Bupropion and Naltrexone in Methamphetamine Use Disorder

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Alkermes provided injectable extended-release naltrexone (Vivitrol®) and matched injectable placebo for CTN-0068 ADAPT and CTN-0054 ADAPT-MD.

Learning Objectives

- Describe the encouraging findings of the Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder (ADAPT) trial and how they supported the development of the Accelerated Development of Additive Treatment for Methamphetamine Use Disorder (ADAPT-2) trial.
- List the ways in which combination Bupropion + Naltrexone therapy contribute to the ongoing health crisis of methamphetamine use disorder.

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

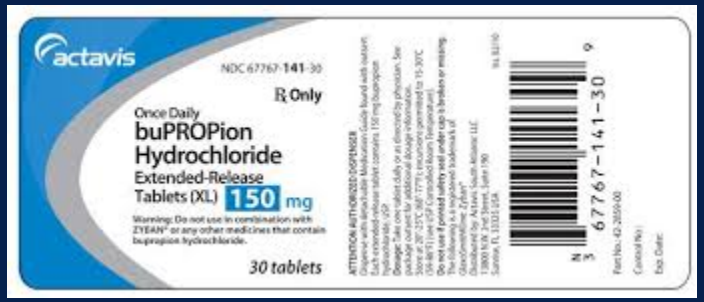
ADAPT-2 Background and Rationale

- 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



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ADAPT-2 Study Objectives

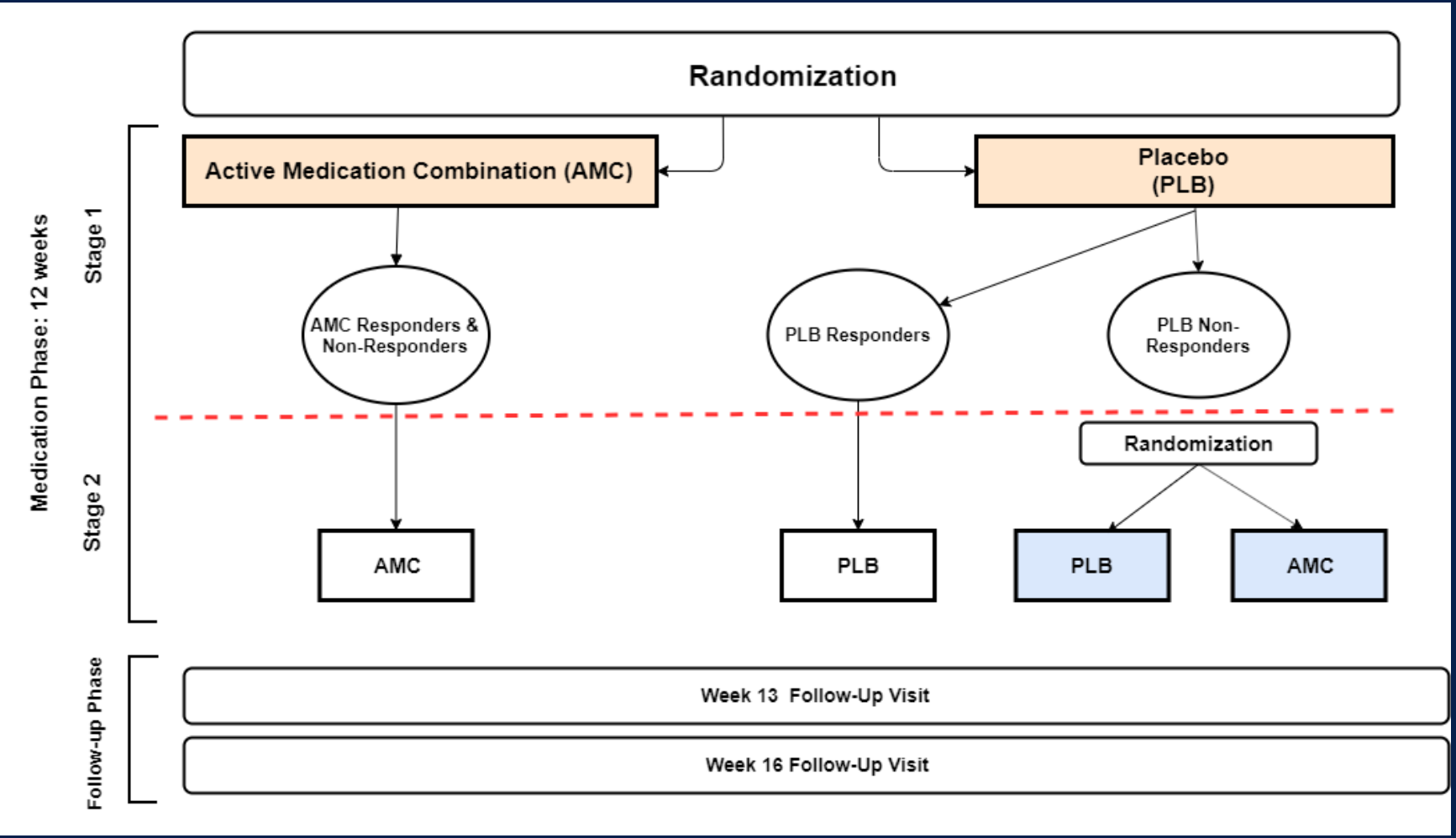
Primary Aim:

