# Advances in Treatments for Methamphetamine Use Disorder

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# Disclosure Information

## Advances in Treatments for Methamphetamine Use Disorder

Friday, April 1, 2022, 10:30 – 11:30 AM

Madhukar H. Trivedi, M.D.

Dr. Trivedi is or has been an advisor/consultant and received fees from: Acadia Pharmaceuticals, Inc., Alkermes Inc, Axsome Therapeutics, Biogen MA Inc., Circular Genomics Inc., GH Research Limited, Heading Health Inc., Janssen, Legion Health Inc, Merck Sharp & Dohme Corp., Mind Medicine (MindMed) Inc., Neurocrine Biosciences Inc, Noema Pharma AG, Orexo US Inc, Otsuka American Pharmaceutical Inc., Otsuka Canada Pharmaceutical Inc, Otsuka Pharmaceutical Development & Commercialization Inc., SAGE Therapeutics, Takeda Pharmaceutical Company Ltd., and Titan Pharmaceuticals Inc.

# Learning Objectives

- Demonstrate an increased knowledge of pharmacotherapy options for the management of methamphetamine use disorder.
- Discover the mechanisms and utility of brain stimulation techniques including transcranial magnetic stimulation in the management of methamphetamine use disorder.
- Articulate the role of glutamatergic dysregulation in methamphetamine use disorder, and potential therapeutic options to address this problem.

# Methamphetamine Crisis

- Methamphetamine use disorder is persistently rising in the United States
- Methamphetamine is a leading cause of overdose deaths in the Midwest and West
- Despite this crisis being identified as a public health goal, there is no FDA-approved medication for methamphetamine use disorder

Hedegaard et al., 2017; Ellis et al., 2018; Ashok et al., 2017; Soares and Pereira, 2019

# ADAPT Pilot Results

## Assessments of Medication Adherence and Quality of Life (TEA) Functional Outcomes

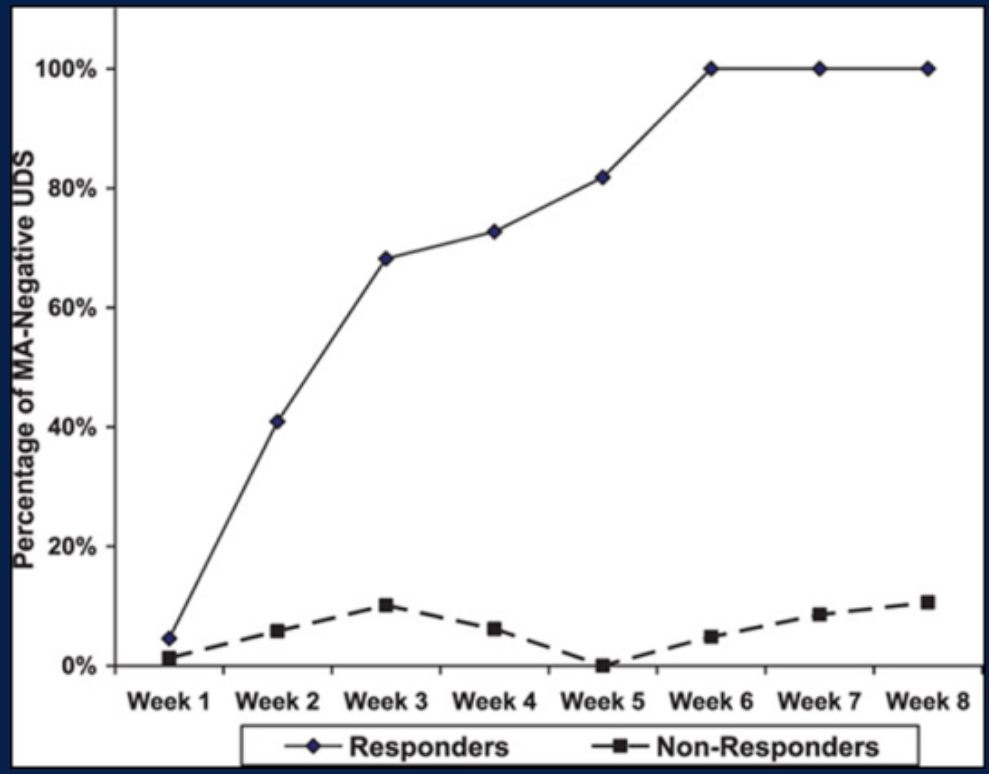
| Adherence Measure | Responder (n = 11) | Nonresponder (n = 38) | Total (N = 49) |
|---|---|---|---|
| % of dispensed BRP doses taken based on participant self-report | 97.6% | 92.1% | 93.6% |
| % of dispensed BRP doses* taken as confirmed by dosing video or in-person observation | 95.2% | 83.4% | 86.6% |
| % Participants who received XR-NTX injection #2 | 100% | 78.9% | 83.7% |
| % Participants with detectable BRP blood levels (>0.50 ng/mL) at weeks 5 and 8† | 100% | 69.7% | 76.5% |
| % Participants with detectable hydroxybupropion blood levels (>1.00 ng/mL) at weeks 5 and 8† | 100% | 75.0% | 80.6% |

**Functional Outcomes: Quality of Life (TEA)**

| TEA Item(s) | Responder (n = 11) | Nonresponder (n = 31)‡ | P |
|---|---|---|---|
| Baseline assessments | | | |
| Total score | 16.4 (7.2) | 17.7 (7.1) | 0.54 |
| Substance abuse | 3.5 (1.9) | 3.8 (2.7) | 0.87 |
| Health | 3.7 (2.1) | 4.5 (2.2) | 0.28 |
| Lifestyle/personal responsibility | 3.5 (2.5) | 4.6 (2.2) | 0.10 |
| Community | 5.5 (2.3) | 4.8 (2.4) | 0.26 |
| Week 9 assessments | | | |
| Total TEA score | 36.9 (3.5) | 23.7 (9.1) | 0.00002 |
| Substance abuse | 9.7 (0.65) | 5.4 (2.8) | 0.004 |
| Health | 9.4 (1.0) | 6.0 (2.6) | 0.0002 |
| Lifestyle/personal responsibility | 8.8 (1.2) | 5.7 (2.6) | 0.0007 |
| Community | 9.0 (1.7) | 6.6 (2.4) | 0.002 |

*Dose dispensed is adjusted as a result of dose reductions and early medication discontinuation.
†There were 11 responders for weeks 5 and 8; nonresponders in weeks 5 and 8 were 34 and 31, respectively.
‡Seven participants in the nonresponder group missed the week 9 visit. *P* values were obtained from Wilcoxon test.
BRP, bupropion; TEA, Treatment Effectiveness Assessment; XR-NTX, extended-release injectable naltrexone.

