AR19 (amphetamine sulfate) 
Manipulation-Resistant, Immediate-Release Capsules for the Treatment of ADHD 
October 8, 2020 
Arbor Pharmaceuticals 
Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
Summary Presentation

Evan Scullin, MD
Vice President, Medical Affairs
Arbor Pharmaceuticals
AR19: First IR ADHD Rx Stimulant with Physical, Chemical Barriers Designed to Resist Manipulations Required for Snorting, Smoking, Injecting

- Pellets-in-capsule form of FDA-approved amphetamine sulfate
- Meets standard for approval in pediatric and adult patients with ADHD
Propose “Manipulation-Resistant” Terminology for AR19, Not “Abuse-Deterrent”

- “Abuse-deterrent” terminology
  - May stigmatize patients
  - May lead to false perceptions that product is “abuse-proof”
- Manipulation-resistant terminology
  - Barriers to conversion for non-oral use

Physicians recognize need for treatment option like AR19 to provide protections for at-risk patients
Arbor Proposes to Eliminate 40 mg Dose

- Originally formulated 7 dose strengths to provide clinicians flexible dosing options for pediatric and adult patients
  - 2.5, 5, 10, 15, 20, 30, and 40 mg
- 30 mg would be highest strength dose
  - Commonly prescribed dose of IR amphetamine products
Arbor Committed to Ensure Patient Access

- Public comments in *Federal Register*
  - Concerns about patient access and cost
- AR19 must be accessible to have intended public health impact
- To be priced consistent with marketed ADHD medications
FDA Question 1

“Considering the patterns of prescription stimulant nonmedical use in the United States, please discuss the potential public health impact of prescription stimulants formulated to be abuse-deterrent.”

Stephen Faraone, PhD
Vice Chair for Research, Department of Psychiatry
Distinguished Professor of Psychiatry
Distinguished Professor of Neuroscience & Physiology
SUNY Upstate Medical University
Epidemiology of Non-Oral Use Identifies Target Populations and Medications

- Older adolescents, young adults with ADHD have highest prevalence of prescription stimulant NMU
- 45% of college students prescribed a stimulant for ADHD reported snorting it

- Non-oral prescription stimulant use more common with
  - IR than ER
  - Amphetamine than methylphenidate

# High Rate of Non-Oral Use of Prescription Stimulants

<table>
<thead>
<tr>
<th></th>
<th>Adolescents&lt;sup&gt;1&lt;/sup&gt; (196 users)</th>
<th>College Students&lt;sup&gt;2&lt;/sup&gt; (641 users)</th>
<th>Adults&lt;sup&gt;3&lt;/sup&gt; (1,284 users)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any non-oral Use</strong></td>
<td>27 (14%) 1 in 7</td>
<td>135 (21%) 1 in 5</td>
<td>207 (16%) 1 in 6</td>
</tr>
<tr>
<td><strong>Snorting</strong></td>
<td>19 (10%)</td>
<td>120 (19%)</td>
<td>188 (15%)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>8 (4%)</td>
<td>33 (5%)</td>
<td>29 (2%)</td>
</tr>
<tr>
<td><strong>Injecting</strong></td>
<td>2 (1%)</td>
<td>21 (3%)</td>
<td>27 (2%)</td>
</tr>
</tbody>
</table>

Non-Oral Use Associated with More Severe Clinical Outcomes than Oral Use

- Significant medical outcomes: Acute cardiac, CNS or neuropsychiatric events, pulmonary complications, psychological dependence

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Snorting (95% CI)</th>
<th>Injecting (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major effect (Life-threatening)</td>
<td>2.9 (1.9, 4.4)</td>
<td>7.5 (4.7, 12.8)</td>
</tr>
<tr>
<td>Death</td>
<td>9.9 (2.3, 105.1)</td>
<td>24.2 (5.3, 308.8)</td>
</tr>
</tbody>
</table>

Faraone, 2019.
Non-Oral Use of CNS-Active Drugs Delivers Faster, Greater Euphoric Effects than Oral Use

