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

Target Population

- 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[1]

Target Medications

- Non-oral prescription stimulant use more common with
  - IR than ER[1-4]
  - Amphetamine than methylphenidate[5]

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

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%)** ***1 in 7***	**135 (21%)** ***1 in 5***	**207 (16%)** ***1 in 6***
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).

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

	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.

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]

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

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

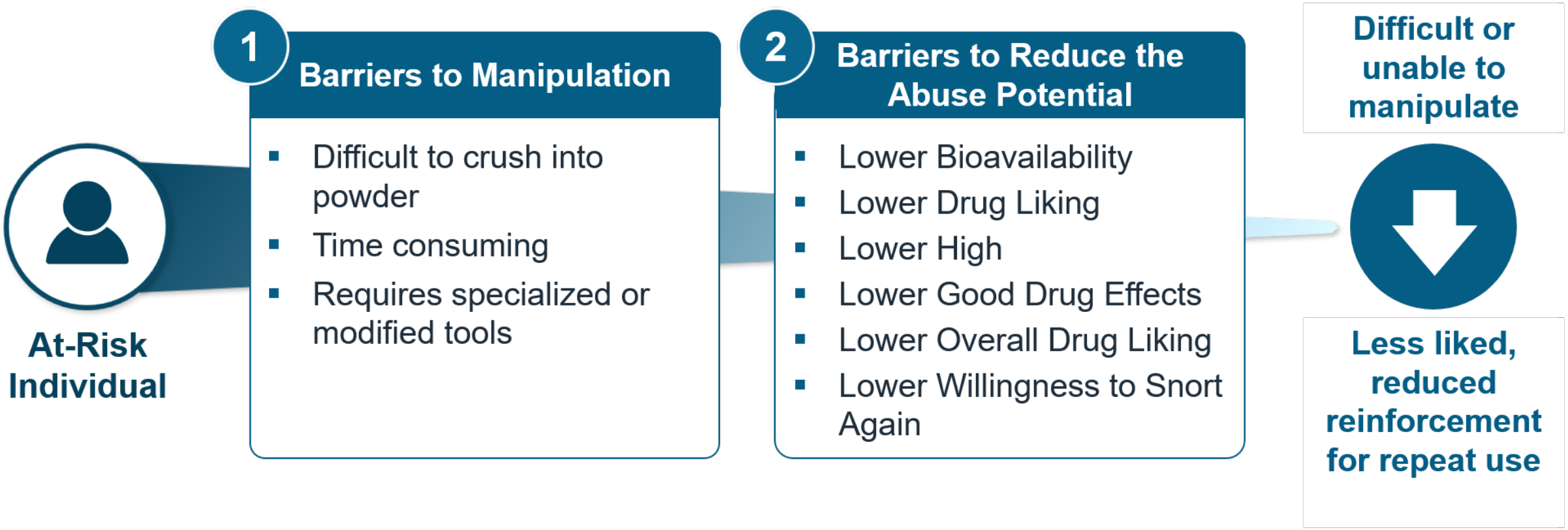
“Based on the information provided, including the intranasal study comparing this product to amphetamine sulfate, has the Applicant provided adequate evidence that the formulation of AR19 would deter IN use?”

