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United States Patent and Trademark Office

January 08, 2024

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***63/463,169***
FILING DATE: ***May 01, 2023***

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS ***US63/463,169***

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Application Number: 63463169 Document Date: 05/01/2023

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. _____

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)

Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max):

COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☒ The address corresponding to Customer Number: 26191

OR

☐ Firm or Individual Name

Address

City	State	Zip
Country	Telephone	Email

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Application Data Sheet. See 37 CFR 1.76

☐ CD(s), Number of CDs _____

☒ Drawing(s) *Number of Sheets* 7

☐ Other (specify) _____

☒ Specification (e.g. description of the invention) *Number of Pages* 100

Fees Due: Filing Fee of $300 ($150 for small entity) ($75 for micro entity). If the specification and drawings exceed 100 sheets of paper, an application size fee is also due, which is $420 ($210 for small entity) ($105 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

METHOD OF PAYMENT OF THE FILING FEE AND APPLICATION SIZE FEE FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ Applicant claims small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Applicant must attach form PTO/SB/15A or B or equivalent.

☐ A check or money order made payable to the *Director of the United States Patent and Trademark Office* is enclosed to cover the filing fee and application size fee (if applicable).

☐ Payment by credit card. Form PTO-2038 is attached

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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 10 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET – Page 2 of 2

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government. (NOTE: Providing this information on a provisional cover sheet, such as this Provisional Application for Patent Cover Sheet (Form PTO/SB/16), does not satisfy the requirement of 35 U.S.C. 202(c)(6), which requires that the specification contain a statement specifying that the invention was made with Government support and that the Government has certain rights in the invention.)

☒ No.

☐ Yes, the invention was made by an agency of the U.S. Government. The U.S. Government agency name is: _____

☐ Yes, the invention was made under a contract with an agency of the U.S. Government.

The contract number is: _____

The U.S. Government agency name is: _____

In accordance with 35 U.S.C. 2020(c)(6) and 37 CFR 401.14(f)(4), the specifications of any United States patent applications and any patent issuing thereon covering the invention, including the enclosed provisional application, must state the following:

"This invention was made with government support under [IDENTIFY THE CONTRACT] awarded by [IDENTIFY THE FEDERAL AGENCY]. The government has certain rights in the invention."

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Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

SIGNATURE /William T. Spencer, Reg. No. 73,609/ Date 5/1/2023

TYPED or PRINTED NAME William T. Spencer REGISTRATION NO. 73,609 *(if appropriate)*

TELEPHONE +1 (212) 641-2270 Docket Number: 54925-0003P02

51193455.doc

PTO/AIA/14 (01-22)
Approved for use through 05/31/2024. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0003P02
	Application Number	
Title of Invention	COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix

Residence Information (Select One) ● US Residency Non US Residency Active US Military Service

City	State/Province	Country of Residence

Mailing Address of Inventor:

Address 1	
Address 2	
City	State/Province
Postal Code	Country

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	26191		
Email Address	apso@fr.com	Add Email	Remove Email

Application Information:

Title of the Invention	COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME		
Attorney Docket Number	54925-0003P02	Small Entity Status Claimed	☒
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	7	Suggested Figure for Publication (if any)	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0003P02
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Title of Invention	COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
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Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	26191		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0003P02
	Application Number	
Title of Invention	COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME	

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

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Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0003P02
	Application Number	
Title of Invention	COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0003P02
	Application Number	
Title of Invention	COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
● Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	MAPS Public Benefit Corporation		
Mailing Address Information For Applicant:			
Address 1	3141 Stevens Creek Blvd # 40547		
Address 2			
City	San Jose	**State/Province**	CA
Country	US	Postal Code	95117
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	54925-0003P02
	Application Number	
Title of Invention	COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

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Signature:

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This Application Data Sheet must be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/William T. Spencer, Reg. No. 73,609/			Date (YYYY-MM-DD)	2023-05-01
First Name	William	Last Name	Spencer	Registration Number	73609

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Approved for use through 05/31/2024. OMB 0651-0032
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The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME

FIELD

The present invention generally relates to 3,4-methylenedioxymethamphetamine (MDMA) particles, dosage forms, and uses thereof.

BACKGROUND

Central nervous system (CNS) disorders can have a devastating impact on the afflicted individuals, their families, and society at large. These disorders can be challenging to treat, as the therapies often have significant undesired side effects. As such, novel treatments for such disorders are needed.

MDMA has been studied in late stage clinical trials for the treatment of subjects with post-traumatic stress disorder (PTSD). Earlier-stage clinical trials exploring its efficacy in treating a variety of disorders are ongoing.

MDMA has multiple solid-state forms, including a MDMA hydrochloride hydrate (MDMA·HCl hydrate) that readily forms under ambient conditions, particularly during grinding and in high-humidity environments. In addition, the free base of MDMA is an oil at room temperature. This results in significant difficulty in preparing consistent, stable, safe, and effective dosage forms of MDMA. As such, novel MDMA formulations are needed.

SUMMARY

The present disclosure is based, in part, on surprising and unexpected discoveries related to particle size in formulations of MDMA and use of such formulations in therapy.

Some embodiments provide a composition comprising 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, wherein the average particle size of the MDMA is from about 50 μm to about 400 μm.

Some embodiments provide a dosage form comprising a composition comprising 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, wherein the average particle size

of the MDMA is from about 50 μm to about 400 μm, and optionally one or more additional pharmaceutically acceptable excipients.

Some embodiments provide a method of treating a subject in need thereof, comprising administering to the subject a dosage form as described herein (i.e., comprising MDMA or a pharmaceutically acceptable salt and/or solvate thereof and one or more pharmaceutically acceptable excipients).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows exemplary coarse MDMA hydrochloride particles isolated from the synthetic process.

FIG. 2 shows exemplary particles comprising MDMA after milling.

FIG. 3 shows the particle size distribution (PSD) of the milled particles of FIG. 2.

FIG. 4 shows an HPLC chromatogram for coarse MDMA particles isolated from the synthetic process.

FIG. 5 shows the XRPD spectra of MDMA·HCl monohydrate (5A), MDMA Form III (5B), and MDMA Form II (5C).

FIG. 6 shows the schedule of dosing and psychotherapy sessions for MDMA·HCl, in which the doses are expressed on a free base basis of MDMA.

FIG. 7 shows an integrated forest plot of treatment effect for the MAPP1 and MAPP2 clinical trials.

DETAILED DESCRIPTION

Reference will now be made in detail to certain embodiments of the present disclosure, examples of which are illustrated in the accompanying structures and formulas. While the present disclosure will be described in conjunction with the enumerated embodiments, it will be understood that the present disclosure is not limited to these embodiments. On the contrary, the present disclosure is intended to cover all alternatives, modifications, and equivalents that can be included within the scope of the present disclosure as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present disclosure.

Any of the embodiments described herein, including those described under different aspects of the present disclosure and different parts of the specification (including embodiments described only in the Examples) can be combined with one or more other embodiments of the present disclosure, unless explicitly disclaimed or improper. Combinations of embodiments are not limited to the specific combinations claimed via the multiple dependent claims.

Definitions

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts. A composition can refer to a product suitable for administration to a subject, but for clarity, compositions for pharmaceutical use are generally referred to as "dosage forms" herein.

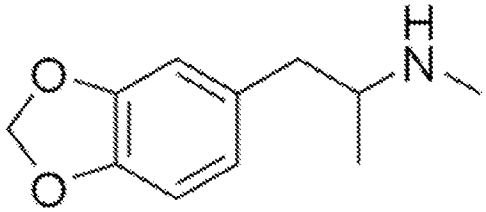
As particles are often non-spherical, it is difficult and complex to provide dimensional descriptions of these non-spherical particles. As used herein, "volume diameter" refers to the diameter of a sphere with a volume equivalent to that of the non-spherical particle. In some embodiments, the particle sizes described herein are measured using a laser diffraction technique that correlates light scattering to particle volume, from which effective length or effective diameter is calculated. The distribution is based on a measurement of thousands of particles. Particle samples can be in dry form, in slurry form, or in the form of suspension. In one embodiment, the particle sample is suspended in a solution of cyclohexane. In another embodiment, the instrument used to determine particle size and distribution is Malvern Mastersizer 3000.

As use herein, particle size is expressed in terms of volume diameter and the particle size distribution is expressed in terms of Dv50, Dv10, and Dv90. A Dv90 value, for example, represents that 90% of particles formed are below a certain threshold. For instance, a Dv90 below 420 μm means that 90% of particles formed have a lower diameter than 420 μm. As used herein, "Dv50", also known as the median particle diameter, corresponds to the value for which 50% of the particles have a lower volume diameter, and 50% of the particles have a higher volume diameter. "Dv90" corresponds to the value for which 90% of the particles have a lower volume diameter, and 10% of the particles have a higher volume diameter. "Dv10" corresponds to the value for which 10% of the particles have a lower volume diameter, and 90% of the particles have a higher volume diameter.

As used herein, "particle size range" corresponds to a value obtained by subtracting the Dv10 from the Dv90. The "Dv10 – Dv90 range" may be calculated from the Dv10 and Dv90 obtained from a single sample, or it may be calculated by averaging the Dv10 and Dv90 values obtained, individually, from a plurality of samples taken from the same batch.

Unless specifically stated or obvious from context, as used herein, the term "about" is understood as within a range of normal tolerance in the art, for example, within 20% of the stated value. As used herein, "about" a specific value also includes the specific value, for example, about 10% includes 10%.

As used herein, the term "MDMA" refers to the compound 3,4-methylenedioxymethamphetamine, having the structure:



In some embodiments, the MDMA is racemic. In some embodiments, the MDMA is (S)-MDMA, in some embodiments, the MDMA is (R)-MDMA. In some embodiments, the MDMA is a non-racemic (i.e., scalemic) mixture of (S)-MDMA and (R)-MDMA.

The term "treating" refers to administering a therapy in an amount, manner, or mode effective to improve a condition, symptom, or parameter associated with a disease or disorder. The term "treating" or "treatment" covers the treatment of a disease or disorder described herein, in a subject, such as a human, and includes: (i) inhibiting a disease or disorder, *i.e.*, arresting its development; (ii) relieving a disease or disorder, *i.e.*, causing regression of the disease or disorder; (iii) slowing progression of the disease or disorder; and/or (iv) inhibiting, relieving, or slowing progression of one or more symptoms of the disease or disorder.

The term "therapeutic" as used herein means a treatment. A therapeutic effect is obtained by suppression, remission, or eradication of a disease state.

The term "prevent" or "preventative" as used herein means a prophylactic treatment. A preventative effect is obtained by delaying the onset of a disease state or decreasing the severity of a disease state when it occurs.

The term "therapeutically effective amount", "prophylactically effective amount", or "effective amount" refers to an amount of the agent that, when administered, is sufficient to cause

the desired effect. For example, an effective amount of MDMA may be an amount sufficient to have a beneficial effect on the subject (*e.g.*, to lessen symptoms of disease or disorder). The therapeutically effective amount of the agent may vary depending on the tumor being treated and its severity as well as the age, weight, etc., of the subject to be treated. In the methods described herein, the therapeutic compounds may be administered to a subject having one or more signs or symptoms of a disease or disorder.

The term "pharmaceutically acceptable" indicates that the compound, or salt or composition thereof is compatible chemically and/or toxicologically with the other ingredients comprising a formulation and/or the subject being treated therewith.

As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. These pharmaceutically acceptable salts may be prepared in situ during the final isolation and purification of the compound, or by separately reacting the purified compound in its free base form with a suitable acid. Suitable acids include pharmaceutically acceptable inorganic acids and pharmaceutically acceptable organic acids. Representative pharmaceutically acceptable acid addition salts include hydrochloride, hydrobromide, nitrate, methylnitrate, sulfate, bisulfate, sulfamate, phosphate, acetate, hydroxyacetate, phenyl acetate, propionate, butyrate, isobutyrate, valerate, maleate, hydroxymaleate, acrylate, fumarate, malate, tartrate, citrate, salicylate, p-aminosalicyclate, glycollate, lactate, heptanoate, phthalate, oxalate, succinate, benzoate, o-acetoxybenzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, mandelate, tannate, formate, stearate, ascorbate, palmitate, oleate, pyruvate, pamoate, malonate, laurate, glutarate, glutamate, estolate, methanesulfonate (mesylate), ethanesulfonate (esylate), 2-hydroxyethanesulfonate, benzenesulfonate (besylate), p-aminobenzenesulfonate, p-toluenesulfonate (tosylate),napthalene-2-sulfonate, ethanedisulfonate, and 2,5-dihydroxybenzoate.

The term "psychotherapy session" refers to a period of time during which communication (e.g., oral communication) between a subject and a psychotherapist to improve psychological functioning, well-being, and coping mechanisms in the subject occurs. In some embodiments, the psychotherapist is a person who has received training to administer psychotherapy (e.g., a psychiatrist, psychologist, or licensed social worker).

The term "administering" or "administration" of a therapy (*e.g.*, MDMA) to a subject includes any route of introducing or delivering a compound to a subject to perform its intended function. Administration can be carried out by any suitable route, including orally, intranasally, parenterally (intravenously, intramuscularly, intraperitoneally, or subcutaneously), or topically. Administration includes self-administration and administration by another person.

The term "subject" refers to any animal amenable to the methods described herein. In some embodiments, the subject is a mammal. In some embodiments, the mammal is a mouse, a rat, a guinea pig, a non-human primate, a dog, a cat, or a domesticated animal (*e.g.*, horse, cow, pig, goat, sheep). In some embodiments, the subject is a human.

"Optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where the event or circumstance occur and instances where it does not.

The term "substantially" is used herein to refer to greater than 90% (e.g., greater than 92%, greater than 94%, greater than 96%, greater than 98%, or greater than 99%). For example, the composition is substantially free of MDMA·HCl hydrate, i.e., of the MDMA present in the composition, less than 10% is MDMA·HCl hydrate (e.g., less than 8%, less than 6%, less than 4%, less than 2%, or less than 1% is MDMA·HCl hydrate). For example, the MDMA is "substantially pure", meaning that the MDMA contains less than 10% of compounds or substances that are not MDMA (e.g., less than 8%, less than 6%, less than 4%, less than 2%, or less than 1% of compounds or substances that are not MDMA). In some embodiments, substantially pure MDMA contains greater than 90% (e.g., greater than 92%, greater than 94%, greater than 96%, greater than 98%, or greater than 99%) of a single solid form (e.g., polymorph), a single salt, or a single solvate of MDMA.

To provide a more concise description, some of the quantitative expressions herein are recited as a range from about amount X to about amount Y, wherein "X" is one numerical limit of the range and "Y" is the other numerical limit of the range. It is understood that wherein a range is recited, the range is not limited to the recited upper and lower bounds, but rather includes the full range from about amount X through about amount Y, or any range therein.

Particles of MDMA

Consistent dosing to provide safe and effective MDMA levels for treatment has been challenging. Current manufacturing and formulation protocols for therapeutic MDMA provides formulations containing particles with an average particle size greater than 600 micrometers (μm or micron) (e.g., as determined by laser diffraction). Formulation testing revealed that these larger particles are inadequate for batch consistency and do not have desirable dissolution parameters, creating the need for MDMA solids with reduced particle size and improved particle size uniformity.

MDMA has multiple solid-state forms, including MDMA·HCl hydrate that readily forms under ambient conditions, particularly during grinding and in high-humidity environments. The hydrate is significantly more hygroscopic than the MDMA, and can adsorb up to two additional molar equivalents of surface moisture when fine particles are exposed to a high-humidity environment for an extended period of time. It is therefore necessary to reduce MDMA particle size in an environment that is unfavorable for hydrate formation.

The present disclosure provides a solution to these problems.

Some embodiments provide particles of 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof having an average particle size from about 50 μm to about 400 μm.

In some embodiments, the particles have desirable bulk properties and processability for preparing dosage forms suitable for administration to a subject.

MDMA isolated from chemical synthesis is a highly pure, coarse solid with varying particle size. The coarse MDMA, with a typical Dv90 from 800 to 1600 μm and a typical particle size range from 500 μm to 1100 μm, does not yield a uniform blend. The particle size distribution of the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, in the resulting dosage form is uneven, leading to an unacceptably high rate of batch failure.

In some embodiments, the particles are substantially smaller than about 610 μm. In some embodiments, substantially all of the particles have particle sizes and/or volume diameters below about 610 μm. In some embodiments, substantially all of the particles have at least one dimension smaller than about 610 μm.

In some embodiments, the average particle size of the MDMA is from about 50 μm to about 400 μm. In some embodiments, the average particle size of the composition is from about 50 μm to about 100 μm, 100 μm to about 150 μm, 150 μm to about 200 μm, 200 μm to about 250

μm, 250 μm to about 300 μm, 350 μm to about 400 μm, 50 μm to about 150 μm, 150 μm to about 250 μm, 250 μm to about 400 μm, 200 μm to about 400 μm, 100 μm to about 300 μm, or 200 μm to about 400 μm.

In some embodiments, the particles have a Dv10 from about 5 μm to about 40 μm, a Dv50 from about 100 μm to about 200 μm, a Dv90 from about about 250 μm to about 420 μm, to a particle size range from about 250 μm to about 350 μm.

In some embodiments, the Dv10 value of the particles is from about 5 μm to about 40 μm, about 5 μm to about 30 μm, about 5 μm to about 20 μm, about 5 μm to about 15 μm, about 10 μm to about 40 μm, about 15 μm to about 40 μm, about 20 μm to about 40 μm, about 25 μm to about 40 μm, about 10 μm to about 35 μm, about 15 μm to about 35 μm, about 18 μm to about 32 μm, about 20 μm to about 30 μm, about 20 μm to about 25 μm, about 25 μm to about 30 μm, about 5 μm, about 10 μm, about 15 μm, about 20 μm, about 21 μm, about 22 μm, about 23 μm, about 24 μm, about 25 μm, about 26 μm, about 27 μm, about 28 μm, or about 29 μm.

In some embodiments, the Dv50 value of the particles is from about 100 μm to about 200 μm, about 110 μm to about 190 μm, about 120 μm to about 180 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, or about 100 μm to about 200 μm.

In some embodiments, the Dv90 value of the particles is from about 0.01 μm to about 400 μm, from about 250 μm to about 420 μm, from about 250 μm to about 400 μm, from about 250 μm to about 380 μm, from about 270 μm to about 380 μm, from about 270 μm to about 360 μm, from about 270 μm to about 350 μm, from about 270 μm to about 420 μm, from about 290 μm to about 420 μm, from about 290 μm to about 400 μm, from about 290 μm to about 380 μm, from about 310 μm to about 420 μm, from about 310 μm to about 400 μm, from about 310 μm to about 380 μm, from about 330 μm to about 420 μm, from about 330 μm to about 400 μm, from about 330 μm to about 380 μm, from about 350 μm to about 420 μm, from about 350 μm to about 400 μm, or from about 370 μm to about 420 μm.

In some embodiments, the particles are more uniformly distributed (e.g., have a smaller particle size range) than are the crude MDMA particles isolated from the synthetic process. In some embodiments, the particles have a particle size range that is less than about 600 μm (e.g., less than about 500 μm, less than about 420 μm, or less than about 400 μm). In some embodiments,

the particle size range is about 5 μm to about 500 μm (e.g., about 5 μm to about 420 μm, about 20 μm to about 353 μm, about 20 μm to about 326 μm, about 21 μm to about 353 μm, about 21 μm to about 342 μm, about 21 μm to about 326 μm, about 24 μm to about 353 μm, about 29 μm to about 342 μm, about 34 μm to about 341 μm, about 200 μm to about 400 μm, about 230 μm to 380 μm, or about 250 μm to 350 μm.

In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof are synthesized using the cGMP process disclosed in, for example, Scheme 1 of Nair, et al., ACS Omega 20022, 7, pp. 900-907, which is herein incorporated by reference in its entirety for all purposes, including all figures, drawings, and supplemental information.

In some embodiments, the present disclosure provides, in part, particles smaller than about 610 μm in the composition as well as in the dosage form. More specifically, MDMA particles with reduced particle size and increased particle size uniformity with a Dv90 below about 420 μm provide acceptable batch consistency enabling the production of pharmaceutically acceptable dosage forms.

Some embodiments provide a method of producing particles of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, wherein substantially all of the particles are smaller than about 610 μm, with a Dv90 less than 420 μm and a particle size range of less than 400 μm. In some embodiments, the method produces substantially no MDMA·HCl hydrate. In some embodiments, the particles produced have a higher flowability than coarse MDMA particles.

Some embodiments provide a dosage form manufactured from the composition described herein, i.e., comprising MDMA particles substantially smaller than about 610 μm, with a Dv90 below 420 μm and a particle size range of less than 400 μm.

Some embodiments provide dosage forms manufactured from MDMA particles larger than 610 μm, but are reduced to the desired particle size of less than 610 μm with a Dv90 below 420 μm during the manufacturing of the finished product by milling or other means with one or more pharmaceutically acceptable excipients.

In some embodiments, substantially all of the particles are (i) smaller than about 610 μm, and (ii) have a Dv90 below about 400 μm. In some embodiments, the Dv90 is from about 0.01 μm to about 400 μm. In some embodiments, less than 10% of the particles have a particle size below about 10 μm (i.e., the particles have a Dv10 of about 10 μm). In some embodiments, from about

0% to about 10% of the particles have a particle size (Dv10) from about 0.01 μm to about 10 μm. In some embodiments, the median particle size (Dv50) is from about 100 μm to about 200 μm.

In some embodiments, the particles described herein are substantially free of MDMA·HCl monohydrate.

In some embodiments, the dissolution rate in water is greater than or equal to 50% (e.g., 60%, 70%, 80%, 85%, 90%, 95%, 98%, or 99%) of the mass of the MDMA in 30 minutes. In some embodiments, the dissolution rate in water is greater than or equal to 80% of the mass of the MDMA in 30 minutes.

In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is amorphous. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is substantially amorphous. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is crystalline. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is substantially crystalline. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is free of MDMA monohydrate. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is substantially free of MDMA monohydrate. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is present in one or more forms as described in Nair, et al., supra.

In some embodiments, the particles are prepared by a process comprising screen milling coarse particles under an inert atmosphere to reduce the particle size and increase the particle size uniformity of the coarse particles. In some embodiments, the coarse particles are particles isolated from the chemical synthesis of the MDMA. In some embodiments, the coarse particles do not undergo an additional size-reducing process.

In some embodiments, the median particle size (Dv50) of the coarse particles is greater than 400 μm. In some embodiments, the coarse particles are substantially free of a hydrate (e.g., monohydrate) of a pharmaceutically acceptable salt of MDMA. In some embodiments, the coarse particles are substantially free of MDMA·HCl monohydrate.

In some embodiments, the coarse particles are heated to a temperature of 50-70 °C in an environment having an ambient pressure below 1 atmosphere, before entering the screen mill. In some embodiments, the coarse particles are fed into the screen mill in the absence of applied pressure. In some embodiments, the inert atmosphere is substantially free of moisture. In some

embodiments, the inert atmosphere comprises substantially dry nitrogen gas. In some embodiments, the inert atmosphere comprises substantially dry argon gas.

In some embodiments, the particles consist essentially of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

In certain embodiments, the coarse MDMA crystals used to form the MDMA particles of the present disclosure are synthesized using the cGMP process disclosed in, for example, Scheme 1 of Nair *et. al.*, ACS Omega 2022, 7, 1, 900–907, which is incorporated herein in its entirety by reference. The chemical purity of these coarse MDMA crystals as determined by a validated HPLC methodology may exceed 98% of total peak area. In some embodiments, the chemical purity of the coarse MDMA crystals exceeds 99% of total peak area. In some embodiments, the chemical purity of the coarse MDMA crystals exceeds 99.5% of total peak area. In some embodiments, the chemical purity of the coarse MDMA crystals exceeds 99.9% of total peak area.