- Non-oral use circumvents first-pass metabolism and allows drug to enter brain more quickly\(^1\)-\(^3\)
  - Accelerates and intensifies effects
  - Highly-reinforcing effects may lead to compulsive use and addiction
- Progression of behaviors well documented in professional guidelines and psychopharmacology textbooks\(^1\)-\(^3\)

Potential Public Health Impact of AR19

- Targets for intervention: Older adolescents and young adults; IR amphetamines
- Important not to minimize prevalence of non-oral use; 45% of college students with ADHD snort
- Serious health outcomes from more dangerous, non-oral routes
- Non-orally using CNS active drugs puts users at higher risk for compulsive use and addiction
- Barriers to manipulations expected to reduce non-oral use, resulting in harm reduction
FDA Question 2

“Based on the information provided, including the intranasal study comparing this product to amphetamine sulfate, has the Applicant provided adequate evidence that the formulation of AR19 would deter IN use?”

Beatrice Setnik, PhD
Chief Scientific Officer
Altasciences
# Rationale for Manipulation-Resistant Formulations

## Barriers to Manipulation

1. **Difficult to crush into powder**
2. **Time consuming**
3. **Requires specialized or modified tools**

## Barriers to Reduce the Abuse Potential

- Lower Bioavailability
- Lower Drug Liking
- Lower High
- Lower Good Drug Effects
- Lower Overall Drug Liking
- Lower Willingness to Snort Again

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**Difficult or unable to manipulate**

**Less liked, reduced reinforcement for repeat use**
AR19 Extremely Difficult to Manipulate; Not Successful Without Modified Tool

* Small particles defined by FDA Guidance (2017) as <500 microns

Modified Tool 7
- Extensive exploratory studies to identify enhancements
- Multi-step, 20-minute procedure
- Additional equipment required
- AR19 not reduced to fine powder
AR19 Could Not Be Reduced to a Fine Powder

Evekeo Tool 3
~30-second process

AR19 Modified Tool 7
~20-minute process

Photographs taken at same magnification
HAP Studies Evaluate Pharmacological Effects of Drugs Prepared in Advance for Snorting

At-Risk Individual

Drugs Prepared in Advance by Pharmacy Staff

Lower Bioavailability
Lower Drug Liking
Lower High
Lower Good Drug Effects
Lower Overall Drug Liking
Lower Willingness to Snort Again

Barriers to Reduce the Abuse Potential

Barriers to Manipulation
Difficult to crush into powder
Time consuming
Requires specialized or modified tools

Unlikely that typical individual would perform

HAP = Human Abuse Potential
Interpreting HAP Study Findings

“The overall assessment of abuse potential should be based on the pattern of findings across all of the measures.”


- Sponsor analyses pre-specified, reflect all completers
- FDA analyses post-hoc, exclude data from several subjects
Lower $d$-Amphetamine Concentrations Through 12 Hours for AR19

Mean $d$-amphetamine Plasma Concentration (ng/mL) [95% CI]

- Intranasal Amphetamine API 40 mg (N=39)
- Intranasal AR19 40 mg (N=38)
Primary Endpoint: Drug Liking $E_{\text{max}}$

Q: At this moment, my liking for this drug is...

Difference = 9.2 (95% CI: 2.5-15.9)
Superiority with margin* $p = 0.026$

*Margin = 10%*(μ$_{\text{API}}$ – 50)
Lower Mean Drug Liking Over Time for AR19 Compared to Intranasal Amphetamine

Q: At this moment, my liking for this drug is…

- Strong Liking
- Neither Like nor Dislike
- Strong Disliking

Mean Drug Liking VAS Score

- Intranasal Amphetamine API 40 mg
- Intranasal AR19 40 mg
- Placebo

Time (Hours)
Two-Sided P-value

Drug High $E_{\text{max}}$  
Good Drug Effects $E_{\text{max}}$  
Overall Drug Liking $E_{\text{max}}$  
Take Drug Again $E_{\text{max}}$  

AR19 Liked Less

Mean Difference (AR19 vs Amphetamine API)  
[95% CI]

All significance tests conducted at two-sided 0.05 significance level.
AR19 Difficult to Manipulate and Less Rewarding to Snort

