

**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

Introduction

Evan Scullin, MD

Vice President, Medical Affairs
Arbor Pharmaceuticals



Arbor and FDA Agree About Scope of Problem

1. Prescription stimulant nonmedical use (NMU) is public health concern
2. Patients with ADHD at greater risk for NMU and substance use disorder (SUD)
3. Most NMU of prescription stimulants occurs in adolescents and young adults
4. Non-oral NMU leads to more severe medical outcomes than oral NMU

Manipulation-Resistant Formulations Are a Harm Reduction Strategy for Non-Oral Use

Impact of New Formulation	Rationale
<i>Cannot</i> address oral nonmedical use	<ul style="list-style-type: none"> ▪ Must work as a medication when taken by intended route of administration
<i>Cannot</i> address addiction	<ul style="list-style-type: none"> ▪ Potential for addiction at level of API, not formulation
<i>Cannot</i> address polysubstance use	<ul style="list-style-type: none"> ▪ No formulation can prevent individual from using other drugs or substances

***Can* reduce harm by impeding nonmedical use of that specific product by non-oral routes**

AR19: First IR ADHD Rx Stimulant with Physical, Chemical Barriers Designed to Resist Manipulations Required for Snorting, Smoking, Injecting

- Form of FDA-approved amphetamine sulfate
- Capsules contain pellets ~1.2 mm in diameter
- 505(b)(2) application using Evekeo® as reference drug



Arbor Agrees 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

Target Population to Gain Most Benefit: Older Adolescents, Young Adults with ADHD

- This patient population has highest prevalence of misuse and abuse of prescription stimulants
- Part of harm reduction strategy with this vulnerable population
 - Manipulation difficult, non-oral use less rewarding
- Education programs for physicians, patients, families
 - Focus on oral and non-oral misuse and abuse

Attributes of AR19 that Resist Administration by Non-Oral Routes

Design Attribute	Feature
Pellets-in-capsule formulation	<ul style="list-style-type: none"> ▪ Difficult to handle for physical manipulation ▪ Increased surface area of pellets maximizes gelling properties
Hard, non-brittle pellets	<ul style="list-style-type: none"> ▪ Provides resistance to particle size reduction
Manipulation-resistant excipients	<ul style="list-style-type: none"> ▪ Gels in small volume, making injection difficult ▪ Reduces intranasal bioavailability

Overview of Development Program

Biopharmaceutics

AR19-002

Comparative bioavailability study of AR19 and Evekeo

AR19-003

Food-effect bioavailability study of AR19

AR19-005

PK dose proportionality study of AR19

Efficacy and Safety

AR19-004

Randomized, double-blind, placebo-controlled study of AR19 in adults

- AR19 safe and effective for use in adult and pediatric patients with ADHD
 - All excipients included in other FDA-approved oral medications

Manipulation Resistance

AR19-001

Randomized, double-blind, active- and placebo-controlled intranasal HAP study

In Vitro

Manipulation studies for snorting, smoking and injection

Nonclinical IV Safety

In vitro hemolytic potential and In vivo nonclinical IV safety studies

Broader Public Health Issues and Arbor Recommendations

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
- Non-oral stimulant use is often misuse, not abuse

MISUSE

- *Using medication in way other than intended to get therapeutic effect*

ABUSE

- *Using medication for non-therapeutic purpose, like to get high*

Arbor Will Use Enhanced Pharmacovigilance to Monitor Misuse and Abuse Patterns, Safety Signals

Data Source	Description
Pharmacovigilance Monitoring	Submit all reported adverse events to FDA
Medical Literature Monitoring	Sentinel occurrences
Internet Monitoring	Sentinel occurrences
News Media Monitoring	Sentinel occurrences
Proactive Signal Trending Reports	Individual case review and signal trending
National Poison Data System	Calls to US poison control centers

- Allow Arbor and FDA to take prompt action to address any safety signals
- Post-marketing plan submitted to FDA, to evaluate real world impact

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

Agenda

Public Health Need for Manipulation-Resistant Prescription Stimulants

Stephen Faraone, PhD

Distinguished Professor of Psychiatry
SUNY Upstate Medical University

In Vitro Manipulation-Resistant Studies

Eric Kinzler, PhD

President and Founder
Pellucid Advantage, LLC

Intranasal Human Abuse Potential (HAP) Study

Beatrice Setnik, PhD

Chief Scientific Officer
Altasciences

Nonclinical Safety Studies

John Dillberger, DVM, PhD

President
J. Dillberger, LLC

Clinical Relevance and Benefit-Risk Assessment

Anthony Rostain, MD, MA

Chair of Psychiatry and Behavioral Health
Cooper University Healthcare

Topics for Consideration Based on FDA Briefing Document

Topic	Points to Consider
Stimulants are Not Opioids	<ul style="list-style-type: none"> Different pharmacology, patterns of NMU, and patients
Impact of a Single Product	<ul style="list-style-type: none"> Many physicians expressed desire for treatment option with barriers to manipulation Importance of improving medications for public health
Difficulty of Manipulation	<ul style="list-style-type: none"> Extensive equipment, time, and effort required for manipulation Not permitted opportunity to share confidential methods
Interpretation of HAP Study	<ul style="list-style-type: none"> FDA review based on post-hoc analyses, removing outliers Arbor will show prespecified analyses, no outliers removed

Public Health Need for Manipulation-Resistant Prescription Stimulants

Stephen Faraone, PhD

Vice Chair for Research, Department of Psychiatry

Distinguished Professor of Psychiatry

Distinguished Professor of Neuroscience & Physiology

SUNY Upstate Medical University



Prescription Stimulants Shown to Reduce Poor Outcomes Associated with ADHD

- Disruptive behaviors
- Poor social skills, impaired family relationships
- Lower quality of life and self-esteem
- Underachievement in school and work
- Delinquency and criminality
- Substance use disorders
- Accidents and injuries
- Suicide

Faraone, 2015. Cortese, 2020.

Misuse and Abuse of Prescription Stimulants Is a Serious Public Health Issue

- 5.1 million individuals ≥ 12 years misused or abused prescription stimulants¹
 - 370,000 adolescents (12-17)
 - 2.2 million young adults (18-25)
 - 2.5 million adults (26+)
- Conservative estimates of non-oral users of prescription stimulants²
 - Snorting: 550,000
 - Smoking: 50,000
 - Injecting: 50,000

1. National Survey on Drug Use and Health, 2018. 2. Faraone, 2019.

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

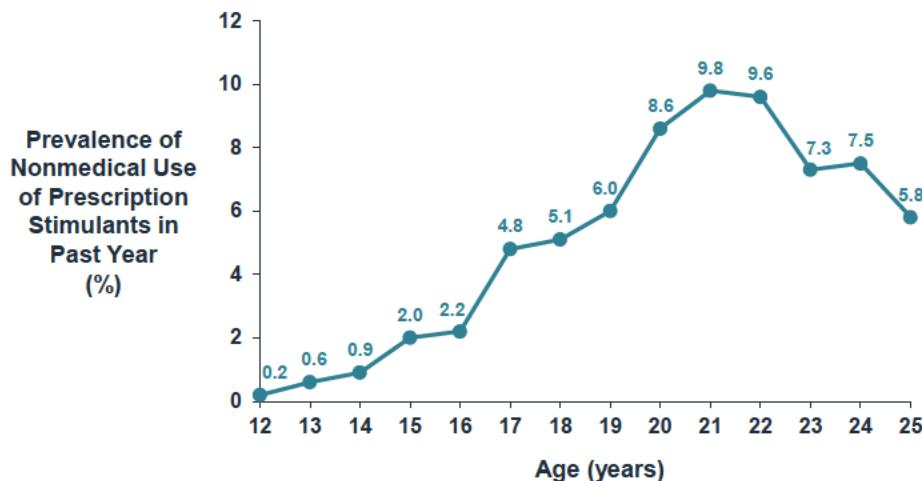
- Non-oral use circumvents first-pass metabolism and allows drug to enter brain more quickly¹⁻³
 - Accelerates and intensifies effects
 - Highly-reinforcing effects may lead to compulsive use and addiction
- Progression of behaviors well documented in professional guidelines and psychopharmacology textbooks¹⁻³

