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Supplementary information

MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study

In the format provided by the authors and unedited

SUPPLEMENTARY DATA TABLES

Supplementary Data Table 1. Missing Data from mITT Set Based on Reasons for Post-Randomization Withdrawal

<table>
<tr><th>Post-randomization Events</th><th>Available Data Post-Withdrawal</th><th>Treatment Assignment</th><th>Summary of Missing Data and Inclusion in de jure Estimand by Visit</th></tr>
<tr><td rowspan="2">Discontinue Study, Withdraw Consent</td><td rowspan="2">No data</td><td>MDMA</td><td>
<table>
<tr><th>Reason</th><th>Participant #</th><th>Missed Visits</th><th>De jure estimand</th></tr>
<tr><td>COVID</td><td>0807[A]
1211[A]</td><td>T3, T4</td><td>Included T1, T2</td></tr>
<tr><td>Perceived early efficacy</td><td>0611[B]</td><td>T3, T4</td><td>Included T1, T2</td></tr>
<tr><td>Did not want to complete CAPS due to triggering (primary); AE-depressed mood (secondary)</td><td>0213[B]</td><td>T3, T4</td><td>Included T1, T2</td></tr>
</table>
</td></tr>
<tr><td>Placebo</td><td>
<table>
<tr><th>Reason</th><th>Participant #</th><th>Missed Visits</th><th>De jure estimand</th></tr>
<tr><td>SAE- suicidal ideation</td><td>0104[B]</td><td>T3, T4</td><td>Included T1, T2</td></tr>
<tr><td>COVID</td><td>0707[A]</td><td>T3, T4</td><td>Included T1, T2</td></tr>
<tr><td>Choice</td><td>0711[B]</td><td>T3, T4</td><td>Included T1, T2</td></tr>
<tr><td>AE- insomnia</td><td>0211</td><td>T4</td><td>Included T1, T2, T3</td></tr>
</table>
</td></tr>
<tr><td rowspan="2">Discontinue Intervention (or experiences long delay) and does not receive Rescue Medication</td><td rowspan="2">Data collection continues whenever possible via remote visits</td><td>MDMA</td><td>None Observed</td></tr>
<tr><td>Placebo</td><td>
<table>
<tr><th>Reason</th><th>Participant #</th><th>Missed Visits</th><th>De jure estimand</th></tr>
<tr><td>COVID[A]</td><td>1502[A]</td><td>None</td><td>Included T1, T2, T3</td></tr>
</table>
</td></tr>
<tr><td rowspan="2">Discontinue Intervention (or experiences long delay) and receives Rescue Medication</td><td rowspan="2">Data collection continues whenever possible via remote visits</td><td>MDMA</td><td>None Observed</td></tr>
<tr><td>Placebo</td><td>
<table>
<tr><th>Reason</th><th>Participant #</th><th>Missed Visits</th><th>De jure estimand</th></tr>
<tr><td>SAE- suicide attempt</td><td>0203</td><td>T3</td><td>Included T1, T2</td></tr>
<tr><td>AE- increased anxiety</td><td>0102</td><td>T2, T3</td><td>Excluded [C]</td></tr>
</table>
</td></tr>
<tr><td>Death</td><td>No data</td><td>MDMA</td><td>None Observed</td></tr>
<tr><td></td><td></td><td>Placebo</td><td>None Observed</td></tr>
<tr><td rowspan="2">Suicide</td><td rowspan="2">No data</td><td>MDMA</td><td>None Observed</td></tr>
<tr><td>Placebo</td><td>None Observed</td></tr>
</table>

[A] COVID, participants for which participation was terminated due to study closure related to the COVID-19 pandemic

[B] Discontinued participation and withdrew consent which led to missing data.

[C] Participant completed only Baseline T1, discontinue intervention and received rescue medication, and T4. As no endpoint assessment was collected prior to treatment discontinuation, this participant is excluded from the *de jure* estimand but included in the *de facto* estimand sensitivity analysis.

Supplementary Data Table 2. Analysis Effects on Primary Results

MMRM Results for Fixed Effects		
Effect	**F-Value**	**Pr > F**
Treatment	12.6	0.0007
Baseline CAPS-5 Score	0.13	0.7219
Study Visit	51.54	<.0001
Treatment x Study Visit	8.75	0.0004
Dissociative Subtype	2.03	0.159
Study Site	1.6	0.1003
Analysis of Covariate Effects on Primary Results		
Variable	**p-value main effect**	**p-value interaction w/Tx**
Age (continuous)	0.2491	0.8291
Sex biological	0.6281	0.9376
Disabled (yes/no)	0.9883	0.4444
Covid-19 (pre/during)	0.7701	0.9633
Prior SSRI Usage (yes/no)	0.6114	0.7650
PTSD Duration (continuous)	0.6688	0.3795
Dissociative Subtype (yes/no)	0.0350	0.0044
BDI (>=23)	0.1003	0.6373
ACE (>=4)	0.5198	0.5127
AUDIT (>=5)	0.4975	0.4071
DUDIT (>=5)	0.6420	0.6441

Supplementary Data Table 2: Each of these covariates were added one-at-a-time as fixed effects to the primary efficacy model and analyzed as 2-sided F-tests without correction for multiple comparisons. The p-values associated with their coefficient estimates are reported.

Supplementary Data Table 3: Treatment Emergent Adverse Events Related to MDMA

Adverse Event (PT)	MDMA-assisted therapy (n=46)	Placebo with therapy (n=44)
Muscle Tightness	29 (63.0%)	5 (11.4%)
Decreased Appetite	24 (52.2%)	5 (11.4%)
Nausea	14 (30.4%)	5 (11.4%)
Hyperhidrosis	9 (19.6%)	1 (2.3%)
Feeling Cold	9 (19.6%)	3 (6.8%)
Restlessness	7 (15.2%)	0
Mydriasis	7 (15.2%)	0
Dizziness Postural	6 (13.0%)	2 (4.5%)
Bruxism	6 (13.0%)	1 (2.3%)
Nystagmus	6 (13.0%)	0
Blood Pressure Increased	5 (10.9%)	0
Feeling Jittery	5 (10.9%)	0
Non-Cardiac Chest Pain	5 (10.9%)	1 (2.3%)
Dry Mouth	5 (10.9%)	2 (4.5%)
Vision Blurred	4 (8.7%)	1 (2.3%)
Pollakiuria	4 (8.7%)	1 (2.3%)
Intrusive Thoughts	4 (8.7%)	0
Vomiting	4 (8.7%)	0
Stress	4 (8.7%)	0
Musculoskeletal Pain	4 (8.7%)	0
Pyrexia	3 (6.5%)	1 (2.3%)
Chills	3 (6.5%)	0
Substance Use (*cannabis)*	3 (6.5%)	0
Micturition urgency	3 (6.5%)	0
Muscle Twitching	3 (6.5%)	0
Somnolence	3 (6.5%)	0
Nervousness	3 (6.5%)	0

Supplementary Data Table 3. Treatment Emergent Adverse Events (TEAEs). AEs that occurred from the first experimental session to study termination based on participant level incidence were termed TEAE. Relationship to MDMA was determined based on relative incidence of TEAEs with at least two-fold difference between MDMA vs. placebo. Listed here are the most common (>5% of subjects) TEAEs related to MDMA.

Supplementary Data Table 4: Changes in Vital Signs During the Experimental Sessions