Methods of Manufacturing MDMA

The MDMA particles of the present disclosure can be prepared by any suitable processes known in the art. In certain embodiments, the MDMA particles of the present disclosure are prepared by a process described herein.

In one aspect, the present disclosure provides new processes for preparing the MDMA particles of the present disclosure.

MDMA isolated from the current chemical synthesis is a highly pure, coarse solid with varying particle size. The coarse MDMA, having a typical Dv90 from 800 μm to 1600 μm and a typical particle size range from 500 μm to 1100 μm, does not yield a uniform blend. The distribution of the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, in the resulting dosage form is uneven, leading to an unacceptably high rate of batch failure. In some embodiments, the median particle size (Dv50) of the coarse particles is greater than 400 μm. In some embodiments, the coarse particles are substantially free of MDMA·HCl monohydrate.

In one embodiment, the process comprises the step of reducing MDMA particle size by screen milling under an inert atmosphere. Screen milling processes known in the art can be used in the processes of the present disclosure. In one embodiment, screen milling in the processes of the present disclosure is performed using a conical screen miller, *e.g.*, a Ytron-Quadro Comill.

One process of the present disclosure comprises the step of screen milling a batch of coarse particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, until the desired particle size reduction and increased particle uniformity are achieved.

In a first process, the coarse particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are substantially dried under a vacuum at 50-70 °C, then fed into a screen mill under an inert atmosphere that may comprise substantially dry nitrogen or any other substantially dry gas. The solids are fed into the mill in the absence of applied pressure, and captured in a collection bag upon exit.

In certain embodiments, the coarse particles comprising crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, are fed into the screen mill in batches of approximately 250 grams, 500 grams, 1000 grams, or 2000 grams. In certain embodiments, the milling process is conducted at a rate of approximately 10 grams per minute, 15 grams per minute, 20 grams per minute, 25 grams per minute, or 50 grams per minute.

In certain embodiments, the screen milling in the processes described above is carried out by hand-feeding the coarse crystalline MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, into the screen mill to avoid compacting and buildup within the mill.

In certain embodiments, a mill speed of 3000, 4000, 5000, 6000, 7000, or 8000 rpm is used.

In certain embodiments, the screen used in the processes described above is a stainless-steel conical screen.

In some embodiments, any one of the processes described above further comprises recovering and storing the MDMA particles after the screen milling step.

Particles of MDMA and Excipient(s)

Some embodiments provide a composition comprising 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, wherein the average particle size of the composition is from about 50 μm to about 400 μm. The excipients can be any excipients described herein, for example, magnesium stearate and/or mannitol.

In some embodiments, the average particle size of the composition is from about 50 μm to about 100 μm, 100 μm to about 150 μm, 150 μm to about 200 μm, 200 μm to about 250 μm, 250

μm to about 300 μm, 350 μm to about 400 μm, 50 μm to about 150 μm, 150 μm to about 250 μm, 250 μm to about 400 μm, 200 μm to about 400 μm, 100 μm to about 300 μm, or 200 μm to about 400 μm.

In some embodiments, the composition has desirable bulk properties and processability for preparing dosage forms suitable for administration to a subject.

MDMA isolated from the current chemical synthesis is a highly pure, coarse solid with varying particle size. The coarse MDMA, having a typical Dv90 from 800 μm to 1600 μm and a typical particle size range from 500 μm to 1100 μm, does not yield a uniform blend. The distribution of the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, in the resulting dosage form is uneven, leading to an unacceptably high rate of batch failure.

It was initially proposed that acceptable MDMA particle size could be achieved by ball-milling the coarse MDMA particles in the presence of a non-aqueous liquid dispersant. This was undesirable due to the high purity of the MDMA isolate, which was suitable for formulation without an additional purification step. It was unexpectedly discovered that MDMA particles with the reduced particle size and more uniform particle size range necessary for drug product manufacturing can be produced under dry conditions using a screen mill, under an inert atmosphere. Alternatively, particles of the desired particle size can be produced by milling of the blends of the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and other pharmaceutically acceptable excipient(s) or by other processes such as wet granulation, forming particles of a composition comprising MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients.

In some embodiments, the composition particles are substantially smaller than about 610 μm. In some embodiments, substantially all of the particles may have volume diameters below about 610 μm. In some embodiments, substantially all of the particles may have at least one dimension smaller than about 610 μm.

In some embodiments, the Dv10 value of the particles is from about 5 μm to about 40 μm, about 5 μm to about 30 μm, about 5 μm to about 20 μm, about 5 μm to about 15 μm, about 10 μm to about 40 μm, about 15 μm to about 40 μm, about 20 μm to about 40 μm, about 25 μm to about 40 μm, about 10 μm to about 35 μm, about 15 μm to about 35 μm, about 18 μm to about 32 μm, about 20 μm to about 30 μm, about 20 μm to about 25 μm, about 25 μm to about 30 μm, about 5

μm, about 10 μm, about 15 μm, about 20 μm, about 21 μm, about 22 μm, about 23 μm, about 24 μm, about 25 μm, about 26 μm, about 27 μm, about 28 μm, or about 29 μm.

In some embodiments, the Dv50 value of the particles is from about 100 μm to about 200 μm, about 110 μm to about 190 μm, about 120 μm to about 180 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, about 100 μm to about 200 μm, or about 100 μm to about 200 μm.

In some embodiments, the Dv90 value of the particles is from about 0.01 μm to about 400 μm, from about 250 μm to about 420 μm, from about 250 μm to about 400 μm, from about 250 μm to about 380 μm, from about 270 μm to about 380 μm, from about 270 μm to about 360 μm, from about 270 μm to about 350 μm, from about 270 μm to about 420 μm, from about 290 μm to about 420 μm, from about 290 μm to about 400 μm, from about 290 μm to about 380 μm, from about 310 μm to about 420 μm, from about 310 μm to about 400 μm, from about 310 μm to about 380 μm, from about 330 μm to about 420 μm, from about 330 μm to about 400 μm, from about 330 μm to about 380 μm, from about 350 μm to about 420 μm, from about 350 μm to about 400 μm, or from about 370 μm to about 420 μm.

In some embodiments, the composition particles are more uniformly distributed (e.g., have a smaller particle size range) than are the crude MDMA particles isolated from the synthetic process (i.e., the coarse particles). In some embodiments, the composition particles have a particle size range that is less than about 600 μm (e.g., less than about 500 μm, less than about 420 μm, or less than about 400 μm). In some embodiments, the particle size range is about 5 μm to about 500 μm (e.g., about 5 μm to about 420 μm, about 20 μm to about 353 μm, about 20 μm to about 326 μm, about 21 μm to about 353 μm, about 21 μm to about 342 μm, about 21 μm to about 326 μm, about 24 μm to about 353 μm, about 29 μm to about 342 μm, about 34 μm to about 341 μm, about 200 μm to about 400 μm, about 230 μm to 380 μm, or about 250 μm to 350 μm.

In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, used to form the particles are synthesized using the cGMP process disclosed in, for example, Scheme 1 of Nair, et al., supra.

In some embodiments, the present disclosure provides, in part, particles smaller than about 610 μm in the composition as well as the dosage form. More specifically, composition particles with reduced particle size and increased particle size uniformity with a Dv90 below about 420 μm

provide acceptable batch consistency enabling the production of pharmaceutically acceptable dosage forms.

Some embodiments provide a method of producing a composition comprising particles substantially smaller than about 610 μm, with a Dv90 less than 420 μm and a particle size range of less than 400 μm, wherein the particles comprise MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients. In some embodiments, the method produces substantially no hydrate (e.g., monohydrate) of a pharmaceutically acceptable salt of MDMA (e.g., MDMA·HCl). In some embodiments, the particles produced have a higher flowability than coarse MDMA particles.

Some embodiments provide a dosage form prepared from a composition described herein. In some embodiments, the composition comprises particles substantially smaller than about 610 μm, with a Dv90 below 420 μm and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a composition comprising particles substantially smaller than about 610 μm, with a Dv90 less than 420 μm and a particle size range of less than 400 μm, wherein the particles comprise MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients.

Some embodiments provide a dosage form prepared by a method comprising:

blending particles having an average particle size greater than 610 μm with one or more pharmaceutically acceptable excipients;

changing the average particle size of the particles to less than 610 μm and a Dv90 below 420 μm;

wherein the particles comprise MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients.

In some embodiments, the changing comprises milling the particles with the one or more pharmaceutically acceptable excipients.

In some embodiments, substantially all of the particles are (i) smaller than about 610 μm, and (ii) have a Dv90 lesser than about 400 μm. In some embodiments, the Dv90 is from about 0.01 μm to about 400 μm. In some embodiments, less than 10% of the particles have a particle size (Dv10) below about 10 μm. In some embodiments, from about 0% to about 10% of the particles have a particle size (Dv10) from about 0.01 μm to about 10 μm. In some embodiments, the median particle size (Dv50) is from about 100 μm and about 200 μm.

In some embodiments, the particles are substantially free of MDMA·HCl monohydrate.

In some embodiments, at least 80% of the mass of the MDMA particles dissolves in water in 30 minutes or less.

In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is amorphous. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is substantially amorphous. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is crystalline. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is substantially crystalline. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is free of MDMA·HCl monohydrate. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, is substantially free of MDMA·HCl monohydrate. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof, comprises one or more forms as described in Nair, et al., supra.

In any of the compositions described herein, the particles of the composition are prepared by a process comprising a step of reducing average particle size and increasing particle size uniformity by screen-milling under an inert atmosphere.

In some embodiments, the composition includes a diluent. In some embodiments, the diluent is a sugar alcohol. In some embodiments, the diluent has a moisture content of less than 0.25% by mass, prior to blending with the MDMA, or a pharmaceutically acceptable salt and/or hydrate thereof.

In some embodiments, in the compositions described herein the desired particle size and particles size uniformity is achieved in the process of making the finished dosage form by milling or other means.

In some embodiments, the compositions described herein can additionally include a lubricant. In some embodiments, the lubricant includes a pharmaceutically acceptable salt of a saturated fatty acid.

In some embodiments, the particles are prepared by a process comprising the step of reducing particle size and increasing particle size uniformity by screen milling. In some embodiments, the coarse particles do not undergo an additional size-reducing process.

In some embodiments, the median particle size (Dv50) of the coarse particles is greater than 400 μm. In some embodiments, the coarse particles are substantially free of MDMA·HCl monohydrate.

In some embodiments, the coarse particles are heated to a temperature of 50-70 °C in an environment having an ambient pressure below 1 atmosphere, before entering the screen mill. In some embodiments, the coarse particles are fed into the screen mill in the absence of applied pressure. In some embodiments, the inert atmosphere is substantially free of moisture. In some embodiments, the inert atmosphere comprises substantially dry nitrogen gas. In some embodiments, the inert atmosphere comprises substantially dry argon gas.

In some embodiments, the particles consist essentially of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients.

Dosage Forms

Some embodiments provide a dosage form comprising a composition comprising 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, wherein the average particle size of the composition in the dosage form is from about 50 μm to about 400 μm.

Some embodiments provide a dosage form comprising a composition comprising 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, wherein the average particle size of the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is from about 50 μm to about 400 μm.

Exemplary, non-limiting pharmaceutically acceptable excipients are described below. Additional excipients and general methods for preparing the types of dosage forms described herein can be found in, for example, Remington: The Science and Practice of Pharmacy, 23rd Edition (Elsevier Science, Amsterdam, NL. 2020). Such pharmaceutically acceptable excipients include, but are not limited to, binders, glidants, disintegrants, lubricants, carriers, diluents, buffers, tonicity modifying agents, polymers, thickening agents, penetration enhancers, surfactants, and solubility enhancers. *See, e.g.*, Remington's, *supra*. Some pharmaceutically acceptable excipients can be in more than one of the foregoing sub-categories. Pharmaceutically acceptable excipients

also include dosage form coatings, for example, an extended release coating, abuse-deterrent coating, or a film-coating.

In some embodiments, pharmaceutically acceptable excipients used herein have reduced hygroscopicity and/or low residual moisture content.

In some embodiments, the pharmaceutically acceptable excipients used herein are independently selected from the group consisting of: microcellulose, lactose (e.g., α-lactose monohydrate), starch, mannitol, calcium hydrogen phosphate anhydrous, silicon dioxide, calcium carbonate, microcellulose, talc, sodium starch glycolate, croscarmellose sodium, povidone, copovidone or hydroxyl propyl cellulose, magnesium stearate, sodium stearyl fumarate, and colloidal silicon dioxide. In some embodiments, the pharmaceutically acceptable excipient comprises α-lactose monohydrate. In some embodiments, the pharmaceutically acceptable excipient comprises magnesium stearate and mannitol.

In some embodiments, the dosage form comprises particles substantially smaller than about 610 μm, with a Dv90 below 420 μm and a particle size range of less than 400 μm. The dosage forms comprise MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, in accordance with any embodiment as described herein. The dosage forms may be intended for topical, oral, nasal, mucosal, respiratory, transdermal, or parenteral administration.

The dosage forms provided herein include, but are not limited to, solid formulations such as tablets, capsules, pills, wafers, films, and lozenges, or liquid formulations such as aqueous solutions, elixirs, and syrups. Solid and liquid formulations in accordance with the present invention may also be incorporated into liquid or solid comestibles.

In some embodiments, the dosage form comprises encapsulated pharmaceutical formulations provided by any other embodiment as described herein. Capsules used for the dosage form may be hard-shelled or soft-shelled. The capsules may comprise collagenous gelatin, fish gelatin, hydroxypropyl methylcellulose, starch, pullulan, polyvinyl acetate, or any other material known to a person skilled in the art to be useful for encapsulating dosage forms.

In some embodiments, the dosage form comprises liquid formulations formulated for topical administration, such as aqueous solutions and emulsions, which may be applied directly to the skin and/or mucous membranes, or aerosolized for respiratory administration. Alternatively, topical dosage forms provided by the present invention may be formulated as creams, foams, gels, lotions, and ointments.

In some embodiments, the dosage form comprises solid compositions formulated for respiratory or inhalation administration, for example, for use in dry-powder inhalers, or liquid compositions formulated for use in metered-dose inhalers or nebulizers.

In some embodiments, the dosage form comprises a liquid solutions formulated for parenteral administration, such as suspensions, emulsions, or reconstituted lyophilized powders, suitable for administration by injection.

In some embodiments, the dosage form is in the form of a capsule, for example a cellulose-based capsule containing the composition described herein. In some embodiments, the dosage form is a hydroxypropylmethylcellulose (HPMC) capsule. In some embodiments, the capsule is a gelatin capsule.

In some embodiments, the dosage form comprises about 1 mg to about 150 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA. In some embodiments, the dosage form comprises about 17 mg to about 126 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA. In some embodiments, the dosage form comprises about 1 mg to about 50 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA. In some embodiments, the dosage form comprises about 68 mg to about 100 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA. In some embodiments, the dosage form comprises about 50 mg to about 130 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA. In some embodiments, the dosage form comprises about 25 mg to about 75 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA. In some embodiments, the dosage form comprises about 50 mg to about 100 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA. In some embodiments, the dosage form comprises about 75 mg to about 125 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA. In some embodiments, the dosage form comprises about 100 mg to about 150 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA.

In some embodiments, the amount of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is expressed on a free base basis of MDMA.

In some embodiments, the dosage form comprises about 12.5 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 37.5 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 62.5 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, or about 150 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA.

In some embodiments, the dosage form comprises 12.5 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 37.5 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 62.5 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, or 150 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA.

In some embodiments, the dosage form comprises about 12.5 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 37.5 mg, about 40 mg, about 50 mg, about 60 mg, about 62.5 mg, about 75 mg, about 80 mg, about 100 mg, or about 125 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA.

In some embodiments, the dosage form comprises 12.5 mg, 15 mg, 20 mg, 25 mg, 30 mg, 37.5 mg, 40 mg, 50 mg, 60 mg, 62.5 mg, 75 mg, 80 mg, 100 mg, or 125 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA.

In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof is MDMA hydrochloride (MDMA·HCl). In some embodiments, the dosage form comprises about 1 mg to about 180 mg (e.g., about 20 mg to about 150 mg, about 30 mg to about 140 mg, about 40 mg to about 130 mg, about 30 mg to about 70 mg, about 40 mg to about 60 mg, about 80 mg to about 120 mg, about 120 mg to about 180 mg, about 30 mg to about 50 mg, about 35 mg to about 45 mg, about 55 mg to about 65 mg, about 20 mg, about 40 mg, about 60 mg, about 80 mg, about 120 mg, about 150 mg, or about 180 mg) MDMA·HCl. In some embodiments, the dosage form comprises about 120 mg to about 180 mg MDMA·HCl. In some embodiments, the dosage form comprises about 20 mg to about 150 mg MDMA·HCl. In some embodiments, the dosage form comprises about 80 mg to about 120 mg MDMA·HCl. In some embodiments, the dosage form comprises about 40 mg to about 60 mg MDMA·HCl. In some embodiments, the dosage form comprises about 20 mg MDMA·HCl. In some embodiments, the dosage form

comprises about 40 mg MDMA·HCl. In some embodiments, the dosage form comprises about 60 mg MDMA·HCl. In some embodiments, the dosage form comprises about 80 mg MDMA·HCl. In some embodiments, the dosage form comprises about 100 mg MDMA·HCl. In some embodiments, the dosage form comprises about 120 mg MDMA·HCl. In some embodiments, the dosage form comprises about 150 mg MDMA·HCl. In some embodiments, the dosage form comprises about 180 mg MDMA·HCl.

In some embodiments, the dosage form comprises particles substantially smaller than about 610 μm, with a Dv90 below 420 μm and a particle size range of less than 400 μm, and one or more pharmaceutically acceptable excipients.

In some embodiments, the dosage form comprises particles substantially smaller than about 610 μm that are prepared by a product comprising milling a mixture of MDMA with one or more pharmaceutically excipients as described herein.

In some embodiments, the dosage form comprises particles substantially smaller than about 610 μm, with a Dv90 below 420 μm and a particle size range of less than 400 μm, a binder comprising a polyalcohol, and a lubricant comprising a pharmaceutically acceptable salt of a saturated fatty acid.

In some embodiments, the dosage form is substantially free of a hydrate of a pharmaceutically acceptable salt of MDMA. In some embodiments, the dosage form is substantially free of MDMA·HCl monohydrate. In some embodiments, the dosage form comprises no detectable MDMA·HCl monohydrate.

In some embodiments, each of the dosage form is a tablet. In some embodiments, the dosage form is a capsule. In some embodiments, the dosage form includes one or more individual dosage units, for example, in some embodiments, the dosage form is a blister pack. In some embodiments, the dosage form includes one individual dosage unit. In some embodiments, the dosage form includes at least two individual dosage units. In some embodiments, the dosage form includes three individual dosage units. In some embodiments, the dosage form includes at least three individual dosage units. In some embodiments, each of the one or more individual dosage units comprises a capsule. In some embodiments, each of the one or more individual dosage units comprises a tablet. In some embodiments, each of the one or more individual dosage units comprises a capsule. In some embodiments, each of the one or more individual dosage units is a tablet. In some embodiments, each of the one or more individual dosage units is a capsule.

In some embodiments, the one or more individual dosage units are administered during a single psychotherapy session. In some embodiments, the one or more individual dosage units are administered at different times during the single psychotherapy session.

As used herein, an individual dosage unit (i.e., a tablet or capsule provided in a blister pack) has the same characteristics of the dosage forms described herein that are not comprised of individual dosage units (i.e., the dosage forms such as tablets, capsules, and the like). As such, each individual dosage unit is a dosage form comprising MDMA, or a pharmaceutically acceptable salt and/or solvate thereof (for example, about 40 mg MDMA·HCl; or about 60 mg MDMA·HCl).

Some embodiments provide a dosage form comprising a capsule comprising gelatin, wherein the capsule contains a composition comprising:

MDMA, wherein substantially all of the MDMA particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm; and

α-lactose monohydrate.

Some embodiments provide a dosage form comprising a capsule comprising gelatin, wherein the capsule contains a composition comprising:

MDMA; and

α-lactose monohydrate;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a capsule comprising gelatin, wherein the capsule contains a composition comprising:

MDMA·HCl, wherein substantially all of the MDMA·HCl particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm; and

α-lactose monohydrate.

Some embodiments provide a dosage form comprising a capsule comprising gelatin, wherein the capsule contains a composition comprising:

MDMA·HCl; and

α-lactose monohydrate;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a capsule comprising gelatin, wherein the capsule contains a composition comprising:

about 20 mg to about 150 mg MDMA·HCl, wherein substantially all of the MDMA·HCl particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm; and

α-lactose monohydrate.

Some embodiments provide a dosage form comprising a capsule comprising gelatin, wherein the capsule contains a composition comprising:

about 20 mg to about 150 mg MDMA·HCl; and

α-lactose monohydrate;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 40 mg to about 60 mg MDMA·HCl, wherein substantially all of the MDMA·HCl particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 40 mg to about 60 mg MDMA·HCl;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 40 mg MDMA·HCl, wherein substantially all of the MDMA·HCl particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 40 mg MDMA·HCl;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 60 mg MDMA·HCl, wherein substantially all of the MDMA·HCl particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 60 mg MDMA·HCl;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 34 mg MDMA on a free base basis of MDMA, wherein substantially all of the MDMA particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 34 mg MDMA on a free base basis of MDMA;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 50 mg MDMA on a free base basis of MDMA, wherein substantially all of the MDMA particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 50 mg MDMA on a free base basis of MDMA;

about 0.1% to about 10% by weight of magnesium stearate; and

about 25% to about 75% by weight of mannitol;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

In some embodiments, the dosage form comprises about 0.1% to about 10% (e.g., about 0.1% to about 8%, about 0.1% to about 5%, about 0.1% to about 4%, about 0.1% to about 2%, about 0.5% to about 1.5%, or about 1%) by weight of magnesium stearate. In some embodiments, the dosage form comprises about 1% by weight of magnesium stearate.

In some embodiments, the dosage form comprises about 25% to about 75% (e.g., about 25% to about 65%, about 25% to about 55%, about 25% to about 50%, about 25% to about 35%, about 35% to about 75%, about 50% to about 75%, about 35% to about 65%, about 40% to about

60%, about 45% to about 55%, or about 49%) by weight of mannitol. In some embodiments, the dosage form comprises about 49% by weight of mannitol.

In some embodiments, the dosage form comprises about 25% to about 75% (e.g., about 25% to about 65%, about 25% to about 55%, about 25% to about 50%, about 25% to about 35%, about 35% to about 75%, about 50% to about 75%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55%, or about 50%) by weight of MDMA·HCl. In some embodiments, the dosage form comprises about 50% by weight of MDMA·HCl.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 60 mg MDMA·HCl, wherein substantially all of the MDMA·HCl particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm;

about 1% by weight of magnesium stearate; and

about 49% by weight of mannitol.

Some embodiments provide a dosage form comprising a capsule comprising hydroxypropylmethylcellulose (HPMC), wherein the capsule contains a composition comprising:

about 60 mg MDMA·HCl;

about 1% by weight of magnesium stearate; and

about 49% by weight of mannitol;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Methods of Use

Some embodiments provide a method of treating a subject in need thereof, comprising administering to the subject a dosage form as described herein (i.e., comprising MDMA or a pharmaceutically acceptable salt and/or solvate thereof and one or more pharmaceutically acceptable excipients).

