Midomafetamine-Assisted Therapy (MDMA-AT) for Treatment of Post-Traumatic Stress Disorder (PTSD)

June 4, 2024

Lykos Therapeutics

Psychopharmacologic Drugs Advisory Committee (PDAC)

Introduction

Amy Laverdiere, MBA

Program Lead

Lykos Therapeutics

PTSD is a Serious Mental Health Condition with Few Effective Treatment Options

- PTSD can develop after a person experiences or witnesses a traumatic event[1]
- Debilitating and lasting symptoms related to the trauma, which negatively impact all aspects of an individual's life[2]
- Anxiety, depression, substance use disorder and suicidal ideation are common[3]
- No FDA approved treatments in > 20 years
- Insufficient treatment options

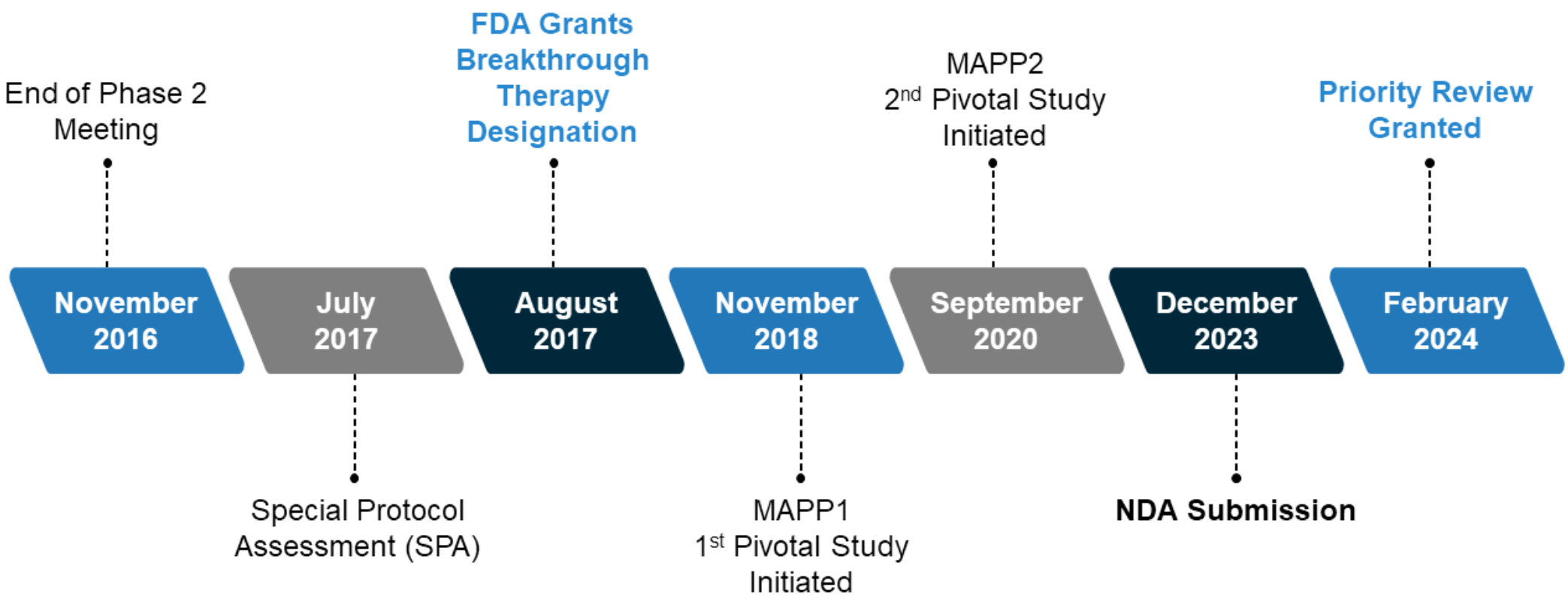
1. Yehuda et al., 2015; 2. Dorrington et al. 2014; 3. Stanley, 2021

Cumulative Experience with MDMA Informed Development Program

- 1970s – 1980s MDMA used in conjunction with talk therapy
- Early research suggested that MDMA can provide a benefit in psychiatric treatment[1]
- ~ 4,000 people documented to have taken MDMA in earlier clinical practice
- More recently MDMA utilized in ~ 2,000 participants in research studies
- Experience informed overall design of clinical program

1. Stolaroff, 2004

MDMA-AT Key Regulatory and Study Milestones



MDMA-AT studied across 17 clinical Phase 1, 2, and 3 studies, with 427 participants exposed to MDMA

MDMA Catalyzes Effective Psychotherapy for PTSD

MDMA

- Facilitates memory recollection
- Extends tolerance for revisiting distressing thoughts or experiences
- Increases self-awareness leading to introspection and personal reflection

Psychological Intervention

- Prioritizes safety and well-being
- Patient-centered
- Trauma informed
- Supports processing of traumatic memories

Medication Session

Proposed Indication

Midomafetamine is an entactogen indicated for the treatment of post-traumatic stress disorder (PTSD) in combination with psychological intervention in adults

Data Support Positive Benefit-Risk Profile for MDMA-AT with Appropriate Risk Mitigation

Efficacy

- Statistically significant and clinically meaningful improvement in PTSD symptoms and functional impairment
- Consistent results across two Phase 3 trials
- Durable results > 6 months

Safety

- Well-tolerated with mostly transient, mild to moderate, self-limiting AEs
- Low discontinuation rates
- Single-dose packaging for acute treatment
- REMS with patient monitoring and registry

Post-approval plan:
REMS, controlled distribution, labeling, therapist training, prescriber / patient education, and post-marketing studies

Agenda

Unmet Need	**Jerry Rosenbaum, MD** Director, Center for the Neuroscience of Psychedelics at Massachusetts General Hospital Research Institute Stanley Cobb Professor Psychiatry at Harvard Medical School
Efficacy	**Berra Yazar-Klosinski, PhD** Chief Scientific Officer Lykos Therapeutics
Safety	**Alia Lilienstein, MD, MPH** Senior Medical Director Lykos Therapeutics
Clinical Perspective	**Kelley O'Donnell, MD, PhD** Research Assistant Professor of Psychiatry, NYU School of Medicine Director of Clinical Training, NYU Langone Center for Psychedelic Medicine
Benefit-Risk Summary	**Berra Yazar-Klosinski, PhD** Chief Scientific Officer Lykos Therapeutics

Additional External Experts

Jason Connor, PhD
President and Lead Statistical Scientist
ConfluenceStat, LLC

Sarah Kleiman, PhD
Clinical Psychologist
Precision Psychological Assessments, LLC

Rebecca Blanchard, PhD
Clinical Pharmacologist
Rebecca Blanchard Consulting, LLC

Peter Kowey, MD
Professor of Medicine and Clinical Pharmacology
Sidney Kimmel Medical College at Thomas Jefferson University
William Wikoff Smith Chair in Cardiovascular Research

Keith Heinzerling, MD, MPH
Director Addiction Medicine
Pacific Neuroscience Institute

Unmet Need

Jerry Rosenbaum, MD

Director, Center for the Neuroscience of Psychedelics at Massachusetts General Hospital Research Institute

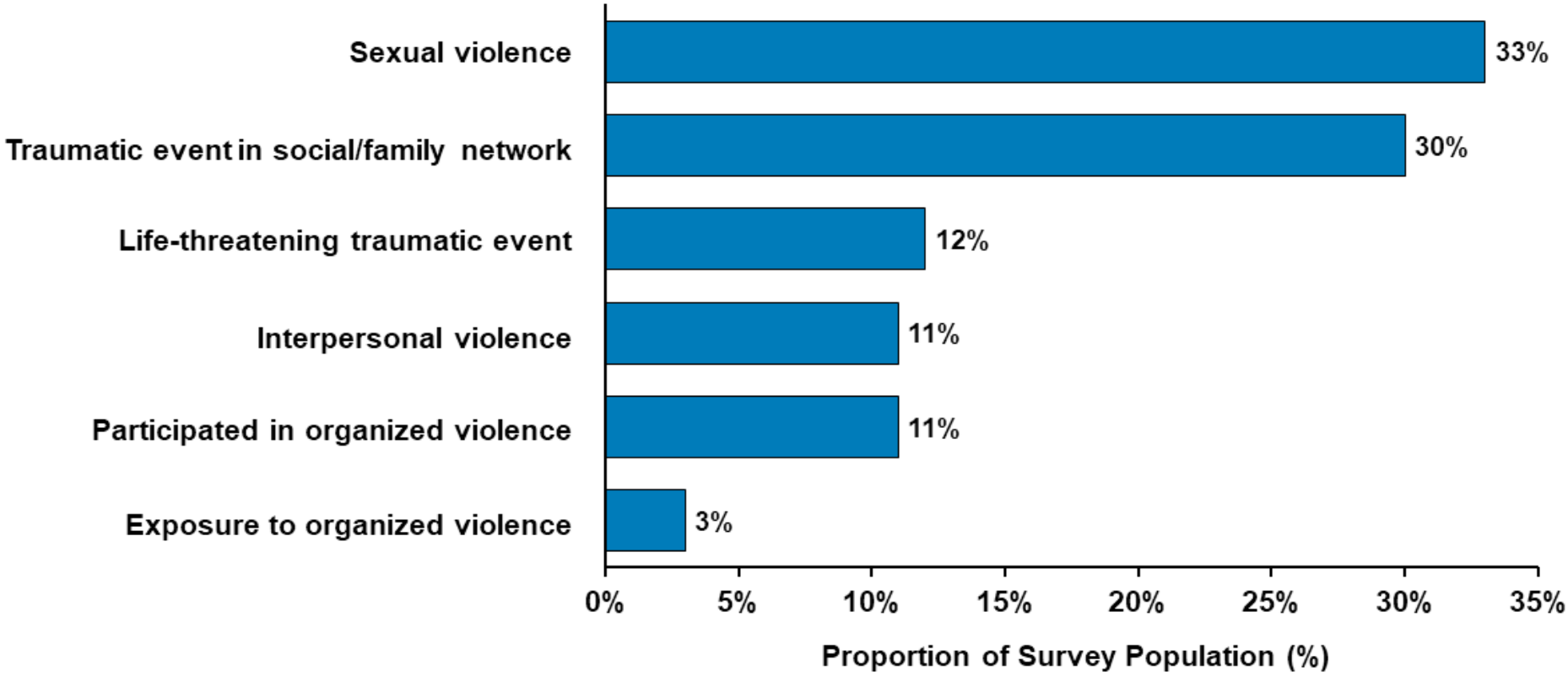
Stanley Cobb Professor Psychiatry at Harvard Medical School

PTSD is a Serious, Life-Threatening Mental Health Condition

13 million	Adults with PTSD in US[1]
6 years	Average duration of PTSD symptoms[2]
40 – 60%	Patients remain symptomatic despite treatment[3,4,5]
48%	Patients remain untreated[6]
47%	Greater risk of mortality[7]

1. U.S. Department of Veterans Affairs, 2020; 2. Kessler et al. 2017; 3. Steenkamp et al. 2015; 4. Bradley et al, 2005; 5. Brady et al, 2000; 6. Rodriguez et al. 2003; 7. Nilaweera et al. 2023

Different Types of Trauma Can Lead to PTSD



WHO World Mental Health Survey (N = 47,566)
Adapted from Kessler, 2014

PTSD Diagnosed Using Well-Established DSM-5 Criteria

Description	Requirement
Exposure to actual or threatened death, serious injury, or sexual violence	Required
Duration of disturbance	≥ 1 month
Presence of intrusion symptoms	≥ 1 symptom
Persistent avoidance	≥ 1 symptom
Negative alterations in cognitions and mood	≥ 2 symptoms
Alterations in arousal and reactivity	≥ 2 symptoms
Clinically significant distress/impairment	Required
Not attributable to effects of substance (e.g. alcohol, medication) or other medical diagnosis	Required

American Psychiatric Association, 2022

PTSD is Characterized by Four Symptom Clusters

Avoidance of Triggers	▪ Avoidance of distressing thoughts or feelings associated with the trauma ▪ Avoidance or efforts to avoid external reminders, or close associations with the trauma
Intrusion	▪ Recurrent, involuntary, and intrusive distressing memories or dreams ▪ Dissociative reactions
Negative Thoughts and Feelings	▪ Persistent and exaggerated negative beliefs and inability to experience positive emotions ▪ Self-blame or blaming others ▪ Noticeably diminished interest or participation in important activities
Arousal and Reactivity	▪ Hypervigilance and sleep disturbance ▪ Irritable behavior/angry outbursts ▪ Reckless or self-destructive behavior

PTSD Occurs in a Complex Patient Population With Comorbid Psychiatric Conditions[1-3]

59%	Anxiety disorders[1]
52%	Major depressive disorder[2]
46%	Substance use disorders[1]
42%	Suicidal ideation[3]

1. Pietrzak et al. 2011; 2. Rytwinski et al. 2013; 3. Rojas SM et al. 2014

Current Therapies for PTSD Can Be Difficult to Tolerate and Can Be Ineffective for Some Patients

	Psychotherapy	SSRI or SNRI
Benefit	▪ Clinically meaningful PTSD symptom reduction using trauma-focused therapy (PE, CPT, EMDR*)	▪ FDA-approved treatment for PTSD ▪ Demonstrated greater efficacy than placebo based on clinician-assessed scale for PTSD symptom
Challenge	▪ High dropout rates due to exacerbation of distress and often takes months/years ▪ Highly variable outcomes ▪ Limited access	▪ Response rates rarely exceed 60%[1] ▪ Side effect profiles ▪ Often polypharmacy with off-label agents ▪ Target symptoms only

*PE = Prolonged Exposure; CPT = Cognitive Processing; EMDR = Eye Movement Desensitization and Reprocessing; 1. Berger 2009

Summary of Unmet Need

- PTSD is a serious, debilitating disorder
- Patients experience chronic symptoms that disrupt quality of life and can be life-threatening
- Current treatments have limitations
  - Psychotherapy: high drop-out rates
  - Pharmacotherapy: does not address underlying cause of PTSD

Need effective intervention to better support patients with PTSD

Efficacy

Berra Yazar-Klosinski, PhD

Chief Scientific Officer

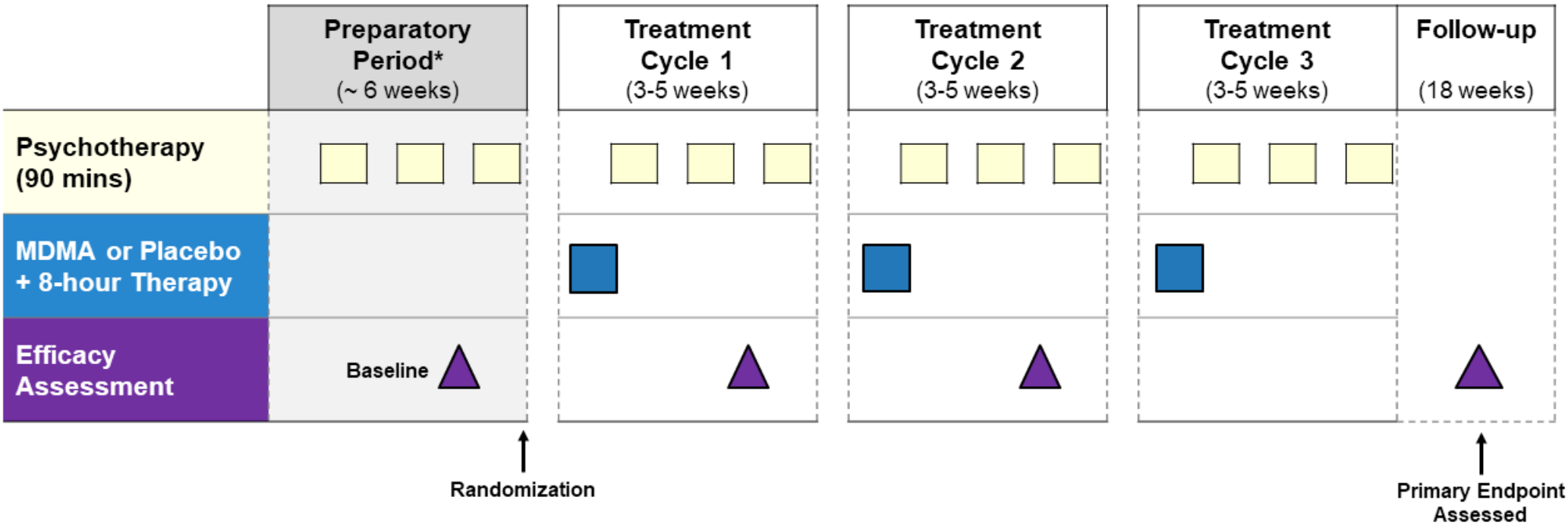
Lykos Therapeutics

Two Pivotal Phase 3 Studies Demonstrate Efficacy of MDMA-AT

MAPP1	**Phase 3, multi-site, randomized, placebo-controlled with at least severe PTSD Dose*: 120 mg at session 1; 180 mg at session 2 and 3**
MAPP2	**Phase 3, multi-site, randomized, placebo-controlled with at least moderate PTSD Dose*: 120 mg at session 1; 180 mg at session 2 and 3**

*Phase 3 trials specified dose of the hydrochloride salt of MDMA

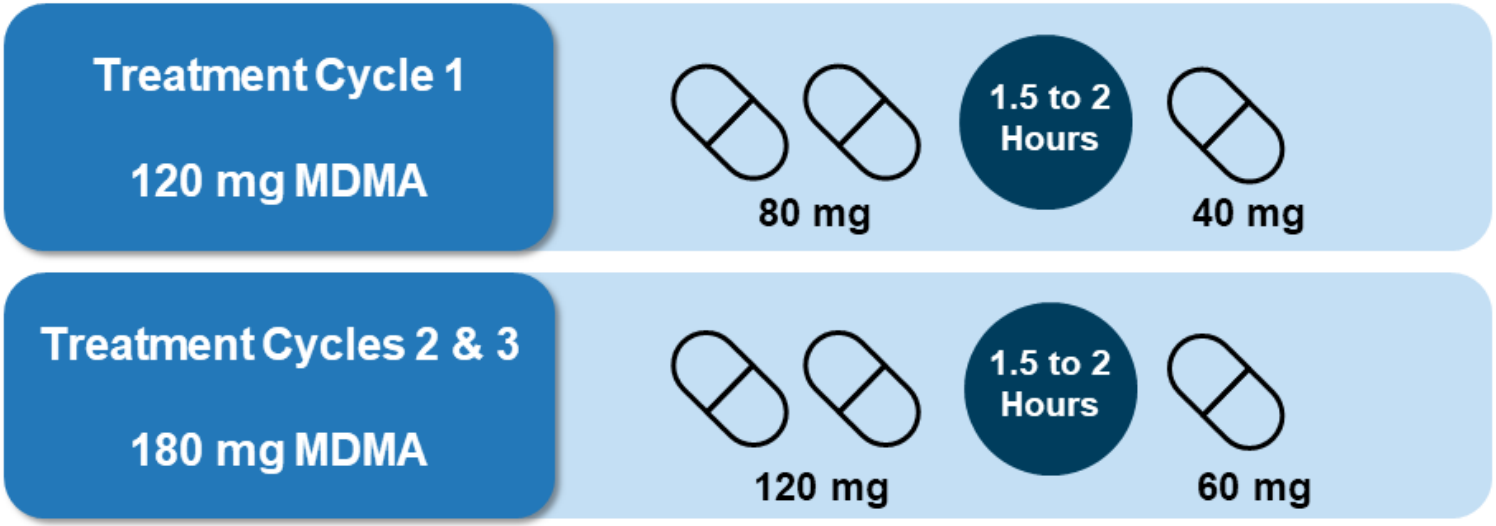
MAPP1 and MAPP2 Clinical Design



*1:1 randomization and baseline endpoint evaluations were conducted following first independent rater (IR) video assessment

Dosing of MDMA Informed by Phase 2 Studies, Literature and Pharmacokinetic Modeling

- MDMA does not require daily dosing or steady state plasma levels to be effective in PTSD
- Onset of action: ~ 0.5 hours post-dose
- Subjective effects: peak ~ 1.5 hours, persists for 3-6 hours



Phase 3 trials specified dose of the hydrochloride salt of MDMA

Therapeutic Program Informed by Nine Phase 2 Studies

- Greater mean reduction in CAPS for 3 medication sessions vs 2 with comparable safety
  - No further effect observed with 4 to 6 medication sessions
- Tested 6 to 8-hour medication sessions
- Time (> 21 days) between medication sessions allows
  - Sufficient time for processing and integration of insights
  - Three 90-minute integration psychotherapy visits

MDMA-AT Provides Personalized Experience and Develops Therapeutic Alliance

- Comfortable sitting room with option for music
- Standardized therapeutic program conducted per therapy manual
- Goal is to express and process memories and emotions
- Therapists encourage use of stress coping techniques, as needed

Yehuda Lab MDMA-AT treatment room at James J Peters VAMC, New York

Provides personalized patient directed therapy session

Study Personnel Had Different Roles and Responsibilities to Support Patients

CO-25

Site Physician / Principal Investigator	▪ Accountable for conduct of study ▪ DEA license holder ▪ Eligibility determination ▪ Responsible for safety oversight and AE reporting
Site Therapists	▪ Therapy team conducted MDMA-AT similarly across all patients, following treatment manual and study protocol ▪ Not involved in administration of efficacy assessments
Independent Raters (IR)	▪ Trained to administer blinded primary and key secondary outcomes per guidelines, in a reliable, neutral, non-leading manner ▪ No IR to assess the same patient more than once on the CAPS-5
Study Oversight Personnel	▪ Oversight of therapy sessions to ensure consistency ▪ Quality control of endpoint assessments conducted by Independent Raters

MAPP1 and MAPP2: Primary and Key Secondary Endpoint

Primary Endpoint	Change in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total severity score from Baseline to Week 18
Key Secondary Endpoint	Change in clinician-rated functional impairment, measured by mean of Sheehan Disability Scale (SDS) items from Baseline to Week 18

CAPS-5: Validated Clinician-Administered Measure for PTSD Diagnosis and Symptom Severity

20 Symptoms Across 4 Domains			
Intrusion	Avoidance	Cognitions and mood	Arousal and reactivity

CAPS-5 Total Severity Score Categories

Asymptomatic	Mild	Moderate	Severe	Extreme
0 – 10	11 – 22	23 – 34	35 – 46	47 – 80

Weathers et al. 2018

Measures Taken to Address Functional Unblinding and Expectation Bias

- CAPS-5 is a more objective evaluation than many patient-reported outcome measures
- Primary endpoint assessed 6-8 weeks after last medication session
- Administered by blinded independent raters who ask standardized in-depth questions about each PTSD symptom
  - Elicits a detailed and largely behavioral description
  - Received training at beginning and throughout study
  - Blinded to study design and treatment
  - Remote, not present at or affiliated with any sites
- Participants trained and assessed by different raters at each timepoint

Pre-Specified Primary Endpoint Statistical Analysis

- Analysis population: modified intent-to-treat (mITT) population
  - Randomized, received ≥ 1 dose in one treatment cycle and had ≥ 1 post baseline CAPS-5 assessment
- Analysis: mixed-model for repeated measures (MMRM)
  - De jure estimand: includes CAPS-5 assessments while adhering to treatment
  - Sensitivity analysis: de facto estimand which includes all CAPS-5 assessments regardless of treatment adherence

MAPP1 and MAPP2 Similar Key Enrollment Criteria

Inclusion Criteria

- Age ≥ 18 years
- Met DSM-5 for current PTSD with symptom duration ≥ 6 months
- PTSD symptom severity
  - **MAPP1:** CAPS-5 ≥ 35 (≥ severe)
  - **MAPP2:** CAPS-5 ≥ 28 (≥ moderate)

Exclusion Criteria

- Potential for re-exposure to trauma
- Recent or extensive pre-trial use of illicit MDMA
- Engaged in litigation related to PTSD
- Without social support or stable living conditions
- Unable to taper off medications used to treat PTSD
- Current or history of primary psychotic disorder, bipolar disorder 1, or dissociative identity disorder
- Uncontrolled essential hypertension (140/90 mmHg or higher)
- History of any medical condition to make sympathomimetic drug harmful due to increases in blood pressure and heart rate

MAPP1 and MAPP2 Phase 3 Study Results

Pivotal Studies: Baseline Patient Demographics

Characteristic	MAPP1		MAPP2	
	MDMA-AT N = 46	Placebo + Therapy N = 44	MDMA-AT N = 53	Placebo + Therapy N = 51
Age, mean (SD) **(years)**	**43.6** (12.9)	**38.2** (10.4)	**38.2** (11.0)	**40.0** (9.6)
Female	59%	73%	60%	82%
Race*				
White	85%	68%	70%	63%
Black or African American	0	5%	9%	6%
Asian	4%	11%	9%	12%
Other	7%	0	0	6%
Multiple	4%	14%	11%	14%
Hispanic or Latino	11%	7%	32%	22%
BMI, mean (SD)	**26.0** (4.8)	**24.8** (4.2)	**26.3** (5.6)	**24.7** (4.9)

*1 placebo patient with missing race; mITT population

Pivotal Studies: Baseline PTSD Characteristics Similar Across Arms

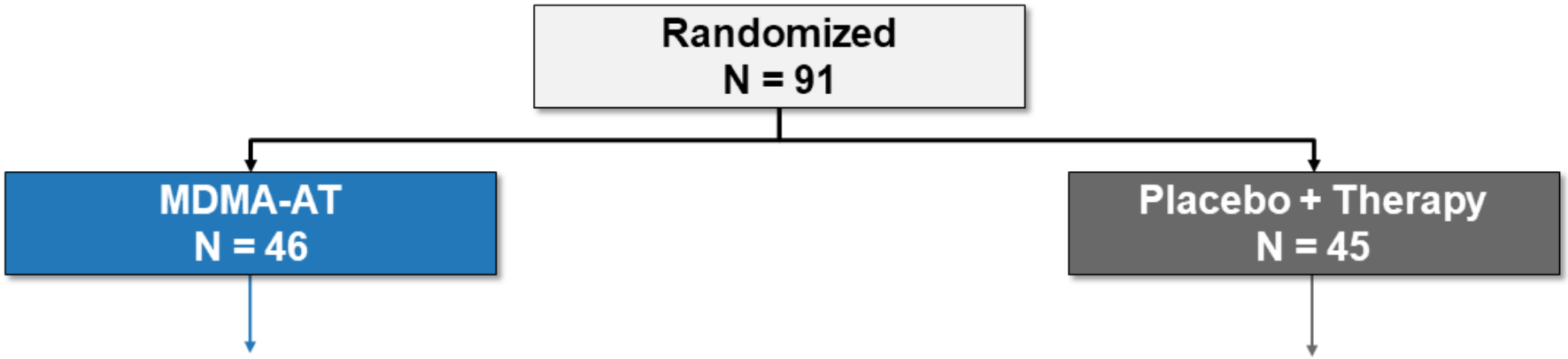
Characteristic	MAPP1		MAPP2	
	MDMA-AT N = 46	Placebo + Therapy N = 44	MDMA-AT N = 53	Placebo + Therapy N = 51
PTSD Duration (years), mean (SD)	**14.8** (11.6)	**13.3** (11.4)	**16.3** (14.3)	**16.1** (12.4)
Trauma History				
Developmental trauma event	**87%**	**82%**	**92%**	**84%**
Veteran	**22%**	**14%**	**17%**	**14%**
Served in combat area	**13%**	**11%**	**17%**	**12%**
Multiple trauma	**89%**	**86%**	**75%**	**88%**
Pre-study PTSD medication				
Sertraline	**26%**	**25%**	**28%**	**20%**
Paroxetine	**9%**	**9%**	**2%**	**2%**
Any previous psychotherapy	**98%**	**98%**	**96%**	**96%**
CAPS-5 total severity score, mean (SD)	**44.0** (6.0)	**44.2** (6.2)	**39.4** (6.6)	**38.7** (6.7)
SDS total score, mean (SD)	**6.8** (2.1)	**7.4** (1.6)	**6.0** (1.8)	**6.1** (1.8)

mITT population

Pivotal Studies: Psychiatric Medical History

Psychiatric Disorders Preferred Term ≥ 25%	MAPP1		MAPP2	
	MDMA-AT N = 46	Placebo + Therapy N = 44	MDMA-AT N = 53	Placebo + Therapy N = 51
Suicidal ideation	91%	93%	83%	92%
Major depression	91%	91%	93%	100%
Insomnia	83%	70%	68%	67%
Anxiety	57%	46%	55%	51%
Suicide attempt	35%	23%	19%	24%
Attention deficient / hyperactivity disorder	33%	14%	26%	20%
Nightmare	30%	32%	51%	35%
Social anxiety disorder	28%	30%	25%	24%
Generalized anxiety disorder	28%	23%	32%	26%
Intentional self-injury	26%	16%	21%	29%

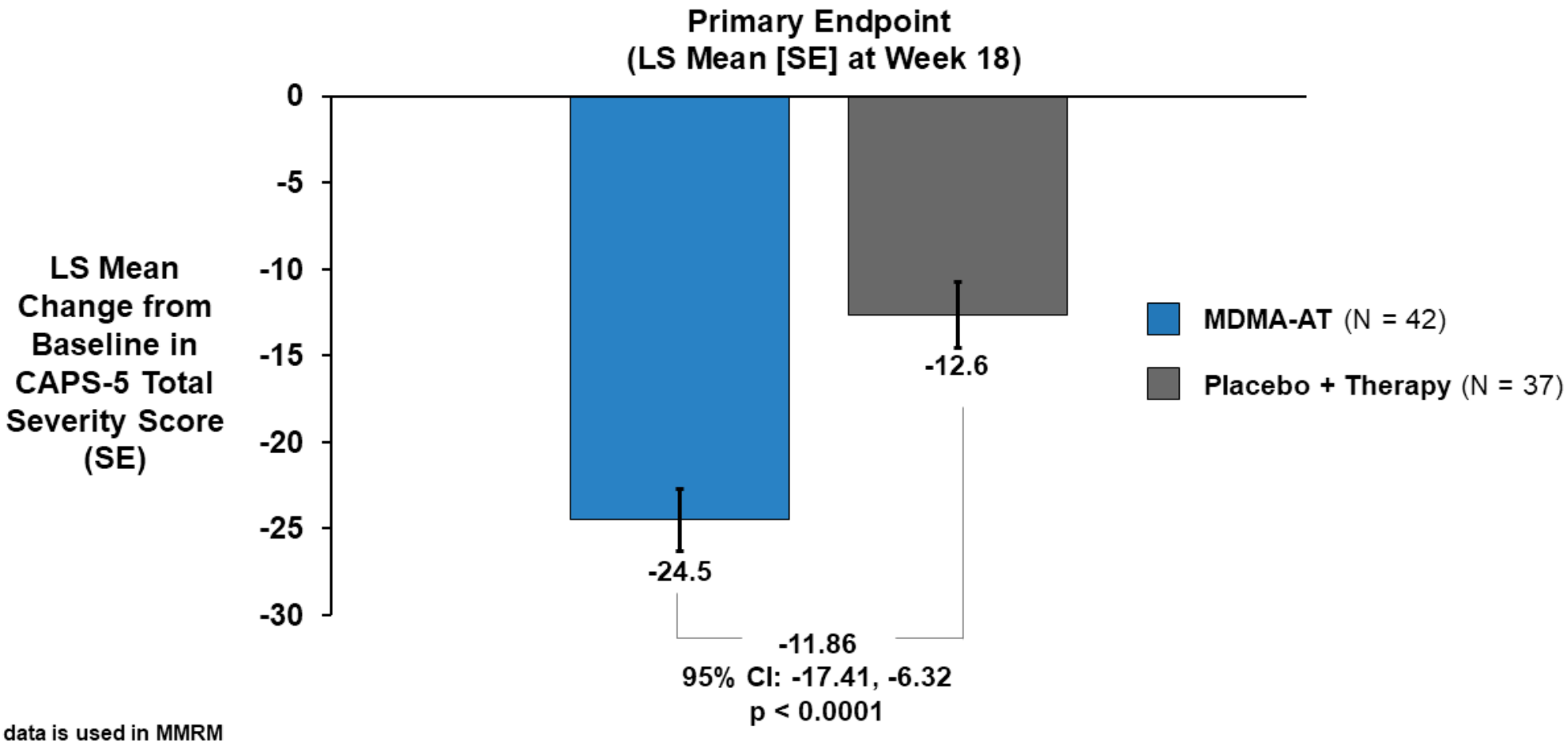
MAPP1: Patient Disposition



MDMA-AT N = 46		Placebo + Therapy N = 45
0	Adverse event	3
1	Administrative reason	1
1	Investigator chose to discontinue treatment	0
1	Patient chose to discontinue treatment	1
0	Patient declined participation	1
1	Withdrawal of consent	1
0	Other	1
42 (91%)	Completed Study	37 (82%)

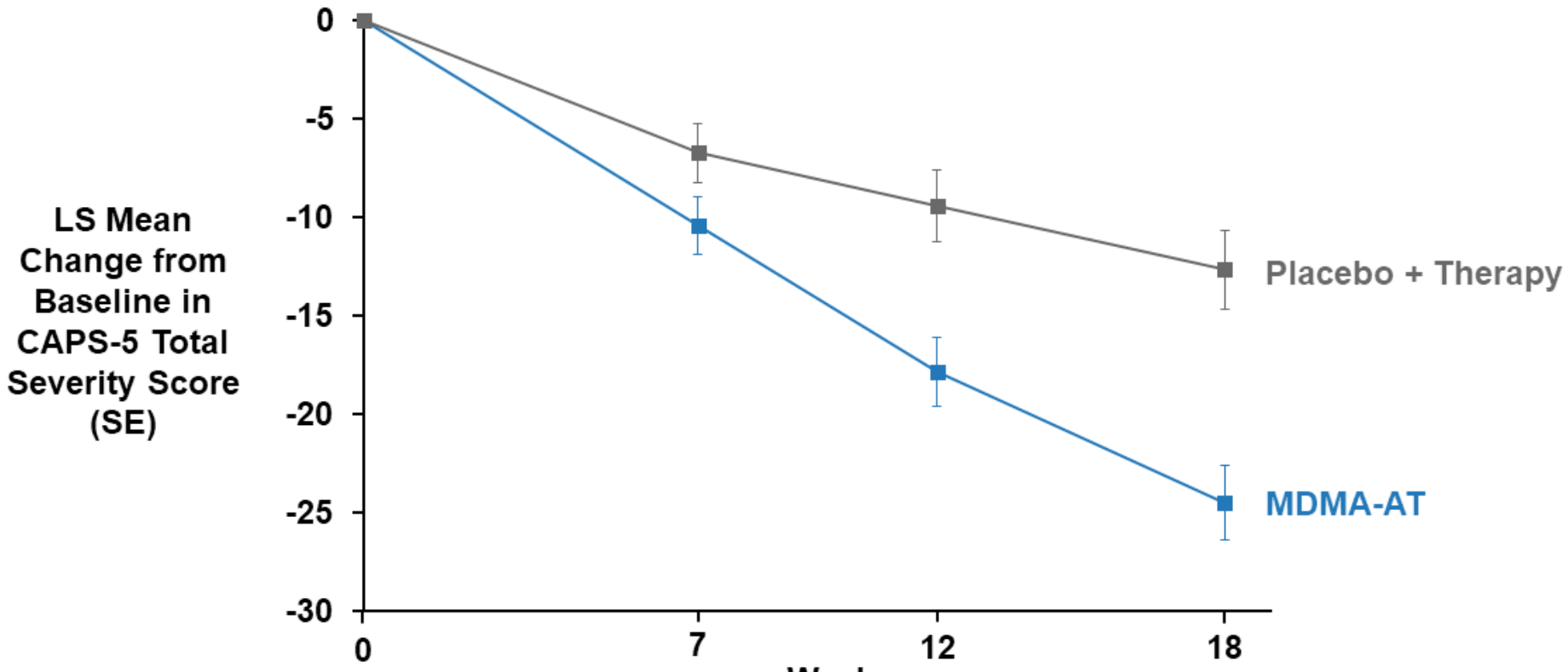
mITT population

MAPP1: Primary Endpoint Met – Statistically Significant Improvement vs Placebo in CAPS-5



All data is used in MMRM

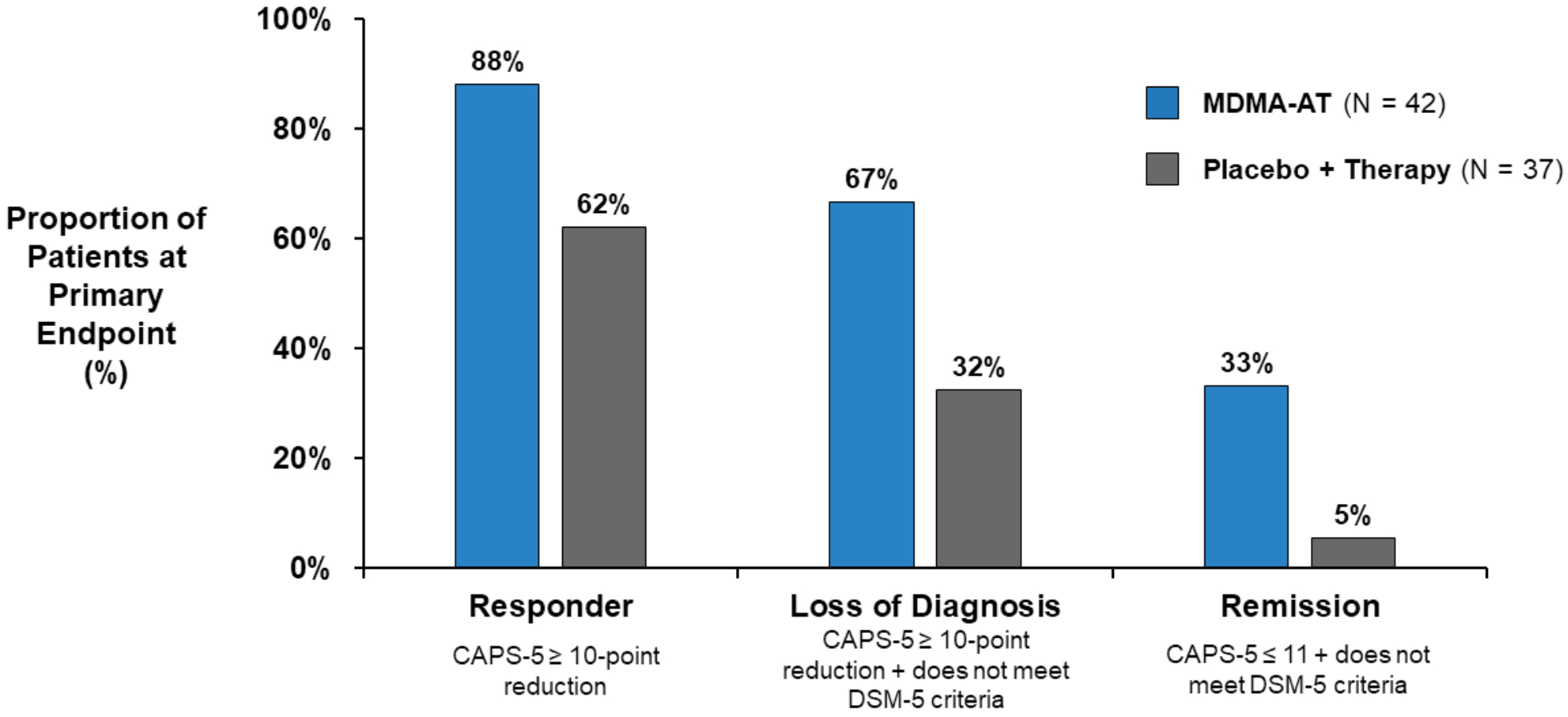
MAPP1: MDMA-AT Separates Early and Effect Maintained Through Week 18 Compared to Placebo



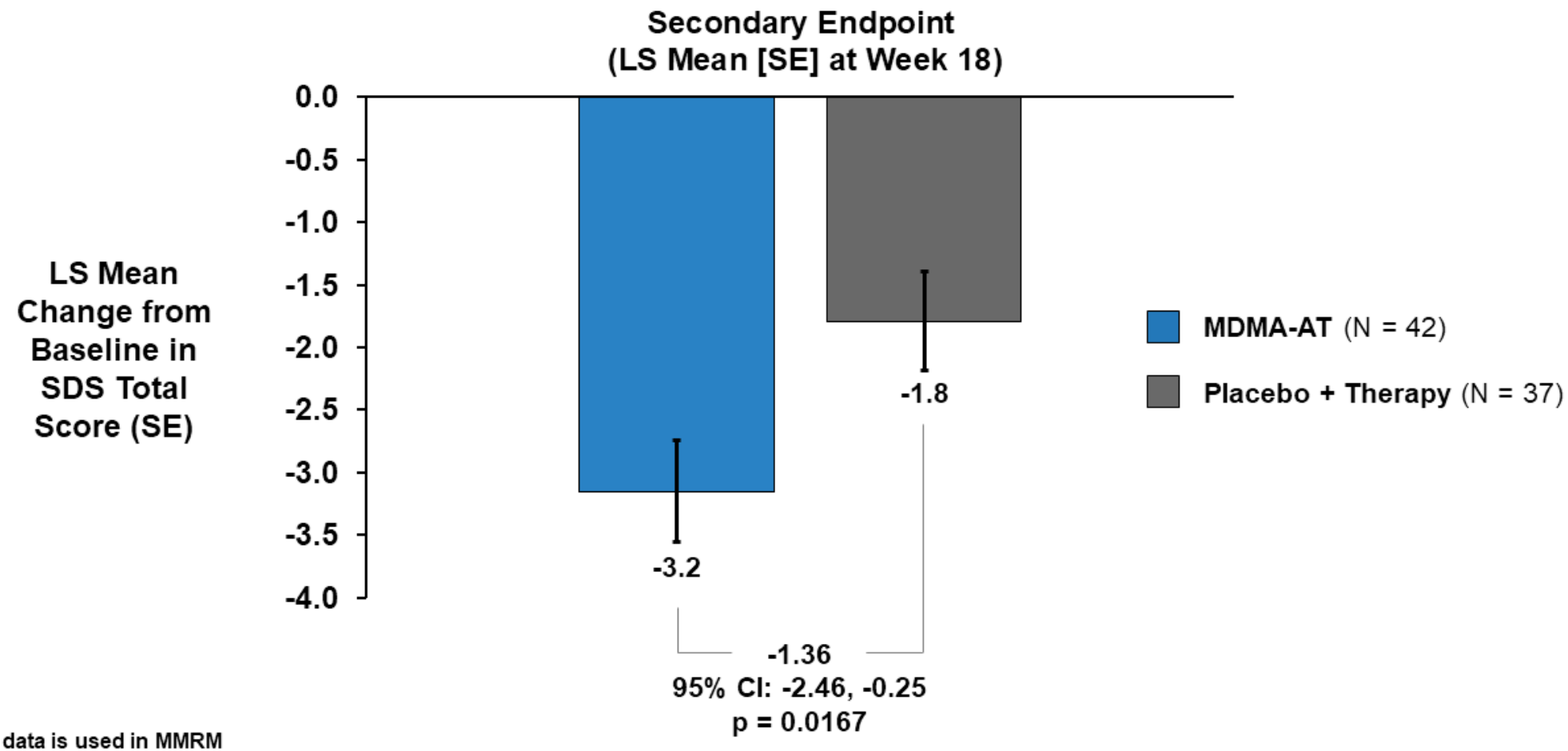
MDMA-AT N	46	46	42	42
Placebo N	44	43	39	37

All data is used in MMRM

MAPP1: MDMA-AT Associated with Greater Rates of Response, Loss of PTSD Diagnosis, and Remission vs Placebo

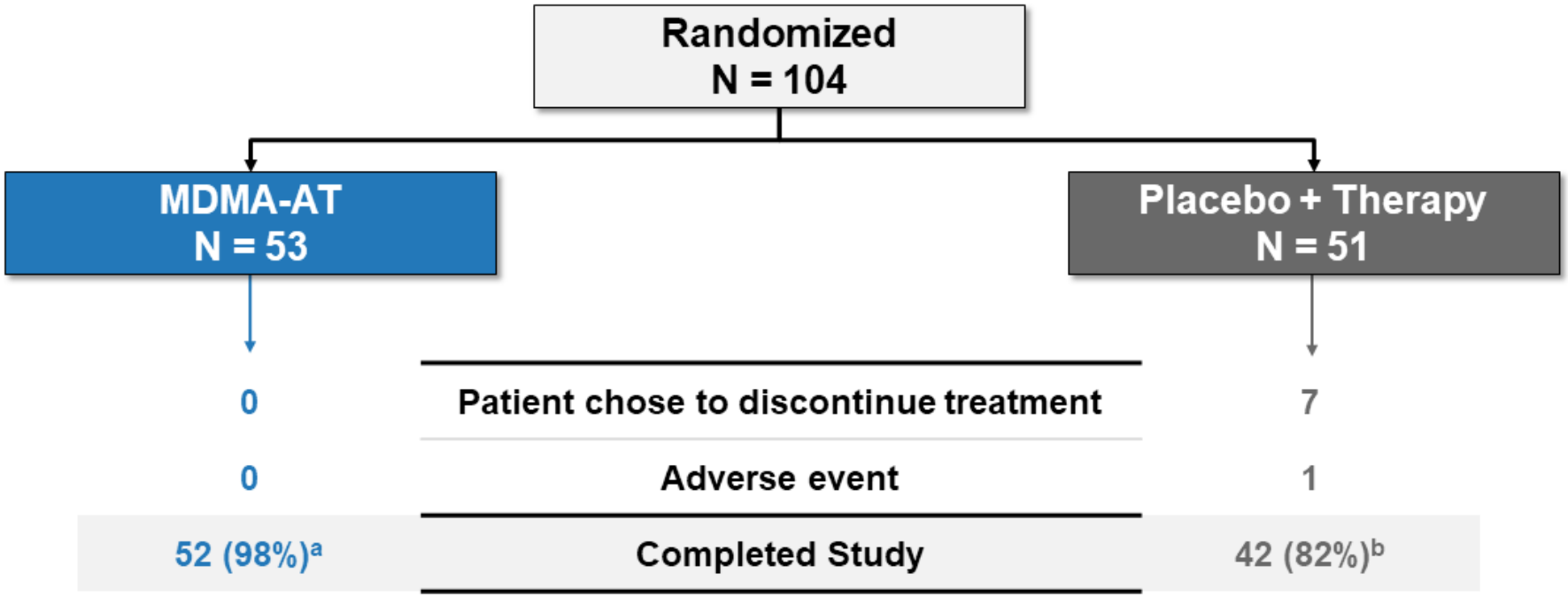


MAPP1: Key Secondary Endpoint Met Demonstrating Functional Improvements



All data is used in MMRM

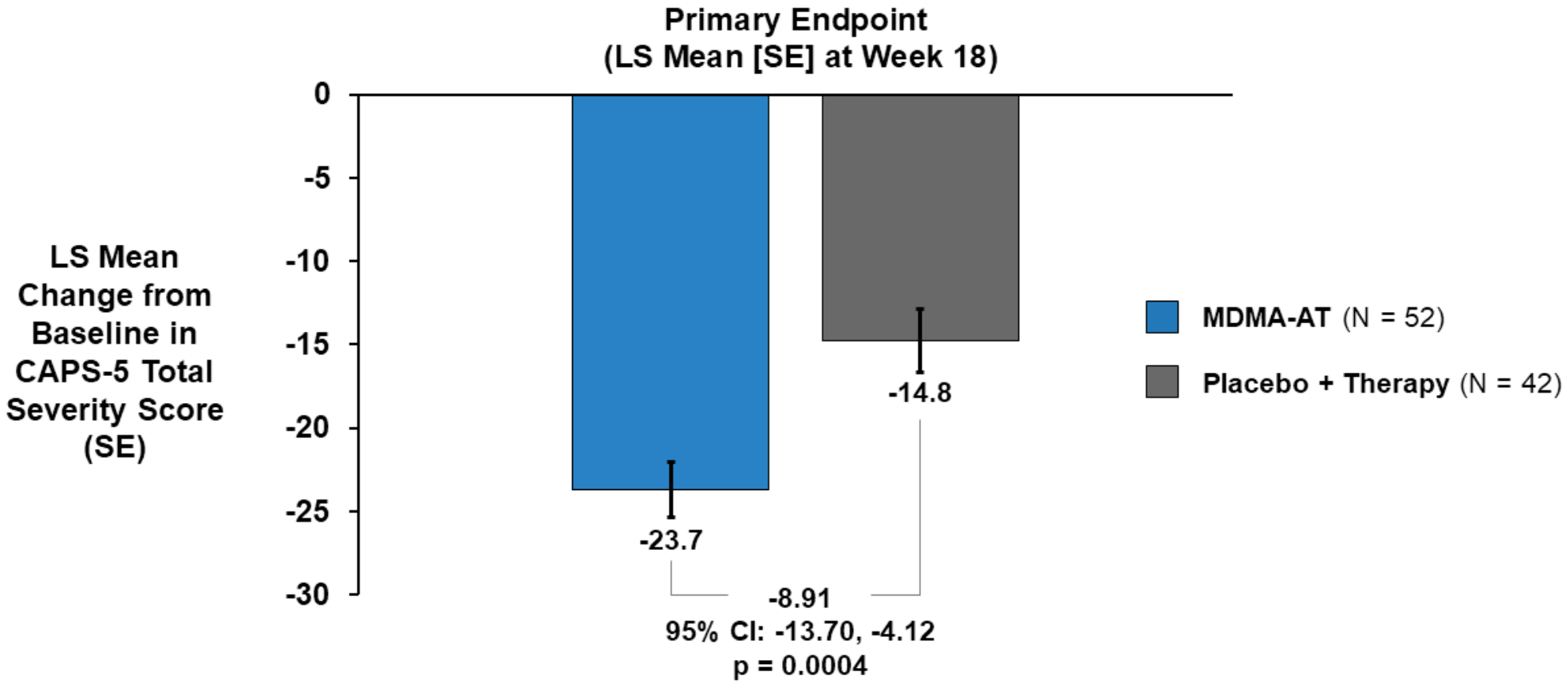
MAPP2: Patient Disposition



mITT population

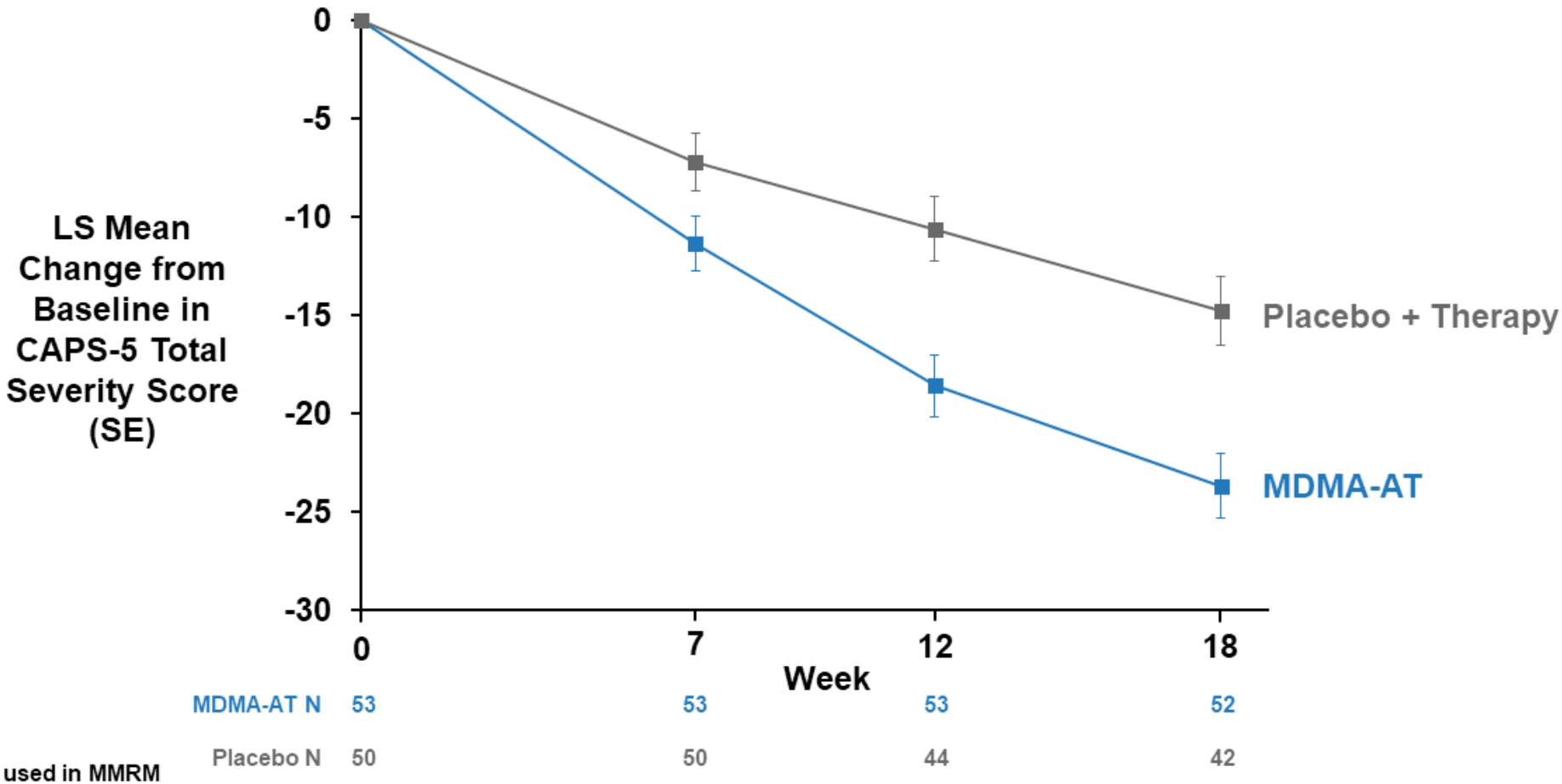
a. One patient completed 3 medication sessions but not primary endpoint assessment; b. 1 patient completed study but had no outcome assessment

MAPP2: Primary Endpoint Met – Statistically Significant and Clinically Meaningful Improvement with MDMA-AT



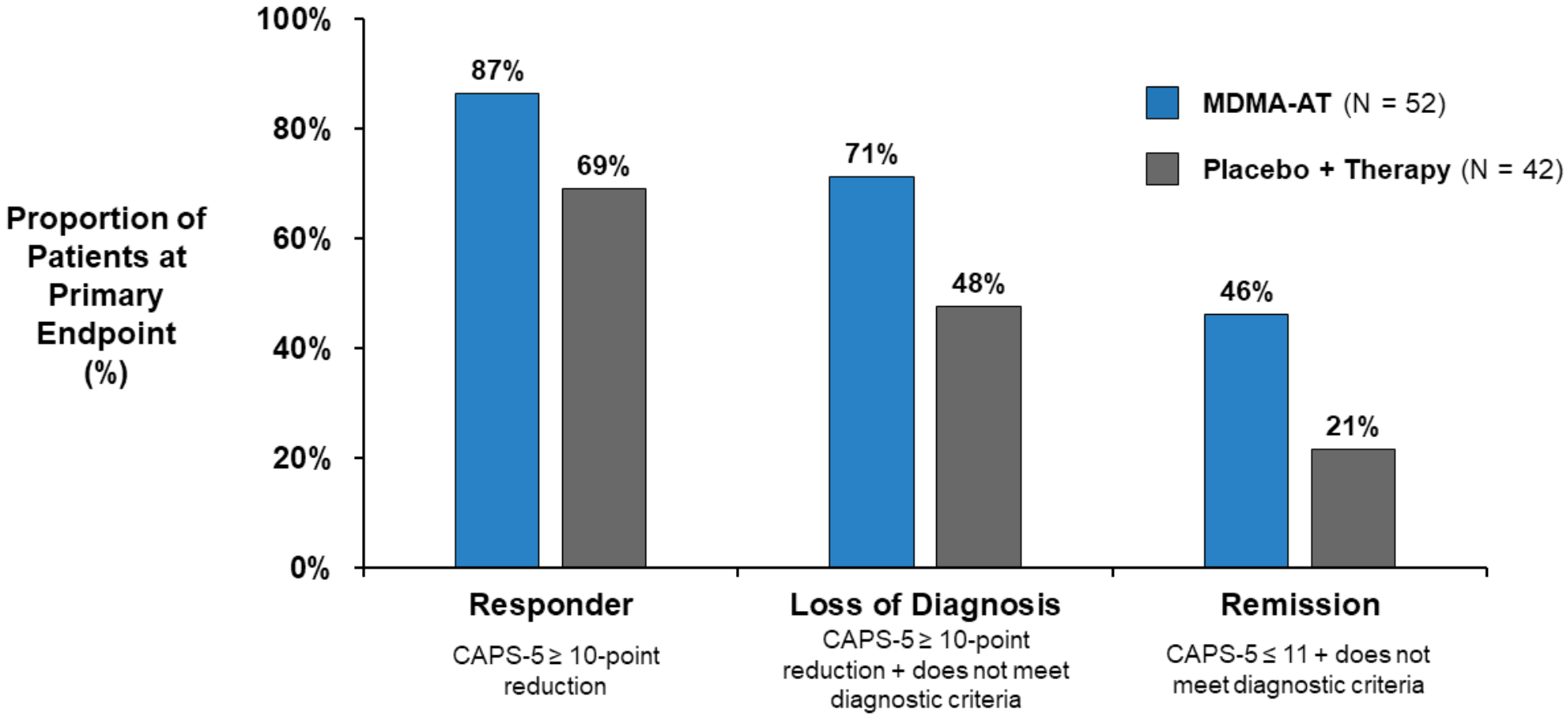
All data is used in MMRM

MAPP2: MDMA-AT Separates Early and Effect Maintained Through Week 18 Compared to Placebo

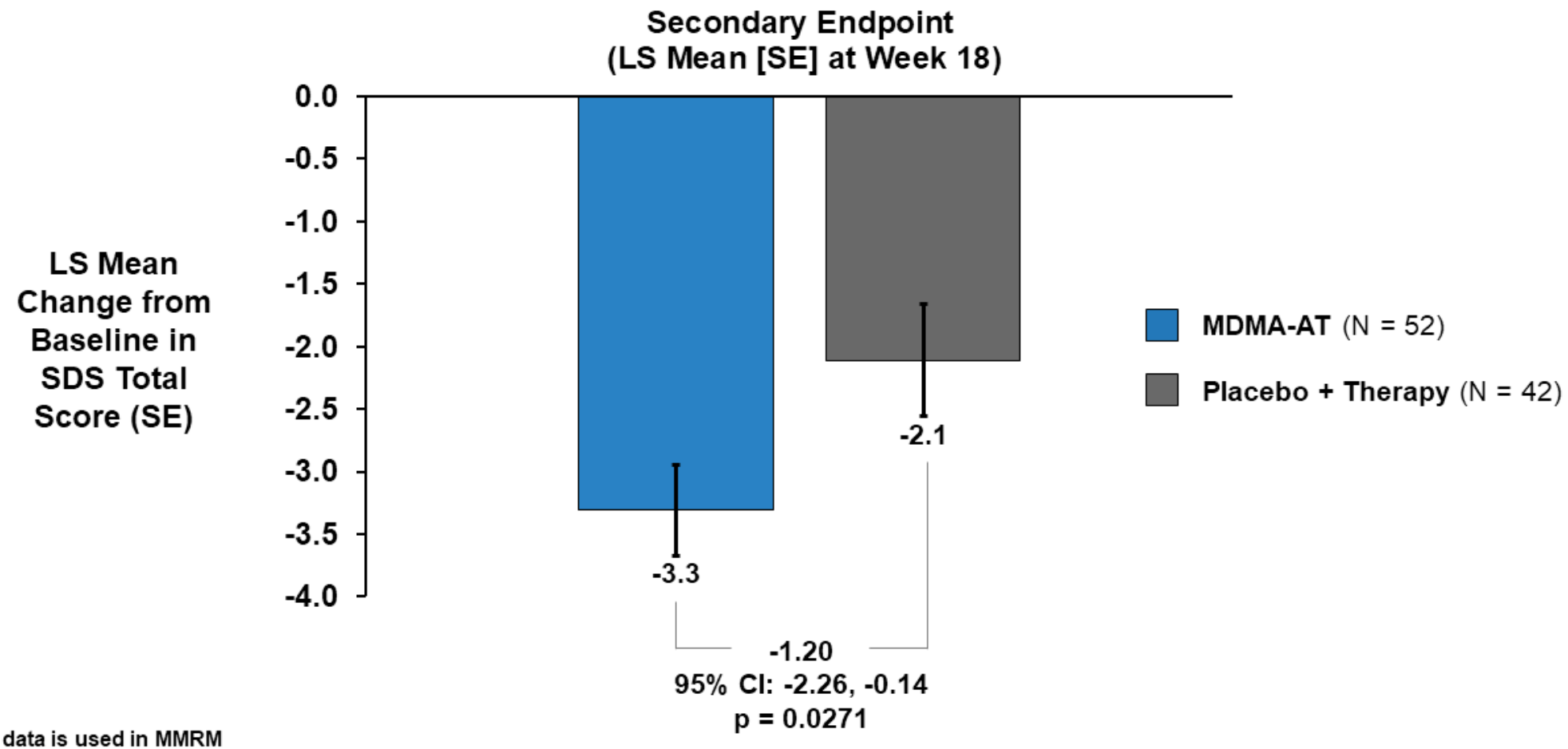


All data is used in MMRM

MAPP2: Greater Rates of Treatment Response, Loss of PTSD Diagnosis, and Remission in MDMA-AT Patients



MAPP2: Key Secondary Endpoint Met Demonstrating Functional Improvements



All data is used in MMRM

MPLONG Long-Term Follow-Up Study

MPLONG: Long-Term Observational Study

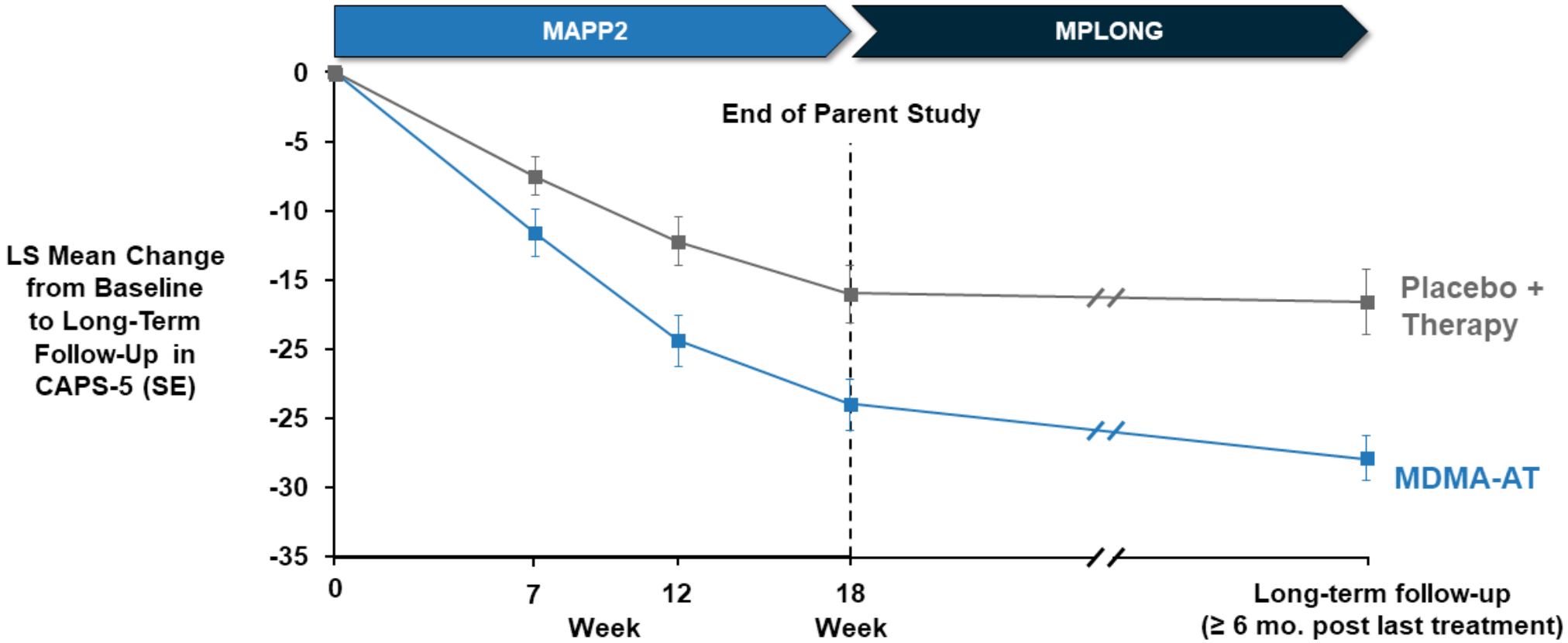
- Long-term follow-up with assessments conducted at least 6 months after completion of MAPP1 / MAPP2
- Open for enrollment ~ 7 months after last medication session in MAPP1 and open throughout MAPP2
  - MAPP1 patients unblinded: 67% of patients participated (60/90); 30 MDMA, 30 placebo
  - MAPP2 patients blinded: 80% of patients participated (82/103); 45 MDMA, 37 placebo
- CAPS-5 assessment at least 6 months after parent study

MPLONG: Patient Demographics and Characteristics (MAPP2 Patients)

Characteristic	MDMA-AT N = 45	Placebo + Therapy N = 37
Age, mean (SD) **(years)**	**38.0** (11.5)	**40.0** (9.9)
Female	**60%**	**78%**
White	**64%**	**62%**
Hispanic or Latino	**33%**	**22%**
CAPS-5, mean (SD)		
Baseline	**39.1** (6.2)	**38.9** (6.8)
Study Termination	**14.9** (12.2)	**23.2** (13.0)
SDS, mean (SD)		
Baseline	**6.1** (1.6)	**6.1** (1.7)
Study Termination	**2.6** (2.6)	**3.7** (2.8)
Time of follow-up, mean (SD) **(months)**[1]	**10.2** (3.3)	**9.6** (3.4)

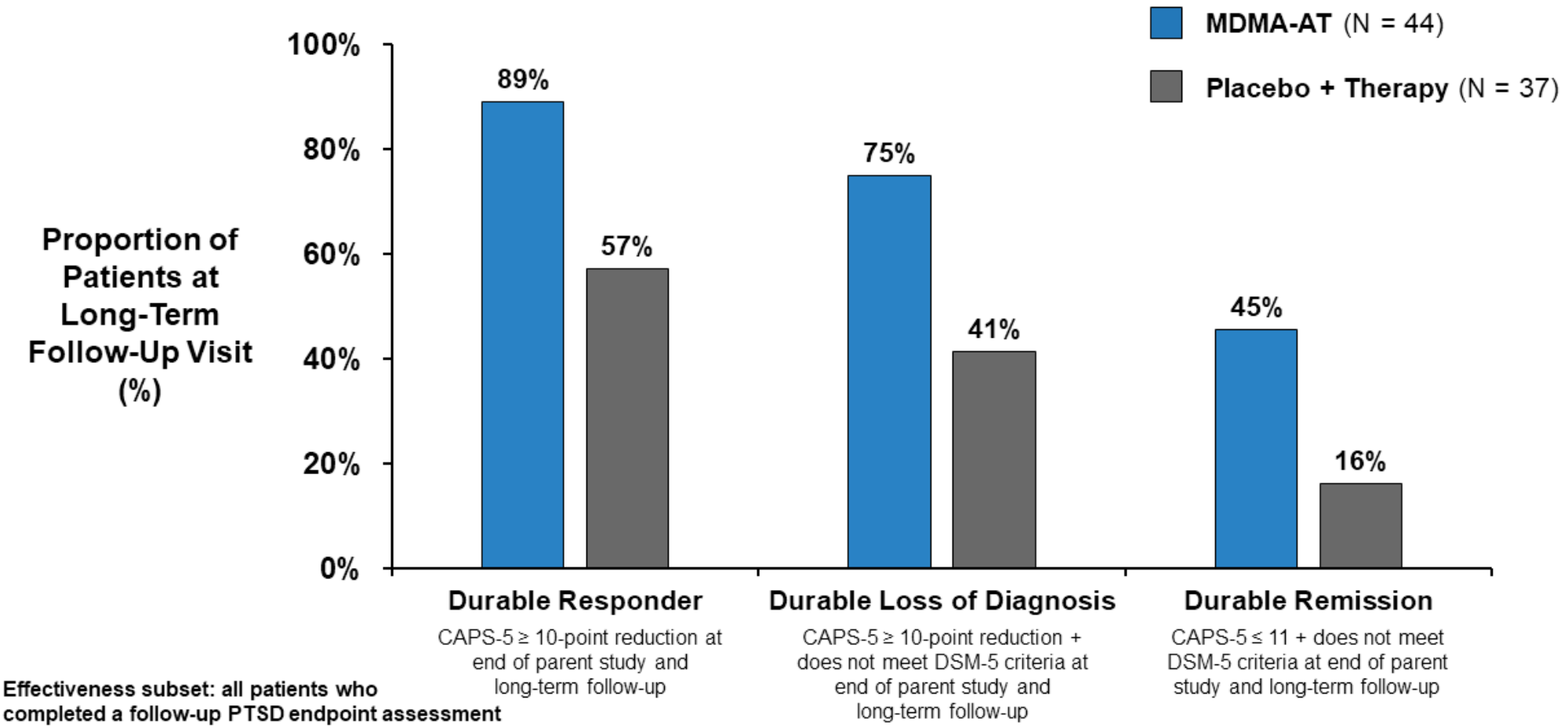
1. MDMA-AT (n = 43) and Placebo + Therapy (n = 36), based on CAPS-5 completion

MPLONG: MDMA Offers Durable Effect Compared to Placebo (MAPP2 Patients)



Effectiveness subset: all patients who completed a follow-up PTSD endpoint assessment

MPLONG: Continued Greater Rates of Treatment Response, Loss of PTSD Diagnosis, and Remission (MAPP2 Patients)



Effectiveness subset: all patients who completed a follow-up PTSD endpoint assessment

Summary of Overall Efficacy

- MAPP1 and MAPP2 met CAPS-5 primary endpoint and SDS key secondary endpoint
- CAPS-5 and SDS showed separation post-baseline at first assessment with evidence of durability
- Greater proportion of MDMA-AT patients classified as responders, loss of PTSD diagnosis and in remission compared to placebo
- All sensitivity analyses support the primary and key secondary endpoint conclusions

MDMA-AT provides statistically significant and clinically meaningful improvement in PTSD symptoms and functional impairment

Safety

Alia Lilienstein, MD, MPH

Senior Medical Director, Head of Clinical Science

Lykos Therapeutics

Safety Database

Known safety profile

Muscle tightness, decreased appetite, nausea, hyperhidrosis, blood pressure / heart rate increases, neuropsychological effects

MDMA Safety Database: N = 477 across 18 studies*
N = 287 with PTSD received MDMA

Phase 1	Phase 2	Pivotal Phase 3	Follow up / Cross over
(4 studies*)	(9 studies)	(2 studies)	(3 studies)
N = 190	N = 148	N = 99	N = 40

***Includes NIDA Study N = 50**

Most Patients Received Intended Dosing Regimen of MDMA in Phase 3 Studies

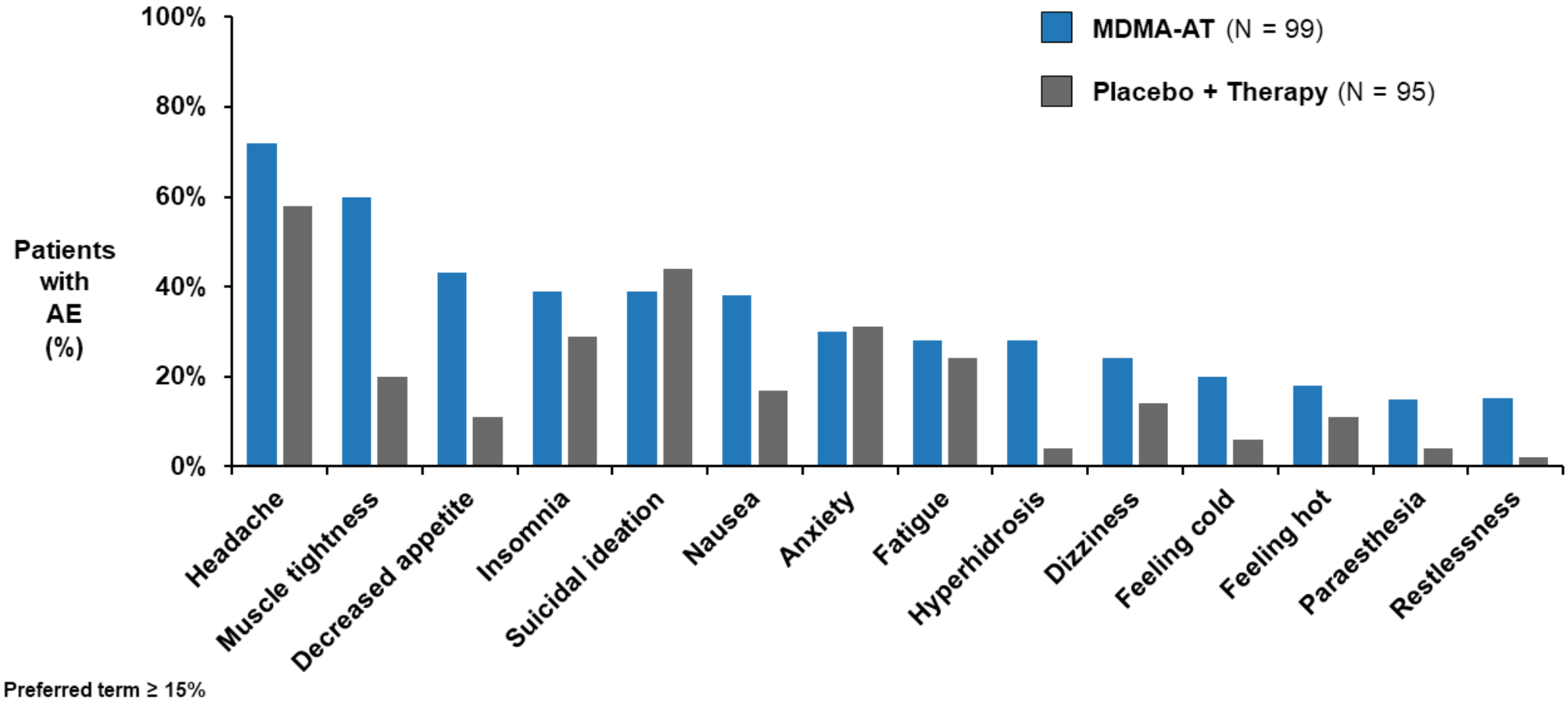
Split dose	Treatment Cycle 1	Treatment Cycle 2		Treatment Cycle 3	
1st part	80 mg N = 99 (100%)	120 mg N = 94 (95%)	80 mg N = 2 (2%)	120 mg N = 92 (93%)	80 mg N = 3 (3%)
2nd part	40 mg N = 96 (97%)	60 mg N = 93 (94%)	40 mg N = 2 (2%)	60 mg N = 91 (92%)	40 mg N = 3 (3%)

Phase 3 trials specified dose as the hydrochloride salt of MDMA

Pooled Phase 3 Studies: Overall Summary of Adverse Events

Patients with ≥ 1 event	MDMA-AT N = 99	Placebo + Therapy N = 95
AE	100%	98%
Severe AE	9%	9%
SAE	0	2%
AEs leading to discontinuation	1%	5%
Death	0	0

Pooled Phase 3 Studies: Most Common Adverse Events



Preferred term ≥ 15%

Key Observed and Potential Risks

Neuropsychological and Physiologic Effects

- Temporary alterations in mental state may result in patient impairment
  - Increase feelings of empathy, openness, and connectedness
  - Decrease in sensitivity to fear or anger
- Risks related to perceptual changes and physiologic effects
  - Dizziness (24%), mydriasis (13%), nystagmus (13%), blurred vision (12%), and gait disturbance (5%)
- Measures to mitigate risk in Phase 3 trials
  - Preparatory therapy sessions to establish rapport
  - Licensed and trained therapists
  - Support during medication sessions and driving restrictions

Emergence or Exacerbation of Suicidality Assessed

- Patients excluded
  - Serious imminent suicidal risk
  - Likely to be re-exposed to their index trauma or other significant trauma
- Lifetime suicidal ideation assessed by C-SSRS (Phase 3 pooled)
  - Any ideation: MDMA 87%, placebo 88%
  - Serious ideation: MDMA 35%, placebo 37%
  - Suicidal behavior: MDMA 27%, placebo 31%

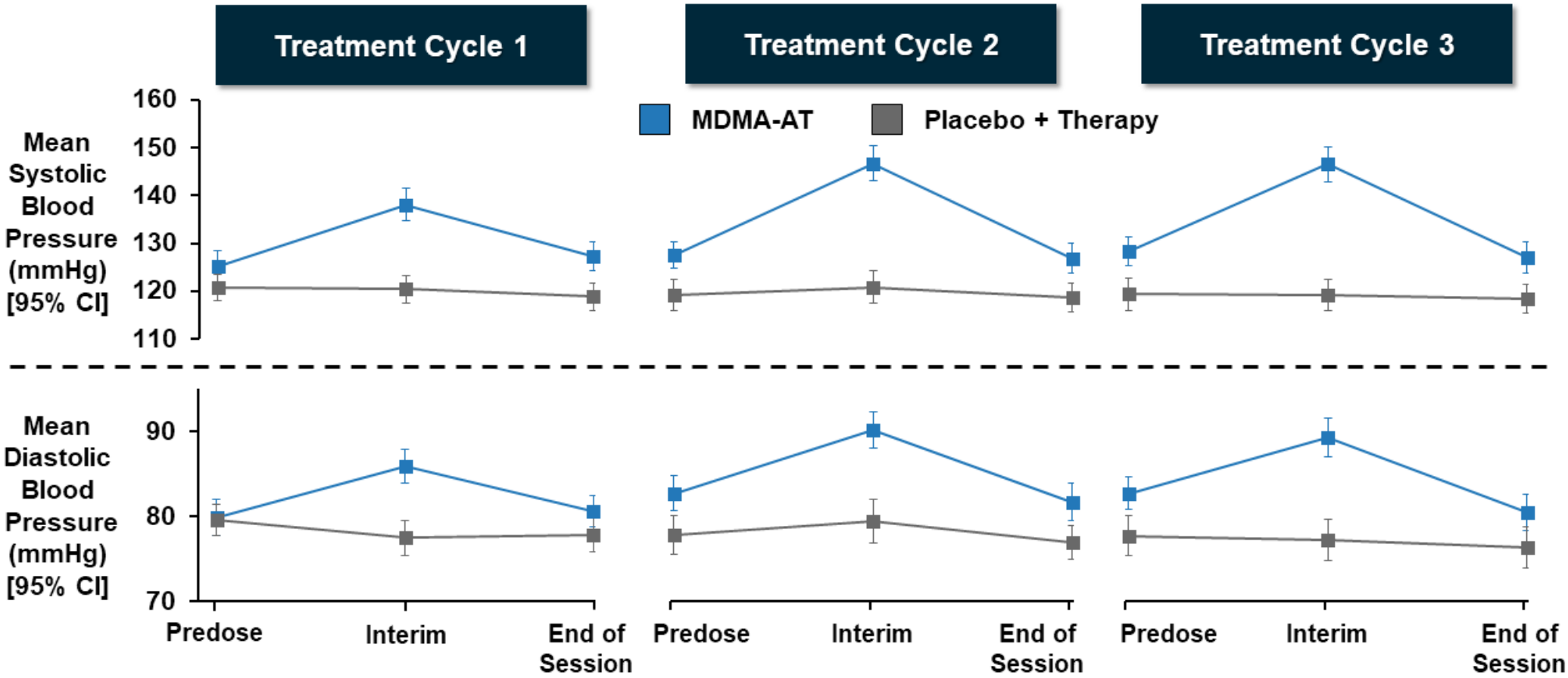
Suicidality AEs Comparable in Both Groups

Preferred Term, %	MDMA-AT N = 99	Placebo + Therapy N = 95
Suicidal ideation	39%	44%
Intentional self-injury	3%	5%
Suicidal behavior	0	2%
Suicide attempt	0	1%

Pooled Phase 3 Studies: MDMA is Known to Increase Blood Pressure and Heart Rate

- Patients with moderate CV risk underwent additional screening measures, including stress testing
  - e.g. well-controlled hypertension or diabetes
- Patients excluded with relevant underlying medical conditions
  - Uncontrolled hypertension
  - Significant cardiovascular or cerebrovascular disease
  - Atrial and ventricular tachyarrhythmias
- Vital signs measured pre-dose, interim, and at end of medication sessions

Transient Self-Limiting Dose-Dependent Blood Pressure Increases

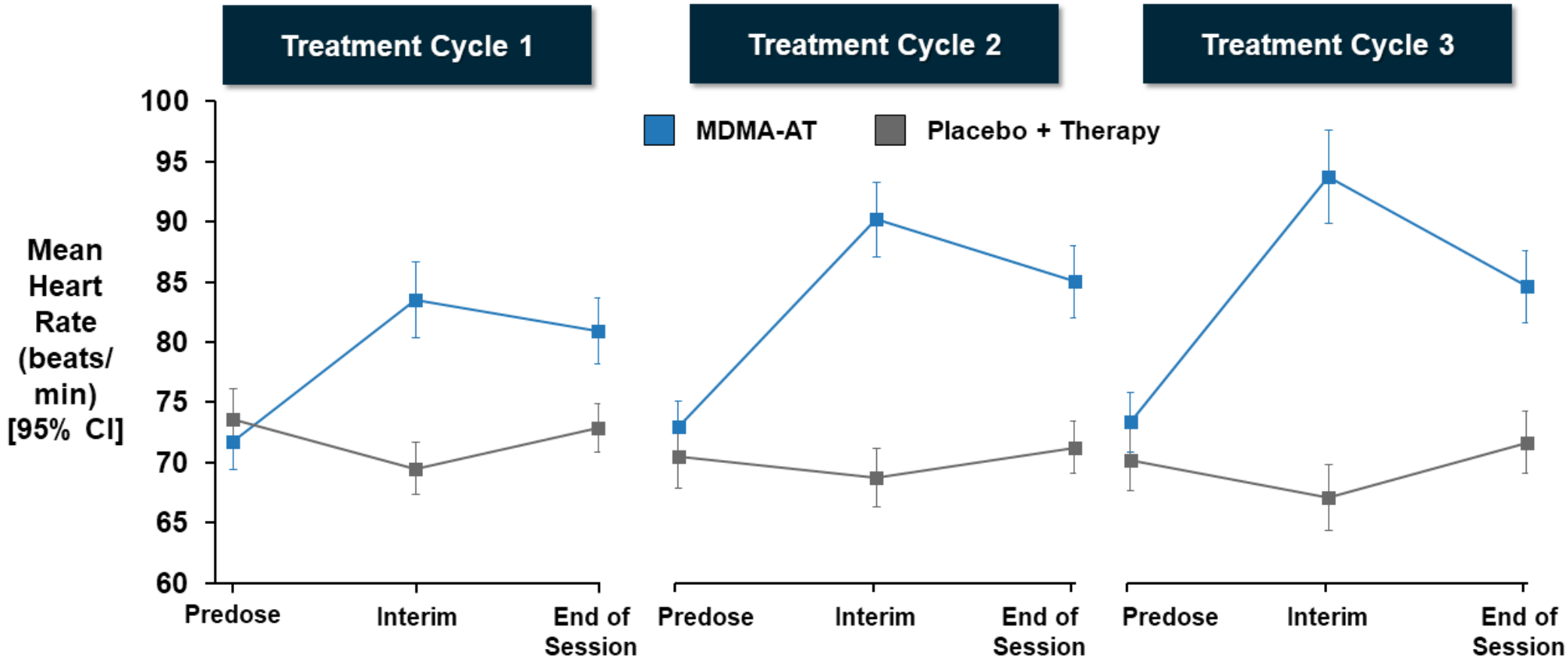


Interim: 1.5 – 2 hours after first part of split dose; end of session: 7.5 hours after first part of split dose