1. AR19: Barriers to Manipulation
   - Cannot be prepared with common household tools
   - Laboratory procedure:
     - Not intuitive
     - Modified tool
     - Specific accessories
     - Considerable time, effort
   - Not reduced to fine powder

2. AR19: Reduced Abuse Potential
   - Lower Bioavailability
   - Lower Drug Liking
   - Lower High
   - Lower Good Drug Effects
   - Lower Overall Drug Liking
   - Lower Willingness to Snort Again

Unlikely that typical individual would perform

Limit reinforcing effects even when barriers removed

Multiple barriers

Expected to reduce nasal use
FDA Question 3

“Based on the information provided, including the syringeability study, has the Applicant provided adequate evidence that the formulation of AR19 would deter IV use?”

Eric Kinzler, PhD
President and Founder
Pellucid Advantage, LLC
Study Director
DRUGSCAN
Goal of IV User Is To Inject a Dose That Will Achieve Their Desired Effect

- FDA: minimum reinforcing IV dose 10 mg dextroamphetamine\(^1\)
- IV amphetamine dose sought by users\(^2\)
  - Individuals initiating IV use: 20-40 mg
  - Experienced IV users: 100-300 mg, multiple injections/day

Background on Interpretation of Small Volume Extraction and Syringeability Results

- Incentive for injection depends on two factors
  - **Input**: time, effort, materials required
  - **Output**: API recovery (IV dose)

- Testing includes range of methods
  - Real-world techniques of IV users
  - Advanced methods requiring laboratory tools & techniques
Summary of Small Volume Extraction and Syringeability Studies

- Not feasible to prepare AR19 for injection using standard methods
- Most conditions yielded trace amphetamine or none
- 1-hour laboratory method with AR19 40 mg achieved 20 mg (50%)
  - Optimal manipulation, pretreatment, extraction at near boiling temperature with vigorous agitation, large needle, lab filter
- Multi-capsule extraction not feasible
- Dropping 40 mg strength would reduce maximum recovery possible

In vitro experiments suggest it is not feasible to prepare a highly rewarding amphetamine dose for injection with AR19
FDA Question 4

“Based on the information provided, has the Applicant adequately characterized the safety of AR19?”

John Dillberger, DVM, PhD
President
J. Dillberger, LLC
Fellow, International Academy of Toxicologic Pathology
All AR19 Excipients Safe for Oral Use

- Well-established safety profile for all ages when taken orally
- All excipients included in other FDA-approved medications
Excipients of FDA Concern Contained in Currently Approved Prescription Stimulants

- Concerta® (methylphenidate HCl) includes 7M PEO
  - No TMA, TTP, or MAHA observed in >85 million prescriptions\(^1,2\)
- Other FDA-approved prescription stimulants contain talc
  - Ritalin® (methylphenidate HCl)
  - Adderall® XR (amphetamine)
- AR19 talc safety margin ~2600 capsules snorted over 6 months
- IV talc toxicity typically associated with thousands of injections\(^3\)

7M PEO and talc do not pose unique risk for AR19

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TMA = thrombotic microangiopathy. TTP = thrombotic thrombocytopenic purpura. MAHA = microangiopathic hemolytic anemia.
## Summary of Nonclinical Safety Studies

### In Vitro
- No evidence of in vitro hemolysis of any AR19 extract
- Hemolysis findings with PEO 7M consistent with published reports

### In Vivo
- Injection of PEO 7M
  - TMA-like effects in pilot study
  - Lethality in pivotal study
- Injection with AR19 extract at human equivalent of 3 capsules/day well tolerated
FDA Question 5

“Discuss whether the benefits of AR19 outweigh the risks for the proposed indication.”