## Percentage methamphetamine-negative urine drug screen by responder status by study week




Mooney et al., 2016

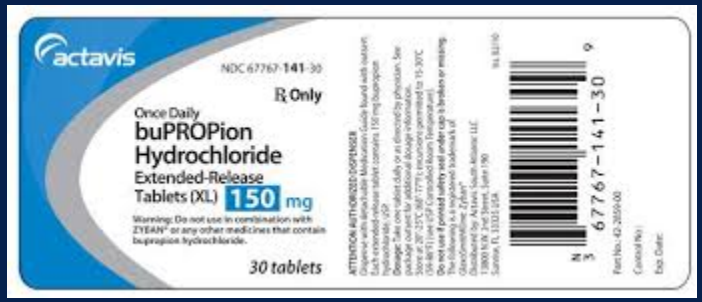
# ADAPT-2 Background and Rationale

- Promising candidates showing preliminary clinical utility include naltrexone and bupropion
- Combination of bupropion + naltrexone predicated on potentially complementary effects as shown in clinical research
- CTN-0054 ADAPT-MD pilot trial: Open-label study using bupropion + naltrexone for MA dependent participants showed promising results

Hanson, 2004; Newton et al., 2006; Ornellas & Chavez, 2011

# ADAPT-2 Study Medications

- Naltrexone appears to:
  - Reduce reinforcing effects of amphetamine
  - Reduce likelihood of relapse
  - Decrease craving




- Bupropion (typically 300mg/day) appears to:
  - reduce cue-craving
  - decrease methamphetamine use

# ADAPT-2 Study Objectives

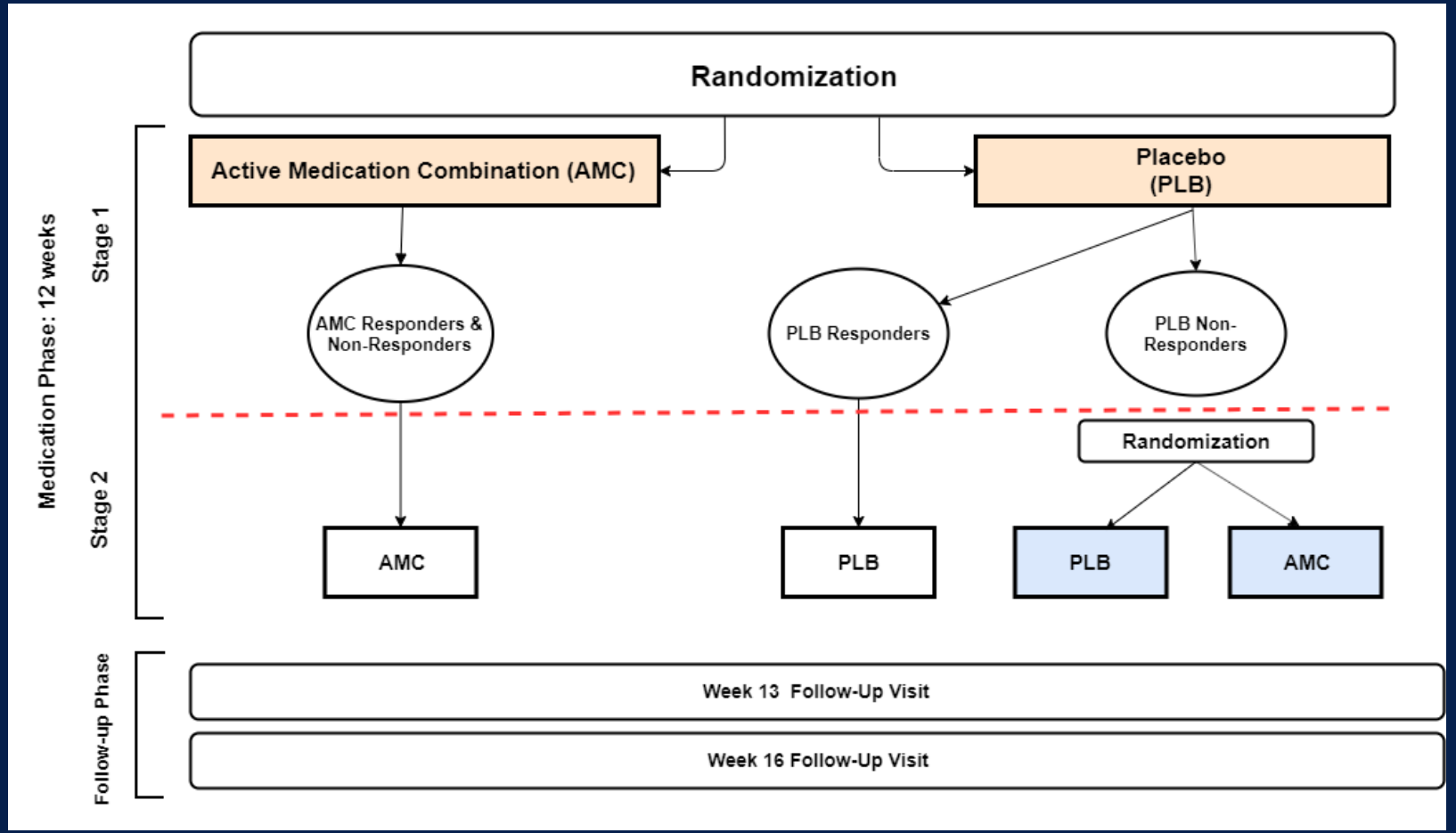
**Primary Aim:**

- Assess efficacy of extended-release injectable naltrexone (380 mg) + extended release oral bupropion (450 mg) as combination pharmacotherapy for methamphetamine use disorder

**Secondary Aims:**

- Assess safety
- Assess efficacy on other SUD outcomes, depression symptom scores, quality of life ratings