Beatrice Setnik, PhD

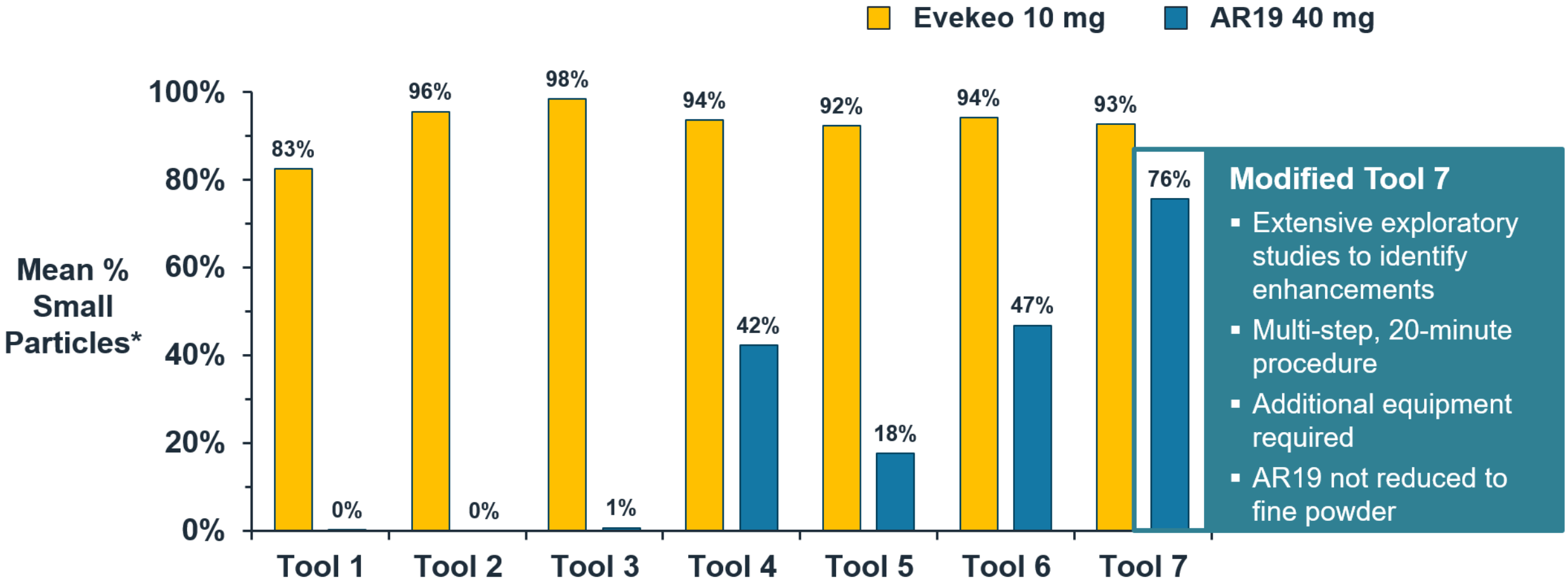
Chief Scientific Officer

Altasciences

Rationale for Manipulation-Resistant Formulations



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