Anthony Rostain, MD, MA
Chair of Psychiatry and Behavioral Health
Cooper University Healthcare
Limitations and Potential Benefits of Manipulation-Resistant Formulations

**Limitations**
- Cannot prevent oral misuse or abuse
- Cannot be “abuse-proof” by any route

**Potential Benefits**
- Make manipulation difficult
- Reduce positive reinforcement
- Reduce harmful medical outcomes

Meaningful barriers would make non-oral use:
(1) more difficult and (2) less rewarding
## Clinical Relevance of AR19 Barriers for Non-Oral Use, By Route

<table>
<thead>
<tr>
<th>Route</th>
<th>More Difficult to Manipulate?</th>
<th>Less Rewarding?</th>
</tr>
</thead>
</table>
| **Snorting** | - Required modified tool, additional accessories, extensive time and effort  
- Could not be reduced to fine powder  | - Reduced nasal bioavailability  
- Lower liking, high, good effects, and willingness to take again  |
| **Smoking** | - Required modified tool, additional accessories, extensive time and effort  
- Could not be reduced to fine powder  | - Very low recoveries of volatilized amphetamine  
- Not feasible route  |
| **Injecting** | - All typical IV methods failed  
- Advanced techniques required for injectable amphetamine  | - Low IV dose required multiple steps, lab equipment, substantial time and effort  
- Multiple-dose extraction to increase IV dose failed  |

AR19 physical and chemical barriers make snorting, smoking, and injecting (1) more difficult **and** (2) less rewarding.
AR19 Not Expected to Lead to Increase in Illicit Stimulant Use

- No consistent evidence between ADF opioids and increase in illicit drug use\(^1\)
- Stimulants and opioids fundamentally different
  - Opioids may cause physical dependence; stimulants do not
  - Different motivations for nonmedical use
- AR19 would be treatment option
  - Not reformulation of entire market
- At-risk population comfortable non-orally using prescription stimulants because they are perceived as safe\(^2\)
  - Initiation of “street drugs” unlikely because they are perceived as dangerous

AR19 Has Positive Benefit-Risk Profile for Patients and for Public Health

Taking Medication as Intended

Mitigating Potential for Misuse and Abuse

Reduce harms by imposing meaningful barriers to non-oral use

Discourage progression down a path of dangerous drug-taking behaviors
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Back-up Slides shown
NMU of Rx Stimulants and Rx Opioids More Common in Individuals with ADHD

- NMU of Rx stimulants and opioids was greater among those with ADHD

- Psychiatric comorbidities were more common among individuals with use of Rx stimulants nonmedically
  - e.g., ADHD, depression, anxiety

ADHD = attention deficit hyperactivity disorder
NMU = nonmedical use
Rx = prescription

Source: FDA-generated figure. Nonmedical Use of Prescription Medications among the General Population (AR19.MA004), an Applicant-submitted online survey of the general U.S. population aged 18 to 49 years conducted by the internet panel company YouGov
Figure 8: Primary Endpoint – Drug Liking Emax (AR19.001)

Q: At this moment, my liking for this drug is...

Difference = 9.2 (95% CI: 2.5-15.9)
Superiority with margin* p = 0.026

Mean Drug Liking
E_{max}
[95% CI]

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Mean Liking</th>
<th>Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intranasal Amphetamine API 40 mg</td>
<td>78</td>
<td>7.8</td>
</tr>
<tr>
<td>Intranasal AR19 40 mg</td>
<td>69</td>
<td>6.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

* Margin = 10% x (μ_{API} - 50).
AR19 Extracts Containing High Molecular Weight PEO are not Injectable

- Extracts 3, 4, 5, 7 have similar consistency
- Solidification when cooling to body temperature (37°C)

From left to right: Extracts 3, 4, 5, 7
Pre-Specified Statistical Analyses for Drug Liking $E_{\text{max}}$

<table>
<thead>
<tr>
<th>Drug Liking $E_{\text{max}}$ Analysis</th>
<th>Treatment Difference (Lower 97.5% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation Test</td>
<td>24.0 (15.0, infinity)</td>
<td>0.04</td>
</tr>
<tr>
<td>Superiority Test with 10% margin</td>
<td>9.2 (2.5, infinity)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

IN AR19 Liked More  IN AR19 Liked Less

Margin = 10% of absolute IN API drug effect

Drug Liking $E_{\text{max}}$ of API = 78
78 - 50 (neutral) = 28
10% * 28 = 2.8