In some embodiments, the dosage form is administered in a therapeutic setting, for example, in an in-patient and/or out-patient setting. In some embodiments, the dosage form is administered in a psychotherapy session (e.g., a single psychotherapy session).

Some embodiments provide a method of treating a subject having one or more central nervous system (CNS) disorders, comprising administering to the subject a dosage form as described herein (i.e., comprising MDMA or a pharmaceutically acceptable salt and/or solvate thereof and one or more pharmaceutically acceptable excipients).

In some embodiments, the one or more CNS disorders are independently mood, anxiety, or trauma-linked disorders.

In some embodiments, the one or more CNS disorders are independently autism spectrum disorders, neuropsychiatric diseases or disorders; or neurodegenerative diseases.

In some embodiments, the one or more CNS disorders are independently post-traumatic stress disorder (PTSD), anxiety disorder, major depressive disorder, obsessive compulsive disorder, bipolar disorder, dysthymic disorder; Parkinson's disease, epilepsy, recurrent migraines, stroke, or post-concussion syndrome; alcohol use disorder; attention deficit hyperactivity disorder (ADHD), anorexia nervosa, bulimia, binge eating disorder, or autism.

In some embodiments, the one or more CNS disorders is PTSD. In some embodiments, the one or more CNS disorders is treatment-resistant PTSD.

The dosage form may be administered in any pharmaceutically acceptable dosage form, including dosage forms provided in accordance with any embodiment as described herein. The dosage form may be administered on one occasion, or on multiple individual occasions.

In some embodiments, the dosage form is administered during individual psychotherapy. The individual psychotherapy sessions may occur at regular intervals, *e.g.*, every two weeks, or at non-regular intervals that may vary in accordance with a subject's individual needs or protocols established for treating the subject's indicated disease or disorder.

In some embodiments, the dosage form in accordance with any embodiment is orally administered to a subject suffering from a central nervous system disease or disorder. The dosage form is administered in a therapeutic setting during multiple individual psychotherapy sessions, wherein at least one therapist is present.

In some embodiments, the dosage form is orally administered in two separate dosage components, an initial dose and a supplementary dose, during the same psychotherapy session. The initial dose may comprise about 25 to about 150 mg of MDMA or a pharmaceutically acceptable salt and/or solvate thereof, and the supplementary dose may comprise about 10 mg to about 70 mg of MDMA or a pharmaceutically acceptable salt and/or solvate thereof. In some

embodiments, the initial and supplementary dosage components are physically separated from each other (*e.g.*, as two capsules, two tablets, or one capsule and one tablet) and are provided in a kit (*e.g.*, a blister pack). In some embodiments, initial and supplementary dosage components are both part of one dosage form (*e.g.*, a pill, a tablet, or a capsule).

In some embodiments, the central nervous system disorder is a trauma-linked disorder or a stressor-linked disorder. In some embodiments, the central nervous system disorder is a mood disorder. In some embodiments, wherein the central nervous system disorder is an anxiety disorder. In some embodiments, the central nervous system disorder is post-traumatic stress disorder.

In some embodiments, the administering is performed during a psychotherapy session. In some embodiments, a dosage form comprising about 100 mg of MDMA is administered. In some embodiments, about 100 mg of MDMA is administered in one dose. In some embodiments, about 100 mg of MDMA is administered in two doses.

In some embodiments, a dosage form comprising about 120 mg of MDMA is administered. In some embodiments, about 120 mg of MDMA is administered in one dose. In some embodiments, the about 120 mg of MDMA is administered in two doses.

In some embodiments, the dosage form comprising about 140 mg of MDMA is administered. In some embodiments, about 140 mg of MDMA is administered in one dose. In some embodiments, the about 140 mg of MDMA is administered in two doses.

In some embodiments, the dosage form comprising about 160 mg of MDMA is administered. In some embodiments, the about 160 mg of MDMA is administered in one dose. In some embodiments, the about 160 mg of MDMA is administered in two doses.

In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day is about 80 mg to about 170 mg on a free base basis of MDMA. In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day is about 102 mg to about 150 mg on a free base basis of MDMA. In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day is about 102 mg on a free base basis of MDMA. In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day is about 150 mg on a free base basis of MDMA. In some embodiments,

the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day should not exceed about 150 mg on a free base basis of MDMA.

In some embodiments, the dose of MDMA·HCl, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day is about 90 mg to about 210 mg, on a free base basis of MDMA. In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day is about 120 mg to about 180 mg, on a free base basis of MDMA. In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day is about 120 mg, on a free base basis of MDMA. In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day is about 180 mg, on a free base basis of MDMA. In some embodiments, the dose of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, administered in one day should not exceed about 180 mg, on a free base basis of MDMA.

In some embodiments, the dosage form comprising the therapeutically effective amount of MDMA is orally administered. In some embodiments, the dosage form comprising the therapeutically effective amount of MDMA is administered in a capsule. In some embodiments, the dosage form comprising the therapeutically effective amount of MDMA is administered in a tablet.

In some embodiments, the dosage form comprising the therapeutically effective amount of MDMA is administered as one or more individual dosage units during a single psychotherapy session. In some embodiments, the dosage form comprising the therapeutically effective amount of MDMA is administered at different times during a single psychotherapy session.

Some embodiments provide a method of treating PTSD in a subject in need thereof, comprising:

administering one or more individual dosage units during a psychotherapy session;

wherein each individual dosage unit comprises a composition comprising about 20 mg to about 150 mg MDMA and/or a pharmaceutically acceptable salt or solvate thereof on a free base basis of MDMA;

wherein substantially all of the MDMA particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a method of treating PTSD in a subject in need thereof, comprising:

administering one or more individual dosage units during a psychotherapy session;

wherein each individual dosage unit comprises a composition comprising about 20 mg to about 150 mg MDMA and/or a pharmaceutically acceptable salt or solvate thereof on a free base basis of MDMA;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a method of treating PTSD in a subject in need thereof, comprising:

administering one or more individual dosage units during a first psychotherapy session;

administering one or more individual dosage units during a second psychotherapy session at least 21 days after the first psychotherapy session;

administering one or more individual dosage units during a third psychotherapy session at least 21 days after the second psychotherapy session;

wherein each individual dosage unit comprises a composition comprising about 20 mg to about 150 mg MDMA and/or a pharmaceutically acceptable salt or solvate thereof on a free base basis of MDMA;

wherein substantially all of the MDMA particles have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

Some embodiments provide a method of treating PTSD in a subject in need thereof, comprising:

administering one or more individual dosage units during a first psychotherapy session;

administering one or more individual dosage units during a second psychotherapy session at least 21 days after the first psychotherapy session;

administering one or more individual dosage units during a third psychotherapy session at least 21 days after the second psychotherapy session;

wherein each individual dosage unit comprises a composition comprising about 20 mg to about 150 mg MDMA and/or a pharmaceutically acceptable salt or solvate thereof on a free base basis of MDMA;

wherein substantially all of the particles of the composition have a particle size smaller than about 610 μm, a Dv90 below 420 μm, and a particle size range of less than 400 μm.

In some embodiments, the one or more individual dosage units administered during a psychotherapy session is one individual dosage unit. In some embodiments, the one or more individual dosage units administered during a psychotherapy session is two individual dosage units. In some embodiments, the one or more individual dosage units administered during a psychotherapy session is three individual dosage units.

In some embodiments, when the one or more individual dosage units is two or more individual dosage units, the method comprises administering the individual dosage units at different times during the psychotherapy session. In some embodiments, when the one or more individual dosage units is two or more individual dosage units, the method comprises administering the individual dosage units at the same time during the psychotherapy session.

In some embodiments, the one or more individual dosage units is three individual dosage units; two of the individual dosage units are administered at the same time; and the third individual dosage unit is administered at a different time during the psychotherapy session. In some embodiments, the one or more individual dosage units is three individual dosage units; the first and second of the individual dosage units are administered at the same time; and the third individual dosage unit is administered after the first and second individual dosage units during the psychotherapy session. In some embodiments, the third individual dosage unit is administered about 5 minutes to about 5 hours (e.g., about 15 minutes to about 5 hours, about 30 minutes to about 5 hours, about 1 hour to about 5 hours, about 1.5 hours to about 5 hours, about 2 hours to about 5 hours, about 3 hours to about 5 hours, about 5 minutes to about 4 hours, about 5 minutes to about 3 hours, about 5 minutes to about 2 hours, about 5 minutes to about 1 hour, about 30 minutes to about 4 hours, about 45 minutes to about 3 hours, about 1 hour to about 2.5 hours, about 1 hour to about 2 hours, about 1 hour and 15 minutes to about 1 hour and 45 minutes, about 1 hour and 15 minutes to about 2 hours and 15 minutes, about 1.5 hours to about 2 hours, about 1.5 hours, about 1 hour and 45 minutes, or about 2 hours) after the first and second individual dosage units. In some embodiments, the third individual dosage unit is administered about 1.5 hours to about 2 hours after the first and second individual dosage units.

In some embodiments, each individual dosage unit comprises a capsule. In some embodiments, the capsule comprises hydroxypropylmethylcellulose (HPMC). In some

embodiments, the capsule contains a composition comprising about 20 mg to about 150 mg MDMA and/or a pharmaceutically acceptable salt or solvate thereof on a free base basis of MDMA. In some embodiments, the composition comprises about 0.1% to about 10% by weight of magnesium stearate and about 25% to about 75% by weight of mannitol.

In some embodiments, the composition comprises about 0.1% to about 10% (e.g., about 0.1% to about 8%, about 0.1% to about 5%, about 0.1% to about 4%, about 0.1% to about 2%, about 0.5% to about 1.5%, or about 1%) by weight of magnesium stearate. In some embodiments, the composition comprises about 1% by weight of magnesium stearate.

In some embodiments, the composition comprises about 25% to about 75% (e.g., about 25% to about 65%, about 25% to about 55%, about 25% to about 50%, about 25% to about 35%, about 35% to about 75%, about 50% to about 75%, about 35% to about 65%, about 40% to about 60%, about 45% to about 55%, or about 49%) by weight of mannitol. In some embodiments, the composition comprises about 49% by weight of mannitol.

In some embodiments, the composition comprises about 34 mg to about 50 mg MDMA or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA. In some embodiments, the composition comprises about 34 mg MDMA or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA. In some embodiments, the composition of the one or more individual dosage units administered during the first psychotherapy session comprises about 34 mg MDMA or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA. In some embodiments, the composition comprises about 50 mg MDMA or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA. In some embodiments, the composition of the one or more individual dosage units administered during the second and third psychotherapy sessions comprises about 50 mg MDMA or a pharmaceutically acceptable salt and/or solvate thereof on a free base basis of MDMA.

In some embodiments, the MDMA or a pharmaceutically acceptable salt and/or solvate thereof is MDMA·HCl. In some embodiments, the composition comprises about 1 mg to about 180 mg (e.g., about 20 mg to about 150 mg, about 30 mg to about 140 mg, about 40 mg to about 130 mg, about 30 mg to about 70 mg, about 40 mg to about 60 mg, about 80 mg to about 120 mg, about 120 mg to about 180 mg, about 30 mg to about 50 mg, about 35 mg to about 45 mg, about 55 mg to about 65 mg, about 20 mg, about 40 mg, about 60 mg, about 80 mg, about 120 mg, about 150 mg, or about 180 mg) MDMA·HCl. In some embodiments, the composition comprises about

120 mg to about 180 mg MDMA·HCl. In some embodiments, the composition comprises about 20 mg to about 150 mg MDMA·HCl. In some embodiments, the composition comprises about 80 mg to about 120 mg MDMA·HCl. In some embodiments, the composition comprises about 40 mg to about 60 mg MDMA·HCl. In some embodiments, the composition comprises about 20 mg MDMA·HCl. In some embodiments, the composition comprises about 40 mg MDMA·HCl. In some embodiments, the composition comprises about 60 mg MDMA·HCl. In some embodiments, the composition comprises about 80 mg MDMA·HCl. In some embodiments, the composition comprises about 100 mg MDMA·HCl. In some embodiments, the composition comprises about 120 mg MDMA·HCl. In some embodiments, the composition comprises about 150 mg MDMA·HCl. In some embodiments, the composition comprises about 180 mg MDMA·HCl. In some embodiments, the composition of the one or more individual dosage units administered during the first psychotherapy session comprises about 40 mg MDMA·HCl. In some embodiments, the composition of the one or more individual dosage units administered during the second and third psychotherapy sessions comprises about 60 mg MDMA·HCl.

In some embodiments, the second psychotherapy session is at least 21 days (e.g., at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, about 3 weeks to about 4 weeks, about 3 weeks to about 5 weeks, or about 3 weeks to about 6 weeks) after the first psychotherapy session. In some embodiments, the second psychotherapy session is about 3 weeks to about 5 weeks after the first psychotherapy session.

In some embodiments, the third psychotherapy session is at least 21 days (e.g., at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, about 3 weeks to about 4 weeks, about 3 weeks to about 5 weeks, or about 3 weeks to about 6 weeks) after the second psychotherapy session. In some embodiments, the third psychotherapy session is about 3 weeks to about 5 weeks after the second psychotherapy session.

In some embodiments, the subject consumed no food for at least 5 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. For example, in some embodiments, the subject consumed no food for at least 6 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the subject consumed no food for at least 8 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. For example, in some embodiments, the subject consumed no food for at least 10 hours before administering the MDMA, or a

pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the subject consumed no food for at least 10 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. For example, in some embodiments, the subject consumed no food for at least 12 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the subject consumed no food for at least 14 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. For example, in some embodiments, the subject consumed no food for at least 16 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the subject consumed no food for at least 18 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. For example, in some embodiments, the subject consumed no food for at least 20 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the subject consumed no food for at least 22 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof. For example, in some embodiments, the subject consumed no food for at least 24 hours before administering the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

In some embodiments, the subject consumed food up to about 6 hours before administering the MDMA. For example, the subject consumed food up to about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 30 minutes, about 20 minutes, about 15 minutes, about 10 minutes, about 5 minutes, about 1 minute, about 30 seconds, or about 5 seconds before administering the MDMA. For example, the subject consumed food concurrently with administering the MDMA.

In some embodiments, the dose of the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof is 50 mg on a free base basis of MDMA. In some embodiments, the dose of the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof is 100 mg on a free base basis of MDMA. In some embodiments, the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof is MDMA hydrochloride.

In some embodiments, the dose of the MDMA hydrochloride is 120 mg. In some embodiments, the method comprises measuring a C_{max} of about 100 ng/mL to about 500 ng/mL in the subject after administering the MDMA·HCl. In some embodiments, the dose of the MDMA hydrochloride may be about 112 mg, about 114 mg, about 116 mg, about 118 mg, about 120 mg,

about 122 mg, or about 124 mg. In some embodiments, the method comprises measuring a C_{max} of about 150 ng/mL to about 450 ng/mL, about 175 ng/mL to about 400 ng/mL, about 200 ng/mL to about 320 ng/mL, about 220 ng/mL to about 300 ng/mL, about 240 ng/mL to about 280 ng/mL, about 250 ng/mL to about 275 ng/mL, about 255 ng/mL to about 270 ng/mL, or about 158 ng/mL to about 164 ng/mL. In some embodiments, the method comprises measuring a C_{max} of about 261 ng/mL. The subranges and specific values may be selected based on factors such as the participant's weight, age, and overall health, as well as the desired therapeutic effect and potential side effects of the MDMA.

In some embodiments, the method comprises measuring an AUC_{0-t} in the subject after administering MDMA·HCl. In some embodiments, the measured AUC_{0-t} is about 2500 h*ng/mL to about 5000 h*ng/mL, about 3000 h*ng/mL to about 4500 h*ng/mL, about 3000 h*ng/mL to about 4200 h*ng/mL, about 3300 h*ng/mL to about 4000 h*ng/mL, about 3570 h*ng/mL to about 3770 h*ng/mL, about 3500 h*ng/mL to about 3600 h*ng/mL, about 3520 h*ng/mL to about 3580 h*ng/mL, about 3620 h*ng/mL to about 3730 h*ng/mL, or about 3670 h*ng/mL. In some embodiments, the measured AUC_{0-t} is about 3550 h*ng/mL. In some embodiments, the measured AUC_{0-t} is about 3670 h*ng/mL.

In some embodiments, the method comprises measuring an AUC_{0-72} in the subject after administering MDMA·HCl. In some embodiments, the measured AUC_{0-72} is about 2500 h*ng/mL to about 5000 h*ng/mL, about 3000 h*ng/mL to about 4500 h*ng/mL, about 3500 h*ng/mL to about 4200 h*ng/mL, about 3700 h*ng/mL to about 3900 h*ng/mL, about 3750 h*ng/mL to about 3850 h*ng/mL, about 3800 h*ng/mL to about 4000 h*ng/mL, about 3870 h*ng/mL to about 3900 h*ng/mL, or about 3880 h*ng/mL. In some embodiments, the measured AUC_{0-72} is about 3800 h*ng/mL. In some embodiments, the measured AUC_{0-inf} is about 3880 h*ng/mL. In some embodiments, the method comprises measuring an AUC_{0-inf} in the subject after administering MDMA·HCl. In some embodiments, the measured AUC_{0-inf} is about 2500 h*ng/mL to about 5000 h*ng/mL, about 3000 h*ng/mL to about 4500 h*ng/mL, about 3500 h*ng/mL to about 4200 h*ng/mL, about 3700 h*ng/mL to about 3900 h*ng/mL, about 3750 h*ng/mL to about 3850 h*ng/mL, about 3800 h*ng/mL to about 4000 h*ng/mL, about 3870 h*ng/mL to about 3900 h*ng/mL, or about 3890 h*ng/mL. In some embodiments, the measured AUC_{0-inf} is about 3800 h*ng/mL. In some embodiments, the measured AUC_{0-inf} is about 3890 h*ng/mL.

In some embodiments, the method comprises measuring a T_{max} in the subject after administering MDMA·HCl. In some embodiments, the measured T_{max} is about 30 minutes to about 10 hours, about 30 minutes to about 4 hours, about 45 minutes to about 3 hours, about 2 hours to about 8 hours, about 4 hours to about 10 hours, about 6 hours to about 10 hours, about 2 hours to about 6 hours, about 3 hours to about 5 hours, about 1 hour to about 3 hours, about 1.5 hours to about 2.5 hours, about 1.7 hours to about 2.3 hours, or about 2 hours. In some embodiments, the measured T_{max} is about 4 hours. In some embodiments, the measured T_{max} is about 2 hours.

In some embodiments, the method comprises measuring a $t_{1/2}$ in the subject after administering MDMA·HCl. In some embodiments, the measured $t_{1/2}$ is about 2 hours to about 20 hours, about 3 hours to about 20 hours, about 4 hours to about 20 hours, about 4 hours to about 15 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 4 hours to about 6 hours, about 6 hours to about 20 hours, about 8 hours to about 20 hours, about 10 hours to about 20 hours, about 13 hours to about 20 hours, about 16 hours to about 20 hours, about 18 hours to about 20 hours, about 6 hours to about 12 hours, about 7 hours to about 11 hours, about 8 hours to about 10 hours, about 8 hours to about 8 hours, about 8.36 hours, or about 9 hours. In some embodiments, the measured $t_{1/2}$ is about 8.36 hours. In some embodiments, the measured $t_{1/2}$ is about 9 hours.

In some embodiments, the method comprises measuring a T_{lag} in the subject after administering MDMA·HCl. In some embodiments, the measured T_{lag} is about 0 hours to about 2 hours, about 0.25 hours to about 1.5 hours, about 0.25 hours to about 0.75 hours, about 0.75 hours to about 1.25 hours, about 0.5 hours, about 0.75 hours, or about 1 hour. In some embodiments, the measured T_{lag} is about 0.5 hours. In some embodiments, the measured T_{lag} is about 0.5 hour.

In some embodiments, the method comprises measuring a CL/F in the subject after administering MDMA·HCl. In some embodiments, the measured CL/F is about 1 L/h to about 100 L/h, about 1 L/h to about 70 L/h, about 10 L/h to about 60, about 20 L/h to about 50 L/h, about 30 L/h to about 40 L/h, about 32 L/h to about 36 L/h, about 35 L/h to about 40 L/h, about 34.5 L/h, or about 37.5 L/h. In some embodiments, the measured CL/F is about 368 L/h. In some embodiments, the measured CL/F is about 34.5 L/h. In some embodiments, the measured CL/F is about 368 L/h. In some embodiments, the measured CL/F is about 37.5 L/h.

In some embodiments, the method comprises measuring a Vd/F in the subject after administering MDMA·HCl. In some embodiments, the measured Vd/F is about 100 L to about

800 L, about 200 L to about 700 L, about 300 L to about 600 L, about 400 L to about 500 L, about 400 L to about 420 L, about 410 L to about 450 L, about 420 L to about 440 L, about 425 L to about 435 L, about 412 L, or about 430 L. In some embodiments, the measured Vd/F is about 430 L. In some embodiments, the measured Vd/F is about 412 Vd/F.

Non-limiting examples of diagnostic tests to assess improvement in the symptoms of PTSD in the subject include the Clinician-Administered PTSD scale for DSM-5 (CAPS-5) and Sheehan Disability Scale (SDS). Further information on the CAPS-5 can be found at *Psychol Assess.* **2018** Mar;30(3):383-395, which is incorporated herein in its entirety. Further information on the SDS can be found at *International Clinical Psychopharmacology* **2008**;23(2):70-83, which is incorporated herein in its entirety.

In some embodiments, a reduction (i.e., improvement) in the CAPS-5 is measured in the subject after administering the MDMA in comparison to before administering the MDMA. In some embodiments, a reduction of at least 1 point (e.g., at least 2 points, at least 4 points, at least 6 points, at least 8 points, at least 10 points, at least 12 points, at least 14 points, at least 15 points, at least 16 points, at least 18 points, at least 20 points, at least 23 points, at least 25 points, at least 30 points, at least 40 points) in the CAPS-5 is measured in the subject after administering the MDMA in comparison to before administering the MDMA. In some embodiments, a reduction of at least 6 points in the CAPS-5 is measured in the subject after administering the MDMA in comparison to before administering the MDMA. In some embodiments, a reduction of at least 10 points in the CAPS-5 is measured in the subject after administering the MDMA in comparison to before administering the MDMA. In some embodiments, a reduction of at least 15 points in the CAPS-5 is measured in the subject after administering the MDMA in comparison to before administering the MDMA. In some embodiments, a reduction of at least 20 points in the CAPS-5 is measured in the subject after administering the MDMA in comparison to before administering the MDMA. In some embodiments, a reduction of at least 23 points in the CAPS-5 is measured in the subject after administering the MDMA in comparison to before administering the MDMA. In some embodiments, the CAPS-5 score of the subject after administering the MDMA is less than or equal to 11 (meeting the definition of being in remission).

In some embodiments, a reduction (i.e., improvement) in the SDS is measured in the subject after administering the MDMA in comparison to before administering the MDMA. In some embodiments, a reduction of at least 1 point in the SDS is measured in the subject after

administering the MDMA in comparison to before administering the MDMA. In some embodiments, a reduction of at least 2 points in the SDS is measured in the subject after administering the MDMA in comparison to before administering the MDMA. In some embodiments, a reduction of at least 2 points in the SDS is measured in the subject after administering the MDMA in comparison to before administering the MDMA. In some embodiments, a reduction of at least 3 points in the SDS is measured in the subject after administering the MDMA in comparison to before administering the MDMA. In some embodiments, a reduction of at least 4 points in the SDS is measured in the subject after administering the MDMA in comparison to before administering the MDMA. In some embodiments, a reduction of at least 5 points in the SDS is measured in the subject after administering the MDMA in comparison to before administering the MDMA.

