuse; that is, factors like the extract dose injected and the frequency of injection.

The FDA's briefing document raised concern about the potential toxicity of high molecular weight PEO as well as talc if AR19 was administered via non-oral routes. However, many of the most commonly prescribed prescription stimulants contain these same excipients.

For example, PEO 7 million is a primary excipient in Concerta, which has been FDA-approved for the treatment of ADHD since 2000. Despite methylphenidate products having intravenous abuse liability, there have been no reports in the FDA Adverse Event Reporting System of thrombotic microangiopathy, thrombotic thrombocytopenic purpura, or microangiopathic hemolytic anemia despite more than 85 million prescriptions dispensed.

Also, like AR19, both Ritalin and Adderall XR contain talc. Furthermore, the literature suggests that in order to observe adverse events from talc, an individual would have to prepare and snort about 2600 AR19 capsules over a 6-month period. While no safe dose of intravenous talc has been identified, case studies have suggested that the effect is cumulative over thousands of injections.

Therefore, the two excipients in AR19 that the FDA has raised as potential safety concerns do not pose a unique risk.

Nonetheless, Arbor conducted several in vitro and in vivo IV excipient safety studies to thoroughly evaluate the potential toxicity risks of manipulated AR19 extracts. For the in vitro hemolytic potential study, we selected 9 representative AR19 extracts from the thousands evaluated. We also characterized the PEO content of these representative syringeable AR19 extracts.

Arbor also performed several single- and 7-day, repeat-dose IV safety studies in New Zealand White rabbits.

Before I present the results, it's important to understand the terms syringeability and injectability to describe AR19 extracts. These are not synonymous. An extract is syringeable if it can be drawn up into a syringe at any temperature. An extract is injectable only if it can be drawn up and expelled from the syringe at body temperature, which is suitable for mixing with blood or injection into a blood vessel.

The small volume extraction studies already described by Dr. Kinzler measured the amphetamine content of extracts that were syringeable, regardless of temperature. The in vitro hemolytic potential study evaluated syringeable AR19 extracts, not all of which were directly injectable. And the in vivo study in rabbits that I will describe evaluated the injectable AR19 extract that contained the highest concentration of amphetamine and PEO.

Now I will present the in vitro hemolytic potential study. The in vitro system utilizes a syringe pump to pass human blood mixed with different test materials through a small-diameter needle, which simulates blood flow through arterioles. The concentration of free hemoglobin is measured as an indicator of hemolysis.

We assessed four types of test materials, including: a negative control compound, which was water; a positive control compound, which was PEO with a molecular weight of 8 million Daltons at a blood concentration of 40 micrograms per mL; a comparator compound, PEO with a molecular weight of 7 million Daltons at blood concentrations ranging from 0.1-100 micrograms per mL; and 9 different syringeable AR19 extracts, each obtained by different manipulation and extraction methods. The AR19 extracts were chosen to be representative of different ways someone might try to prepare the product for injection. These included extracts with and without physical manipulation, with and without pretreatment, and extracting with different solvents, volumes, temperatures, times, and with and without agitation.

The in vitro study produced no evidence of meaningful hemolytic potential for the AR19 extracts. This slide shows on the y-axis the mean percentage of free hemoglobin response relative to the positive control of PEO 8 Million, which is represented by the red bar. The study also included a negative control, water, represented by the gray bar. As expected, 7 million PEO produced concentration-related hemolysis. In contrast, there was no evidence of any meaningful hemolysis with any of the AR19 extracts. None of them significantly differed from the water control.

Based on the in vitro hemolytic results, AR19 Extract 8 was selected for evaluation for the in vivo safety study. Let me explain why. All 9 extracts were syringeable, which means they could be drawn up into a syringe at any temperature without regard to whether the extract was also injectable. However, only 5 were injectable, which means they could be expelled from a syringe at a physiological temperature suitable for injection. Of the 5 injectable extracts, we then compared the PEO content. Extract 8 was chosen for the in vivo IV safety study because it had the highest PEO content and it had the highest yield of amphetamine of the entire program.

The PEO content of Extract 8 was then further evaluated, and it was determined that due to the pretreatment required to prepare AR19 for injection, high molecular weight PEO was no longer present. In fact, all PEO was less than 1 million Dalton.

Next, we evaluated the potential effects of intravenous administration of Extract 8 in a series of in vivo safety studies. Following a series of dose-range finding studies, and in consultation with the FDA, we designed a pivotal, 7-day, intravenous safety study in New Zealand White rabbits.

Five treatment groups were evaluated. These included three different doses of AR19 Extract 8. These represented the human equivalent of injecting one, two or three IV doses of the highest strength capsule. There was also a normal saline control and a positive control of PEO 7 million. Fourteen rabbits were included in each treatment group and doses were administered IV daily for 7 days. Subsets of rabbits were euthanized and necropsied after the last dose to evaluate toxicity and two weeks after the last dose to evaluate recovery from any effects.