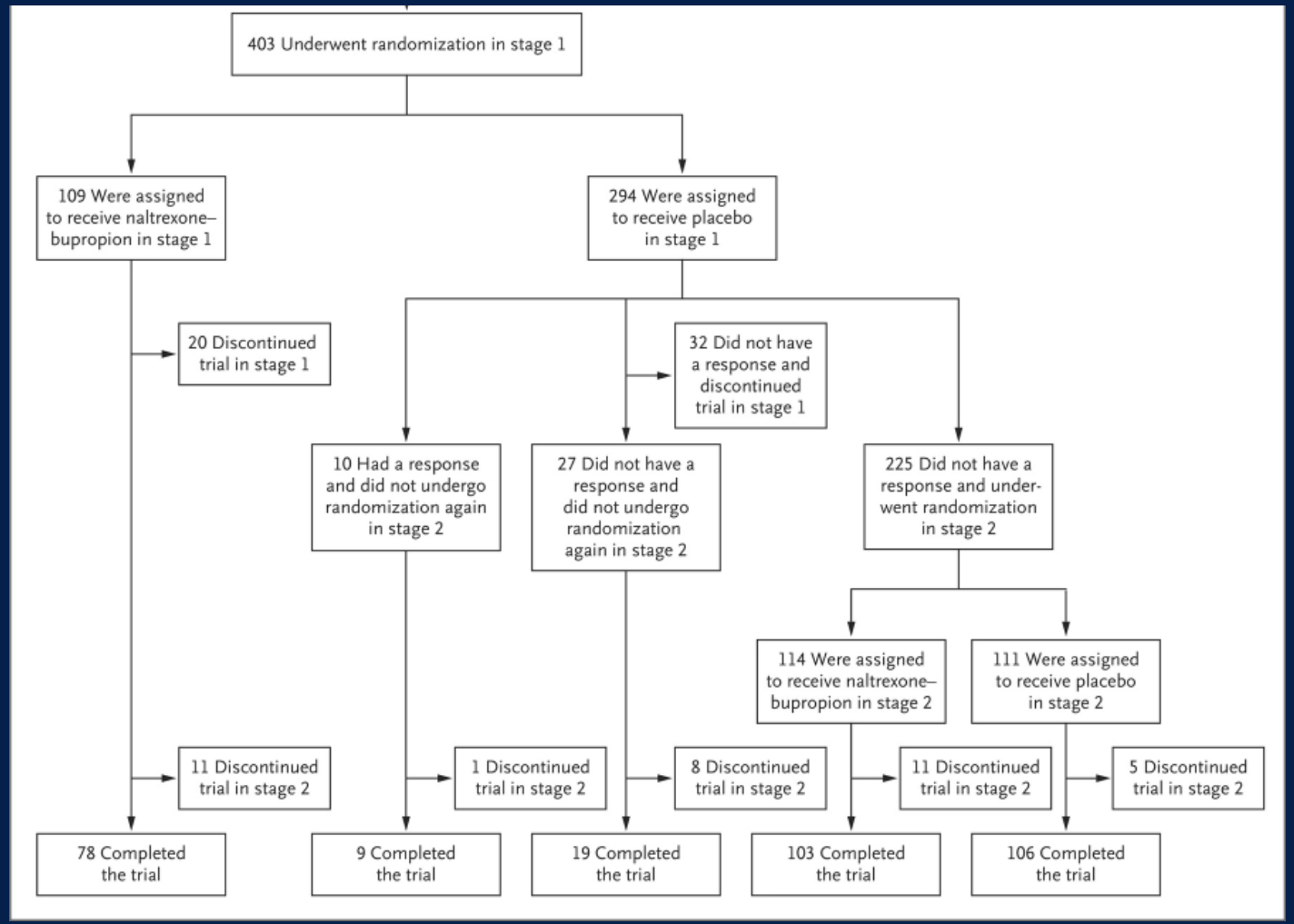
# ADAPT-2 Study Schema: Unmasked



# Primary Outcomes

- **Primary efficacy outcome measure**
  - Methamphetamine negative UDS results in Medication Phase (AMC vs PLB)
- **"Responder":** Participants who provide at least 3 of 4 total UDS negative for methamphetamine during evaluation periods
  - Stage 1 evaluation period: Weeks 5 and 6
  - Stage 2 evaluation period: Weeks 11 and 12
- **Primary safety outcomes**: Adverse Events and Serious Adverse Events

# Screening and Randomization




Trivedi et al., 2021

# ADAPT Primary Outcome Results

# ADAPT Primary Outcome Results

## Baseline Demographics of Participants in the Intention-to-Treat Population

| Characteristic | All Participants | Stage 1 | | Stage 2 | |
|---|---|---|---|---|---|
| | Total (N=403) | Naltrexone–Bupropion (N=109) | Placebo (N=294) | Naltrexone–Bupropion (N=114) | Placebo (N=111) |
| Male — no. (%) | 277 (68.7) | 78 (71.6) | 199 (67.7) | 78 (68.4) | 79 (71.2) |
| Age – yr | 41.0±10.1 | 41.0±10.6 | 41.0±10.0 | 41.0±10.5 | 42.0±9.6 |
| Hispanic or Latino ethnic group — no. (%) | 55 (13.6) | 13 (11.9) | 42 (14.3) | 20 (17.5) | 18 (16.2) |
| Race or ethnic group — no. (%) | | | | | |
| White | 287 (71.2) | 82 (75.2) | 205 (69.7) | 84 (73.7) | 69 (62.2) |
| Black | 48 (11.9) | 10 (9.2) | 38 (12.9) | 8 (7.0) | 22 (19.8) |
| Other | 68 (16.9) | 17 (15.6) | 51 (17.3) | 22 (19.3) | 20 (18.0) |
| High school diploma, GED, or lower education level — no. (%) | 142 (35.2) | 39 (35.8) | 103 (35.0) | 36 (31.6) | 33 (29.7) |

# ADAPT Primary Outcome Results

## Baseline Demographics of Participants in the Intention-to-Treat Population

| Characteristic | All Participants | Stage 1 | | Stage 2 | |
|---|---|---|---|---|---|
| | Total (N=403) | Naltrexone–Bupropion (N=109) | Placebo (N=294) | Naltrexone–Bupropion (N=114) | Placebo (N=111) |
| Marital status — no. (%) | | | | | |
| Married or living with partner | 93 (23.1) | 26 (23.9) | 67 (22.8) | 25 (21.9) | 25 (22.5) |
| Never married | 204 (50.6) | 49 (45.0) | 155 (52.7) | 60 (52.6) | 59 (53.2) |
| Divorced, separated, widowed, or unknown — no. (%) | 106 (26.3) | 34 (31.2) | 72 (24.5) | 29 (25.4) | 27 (24.3) |
| Employed — no. (% | 156 (38.7) | 43 (39.4) | 113 (38.4) | 46 (40.4) | 44 (39.6) |

# ADAPT Primary Outcome Results

## Baseline Methamphetamine Use Characteristics

| Characteristic | All Participants | Stage 1 | | Stage 2 | |
|---|---|---|---|---|---|
| | Total (N=403) | Naltrexone–Bupropion (N=109) | Placebo (N=294) | Naltrexone–Bupropion (N=114) | Placebo (N=111) |
| No. of days that methamphetamine was used in the 30 days before consent | 26.7±4.1 | 27.0±3.9 | 26.5±4.2 | 26.7±4.1 | 26.1±4.3 |
| Most frequent route of use — no. (%) | | | | | |
| Smoking | 293 (72.7) | 80 (73.4) | 213 (72.4) | 83 (72.8) | 79 (71.2) |
| Intravenous | 77 (19.1) | 23 (21.1) | 54 (18.4) | 21 (18.4) | 22 (19.8) |
| Nasal or oral | 33 (8.2) | 6 (5.5) | 27 (9.2) | 10 (8.8) | 10 (9.0) |
| Participants reporting intravenous use ≥1 days in the 30 days before consent — no. (%) | 135 (33.5) | 39 (35.8) | 96 (32.7) | 38 (33.3) | 36 (32.4) |
| Intensity of craving | 66.1±22.3 | 65.7±22.2 | 65.8±21.6 | 66.7±21.3 | 63.7±21.9 |
| Age of first use — yr | 24.8±9.9 | 24.7±10.7 | 24.8±9.6 | 25.5±10.9 | 24.8±9.1 |