1. Lile, 2011. 2. Stahl, 2013. 3. Harstad, 2014.

Epidemiology of Misuse and Abuse of Prescription Stimulants, by Route

CO-21

Peak Prevalence of Stimulant Misuse and Abuse Occurs in Early Adulthood



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

CO-22

High Rate of Non-Oral Use of Prescription Stimulants

	Prevalence (%) Among Prescription Stimulant Users		
	Adolescents ¹ (196 users)	College Students ² (641 users)	Adults ³ (1,284 users)
Any non-oral Use	27 (14%) <i>1 in 7</i>	135 (21%) <i>1 in 5</i>	207 (16%) <i>1 in 6</i>
Snorting	19 (10%)	120 (19%)	188 (15%)
Smoking	8 (4%)	33 (5%)	29 (2%)
Injecting	2 (1%)	21 (3%)	27 (2%)

1. SNAPS, 2019 (N=1,777). 2. Inflexxion – College Study, 2019 (N=1,842). 3. Inflexxion – General Population Study, 2019 (N=12,000).

Epidemiology of Non-Oral Use Identifies Target Populations and Medications

- 45% of college students prescribed a stimulant for ADHD reported snorting it¹
 - Half did so to achieve faster effect on ADHD symptoms¹
- Non-oral prescription stimulant use more common with
 - IR than ER¹⁻⁴
 - Amphetamine than methylphenidate⁵

1. Inflexxion – College Study, 2019 (N=1,842). 2. Inflexxion – General Population Study, 2019 (N=12,000). 3. Bright, 2008. 4. Cassidy, 2015. 5. Harstad, 2014

Snorting Prescription Stimulants Twice as Prevalent as Opioids Among College Students

Prevalence of Nonmedical Use by Route of Administration in College Students (N=1,842) ¹		
	Snorting	Injecting
Prescription Stimulants	120 (6.5%)	21 (1.1%)
Prescription Opioids	64 (3.5%)	25 (1.4%)

1. Inflexxion – College Study, 2019.

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

- Higher risk of significant medical outcomes for non-oral vs oral routes
 - Acute cardiac events, acute CNS events, neuropsychiatric events, pulmonary complications, psychological dependence

Odds Ratio (95% CI) vs Unintentional Oral Use of Prescription Amphetamine		
Adverse Event	Snorting	Injecting
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)

Faraone, 2019.

Unmet Need for Manipulation-Resistant ADHD Stimulants to Reduce Harms of Non-Oral Routes

- No immediate-release ADHD stimulants available to resist manipulation for non-oral use
- Important not to minimize prevalence of snorting, smoking, injecting
- 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
- Targets for intervention: Older adolescents and young adults; IR amphetamines
- Barriers to manipulations expected to reduce non-oral use, resulting in a public health benefit

In Vitro Manipulation-Resistant Studies

Eric Kinzler, PhD

President and Founder
Pellucid Advantage, LLC
Study Director
DRUGSCAN



Overview of Manipulation-Resistant Studies

- Evaluated physical and chemical properties of AR19 to resist manipulation for snorting, smoking, injecting
 - Common household tools and methods
 - Laboratory tools and methods to test to extreme
- Designs informed by FDA Guidance on ADF opioids¹ and real-world techniques
 - Additional conditions evaluated as requested by FDA
- Evekeo, Adderall®, or amphetamine sulfate API comparators

1. FDA. Abuse-Deterrent Opioids – Evaluation and Labeling: Guidance for Industry, 2015.

Snorting Route

Current Prescription Stimulants Easy to Crush and Snort

NO current IR prescription stimulants offer barriers to snorting



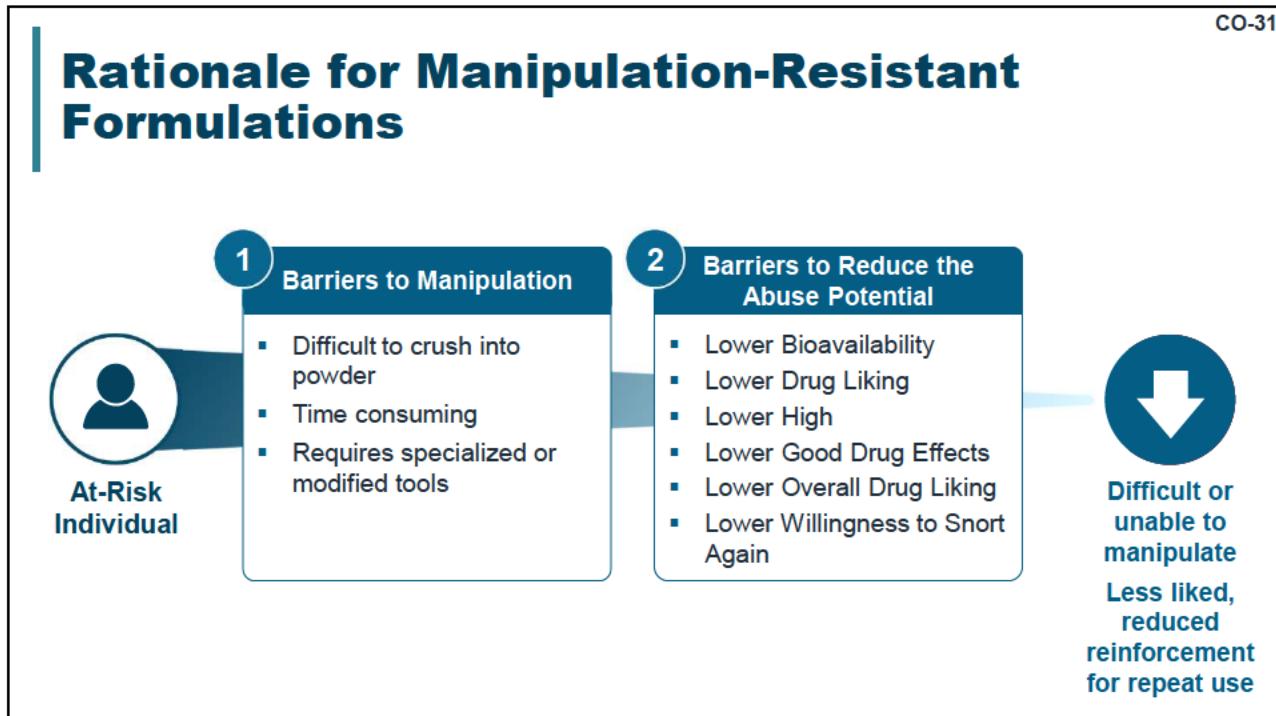
At-Risk Individual

Crush/Snort Tablet

Positive Reinforcement for Repeat Use
Faster Effects



Rationale for Manipulation-Resistant Formulations



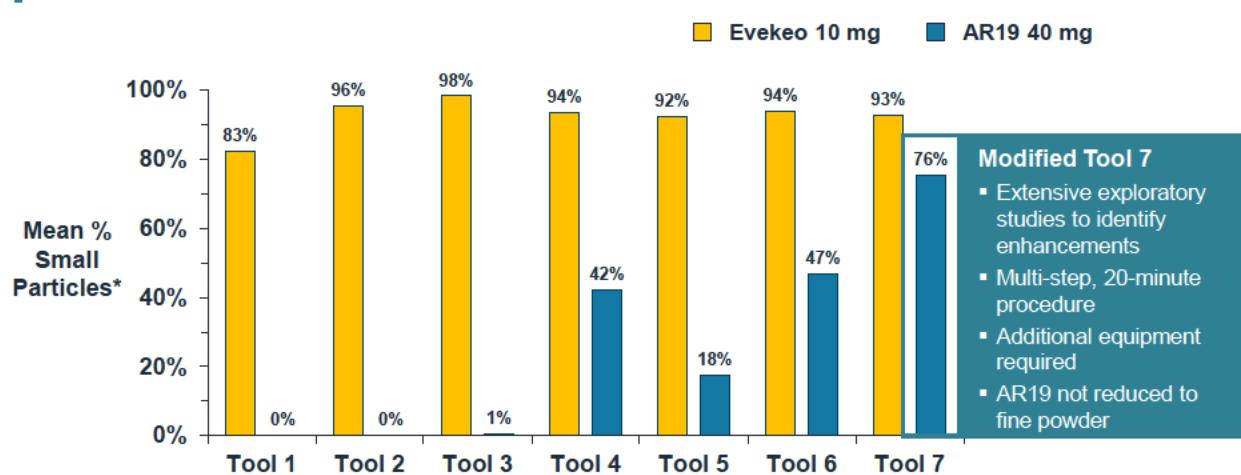
Rationale and Methods for Particle Size Reduction Studies