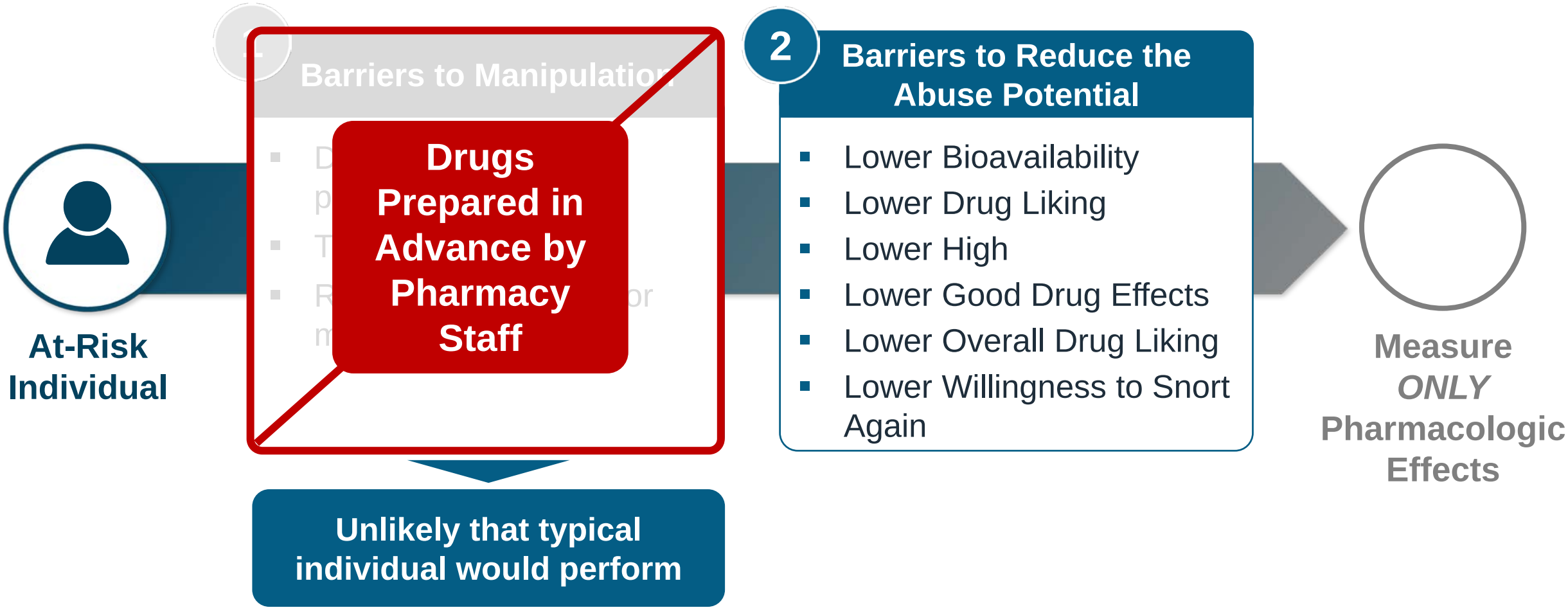
~30-second process

AR19
Modified Tool 7

~20-minute process

Photographs taken at same magnification

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



HAP = Human Abuse Potential