# Primary Outcome Results

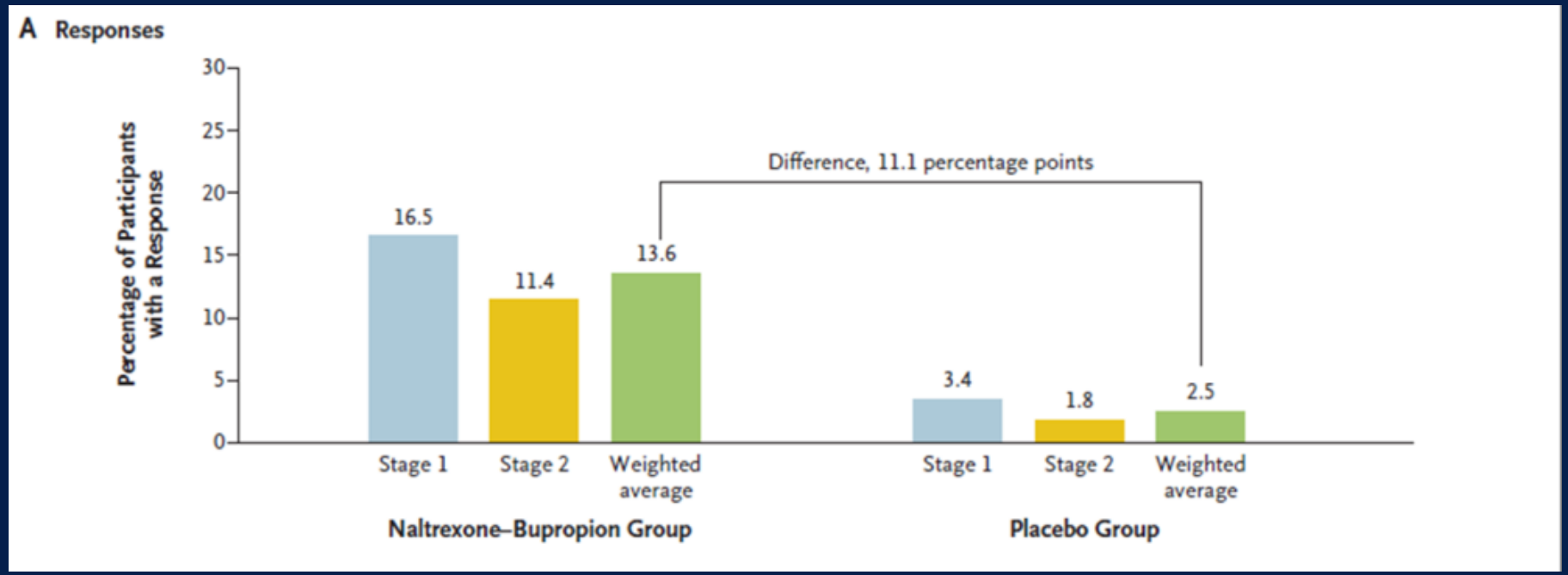
## Primary Outcome Analysis by Stage and Treatment Arm

| Stage 1 | | | Stage 2 | | | Results | | |
|---|---|---|---|---|---|---|---|---|
| N | PLB Responder Rate | AMC Responder Rate | N | PLB Responder Rate | AMC Responder Rate | Treatment Effect | *p*-Value | Number Needed to Treat |
| 403 | **10/294 (3.4%)** | 18/109 (16.5%) | 225 | **2/111 (1.8%)** | 13/114 (11.4%) | 0.1111 | **<0.0001** | **9** |

Note: Rate of continuation into Stage 2 among PLB non-responders was 0.7923

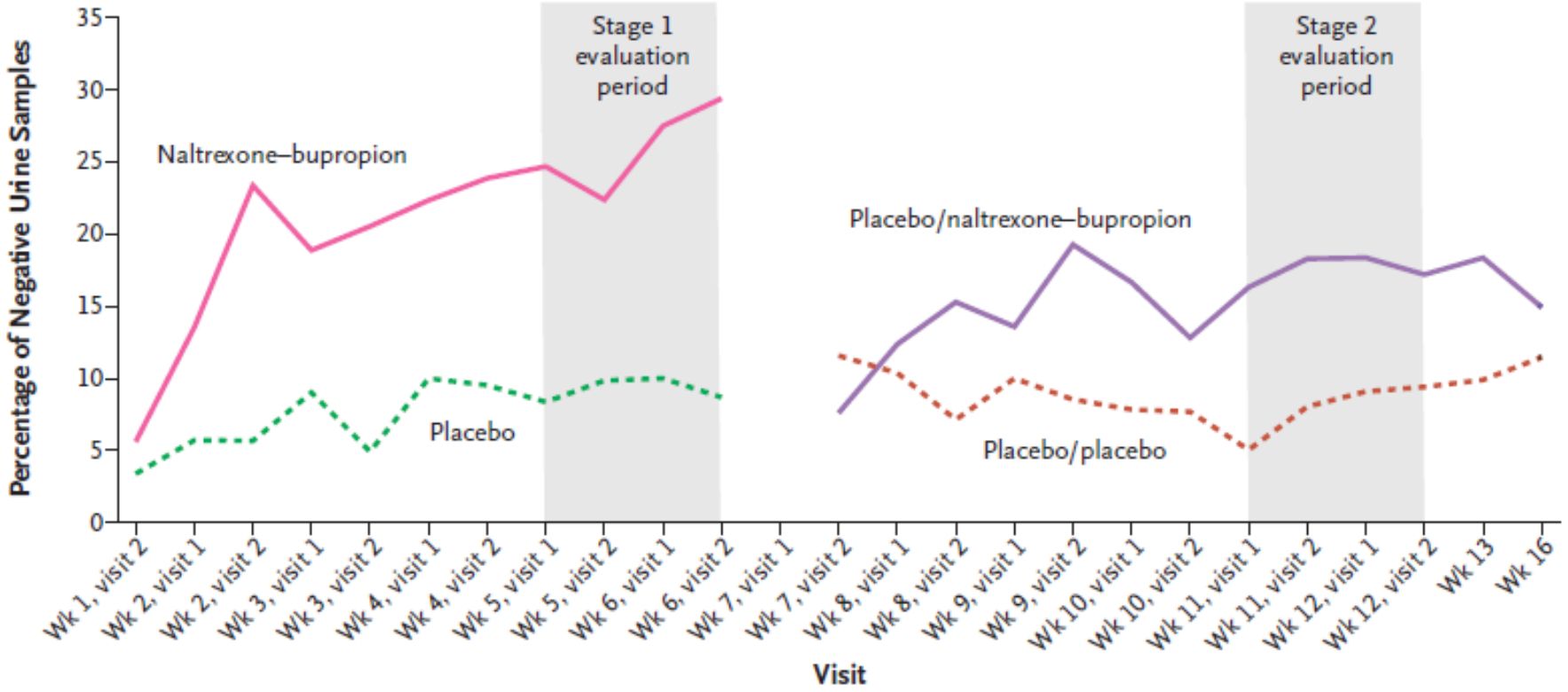
The primary efficacy outcome was statistically significant.

