



## Clinical trial results:

### An Open- Label, Phase 2, Multicenter Feasibility Study of Manualized MDMA-Assisted Psychotherapy with an fMRI sub-study Assessing Changes in Brain Activity in Subjects with Posttraumatic Stress Disorder.

#### Summary

EudraCT number	2018-001718-13
Trial protocol	NL CZ NO DE GB ES
Global end of trial date	15 December 2023

#### Results information

Result version number	v2 (current)
This version publication date	02 February 2025
First version publication date	05 January 2025
Version creation reason	<ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Updating to correct an error in the sample size reported for primary and secondary endpoint analyses. Sample size is currently reported as n=20 due to a misunderstanding that the analysis did not include data from a participant who withdrew prior to completion of the endpoint assessments. As an mITT analysis was conducted for both endpoints, available data from this participant is, in fact, included in the analyses so the correct sample size is n=21.

#### Trial information

##### Trial identification

Sponsor protocol code	MP18
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04030169
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	MAPS Europe B.V.
Sponsor organisation address	Tine van Dethstraat 83, 2331CD, Leiden, Netherlands,
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Notes:

##### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

Notes:

**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	15 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2023
Global end of trial reached?	Yes
Global end of trial date	15 December 2023
Was the trial ended prematurely?	No

Notes:

**General information about the trial**

Main objective of the trial:

The overall objective of this study is to use standard clinical measures to explore the safety and effects of open-label manualized MDMA-assisted psychotherapy with a flexible dose of MDMA in participants with severe PTSD, and to serve as an opportunity for supervision of therapy teams selected to conduct Phase 3 MDMA-assisted psychotherapy research.

The primary objective of this study is to evaluate the effectiveness of MDMA-assisted psychotherapy for treatment of PTSD, as measured by the estimand of change in CAPS-5 Total Severity Score from baseline to 13 weeks post-baseline.

Protection of trial subjects:

During Screening, throughout MDMA-assisted psychotherapy, and during assessment of study measures, participants will be asked to think about and discuss their thoughts and emotions relating to the traumatic event or events associated with their PTSD. They may experience intense emotional responses or suicidal ideation as a result of recalling and speaking about this material. The therapy team will minimize risks by carefully evaluating all participants to determine if there is a current risk of suicidal behavior. A qualified study team member will administer the C-SSRS, a validated measure for assessing suicide risk, at regular, protocol-specified intervals and as needed to monitor for the development and intensity of suicidal ideation and/or behavior. Study teams will implement a protocol-defined plan to address elevated or imminent suicide risk, including continued monitoring and assessment of risk via regular check-ins until the participant stabilizes, discontinuation of study treatment, and/or escorting the participant to the appropriate health services depending on the degree of risk as assessed by the C-SSRS.

MDMA is known to transiently increase heart rate and blood pressure in a dose-dependent manner that is generally not problematic for physically healthy individuals. Before and after drug administration in Experimental Sessions, the study teams monitor vital signs. Should the participant experience signs or symptoms indicative of a cardiac event, the study physician will be contacted immediately and the participant will be taken to emergency services. Pending transport to the hospital the site team may take any measures ordered by the site physician including administering medication such as aspirin or nitroglycerin or providing supplemental oxygen per local standards.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Norway: 2
Worldwide total number of subjects	21
EEA total number of subjects	15

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	21
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited by 7 study centers in the United Kingdom, Germany, Norway, the Czech Republic, and the Netherlands through referrals from other psychiatrists, psychotherapists, or physicians, print and internet advertisements, and by word of mouth.

### Pre-assignment

Screening details:

Inclusion: Aged at least 18 years old; Able to swallow pills; current, chronic, severe PTSD; Current alcohol or substance use disorder without safety concern

Exclusion: Current serious suicide risk; Any medical condition that could make receiving a sympathomimetic drug harmful (due to increase in blood pressure and heart rate)

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label trial. Therefore, blinding implementation details are not applicable.