EMBODIMENTS

1. Particles comprising 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, wherein the particle is substantially smaller than about 610 μm.

2. The particles of embodiment 1, wherein the particles have a Dv90 less than about 420 μm,and a particle size range (Dv90-Dv10) less than about 400 μm.

3. The particles of embodiment 2, wherein the particles have a Dv90 less than about 400 μm.

4. The particles of any one of embodiments 1-3, wherein 0-10% of the particles have a particle size (Dv10) from about 0.01 μm to about 10 μm.

5. The particles of any one of the preceding embodiments, wherein the particles have a median particle size (Dv50) from about 100 μm to about 200 μm.

6. The particles of any one of the preceding embodiments, wherein the chemical purity of the particles is from about 98-100% and no single impurity is present in an amount of from about 0.5% to about 100% as determined by HPLC.

7. The particles of any one of the preceding embodiments, wherein the chemical purity of the particles is from 99-100% and no single impurity is present in an amount of from about 0.5% to about 1% as determined by HPLC.

8. The particles of any one of embodiments 1-7, wherein the particles are prepared by a process comprising a step of reducing particle size and increasing particle size uniformity of coarse particles by screen-milling using a screen mill.

9. The particles of embodiment 8, wherein the coarse particles do not undergo an additional size-reducing process.

10. The particles of embodiment 8 or 9, wherein substantially all of the particles are smaller than about 610 μm.

11. The particles of any one of embodiments 8-10, wherein the median particle size (Dv50) of the coarse particles is from about 300 μm to about 900 μm.

12. The particles of embodiment 11, wherein the coarse particles are substantially free of MDMA·HCl monohydrate.

13. The particles of any of embodiments 8-12, wherein the coarse particles are heated to a temperature of 50-70 °C in an environment with an ambient pressure of from about 0.1-1 atmosphere, before entering the screen mill.

14. The particles of any one of embodiments 8-13, wherein the coarse particles are fed into the screen mill in the absence of applied pressure.

15. The particles of any one of embodiments 8-14, wherein the milling method is conducted in an inert atmosphere that is substantially free of moisture.

16. The particles of embodiment 15, wherein the inert atmosphere comprises substantially dry nitrogen gas.

17. The particles of any one of the preceding embodiments, wherein the particles are substantially free of MDMA·HCl monohydrate.

18. A dosage form comprising the particles of any one of the preceding embodiments and one or more pharmaceutically acceptable excipients.

19. The dosage form of embodiment 18, comprising about 1 mg to about 150 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA.

20. The dosage form of embodiment 18 or 19, comprising about 35 mg to about 45 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA.

21. The dosage form of any one of embodiments 18-20, comprising about 55 mg to about 65 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA.

22. The dosage form of any one of embodiments 18-21, comprising about 75 mg to about 85 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA.

23. The dosage form of any one of embodiments 18-22, comprising about 95 mg to about 105 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA.

24. The dosage form of any one of embodiments 18-23, comprising about 115 mg to about 125 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA.

25. The dosage form of any one of embodiments 18-24, wherein the dissolution rate in water is greater than or equal to 80% of the mass of the MDMA in 30 minutes.

26. The dosage form of any one of embodiments 18-25, wherein the particles are prepared by a process comprising a step of reducing the particle size and increasing particle size uniformity by screen-milling under an inert atmosphere.

27. The dosage form of any one of embodiments 18-26, wherein the dosage form comprises a diluent.

28. The dosage form of embodiment 27, wherein the diluent is a sugar alcohol.

29. The dosage form of embodiment 27 or 28, wherein the diluent has a moisture content from 0% to about 0.25% by mass, prior to blending.

30. The dosage form of embodiment 18, wherein the composition additionally comprises a lubricant.

31. The dosage form of embodiment 30, wherein the lubricant comprises a pharmaceutically acceptable salt of a saturated fatty acid.

32. The dosage form of any one of embodiments 18-31, wherein substantially all of the particles are smaller than about 610 μm.

33. The dosage form of any one of embodiments 18-32, wherein the Dv90 of the particles is from about 0.01 μm to about 400 μm.

34. The dosage form of any one of embodiments 18-33, wherein from about 0-10% of the particles have a particle size (Dv10) from about 0.01 μm to about 10 μm.

35. The dosage form of any one of embodiments 18-34, wherein the median particle size (Dv50) of the particles is from 100 μm to 200 μm.

36. The dosage form of any one of embodiments 18-35, wherein the chemical purity of the particles is from about 98-100% and no single impurity is present in an amount of from about 0.5% to about 100% as determined by HPLC.

37. The dosage form of any one of embodiments 18-36, wherein the chemical purity of the particles is from about 99-100% and no single impurity is present in an amount of from about 0.5% to about 100% as determined by HPLC.

38. The dosage form of any one of embodiments 18-36, wherein the dosage form is a capsule or a tablet.

39. The dosage form of any one of embodiments 18-38, wherein the dosage form is a capsule.

40. The dosage form of any one of embodiments 18-38, wherein the dosage form is a tablet.

41. The dosage form of any one of embodiments 18-40, comprising one or more individual dosage units.

42. The dosage form of embodiment 41, comprising one individual dosage unit.

43. The dosage form of embodiment 42, comprising at least two individual dosage units.

44. The dosage form of embodiment 43, comprising at least three individual dosage units.

45. The dosage form of any one of embodiments 41-44, wherein each of the one or more individual dosage units comprises a capsule.

46. The dosage form of any one of embodiments 41-45, wherein the one or more individual dosage units are administered during a single psychotherapy session.

47. The dosage form of any one of embodiments 41-46, wherein the one or more individual dosage units are administered at different times during the single psychotherapy session.

48. A method of treating a central nervous system disorder in a subject, the method comprising: administering to the subject a therapeutically effective amount of the particles of any one of embodiments 1-17 or the dosage form of any one of embodiments 18-47.

49. The method of embodiment 48, wherein the central nervous system disorder is a trauma-linked disorder or a stressor-linked disorder.

50. The method of embodiment 48, wherein the central nervous system disorder is a mood disorder.

51. The method of embodiment 48, wherein the central nervous system disorder is an anxiety disorder.

52. The method of embodiment 48, wherein the central nervous system disorder is post-traumatic stress disorder.

53. The method of any one of embodiments 48-52, wherein the administering is performed during a psychotherapy session.

54. The method of any one of embodiments 48-53, wherein about 100 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, , on a free base basis of MDMA is administered.

55. The method of embodiment 54, wherein the about 100 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, , on a free base basis of MDMA is administered in one dose.

56. The method of embodiment 54, wherein the about 100 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, , on a free base basis of MDMA is administered in two doses.

57. The method of any one of embodiments 48-53, wherein about 120 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, , on a free base basis of MDMA is administered.

58. The method of embodiment 57, wherein about 120 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA is administered in one dose.

59. The method of embodiment 57, wherein about 120 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA is administered in two doses.

60. The method of any one of embodiments 48-53, wherein about 140 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA is administered.

61. The method of embodiment 60, wherein the about 140 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA is administered in one dose.

62. The method of embodiment 60, wherein the about 140 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA is administered in two doses.

63. The method of any one of embodiments 48-53, wherein about 160 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA is administered.

64. The method of embodiment 63, wherein the about 160 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA is administered in one dose.

65. The method of embodiment 63, wherein the about 160 mg of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA is administered in two doses.

66. The method of any one of embodiments 48-65, wherein the dosage form comprising the therapeutically effective amount of MDMA, on a free base basis of MDMA or a pharmaceutically acceptable salt and/or solvate thereof, is orally administered.

67. The method of embodiment 66, wherein the therapeutically effective amount of the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered in a capsule.

68. The method of embodiment 66, wherein the dosage form comprising the therapeutically effective amount of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered in a tablet.

69. The method form of any one of embodiments 48-68, wherein the dosage form comprising the therapeutically effective amount of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered as one or more individual dosage units during a single dosing session.

70. The method form of any one of embodiments 48-68, wherein the dosage form comprising the therapeutically effective amount of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof, is administered at different times during a single psychotherapy session.

71. The particle, dosage form, or method of any one of embodiments 1-70, wherein the MDMA, or a pharmaceutically acceptable salt and/or hydrate is a pharmaceutically acceptable salt.

72. The particle, dosage form, or method of any one of embodiments 1-71, wherein the MDMA, or a pharmaceutically acceptable salt and/or hydrate is present in the form of the hydrochloride salt.

All publications, patents, patent applications, and information available on the internet and cited in the present disclosure are herein incorporated by reference to the same extent as if each individual publication, patent, patent application, or item of information was specifically and individually indicated to be incorporated by reference. To the extent publications, patents, patent applications, and items of information incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

EXAMPLES

These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Example 1. Preparation of High-Purity MDMA

This example provides methods of preparing high-purity MDMA. To a 50 L reaction vessel were added 4107.3 g crude MDMA·HCl and 41000 mL 2-propanol. The batch temperature was raised to 67.2 °C, while stirring, and the mixture was then stirred for 30 minutes at 67.2 °C until all of the solids dissolved. Stress-tests had demonstrated stability for 72 hours at 70-80 °C, proving the thermal stability of MDMA·HCl.

The batch was then transferred through a 1.2 μm in-line filter capsule, using positive pressure, to a clean, 50 L reaction vessel, fitted with a jacket that had been pre-heated to 66.1 °C. In this new reaction vessel, the batch was cooled to 55.3 °C, over the course of 90 minutes. 41.1 g of MDMA·HCl Form 1 seed crystal (0.18 mol, 0.008 equivalents) were then added, and the batch

was stirred at the same temperature for 30 minutes. The batch was cooled to 15.2 °C at a rate of 3 °C/hour, then stirred at this temperature for an additional 10 hours.

The white suspension was removed from the mother liquor via vacuum filtration over a filter plate fitted with a filter cloth then washed with 8220 mL 2-propanol. The filter cake was transferred to a drying oven, and dried under vacuum (140 mbar) for 19 hours at 56.6 °C. The collected MDMA·HCl was a white solid weighing 3548.3 g (85.5% yield; 99.95% peak area, 99.64% w/w by HPLC). No single impurity exceeded 0.02% of peak area by HPLC, and residual solvents (methanol, <6 ppm; 2-propanol, 490 ppm) were found to be within the target range. **FIG. 1** shows the coarse MDMA hydrochloride particles isolated from the synthetic process, and **FIG. 4** shows an HPLC chromatogram for coarse MDMA particles isolated from the synthetic process. Other polymorphic forms were also prepared. **FIG. 5** shows the XRPD spectra of MDMA·HCl monohydrate (5A), MDMA Form III (5B), and MDMA Form II (5C).

Example 2. General Description of Screen Milling Process

1911 g MDMA, split into four sub-lots, was fed into an Ytron-Quadro Comill with a stainless steel 610 screen and a rounded mixing drive. The solids were fed into the mill under an inert atmosphere, without pressure applied, and passed directly into a polyethylene collection bag with an earthing cable protecting the equipment from static discharge. A mill speed of 6000 rpm was utilized. The feeding of all four batches was conducted by hand and took place over 30 minutes to avoid a significant build up within the mill. The mass of MDMA recovered from the mill was 1880 g, as measured after analytical sampling. Milling was in general rapid and facile. XRPD data indicated no evidence of MDMA·HCl monohydrate formation in any of the four sub-lots. The milled product was found to be 99.9% MDMA by HPLC (100.0% on a dry basis). Particle size of MDMA recovered from this experiment for each sample/lot is shown in Table 1. The results show that each of the four sub-lots consistently showed a Dv90 of less than 400 μm. **FIG. 2** shows exemplary particles comprising MDMA after milling, and **FIG. 3** shows the particle size distribution (PSD) of the milled particles of FIG. 2.

Table 1: Particle Size of MDMA Measured by Laser Diffraction.

Sample	**Dv90**	**Dv50**	**Dv10**
CJS194-1	342 µm	170 µm	29.0 µm
CJS194-2	326 µm	135 µm	20.0 µm
CJS194-3	326 µm	134 µm	20.9 µm
CJS194-4	353 µm	161µm	23.8 µm
CJS194-5 (blend of lots 1-4)	341 µm	151 µm	23.4 µm
Input 201101	844 µm	512 µm	376 µm

Example 3. Dosage Form Specifications.

Description of Drug Product

Two dosage strengths of the drug product are available including 34 mg MDMA (equivalent to 40.5 mg MDMA hydrochloride (MDMA·HCl)) and 50 mg MDMA (equivalent to 59.5 mg MDMA·HCl) in hydroxypropyl methylcellulose (HPMC) capsules. The capsules are imprinted and are filled with a composition comprising MDMA·HCl. The appearance of the 34 mg dosage strength capsule is a Size 2, HPMC Swedish Orange / White Capsule imprinted with "MDMA 34" and the appearance of the 50 mg dosage strengths is a Size 2, HPMC Swedish Orange Capsule imprinted with "MDMA 50". Recipharm Aesica Queenborough Ltd. is the proposed manufacturer for commercial drug product.

Composition of Drug Product

HPMC capsules filled with a powder blend including MDMA·HCl, mannitol, and magnesium stearate. The formulation of the powder blend is a proportional formulation. See Table 2 below for the composition of each of the dosage forms.

Table 2. Composition of the MDMA 34 mg and 50 mg Drug Product.

Component and Quality Standard (and Grade, if Applicable)	**Reference to Standard**	**Function**	**Strength (Label Claim)**			
			MDMA 34 mg Capsule		**MDMA 50 mg Capsule**	
			Quantity per Unit	**[% $^{w}/_{w}$]**	**Quantity per Unit**	**[% $^{w}/_{w}$]**
Active Substances(s)						

Component and Quality Standard (and Grade, if Applicable)	Reference to Standard	Function	Strength (Label Claim)			
			MDMA 34 mg Capsule		MDMA 50 mg Capsule	
			Quantity per Unit	[% w/w]	Quantity per Unit	[% w/w]
MDMA·HCl, milled	In-house	Active API	40.50 mg[1]	50.0	59.50 mg[2]	50.0
Excipients						
Mannitol (Mannogem Powder)	USP / EP	Diluent	39.69 mg	49.0	58.31 mg	49.0
Magnesium Stearate	USP-NF / EP	Lubricant	0.81 mg	1.0	1.19 mg	1.0
Total	---	---	81.00 mg	100.0	119.00 mg	100.0
Size 2, HPMC Swedish Orange / White Capsules	In-house	Capsule	Average capsule weight 57 mg-65 mg	N/A	---	---
Size 2, HPMC Swedish Orange Capsules	In-house	Capsule	---	---	Average capsule weight 57 mg-65 mg	N/A

[1]40.50 mg of MDMA.HCl is equivalent to 34 mg MDMA free base.

[2]59.50 mg of MDMA.HCl is equivalent to 50 mg MDMA free base.

The composition and components of the HPMC capsule shells is provided in Table 3 and Table 4 below.

Table 3. Composition of the Size 2, HPMC Swedish Orange / White Capsules

Component	Body: V44.900, WHITE OP. V900	Cap: V22.905, SWEDISH ORANGE OP. V905
Ferric Oxide, Red, E172, USP-NF	---	1.1817%
Titanium Dioxide, E171, USP/EP	2.0000%	0.4916%
Hypromellose, USP/EP	QSP 100%	QSP 100%

Table 4. Composition of the Size 2, HPMC Swedish Orange Capsules.

Component	Body and Cap: V22.905, SWEDISH ORANGE OP. V905
Ferric Oxide, Red, E172, USP-NF	1.1817%
Titanium Dioxide, E171, USP/EP	0.4916%
Hypromellose, USP/EP	QSP 100%

Printing Ink 10A2 Black

The printing ink consists of shellac, E904 US Pharmacopoeia-National Formulary / European Pharmacopoeia (USP-NF/EP), ferric oxide black, E172 (USP-NF), propylene glycol (USP/EP), strong ammonia solution (USP-NF/EP), and potassium hydroxide (USP-NF/EP).

Container Closure System

The container closure system is an aluminum blister pack consisting of cold-formable aluminum laminate and push-through blister lidding foil.

Example 4. Comparative Dissolution Studies.

This protocol describes experiments that can be performed to compare the dissolution profiles obtained for 40 mg MDMA·HCl capsules and 60 mg MDMA·HCl capsules that can be used in Phase III clinical studies manufactured by Sharp Clinical Services versus 40 mg MDMA·HCl (34 mg MDMA on a free base basis) and 60 mg MDMA·HCl (50 mg MDMA on a free base basis) capsules manufactured by Recipharm QB (RQB). N=12 capsules from each manufacturer can be compared in pH 1.2, 4.5, and 6.8 dissolution media, with all other dissolution and analytical conditions as described in the Dissolution Studies Procedure.

Investigation Strategy

MDMA·HCl capsules (40 mg and 60 mg) and the details of these are listed in Table 5 along with the details of the RQB capsules to be used.

Table 5. MDMA Capsule Details.

Manufacturer	**Dose Strength MDMA·HCl**	**Equivalent Dose Strength MDMA freebase**	**Batch Details**
Sharp Clinical Services	40 mg	34 mg	99441B1
RQB	40 mg	34 mg	RQB200601-010A
Sharp Clinical Services	60 mg	50 mg	99441B2
RQB	60 mg	50 mg	RQB200601-010B

The current RQB analytical method has two sampling timepoints (15 and 30 minutes). An initial dissolution can be performed to establish the suitable sampling timepoints.

Testing to be performed

Dissolution Profile Timepoint Determination

Perform a single dissolution (n=6 capsules) as described in the Dissolution Studies Procedure. Use both strengths of the RQB and Sharp capsules (see Table 5) and sample at the following timepoints: 5, 10, 15, 20, 30, 45, and 60 minutes. Analyse all samples as described in the analytical test method. It is useful to note if coning is observed for either batch of capsules.

Plot the mean % dissolution at each timepoint and use this data to estimate the key timepoints required to describe the dissolution release profile. It may be necessary to interpolate these points. A minimum of 3 timepoints are required. The criteria for the timepoints are:

1) Mean ≤85% dissolution for all but one timepoint
2) CV NMT 20% for timepoints ≤10 minutes
3) CV NMT 10% for timepoints > 10 minutes

The selected timepoints to be used for the dissolution testing need to fulfill these criteria and need to be the same for both strengths and products from both manufacturers. Otherwise, these timepoints must be modified and the analysis repeated based on the profile obtained.

Dissolution Testing

n=12 units of each of both the RQB and Sharp capsule batches in Table 5 is to be tested for dissolution as per the Dissolution Studies Procedure, using each of the media described below and the sampling timepoints established in the Dissolution Studies Procedure.

Standards are to be prepared in the same dissolution media as the samples. Prepare on the day of use. Media preparation can be scaled as required.

pH 1.2 Dissolution Media Preparation

Prepare 15 L of media as follows: Dissolve 26.3 g NaCl and 111 mL (131.3 g) aqueous hydrogen chloride in 15 L of water. Mix well.

pH 4.5 Dissolution Media Preparation

Prepare 15 L of media as follows: Dissolve 204.2 g potassium dihydrogen phosphate in 11.2 L water. Adjust the pH with 0.1 M sodium hydroxide or 0.1 M hydrochloric acid as required. Dilute to 15 L with water.

pH 6.8 Dissolution Media Preparation

Prepare 15 L of media as follows: Mix 3750 mL of 0.2 M potassium dihydrogen phosphate with 1680 mL 0.2 M sodium hydroxide and dilute to 15 L with water.

Calculation of Results

Plot the mean dissolution profile obtained for the Sharp and RQB capsules at each dissolution condition, accounting for the samples removed at the previous timepoints. Compare the mean dissolution profile obtained for the Sharp capsules with the mean dissolution profile obtained for the RQB capsules.

For the comparison of dissolution profiles, where applicable, the similarity factor f2 should be estimated by using the following formula: $f2 = 50 \cdot \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \cdot 100\}$

In the above equation,

f2 is the similarity factor;

n is the number of time points;

R(t) is the mean percent reference drug dissolved at time t after initiation of the study; and

T(t) is the mean percent test drug dissolved at time t after initiation of the study.

Two dissolution profiles are considered similar when the f2 value is ≥50. When both test and reference products demonstrate that ≥85% of the labelled amount of the drug is dissolved in 15 minutes, comparison with an f2 test is unnecessary and the dissolution profiles are considered similar. When the coefficient of variation is too high, f2 calculation is considered inaccurate and a conclusion on similarity in dissolution cannot be made.

If high variability or coning is observed in the paddle apparatus at 50 rpm for both reference and test products, the use of the basket apparatus at 100 rpm is recommended. Additionally,

alternative methods where appropriately justified, may be considered to overcome issues such as coning, if scientifically substantiated.

Example 5. Dissolution Studies Procedure.

Introduction

This method describes the procedure for Dissolution Test of MDMA HCI by High Performance Liquid Chromatography – Ultraviolet (HPLC-UV).

Equipment

- Agilent HPLC with Binary pump & UV detector
- Dissolution Bath, Apparatus 2 (Paddle)
- XBridge Phenyl, 3.5µm, 4.6 x 150mm (Cat. No. 186003335, Waters)
- 0.45 µm GHP membrane filter (Cat. No. WAT200802, Waters)

General Statements

Mobile phase preparations may be scaled up or down as long as the required concentration remains the same.

All glassware used in sampling and testing should be Grade A glassware to limit any untoward interactions and must be thoroughly cleaned prior to use. Agilent HPLC system must be used for the analysis. Mobile Phase A was either Water : TFA – 100 : 0.1 or Acetonitrile : TFA – 100 : 0.1. The Dissolution Media/ Diluent was 0.1N HCl and the needle wash was Water : Acetonitrile 50 : 50. The standard solution of MDMA was 0.1 mg/mL MDMA·HCl in water.

Dissolution Procedure for Samples

Weigh six capsules separately and prepare dissolution sample with the dissolution parameters shown in Table 6.

Table 6. Dissolution Parameters.

Apparatus Type	Apparatus 2, Paddle
Dissolution Media	0.1N HCl
Media volume	500 mL
Bath Temperature	37 ± 0.5°C
Stir Speed	50 RPM

Filter type	0.45 µm GHP Membrane Filter
Sinker Type	Wire Sinker
Volume pulled per time point	5 mL
Sampling time	15 min, 30 min

Chromatographic Conditions

Table 7 shows the HPLC parameters that can be used.

Table 7: HPLC parameters.

Column	XBridge Phenyl 150 x 4.6mm, 3 µm
Column Oven	30 °C
Injection Volume	10 µL
Autosampler Temperature	Ambient
Flow Rate	1.0 mL/min
Detection	UV 235 nm
Mobile Phase program	MPA:MPB 80:20 Isocratic
Needle Wash	Water : MeCN (50 : 50)
Run Time	10 mins

Guideline injection sequence

The below sequence is a guideline only. An injection sequence may be altered as required. However, the following key points must not be altered:

- Inject the blank solution until a stable baseline is achieved.
- Number of standard solution injections prior to sample analysis.
- Standard solution must be injected in duplicate following a maximum of 6 sample injections (not inclusive of diluent blank injections) and at the end of the sequence.

Table 8 shows an injection sequence that can be used.

Table 8: Example injection sequence.