# Weighted Outcome Primary Result




Trivedi et al., 2021

**B** **Methamphetamine-Negative Urine Samples**

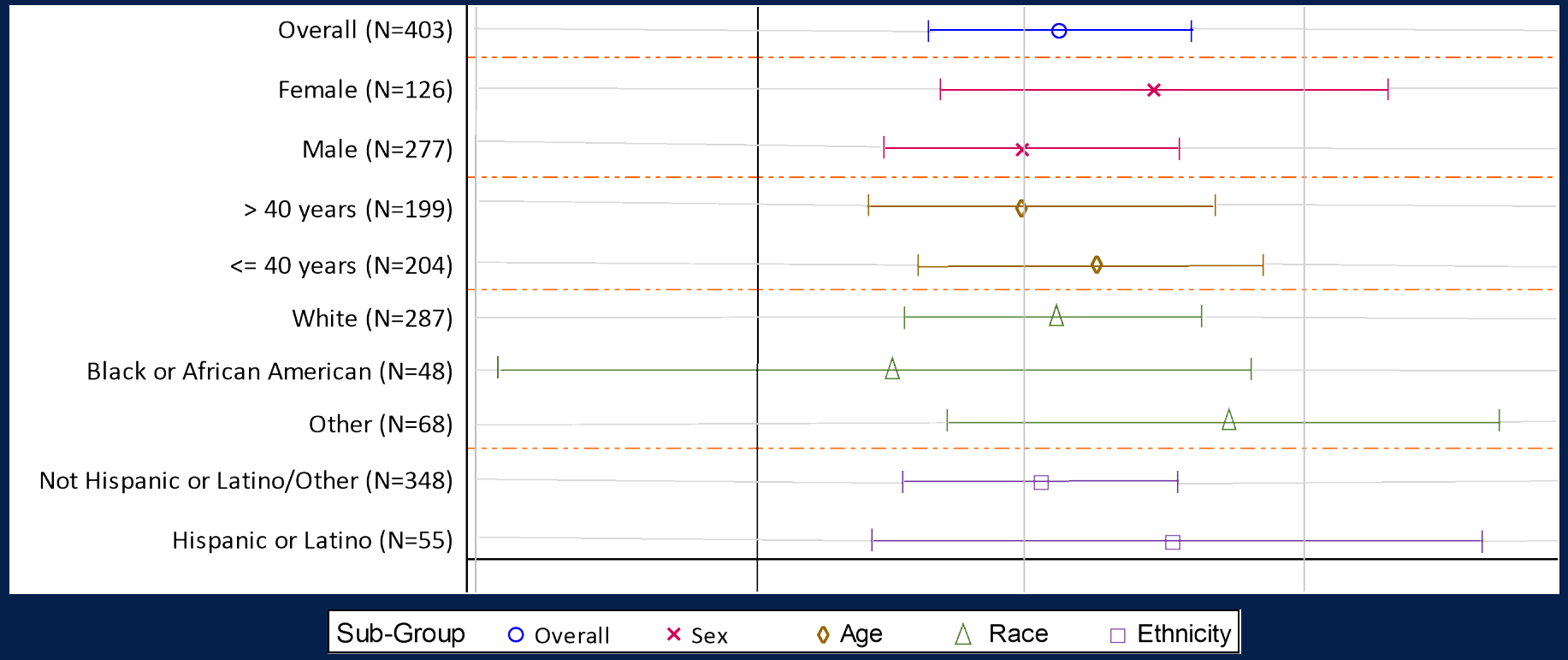



**No. of Urine Samples Obtained at Each Visit**

| | Stage 1 | | | | | | | | | | | Stage 2 | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Naltrexone–bupropion | 89 | 96 | 77 | 90 | 73 | 85 | 67 | 81 | 67 | 80 | 68 | | | | | | | | | | | | | |
| Placebo | 265 | 280 | 229 | 266 | 223 | 260 | 210 | 239 | 203 | 240 | 207 | | | | | | | | | | | | | |
| Placebo/naltrexone–bupropion | | | | | | | | | | | | 92 | 97 | 85 | 103 | 83 | 96 | 78 | 98 | 82 | 98 | 93 | 98 | 87 |
| Placebo/placebo | | | | | | | | | | | | 95 | 106 | 84 | 100 | 82 | 102 | 91 | 99 | 87 | 99 | 85 | 101 | 96 |

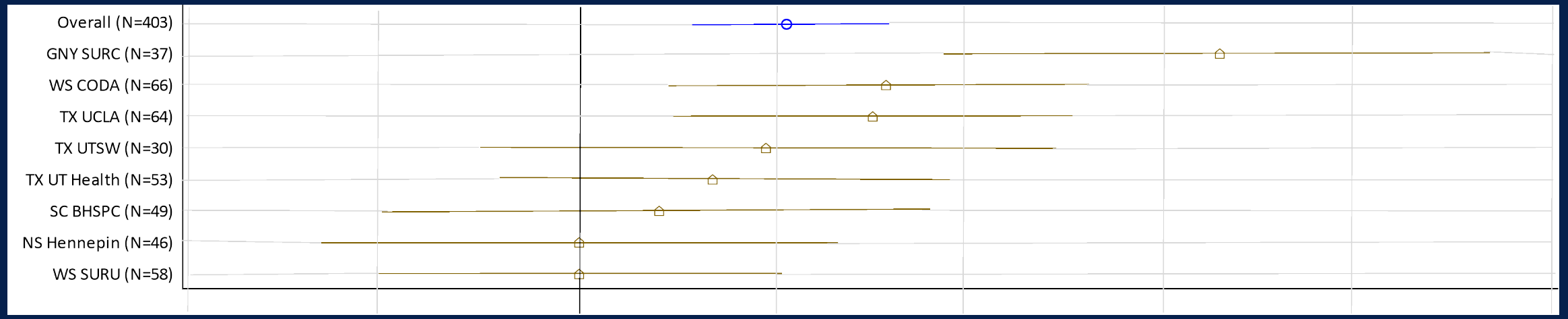
# Repeated Primary Analysis, Separately by Sex, Age, Race, Ethnicity

## Weighted Treatment effect, *h* (95% CI) by Sub-Groups



# Repeated Primary Analysis, Separately by Site

## Weighted Treatment effect, *h* (95% CI) by Sub-groups



# Covariate adjusted model showed results consistent with the primary outcome analysis.

| Primary Outcome Covariate Adjusted Analysis Results: ITT Population | | |
|---|---|---|
| **Model Results** | Treatment Effect | p-value |
| Treatment Effect | 0.1095 | **<0.0001** |
| **Other Covariates in the Model** | | |
| Site | | 0.1108 |
| Age at onset of methamphetamine use | | 0.3037 |
| Baseline number of methamphetamine use days self-reported | | 0.3154 |
| Baseline IV methamphetamine use self-reported | | 0.0911 |
| Number of DSM-5 criteria met during screening | | 0.1859 |
| Baseline number of days of cigarette or e-cigarette use self-reported | | 0.1573 |
| Baseline Treatment Effectiveness Assessment Score | | 0.2301 |
| Baseline average Visual Analog Craving Scale Score | | 0.8640 |

# ADAPT Secondary Outcome Results

## Treatment Effectiveness Score (TES) – proportion of 12 UDS that are MA-negative, within each stage

Other Methamphetamine UDS-Derived Results

| Stage 1 | | Stage 2 | | Results | | |
|---|---|---|---|---|---|---|
| PLB Mean TES | AMC Mean TES | PLB Mean TES | AMC Mean TES | Treatment Effect | Std. Error H | *p*-Value |
| 0.114 | 0.196 | 0.126 | 0.184 | 0.068 | 0.016 | **<0.001** |

Notes: N=403, Weight used 0.43, continuation rate 0.792, test statistic Z 4.254

# ADAPT Secondary Outcome Results

Other Methamphetamine UDS-Derived Results

## Number of visits with methamphetamine negative UDS results, within each stage

| Stage 1 | | Stage 2 | | Results | |
|---|---|---|---|---|---|
| PLB # Visits MA-Negative UDS | AMC # Visits MA-Negative UDS | PLB # Visits MA-Negative UDS | AMC # Visits MA-Negative UDS | Treatment Effect | *p*-Value |
| 1.474 | 2.449 | 1.613 | 2.309 | 0.815 | **<0.001** |