### Arms

Arm title	Open-label MDMA-assisted therapy
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Arm description:

Two open-label sessions of MDMA-assisted therapy, scheduled approximately 1 month apart, with an initial dose of midomafetamine (MDMA) HCl of 80 or 120 mg and optional supplemental dose half that of initial dose (40 or 60 mg) 1.5 to 2 hours later administered at each session.

Arm type	Experimental
Investigational medicinal product name	Midomafetamine HCl
Investigational medicinal product code	
Other name	MDMA HCl, MDMA, 3,4-methylenedioxymethamphetamine, Midomafetamine
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Midomafetamine HCl is administered at 2 experimental sessions occurring approximately one month apart. In the first Experimental Session, the initial dose is 80 mg. In the second Experimental Session, the initial dose may be increased to 120 mg unless tolerability issues emerge with the first dose or the participant declines. In each Experimental Session, 1.5 to 2 hours after the initial dose is given, the participant will be administered a supplemental half-dose (i.e. 40 mg or 60 mg, respectively) unless tolerability issues emerge with the first dose or the participant declines.

<b>Number of subjects in period 1</b>	Open-label MDMA-assisted therapy
Started	21
Completed	20
Not completed	1
Dropout, participant chose to discontinue	1



## Baseline characteristics

### Reporting groups

Reporting group title	Open-label MDMA-assisted therapy
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Reporting group description:

Two open-label sessions of MDMA-assisted therapy, scheduled approximately 1 month apart, with an initial dose of midomafetamine (MDMA) HCl of 80 or 120 mg and optional supplemental dose half that of initial dose (40 or 60 mg) 1.5 to 2 hours later administered at each session.

Reporting group values	Open-label MDMA-assisted therapy	Total	
Number of subjects	21	21	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	21	21	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	44.3		
standard deviation	± 10.15	-	
Gender categorical			
Units: Subjects			
Female	11	11	
Male	10	10	

### Subject analysis sets

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants exposed to study drug

Reporting group values	Safety Set		
Number of subjects	21		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		

Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	21		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical			
Units: Subjects			
Female	11		
Male	10		

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## End points

### End points reporting groups

Reporting group title	Open-label MDMA-assisted therapy
Reporting group description: Two open-label sessions of MDMA-assisted therapy, scheduled approximately 1 month apart, with an initial dose of midomafetamine (MDMA) HCl of 80 or 120 mg and optional supplemental dose half that of initial dose (40 or 60 mg) 1.5 to 2 hours later administered at each session.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: All participants exposed to study drug	

### Primary: Change From Baseline to Visit 14 in CAPS-5 Total Severity Score

End point title	Change From Baseline to Visit 14 in CAPS-5 Total Severity Score <sup>[1]</sup>
End point description: The CAPS-5 is a 30-item semi-structured interview assessing PTSD in the past month through diagnostic and symptom severity scores anchored to a DSM-5 defined traumatic event. The CAPS-5 produces a Total Severity Score based on severity of PTSD domains described in the DSM-5, as well as a categorical rating indicating whether a participant meets PTSD diagnostic criteria. CAPS-5 Total Symptom Severity scores range from 0 to 80 with higher values designating greater symptom severity. CAPS-5 assigns PTSD diagnosis as being present or absent.	
End point type	Primary
End point timeframe: Baseline to 13 weeks post-baseline	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: This was a single-arm, open-label study.	

End point values	Open-label MDMA-assisted therapy			
Subject group type	Reporting group			
Number of subjects analysed	21 <sup>[2]</sup>			
Units: Score on a scale				
least squares mean (confidence interval 95%)	-13.95 (-16.32 to -11.58)			

Notes:  
[2] - The mITT analysis includes one participant with no data available at the primary endpoint assessment

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline to Visit 14 in Sheehan Disability Scale (SDS) Scores

End point title	Change From Baseline to Visit 14 in Sheehan Disability Scale (SDS) Scores
End point description: The Sheehan Disability Scale (SDS) is a clinician-rated assessment of functional impairment for PTSD. The SDS is a 3-item scale measuring the severity of disability (i.e., the degree of impairment) in the domains of work, family life/home responsibilities and social/leisure activities. Responses are recorded	

using an 11-point scale (0 = not at all to 10 = extremely) and 5 verbal tags (not at all, mildly, moderately, markedly, extremely). For participants who are not able to work for reasons unrelated to PTSD, the measure includes an option to skip the work-related impairment item, and the reason was collected. The impact of missing item-level data was mitigated by averaging across the items to obtain a Total Score, rather than a straight sum.