- Particle size reduction is first step in transforming a drug into an abusable form for snorting, smoking, or injecting
- Tested full range of common household tools
- Evaluated all potential mechanisms of physical manipulation
- Performed all in vitro testing three times per condition to ensure reproducibility

Battery of Representative Tools for Particle Size Reduction

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

AR19 Extremely Difficult to Manipulate; Not Successful Without Modified Tool



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

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

AR19.001: Intranasal Human Abuse Potential (HAP) Study

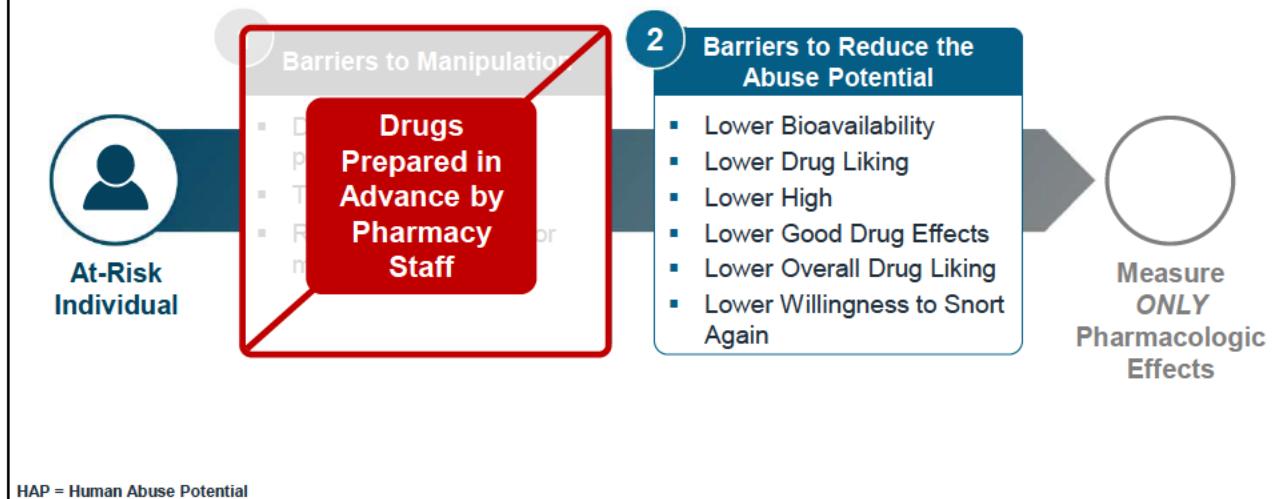
Beatrice Setnik, PhD

Chief Scientific Officer

Altasciences



HAP Studies Evaluate Pharmacological Effects of Drugs Prepared in Advance for Snorting



Intranasal HAP Study Participants (N=37 Completers)

- Non-dependent, recreational stimulant users
- Recent intranasal experience in last 12 weeks
- 18-55 years
- Able to discriminate amphetamine API 40 mg from placebo

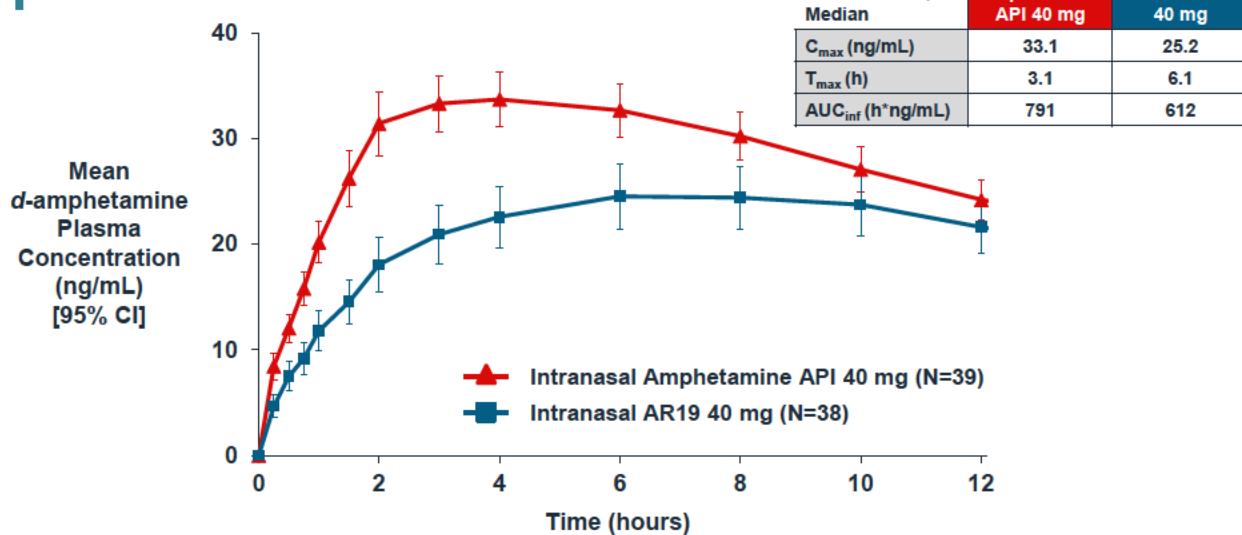
AR19 Not Manipulated by Subjects; Prepared by Trained Pharmacists

- Due to difficulty of optimal manipulation with Modified Tool 7
 - DRUGSCAN sent laboratory scientist to clinical site to teach pharmacists how to manipulate AR19
 - Pharmacists evaluated for ability to manipulate AR19 consistently prior to study

Pharmacokinetics (PK)

CO-41

Lower *d*-Amphetamine Concentrations Through 12 Hours for AR19



CO-42

Pharmacodynamics (PD)

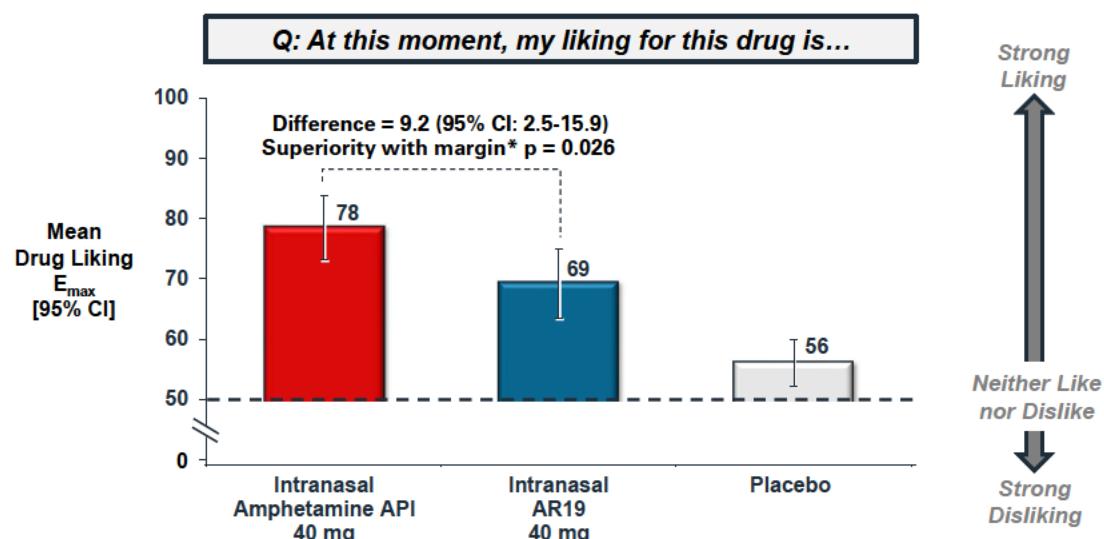
"The overall assessment of abuse potential should be based on the pattern of findings across all of the measures."