Note: N = 403, Weight 0.43, continuation rate 0.792, test statistic (z) 4.026

# ADAPT Secondary Outcome Results

Other Methamphetamine UDS-Derived Results

## Number of consecutive visits with methamphetamine negative UDS

| Stage 1 | | Stage 2 | | Results | |
|---|---|---|---|---|---|
| PLB # Consecutive Visits MA-Negative UDS | AMC # Consecutive Visits MA-Negative UDS | PLB # Consecutive Visits MA-Negative UDS | AMC # Consecutive Visits MA-Negative UDS | Treatment Effect | *p*-Value |
| 1.300 | 2.126 | 1.373 | 2.052 | 0.742 | **<0.001** |

Note: N = 403, Weight 0.43, continuation rate 0.792, test statistic (z) 3.761

# Self-Reported Changes in Methamphetamine Use & Craving

## Use from Timeline Follow Back (TLFB)

| Stage 1: Mean Change from Baseline | | Stage 2: Mean Change from End of Stage 1 | | Results | |
|---|---|---|---|---|---|
| PLB Days of MA Use | AMC Days of MA Use | PLB Days of MA Use | AMC Days of MA Use | Treatment effect | p-value |
| 0.140 | 0.272 | 0.160 | 0.253 | 0.110 | **<0.001** |

Note: Weight 0.43, continuation rate 0.792, test statistic (Z) 5.666

## Craving from VAS

| Stage 1: Mean Change from Baseline | | Stage 2: Mean Change from End of Stage 1 | | Results | |
|---|---|---|---|---|---|
| PLB Days of MA Use | AMC Days of MA Use | PLB Days of MA Use | AMC Days of MA Use | Treatment effect | p-value |
| -21.860 | -29.599 | -20.119 | -31.339 | -9.724 | **<0.001** |

Note: N = 392, Weight 0.43, continuation rate 0.792, test statistic (z) -4.69

# TLFB Selected Results – Alcohol and Cigarettes

## Alcohol

| Stage 1: Mean Change from Baseline | | Stage 2: Mean Change from End of Stage 1 | | Results | |
|---|---|---|---|---|---|
| Placebo Mean Change from Baseline | AMC Mean Change from Baseline | Placebo Mean Change from End of Stage 1 | AMC Mean Change from End of Stage 1 | Treatment effect | p-value |
| -0.054 | -0.016 | -0.035 | -0.035 | 0.016 | 0.089 |

Note: N = 392, Weight 0.43, continuation rate 0.792, test statistic (z) 1.706

## Cigarettes

| Stage 1: Mean Change from Baseline | | Stage 2: Mean Change from End of Stage 1 | | Results | |
|---|---|---|---|---|---|
| Placebo Mean Change from Baseline | AMC Mean Change from Baseline | Placebo Mean Change from End of Stage 1 | AMC Mean Change from End of Stage 1 | Treatment effect | p-value |
| 0.054 | 0.103 | 0.038 | 0.119 | 0.067 | **<0.001** |

Note: N = 392, Weight 0.43, continuation rate 0.792, test statistic (z) 4.353

# Outcomes Related to Life Quality

**Treatment Effectiveness Assessment (TEA)**

- More improvement (from baseline) in AMC than PLB, in both stages
- **Overall significant effect ($p<0.0001$)**

**QoL Outcomes**

- 3 separate types: Physical Health, Mental Health, Activities
- More improvement (from baseline) in AMC than PLB, in both stages
- Not significant

# Depressive Symptoms from PHQ-9

| Stage 1: Mean Change from Baseline | | Stage 2: Mean Change from End of Stage 1 | | Results | |
|---|---|---|---|---|---|
| PLB PHQ-9 | AMC PHQ-9 | PLB PHQ-9 | AMC PHQ-9 | Treatment effect | p-value |
| -2.946 | -4.458 | -3.362 | -4.042 | -1.039 | 0.016 |

Note: N = 403, Weight 0.43, continuation rate 0.792, test statistic (z) -2.41

# Treatment Effectiveness Assessment (TEA)

| Stage 1: Mean Change from Baseline | | Stage 2: Mean Change from End of Stage 1 | | Results | |
|---|---|---|---|---|---|
| PLB TEA Score | AMC TEA Score | PLB TEA Score | AMC TEA Score | Treatment effect | p-value |
| 2.178 | 6.495 | 2.450 | 6.222 | 4.006 | **<0.001** |

Note: N=306, Weight 0.43, continuation rate 0.792, test statistic (z) 4.558

# PHQ-9: Suicide Endorsement

PHQ-9: Suicide Item #9:

Over the past 2 weeks, how often have you been bothered by thoughts that you would be better off dead, or thoughts of hurting yourself in some way?

| Stage 1 | | Stage 2 | | Results | | |
|---|---|---|---|---|---|---|
| Placebo Rate | AMC Rate | Placebo Rate | AMC Rate | Treatment effect | p-value | NNT |
| 0.029 | 0.025 | 0.030 | 0.021 | -0.007 | 0.693 | -140.1 |

Note: N=403, Weight 0.43, randomization fraction 0.37, continuation rate 0.792, test statistic (z) -0.504, 95% Lower limit -0.035

# ADAPT Safety Outcomes

**Table 3. Safety results (in the safety population), by stage and treatment arm.**

| | Stage 1 | | Stage 2 | |
|---|---|---|---|---|
| **Serious Adverse Events (SAE)** | **PBO (N=294)** | **NTX-BPR (N=109)** | **PBO/PBO (N=111)** | **PBO/NTX-BPR (N=114)** |
| Participants with at least one treatment emergent SAE, N (%)[1] | 4 (1.4%) | 1 (0.9%) | 4 (3.6%) | 3 (2.6%) |
| Type of SAE, N (%)[2] | | | | |
| Inpatient hospital admission or prolongation of existing hospitalization | 3 (75.0%) | 1 (100.0%) | 4 (100.0%) | 4 (100.0%) |
| Seizure | 1 (25.0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Adverse Events (AE)[3]** | **PBO (N=294)** | **NTX-BPR (N=109)** | **PBO/PBO (N=111)** | **PBO/NTX-BPR (N=114)** |
| Participants with at least one moderate or severe treatment emergent AE, N (%)[1] | 26 (8.8%) | 26 (23.9%) | 2 (1.8%) | 9 (7.9%) |
| Treatment emergent AEs, N | | | | |
| Grade 2 – Moderate, N (%) | 45 (100.0%) | 38 (100.0%) | 2 (100.0%) | 11 (91.7%) |
| Grade 3 – Severe, N (%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (8.3%) |
| AEs related to oral medication, N (%)[3] | 27 (60.0%) | 23 (60.5%) | 1 (50.0%) | 3 (25.0%) |
| AEs related to injectable medication, N (%)[3] | 27 (60.0%) | 18 (47.4%) | 1 (50.0%) | 10 (83.3%) |

Trivedi et al., 2021

# Stage 1 Adverse Events

| Summary of Treatment Emergent Adverse Events By Treatment Arm in Stage 1 | | | |
|---|---|---|---|
| | Placebo (N=294) | AMC (N=109) | Total (N=403) |
| Number of participants with treatment emergent adverse events in Stage 1[1] | 245 | 99 | 344 |
| Number of treatment emergent adverse events | 839 | 417 | 1256 |
| Severity of adverse event | | | |
| Missing | 0 | 2 | 2 |
| Grade 1 - Mild | 679 | 328 | 1007 |
| Grade 2 - Moderate | 149 | 86 | 235 |
| Grade 3 - Severe | 11 | 1 | 12 |
| Relationship of treatment emergent adverse event to oral study medication | | | |
| No | 683 | 269 | 952 |
| Yes | 156 | 148 | 304 |
| Relationship of treatment emergent adverse event to injectable study medication | | | |
| No | 741 | 341 | 1082 |
| Yes | 98 | 76 | 174 |

[1] Stage 1 AEs include adverse events occurring before the date of re-randomization for re-randomized participants and in Weeks 1-6 for non-re-randomized participants.