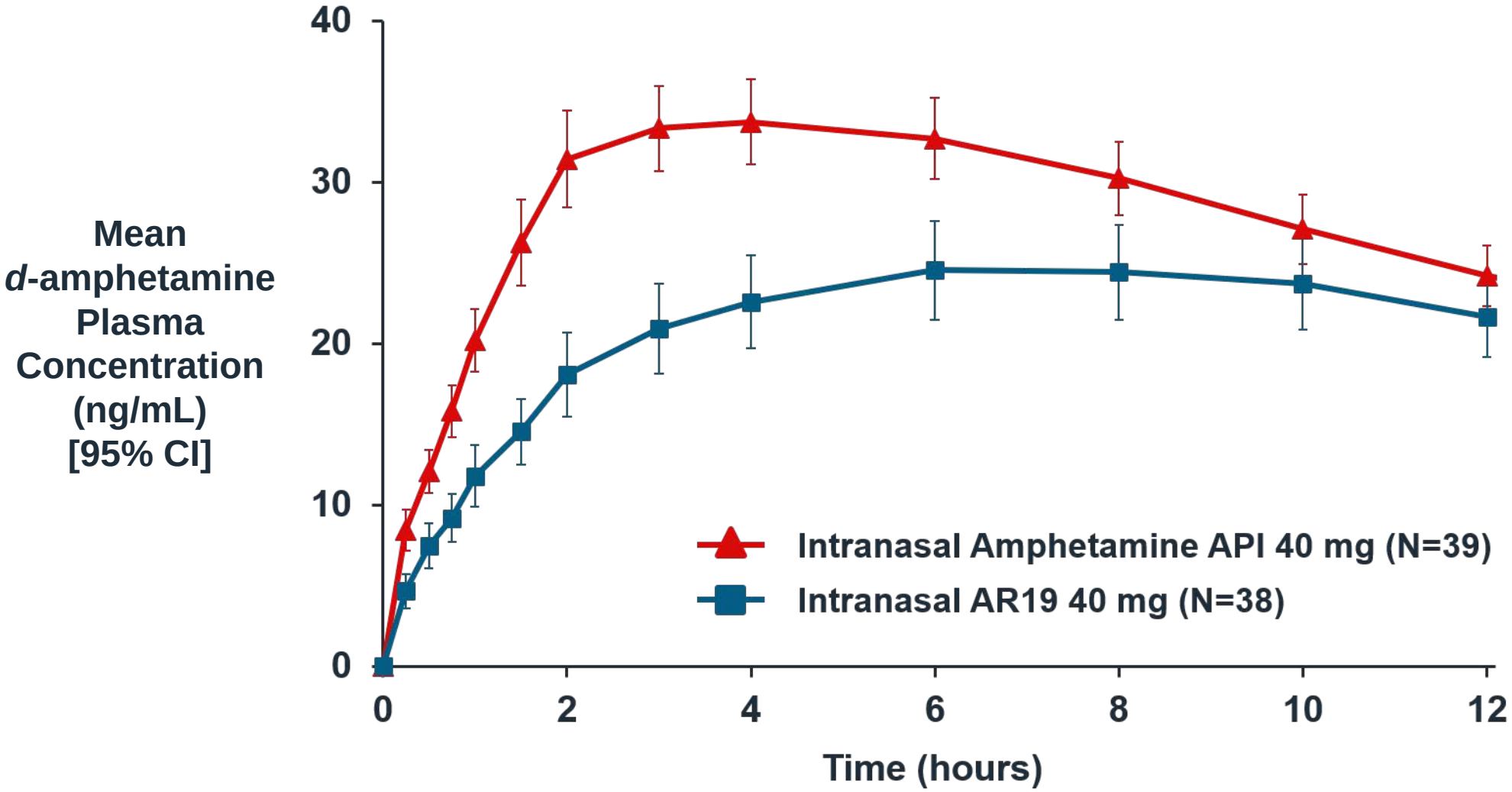
Interpreting HAP Study Findings

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

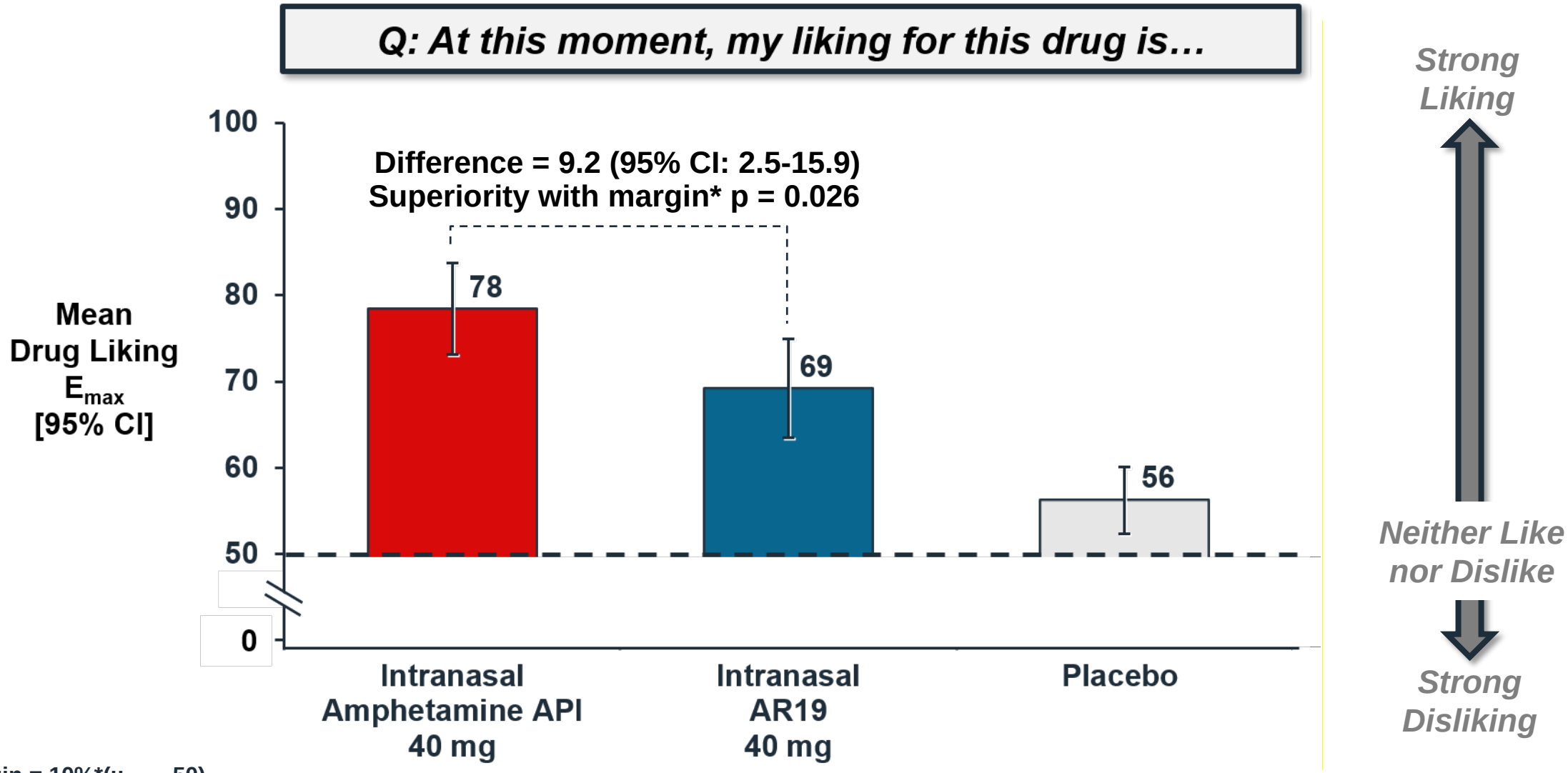
FDA Guidance Document (2015)