FDA Guidance Document (2015)

Important Differences Between Sponsor and FDA Statistical Analyses of PD Endpoints

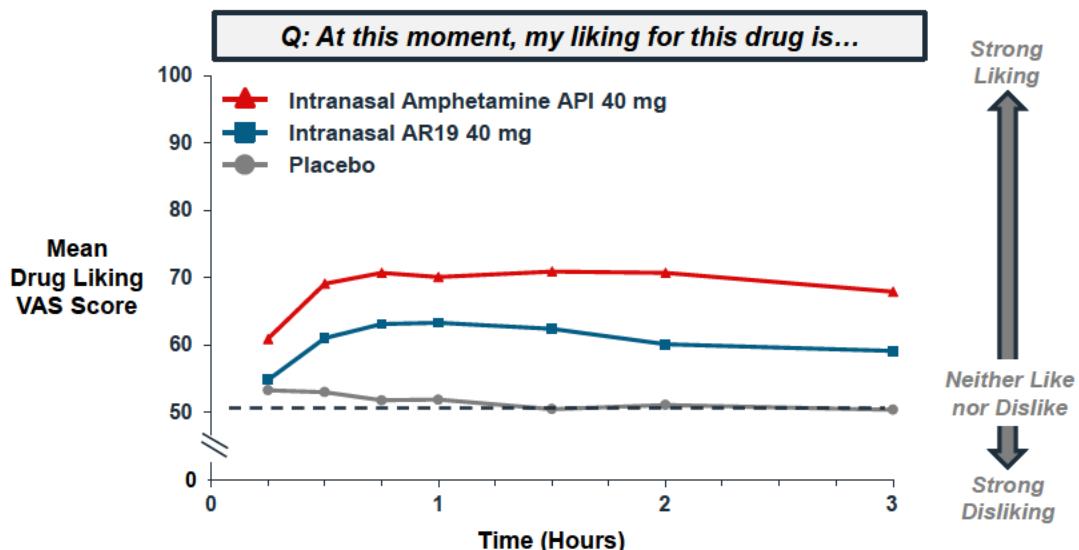
- FDA's review based on statistical analyses
 - Post-hoc
 - Conducted in modified population, not prespecified
- Sponsor's review based on statistical analyses
 - Prespecified in study protocol
 - All completers representing totality of data
 - No outliers removed from any analyses to be presented

Primary Endpoint: Drug Liking E_{max}



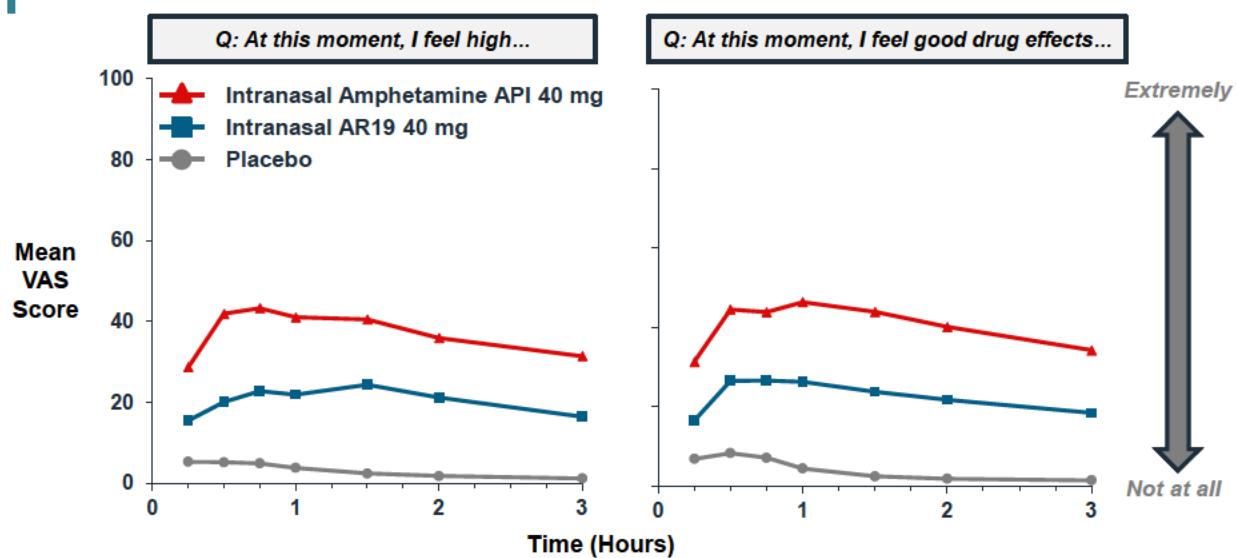
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Lower Mean Drug Liking Over Time for AR19 Compared to Intranasal Amphetamine

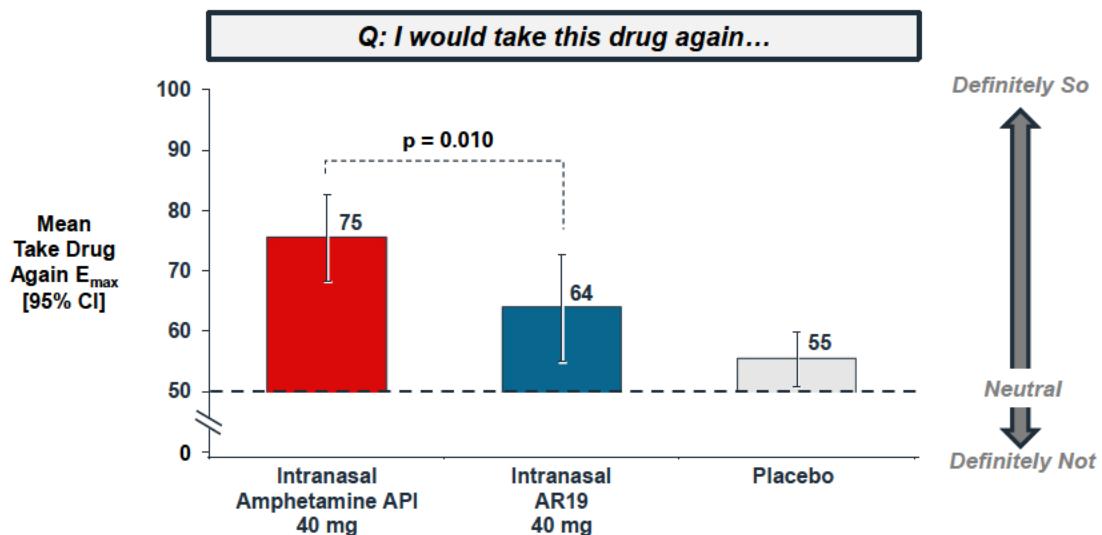


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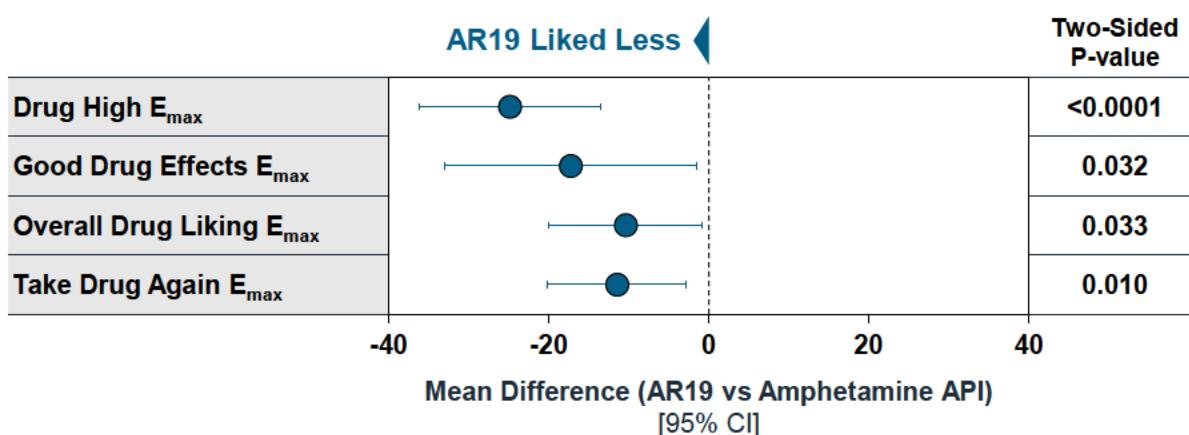
Lower Mean High and Good Effects Over Time for AR19 Compared to Intranasal Amphetamine