# Stage 1: No Study Medication Related SAEs

| Summary of Treatment Emergent Serious Adverse Events (SAEs) by Treatment Arm in Stage 1 | Placebo (N=294) | AMC (N=109) | Total (N=403) |
|---|---|---|---|
| Number of participants with treatment emergent serious adverse events in Stage 1[1] | 4 | 1 | 5 |
| Number of treatment emergent serious adverse events | 4 | 1 | 5 |
| Type of treatment emergent serious adverse event | | | |
| Inpatient admission to hospital or prolongation of existing hospitalization | 3 | 1 | 4 |
| Seizure | 1 | 0 | 1 |
| Death | 0 | 0 | 0 |
| Life-threatening event | 0 | 0 | 0 |
| Persistent or significant incapacity | 0 | 0 | 0 |
| Congenital anomaly or birth defect | 0 | 0 | 0 |
| Important medical event that required intervention to prevent any of the above | 0 | 0 | 0 |
| Relationship of treatment emergent serious adverse event to oral study medication | | | |
| No | 4 | 1 | 5 |
| Yes | **0** | **0** | **0** |
| Relationship of treatment emergent serious adverse event to injectable study medication | | | |
| No | 4 | 1 | 5 |
| Yes | **0** | **0** | **0** |

[1] Stage 1 SAEs include serious adverse events occurring before the date of re-randomization for re-randomized participants and in Weeks 1-6 for non-re-randomized participants

# Stage 1 SAEs by MedDra Class

| Summary of Treatment Emergent MedDRA Coded Serious Adverse Events | | | |
|---|---|---|---|
| System Organ Class/ Preferred Term (MedDRA v22.1) | Placebo (N=294) | AMC (N=109) | Total (N=403) |
| Participants with at least one serious adverse event in Stage 1[1] | 4 | 1 | 5 |
| Psychiatric disorders | 2 | 0 | 2 |
| Substance-induced psychotic disorder | 1 | 0 | 1 |
| Paranoia | 1 | 0 | 1 |
| Nervous system disorders | 1 | 0 | 1 |
| Seizure | 1 | 0 | 1 |
| Infections and infestations | 0 | 1 | 1 |
| Gastroenteritis | 0 | 1 | 1 |
| Gastrointestinal disorders | 1 | 0 | 1 |
| Pancreatitis | 1 | 0 | 1 |

# Stage 2 Adverse Events

Table Summary of Treatment Emergent Adverse Events by Treatment Arm in Stage 2

| | Re-randomized | | Not Re-randomized | | |
|---|---|---|---|---|---|
| | Placebo/Placebo (N=111) | Placebo/AMC (N=114) | Placebo (N=69) | AMC (N=109) | Total (N=403) |
| Number of participants with treatment emergent adverse events in Stage 2[1] | 77 | 88 | 15 | 59 | 239 |
| Number of treatment emergent adverse events | 206 | 295 | 34 | 148 | 683 |
| Severity of adverse event | | | | | |
| Missing | 0 | 1 | 0 | 0 | 1 |
| Grade 1 - Mild | 151 | 246 | 24 | 104 | 525 |
| Grade 2 - Moderate | 45 | 40 | 7 | 35 | 127 |
| Grade 3 - Severe | 10 | 8 | 3 | 9 | 30 |
| Relationship of treatment emergent adverse event to oral study medication | | | | | |
| No | 182 | 254 | 32 | 122 | 590 |
| Yes | 24 | 41 | 2 | 26 | 93 |
| Relationship of treatment emergent adverse event to injectable study medication | | | | | |
| No | 195 | 233 | 33 | 135 | 596 |
| Yes | 11 | 62 | 1 | 13 | 87 |

# Stage 2: One SAE related to Study Medications

Summary of Treatment Emergent Serious Adverse Events by Treatment Arm in Stage 2

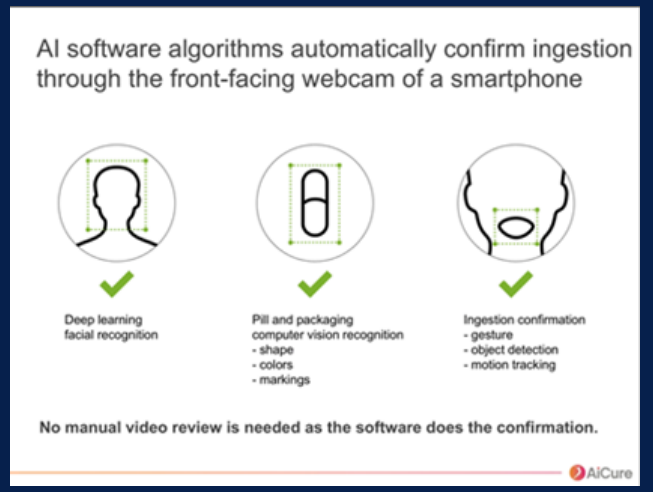
| | Re-randomized | | Not Re-randomized | | |
|---|---|---|---|---|---|
| | Placebo/Placebo (N=111) | Placebo/AMC (N=114) | Placebo (N=69) | AMC (N=109) | Total (N=403) |
| Number of participants with trt emergent SAEs in Stage 2[1] | 4 | 3 | 1 | 3 | 11 |
| Number of treatment emergent SAEs | 4 | 4 | 1 | 3 | 12 |
| Type of treatment emergent serious adverse event | | | | | |
| Inpatient admission to hospital or prolongation of existing hospitalization | 4 | 4 | 1 | 3 | 12 |
| Death | 0 | 0 | 0 | 0 | 0 |
| Life-threatening event | 0 | 0 | 0 | 0 | 0 |
| Persistent or significant incapacity | 0 | 0 | 0 | 0 | 0 |
| Congenital anomaly or birth defect | 0 | 0 | 0 | 0 | 0 |
| Important medical event that required intervention to prevent any of the above | 0 | 0 | 0 | 0 | 0 |
| Seizure | 0 | 0 | 0 | 0 | 0 |
| Relationship of treatment emergent serious adverse event to oral study medication | | | | | |
| No | 4 | 4 | 1 | 2 | 11 |
| Yes | **0** | **0** | **0** | **1** | **1** |
| Relationship of treatment emergent serious adverse event to injectable study medication | | | | | |
| No | 4 | 4 | 1 | 3 | 12 |
| Yes | **0** | **0** | **0** | **0** | **0** |