- 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

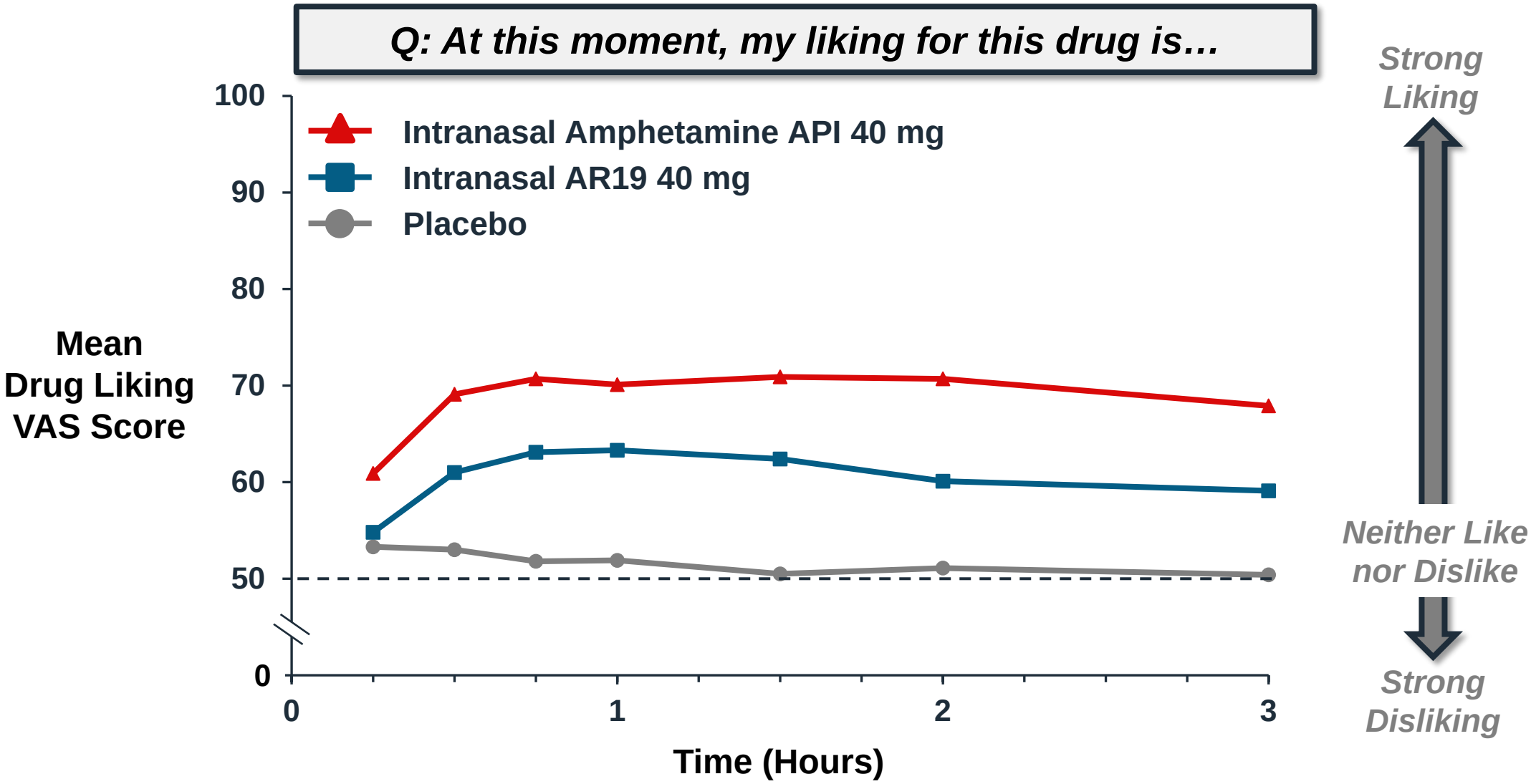


Primary Endpoint: Drug Liking E_{max}

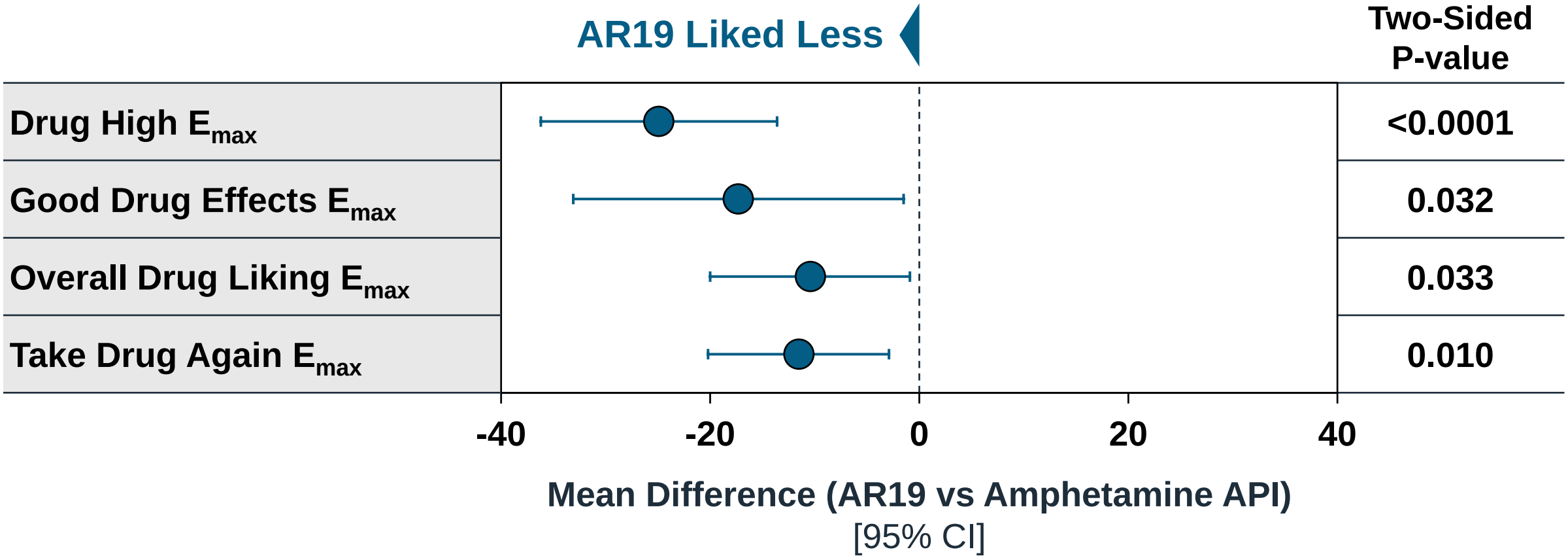


Margin = 10%(μ_{API} – 50)