FDA noted in their briefing document that this study was limited in terms of the duration of treatment and the number of injections. While it's true that we could have injected extracts numerous times per day for the duration of the rabbits' lives, this was not the purpose of the study. The study was designed to exaggerate a real-world situation. As Dr. Kinzler mentioned earlier, the time to produce a single extract of a single capsule takes approximately 1 hour, and the maximum dose that can be achieved for injection is low. Therefore, AR19 is highly unlikely to be used repeatedly via the IV route.

The study design, including the duration of treatment, was refined based on suggestions from the FDA, all of which we accepted. It is also important to note that TMA effects were able to be produced with fewer animals and in a shorter treatment duration in prior studies, such as the Hunt study as well as Arbor's own dose-finding study.

After the first dose of positive control PEO 7 million, all of the animals died or were euthanized due to moribund conditions. Postmortem evaluation showed clotted blood in the atria and ventricles of the heart. We knew from our pilot studies that there was a very small difference between a dose that would produce no effect in rabbits, a dose that would produce TMA-like effects, and a dose that was lethal. For the pivotal study, we chose a PEO 7 million dose that we thought would be low enough to be tolerated but high enough to produce the TMA-like effects we saw in our pilot studies. As it turned out, the PEO 7 million dose level resulted in death before TMA-like effects could occur. Nevertheless, as the FDA noted, we did produce TMA-like effects in rabbits in a pilot study by injecting PEO 7 million, confirming that rabbits are a suitable species to screen for such effects.

In contrast to the PEO 7 million dosing group in the pivotal study, all animals in the AR19 extract groups survived to the end of the study. In fact, they tolerated daily doses of AR19 Extract 8 without any effects.

The FDA has noted that the IV safety studies with Extract 8 do not appear to yield reproducible results. We disagree. For background, a pilot study uses small groups of animals to identify adverse findings that could potentially be drug

related. Pilot studies are not intended to reach conclusions about drug-relatedness.

A subsequent pivotal study uses larger groups of animals to see if any of those adverse findings are reproduced. If so, then one concludes that they are drug related. If they are not reproduced, then one concludes that the findings in the pilot study were due to chance rather than the drug. One does not conclude that the pivotal study failed. To put it another way, a pilot study is done to generate hypotheses, while a pivotal study is done to confirm or refute those hypotheses.

To summarize, the AR19 excipients of concern raised by FDA, PEO 7 million and talc, are contained in other FDA-approved prescription stimulants. Based on the available data, thousands of intranasal or intravenous AR19 exposures would be required to cause talc toxicity. In light of the difficulty of manipulation and lack of incentive to do so, talc toxicity with AR19 is unlikely. For these practical reasons and based on the studies conducted by Arbor, PEO toxicity is unlikely as well. First, there was no evidence of in vitro hemolysis with any AR19 Extract. And second, injection of rabbits with AR19 Extract at the human equivalent of three 40 milligram capsules per day for 7 days was well tolerated, possibly because the PEO molecular weight was less than 1 million Dalton. Thank you, I will now turn the presentation over to Dr. Rostain.

Applicant Presentation – Anthony Rostain

Thank you. My name is Anthony Rostain, and I'm the Chair of Psychiatry and Behavioral Health at Cooper University Health Care and have been involved in the care of patients with ADHD for close to 40 years. I have also been professionally involved in addressing the growing trend toward nonmedical use of stimulants for years. Based on my personal experience working with young people with ADHD, I can attest that they underappreciate the risks of misusing and abusing what they see as a safe medication prescribed by a doctor.

The misuse and abuse of prescription stimulants is a serious public health issue. Snorting, smoking, and injecting is occurring at alarming rates, particularly among young people.

By using non-orally, individuals may be seeking a more rapid and profound effect to get faster relief from their ADHD symptoms, to stay up late to study for a test, or to get high at a party. And I know not just from the data, but from patients in my practice, that this dangerous behavior can result in hospitalizations and severe medical outcomes, including strokes and cardiac events, as well as the development of a substance use disorder. Unfortunately, all immediate-release prescription stimulants on the market today are easy to manipulate for snorting, smoking, and injecting, which leads me to the benefit-risk assessment for AR19. For that, we must consider both the impact on an individual patient who takes the medication as intended, as well as its potential to mitigate misuse and abuse in the general population.

Let's begin with individual patients taking the medication as intended. The data demonstrate that AR19 would be safe and effective for the treatment of ADHD in children and adults. As Dr. Faraone reviewed, and as highlighted by the FDA, effective treatment of ADHD with prescription stimulants like AR19 reduces many impairments of the disorder and has been shown to meaningfully improve patient's lives: increasing achievement in school and at work, and reducing the risks for nonmedical use, substance use disorders, accidents, and premature death.