Significantly Lower Willingness to Snort AR19 Again than Amphetamine API

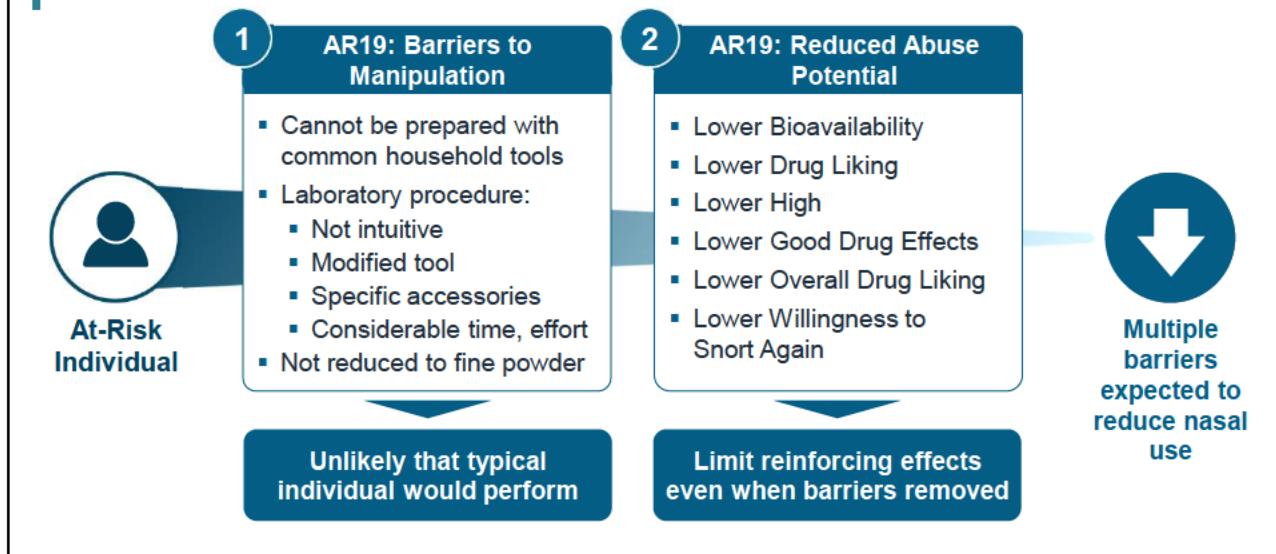


Totality of Data: Consistent Results Across Secondary Pharmacodynamic Endpoints with AR19



All significance tests conducted at two-sided 0.05 significance level.

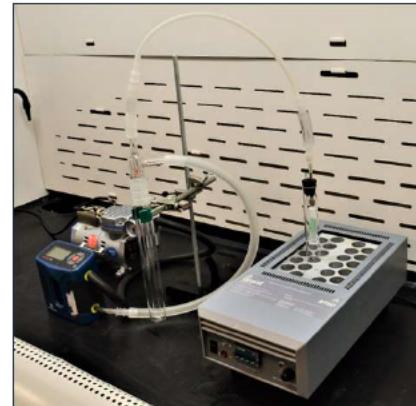
AR19 Difficult to Manipulate and Less Rewarding to Snort



Smoking Simulation Studies

Smoking Not a Feasible Route of Administration for AR19

- Simulated smoking apparatus with optimized times, temperatures
- Up to 58% of amphetamine API volatilized
- ≤11% of amphetamine volatilized from Evekeo or AR19 at any temperature
- Experiments with an open flame (real-world) resulted in <5% volatilized API from AR19



Small Volume Extraction and Syringeability Studies

Background on Interpretation of Small Volume Extraction and Syringeability Results

- ADHD stimulants must be bioavailable when taken as intended
- Incentive for injection depends on two factors
 - Input: time, effort, materials required
 - Output: API recovery
- Testing includes range of methods
 - Real-world techniques of IV users
 - Advanced methods requiring laboratory tools & techniques

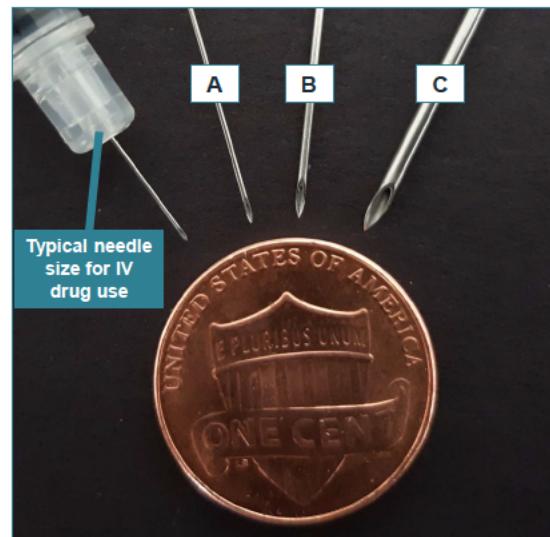
Goal of IV User Is To Inject Dose That Will Achieve Desired Effect

- Dose (mg) is more important than percent extraction for IV user
- FDA: minimum reinforcing IV dose 10 mg dextroamphetamine¹
- IV amphetamine dose sought by users²
 - Individuals initiating IV use: 20-40 mg
 - Experienced IV users: 100-300 mg, multiple injections/day
- Will show syringeable recovery for
 1. Percentage of API
 2. Dose in mg

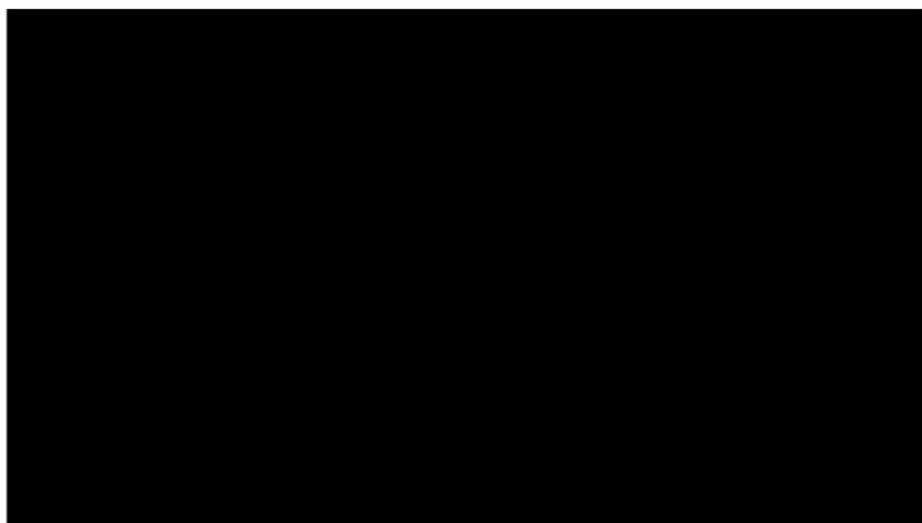
1. Fischman, 1976. 2. Barceloux, 2012.