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

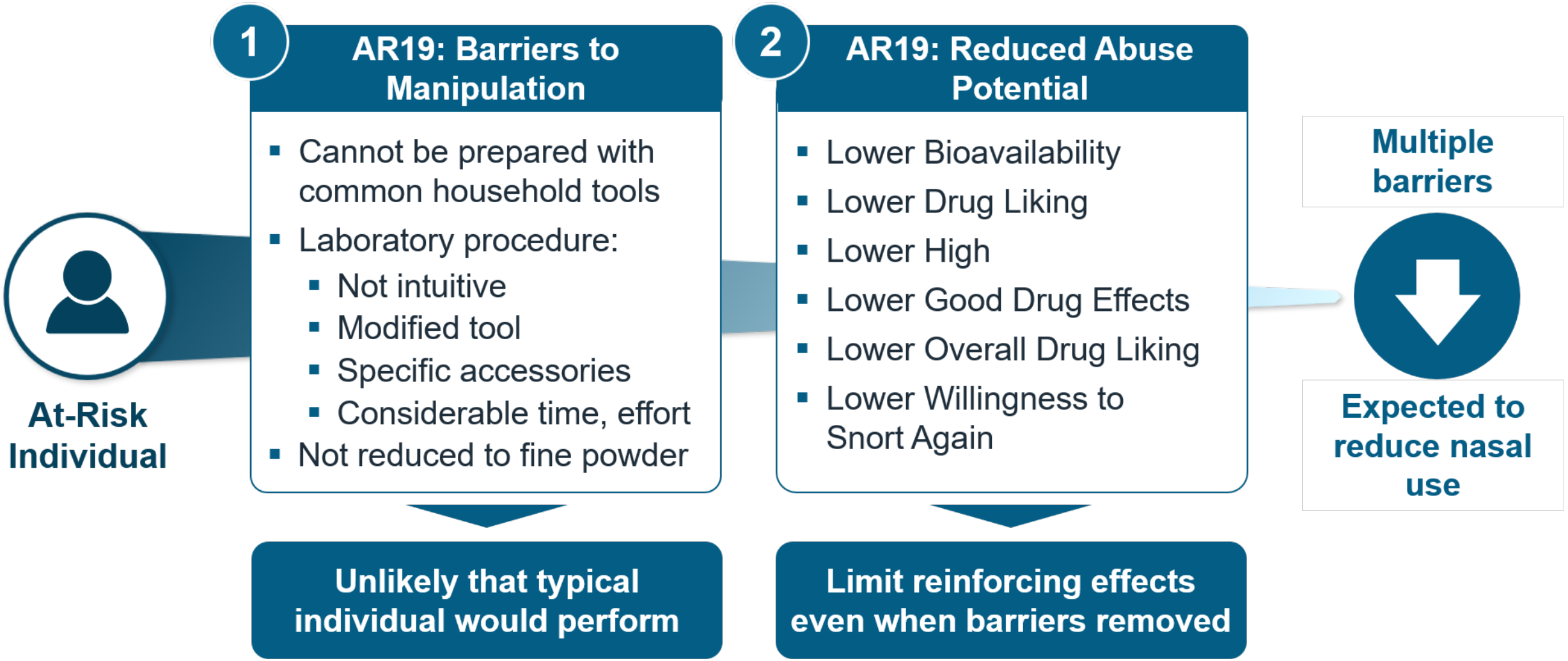


Totality of Data: Consistent Results Across Secondary Pharmacodynamic Endpoints with AR19