End point type	Secondary
End point timeframe:	
Baseline to 13 weeks post-baseline	

End point values	Open-label MDMA-assisted therapy			
Subject group type	Reporting group			
Number of subjects analysed	21 <sup>[3]</sup>			
Units: Score on a scale				
least squares mean (confidence interval 95%)				
Family Life/Home	-1.18 (-2.14 to -0.22)			
Social/Leisure Activities	-1.45 (-2.32 to -0.58)			
Work/School	-1.45 (-2.36 to -0.53)			
Total Score	-1.30 (-2.17 to -0.43)			

Notes:

[3] - The mITT analysis includes one participant with no data available at the primary endpoint assessment

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events, defined as adverse events that occurred during the study treatment period from the first experimental session to the last integrative session.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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### Reporting groups

Reporting group title	Open-label MDMA-assisted therapy
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Reporting group description:

Two open-label sessions of MDMA-assisted therapy, scheduled approximately 1 month apart, with an initial dose of midomafetamine (MDMA) HCl of 80 or 120 mg and optional supplemental dose half that of initial dose (40 or 60 mg) 1.5 to 2 hours later administered at each session.

Serious adverse events	Open-label MDMA-assisted therapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 21 (9.52%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal behaviour			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Open-label MDMA-assisted therapy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 21 (100.00%)		
Investigations			

Blood pressure increased subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 3		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)  Dizziness subjects affected / exposed occurrences (all)  Paraesthesia subjects affected / exposed occurrences (all)  Tension headache subjects affected / exposed occurrences (all)	15 / 21 (71.43%) 34  2 / 21 (9.52%) 3  2 / 21 (9.52%) 3  2 / 21 (9.52%) 2		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)  Feeling cold subjects affected / exposed occurrences (all)  Feeling hot subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 4  2 / 21 (9.52%) 2  2 / 21 (9.52%) 2		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 3		
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all)	8 / 21 (38.10%) 12		
Dry mouth subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 3		
Vomiting subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 5		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 4		
Insomnia subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 5		
Suicidal ideation subjects affected / exposed occurrences (all)	7 / 21 (33.33%) 16		
Emotional disorder subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Musculoskeletal and connective tissue disorders Muscle tightness subjects affected / exposed occurrences (all)	8 / 21 (38.10%) 13		
Back pain subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 3		
Myalgia subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 5		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 March 2021	Changes to the protocol incorporated in the amendment dated 29MAR2021 included: <ul style="list-style-type: none"><li>- Removal of the dissociative subtype of PTSD from the list of exclusion criteria</li><li>- Addition of a requirement that participants not begin a new form of mental healthcare during the screening or treatment phases of the trial without consulting with the study team</li><li>- Removal of the International Personality Disorder Examination (IDPE) as a screening measure to instead use the Structured Clinical Interview for DSM-5 - Personality Disorders (SCID-PD) across all study sites</li><li>- Updates to protocol safety information to reflect current Investigator Brochure</li></ul>
22 November 2022	Changes to the protocol incorporated in the amendment dated 22NOV2022 included: <ul style="list-style-type: none"><li>- Updates to reflect a change in IMP packaging from bulk bottles to containers with IMP for a single experimental session</li><li>- Updates to indicate that audio/video recordings from study visits would be deleted following completion of the required reviews and would not be retained for future research or educational use</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This was an open-label, feasibility study in a small sample, limiting interpretation of the results.

Notes: