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

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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\(^1\)
- \(\sim 4,000\) people documented to have taken MDMA in earlier clinical practice
- More recently MDMA utilized in \(\sim 2,000\) participants in research studies
- Experience informed overall design of clinical program

1. Stolaroff, 2004
MDMA-AT Key Regulatory and Study Milestones

- **End of Phase 2 Meeting**: November 2016
- **FDA Grants Breakthrough Therapy Designation**: July 2017
- **Special Protocol Assessment (SPA)**: August 2017
- **MAPP1 1st Pivotal Study Initiated**: November 2018
- **MAPP2 2nd Pivotal Study Initiated**: September 2020
- **NDA Submission**: December 2023
- **Priority Review Granted**: February 2024

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
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\(^7\) |

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Different Types of Trauma Can Lead to PTSD

- Sexual violence: 33%
- Traumatic event in social/family network: 30%
- Life-threatening traumatic event: 12%
- Interpersonal violence: 11%
- Participated in organized violence: 11%
- Exposure to organized violence: 3%

WHO World Mental Health Survey (N = 47,566)
Adapted from Kessler, 2014
# PTSD Diagnosed Using Well-Established DSM-5 Criteria

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

American Psychiatric Association, 2022
# PTSD is Characterized by Four Symptom Clusters

| Avoidance of Triggers | Avoidance of distressing thoughts or feelings associated with the trauma  
<table>
<thead>
<tr>
<th></th>
<th>Avoidance or efforts to avoid external reminders, or close associations with the trauma</th>
</tr>
</thead>
</table>
| 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  
<p>|                        | Irritable behavior/angry outbursts                                               |
|                        | Reckless or self-destructive behavior                                            |</p>
<table>
<thead>
<tr>
<th>Percentage</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>59%</td>
<td>Anxiety disorders</td>
</tr>
<tr>
<td>52%</td>
<td>Major depressive disorder</td>
</tr>
<tr>
<td>46%</td>
<td>Substance use disorders</td>
</tr>
<tr>
<td>42%</td>
<td>Suicidal ideation</td>
</tr>
</tbody>
</table>

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

**Psychotherapy**
- Clinically meaningful PTSD symptom reduction using trauma-focused therapy (PE, CPT, EMDR*)

**SSRI or SNRI**
- FDA-approved treatment for PTSD
- Demonstrated greater efficacy than placebo based on clinician-assessed scale for PTSD symptom

**Benefit**
- High dropout rates due to exacerbation of distress and often takes months/years
- Highly variable outcomes
- Limited access

**Challenge**
- Response rates rarely exceed 60%
- 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

<table>
<thead>
<tr>
<th></th>
<th>Preparatory Period* (~ 6 weeks)</th>
<th>Treatment Cycle 1 (3-5 weeks)</th>
<th>Treatment Cycle 2 (3-5 weeks)</th>
<th>Treatment Cycle 3 (3-5 weeks)</th>
<th>Follow-up (18 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotherapy (90 mins)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDMA or Placebo + 8-hour Therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy Assessment</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Randomization*

*Primary Endpoint Assessed*

*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

**Treatment Cycle 1**
- 120 mg MDMA
  - 80 mg
  - 40 mg
  - 1.5 to 2 Hours

**Treatment Cycles 2 & 3**
- 180 mg MDMA
  - 120 mg
  - 60 mg
  - 1.5 to 2 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

Provides personalized patient directed therapy session

Yehuda Lab MDMA-AT treatment room at James J Peters VAMC, New York
Study Personnel Had Different Roles and Responsibilities to Support Patients

- **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

<table>
<thead>
<tr>
<th>20 Symptoms Across 4 Domains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrusion</td>
</tr>
</tbody>
</table>

### CAPS-5 Total Severity Score Categories

- **Asymptomatic**: 0 – 10
- **Mild**: 11 – 22
- **Moderate**: 23 – 34
- **Severe**: 35 – 46
- **Extreme**: 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