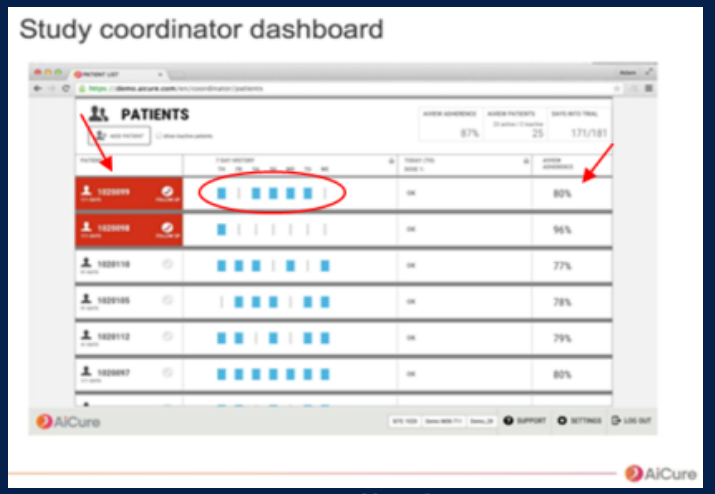
# Stage 2 SAEs by MedDRA Class

| Summary of Treatment Emergent MedDRA Coded Serious Adverse Events | | | | | |
|---|---|---|---|---|---|
| | Re-randomized | | Not Re-Randomized | | Total |
| System Organ Class/ Preferred Term (MedDRA v22.1) | Placebo/Placebo (N=111) | Placebo/AMC (N=114) | Placebo (N=69) | AMC (N=109) | Total (N=403) |
| Participants with at least one SAE in Stage 2[1] | 4 | 3 | 1 | 3 | 11 |
| Infections and infestations | 3 | 1 | 1 | 1 | 6 |
| Pneumonia | 1 | 0 | 0 | 1 | 2 |
| Urosepsis | 1 | 0 | 0 | 0 | 1 |
| Gastroenteritis shigella | 1 | 0 | 0 | 0 | 1 |
| Cellulitis | 0 | 1 | 0 | 0 | 1 |
| Appendicitis | 0 | 0 | 1 | 0 | 1 |
| Psychiatric disorders | 0 | 1 | 0 | 1 | 2 |
| Homicidal ideation | 0 | 1 | 0 | 0 | 1 |
| Depression | 0 | 0 | 0 | 1 | 1 |
| Social circumstances | 1 | 0 | 0 | 0 | 1 |
| Victim of crime | 1 | 0 | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | 0 | 1 | 0 | 0 | 1 |
| Neck pain | 0 | 1 | 0 | 0 | 1 |
| Metabolism and nutrition disorders | 0 | 1 | 0 | 0 | 1 |
| Hyperglycaemia | 0 | 1 | 0 | 0 | 1 |
| Cardiac disorders | 0 | 0 | 0 | 1 | 1 |
| Cardiac failure acute | 0 | 0 | 0 | 1 | 1 |

# Adherence Measures

- Study Medication Dosing Logs
- Injection Administration Form
- Oral Study Medication Blood Levels
- Video observed therapy via AiCure app

# Medication Adherence

| Summary of Treatment Exposure by Site | | | | |
|---|---|---|---|---|
| | | Tablets[1] | Injections[2] | Overall Treatment Exposure[3] |
| Site | Participants Randomized | % | % | % |
| SC BHSPC | 49 | 56% | 70% | 63% |
| WS CODA, Inc. | 66 | 63% | 77% | 70% |
| GNY SURC - Columbia | 37 | 63% | 80% | 71% |
| NS Hennepin Healthcare | 46 | 61% | 77% | 69% |
| WS SURU - SFDPH | 58 | 61% | 78% | 70% |
| TX UCLA CBAM | 64 | 66% | 86% | 76% |
| TX UT Health CNRA | 53 | 65% | 81% | 73% |
| TX UTSW | 30 | 76% | 92% | 84% |
| Total | 403 | 63% | 80% | 72% |

[1] Three tablets per day were expected during the 12-week treatment period.
[2] Four injections were expected during the 12-week treatment period.
[3] Overall treatment exposure percentage is an average of the percentage for tablets and percentage for injections. This percentage represents medication adherence across all treatment groups (i.e., Placebo, AMC, Placebo/Placebo, Placebo/AMC).

# Summary of Treatment Exposure by Site

| Summary of Treatment Exposure by Site | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Tablets[1] | | | Injections[2] | | | Overall Treatment Exposure[3] |
| Site | Participants Randomized | Taken | Expected | % | Administered | Expected | % | % |
| SC BHSPC | 49 | 6,933 | 12,348 | 56.1% | 138 | 196 | 70.4% | 63.3% |
| WS CODA | 66 | 10,539 | 16,632 | 63.4% | 203 | 264 | 76.9% | 70.1% |
| GNY SURC | 37 | 5,864 | 9,324 | 62.9% | 118 | 148 | 79.7% | 71.3% |
| NS Hennepin | 46 | 7,059 | 11,592 | 60.9% | 142 | 184 | 77.2% | 69.0% |
| WS SURU | 58 | 8,871 | 14,616 | 60.7% | 182 | 232 | 78.4% | 69.6% |
| TX UCLA | 64 | 10,659 | 16,128 | 66.1% | 219 | 256 | 85.5% | 75.8% |
| TX UT Health | 53 | 8,684 | 13,356 | 65.0% | 172 | 212 | 81.1% | 73.1% |
| TX UTSW* | 30 | 5,719 | 7,560 | 75.6% | 110 | 120 | 91.7% | 83.7% |
| **Total** | 403 | 64,328 | 101,556 | **63.3%** | 1284 | 1612 | **79.7%** | **71.5%** |

[1] Three tablets per day were expected during the 12-week treatment period.

[2] Four injections were expected during the 12-week treatment period.

[3] Overall treatment exposure percentage is an average of the percentage for tablets and percentage for injections. This percentage represents medication adherence across all treatment groups (i.e., Placebo, AMC, Placebo/Placebo, Placebo/AMC).

*TX UTSW added as an 8th site in July 2018.
All other sites endorsed for enrollment in May 2017.

# Oral Bupropion Blood Levels

| Summary of Oral Medication Blood Levels in AMC Participants by Stage | | | | |
|---|---|---|---|---|
| | | Stage 2 | | |
| | Stage 1 | Re-randomized | Not Re-randomized | Total |
| | AMC (N=109) | Placebo/AMC (N=114) | AMC (N=109) | (N=223) |
| **Bupropion adherence[1]** | | | | |
| Visit 0401 | 72/76 | | | |
| Visit 0701 | 65/68 | | | |
| Visit 1001 | | 73/80 | 50/56 | 123/136 |
| Visit 1202 | | 77/80 | 55/55 | 132/135 |
| **Hydroxybupropion adherence[2]** | | | | |
| Visit 0401 | 75/76 | | | |
| Visit 0701 | 68/68 | | | |
| Visit 1001 | | 79/80 | 54/56 | 133/136 |
| Visit 1202 | | 77/80 | 55/55 | 132/135 |

[1] A participant was considered adherent if bupropion blood level was greater than 0.500 ng/mL.
[2] A participant was considered adherent if hydroxybupropion blood level was greater than 1.00 ng/mL.

# Final Takeaways

- Even in face of grim mortality rates due to methamphetamine disorder in the US, there is still no FDA-approved treatment.
- This is the first large study to present promising results.
- A treatment that involves multiple on-site injections would be more promising than sending patients home with oral medication, where there is no confirmation of consumption.
- Future directions include examination other interventions to increase adherence and/or are fast acting.

# References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# Questions?

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