Solution	**Number of Injections**
Diluent blank	3
Standard 1	5
Standard 2	1
Standard 1 (Bracketing STD)	2
Sample Solution (Up to 6 samples)	1 per Sample Solution
Standard 1 (Bracketing STD)	2

Column Cleaning

After each use, the column must be thoroughly cleaned to ensure that it is ready for use on a subsequent occasion. Purge the column with a solvent system including 50% water and 50% acetonitrile (CAN) for 30 mins at 0.5 mL/min. Purge the column with a solvent system including 25% water and 75% ACN for 30 mins at 0.5 mL/min. Purge the column with 100% ACN for 1 hour at 0.5 mL/min. Store the column in 100% ACN.

System suitability criteria

- Diluent used in injection prior to the Standard 1 injection must not have significant interferences (> 0.5% of the average area of five injection of STD 1) with the MDMA·HCl peak.
- The percentage relative standard deviation (RSD) of MDMA·HCl peak area for first five STD 1 injection must be < 2.0%
- The United States Pharmacopeia (USP) tailing factor for the MDMA·HCl peak in the first STD 1 injection must be < 3.0.
- The number of USP theoretical plates for the MDMA·HCl peak in the first injection of STD 1 must be > 1500.
- The ratio of check standard solution (STD 2) response to the average response of first five STD 1 injection must be 98.0% - 102.0%.

Calculations

The dissolution calculation for MDMA·HCl is

% dissolved = (PA_{SMP} x C_{STD} x VOL_{VES} x 100) / (PA_{STD} x LC)

where:

PA_{SMP} is sample peak area (MDMA·HCl peak)

VOL_{VES} is volume of dissolution media in the vessel (mL)

C_{STD} is concentration of MDMA·HCl reference standard in the working standard 1 preparation considering the purity of the reference standard (in mg/mL)

PA_{STD} is mean MDMA·HCl peak area of the bracketing assay standard solution 1 injections

LC is labelled claim per capsule (40 mg or 60 mg)

Example 6. Dosage, Administration, and Prescription Information.

Dosage and Administration

Recommended Dosage

The total dosage of MDMA·HCl includes 3 doses in combination with treatment sessions (dose 1: 102 mg; doses 2 and 3: 150 mg each) with interim periods of at least 21 days between doses. The total dose of MDMA·HCl at each of these treatment sessions is provided in an individual package containing 3 capsules. Patients take 2 capsules at the start of the session and take the third capsule 1½ to 2 hours after the first dose. Patients may need to set an alarm to take the second dose.

The MDMA·HCl is for oral use only. The capsules should be swallowed whole and not crushed or chewed. MDMA·HCl may be taken without regard to timing of meals. It is recommended to not exceed 150-mg MDMA·HCl per day.

FIG. 6 shows the schedule of dosing and therapy sessions for MDMA·HCl.

Administration Instructions

Instruct patients to follow these administration instructions and read the instructions for use before self-administration. Instruct the patients to take the unopened package with them to the treatment session. At the start of the psychotherapy session, patients should:

- Push 2 capsules through the foil and take with a sip of water.
- Sit or lay down in a comfortable position.
- Protect eyes from bright light.
- Rest and proceed with the treatment session for 1½ to 2 hours
- After 1½ to 2 hours have elapsed, sit up and push remaining capsule through foil. Take 1 capsule with a sip of water.
- Sit or lay down in a comfortable position.
- Protect eyes from bright light.
- Rest and proceed with the treatment session.
- Remain in the facility until effects have worn off.
- Do not engage in potentially hazardous activities such as driving until the next day.

Important Considerations Prior to Initiating and Between MDMA·HCl Treatments

Before initiating treatment, instruct the patient that MDMA·HCl must be self-administered under the direct observation of a health care provider during a treatment session. Also instruct the patient not to engage in potentially hazardous activities, such as driving or operating machinery, until the next day after each treatment.

Blood Pressure Assessment Before Initiating Treatment

- Assess blood pressure prior to prescribing MDMA·HCl.
- If baseline blood pressure is elevated (e.g., >140 mm Hg systolic, >90 mm Hg diastolic), consider the risks of short-term increases in blood pressure and benefit of MDMA·HCl treatment in patients with PTSD.

Important Considerations Prior to Prescribing Each MDMA·HCl Dose

- Assess cardiovascular status of patients being considered for treatment with MDMA·HCl. Before initiating treatment, conduct a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and a physical exam to assess for the presence of cardiac disease with further cardiac evaluation when warranted.
- Before prescribing the second and third doses of MDMA·HCl, collect any additional cardiac history to assess for a change in cardiovascular status. Also review concomitant medications to ensure that patients are not taking any contraindicated medications (e.g., monoamine oxidaze inhibitors (MAOIs)) before prescribing each dose of MDMA·HCl.

Therapeutic Program

The safety and efficacy of MDMA·HCl were examined in combination with a specific therapeutic program. Physicians should advise patients that each dose of MDMA·HCl must be self-administered under the direct observation of an appropriately-trained health care provider during a treatment session. The prescriber should discuss the following elements of the therapeutic program.

Preparatory Sessions

Preparatory session(s) (talk therapy or psychotherapy) address the patient questions and concerns, as well as to prepare them for upcoming treatment sessions with MDMA·HCl. In clinical trials, preparation included multiple preparatory sessions.

Sessions with MDMA·HCl

At the beginning of each of the 3 treatment sessions with MDMA·HCl, the planned approach and the range of experiences that may occur during the session should be reviewed with the trained health care provider.

Integration Sessions Following Sessions with MDMA·HCl

Follow-up contact with the trained health care provider should be conducted to support successful integration. In clinical trials, integration included 3 sessions (talk therapy or psychotherapy) after each session with MDMA·HCl.

Post-Administration Observation

During and after MDMA·HCl self-administration at each session, a health care provider should observe the patient for approximately 6 hours from first dose of the split dose. Patients should understand that they should not leave the physical setting while still experiencing effects of MDMA·HCl at treatment sessions. Patients should also understand that additional time may be required beyond the planned length of the sessions, if the patient needs additional support. The patient must also agree to accept transport home from treatment sessions with MDMA·HCl.

Missed Treatment Session(s)

If a patient misses treatment session(s), provided there is no evidence of diversion or abuse, the patient should be counseled to re-schedule the missed session and to continue the current psychotherapy schedule. Healthcare providers should reiterate the importance of psychological intervention in combination with MDMA·HCl treatment.

Use of MDMA·HCl with Reversible MAOIs Such as Linezolid or Methylene Blue

Do not start MDMA·HCl in a patient who is being treated with a reversible MAOI such as linezolid or intravenous methylene blue. Drug interactions can increase the risk of hypertensive

reactions. In some cases, a patient already receiving psychotherapy with MDMA·HCl may require urgent treatment with MAOIs. MDMA·HCl should not be administered again until 5 to 10 times the half life after the last dose of MAOIs, whichever comes first.

Dosage Forms snd Strengths

MDMA·HCl is supplied as single-dose, foil-wrapped capsules in 2 total dosage strengths:

- 102 mg total dose: midomafetamine (MDMA) HCl 34 mg, 3 Swedish Orange/White, Size 2 capsules imprinted with "MDMA 34".
- 150 mg total dose: midomafetamine HCl 50 mg, 3 Swedish Orange, Size 2 capsules imprinted with "MDMA 50".

Contraindications

Table 9: MDMA·Contraindications

Contraindication	**Notes**
Use of MAOIs	Concomitantly or within 14 days of discontinuing treatment with MDMA, including reversible MAOIs such as linezolid or intravenous methylene blue
Known hypersensitivity	To MDMA or any of the other components of the formulation

Drug Interactions

Drugs Metabolized by CYP2D6

Midomafetamine HCl is a strong CYP2D6 inhibitor. Therefore, coadministration of MDMA·HCl with drugs that are primarily metabolized by CYP2D6 may increase the exposures of those drugs. Such drugs include certain antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, and sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone and flecainide). When used concomitantly with MDMA·HCl, it may be necessary to decrease the dose of these CYP2D6 substrates or temporarily halt administration, particularly for drugs with a narrow therapeutic index. Drugs that require metabolic activation by CYP2D6 to be effective (e.g., tamoxifen and codeine) theoretically could have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as MDMA·HCl. Patients treated concomitantly with MDMA·HCl and such drugs may require temporarily increased doses of the drug.

Psychostimulants

Concomitant use with psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) may increase blood pressure. Closely monitor blood pressure with concomitant use of MDMA·HCl with psychostimulants.

Monoamine Oxidase Inhibitors (MAOIs)

Concomitant use of MDMA·HCl and other monoamine oxidase inhibitors (MAOIs) within 14 days is contraindicated because of an increased risk of causing hypertensive reactions. At least 14 days should elapse between discontinuation of an MAOI and treatment with MDMA·HCl. Conversely, at least 14 days should be allowed after taking MDMA·HCl before starting an MAOI.

Serotonergic Drugs

Co-administration with serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) may eliminate or greatly attenuate the effects of MDMA·HCl, and these medications should be tapered in line with the prescriber's clinical judgment.
once obtained at a lower dose).

Pharmacokinetics

MDMA·HCl is a racemic mixture. Both enantiomers are pharmacologically active. 3,4-methylendioxyampetamine (MDA) is a metabolite of MDMA and is also pharmacologically active. Peak plasma levels and $AUC_{0\text{-}inf}$ of MDA are less than 10% of the corresponding parameters for MDMA. MDA may contribute to the pharmacological effects of MDMA·HCl. The pharmacokinetics of MDMA are non-linear with higher than dose proportional increases in plasma concentration due to auto-inhibition of CYP2D6. The elimination half life of a single 120 mg dose of MDMA·HCl was 9 hours.

Absorption

The absolute bioavailability of MDMA·HCl in humans is not known because pharmacokinetic studies have not been conducted following intravenous (iv) administration of MDMA·HCl. MDMA·HCl exhibits high solubility and permeability and appears to be well absorbed. In humans, following a single 120 mg dose of MDMA·HCl, peak plasma concentration of MDMA was generally achieved within 2 hours and C_{max} was 261 ng/mL. The $AUC_{0\text{-}inf}$ of MDMA was 3890 h*ng/mL following a single 120 mg dose of MDMA·HCl. Peak plasma levels (C_{max}) of MDA were 13.3 ng/mL and occurred at 6 hours post dose. The $AUC_{0\text{-}inf}$ of MDA was 374 h*ng/mL following a single 120 mg dose of MDMA·HCl.

Table 10. Pharmacokinetics of MDMA and MDA following a single 120 mg dose of MDMA·HCl administered to fasting healthy males and females

PK Parameter	**MDMA**	**MDA**
C_{max} ng/mL (CV%)	261 (27.0)	13.3 (27.6)
T_{max} h (min, max)	2.00 (2.00, 8.00)	6.00 (2.00, 8.00)
$AUC_{0\text{-}inf}$ h*ng/mL (CV%)	3890 (39.1)	374 (38.1)
$t_{1/2}$ h (CV%)	9.10 (19.6)	12.8 (19.2)

Effect of Food

The C_{max} and AUC data from a food-effect study involving administration of MDMA·HCl to healthy volunteers under fasting conditions and with a high-fat meal indicated that exposure to the drug is not affected by food. A high fat meal had no effect on the pharmacokinetics of a single 120 mg dose of MDMA·HCl in healthy males and females.

Distribution

In vitro studies have demonstrated that MDMA is X% bound to human plasma proteins at concentrations up to Y. MDMA is not a substrate of BCRP, MDR1, OATP1B1, or OATP1B3. A single 120 mg dose of MDMA·HCl resulted in a volume of distribution of 430 L.

Elimination

Metabolism

MDMA is extensively metabolized in humans. Several parallel metabolic pathways contribute to the metabolism of MDMA including CYP2D6, CYP1A2, CYP3A4, CYP2C19, and CYP2B6. MDMA is a strong inhibitor of CYP2D6 and thus auto-inhibits its own metabolism, leading to higher than dose proportional pharmacokinetics of MDMA.

N-demethylation of MDMA forms an active metabolite, 3,4-methylenedioxyamphetamine (MDA). The parent compound and MDA are further O-demethylated to 3,4-dihydroxymethamphetamine (HHMA) and 3,4-dihydroxyamphetamine (HHA), respectively. Both HHMA and HHA are subsequently O-methylated mainly to 4-hydroxy-3-methoxymethamphetamin (HMMA) and 4-hydroxy-3-methoxyamphetamine (HMA). MDMA is a strong inhibitor of CYP2D6 and thus auto-inhibits its own metabolism, leading to higher than dose proportional pharmacokinetics of MDMA.

Excretion

Formal ADME studies evaluating the recovery of labeled MDMA have not been conducted. The percentage of unchanged MDMA excreted in urine following orally administered doses of 1.0 and 1.6 mg/kg MDMA was 8% and 11%, respectively. The majority of the dose recovered in the urine was conjugated metabolites.

Potential for Other Drugs to Affect MDMA·HCl

MDMA·HCl is metabolized via several parallel Cytochrome P450 (CYP) pathways. Therefore, the potential that inhibition of any one pathway will impact the pharmacokinetics of MDMA·HCl in a clinically meaningful way is minimized. Paroxetine administered 20 mg a day for three days to 7 healthy males increased the $AUC_{0\text{-}inf}$ of a single 100 mg dose of MDMA by 27% and C_{max} by 17%. Bupropion 150 mg per day for three days followed by 300 mg a day for four days administered to 16 healthy male and female Caucasian subjects increased the $AUC_{0\text{-}24hr}$ of a single 125 mg dose of MDMA by 33% and C_{max} by 14%.

Potential for MDMA·HCl to Affect Other Drugs

MDMA·HCl is a strong CYP2D6 inhibitor. Therefore, when administered in combination with sensitive CYP2D6 substrates, MDMA·HCl may cause significant increase in the plasma levels of those drugs. A single 1.5 mg/kg dose of MDMA administered to 15 healthy males 4 hours before 30 mg dextromethorphan (Days 1, 2, 3, 4, 5 and 8) increased the $AUC_{0\text{-}8hr}$ of dextromethorphan 9.5-fold and C_{max} 8.5-fold. A single 1.5 mg/kg dose of midomafetamine HCl administered 4 hours before 30 mg dextromethorphan (Days 1, 2, 5, 8 and 11) to 12 healthy Caucasian females increased the $AUC_{0\text{-}inf}$ of dextromethorphan 13.6-fold and C_{max} 8.3-fold. A single 100 mg dose of MDMA administered to 7 healthy males increased the $AUC_{0\text{-}8hr}$ of paroxetine (20 mg) 3-fold and increased C_{max} 2.5-fold (Segura 2005). MDMA·HCl is not an inducer of CYPs and did not inhibit CYPs other than CYP2D6 in a clinically meaningful manner.

Example 7. Clinical Pharmacokinetics of MDMA from Study MPKF and the National Institute on Drug Abuse (NIDA) Study.

Introduction:

The MPKF is a Phase 1, open-label, randomized sequence, multi-dose, 2-period crossover food effect study in 16 healthy individuals. The MPKF study evaluated plasma concentrations of both MDMA and the active metabolite 3,4-methylenedioxyamphetamine (MDA). Summary PK Parameters of the preliminary data was based on interim analysis are presented in Table 12, and Table 13 for MDMA and MDA, respectively.

The NIDA study 7 days of individual-level blood plasma data were collected for 46 participants receiving a low MDMA dose (1.0 mg/kg) and 41 participants receiving a high MDMA dose (1.6 mg/kg, 150 mg maximum).

Materials and methods:

The MPKF study:

Formulation: d,l-MDMA·HCl (50/50 racemic mixture) encapsulated with excipients listed in Table 11. The API, synthesized by Onyx Scientific, was a white crystalline powder of pharmaceutical quality, made according to current Good Manufacturing Practices for human use. This formulation is the highest dosage strength equivalent to the formulation intended for marketing.

Participants: Sixteen healthy individuals were recruited for the study.

Intervention: The study was conducted as a Phase 1, open-label, randomized sequence, multi-dose, 2-period crossover food effect study. Each participant received multiple doses of MDMA, and plasma concentrations of both MDMA and the active metabolite MDA were measured.

Sample Collection: Blood samples were collected at various time points up to 72 hours after dosing. The samples were analyzed using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods.

Pharmacokinetic Analysis: Plasma pharmacokinetic parameters, such as area under the concentration-time curve from time 0 to the last quantifiable concentration (AUC0-t), area under the concentration-time curve from time 0 to 72 hours (AUC0-72), area under the concentration-time curve from time 0 to infinity (AUC0-inf), maximum concentration (Cmax), time to maximum concentration (Tmax), elimination half-life (t1/2), lag time (Tlag), clearance (CL/F), and volume of distribution (Vd/F) were calculated using non-compartmental methods.

Data Analysis: The summary PK parameters were presented in Table 12 for MDMA and Table 13 for MDA. The data were analyzed using descriptive statistics, and the mean and standard deviation were calculated. The results were compared between the two periods and analyzed for food effects. Statistical analyses were performed using appropriate methods, such as analysis of variance (ANOVA) and paired t-tests. A p-value of less than 0.05 was considered statistically significant. Results are shown in table 12 and 13.

Table 11. 60 mg MDMA·HCl Formulation Used in Study MPKF.

Component	**Amount (mg) MPKF Capsules**	**Proportion relative to core weight (% w/w) MPKF Capsules**
MDMA·HCl	59.5[1]	50.0%
Mannitol (filler)	58.3[1]	49.0%
Mg Stearate (lubricant)	1.19	1.0%
Total	**119.00**	**100.0%**

[1] equivalent to 50 mg MDMA free base

The NIDA study:

Formulation: d,l-MDMA·HCl (50/50 racemic mixture) encapsulated without excipients. The API, synthesized by Lipomed; Arlesheim, Switzerland, was a white crystalline powder of pharmaceutical quality, made according to current Good Manufacturing Practices for human use.

Participants: Healthy adult volunteers were recruited for each study.

Intervention: A single oral dose of MDMA (1.0 mg/kg (low), or 1.6 mg/kg (high))) was administered to participants.

Sample collection: Blood samples were collected at various time points up to 3 hours after dosing. Urine samples were collected at various time points up to 120 hours after dosing.

Pharmacokinetic Analysis: The samples were analyzed using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods to determine the plasma pharmacokinetic parameters, such as AUC-0, Cmax, and Tmax. The samples were analyzed using validated gas chromatography-mass spectrometry (GC-MS) and LC-MS/MS methods to determine the % of oral MDMA dose excreted in urine over the 0-120 hour period post-dose.

Data Analysis: The results show a comprehensive understanding of the disposition of MDMA and its metabolites in blood and urine. The data were analyzed using descriptive statistics, and the mean and standard deviation were calculated. Statistical analyses were performed using appropriate methods, such as ANOVA and paired t-tests. A p-value of less than 0.05 was considered statistically significant. Results are shown in table 14 and 15.

Table 12. Preliminary Plasma PK Parameters of MDMA Following a Single 120 mg Oral Dose of MDMA·HCl Under Fasting or Fed Conditions (Study MPKF).

		120 mg MDMA Treatment	
MDMA PK Parameters[a]	**Units**	**Fasted N = 11**	**Fed N = 11**
AUC_{0-t}	h*ng/mL	3670 (43.2);11	3550 (54.4);11
AUC_{0-72}	h*ng/mL	3880 (38.2);11	3800 (48.5);11
AUC_{0-inf}	h*ng/mL	3890 (39.1);11	3800 (50.7);11
C_{max}	ng/mL	261 (27.0);11	242 (24.2);11
T_{max}[b]	h	2.00 (2.00, 8.00);11	4.00 (4.00, 6.00);11
$t_{1/2}$	h	9.10 (19.6);11	8.36 (28.3);11
Tlag[b]	h	0.50 (0.00, 1.00);11	0.50 (0.00, 1.00);11
CL/F	L/h	34.5 (33.7);11	37.5 (39.8);11
Vd/F	L	430 (18.7);11	412 (20.4);11

[a] Arithmetic Mean (Arithmetic CV%);N
[b] Median (Min; Max);N

Table 13. Preliminary Plasma PK Parameters of MDA Following a Single 120 mg Oral Dose of MDMA·HCl Under Fasting or Fed Conditions (Study MPKF).

		120 mg MDMA Treatment	
MDA PK Parameters[a]	**Units**	**Fasted N = 13**	**Fed N = 13**

AUC_{0-t}	h*ng/mL	324 (41.4);13	287 (50.5);13
AUC_{0-72}	h*ng/mL	342 (36.3);13	308 (42.9);13
AUC_{0-inf}	h*ng/mL	374 (38.1);10	388 (37.1);8
C_{max}	ng/mL	13.3 (27.6);13	12.2 (23.9);13
T_{max}[b]	h	6.00 (2.00, 8.00);13	8.00 (4.00, 12.00);13
$t_{1/2}$	h	12.8 (19.2);10	13.2 (25.8);8
Tlag[b]	h	0.50 (0.00, 1.00);13	1.00 (0.00, 1.00);13
CL/F	L/h	368 (41.6);10	339 (29.4);8
Vd/F	L	6510 (31.0);10	6140 (22.8);8

[a] Arithmetic Mean (Arithmetic CV%);N
[b] Median (Min; Max);N

Table 14. Summary Plasma PK Parameters of MDMA Following a Single Oral Dose of MDMA (1.0 or 1.6 mg/kg) in the NIDA study.

		1.0 mg/kg		**1.6 mg/kg**	
PK Parameters	**Units**	**Blood**	**Plasma**	**Blood**	**Plasma**
AUC_{0-3h}[a]	h*ng/mL	248.9 [120.0-536.4] n = 45	220.7 [98.7-480.7] n = 45	419.0 [20.0-831.7] n = 40	352.7 [16.2-846.3] n = 42
Cmax[a]	ng/mL	144.9 [90.3-358.2] n =46	126.3 [66.9-276.1] n = 46	241.6 [58.5-461.9] n = 41	205.1 [46.3-465.3] n = 41
Tmax[a]	h	2.5 [1.5-3.0] n = 46	2.5 [1.5-3.0] n = 46	2.5 [1.0-3.0] n = 41	2.5 [1.0-3.0] n = 42
% of oral MDMA Dose Excreted in Urine (0-120 h post-dose)[b]	%	10.4 [6.3-17.5] n = 5		17.0 [9.0-25.4] n = 9	
% of oral MDMA Dose Excreted in Urine (0-120 h post-dose)[c]	%	8.1, n = 10		11.2, n = 10	

Data presented as median [range] n
[a] Plasma PK data from (Hartman RL, Desrosiers NA, Barnes AJ, et al. 3,4-Methylenedioxymethamphetamine (MDMA) and metabolites disposition in blood and plasma following controlled oral administration. Anal Bioanal Chem. 2014;406(2):587-99).
[b] Urine PK data from (Abraham TT, Barnes AJ, Lowe RH, et al. Urinary MDMA, MDA, HMMA, and HMA excretion following controlled MDMA administration to humans. Journal of analytical toxicology.2009;33(8):439-46).
[c] Urine PK data from (Schwaninger AE, Meyer MR, Barnes AJ, et al. Urinary excretion kinetics of 3,4- methylenedioxymethamphetamine (MDMA, ecstasy) and its phase I and phase II

metabolites in humans following controlled MDMA administration. Clinical chemistry. 2011;57(12):1748-56) (range not available).

Table 15. Summary Plasma PK Parameters of MDA Following a Single Oral Dose of MDMA (1.0 or 1.6 mg/kg) in the NIDA study.