- 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

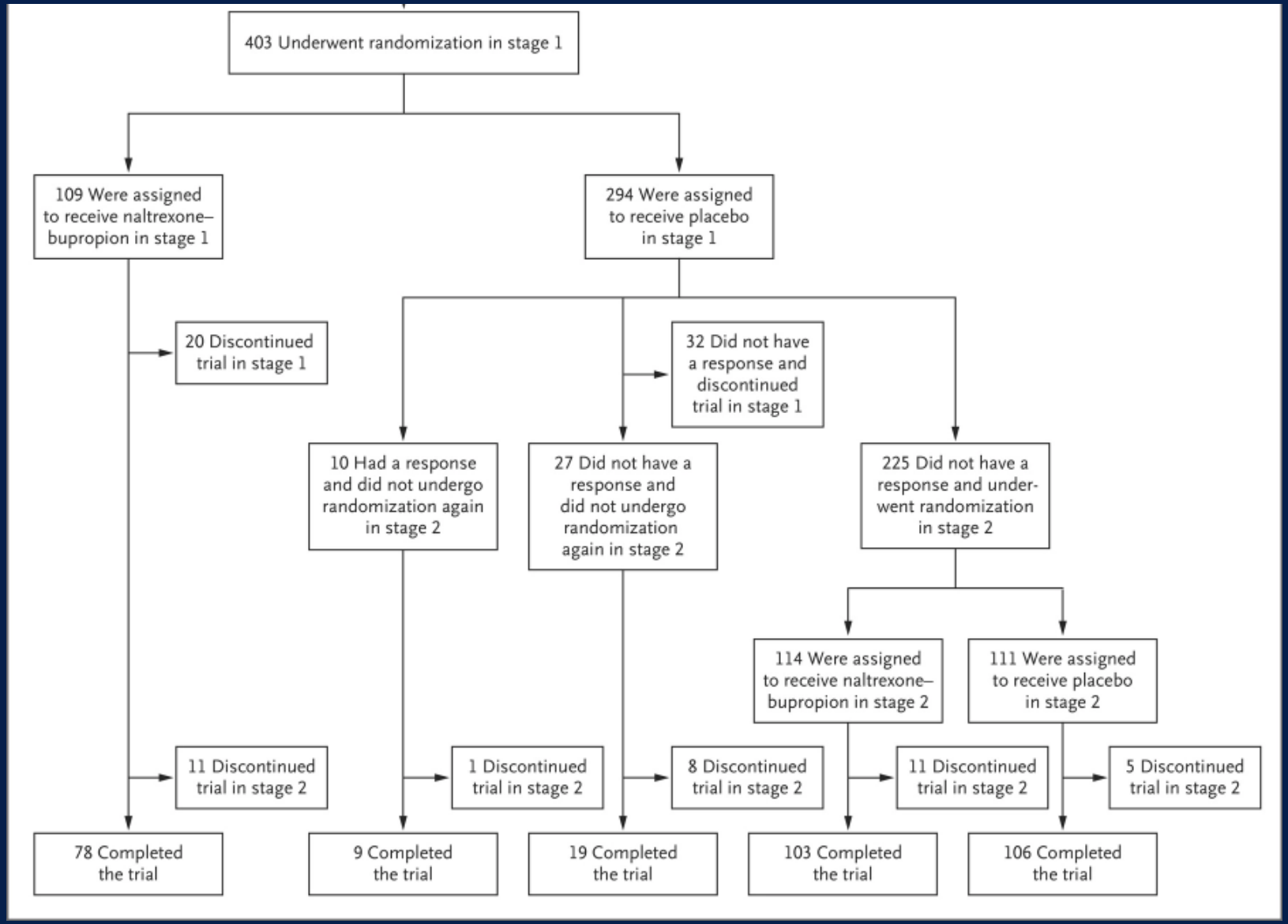
ADAPT-2 Study Schema: Unmasked



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



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ADAPT Primary Outcome Results

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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)

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)

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

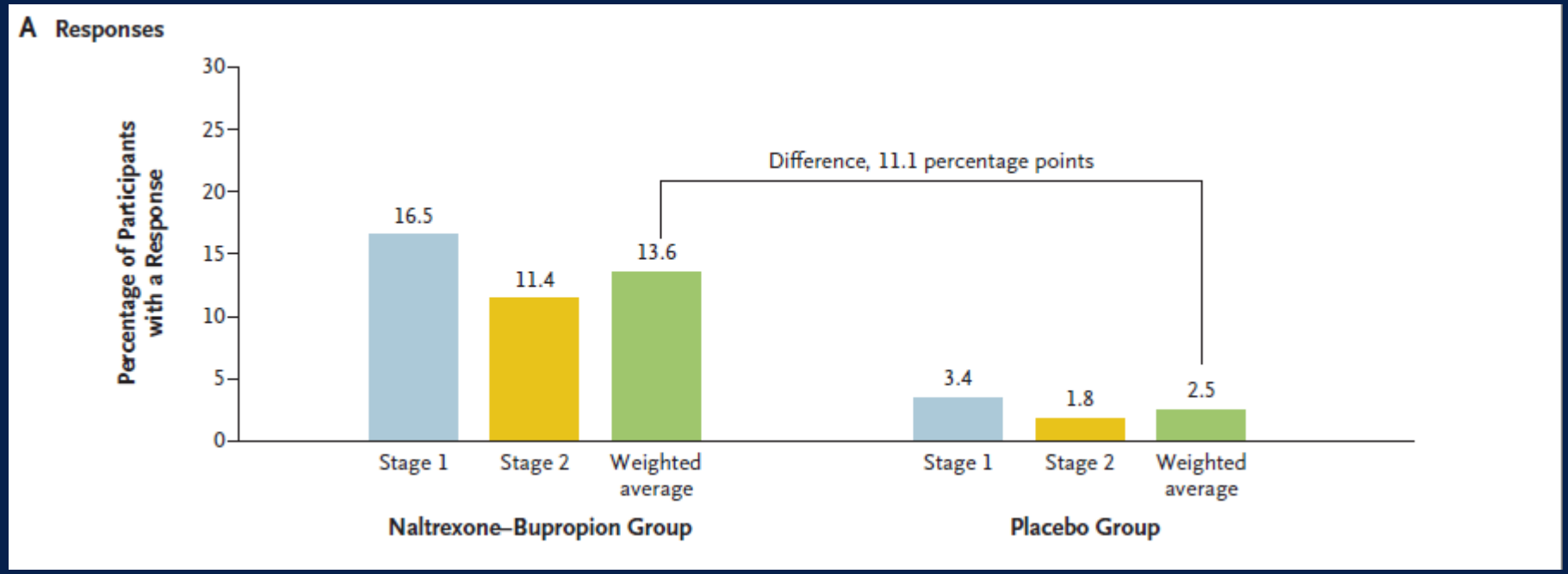
Primary Outcome Results

The primary efficacy outcome was statistically significant.

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

Weighted outcome primary result



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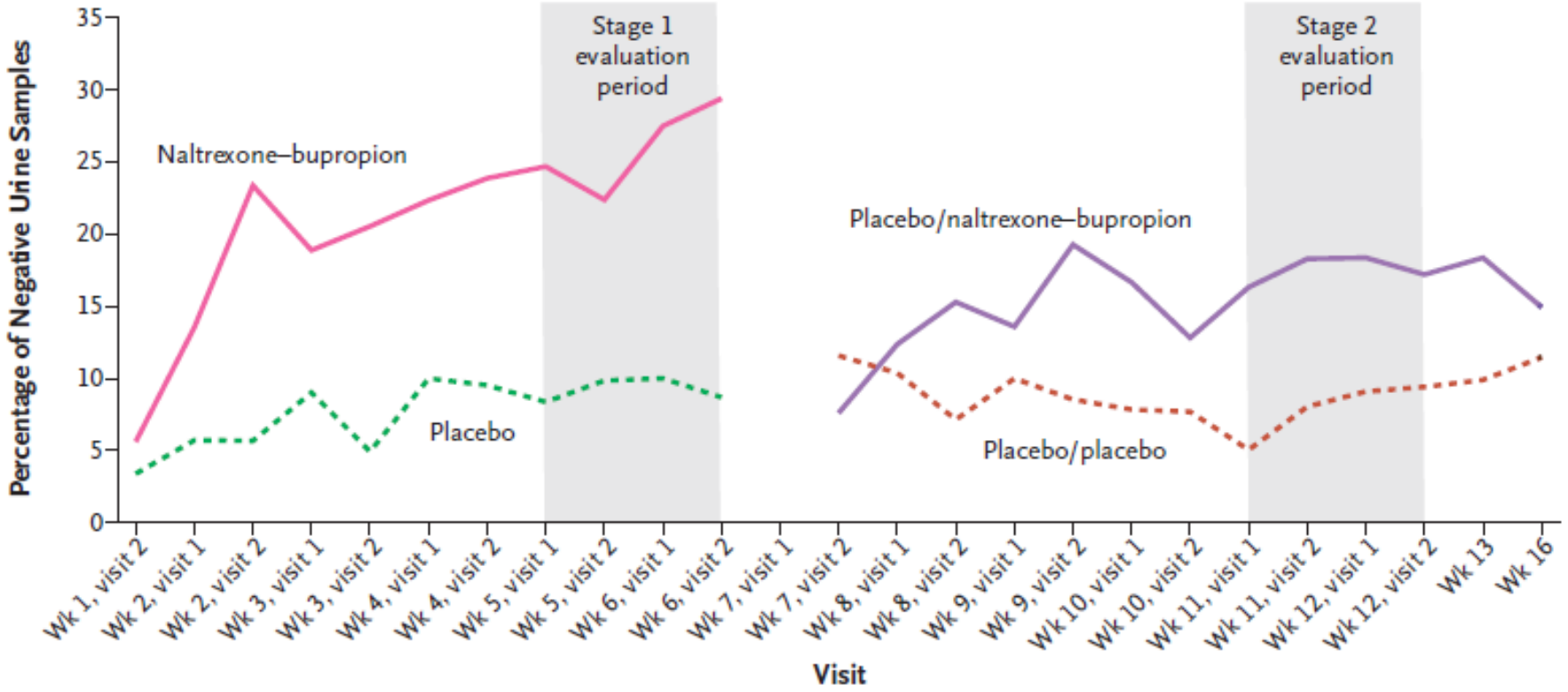
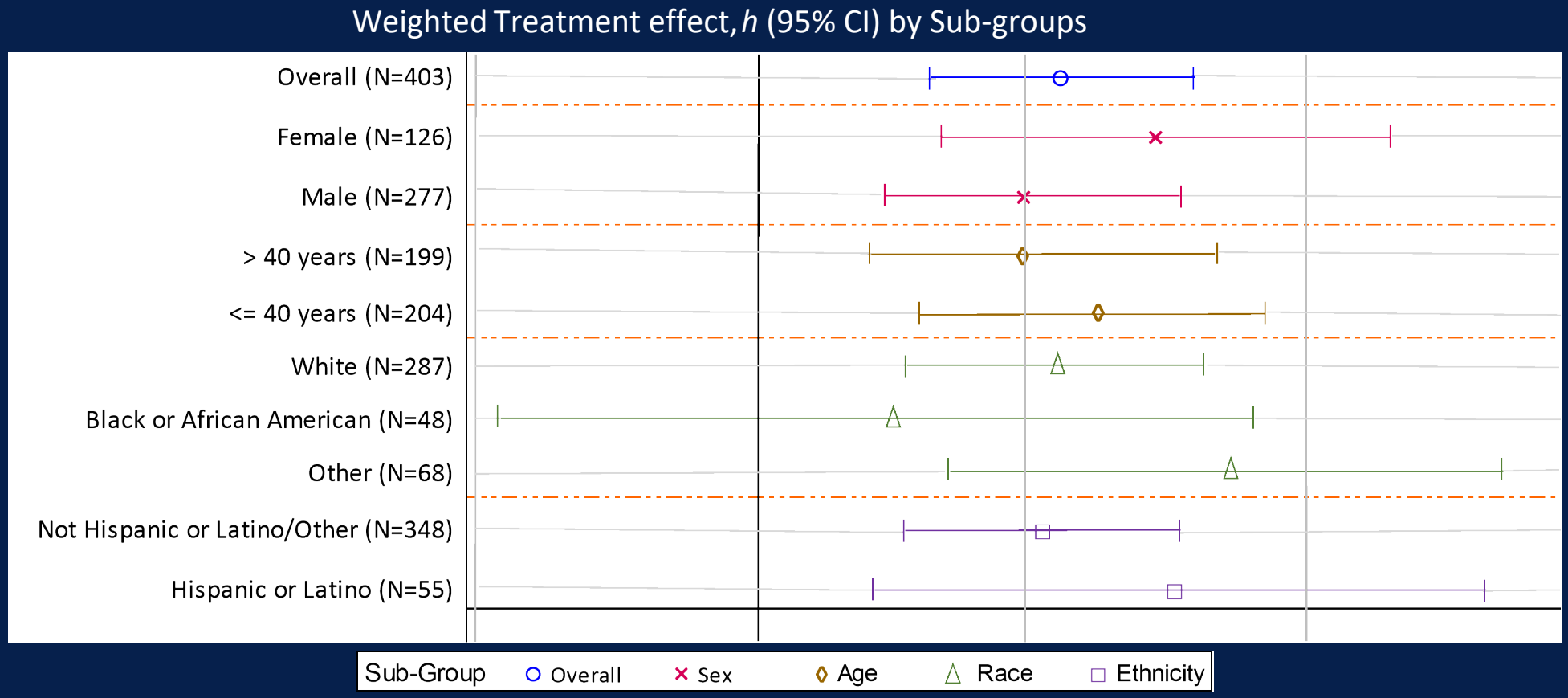
B Methamphetamine-Negative Urine Samples



No. of Urine Samples Obtained at Each Visit

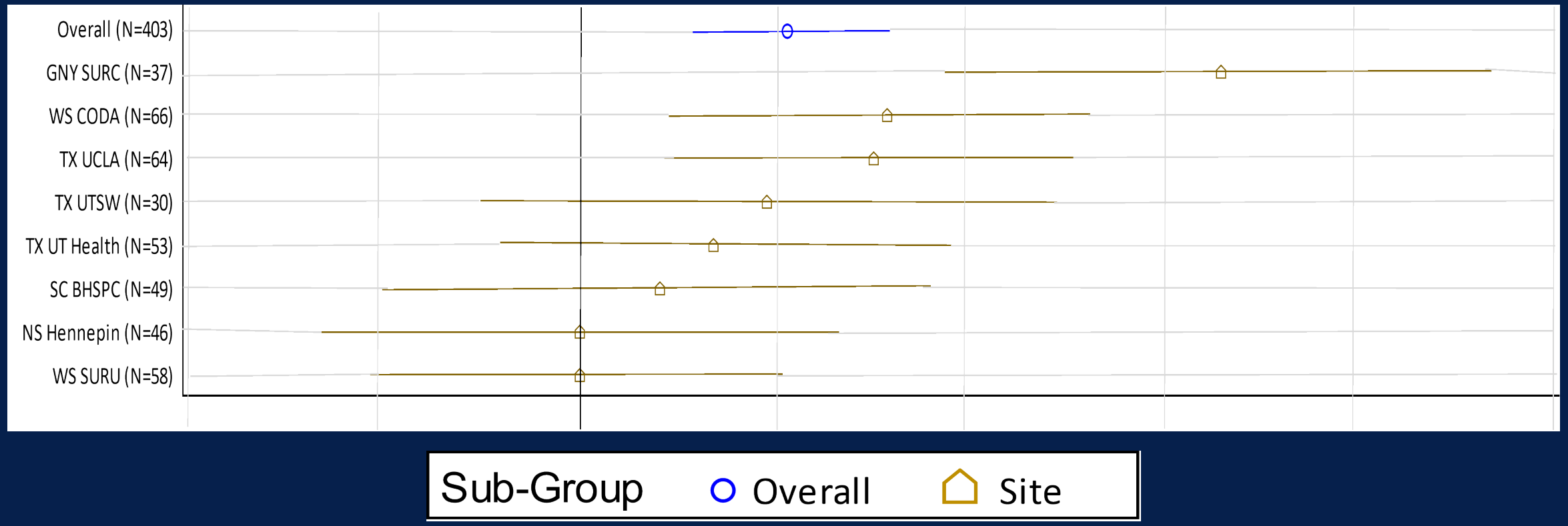
	Stage 1											Stage 2												
Naltrexone–bupropion	89	96	77	90	73	85	67	81	67	80	68													
Placebo	265	280	229	266	223	260	210	239	203	240	207													
Placebo/naltrexone–bupropion												92	97	85	103	83	96	78	98	82	98	93	98	87
Placebo/placebo												95	106	84	100	82	102	91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

Repeated primary analysis, separately by Sex, Age, Race, Ethnicity



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 Outcomes

Other Methamphetamine UDS Derived Results

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

Stage 1		Stage 2		Results		
PLB Mean TES	AMC Mean TES	Placebo 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**

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

Other Methamphetamine UDS Derived Results

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

Stage 1		Stage 2		Results	
Placebo # visits MA negative UDS	AMC # visits MA negative UDS	Placebo # 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

Other Methamphetamine UDS Derived Results

Number of consecutive visits with methamphetamine negative UDS

Stage 1		Stage 2		Results	
Placebo # consecutive visits MA negative UDS	AMC # consecutive visits MA negative UDS	Placebo # 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%)

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

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.

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Questions?

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