While the FDA briefing document questioned the impact of a product like AR19, saying that immediate-release racemic amphetamine sulfate products account for a small percentage of the overall stimulant market, I know from my experience that immediate-release amphetamine formulations are therapeutically interchangeable. I would consider AR19 for any patient in need of an immediate-release amphetamine medication.

Next, we need to consider the benefit-risk for public health, including AR19's manipulation-resistant properties and any potential unintended consequences.

First, it's important to be clear about what a manipulation-resistant formulation like AR19 can be expected to do, and also what it can't. Let's start with the fact that no formulation can prevent oral misuse or abuse. Also, no formulation can be abuse-proof. With sufficient time and effort, the physical and chemical barriers can be partially overcome.

With those limitations in mind, a successful manipulation-resistant formulation would make it difficult to convert the medication into a form that could be snorted, smoked or injected; it would reduce the positive reinforcement of non-oral routes by diminishing the pharmacological effects; and, reduce the harmful medical outcomes that result from use by the most dangerous routes. Taken together, a successful manipulation-resistant formulation should demonstrate meaningful barriers that, first, make non-oral use more difficult and, second, make the behavior less rewarding than currently available products.

So, let's review the clinical relevance of AR19's barriers using that paradigm. For snorting, no common household tool could get AR19 into a snortable form. Even with an extreme manipulation method, AR19 could not be reduced to a fine powder that is easily produced with tablets available today. If someone was willing to perform the multi-step procedure, the human abuse potential study showed that AR19 reduced the positive reinforcement of snorting. The clinical relevance is clear. AR19 can be expected to reduce snorting because individuals simply can't get a big, fast effect in a short amount of time.

For smoking, the process to manipulate AR19 required the same difficulty as for snorting. In terms of reward, since there were very low recoveries of volatized amphetamine from AR19, smoking is not feasible.

The process to prepare AR19 for injection required even more steps. All typical methods failed. Getting any injectable amphetamine required a set of highly advanced techniques. Most important is the fact that the required effort – including multiple steps, laboratory equipment and substantial time and effort – only produced a low dose. And, using the contents of multiple capsules to increase the dose also failed. Bottom line, the physical and chemical barriers in AR19 make snorting, smoking and injecting both more difficult and less rewarding.

Let's also evaluate potential public health risks. A major issue is the concern that a high price will result in limited access and therefore, limited public health impact. For this, the sponsor stated a commitment to price AR19 consistent with currently marketed prescription stimulants.

Next is a concern that labelling will lead to a false sense of security. The sponsor is suggesting the term "manipulation-resistant" rather than "abuse-deterrent" to better reflect what AR19 is designed to do and has outlined a robust physician education plan.

There is a concern that a reformulation could shift someone from snorting to injecting. AR19 was developed to provide robust resistance to all non-oral routes, including injection.

There is also the question about whether a formulation's excipients will cause serious health consequences if injected. The AR19 studies found no evidence of IV toxicity, in vitro or in vivo.

And lastly, there is the potential for consequences both unintended and unforeseen. For this, Arbor will conduct an enhanced pharmacovigilance program and post-market studies.

Finally, I'd like to speak to the assertion made by FDA that individuals prescribed a manipulation-resistant formulation may seek an illicit stimulant like methamphetamine. I suspect this is based on assertions to what was presumed to have occurred following the reformulation of OxyContin, an extended-release oxycodone product.

A recent New England Journal of Medicine article published by the National Institute on Drug Abuse has stated that there is no consistent evidence of an association between the implementation of policies related to prescription opioids, including the advancement of abuse-deterrent formulations, and increases in the rates of illicit drugs.

But nonetheless, it is important to underscore that stimulants and opioids are fundamentally different in many ways. Their pharmacodynamic effects are vastly different. Opioids can cause physical dependence. Stimulants do not. And, the motivations for nonmedical use are distinct: primarily performance enhancement for stimulants and pain relief and euphoria for opioids. Another important difference is that AR19 would be an option among many, not a reformulation of the entire market.

Let us also consider the context of the at-risk population. We are talking about older adolescents and college students. Research has shown that individuals are primarily using these medications non-orally to treat their ADHD or for performance enhancement. The reason they feel comfortable misusing or abusing these drugs in the first place is because they are prescription medications and are perceived as safe. So, the likelihood that AR19 would prompt young individuals to initiate use of illicit stimulants, like cocaine and methamphetamine, is unlikely, because they are street drugs and perceived as dangerous.

And so, based on a careful review of the studies as well as an assessment of the broader public health issues, I conclude that AR19 has a positive benefit-risk profile for patients taking the drug as intended as well as for public health.

AR19 imposes meaningful barriers that can be expected to reduce the harms associated with non-oral use and discourage progression down a path of more dangerous drug-taking behaviors. I see AR19 as an important option for physicians who are seeking appropriate medications for their patients and parents who would appreciate extra levels of protection for their child with ADHD.

Thank you. That concludes the presentation.