		1.0 mg/kg		**1.6 mg/kg**	
PK Parameters	**Units**	**Blood**	**Plasma**	**Blood**	**Plasma**
AUC_{0-3h}[a]	h*ng/mL	12.9 [4.1-26.4] n = 45	8.8 [2.5-15.2] n = 45	19.4 [0.8-43.6] n = 40	11.9 [0.5-36.6] n = 42
Cmax[a]	ng/mL	8.0 [4.0-18.3] n = 46	5.5 [2.3-11.3] n = 46	13.0 [3.0-24.1] n = 41	8.6 [2.0-21.0] n = 42
Tmax[a]	h	3.0 [1.5-3.0] n = 45	3.0 [2.0-3.0] n = 46	3.0 [1.5-3.0] n = 41	3.0 [2.0-3.0] n = 42
% of oral MDMA Dose Excreted in Urine (0-120 h post-dose)[b]	%	0.9 [0.6-2.2] n = 5		1.6 [0.9-2.7] n = 9	
% of oral MDMA Dose Excreted in Urine (0-120 h post-dose)[c]	%	0.6, n = 10		1.2, n = 10	

Data presented as median [range] n
[a] Plasma PK data from (Hartman et al, 2014)
[b] Urine PK data from (Abraham et al, 2009)
[c] Urine PK data from (Schwaninger et al, 2011) (range not available)

Discussion:

MDMA exhibits high PK variability. The unbound maximum concentration (C_{max}) of MDMA following a single 120 mg dose is estimated to be 0.66 μM, based on the PK data from the MPKF study demonstrating a C_{max} of 261 ng/ml following a single 120 mg dose of MDMA, and literature reporting that in humans MDMA is 51% bound to plasma proteins (Wan Aasim WR, Tan SC, Gan SH. Interspecies In Vitro Evaluation of Stereoselective Protein Binding for 3, 4-Methylenedioxymethamphetamine. Journal of Chemistry. 2017;2017).

Example 8. Population PK (PopPK) Analysis

Introduction:

PopPK analyses of MPKF and NIDA concentration-time data will be carried out according

to the FDA Guidances for Industry: *Population Pharmacokinetics* (February 2022) and *Exposure-Response Relationships Study Design, Data Analysis, and Regulatory Applications* (May 2003) and European Medicines Agency (EMA) Guideline on *Reporting the Results of Population Pharmacokinetic Analyses* (Jan 2008). The objectives will include development of population PK models for MDMA and MDA, characterization of the extrinsic and intrinsic factors affecting the exposure of MDMA and MDA, and simulate the dosing scenarios to inform the development of prescribing information in the product label. Table 7 shows the data from MPKF and the NIDA studies (see Example 7) that will be included in the population PK analysis of MDMA and MDA.

Table 16. Clinical Studies that will be included in the population PK analysis.

Study Design	**Number of Subjects**	**Drug Dose and Regimen**	**PK Sampling**
NIDA: Placebo-controlled, double-blind, crossover study in healthy volunteers	N = 50 unique participants with PK data N = 46 1.0 mg/kg MDMA N = 41 1.6 mg/kg MDMA N = 17 completers (all 3 dosing sessions)	Participants received 3 dosing sessions: 1.0mg/kg MDMA, 1.6 mg/kg MDMA, and placebo in randomized order	−0.25 (Pre-dose), 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 4.5, 5.0, 7.0, 9.0, 11, 13, 15, 23, 29, 34, 39, 47, 71, 95, 119, 143, and 167 hour Predose through 47-hour specimens were collected from all participants; the exact number of later collections depended on the length of residential stay.
MPKF: Single-center, open label, randomized sequence, 2-period cross-over study to determine the effect of food on the relative BA of MDMA oral formulation in healthy volunteers	N = 16 evaluable unique participants with PK data N = 14 participants completed both study periods.	A dose of 100 mg MDMA (equivalent to 120 mg MDMA·HCl) for each dosing session. Total cumulative dose is 200 mg.	Pre-dose, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, and 72 hour for each dosing session

Data Analysis:

Nonlinear mixed-effects modeling software (NONMEM®; version 7.3 or higher; ICON, Hanover, MD, US) or Phoenix NLME version 8.0 or higher (Certara, Princeton, NJ, US) will be

used for popPK analysis. NONMEM, Phoenix, and/or R (version 3.3.0 or higher) will be used for simulations. SAS or R will be used for data preparation, graphical analysis, model diagnostics, and statistical summaries. Xpose®, Perl-speaks-NONMEM (PsN; Department of Pharmacy, Uppsala University, Uppsala, Sweden), and/or Pirana (Certara, Princeton, NJ, US) may also be used for model diagnostics and facilitation of tasks such as model running and covariate testing.

Modeling will proceed in a stepwise manner with additional model complexity added as indicated by the data. Separate or sequential models of MDA may be developed. The models will include inter-individual random effects and residual error. The covariates listed in Table 8 may be evaluated for effects on the PK of MDMA and MDA, as data allow.

Table 17. Description of Covariates and Associated Derivation Methods.

<table>
<tr><th>Covariate (Abbreviation)</th><th>MDMA Parameters</th><th>MDA Parameters</th></tr>
<tr><td>Body size (e.g., body weight, LBM, body surface area, and BMI)</td><td colspan="2" rowspan="5">Clearance and central volume of distribution</td></tr>
<tr><td>Age</td></tr>
<tr><td>Race</td></tr>
<tr><td>Clearance and central volume of distribution</td></tr>
<tr><td>Albumin</td></tr>
<tr><td>Hepatic impairment/liver function tests (e.g., AST, ALT, serum bilirubin, or NCI liver dysfunction category)</td><td colspan="2" rowspan="2">Clearance</td></tr>
<tr><td>Renal function (eGFR and CrCl)</td></tr>
<tr><td>Fasting status</td><td>Absorption constant rate</td><td>NA</td></tr>
</table>

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; LBM = lean body mass; NA=not applicable; NCI = National Cancer Institute;

Model evaluation and selection will proceed by inspecting change in objective function value, condition number, goodness-of-fit plots, plausibility, and precision of model parameters, among other measures. A nonparametric bootstrap and visual predictive checks of the final model will be conducted to evaluate the stability and predictive ability of the model.

The final popPK models will be used to simulate rich concentration-time profiles for MDMA and MDA based on subject-level posterior Bayes estimates of the PK parameters. Dosing regimens tested in Phase 2 and 3 studies as well as the proposed clinical dosing regimen may be simulated. Exposure metrics, such as AUC, C_{min}, and C_{max} at steady state will be derived based on these concentration-time profiles. Descriptive statistics will be derived, and results summarized. Results will also be summarized within subgroups based on clinically important covariates that

were identified during the covariate analysis.

Foreseeable limitations to the population PK analysis are listed in Table 18. Namely these limitations pertain to formulation differences between MPKF and NIDA studies (confounded by study and subject population), carryover effects of CYP2D6 enzyme inhibition (due to potential insufficient washout period of 7 days for prior therapies/drug use or MDMA administration within the study), and differences in food intake during dosing days between MPKF and NIDA. Published PK parameters from the NIDA study (Table 14 and Table 15) show several fold range in both AUC and C_{max}, demonstrating high variability in this dataset.

Table 18. Comparison of Design Elements Impacting PopPK Analysis.

Design Element	**MPKF**	**NIDA**	**PopPK Limitation**
Formulation	120 mg MDMA·HCl	d,l-MDMA·HCl (Lipomed, Arlesheim, Switzerland)	Formulation is confounded by study and subject population (MDMA-naïve, vs. drug users and MDMA users).
Population	MDMA-naïve	**Non-drug users** (n = 18): no cannabis usage in the prior 2 years; lifetime cannabis usage not to exceed 10 times **Drug (cannabis) users/non-MDMA** (n = 18): self-reported drug use and confirmation blood/urine test. **MDMA users** (n = 18): participants must have a positive test for amphetamine or MDMA within 90 days of the first dose	Prior drug use within 10 days of study drug administration may result in altered CL due to CYP2D6 inhibition.
Design	Group 1: fasted followed by a fed treatment Group 2: fed followed fasted treatment. A minimum of 14 days between treatments	Participants received low (1.0 mg/kg, ~70 mg) and high dose (1.6 mg/kg, ~112 mg) MDMA and placebo capsules during 3 dosing sessions. Administration of the 3 doses was randomized and balanced with a minimum of 7 days between sessions.	Washout period in NIDA study may be insufficient for CYP2D6 activity to return to baseline and may result in carry-over effects between dosing occasions. Altered CL due to CYP2D6 inhibition is likely.
Controlled Fed/Fasted Dosing	Yes	No	Food consumption immediately prior to dosing was not specified in the NIDA protocol.

Example 9. Evaluation of MDMA tolerability in subjects with moderate Hepatic Impairment Compared to Matched Control Subjects with Normal Hepatic Function.

Introduction:

This study aims to evaluate the effect of moderate hepatic impairment on the PK of oral MDMA and its active metabolite, MDA, and to assess the safety and tolerability of oral MDMA in individuals over the age of 18 with moderate hepatic impairment compared to matched control subjects with normal hepatic function. It is a Phase I, open-label study that will enroll a total of 16 eligible participants, with 8 participants who meet the diagnosis of moderate hepatic impairment (class B according to Child-Pugh's criteria), and 8 participants with normal hepatic function.

Materials and Methods:

Participants will be administered a single oral dose of 125 mg MDMA. Blood samples will be collected at pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose. The plasma concentrations of MDMA and MDA will be analyzed using validated analytical methods. Safety and tolerability will be evaluated by monitoring adverse events, vital signs, and electrocardiograms (ECGs).

Data Analysis:

The primary objective of the study is to compare the PK parameters of MDMA and MDA in participants with moderate hepatic impairment versus matched control subjects with normal hepatic function. The PK parameters that will be evaluated include Cmax, time to reach Tmax, AUC, and t1/2. The PK parameters will be compared between the two groups using analysis of variance (ANOVA) or non-parametric tests, as appropriate. Safety and tolerability will be assessed by comparing the incidence and severity of adverse events between the two groups. The data will be summarized using descriptive statistics, and statistical analyses will be performed using appropriate methods. Statistical tests will be two-sided, and a p-value of less than 0.05 will be considered statistically significant. The number of participants reported below is the cumulative number of participants accrued as of the reporting period.

Example 10. Method of Treating a Subject with MDMA-Assisted Therapy (MDMA-AT)

Across 12 U.S. study sites and 2 Canadian sites, a total of 37 unique cotherapist dyads provided MDMA-assisted therapy (MDMA-AT) for treatment under clinical supervision among participants with severe post-traumatic stress disorder (PTSD). Study sites included private

practice clinics in Charleston (SC), Boulder (CO), Fort Collins (CO), Los Angeles (CA), New Orleans (LA), San Francisco (CA), New York (NY), Boston (MA), Vancouver (British Columbia, Canada), and Montreal (Quebec, Canada); and the University of California, San Francisco (UCSF, CA), University of Connecticut (UC, CT), University of Wisconsin Madison (WI), and New York University (NY). Sites ranged from one to four cotherapist dyads, and each unique dyad treated one participant. Study participants were recruited from November 2017 to March 2019 via internet advertisements, provider referrals, and by word-of-mouth. Study sites conducted telephone screenings to assess initial eligibility prior to inviting participants on-site for further screening.

Eligibility criteria included confirmation of severe PTSD, which was defined as having a CAPS-5 Total severity score of 35 or greater. Participants were asked to agree to the study protocol including lifestyle modifications. Exclusionary criteria included past or present psychotic disorder, bipolar I disorder, pregnancy or lactation, current diagnosis of a substance use disorder (except for caffeine or nicotine), uncontrolled hypertension, weighing less than 48 kg, and other medical conditions contraindicated for MDMA such as cardiac conditions or cerebrovascular disease. Participants who were at serious risk of suicide or posed a risk to others were also ineligible. Participants with controlled hypertension underwent additional screening to confirm the absence of clinically significant underlying cardiovascular disease. Participants who were enrolled into the study were asked, under the supervision of a physician, to taper off psychiatric medications and any other medications that might have interfered with the effects or metabolism of MDMA.

Treatment

The MDMA-AT therapeutic approach is detailed in the "Manual for MDMA-Assisted Therapy in the Treatment of PTSD," published by MAPS (MDMA Treatment Manual, available at maps.org/treatment-manual). MDMA-AT was conducted over a duration of 9 to 15 weeks. Treatment periods consisted of three preparatory sessions before the first administration of MDMA and three MDMA experimental sessions, in which each session was followed by three integrative sessions. In preparatory sessions, participants met with their cotherapist dyad to develop therapeutic rapport, discuss their PTSD symptoms, and the upcoming MDMA-AT session. Therapists provided information on what to expect during the MDMA-AT sessions, including drug effects and strategies to manage any challenging experiences that may emerge.

Participants were offered a total of three MDMA-AT sessions that were scheduled 3 to 5 weeks apart. In the first experimental session, participants were administered a divided dose of 80 mg MDMA·HCl initial + 40 mg MDMA·HCl supplemental. Supplemental doses were administered 1.5 to 2 hours after the initial dose. The purpose of the supplemental dose was to enable a longer period to process trauma during MDMA-AT sessions without significantly impacting the intensity or total duration of pharmacodynamic effects. The second and third experimental sessions offered a dose escalation to divided doses of 80 mg MDMA·HCl + 40 mg MDMA·HCl or 120 mg MDMA·HCl + 60 mg MDMA·HCl. The nominal difference in MDMA doses between countries was due to drug availability and challenges in import/export of a controlled substance, where U.S. participants received racemic MDMA synthesized by David Nichols, Ph.D. (Purdue University) and Canadian participants received racemic MDMA from Lipomed AG Switzerland.

Therapy during MDMA-AT sessions consisted of periods of introspection alternating with periods of communication between the participant and the cotherapist dyad. Participants were encouraged to remain with trauma-related memories, feelings, and/or thoughts as the cotherapist dyad provided support. MDMA-AT sessions lasted 6 to 8 hours and ended after drug effects returned to baseline. Participants remained overnight at the site with a night attendant, except for four participants who did not stay overnight as part of a safety substudy. After each MDMA-AT session, participants received several follow-up visits, including three integrative sessions, where therapists facilitated participants' continued emotional processing, addressed any difficulties following the MDMA-AT session, and helped participants to apply any benefits gained in the MDMA-AT sessions to daily life. Participants worked with the same cotherapist dyad throughout the entire treatment period. The therapeutic approach is detailed in the MDMA Treatment Manual.

Example 11. MAPP1 Clinical Trial Summary.

MAPP1 was a Phase 3 randomized, placebo-controlled, 2-arm, double-blind, multi-site study conducted to investigate the efficacy and safety of MDMA-AT in participants with severe PTSD. This study included 3 experimental sessions of therapy combined with either MDMA·HCl or placebo. During Experimental Session 1, participants received a split dose of 120 mg (80 mg + 40 mg).

Participants received an escalated split dose of 180 mg during Experimental Sessions 2 and 3 unless there were tolerability issues or the participant declined. The primary

outcome measure, the CAPS-5, evaluated changes in PTSD symptom severity and the secondary outcome measure, the SDS, evaluated changes in functional impairment. Both measures were assessed by a blinded centralized language-specific IR pool.

Study Population

Overall, 91 participants were randomized in the study (MDMA: 46 participants; placebo: 45 participants) (Table 19). The majority of participants completed Experimental Session 3
(MDMA: 91.3%; placebo: 84.1%). A total of 8 participants (MDMA: 2 participants; placebo: 6 participants) in the MDMA-AT and 6 participants in the placebo with therapy group) terminated treatment early after randomization:

- Two placebo participants terminated the study early due to adverse events (AEs) as the primary reason (1 participant with a moderate AE of anxiety and 1 participant with a severe treatment emergent adverse event (TEAE) of insomnia). An additional placebo participant terminated early due to participant choice as the primary reason; however, an AE was included as the secondary reason (severe TEAE of suicide attempt).
- Two participants (1 in each treatment group) terminated early due to administrative reasons as the primary reason; secondary reasons for both participants included COVID-19.
- One MDMA participant terminated early due to investigator choice; secondary reasons included subject choice, investigator choice, and COVID-19.
- One placebo participant terminated early due to risk of COVID-19 contraction as the primary reason.
- One participant was randomized to receive placebo but terminated early due to participant declined to participate. This participant did not receive any IP and was not included in the Safety Set.

A total of 4 participants dropped out (2 participants in each group). One placebo participant dropped out due to AEs as the primary reason (severe TEAE of suicidal ideation), 1 MDMA participant dropped out due to participant choice; however,

an AE was included as the secondary reason for dropout (severe TEAE of depression), and 2 participants (1 MDMA and 1 placebo) withdrew consent.

Table 19. Participant Disposition (All Screened).

n (%)	MDMA N = 46	Placebo N = 45
Randomized	46	45
Safety Set[a]	46	44
mITT Set[b]	46	44
Visit Completion		
Experimental Session 1	46 (100.0)	44 (100.0)
Experimental Session 2	43 (93.5)	41 (93.2)
Experimental Session 3	42 (91.3)	37 (84.1)
Study Termination (Visit 20)	46 (100.0)	44 (100.0)
Reason for Study Termination and Primary Reason for Early Termination		
Post-randomization Early Termination	2 (4.3)	6 (13.3)
Adverse Event or Death	0	2 (4.4)
Subject Chose to Discontinue Treatment	0	1 (2.2)
Investigator Chose to Discontinue Treatment	1 (2.2)	0
Administrative Reason	1 (2.2)	1 (2.2)
Subject Declined to Participate	0	1 (2.2)
Other	0	1 (2.2)
Dropout	2 (4.3)	2 (4.4)
Subject Chose to Discontinue Treatment	1 (2.2)	0
AE or Death	0	1 (2.2)
Withdrawal of Consent	1 (2.2)	1 (2.2)
Lost to follow up	0	0

MDMA = 3,4-methylenedioxymethamphetamine; mITT = modified Intent-To-Treat; N = total number of participants in each group; n = number of participants.

A Post-Randomization Early termination refers to a participant that was enrolled and randomized and then stopped all therapy visits and experimental sessions, however CAPS-5 Assessment visits (V8, V13, V19) may have been completed before termination.

A drop out refers to a participant who was enrolled, randomized, and treated but then withdrew consent for all other protocol activities.

Only primary reason for early termination and dropout are included in the table.

Participants may have had secondary reasons for study treatment discontinuation.

a. Received any IMP.

b. Had at Least 1 CAPS-5

Assessment

The majority of participants in the Safety Set were white (76.7%), not Hispanic or Latino (90.0%), and female (65.6%) (Table 20). The mean age at baseline was 40.93 years (range of 20.9 to 71.2 years). In general, the demographic characteristics of the treatment groups were similar with the exception of sex; there was a higher percentage of females in the placebo group (72.7%) than in the MDMA-AT group (58.7%).

Table 20. Demographics and Baseline Characteristics (Safety Set).

	MDMA N = 46	**Placebo N = 44**	**Total N = 90**
Gender, n (%)			
Male	19 (41.3)	12 (27.3)	31 (34.4)
Female	27 (58.7)	32 (72.7)	59 (65.6)
Age, years			
Mean (SD)	43.55 (12.863)	38.19 (10.361)	40.93 (11.950)
Median (Min, Max)	39.10 (24.9, 71.2)	36.59 (20.9, 62.9)	38.58 (20.9, 71.2)
Ethnicity, n (%)			
Hispanic or Latino	5 (10.9)	3 (6.8)	8 (8.9)
Not Hispanic or Latino	41 (89.1)	40 (90.9)	81 (90.0)
Unknown	0	1 (2.3)	1 (1.1)
Race, n (%)			
American Indian or Alaska Native	3 (6.5)	0	3 (3.3)
Asian	2 (4.3)	5 (11.4)	7 (7.8)
Black or African American	0	2 (4.5)	2 (2.2)
Native Hawaiian or Other Pacific Islander	0	0	0
White	39 (84.8)	30 (68.2)	69 (76.7)
Multiple	2 (4.3)	6 (13.6)	8 (8.9)

Max = maximum; MDMA = 3,4-methylenedioxymethamphetamine; Min = minimum; N = total number of participants; n = number of participants; SD = standard deviation.

Source: Table 14.1.3.1.

At baseline, the mean (SD) duration of PTSD was 14.04 (11.473), with a maximum duration of 48.8 years (Table 21). Based on enrollment criteria, all participants had a duration of at least 0.5 years. The majority of patients had trauma histories that included developmental trauma events (84.4%) and/or multiple trauma events (87.8%). Both duration of PTSD and trauma histories were similar across treatment groups. History of major depression (MDMA: 91.3%; placebo: 90.9%) was additionally similar across treatment groups.

Per enrollment criteria all participants had severe PTSD (mean CAPS-5 Total Severity score at baseline: 44.1) and 21.1% of participants had the dissociative subtype of PTSD. In addition, the high mean SDS score (6.8 in MDMA-AT group and 7.4 in placebo with therapy group, (Table 20) indicates that most also had severe functional impairment.

Most participants (97.8%) had previously tried therapy for PTSD, the most common of which were other, EMDR, CBT, and group psychotherapy (Table 21). Other types of therapy included the general term of talk therapy and psychotherapy as well as other specific types of therapy. Histories of pharmacologic and non-pharmacologic interventions were similar across treatment groups.

Baseline PTSD Characteristics (Safety Set)

Table 21. Baseline Disease Characteristics (Safety Set).

	MDMA N = 46	**Placebo N = 44**	**Total N = 90**
Trauma History, n (%)			
Veteran Status	10 (21.7)	6 (13.6)	16 (17.8)
Served in a combat area	6 (13.0)	5 (11.4)	11 (12.2)
Multiple trauma events	41 (89.1)	38 (86.4)	79 (87.8)
Developmental trauma events	40 (87.0)	36 (81.8)	76 (84.4)
Baseline BDI-II Total Score			
Mean (SD)	30.5 (13.11)	34.9 (12.57)	32.7 (12.97)
Median (Min, Max)	30.0 (3, 53)	36.5 (10, 56)	33.5 (3, 56)
Baseline PTSD Duration (years)			
Mean (SD)	14.80 (11.615)	13.25 (11.401)	14.04 (11.473)
Median (Min, Max)	12.61 (0.6, 48.8)	9.58 (0.7, 46.1)	10.86 (0.6, 48.8)

Pre-Study PTSD Medication, n (%)			
Paroxetine	4 (8.7)	4 (9.1)	8 (8.9)
Sertraline	12 (26.1)	11 (25.0)	23 (25.6)
Baseline CAPS-5 Total Severity Score			
Mean (SD)	44.0 (6.01)	44.2 (6.15)	44.1 (6.04)
Median (Min, Max)	43.5 (35, 57)	44.0 (35, 62)	44.0 (35, 62)
Baseline Disease Severity (based on CAPS-5), n (%)			
Severe (≥ 35)	46 (100.0)	44 (100.0)	90 (100.0)
Baseline CAPS-5 Dissociative Subtype, n (%)			
No	40 (87.0)	31 (70.5)	71 (78.9)
Yes	6 (13.0)	13 (29.5)	19 (21.1)
Prior Psychotherapy, n (%)			
Participants with any previous psychotherapy	45 (97.8)	43 (97.7)	88 (97.8)
Cognitive Processing Therapy	0	1 (2.3)	1 (1.1)
Dialectical Behavioral Therapy	2 (4.3)	2 (4.5)	4 (4.4)
Eye Movement Desensitization Reprocessing	24 (52.2)	14 (31.8)	38 (42.2)
Group Psychotherapy	21 (45.7)	14 (31.8)	35 (38.9)
Holotropic Breathwork	2 (4.3)	0	2 (2.2)
Other Cognitive Behavioral Therapy	14 (30.4)	23 (52.3)	37 (41.1)
Prolonged Exposure	2 (4.3)	0	2 (2.2)
Psychodynamic	12 (26.1)	11 (25.0)	23 (25.6)
Other	38 (82.6)	36 (81.8)	74 (82.2)

BDI-II = Beck Depression Inventory II; CAPS-5 = Clinician-administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders version 5; Max = maximum; MDMA = 3,4-methylenedioxymethamphetamine;
Min = minimum; PTSD = Posttraumatic Stress Disorder; SD = standard deviation. Source Table 14.1.3.1 and 14.1.7

Efficacy

Primary Endpoint Analyses

A *de jure estimand* of treatment efficacy was used to estimate the causal effect of MDMA-AT on PTSD symptom severity as measured by the change from Baseline to Visit 19 in CAPS-5 total severity scores in the mITT analysis set. An MMRM analysis of the *de jure estimand* showed a statistically significant difference ($p < 0.0001$) between treatment arms, with a greater reduction in CAPS-5 total severity scores in participants receiving MDMA (-24.50) compared to placebo (-12.64) (Table 22). Differences in

treatment effect among demographic, dissociative sub-type, and overnight stay subgroups were not observed.