Wide Range of Testing Captured Standard and Advanced Laboratory Methods

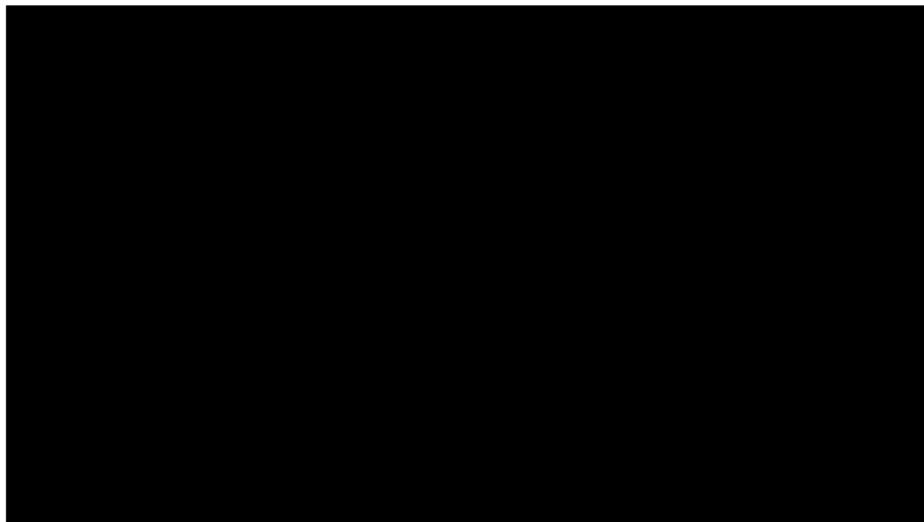
- IV users typically inject 0.5 to 1.0 mL with 1 cc insulin syringes
 - AR19 testing included several-fold larger volumes and needles
- Simple filters not feasible with AR19
 - Laboratory filter needed



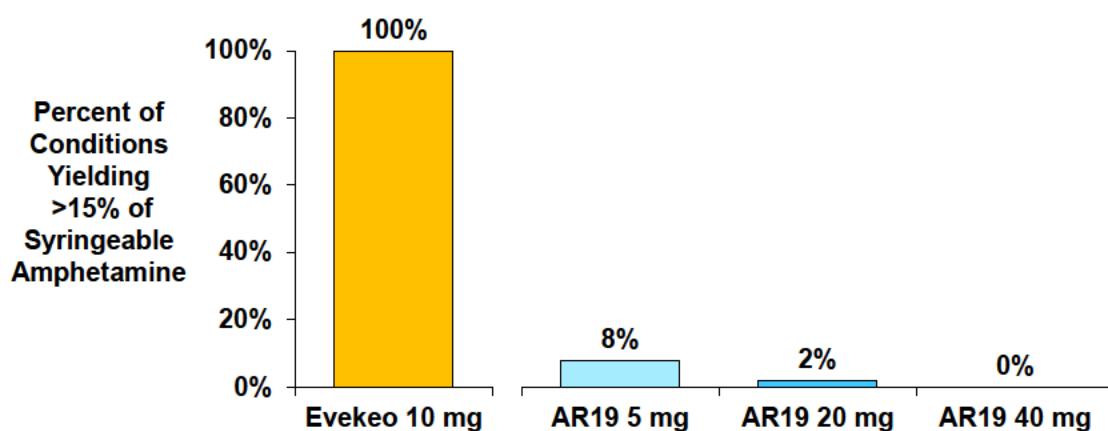
Example of Typical IV Preparation (Evekeo)



Typical IV Preparation Conditions Unsuccessful with AR19



AR19 Could Not Be Prepared for Injection with Small Volume and Needle Gauge A



N=48 sets of conditions

Advanced, Laboratory Conditions Provided Low Yields of Syringeable Amphetamine

Advanced Conditions	Number of Combinations of Conditions	Syringeable Amphetamine from AR19 40 mg	
		Median (Range) mg	Median (Range) %
Level 1	96	0 mg (0-11.8)	0% (0-29.6)
Level 2	96	0 mg (0-16.8)	0% (0-42.0)
Level 3	96	3.5 mg (0-17.3)	8.7% (0-43.4)
Level 4	106	3.8 mg (0-20.1)	9.5% (0-50.2)

~60 Minutes to Perform

Physical Manipulation

Pretreatment

Long Extraction Time

Elevated Temperature

Larger Needles

Important Considerations for PEO in AR19

- PEO 7M associated with IV safety issues with Opana® ER¹⁻³
 - Thrombotic microangiopathy (TMA)
- Opana® ER formulated primarily to prevent snorting
- AR19 formulated to prevent snorting, smoking, and injecting
 - Development program designed to assess benefits and risks by non-oral routes

1. Hunt, 2017. 2. CDC, 2013. 3. CDC, 2015.
PEO 7M = Polyethylene Oxide 7 Million Dalton

Important Differences Between AR19 and Opana® ER in Pharmacology and Formulation

- Differences between AR19 and Opana® ER impact relative IV abuse liability and risks for unintended consequences
 - **Formulation**
 - AR19 pellets increase surface area exposed to small volume of injectable solvent relative to a tablet
 - Additional gelling agent included in AR19 to increase resistance to injection
- **Pharmacology**
- Relative bioavailability of amphetamine vs oxymorphone by oral vs IV route

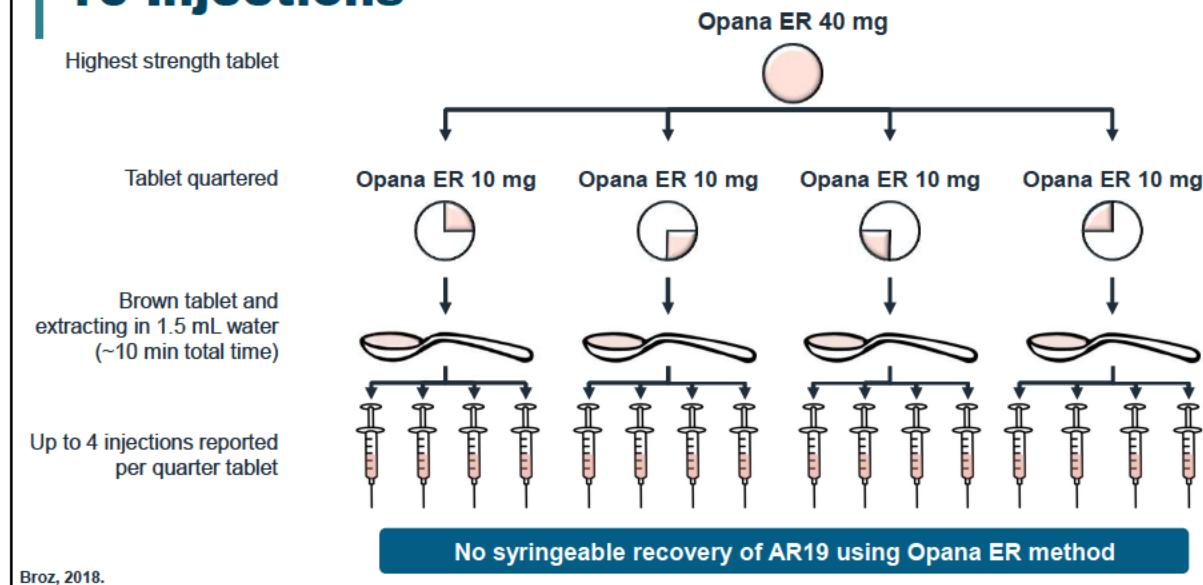
Higher Relative Bioavailability IV than Orally for Oxymorphone than Amphetamine

Characteristic	Amphetamine	Oxymorphone
Oral bioavailability (BA)	75% ^{1,2}	10% ³
Calculation (100% IV BA ÷ oral BA)	100% ÷ 75%	100% ÷ 10%
Relative bioavailability IV : oral	1.33x greater	10x greater

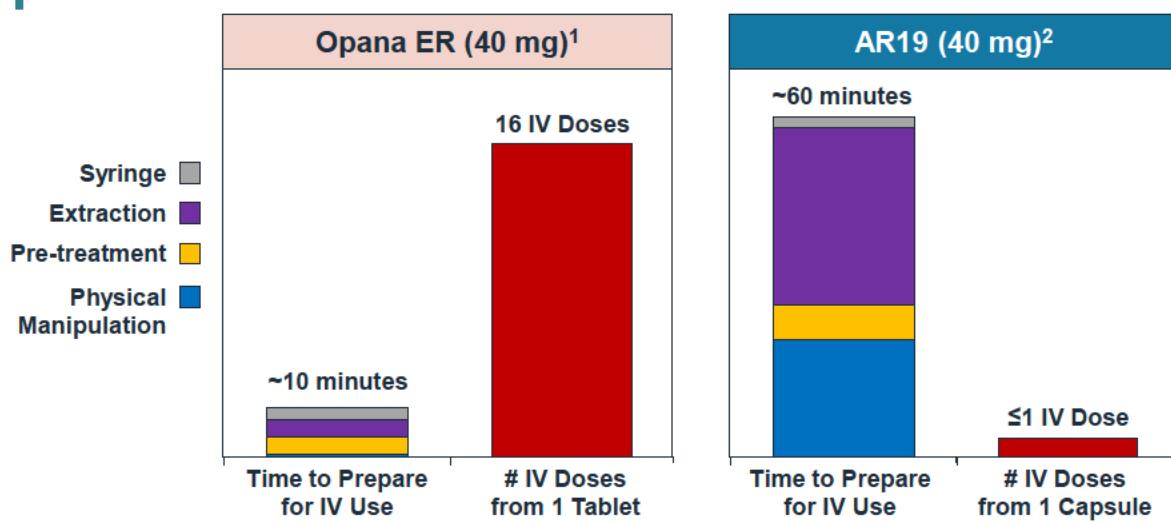
- Substantial inherent motivation for IV use
- Explains how a single Opana ER tablet could make multiple IV doses

1. Markowitz, 2017. 2. Adderall® Prescribing Information. 3. Sloan, 2005.

Single Opana® ER Tablet Provided Up to 16 Injections

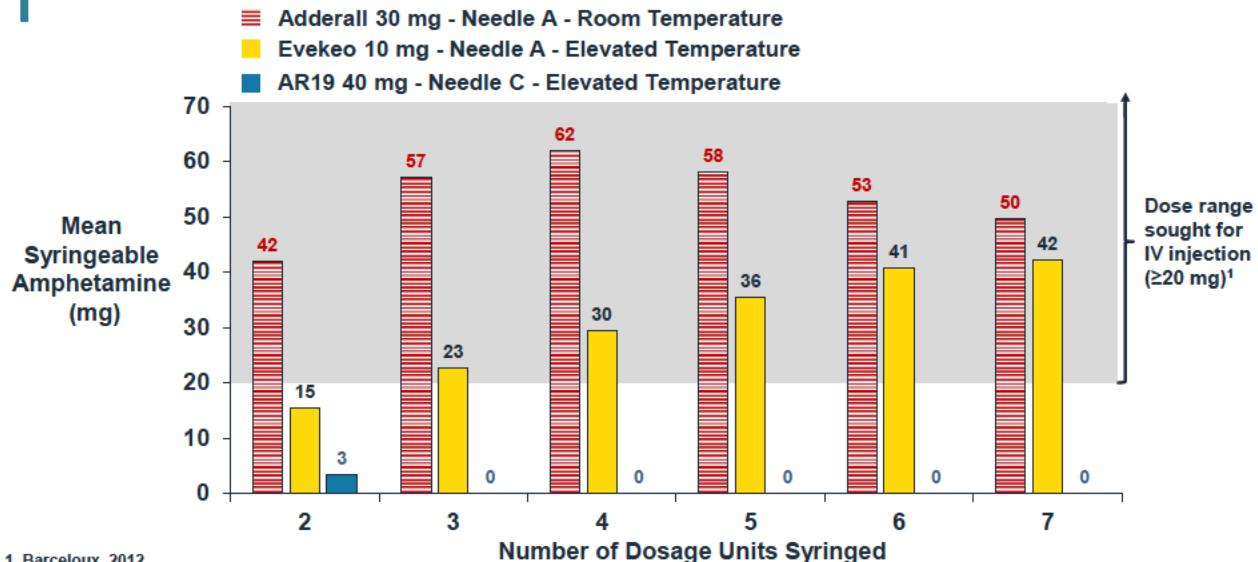


No Incentive for Additional Time and Effort Needed to Prepare AR19 for Injection



1. Broz, 2018. 2. Method providing highest yield of syringeable amphetamine.

Not Feasible to Prepare Multiple AR19 Capsules for Injection



AR19 Demonstrated Resistance to Manipulation for Non-Oral Routes

Snorting

- Cannot be successfully prepared with common household tools
- Optimal manipulation required modified tool, accessories and extensive effort
- Lower abuse potential than amphetamine sulfate

Smoking

- Could not be successfully volatilized
- Not a feasible route

Injecting

- Not possible to prepare using typical IV methods
- Low IV dose required
 - Multiple steps
 - Lab equipment
 - Substantial time and effort

Nonclinical Safety Studies

John Dillberger, DVM, PhD

President

J. Dillberger, LLC

Fellow, International Academy of
Toxicologic Pathology



Rationale for Excipient Safety Studies

- TMA observed with repeated IV use of Opana® ER¹
 - Likely due to changes in blood flow in small blood vessels from injection of high molecular weight PEO²
 - Led to hemolysis
- Investigated two questions for manipulated AR19 extracts
 1. Potential to cause TMA
 2. Potential to cause other adverse effects

TMA = thrombotic microangiopathy

1. CDC, 2013. 2. Hunt, 2017.

Differential Risks Associated with PEO-Containing Extracts

- FDA¹: differential risk could theoretically be based on
 - Differences in manufacturing processes, curing methods, heat, additives, etc.
 - Differences in molecular weight of PEO
 - Differences in methods to prepare products for IV abuse
 - Differential patterns of abuse of drug substances and/or drug products

1. FDA, 2018.

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 injections³

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

1. FAERS Database, 2020. 2. IQVIA NPS Audit, 2000-2020. 3. Matrosovich, 2017.

TMA = thrombotic microangiopathy. TTP = thrombotic thrombocytopenic purpura. MAHA = microangiopathic hemolytic anemia.

Arbor Conducted Several In Vitro and In Vivo IV Excipient Safety Studies

- In vitro hemolytic potential study
 - 9 representative AR19 extracts
- Characterization of PEO content of syringeable AR19 extracts
- Single- and 7-day, repeat-dose IV safety studies in rabbits

Important Distinction Between Syringeability and Injectability

Syringeability

Can be drawn up into a syringe at any temperature

Injectability

Can be drawn up and expelled from syringe at body temperature

- Small volume extraction and syringeability
- In vitro hemolytic potential
- In vivo IV safety

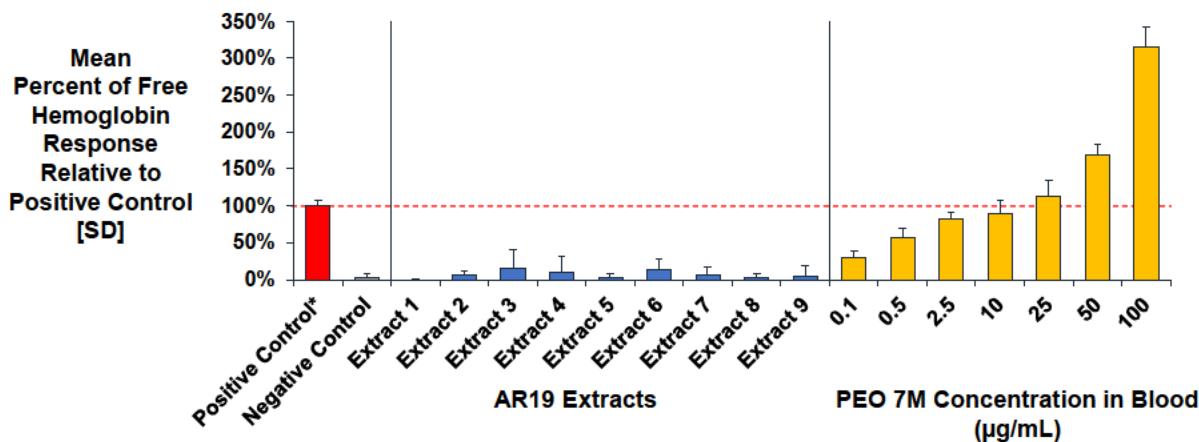
In Vitro Hemolytic Potential Study

- Syringe pump to pass human blood with different test materials through small needle to simulate blood flow through arterioles
- Concentration of free hemoglobin measured as indicator of hemolysis