Pooled Phase 3 Studies: Blood Pressure Results by Clinically Relevant Thresholds

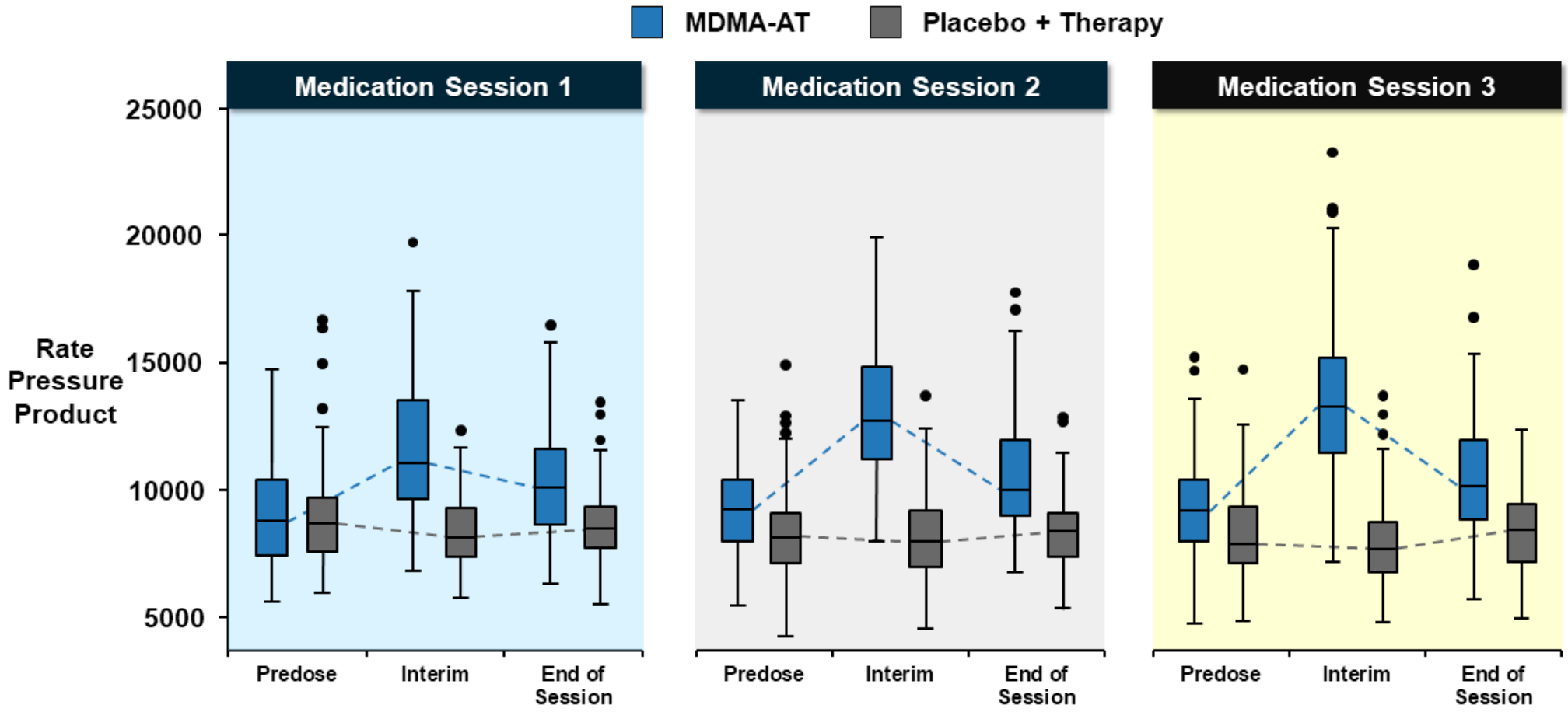
Category, %	MDMA-AT 80 mg N = 99	MDMA-AT 120 mg N = 95		Placebo + Therapy N = 95
		Session 2 N = 94	Session 3 N = 92	Sessions 1, 2, or 3
Systolic blood pressure				
≥ 140 mmHg	46%	62%	57%	26%
≥ 180 mmHg	2%	3%	1%	0
≥ 140 mmHg and increase of ≥ 20 mmHg	21%	34%	37%	10%
Diastolic blood pressure				
≥ 90 mmHg	39%	60%	55%	37%
≥ 110 mmHg	1%	3%	1%	1%
≥ 100 mmHg and increase of ≥ 20 mmHg	3%	6%	4%	2%

Pooled Phase 3 Studies: Heart Rate by Treatment Cycle



Interim: 1.5 – 2 hours after first part of split dose; end of session: 7.5 hours after first part of split dose

Pooled Phase 3 Studies: Rate Pressure Product



Interim: 1.5 – 2 hours after first part of split dose; end of session: 7.5 hours after first part of split dose

Pooled Phase 3 Studies: Rate Pressure Product

Hemodynamic Response	Rate Pressure Product*	MDMA N = 99	Placebo N = 95
High	> 30,000	0	0
High Intermediate	25,000 – 29,999	0	0
Intermediate	20,000 – 24,999	4	0
Low Intermediate	15,000 – 19,999	31	0
Low	10,000 – 14,999	54	22
Less < 10,000	< 10,000	10	73

*Rate pressure product summarized is the maximum value for each patient at the interim time point across the three sessions

Abuse Potential of MDMA

- MDMA has moderately high potential for abuse
- Illicit MDMA use is primarily episodic based on epidemiologic data
- Low rates of treatment for substance use disorder
  - MDMA is primarily serotonergic
  - Unlikely to produce physical dependence or withdrawal syndrome
- Morbidity and mortality with illicit MDMA
  - Considerably lower than methamphetamine
  - Similar to amphetamine
  - Higher than methylphenidate

Proposed REMS to Evaluate and Mitigate Risk of Serious Harm Resulting from Patient Impairment

- Only dispensed in certified healthcare settings
- Evidence of safe-use conditions required
  - Training for healthcare setting (e.g., prescribers, pharmacists, therapists)
  - Patient counseling
- Intrasession and post-session patient monitoring
- Mandatory enrollment in Midomafetamine Drug Registry

Proposed Risk Management to Support Safe Use of MDMA-AT Post Approval

Risk	Patient Monitoring	Proposed Label	Prescriber / HCP Education
Neuropsychological and Physiological Effects	✓	✓	✓
Suicidality	✓	✓	✓
Blood Pressure / Heart Rate Increases	✓	✓	✓
Nonmedical Use / Substitution	✓	✓	✓

Additional Efforts to Support Use in Clinical Practice

- Limited sites initially to effectively and safely deliver MDMA-AT
- Therapists will be trained in therapeutic approach used in Phase 3 studies
- Single-dose packaging of acute treatment

Summary of Overall Safety

- AEs consistent with known safety profile
- AEs mostly mild to moderate and transient
- No deaths or SAEs with MDMA-AT in Phase 3 studies
- Key risks manageable with labeling and REMS
- Inherent safeguards of acute treatment limit nonmedical use
- Post-marketing studies and surveillance to further support safety in clinical setting

Clinical Perspective

Kelley O'Donnell, MD, PhD

Research Assistant Professor of Psychiatry
NYU Grossman School of Medicine
Director of Clinical Training
NYU Langone Center for Psychedelic Medicine

Patients with PTSD Need Additional Treatment Options

- PTSD associated with significant increased risk of mortality
  - Medical and psychiatric comorbidities
  - Increased risk of suicide
- Treatments available for PTSD are insufficient
- Pharmacotherapy
  - Low-to-moderate efficacy
  - Polypharmacy
- Evidence-based psychotherapy
  - Associated with high drop-out rates
  - Slow-acting

MDMA Assists the Psychotherapy

May increase patient's sense of empathy and connectedness

May foster patient's sense of safety and trust

May increase recall of affectively charged memories

Serotonergic effects of MDMA often translate to transiently reduced anxiety

Meaningful Clinical Improvement

- Meaningful symptom reduction was associated with functional improvement
  - Increased ability to pursue goals, meaningful relationships
- Patients with residual symptoms continued to process trauma after treatment
  - Often reported greater sense of safety, trust, self-efficacy

MDMA-AT to Fill Serious and Urgent Unmet Need for Patients with PTSD

- Close scrutiny is appropriate in this vulnerable patient population
- With risk mitigation strategies in place, MDMA would be a welcome addition to available treatment options
  - May strengthen therapeutic alliance, and facilitate recall and processing of traumatic memories
  - May facilitate development of durable insights and skills
  - Acute treatment
  - Potential for durable response
- Tolerable safety profile and low drop-out rate

Benefit / Risk Summary

Berra Yazar-Klosinski, PhD

Chief Scientific Officer

Lykos Therapeutics

Positive Benefit-Risk for Treatment of a Life-Threatening Disorder with High Unmet Need

Benefits

- Statistically significant and clinically meaningful improvement in PTSD symptoms and functional impairment
- Durability of effect at least 6 months after completion of treatment
- Consistency of results across studies and over time

Risks and Mitigations

- AEs expected for MDMA
- AEs mostly mild and self-limited
- Labeling and REMS
- Therapist training and limited roll out
- Post-marketing studies and surveillance
- Taken 3 times in presence of HCPs

Midomafetamine-Assisted Therapy (MDMA-AT) for Treatment of Post-Traumatic Stress Disorder (PTSD)

June 4, 2024

Lykos Therapeutics

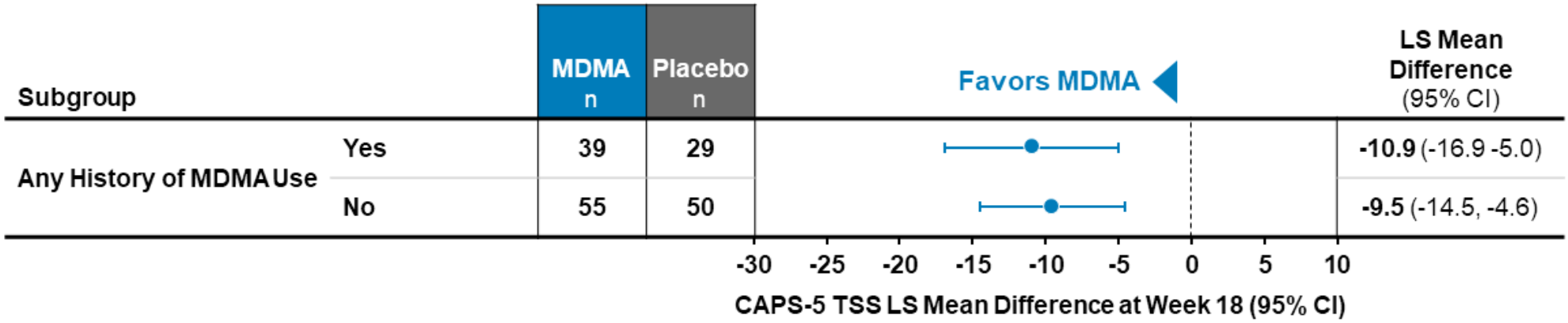
Psychopharmacologic Drugs Advisory Committee (PDAC)

Back-up Slides Shown

History of Alcohol or Substance Abuse, or Illicit MDMA Use Prior to Phase 3 Studies

	MDMA-AT N = 99	Placebo + Therapy N = 95
History of alcohol or substance abuse	26%	26%
History of illicit MDMA use	40%	39%

Treatment Response on CAPS-5 in Pooled Phase 3 Studies Was Comparable in Patients With and Without Prior MDMA Use



Pooled mITT Population

Phase 3 Disposition (Side-by-side and Pooled)

Reason for Study Termination	MAPP1		MAPP2		Pooled	
	MDMA-AT N = 46	Placebo + Therapy N = 44	MDMA-AT N = 53	Placebo + Therapy N = 50	MDMA-AT N = 99	Placebo + Therapy N = 94
Study completed through all visits	91%	84%	98%	86%	95%	85%
Post-randomization early termination	4%	11%	0	8%	2%	10%
Dropout	4%	5%	2%	6%	3%	5%
Lost to follow-up	0	0	0	0	0	0
Primary reason for early termination and dropout						
Adverse event or death	0	7%	0	2%	0	4%
Administrative reason	2%	2%	0	0	1%	1%
Investigator chose to discontinue treatment	2%	0	0	0	1%	0
Patient chose to discontinue treatment	2%	2%	2%	12%	2%	7%
Withdrawal of consent	2%	2%	0	0	1%	1%
Other	0	2%	0	0	0	1%

mITT population

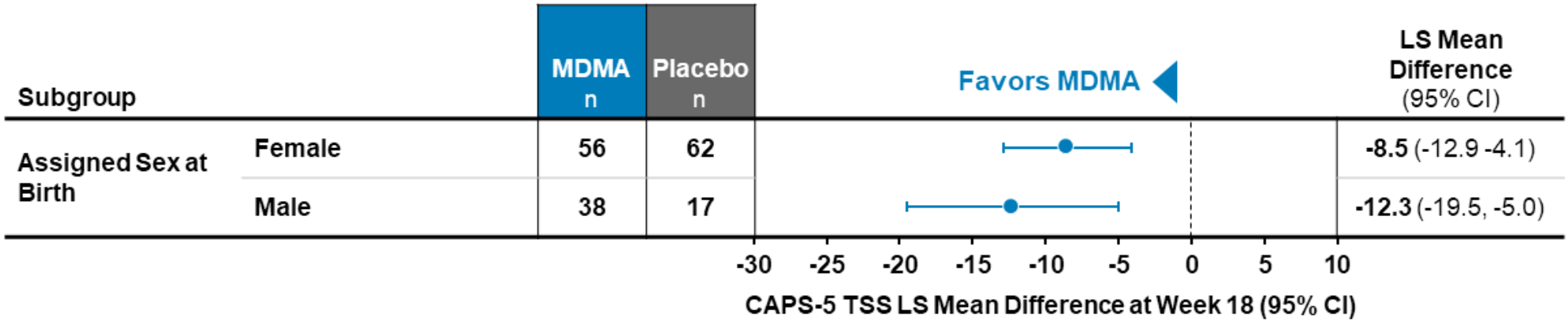
Post-Study Illicit MDMA Use Reported in LTFU Study MPLONG

	MDMA-AT N = 99	Placebo + Therapy N = 95
Ecstasy use in MPLONG, N (%)	**13** (13%)	**7** (7%)
Ecstasy use prior to parent study, n (%)	**6** (46%)	**7** (100%)