Table 22. Change in CAPS-5 Total Severity Scores by Visit - De Jure Estimand (mITT Set).

Statistic by Visit	**MDMA-AT N = 46**	**Placebo with Therapy N = 44**
Baseline CAPS-5 T1 (Visit 3), n	46	44
Mean (SD)	44.0 (6.01)	44.2 (6.15)
Median (min, max)	43.5 (35, 57)	44.0 (35, 62)
CAPS-5 T2 (Visit 8), n	46	43
Mean (SD)	33.7 (12.50)	37.0 (10.70)
Median (min, max)	34.5 (2, 53)	38.0 (8, 62)
CFB to CAPS-5 T2 (Visit 8), n	46	43
Mean (SD)	-10.3 (11.10)	-7.1 (8.69)
Median (min, max)	-9.0 (-39, 8)	-6.0 (-29, 14)
LS mean (95% CI)[a]	-10.40 (-13.29, -7.52)	-6.71 (-9.72, -3.70)
LS mean for treatment difference (95% CI)[a]	-3.69 (-7.93, 0.54)	
CAPS-5 T3 (Visit 13), n	42	39
Mean (SD)	26.2 (12.30)	33.4 (12.79)
Median (min, max)	28.0 (0, 53)	33.0 (3, 60)
CFB to CAPS-5 T3 (Visit 13), n	42	39
Mean (SD)	-17.7 (10.74)	-10.2 (11.94)
Median (min, max)	-17.5 (-41, 4)	-9.0 (-34, 10)
LS mean (95% CI)[a]	-17.83 (-21.33, -14.32)	-9.42 (-13.07, -5.77)
LS mean for treatment difference (95% CI)[a]	-8.41 (-13.53, -3.29)	
CAPS-5 T4 (Visit 19), n	42	37
Mean (SD)	19.5 (13.50)	29.8 (12.37)
Median (min, max)	18.5 (0, 51)	30.0 (2, 52)
CFB to CAPS-5 T4 (Visit 19), n	42	37
Mean (SD)	-24.4 (11.57)	-13.9 (11.53)
Median (min, max)	-25.0 (-47, 3)	-16.0 (-35, 7)
LS mean (95% CI)[a]	-24.50 (-28.28, -20.71)	-12.64 (-16.61, -8.66)
LS mean for treatment difference (95% CI)[a]	-11.86 (-17.41, -6.32)	
p-value[a]	< 0.0001	

De jure estimand does not include data after subjects discontinue treatment.

CAPS-5 = Clinician-Administered Posttraumatic Stress Disorder Scale for Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = Least Squares; Max = Maximum; MDMA = 3,4-methylenedioxymethamphetamine; min = minimum; mITT = modified Intent-to-treat; SD = Standard Deviation

a. LS Mean, LS Mean difference, 95% CI, and p-value of treatment effect at visit 19 are from an MMRM model with treatment group, visit, treatment group by visit interaction, site, and dissociative subtype as fixed effect, and baseline CAPS-5 as a covariate.

A clinically meaningful reduction in CAPS-5 total severity scores and PTSD diagnostic criteria by visit for mITT Set is presented in Table 23. A total of 37 (88.1%) participants receiving MDMA-AT met the definition of responder, demonstrating a clinically meaningful ≥ 10-point reduction in CAPS-5 total severity score, compared to 23 (62.2%) of participants receiving placebo at Visit 19. Total Severity Scores no longer met PTSD diagnostic criteria in 28 (66.7%) participants receiving MDMA compared to 12 (32.4%) of participants receiving the placebo at Visit 19.

A total of 14 (33.3%) of participants receiving the MDMA met the definition of remission, having both a CAPS-5 total severity score ≤ 11 and no longer meeting PTSD diagnostic criteria compared to 2 (5.4%) of participants receiving placebo at Visit 19.

Table 23. Clinically Meaningful Reduction in CAPS-5 Total Severity Scores and PTSD Diagnostic Criteria by Visit (mITT Set).

Visit	**MDMA-AT N = 46** **n (%)**	**Placebo with Therapy N = 44** **n (%)**
T2 endpoint (Visit 8)	46	43
Responder	21 (45.7)	14 (32.6)
Loss of Diagnosis	11 (23.9)	5 (11.6)
Remission	4 (8.7)	1 (2.3)
Non-Responder	25 (54.3)	29 (67.4)
T3 endpoint (Visit 13)	42	39
Responder	31 (73.8)	18 (46.2)
Loss of Diagnosis	24 (57.1)	7 (17.9)
Remission	5 (11.9)	2 (5.1)
Non-Responder	11 (26.2)	21 (53.8)

T4 (primary) endpoint (Visit 19)	42	37
Responder	37 (88.1)	23 (62.2)
Loss of Diagnosis	28 (66.7)	12 (32.4)
Remission	14 (33.3)	2 (5.4)
Non-Responder	5 (11.9)	14 (37.8)

CAPS-5 = Clinician-Administered PTSD for Diagnostic and Statistical Manual of Mental Disorders, 5th edition; mITT = modified Intent-to-treat; PTSD = Posttraumatic Stress Disorder; SD = Standard Deviation.

Responder: ≥ 10-point reduction in CAPS-5 Total Severity Score.

Non-Responder: < 10-point reduction in CAPS-5 Total Severity Score. Loss of Diagnosis: Does not meet Diagnostic Criteria and is a Responder.

Remission: Does not meet Diagnostic Criteria and CAPS-5 Total Score < = 11.

Key Secondary Endpoint Analyses

The *de jure estimand* of treatment efficacy was used to determine the effect of MDMA-AT on SDS total score. An MMRM analysis of the *de jure estimand* showed a statistically significant difference (p = 0.0167) between treatment arms, with a greater reduction in SDS total scores in participants receiving MDMA (-3.15) compared to placebo (-1.79) (Table 24).

Table 24. SDS Total Scores by Visit (mITT Set).

Statistics	**MDMA-AT N = 46**	**Placebo with Therapy N = 44**
Baseline (Visit 3) (n)	46	44
Mean (SD)	6.8 (2.07)	7.4 (1.63)
Median (min, max)	6.8 (1, 10)	8.0 (4, 10)
Visit 8 (n)	46	43
Mean (SD)	5.0 (2.78)	6.1 (2.25)
Median (min, max)	5.0 (0, 10)	6.7 (0, 9)
Visit 13 (n)	42	39
Mean (SD)	4.1 (2.71)	5.5 (2.37)
Median (min, max)	4.7 (0, 10)	5.3 (0, 9)

Statistics	**MDMA-AT N = 46**	**Placebo with Therapy N = 44**

Visit 19 (Primary Endpoint) (n)	42	37
Mean (SD)	3.8 (2.98)	5.3 (2.31)
Median (min, max)	3.4 (0, 9)	5.7 (1, 9)
CFB (n)	42	37
Mean (SD)	-3.1 (2.63)	-2.0 (2.41)
Median (min, max)	-2.5 (-8, 2)	-1.3 (-7, 3)
LSMean (95% CI)[a]	-3.15 (-3.90, -2.40)	-1.79 (-2.58, -1.00)
LSMean for Treatment Difference (95% CI)[a]	-1.36 (-2.46, -0.25)	-
p-value [a]	0.0167	-

CFB = Change from Baseline; LSM = Least Square Means; Max = Maximum; MDMA = 3,4-methylenedioxymethamphetamine; Min = Minimum; mITT = modified Intent-to-treat; SD = Standard Deviation; SDS = Sheehan Disability Scale.

a. LS Mean, LS Mean difference, 95% CI, and p-value of treatment effect at Visit 19 were from an MMRM model with treatment group, visit, treatment group by visit interaction, site, and dissociative subtype as fixed effect, and baseline SDS as a covariate.

Safety

All participants (100%) reported at least 1 TEAE over the course of the study (Table 25). There were 2 serious TEAEs in the placebo with therapy group (1 participant with 2 events of suicide attempt [1 moderate and 1 severe] and 1 participant with 1 event of suicidal ideation [severe], Listing 14.3.2.2.3). Adverse events of special interest included a subset of AEs involving cardiac function, suicidality, and MDMA abuse. There were 3 (6.5%) participants in the MDMA-AT group and 6 (13.6%) participants in the placebo with therapy group with a TEAE of special interest. The majority of AESIs were associated with suicidality (reported by 9 of 10 participants) and 1 participant in the placebo group reported 2 AESIs that were associated with cardiac function (palpitations and irregular heart rate). There were no AESIs of MDMA abuse. A total of 4 participants discontinued study treatment due to a TEAE (MDMA: 1 participant [severe TEAE of depression]; placebo: 3 participants [1 participant with 2 serious adverse events (SAEs) of suicide attempt, 1 participant with a SAE of suicidal ideation, and 1 participant with 1 severe TEAE of insomnia]. The majority of participants in the MDMA-AT group (97.8%) and the placebo with therapy group (90.9%) had at least 1 temporally related TEAE (TEAEs that occurred during an experiment session or up to 2 days following); none of

these events were SAEs. A listing of all TEAEs from MDMA-AT group with ≥ 5% incidence and twice prevalence of placebo group is provided below in Table 26.

Table 25. Overview of AEs (Safety Set).

	MDMA (N = 46) n (%)	**Placebo (N = 44) n (%)**	**Total (N = 90) n (%)**
Number of subjects with at least 1 TEAE	46 (100.0)	44 (100.0)	90 (100.0)
Number of subjects with at least 1 Severe TEAE	4 (8.7)	7 (15.9)	11 (12.2)
Subjects with serious or other significant TEAEs			
At least one Serious TEAE	0 (0.0)	2 (4.5)	2 (2.2)
At least one Serious TEAE Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)
At least one TEAE of Special Interest	3 (6.5)	6 (13.6)	9 (10.0)
Discontinued study treatment due to any TEAE(s)	1 (2.2)	3 (6.8)	4 (4.4)
Temporally-Related TEAEs			
Participants with at least 1 TEAE during Experimental Sessions and 2 Days Following	45 (97.8)	40 (90.9)	85 (94.4)
Participants with at least 1 SAE during Experimental Sessions and 2 Days Following	0	0	0

TEAEs: AEs starting on or after first day of study intervention through to follow-up visit.

MDMA = 3,4-methylenedioxymethamphetamine; N = total number of participants in each group; n = number of participants; SAE = serious adverse event; TEAE = treatment emergent adverse event.

TEAE of special interest include a subset of AEs involving cardiac function, suicidality, and MDMA abuse.

Discontinued study treatment due to any TEAEs includes all participants that discontinued study treatment due toTEAEs regardless of if AEs were the primary or secondary reason for discontinuing study treatment.

Table 26. Treatment-emergent Adverse Events with MDMA Incidence ≥ 5% and twice the prevalence of Placebo.

	MDMA (N = 46) n (%)	**Placebo (N = 44) n (%)**	**Total (N = 90) n (%)**
Muscle tightness	28 (60.9)	6 (13.6)	34 (37.8)
Decreased appetite	24 (52.2)	5 (11.4)	29 (32.2)
Nausea	14 (30.4)	5 (11.4)	19 (21.1)
Hyperhidrosis	10 (21.7)	1 (2.3)	11 (12.2)

Feeling cold	9 (19.6)	3 (6.8)	12 (13.3)
Mydriasis	7 (15.2)	0	7 (7.8)
Restlessness	7 (15.2)	0	7 (7.8)
Bruxism	6 (13.0)	1 (2.3)	7 (7.8)
Dizziness postural	6 (13.0)	2 (4.5)	8 (8.9)
Nystagmus	6 (13.0)	0	6 (6.7)
Blood pressure increased	5 (10.9)	0	5 (5.6)
Dry mouth	5 (10.9)	2 (4.5)	7 (7.8)
Feeling jittery	5 (10.9)	0	5 (5.6)
Intrusive thoughts	4 (8.7)	0	4 (4.4)
Musculoskeletal pain	4 (8.7)	1 (2.3)	5 (5.6)
Non-cardiac chest pain	4 (8.7)	1 (2.3)	5 (5.6)
Pain	4 (8.7)	1 (2.3)	5 (5.6)
Pollakiuria	4 (8.7)	1 (2.3)	5 (5.6)
Stress	4 (8.7)	0	4 (4.4)
Vision blurred	4 (8.7)	1 (2.3)	5 (5.6)
Vomiting	4 (8.7)	0	4 (4.4)
Chills	3 (6.5)	0	3 (3.3)
Micturition urgency	3 (6.5)	0	3 (3.3)
Muscle twitching	3 (6.5)	0	3 (3.3)
Nervousness	3 (6.5)	0	3 (3.3)
Pyrexia	3 (6.5)	1 (2.3)	4 (4.4)
Somnolence	3 (6.5)	0	3 (3.3)
Substance use	3 (6.5)	0	3 (3.3)

There were no new serious safety concerns found in MAPP1, including no increase in reported adverse events of special interest in the categories of suicidal ideation or behavior, cardiovascular, or MDMA abuse in the MDMA-AT group as compared to the psychotherapy with placebo group. As expected, based on the known sympathomimetic effects of the MDMA, transient increases in heart rate and blood pressure were observed during experimental sessions in a dose-dependent manner. These transient elevations in vitals did not require clinical intervention, including among the subset of participants with well-controlled hypertension.

Example 12. MAPP2 Clinical Trial Summary.

MAPP2 was a Phase 3 randomized, placebo-controlled, 2-arm, double-blind,

multi-site study conducted to investigate the efficacy and safety of MDMA-AT in participants with PTSD of moderate or greater severity. This study included 3 experimental sessions of therapy combined with either MDMA or placebo. During Experimental Session 1, participants received a split dose of 120 mg (80 mg + 40 mg). Participants received an escalated split dose of 180 mg during Experimental Sessions 2 and 3 unless there were tolerability issues or the participant declined.

The primary outcome measure, the CAPS-5, evaluated changes in PTSD symptom severity and the secondary outcome measure, the SDS, evaluated changes in functional impairment. Both measures were assessed by a blinded centralized language-specific IR pool.

Study Population

Overall, 104 participants were randomized in the study (MDMA: 53 participants; placebo: 51 participants). All participants were included in the Safety Set. The majority of participants completed ES3 (MDMA: 100%; placebo: 84.3%) (Table 27). A total of 4 participants (all from the placebo group) terminated treatment after randomization:

- One placebo participant terminated the study early due to AE as the primary reason (1 participant with a moderate TEAE of abdominal pain).
- Three placebo participants terminated the study early due to choosing to discontinue treatment as the primary reason.

A total of 5 participants dropped out (MDMA: 1 participant; placebo: 4 participants) as they chose to discontinue treatment, with 1 placebo participant having an AE included as the secondary reason (mild TEAE of suicidal ideation).

Table 27. Participant Disposition (All Screened).

n (%)	MDMA N = 53	Placebo N = 51
Randomized	53	51
Safety Set[a]	53	51
mITT Set[b]	53	50
Visit Completion		

Experimental Session 1	53 (100.0)	51 (100.0)
Experimental Session 2	53 (100.0)	46 (90.2)
Experimental Session 3	53 (100.0)	43 (84.3)
Study Termination (Visit 20)	53 (100.0)	51 (100.0)
Reason for Study Termination and Primary Reason for Early Termination		
Post-randomization Early Termination	0	4 (7.8)
Adverse Event or Death	0	1 (2.0)
Subject Chose to Discontinue Treatment	0	3 (5.9)
Dropout	1 (1.9)	4 (7.8)
Subject Chose to Discontinue Treatment	1 (1.9)	4 (7.8)
Lost to follow up	0	0

MDMA = 3,4-methylenedioxymethamphetamine; mITT = modified Intent-To-Treat; N = total number of participants in each group; n = number of participants.

Only primary reason for early termination and dropout are included in the table. Participants may have had secondary reasons for study treatment discontinuation (Listing 16.2.1).

a. Received any IMP.

Had at Least 1 CAPS-5 Assessment Post-treatment.

Table 28. Demographics and Baseline Characteristics (Safety Set).

	MDMA N = 53	**Placebo N = 51**	**Total N = 104**
Gender, n (%)			
Male	21 (39.6)	9 (17.6)	30 (28.8)
Female	32 (60.4)	42 (82.4)	74 (71.2)
Age, years			
Mean (SD)	38.20 (11.015)	39.99 (9.595)	39.08 (10.332)
Median (Min, Max)	36.18 (21.3, 70.0)	38.22 (20.9, 66.0)	37.16 (20.9, 70.0)
Ethnicity, n (%)			
Hispanic or Latino	17 (32.1)	11 (21.6)	28 (26.9)
Not Hispanic or Latino	36 (67.9)	39 (76.5)	75 (72.1)
Unknown	0	1 (2.0)	1 (1.0)
Race, n (%)			
American Indian or Alaska Native	0	2 (3.9)	2 (1.9)
Asian	5 (9.4)	6 (11.8)	11 (10.6)
Black or African American	5 (9.4)	3 (5.9)	8 (7.7)
Native Hawaiian or Other Pacific Islander	0	1 (2.0)	1 (1.0)

White	37 (69.8)	32 (62.7)	69 (66.3)
Multiple	6 (11.3)	7 (13.7)	13 (12.5)

Max = maximum; MDMA = 3,4-methylenedioxymethamphetamine; Min = minimum; N = total number of participants; n = number of participants; SD = standard deviation.

At Baseline, the mean (SD) duration of PTSD was 16.19 (13.3) years, with a maximum duration of 51.5 years (Table 29). Based on enrollment criteria, all participants had a duration of at least 0.5 years. Most patients had trauma histories that included developmental trauma exposure (88.5%) and/or multiple trauma (81.7%). Both duration of PTSD and trauma histories were similar across treatment groups. History of major depression (MDMA: 92.5%; placebo: 100%) was additionally similar across treatment groups.

Per enrollment criteria all participants had moderate to severe PTSD (mean [SD] CAPS-5 Total Severity score at baseline: 39.0 [6.64]). Majority of the participants did not have CAPS-5 dissociative subtype at Baseline (76.9%). The 2 currently FDA-approved drugs for PTSD treatment, sertraline and paroxetine, were used pre-study by 24.0% and 1.9% of participants, respectively (Table 29). A total of 100 (96.2%) participants received psychotherapy prior to enrollment (Table 29). Prior to study treatment start, a similar percentage of participants in both treatment groups reported to receive CPT, EMDR, other CBT, and other psychotherapies. Majority of the participants (79.8%) received other psychotherapies prior to IMP.

Table 29. Baseline Disease Characteristics (Safety Set).

	MDMA N = 53	**Placebo N = 51**	**Total N = 104**
Trauma History, n (%)			
Veteran Status	9 (17.0)	7 (13.7)	16 (15.4)
Served in a combat area	9 (17.0)	6 (11.8)	15 (14.4)
Multiple trauma events	40 (75.5)	45 (88.2)	85 (81.7)
Developmental trauma events	49 (92.5)	43 (84.3)	92 (88.5)
Baseline BDI-II Total Score			
Mean (SD)	25.4 (11.89)	25.5 (11.26)	25.5 (11.53)
Median (Min, Max)	26.0 (5, 50)	26.0 (2, 50)	26.0 (2, 50)

Baseline PTSD Duration (years)			
Mean (SD)	16.25 (14.274)	16.14 (12.427)	16.19 (13.335)
Median (Min, Max)	10.14 (2.2, 51.5)	12.93 (1.2, 49.1)	11.15 (1.2, 51.5)
Pre-Study PTSD Medication, n (%)			
Paroxetine	1 (1.9)	1 (2.0)	2 (1.9)
Sertraline	15 (28.3)	10 (19.6)	25 (24.0)
Baseline CAPS-5 Total Severity Score			
Mean (SD)	39.4 (6.64)	38.7 (6.67)	39.0 (6.64)
Median (Min, Max)	39.0 (28, 55)	38.0 (28, 56)	39.0 (28, 56)
Baseline Disease Severity (based on CAPS-5), n (%)			
Moderate (28-34)	13 (24.5)	15 (29.4)	28 (26.9)
Severe (≥ 35)	40 (75.5)	36 (70.6)	76 (73.1)
Baseline CAPS-5 Dissociative Subtype, n (%)			
No	40 (75.5)	40 (78.4)	80 (76.9)
Yes	13 (24.5)	11 (21.6)	24 (23.1)
Prior Psychotherapy, n (%)			
Participants with any previous psychotherapy	51 (96.2)	49 (96.1)	100 (96.2)
Cognitive Processing Therapy	1 (1.9)	1 (2.0)	2 (1.9)
Dialectical Behavioral Therapy	4 (7.5)	2 (3.9)	6 (5.8)
Eye Movement Desensitization Reprocessing	17 (32.1)	18 (35.3)	35 (33.7)
Group Psychotherapy	9 (17.0)	15 (29.4)	24 (23.1)
Holotropic Breathwork	0 (0.0)	3 (5.9)	3 (2.9)
Other Cognitive Behavioral Therapy	15 (28.3)	14 (27.5)	29 (27.9)
Prolonged Exposure	2 (3.8)	0 (0.0)	2 (1.9)
Psychodynamic	15 (28.3)	11 (21.6)	26 (25.0)
Other	41 (77.4)	42 (82.4)	83 (79.8)

BDI-II = Beck Depression Inventory II; CAPS-5 = Clinician-administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders version 5; Max = maximum; Min = minimum; PTSD = Posttraumatic Stress Disorder; SD = standard deviation.

Efficacy

Primary Endpoint Analyses

A *de jure* estimand of treatment efficacy was used to estimate the causal effect of MDMA-AT on PTSD symptom severity as measured by the change from Baseline to Visit 19 in CAPS-5 total severity scores in the mITT analysis set. An MMRM analysis of the *de jure* estimand showed a statistically significant difference (p = 0.0004) between

treatment groups, with a greater reduction in CAPS-5 total severity scores in participants receiving MDMA (-23.69) compared to placebo (-14.78) (Table 30). Differences in treatment effect among demographic, dissociative sub-type, and overnight stay subgroups were not observed.

Table 30. Change in CAPS-5 Total Severity Scores by Visit – *De Jure* (mITT Set).