In Vitro Study Assessed Hemolytic Potential of AR19 Extracts

- **Negative Control** (water)
- **Positive Control** (PEO 8M 40 µg/mL)
- **7M PEO Samples** (fixed concentrations 0.1-100 µg/mL)
- **AR19 Extracts 1-9** (representative AR19 extracts)
 - With and without physical manipulation
 - With and without pretreatment
 - Extractions with different solvents, volumes, temperatures, times, and with and without agitation

No Evidence of Meaningful Hemolytic Potential for AR19 Extracts



* Positive Control PEO 8M at blood concentration of 40 $\mu\text{g/mL}$.

AR19 Extract 8 Selected for Evaluation for In Vivo Safety Study

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	1.74	1.25	4.9
2	Yes	Yes	6.61	BLQ	11.2
3	Yes	No	21.78	13.54	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	2.43	1.58	12.1
8	Yes	Yes	20.64	BLQ	20.1
9	Yes	Yes	9.12	BLQ	11.1

NA = Mass of extract too small to be analyzed

BLQ = Below the limit of quantification

Pretreatment Required to Prepare AR19 Extract 8 for Injection Degrades High Molecular Weight PEO

PEO Molecular Weight Content	PEO Content of 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%	

No high molecular weight PEO in injectable AR19 extract

In Vivo IV Safety Studies

Pivotal 7-day IV Safety Study in New Zealand White Rabbits

Treatment	Once-daily IV Dose (mg/kg)	Infusion Duration (min)	Terminal Necropsy		Recovery Necropsy	
			Male	Female	Male	Female
AR19 Extract 8	1 human equiv. dose*	2	4	4	3	3
AR19 Extract 8	2 human equiv. doses*	2	4	4	3	3
AR19 Extract 8	3 human equiv. doses*	2	4	4	3	3
Saline	0	2	4	4	3	3
PEO 7M	0.35	2	4	4	3	3

*Equivalent dose 1 AR19 40 mg capsule with Extract 8 = 28.3 mg/kg

Adequacy of Pivotal IV Safety Study

- FDA: study limited in terms of duration and number of injections
- Study designed to exaggerate real-world situation
 - ~1 hour to prepare single extract of single capsule
 - Maximum dose that can be achieved for injection is low
 - Repeat IV use highly unlikely
- Design refined based on FDA suggestions
- TMA produced with fewer animals and shorter treatment durations in prior studies^{1,2}

PEO 7M Positive Control Produced Adverse Effects

- After first dose of PEO 7M, all animals died or euthanized due to moribund conditions
 - Postmortem evaluation: clotted blood in atria and ventricles
- Pilot studies found small difference between dose that would produce no effect, TMA, and death
- TMA-like effects produced in pilot study with PEO 7M
 - Rabbits confirmed as suitable species

No Evidence of Toxicity Related to AR19 Extract 8 In-life or Postmortem

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

Interpretability of In Vivo Safety Studies

Pilot Study

Hypotheses Generated

- Small groups of animals
- Intended to identify adverse findings that could be drug-related

Pivotal Study

Hypotheses Confirmed or Refuted

- Larger groups of animals
- Intended to determine causality
 - If finding reproduced: drug-related
 - If finding not reproduced: chance

Summary of Nonclinical Safety Studies

- PEO 7M and talc contained in other FDA-approved stimulants
- Talc toxicity unlikely
- PEO toxicity unlikely
 - No evidence of in vitro hemolysis of any AR19 extract
 - Injection with AR19 extract at human equivalent of 3 capsules/day for 7 days well tolerated
 - Possibly because PEO <1M due to pretreatment

Clinical Relevance and Benefit-Risk Assessment

Anthony Rostain, MD, MA

Chair of Psychiatry and Behavioral Health
Cooper University Healthcare



Misuse and Abuse of Prescription Stimulants is a Serious Public Health Issue

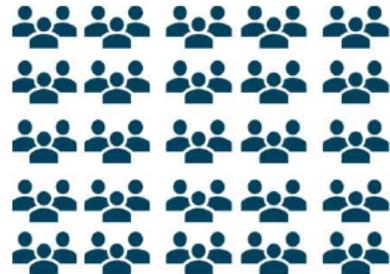
- Alarming rates of non-oral use, particularly among young people
- Using non-orally gives more rapid, profound effect
 - Can result in hospitalizations, severe medical outcomes, greater risk for substance use disorder
- All IR prescription stimulants on market today easy to manipulate for snorting, smoking, and injecting

AR19 Benefit-Risk Assessment for Individual Patients and Public Health

Taking Medication
as Intended



Mitigating Potential for
Misuse and Abuse



Benefit-Risk for Patients Taking Medication As Intended

AR19 Safe and Effective for Treatment of ADHD in Children and Adults

- Prescription stimulants meaningfully improve the lives of patients with ADHD
 - Increasing achievement in school, work
 - Reducing risks for NMU, SUD, accidents, premature death
- AR19 therapeutically interchangeable with other IR amphetamines

Benefit-Risk for Public Health

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

Route	More Difficult to Manipulate?	Less Rewarding?
Snorting	✓	<ul style="list-style-type: none"> ▪ Required modified tool, additional accessories, extensive time and effort ▪ Could not be reduced to fine powder
Smoking	✓	<ul style="list-style-type: none"> ▪ Required modified tool, additional accessories, extensive time and effort ▪ Could not be reduced to fine powder
Injecting	✓	<ul style="list-style-type: none"> ▪ All typical IV methods failed ▪ Advanced techniques required for injectable amphetamine

AR19 physical and chemical barriers make snorting, smoking, and injecting
 (1) more difficult and (2) less rewarding

Evaluation of Potential Public Health Risks

Potential Risks/Concerns	AR19 Evaluation
Limited public health impact from limited access	<ul style="list-style-type: none"> ▪ Priced consistent with marketed ADHD prescription stimulants
False sense of security to prescribers	<ul style="list-style-type: none"> ▪ “Manipulation-resistant” rather than “abuse-deterrent” ▪ Physician education plan
May push individuals to riskier routes of administration of AR19	<ul style="list-style-type: none"> ▪ Substantial barriers to all non-oral routes, including injection
Excipient safety by IV route	<ul style="list-style-type: none"> ▪ No evidence of IV toxicity in vitro or in vivo
Unforeseen unintended consequences	<ul style="list-style-type: none"> ▪ Risk mitigation: enhanced pharmacovigilance and post-market studies

AR19 Not Expected to Lead to Increase in Illicit Stimulant Use

- No consistent evidence between ADF opioids and increase in illicit drug use¹
- Stimulants and opioids fundamentally different
 - Different pharmacodynamic effects
 - 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 safe²
 - Initiation of “street drugs” unlikely because they are perceived as dangerous

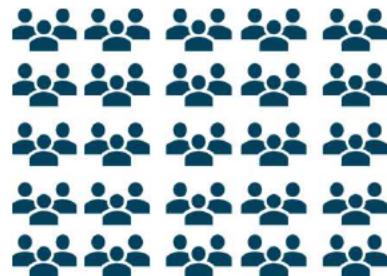
1. Compton, 2016. 2. DeSantis, 2010.

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

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