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

*1 placebo patient with missing race; mITT population
## Pivotal Studies: Baseline PTSD Characteristics Similar Across Arms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MAPP1</th>
<th>MAPP2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTSD Duration (years), mean (SD)</strong></td>
<td>14.8 (11.6)</td>
<td>13.3 (11.4)</td>
</tr>
<tr>
<td><strong>MDMA-AT N = 46</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Placebo + Therapy N = 44</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>MDMA-AT N = 53</strong></td>
<td><strong>Placebo + Therapy N = 51</strong></td>
</tr>
<tr>
<td><strong>MDMA-AT N = 46</strong></td>
<td>16.3 (14.3)</td>
<td>16.1 (12.4)</td>
</tr>
<tr>
<td><strong>PTSD Duration (years), mean (SD)</strong></td>
<td><strong>MDMA-AT N = 53</strong></td>
<td><strong>Placebo + Therapy N = 51</strong></td>
</tr>
<tr>
<td><strong>Developmental trauma event</strong></td>
<td>87%</td>
<td>82%</td>
</tr>
<tr>
<td><strong>Veteran</strong></td>
<td>22%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Served in combat area</strong></td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Multiple trauma</strong></td>
<td>89%</td>
<td>86%</td>
</tr>
<tr>
<td><strong>Pre-study PTSD medication</strong></td>
<td><strong>MDMA-AT N = 53</strong></td>
<td><strong>Placebo + Therapy N = 51</strong></td>
</tr>
<tr>
<td><strong>Sertraline</strong></td>
<td>26%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Paroxetine</strong></td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Any previous psychotherapy</strong></td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td><strong>CAPS-5 total severity score, mean (SD)</strong></td>
<td>44.0 (6.0)</td>
<td>44.2 (6.2)</td>
</tr>
<tr>
<td><strong>SDS total score, mean (SD)</strong></td>
<td>6.8 (2.1)</td>
<td>7.4 (1.6)</td>
</tr>
</tbody>
</table>

mITT population
## Pivotal Studies: Psychiatric Medical History

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

Randomized
N = 91

MDMA-AT
N = 46

- 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

Placebo + Therapy
N = 45

mITT population

37 (82%)
MAPP1: Primary Endpoint Met – Statistically Significant Improvement vs Placebo in CAPS-5

Primary Endpoint
(LS Mean [SE] at Week 18)

LS Mean Change from Baseline in CAPS-5 Total Severity Score (SE)

-24.5
-11.86
95% CI: -17.41, -6.32
p < 0.0001

MDMA-AT (N = 42)
Placebo + Therapy (N = 37)

All data is used in MMRM
MAPP1: MDMA-AT Separates Early and Effect Maintained Through Week 18 Compared to Placebo

**LS Mean Change from Baseline in CAPS-5 Total Severity Score (SE)**

Week: 0, 7, 12, 18

- **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

Proportion of Patients at Primary Endpoint (%)

- **Responder**: CAPS-5 ≥ 10-point reduction
  - MDMA-AT (N = 42): 88%
  - Placebo + Therapy (N = 37): 62%

- **Loss of Diagnosis**: CAPS-5 ≥ 10-point reduction + does not meet DSM-5 criteria
  - MDMA-AT (N = 42): 67%
  - Placebo + Therapy (N = 37): 32%

- **Remission**: CAPS-5 ≤ 11 + does not meet DSM-5 criteria
  - MDMA-AT (N = 42): 33%
  - Placebo + Therapy (N = 37): 5%
MAPP1: Key Secondary Endpoint Met Demonstrating Functional Improvements

Secondary Endpoint (LS Mean [SE] at Week 18)

- MDMA-AT (N = 42)
  - LS Mean Change from Baseline in SDS Total Score (SE): -3.2
  - 95% CI: -2.46, -0.25
  - p = 0.0167

- Placebo + Therapy (N = 37)
  - LS Mean Change from Baseline in SDS Total Score (SE): -1.8

All data is used in MMRM
MAPP2: Patient Disposition

Randomized
N = 104

MDMA-AT
N = 53

- 0: Patient chose to discontinue treatment
- 0: Adverse event
- 52 (98%)\(^a\): Completed Study

Placebo + Therapy
N = 51

- 7: Patient chose to discontinue treatment
- 1: Adverse event
- 42 (82%)\(^b\): Completed Study

mITT population
\(\text{a. One patient completed 3 medication sessions but not primary endpoint assessment; b. 1 patient completed study but had no outcome assessment}\)
MAPP2: Primary Endpoint Met – Statistically Significant and Clinically Meaningful Improvement with MDMA-AT

Primary Endpoint
(LS Mean [SE] at Week 18)

LS Mean Change from Baseline in CAPS-5 Total Severity Score (SE)

MDMA-AT (N = 52)

Placebo + Therapy (N = 42)

-14.8

-23.7

-8.91

95% CI: -13.70, -4.12

p = 0.0004

All data is used in MMRM
MAPP2: MDMA-AT Separates Early and Effect Maintained Through Week 18 Compared to Placebo

LS Mean Change from Baseline in CAPS-5 Total Severity Score (SE)

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>7</th>
<th>12</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDMA-AT N</td>
<td>53</td>
<td>53</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>Placebo N</td>
<td>50</td>
<td>50</td>
<td>44</td>
<td>42</td>
</tr>
</tbody>
</table>

All data is used in MMRM
MAPP2: Greater Rates of Treatment Response, Loss of PTSD Diagnosis, and Remission in MDMA-AT Patients

Proportion of Patients at Primary Endpoint (%)

- **Responder**: CAPS-5 ≥ 10-point reduction
  - MDMA-AT (N = 52): 87%
  - Placebo + Therapy (N = 42): 69%

- **Loss of Diagnosis**: CAPS-5 ≥ 10-point reduction + does not meet diagnostic criteria
  - MDMA-AT (N = 52): 71%
  - Placebo + Therapy (N = 42): 48%

- **Remission**: CAPS-5 ≤ 11 + does not meet diagnostic criteria
  - MDMA-AT (N = 52): 46%
  - Placebo + Therapy (N = 42): 21%
MAPP2: Key Secondary Endpoint Met Demonstrating Functional Improvements

Secondary Endpoint (LS Mean [SE] at Week 18)

-3.3
-2.1

95% CI: -2.26, -0.14
p = 0.0271

MDMA-AT (N = 52)
Placebo + Therapy (N = 42)

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)

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

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)

- **Proportion of Patients at Long-Term Follow-Up Visit (%)**
  - **Durable Responder**
    - MDMA-AT (N = 44): 89%
    - Placebo + Therapy (N = 37): 57%
  - **Durable Loss of Diagnosis**
    - MDMA-AT (N = 44): 75%
    - Placebo + Therapy (N = 37): 41%
  - **Durable Remission**
    - MDMA-AT (N = 44): 45%
    - Placebo + Therapy (N = 37): 16%

*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
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

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Pivotal Phase 3</th>
<th>Follow up / Cross over</th>
</tr>
</thead>
<tbody>
<tr>
<td>(4 studies*)</td>
<td>(9 studies)</td>
<td>(2 studies)</td>
<td>(3 studies)</td>
</tr>
<tr>
<td>( N = 190 )</td>
<td>( N = 148 )</td>
<td>( N = 99 )</td>
<td>( N = 40 )</td>
</tr>
</tbody>
</table>

*Includes NIDA Study \( N = 50 \)
Most Patients Received Intended Dosing Regimen of MDMA in Phase 3 Studies

<table>
<thead>
<tr>
<th>Split dose</th>
<th>Treatment Cycle 1</th>
<th>Treatment Cycle 2</th>
<th>Treatment Cycle 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st part</td>
<td>80 mg N = 99 (100%)</td>
<td>120 mg N = 94 (95%)</td>
<td>80 mg N = 2 (2%)</td>
</tr>
<tr>
<td>2nd part</td>
<td>40 mg N = 96 (97%)</td>
<td>60 mg N = 93 (94%)</td>
<td>40 mg N = 2 (2%)</td>
</tr>
</tbody>
</table>

Phase 3 trials specified dose as the hydrochloride salt of MDMA
# Pooled Phase 3 Studies: Overall Summary of Adverse Events

<table>
<thead>
<tr>
<th>Patients with ≥ 1 event</th>
<th>MDMA-AT N = 99</th>
<th>Placebo + Therapy N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>100%</td>
<td>98%</td>
</tr>
<tr>
<td>Severe AE</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>SAE</td>
<td>0</td>
<td>2%</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Pooled Phase 3 Studies: Most Common Adverse Events

- **Preferred term ≥ 15%**

- **MDMA-AT (N = 99)**
- **Placebo + Therapy (N = 95)**
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

<table>
<thead>
<tr>
<th>Preferred Term, %</th>
<th>MDMA-AT N = 99</th>
<th>Placebo + Therapy N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicidal ideation</td>
<td>39%</td>
<td>44%</td>
</tr>
<tr>
<td>Intentional self-injury</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Suicidal behavior</td>
<td>0</td>
<td>2%</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>0</td>
<td>1%</td>
</tr>
</tbody>
</table>
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

![Graphs showing mean systolic and diastolic blood pressures during treatment cycles.]

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

<table>
<thead>
<tr>
<th>Category, %</th>
<th>MDMA-AT 80 mg N = 99</th>
<th>MDMA-AT 120 mg N = 95</th>
<th>Placebo + Therapy N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Systolic blood pressure]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 140 mmHg</td>
<td>46%</td>
<td>62%</td>
<td>57%</td>
</tr>
<tr>
<td>≥ 180 mmHg</td>
<td>2%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>≥ 140 mmHg and increase of ≥ 20 mmHg</td>
<td>21%</td>
<td>34%</td>
<td>37%</td>
</tr>
<tr>
<td>[Diastolic blood pressure]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 90 mmHg</td>
<td>39%</td>
<td>60%</td>
<td>55%</td>
</tr>
<tr>
<td>≥ 110 mmHg</td>
<td>1%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>≥ 100 mmHg and increase of ≥ 20 mmHg</td>
<td>3%</td>
<td>6%</td>
<td>4%</td>
</tr>
</tbody>
</table>
Pooled Phase 3 Studies: Heart Rate by Treatment Cycle

Treatment Cycle 1

Treatment Cycle 2

Treatment Cycle 3

Mean Heart Rate (beats/min) [95% CI]

Predose | Interim | End of Session
-------------------------------------
MDMA-AT  | Placebo + Therapy

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

![Box plots for three medication sessions showing rate pressure product for MDMA-AT and Placebo + Therapy groups.](image)

- **Medication Session 1**
  - Predose
  - Interim
  - End of Session

- **Medication Session 2**
  - Predose
  - Interim
  - End of Session

- **Medication Session 3**
  - Predose
  - Interim
  - End of Session

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

<table>
<thead>
<tr>
<th>Hemodynamic Response</th>
<th>Rate Pressure Product*</th>
<th>MDMA N = 99</th>
<th>Placebo N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&gt; 30,000</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>High Intermediate</td>
<td>25,000 – 29,999</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>20,000 – 24,999</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Low Intermediate</td>
<td>15,000 – 19,999</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Low</td>
<td>10,000 – 14,999</td>
<td>54</td>
<td>22</td>
</tr>
<tr>
<td>Less &lt; 10,000</td>
<td>&lt; 10,000</td>
<td>10</td>
<td>73</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Risk</th>
<th>Patient Monitoring</th>
<th>Proposed Label</th>
<th>Prescriber / HCP Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropsychological and Physiological Effects</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Suicidality</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Blood Pressure / Heart Rate Increases</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Nonmedical Use / Substitution</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>MDMA-AT N = 99</th>
<th>Placebo + Therapy N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of alcohol or substance abuse</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>History of illicit MDMA use</td>
<td>40%</td>
<td>39%</td>
</tr>
</tbody>
</table>
Treatment Response on CAPS-5 in Pooled Phase 3 Studies Was Comparable in Patients With and Without Prior MDMA Use

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>MDMA n</th>
<th>Placebo n</th>
<th>Favors MDMA</th>
<th>LS Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any History of MDMA Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>29</td>
<td>-10.9</td>
<td>(-16.9, -5.0)</td>
</tr>
<tr>
<td>No</td>
<td>55</td>
<td>50</td>
<td>-9.5</td>
<td>(-14.5, -4.6)</td>
</tr>
</tbody>
</table>

CAPS-5 TSS LS Mean Difference at Week 18 (95% CI)
## Phase 3 Disposition (Side-by-side and Pooled)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study completed through all visits</td>
<td>91%</td>
<td>84%</td>
<td>98%</td>
<td>86%</td>
<td>95%</td>
<td>85%</td>
</tr>
<tr>
<td>Post-randomization early termination</td>
<td>4%</td>
<td>11%</td>
<td>0</td>
<td>8%</td>
<td>2%</td>
<td>10%</td>
</tr>
<tr>
<td>Dropout</td>
<td>4%</td>
<td>5%</td>
<td>2%</td>
<td>6%</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Primary reason for early termination and dropout</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event or death</td>
<td>0</td>
<td>7%</td>
<td>0</td>
<td>2%</td>
<td>0</td>
<td>4%</td>
</tr>
<tr>
<td>Administrative reason</td>
<td>2%</td>
<td>2%</td>
<td>0</td>
<td>0</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Investigator chose to discontinue treatment</td>
<td>2%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td>Patient chose to discontinue treatment</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>12%</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>2%</td>
<td>2%</td>
<td>0</td>
<td>0</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1%</td>
</tr>
</tbody>
</table>

miTT population
### Post-Study Illicit MDMA Use Reported in LTFU Study MPLONG

<table>
<thead>
<tr>
<th></th>
<th>MDMA-AT N = 99</th>
<th>Placebo + Therapy N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecstasy use in MPLONG, N (%)</td>
<td>13 (13%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Ecstasy use prior to parent study, n (%)</td>
<td>6 (46%)</td>
<td>7 (100%)</td>
</tr>
</tbody>
</table>
## MPLONG: Primary Intent of Post-Study Illicit MDMA Use

<table>
<thead>
<tr>
<th>Primary intention for use, n (%)</th>
<th>MDMA-AT N = 75</th>
<th>Placebo + Therapy N = 67</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not use since study</td>
<td>58 (77%)</td>
<td>57 (85%)</td>
</tr>
<tr>
<td>Treatment of mental health condition</td>
<td>5 (7%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Personal growth</td>
<td>4 (5%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Recreation/fun</td>
<td>4 (5%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Satisfy craving</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Missing (Not collected)</td>
<td>4 (5%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>
### MDMA-AT Treatment Response on CAPS-5 Comparable Between Males and Females in Phase 3 Studies

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>MDMA n</th>
<th>Placebo n</th>
<th>LS Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assigned Sex at Birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>56</td>
<td>62</td>
<td>-8.5 (-12.9, -4.1)</td>
</tr>
<tr>
<td>Male</td>
<td>38</td>
<td>17</td>
<td>-12.3 (-19.5, -5.0)</td>
</tr>
</tbody>
</table>

**CAPS-5 TSS LS Mean Difference at Week 18 (95% CI)**

Pooled mITT Population
MAPP2: Results Consistent Between High Expectancy and Low Expectancy Results