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

AR19 Difficult to Manipulate and Less Rewarding to Snort



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

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

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

1. FAERS Database, 2020. 2. IQVIA NPS Audit, 2000-2020. 3. Matrosovich, 2017.
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 <u>and</u> (2) less rewarding

Clinical Relevance of AR19 Barriers for Non-Oral Use, By Route

Route	More Difficult to Manipulate?	Less Rewarding?
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

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

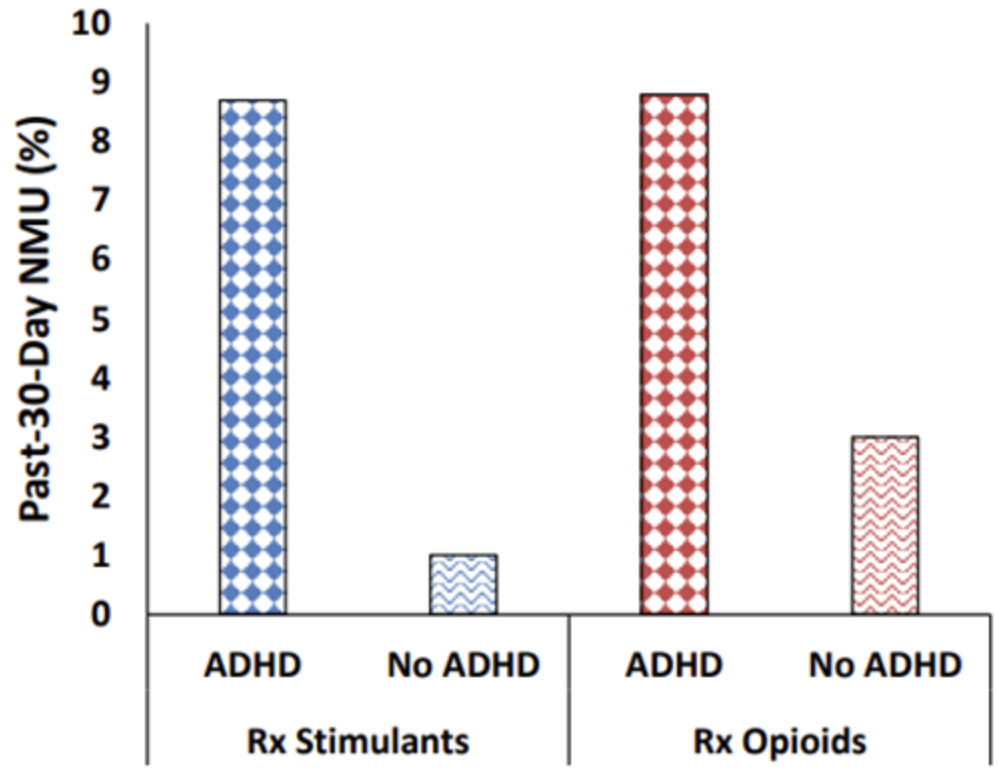
Arbor Pharmaceuticals

Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

Back-up Slides shown

NMU of Rx Stimulants and Rx Opioids More Common in Individuals with ADHD