MPLONG: Primary Intent of Post-Study Illicit MDMA Use

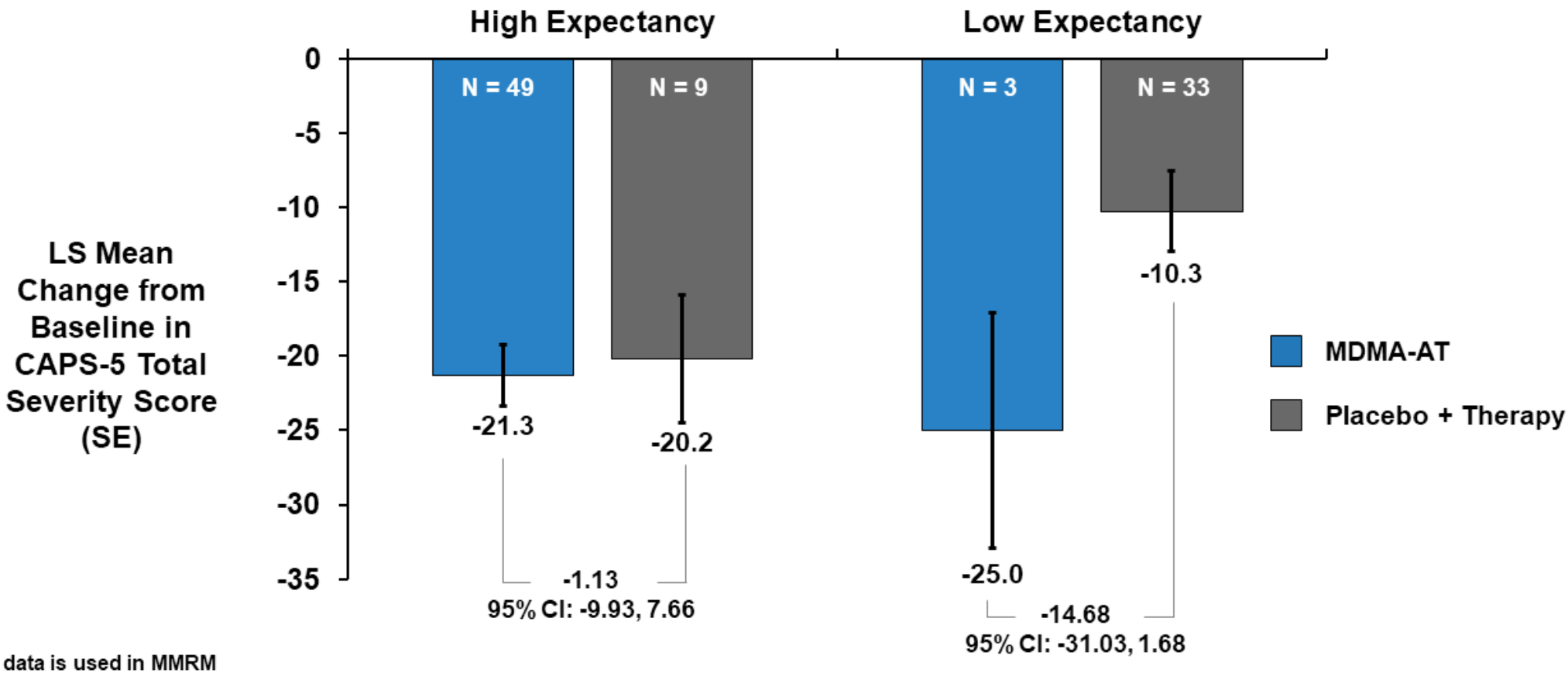
Primary intention for use, n (%)	MDMA-AT N = 75	Placebo + Therapy N = 67
Did not use since study	58 (77%)	57 (85%)
Treatment of mental health condition	5 (7%)	5 (8%)
Personal growth	4 (5%)	1 (2%)
Recreation/fun	4 (5%)	1 (2%)
Satisfy craving	0 (0%)	0 (0%)
Missing (Not collected)	4 (5%)	3 (5%)

MDMA-AT Treatment Response on CAPS-5 Comparable Between Males and Females in Phase 3 Studies



Pooled mITT Population

MAPP2: Results Consistent Between High Expectancy and Low Expectancy Results



All data is used in MMRM
High expectancy denotes participant belief that they received MDMA during study as reported on blinding survey; low expectancy denotes participant belief that they received placebo

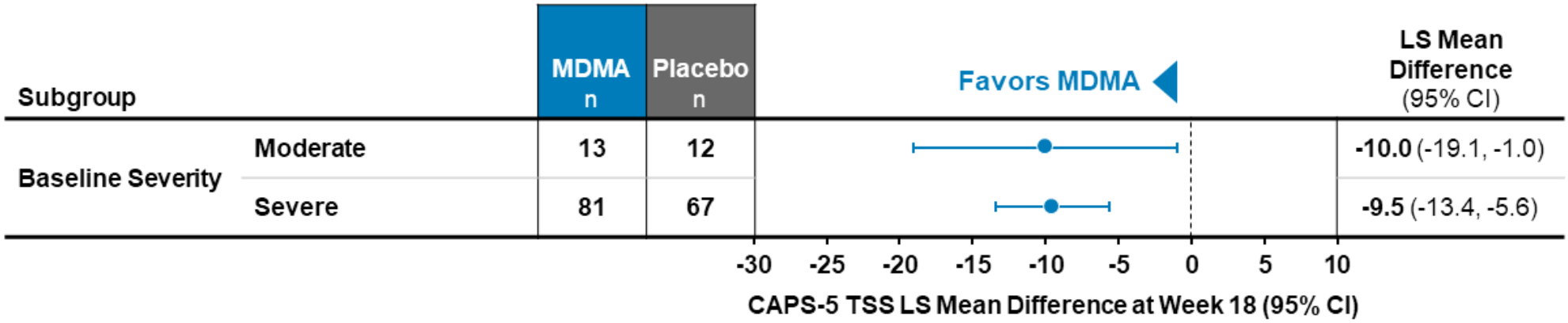
MPLONG Patients Continued to Engage in Mental Health Care after Parent Study

Category	MDMA-AT N = 75	Placebo + Therapy N = 67
Any psychotherapy	83%	70%
Other	69%	51%
Psychodynamic	15%	12%
Eye movement desensitization reprocessing	9%	18%
Other cognitive behavioral therapy	9%	12%
Group psychotherapy	8%	9%
Prolonged exposure	1%	0
Cognitive processing therapy	0	3%
Holotropic breathwork	0	0
Interpersonal therapy	0	2%

MPLONG: Use of Concomitant Medications Generally Similar Between Treatment Groups

Anatomical Therapeutic Chemical (ATC) Class Level 3, %	MDMA N = 75	Placebo N = 67
At least 1 medication	89%	94%
Viral vaccines	48%	30%
Anti-inflammatory and anti-rheumatic products, non-steroids	29%	30%
Anxiolytics	27%	19%
Antidepressants	27%	13%
Vitamin A and D, incl. combinations of the two	24%	18%
Psychostimulants, agents used for ADHD and nootropics	20%	10%
Other mineral supplements	19%	15%
Other nutrients	16%	15%
Other analgesics and anti-pyretics	16%	13%
Direct acting anti-virals	16%	6%

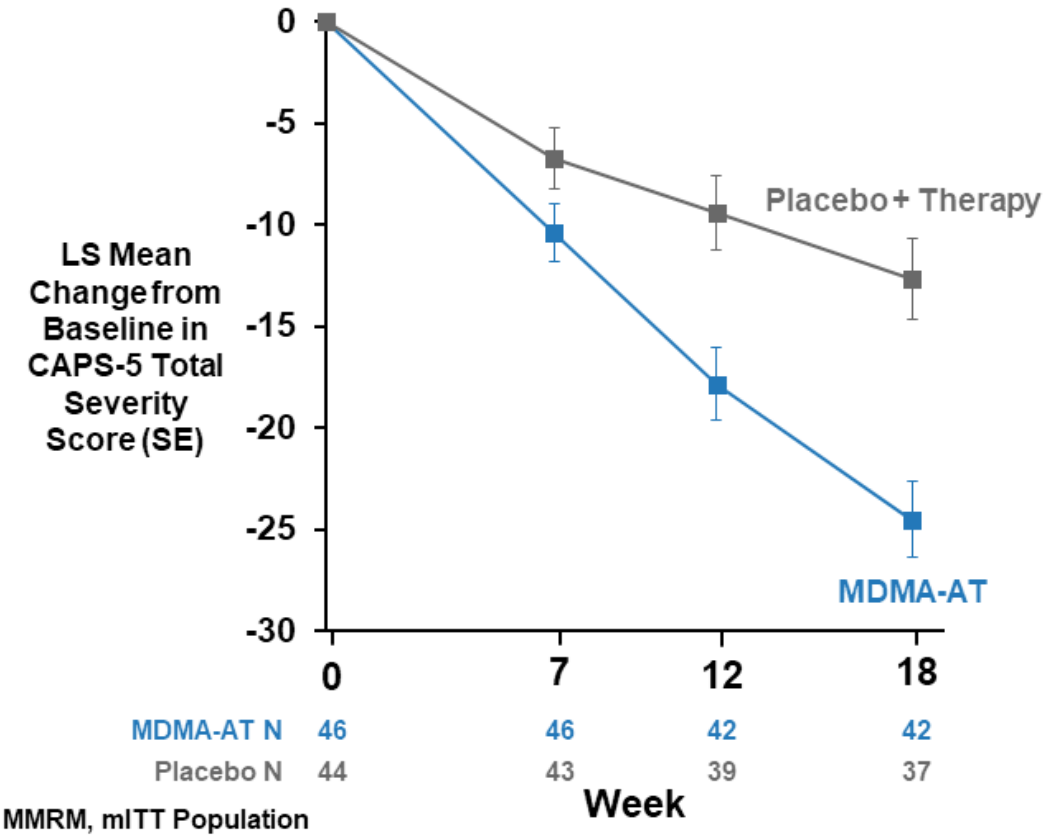
MDMA-AT Treatment Response on CAPS-5 Comparable Across PTSD Severity Groups in Phase 3 Studies



Pooled mITT Population

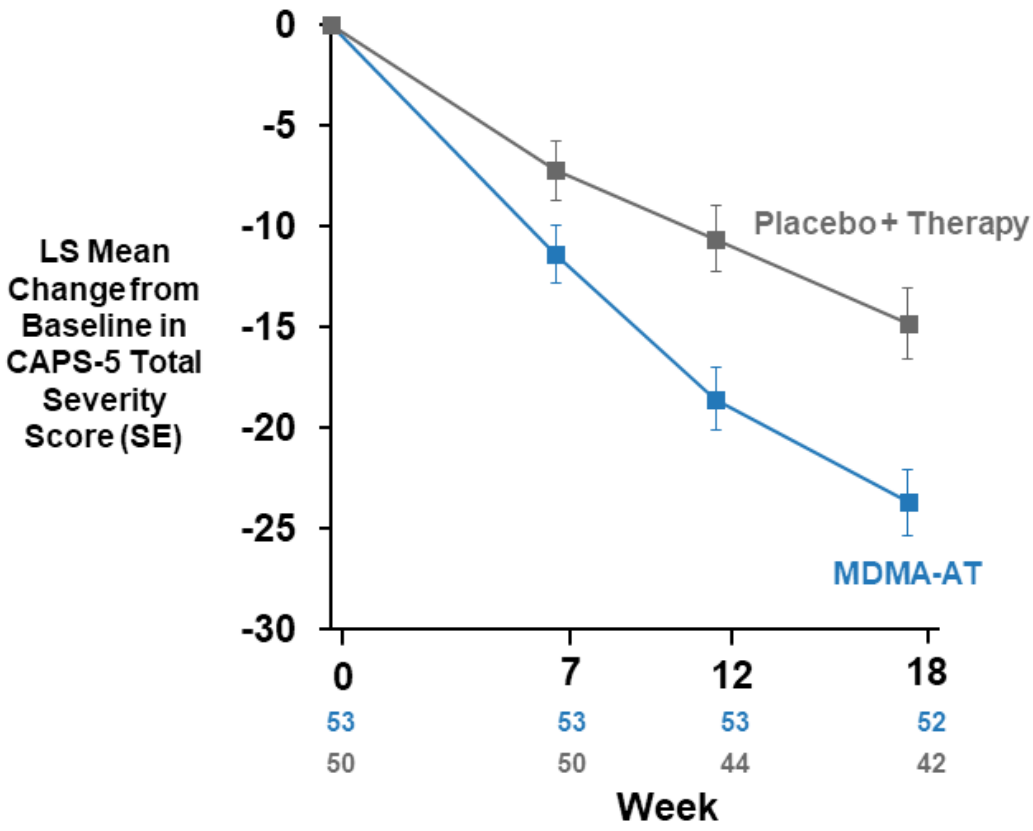
MAPP1 and MAPP2: MDMA-AT Separates Early and Effect Maintained Through Week 18 Compared to Placebo

MAPP1

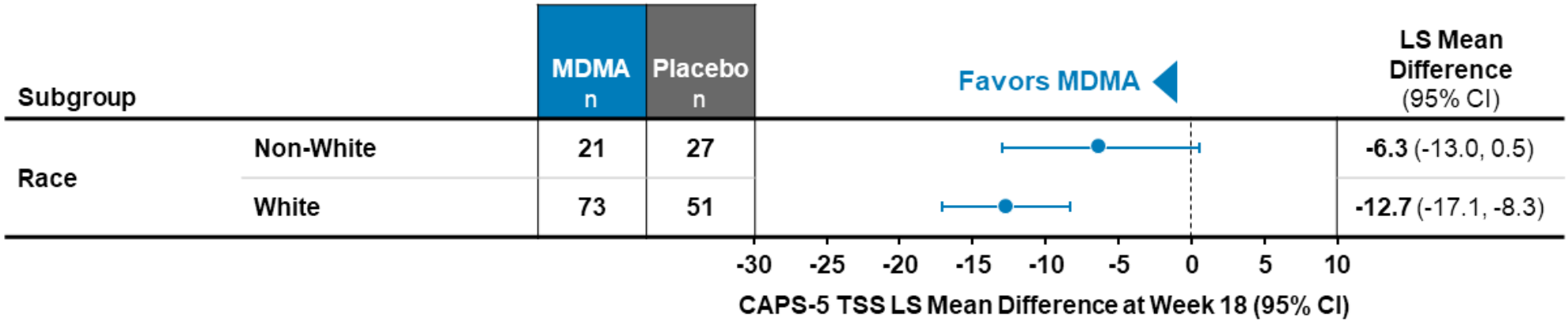


MMRM, mITT Population

MAPP2



MDMA-AT Treatment Response on CAPS-5 Comparable Between Race Groups in Phase 3 Studies



Pooled mITT Population