LS Mean Change from Baseline in CAPS-5 Total Severity Score (SE)

High Expectancy
- N = 49
- N = 9
- N = 3
- N = 33

High Expectancy:
- Mean Change: -21.3
- 95% CI: -9.93, 7.66

Low Expectancy:
- Mean Change: -25.0
- 95% CI: -31.03, 1.68

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

<table>
<thead>
<tr>
<th>Category</th>
<th>MDMA-AT</th>
<th>Placebo + Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any psychotherapy</strong></td>
<td>83%</td>
<td>70%</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>69%</td>
<td>51%</td>
</tr>
<tr>
<td><strong>Psychodynamic</strong></td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Eye movement desensitization reprocessing</strong></td>
<td>9%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Other cognitive behavioral therapy</strong></td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Group psychotherapy</strong></td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Prolonged exposure</strong></td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cognitive processing therapy</strong></td>
<td>0</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Holotropic breathwork</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Interpersonal therapy</strong></td>
<td>0</td>
<td>2%</td>
</tr>
</tbody>
</table>
### MPLONG: Use of Concomitant Medications Generally Similar Between Treatment Groups

<table>
<thead>
<tr>
<th>Anatomical Therapeutic Chemical (ATC) Class Level 3, %</th>
<th>MDMA N = 75</th>
<th>Placebo N = 67</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 medication</td>
<td>89%</td>
<td>94%</td>
</tr>
<tr>
<td>Viral vaccines</td>
<td>48%</td>
<td>30%</td>
</tr>
<tr>
<td>Anti-inflammatory and anti-rheumatic products, non-steroids</td>
<td>29%</td>
<td>30%</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>27%</td>
<td>19%</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>27%</td>
<td>13%</td>
</tr>
<tr>
<td>Vitamin A and D, incl. combinations of the two</td>
<td>24%</td>
<td>18%</td>
</tr>
<tr>
<td>Psychostimulants, agents used for ADHD and nootropics</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Other mineral supplements</td>
<td>19%</td>
<td>15%</td>
</tr>
<tr>
<td>Other nutrients</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td>Other analgesics and anti-pyretics</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Direct acting anti-virals</td>
<td>16%</td>
<td>6%</td>
</tr>
</tbody>
</table>
### MDMA-AT Treatment Response on CAPS-5 Comparable Across PTSD Severity Groups in Phase 3 Studies

<table>
<thead>
<tr>
<th>Baseline Severity</th>
<th>MDMA n</th>
<th>Placebo n</th>
<th>Favors MDMA</th>
<th>LS Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>13</td>
<td>12</td>
<td></td>
<td>-10.0 (-19.1, -1.0)</td>
</tr>
<tr>
<td>Severe</td>
<td>81</td>
<td>67</td>
<td></td>
<td>-9.5 (-13.4, -5.6)</td>
</tr>
</tbody>
</table>

**CAPS-5 TSS LS Mean Difference at Week 18 (95% CI)**

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

**MAPP1**

- LS Mean Change from Baseline in CAPS-5 Total Severity Score (SE)

**MAPP2**

- LS Mean Change from Baseline in CAPS-5 Total Severity Score (SE)

**Week**

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

**Week**

- MDMA-AT N: 63
- MDMA-AT: 63, 53, 52
- Placebo N: 50
- Placebo: 50, 44, 42

MMRM, mITT Population
### MDMA-AT Treatment Response on CAPS-5 Comparable Between Race Groups in Phase 3 Studies

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>MDMA</th>
<th>Placebo</th>
<th>LS Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-White</td>
<td>21</td>
<td>27</td>
<td>-6.3 (-13.0, 0.5)</td>
</tr>
<tr>
<td>White</td>
<td>73</td>
<td>51</td>
<td>-12.7 (-17.1, -8.3)</td>
</tr>
</tbody>
</table>

**CAPS-5 TSS LS Mean Difference at Week 18 (95% CI)**

*Pooled mITT Population*