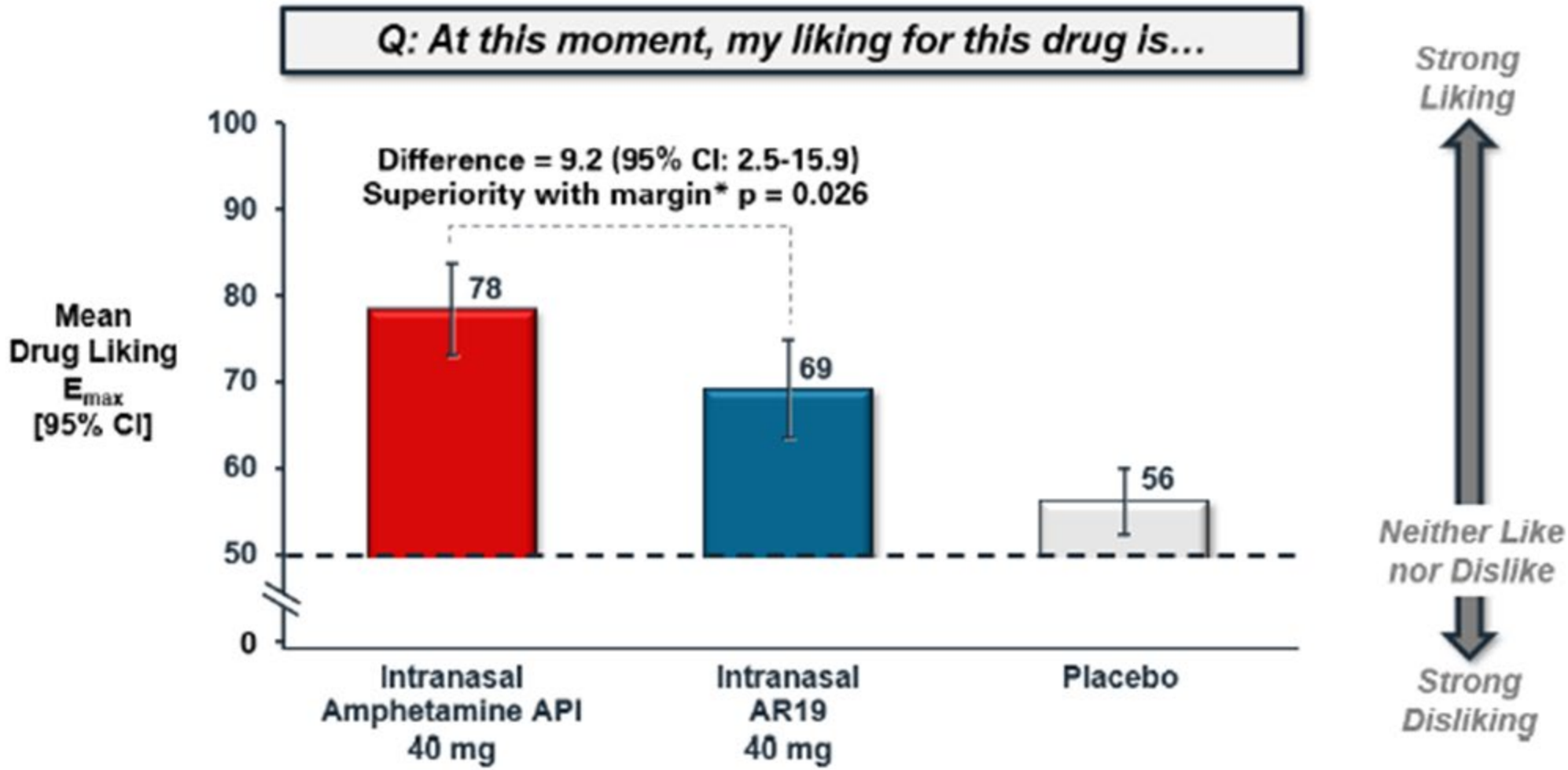
- NMU of Rx stimulants and opioids was greater among those with ADHD
- Psychiatric comorbidities were more common among individuals with use of Rx stimulants nonmedically
  - e.g., ADHD, depression, anxiety



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)



* Margin = 10% × (μ_{API} – 50).

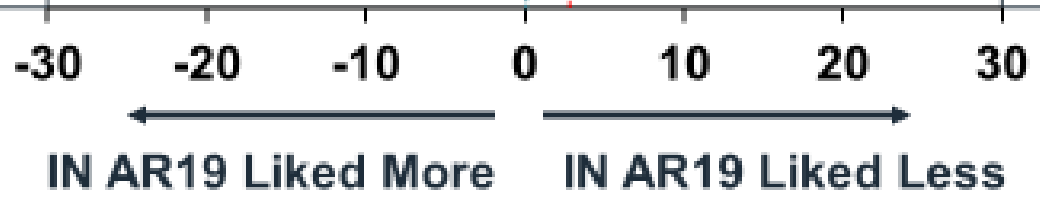
AR19 Extracts Containing High Molecular Weight PEO are not Injectable

- 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_{max}

Drug Liking E_{max} Analysis	Treatment Difference (Lower 97.5% CI)	P-value
Validation Test	**24.0 (15.0, infinity)**	**0.04** (one-sided)
Superiority Test with 10% margin	**9.2 (2.5, infinity)**	**0.026** (one-sided)



Margin = 10% of absolute IN API drug effect

Drug Liking E_{max} of API = 78

78 – 50 (neutral) = 28

10% * 28 = **2.8**