	MDMA (n = 46)	Placebo (n=44)	Total (n=90)
Experimental Session 1			
Predose (n)	46	44	90
Systolic, mean (SD)	126.4 (18.55)	120.2 (13.92)	123.4 (16.65)
Diastolic, mean (SD)	79.4 (11.23)	79.6 (8.76)	79.5 (10.04)
Pulse (beats per minute), mean (SD)	71.0 (11.16)	73.2 (11.20)	72.0 (11.17)
Body temperature (degrees C), mean (SD)	36.6 (0.49)	36.6 (0.39)	36.6 (0.44)
Interim (n)	46	44	90
Systolic, mean (SD)	139.1 (19.70)	122.3 (14.95)	130.9 (19.37)
Diastolic, mean (SD)	85.3 (10.41)	79.1 (11.38)	82.3 (11.28)
Pulse (beats per minute), mean (SD)	82.3 (14.49)	69.6 (11.57)	76.1 (14.56)
Body temperature (degrees C), mean (SD)	36.9 (0.42)	36.7 (0.36)	36. 8 (0.40)
Endpoint (n)	46	44	90
Systolic, mean (SD)	130.8 (16.63)	119.2 (14.77)	125.1 (16.71)
Diastolic, mean (SD)	81.7 (9.63)	77.2 (11.17)	79.5 (10.60)
Pulse (beats per minute), mean (SD)	79.4 (12.51)	73.7 (10.13)	76.6 (11.70)
Body temperature (degrees C), mean (SD)	36.8 (0.51)	36.9 (0.30)	36.8 (0.42)
Experimental Session 2			
Predose (n)	43	41	84
Systolic, mean (SD)	127.2 (14.46)	117.0 (15.33)	122.2 (15.67)
Diastolic, mean (SD)	81.1 (10.35)	76.8 (9.52)	79.0 (10.13)
Pulse (beats per minute), mean (SD)	71.7 (10.44)	67.1 (10.28)	69.5 (10.55)
Body temperature (degrees C), mean (SD)	36.58 (0.44)	36.5 (0.41)	36.6 (0.42)
Interim (n)	43	41	84
Systolic, mean (SD)	146.5 (15.09)	118.1 (18.14)	132.7 (21.85)
Diastolic, mean (SD)	89.1 (10.39)	76.4 (12.45)	82.9 (13.02)
Pulse (beats per minute), mean (SD)	87.3 (12.80)	66.1 (10.61)	77.0 (15.84)
Body temperature (degrees C), mean (SD)	36.9 (0.46)	36.7 (0.30)	36.8 (0.40)
Endpoint (n)	43	41	84
Systolic, mean (SD)	128.8 (17.66)	118.9 (15.12)	123.9 (17.11)
Diastolic, mean (SD)	81.5 (12.36)	75.2 (9.02)	78.4 (11.25)
Pulse (beats per minute), mean (SD)	85.3 (14.66)	69.8 (8.75)	77.7 (14.35)
Body temperature (degrees C), mean (SD)	36.9 (0.48)	36.7 (0.29)	36.8 (0.41)
Experimental Session 3			
Predose (n)	42	37	79
Systolic, mean (SD)	128.5 (15.30)	118.0 (15.79)	123.6 (16.31)
Diastolic, mean (SD)	82.4 (8.00)	76.1 (10.98)	79.4 (9.96)
Pulse (beats per minute), mean (SD)	72.7 (11.80)	69.4 (11.49)	71.2 (11.70)
Body temperature (degrees C), mean (SD)	36.6 (0.46)	36.5585 (0.50)	36.5850 (0.47)
Interim (n)	41	37	78
Systolic, mean (SD)	145.9 (19.23)	117.9 (15.74)	132.6 (22.51)
Diastolic, mean (SD)	86.8 (10.32)	76.2 (10.07)	81.7 (11.45)
Pulse (beats per minute), mean (SD)	91.6 (16.95)	66.4 (12.99)	79.8 (19.75)
Body temperature (degrees C), mean (SD)	37.0 (0.47)	36.7 (0.325)	36.8 (0.44)
Endpoint (n)	42	37	79
Systolic, mean (SD)	127.6 (16.62)	117.5 (13.74)	122.9 (16.06)
Diastolic, mean (SD)	78.4 (11.15)	74.0 (9.39)	76.3 (10.53)
Pulse (beats per minute), mean (SD)	82.1 (14.95)	71.6 (11.84)	77.2 (14.49)
Body temperature (degrees C), mean (SD)	36.9 (0.50)	36.8 (0.40)	36.8 (0.45)

Supplementary Data Table 4. Changes in vital signs during the experimental sessions. Transient increases in blood pressure were observed in the MDMA group, as expected based on Phase 2 data and studies in healthy volunteers.