Statistic by Visit	MDMA N = 53	Placebo N = 50
Baseline CAPS-5 T1 (Visit 3), n	53	50
Mean (SD)	39.4 (6.64)	38.8 (6.63)
Median (Min, Max)	39.0 (28, 55)	39.0 (28, 56)
CAPS-5 T2 (Visit 8), n	53	50
Mean (SD)	28.1 (12.86)	31.4 (10.29)
Median (Min, Max)	30.0 (2, 51)	33.0 (11, 55)
Change from Baseline to CAPS-5 T2 (Visit 8), n	53	50
Mean (SD)	-11.3 (11.69)	-7.5 (8.53)
Median (Min, Max)	-12.0 (-40, 10)	-7.0 (-30, 7)
LS Mean (95% CI)[a]	-11.36 (-14.17, -8.55)	-7.22 (-10.11, -4.32)
LS Mean for Treatment Difference (95% CI)[a]	-4.14 (-8.19, -0.09)	
CAPS-5 T3 (Visit 13), n	53	44
Mean (SD)	20.9 (13.42)	27.7 (11.79)
Median (Min, Max)	19.0 (0, 45)	29.0 (5, 50)
Change from Baseline to CAPS-5 T3 (Visit 13), n	53	44
Mean (SD)	-18.5 (11.82)	-10.8 (10.76)
Median (Min, Max)	-20.0 (-41, 2)	-13.0 (-33, 11)
LS Mean (95% CI)[a]	-18.58 (-21.68, -15.49)	-10.60 (-13.91, -7.29)
LS Mean for Treatment Difference (95% CI)[a]	-7.98 (-12.53, -3.44)	
Primary Outcome CAPS-5 T4 (Visit 19), n	52	42
Mean (SD)	15.8 (12.40)	23.3 (12.79)
Median (Min, Max)	15.5 (0, 44)	21.5 (2, 48)
Change from Baseline to Primary Outcome CAPS-5 T4 (Visit 19), n	52	42
Mean (SD)	-23.5 (12.08)	-15.4 (12.30)
Median (Min, Max)	-25.0 (-44, 9)	-18.0 (-40, 10)

LS Mean (95% CI)[a]	-23.69 (-26.94, -20.44)	-14.78 (-18.28, -11.28)
LS Mean for Treatment Difference (95% CI)[a]	-8.91 (-13.70, -4.12)	
p-value[a]	0.0004	

The *de jure* estimand does not include data after participants discontinued treatment.

CAPS-5 = Clinician Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders version 5; LS = least squares; Max = maximum; MDMA = 3,4-methylenedioxymethamphetamine; Min = minimum; mITT = modified intent-to-treat; MMRM = mixed models repeated measures; PTSD = posttraumatic stress disorder; SD = standard deviation.

a LS Mean, LS Mean difference, 95% CI and p-value of treatment effect at Visit 19 are from an MMRM model with treatment group, visit, treatment group by visit interaction, site, and dissociative subtype as fixed effect, and baseline CAPS-5 as a covariate.

A clinically meaningful reduction in CAPS-5 total severity scores and PTSD diagnostic criteria by visit for mITT Set is presented in Table 31. A total of 45 (86.5%) participants receiving MDMA-AT met the definition of responder, demonstrating a clinically meaningful 10-point reduction in CAPS-5 total severity score, compared to 29 (69.0%) of participants receiving placebo at Visit 19. Total Severity Scores no longer met PTSD diagnostic criteria in 37 (71.2%) participants receiving MDMA compared to 20 (47.6%) of participants receiving the placebo at Visit 19.

A total of 24 (46.2%) of participants receiving the MDMA-AT met the definition of in remission, having both a CAPS-5 total severity score ≤ 11 and no longer meeting PTSD diagnostic criteria compared to 9 (21.4%) of participants receiving placebo at Visit 19.

Table 31. Clinically Significant Reduction in CAPS-5 Total Severity Scores and PTSD Diagnostic Criteria by Visit (mITT Set).

Visit **Responder Criteria**	**MDMA N = 53**	**Placebo N = 50**
10-point reduction in CAPS-5 Total Severity Score		
CAPS-5 T2 (Visit 8)	53	50
Responder	28 (52.8)	21 (42.0)
Non-Responder	25 (47.2)	29 (58.0)
Loss of Diagnosis	21 (39.6)	11 (22.0)
Remission	5 (9.4)	1 (2.0)
CAPS-5 T3 (Visit 13)	53	44
Responder	41 (77.4)	25 (56.8)

Non-Responder	12 (22.6)	19 (43.2)
Loss of Diagnosis	32 (60.4)	15 (34.1)
Remission	14 (26.4)	5 (11.4)
Primary Outcome CAPS-5 T4 (Visit 19)	52	42
Responder	45 (86.5)	29 (69.0)
Non-Responder	7 (13.5)	13 (31.0)
Loss of Diagnosis	37 (71.2)	20 (47.6)
Remission	24 (46.2)	9 (21.4)

CAPS-5 = Clinician Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders version 5; MDMA = 3,4-methylenedioxymethamphetamine; mITT = modified intent-to-treat; PTSD = posttraumatic stress disorder.

Key Secondary Endpoint Analyses

The *de jure* estimand of treatment efficacy was used to determine the effect of MDMA-AT on SDS total score in the mITT analysis set. An MMRM analysis of the *de jure* estimand showed a statistically significant difference (p = 0.0271), with a greater reduction in SDS total scores in participants receiving MDMA (-3.31) compared to placebo (-2.11) (Table 32).

Table 32. SDS Total Scores by Visit (mITT Set).

Statistics	**MDMA-AT N = 53**	**Placebo with Therapy N = 50**
Baseline (Visit 3) (n)	53	50
Mean (SD)	6.0 (1.80)	6.1 (1.79)
Median (min, max)	6.3 (1, 10)	6.2 (2, 10)
Visit 8 (n)	53	50
Mean (SD)	4.1 (2.60)	4.6 (2.36)
Median (min, max)	4.3 (0, 10)	4.3 (0, 9)
Visit 13 (n)	53	44
Mean (SD)	2.9 (2.78)	4.5 (2.77)
Median (min, max)	2.7 (0, 9)	4.8 (0, 10)
Visit 19 (Primary Endpoint) (n)	52	42
Mean (SD)	2.7 (2.67)	4.0 (2.82)
Median (min, max)	2.3 (0, 9)	3.8 (0, 9)
CFB (n)	52	42

Mean (SD)	-3.3 (2.59)	-2.2 (2.91)
Median (min, max)	-4.0 (-7, 7)	-1.8 (-10, 3)
LSMean (95% CI)[a]	-3.31 (-4.03, -2.60)	-2.11 (-2.89, -1.33)
LSMean for Treatment Difference (95% CI)[a]	-1.20 (-2.26, -0.14)	-
p-value[a]	0.0271	-

CFB = Change from BaselineLSM = Least Square Means; Max = Maximum; MDMA = 3,4-methylenedioxymethamphetamine; Min = Minimum; mITT = modified Intent-to-treat; SD = Standard Deviation; SDS = Sheehan Disability Scale.

a. LS Mean, LS Mean difference, 95% CI, and p-value of treatment effect at Visit 19 were from an MMRM model with treatment group, visit, treatment group by visit interaction, site, and dissociative subtype as fixed effect, and baselineSDS as a covariate.

Safety

Overall, 102 (98.1%) participants reported at least 1 TEAE during the study period (Table 33). Of these, 2 (3.9%) participants from the placebo group were discontinued due to TEAE (abdominal pain and suicidal ideation). There were no serious TEAEs or deaths reported during the study. Adverse events of special interest included a subset of AEs involving cardiac function, suicidality, and MDMA abuse. There were 6 (11.3%) participants in the MDMA group and 3 (5.9%) participants in the placebo group with an TEAE of special interest. AESIs related to suicidality were reported in 2 MDMA participants and 2 placebo participants. AESIs related to cardiac function were reported in 4 MDMA participants and 1 placebo participant (all palpitations). There were no AESIs of MDMA abuse. All participants in the MDMA-AT group and the majority of participants in the placebo with therapy group (86.3%) had at least 1 temporally related TEAE (TEAEs that occurred during an experiment session or up to 2 days following). A listing of all TEAEs from MDMA-AT group with ≥ 5% incidence and twice the prevalence of placebo group is provided below in Table 34.

Table 33. Overall Summary of Treatment Emergent Adverse Events, Serious Adverse Events, Discontinuations, and Deaths (Safety Set).

	MDMA N = 53 n (%)	**Placebo N = 51 n (%)**	**Total N = 104 n (%)**
Number of subjects with at least 1 TEAE	53 (100.0)	49 (96.1)	102 (98.1)

Number of subjects with at least 1 Severe TEAE	5 (9.4)	2 (3.9)	7 (6.7)
Subjects with serious or other significant TEAEs			
At least one Treatment-emergent SAE	0 (0.0)	0 (0.0)	0 (0.0)
At least one Treatment-emergent SAE Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)
At least one TEAE of Special Interest	6 (11.3)	3 (5.9)	9 (8.7)
Discontinued study treatment due to any TEAE(s)	0 (0.0)	2 (3.9)	2 (1.9)
Temporally-Related TEAEs			
Participants with at least 1 TEAE during Experimental Sessions and 2 Days Following	53 (100.0)	44 (86.3)	97 (93.3)
Participants with at least 1 SAE during Experimental Sessions and 2 Days Following	0	0	0

Treatment emergent adverse events: AEs starting on or after first day of study intervention through to follow-up visit. MDMA = 3,4-methylenedioxymethamphetamine; N = total number of participants in each group; n = number of participants; SAE = serious adverse event; TEAE = treatment emergent adverse event.
TEAE of special interest include a subset of AEs involving cardiac function, suicidality, and MDMA abuse.
Discontinued study treatment due to any TEAEs includes all participants that discontinued study treatment due to TEAEs regardless of if AEs were the primary or secondary reason for discontinuing study treatment.

Table 34. Treatment-emergent Adverse Events with MDMA Incidence ≥ 5% and twice the prevalence of Placebo.

	MDMA (N = 53) n (%)	**Placebo (N = 51) n (%)**	**Total (N = 104) n (%)**
Muscle tightness	31 (58.8)	13 (25.5)	44 (42.3)
Nausea	24 (45.3)	11 (21.6)	35 (33.7)
Decreased appetite	19 (35.8)	5 (9.8)	24 (23.1)
Hyperhidrosis	18 (34.0)	3 (5.9)	21 (20.2)
Feeling hot	14 (26.4)	6 (11.8)	20 (19.2)
Feeling cold	11 (20.8)	3 (5.9)	14 (13.5)
Paraesthesia	10 (18.9)	1 (2.0)	11 (10.6)
Chest discomfort	9 (17.0)	2 (3.9)	11 (10.6)
Dry mouth	9 (17.0)	4 (7.8)	13 (12.5)
Chills	8 (15.1)	1 (2.0)	9 (8.7)
Feeling jittery	8 (15.1)	0	8 (7.7)
Restlessness	8 (15.1)	2 (3.9)	10 (9.6)
Vision blurred	8 (15.1)	0	8 (7.7)

Bruxism	7 (13.2)	1 (2.0)	8 (7.7)
Nystagmus	7 (13.2)	1 (2.0)	8 (7.7)
Mydriasis	6 (11.3)	0	6 (5.8)
Tremor	6 (11.3)	0	6 (5.8)
Abdominal pain upper	5 (9.4)	1 (2.0)	6 (5.8)
Feeling abnormal	5 (9.4)	2 (3.9)	7 (6.7)
Feeling of body temperature change	5 (9.4)	0	5 (4.8)
Hypoaesthesia	5 (9.4)	1 (2.0)	6 (5.8)
Palpitations	5 (9.4)	1 (2.0)	6 (5.8)
Muscle spasms	4 (7.5)	0	4 (3.8)
Thirst	4 (7.5)	1 (2.0)	5 (4.8)
Dissociation	3 (5.7)	0	3 (2.9)
Flushing	3 (5.7)	1 (2.0)	4 (3.8)
Gait disturbance	3 (5.7)	0	3 (2.9)
Heart rate increased	3 (5.7)	0	3 (2.9)
Panic attack	3 (5.7)	1 (2.0)	4 (3.8)
Visual impairment	3 (5.7)	0	3 (2.9)

There were no new serious safety concerns found in MAPP2, including no increase in reported adverse events of special interest in the categories of suicidal ideation or behavior, cardiovascular, or MDMA abuse in the MDMA-AT group as compared to the psychotherapy with placebo group. As expected, based on the known sympathomimetic effects of the MDMA, transient increases in heart rate and blood pressure were observed during experimental sessions in a dose-dependent manner. These transient elevations in vitals did not require clinical intervention, including among the subset of participants with well-controlled hypertension. FIG. 7 shows an integrated forest plot of treatment effect for the MAPP1 and MAPP2 clinical trials.

Example 13. MPLong Clinical Trial Summary of Results.

MPLONG is an observational long-term follow-up study for MDMA-AT trial participants intended to provide data on treatment durability as measured by the CAPS-5 and Sheehan Disability Scale (SDS). Participants who elect to enroll in MPLONG completed a LTFU visit at least 6 months following their completion of the parent study. MPLONG opened for enrollment 8 months following the last subject visit of the MAPP1 trial and MAPP1 participants entered MPLONG unblinded to their treatment assignment. Enrollees from the second Phase 3 trial

MAPP2, however, complete LTFU with blinding maintained. In all cases, the primary CAPS-5 and secondary SDS assessments are conducted by a centralized blinded independent rater (IR) pool and these data have been maintained in a separate database with restricted access preventing any unplanned analyses. The statistical analysis plan for MPLONG was finalized prior to the sponsor obtaining access to these data.

Overall, 65 participants in the MDMA groups and 57 participants in the placebo groups from the MAPP1 and MAPP2 parent studies contributed to the data for this data cut (27 Feb 2023).

Durable Improvement in CAPS-5

The mean change from baseline (CFB) in CAPS-5 scores at LTFU was -28.7 in participants receiving MDMA and -16.4 in participants receiving placebo during the MAPP2 parent study (Table 35). These data suggest that improvements in CAPS-5 total severity scores were durable from the end of the study to the LTFU in both the MDMA and placebo treatment groups. Similar results were observed when analyzing the CFB in combined participants from the MAPP1 and MAPP2 parent studies.

Table 35. Change from Parent Study (MAPP1 and MAPP2) Baseline in CAPS-5 Total Severity Score.

	MDMA		Placebo	
	Actual	**CFB**	**Actual**	**CFB**
Parent Study Visits (MAPP2 Participants Only)				
Baseline, n	38		28	
Mean (SD)	39.4 (6.29)		38.8 (6.65)	
Median (Min, Max)	38.5 (29, 55)		40.0 (28, 56)	
Visit 8, n	38	38	28	28
Mean (SD)	28.1 (13.11)	-11.3 (11.86)	30.9 (10.46)	-7.9 (8.62)
Median (Min, Max)	30.5 (2, 51)	-12.0 (-40, 10)	32.5 (11, 46)	-8.5 (-26, 7)
Visit 13, n	38	38	27	27
Mean (SD)	19.7 (13.59)	-19.8 (12.57)	26.2 (10.50)	-12.6 (10.55)
Median (Min, Max)	18.0 (0, 45)	-22.0 (-41, 2)	29.0 (5, 41)	-13.0 (-33, 5)
Visit 19, n	37	37	27	27
Mean (SD)	14.8 (12.28)	-24.5 (12.29)	22.7 (12.63)	-16.0 (13.14)
Median (Min, Max)	12.0 (0, 44)	-27.0 (-44, 9)	22.0 (2, 44)	-18.0 (-40, 10)

Long Term Follow Up Study (MAPP2 Participants Only)				
Visit 1, n	38	38	28	28
Mean (SD)	10.7 (9.85)	-28.7 (10.80)	22.4 (14.04)	-16.4 (14.76)
Median (Min, Max)	8.5 (0, 37)	-30.5 (-43, 1)	22.5 (1, 47)	-16.5 (-45, 9)
Parent Study Visits (MAPP1 and MAPP2 Participants)				
Baseline, n	65		57	
Mean (SD)	40.8 (6.09)		41.2 (6.64)	
Median (Min, Max)	40.0 (29, 57)		41.0 (28, 62)	
Visit 8, n	65	65	56	56
Mean (SD)	29.5 (11.81)	-11.3 (10.53)	32.1 (10.22)	-8.9 (8.38)
Median (Min, Max)	31.0 (2, 51)	-12.0 (-40, 10)	34.0 (8, 50)	-8.5 (-29, 7)
Visit 13, n	64	64	55	55
Mean (SD)	22.0 (12.91)	-18.8 (11.40)	28.2 (11.63)	-12.9 (11.32)
Median (Min, Max)	23.0 (0, 45)	-19.0 (-41, 2)	30.0 (3, 53)	-14.0 (-34, 10)
Visit 19, n	63	63	56	56
Mean (SD)	15.9 (12.28)	-24.8 (11.57)	24.9 (12.16)	-16.3 (11.92)
Median (Min, Max)	14.0 (0, 44)	-27.0 (-45, 9)	26.5 (2, 45)	-18.0 (-40, 10)
Long Term Follow Up Study (MAPP1 and MAPP2 Participants)				
Visit 1, n	65	65	57	57
Mean (SD)	11.5 (10.39)	-29.2 (11.28)	24.9 (13.63)	-16.2 (12.99)
Median (Min, Max)	8.0 (0, 40)	-31.0 (-47, 1)	27.0 (1, 58)	-16.0 (-45, 15)

A sensitivity analysis was conducted to determine whether there was a detectable difference in the observed trend dependent on the time elapsed since the parent study (Table 36). There was no observable impact of the time window, as durability was maintained in both those with LFTU within a year and those with LTFU greater than 12 months after study termination.

Table 36. Sensitivity Analysis of Change from Study Termination in CAPS-5 Total Severity Score by Time Window (MAPP1 and MAPP2).

	MDMA		**Placebo**	
	Actual	**Change from Study Termination**	**Actual**	**Change from Study Termination**
Study Termination[a], n	65		57	
Mean (SD)	16.4 (12.57)		25.1 (12.11)	
Median (min, max)	15.0 (0, 44)		27.0 (2, 45)	

LTFU 6-12 Months[b], n	30	30	24	24
Mean (SD)	11.9 (10.29)	-3.7 (6.76)	23.7 (14.07)	0.0 (9.12)
Median (min, max)	9.0 (0, 37)	-2.5 (-19, 8)	24.5 (1, 47)	-0.5 (-16, 26)
LTFU > 12 Months[b], n	35	35	33	33
Mean (SD)	11.2 (10.61)	-5.9 (11.64)	25.8 (13.45)	-0.3 (10.25)
Median (min, max)	6.0 (0, 40)	-5.0 (-30, 17)	28.0 (2, 58)	2.0 (-26, 20)

a Last available assessment in the parent study (MAPP1 or MAPP2) b Each subject was included in 1 of the 2 visit windows only

Assessment of Relapse

Durability of response and frequency of relapse following a treatment response, loss of diagnosis, or remission was also assessed (Table 37). A higher proportion of patients in the MDMA group compared to the placebo group still met the definition of treatment response at LTFU (MDMA: 58 [89.2%]; placebo: 34 [59.6%]), loss of diagnosis (MDMA: 54 [83.1%]; placebo: 23 [40.4%]), or remission (MDMA: 39 [60%]; placebo: 14[24.6%]).

In addition, there was a low incidence of relapse following treatment response or loss of diagnosis (MDMA: 8 [12.3%]; placebo: 14 [24.6%]), and an even lower incidence of relapse following remission (MDMA: 3 [4.6%]; placebo: 3 [5.3%]).

Table 37. Responder Analysis at the LTFU Visit (MAPP1 and MAPP2).

Category	**Response Criteria**	**Statistic**	**MDMA (n = 65) n (%)**	**Placebo (n = 57) n (%)**
Durable Treatment Response	≥ 10 pt reduction in CAPS-5 TSS from BL at study termination and LTFU[a]	Meets criteria	58 (89.2)	34 (59.6)
		Does not meet criteria	7 (10.8)	23 (40.4)
Durable Loss of Diagnosis	≥ 10 pt reduction in CAPS-5 TSS from BL **and** not meeting PTSD diagnostic criteria at LTFU	Meets criteria	54 (83.1)	23 (40.4)
		Does not meet criteria	11 (16.9)	34 (59.6)
Durable Remission	≤ 11 CAPS-5 TSS from BL not meeting PTSD diagnostic criteria at LTFU	Meets criteria	39 (60.0)	14 (24.6)
		Does not meet criteria	26 (40.0)	43 (75.4)
Relapse after Treatment Response	≥ 10 point reduction in CAPS-5 TSS from BL **and** ≥ 10 point increase from study termination at LTFU[a]	Meets criteria	4 (6.2)	7 (12.3)
		Does not meet criteria	61 (93.8)	50 (87.7)
Relapse after Loss	≥ 10 point reduction in CAPS-5 TSS from BL	Meets criteria	4 (6.2)	7 (12.3)

of Diagnosis	**and** not meeting PTSD diagnostic criteria at study termination **and** ≥ 10 point increase and meeting PTSD diagnostic criteria at LTFU[a]	Does not meet criteria	61 (93.8)	50 (87.7)
Relapse of Remission	≤ 11 CAPS-5 TSS from BL **and** not meeting PTSD diagnostic criteria at study termination **and** > 11 CAPS-5 TSS at LTFU[a]	Meets criteria	3 (4.6)	3 (5.3)
		Does not meet criteria	62 (95.4)	54 (94.7)

Note: subjects can be included in more than one category

a Study termination is the visit for the last available assessment in the parent study (MAPP1 or MAPP2)

Various embodiments of the features of this disclosure are described herein. However, it should be understood that such embodiments are provided merely by way of example, and numerous variations, changes, and substitutions can occur to those skilled in the art without departing from the scope of this disclosure. It should also be understood that various alternatives to the specific embodiments described herein are also within the scope of this disclosure.

WHAT IS CLAIMED IS:

1. A composition comprising 3,4-methylenedioxymethamphetamine (MDMA), or a pharmaceutically acceptable salt and/or solvate thereof, and one or more pharmaceutically acceptable excipients, wherein the average particle size is from about 50 μm to about 400 μm.

2. The composition of claim 1, wherein the average particle size is from about 75 μm to about 200 μm.

3. The composition of claim 1 or 2, wherein the average particle size is from about 100 μm to about 200 μm.

4. The composition of any one of claims 1-3, wherein the average particle size is from 100 μm to 200 μm.

5. The composition of any one of claims 1-4, wherein the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof is substantially pure.

6. The composition of any one of claims 1-5, wherein the MDMA, or a pharmaceutically acceptable salt and/or solvate thereof is substantially free of MDMA·HCl monohydrate.

7. A dosage form comprising the composition of any one of claims 1-6, and optionally one or more additional pharmaceutically acceptable excipients.

8. The dosage form of claim 7, wherein the dosage form comprises from about 1 mg to about 150 mg of MDMA or a pharmaceutically acceptable salt and/or solvate thereof, on a free base basis of MDMA, or a pharmaceutically acceptable salt and/or solvate thereof.

9. The dosage form of any one of claims 7-8, wherein the MDMA or a pharmaceutically acceptable salt and/or solvate thereof is MDMA hydrochloride (MDMA·HCl).

10. The dosage form of any one of claims 7-9, wherein the dosage form comprises about 40 mg to about 60 mg MDMA·HCl.

11. The dosage form of any one of claims 7-10, wherein the dosage form comprises one or more additional excipients.

12. The dosage form of any one of claims 7-11, wherein the one or more additional excipients are independently selected from a diluent and a lubricant.

13. The dosage form of any one of claims 7-12, wherein the dosage form comprises a diluent and a lubricant.

14. The dosage form of any one of claims 12-13, wherein the diluent is a sugar alcohol.

15. The dosage form of any one of claims 12-14, wherein the diluent has a moisture content from about 0 to about 0.25% by mass, prior to blending.

16. The dosage form of any one of claims 12-15, wherein the lubricant comprises a pharmaceutically acceptable salt of a saturated fatty acid.

17. The dosage form of any one of claims 12-16, wherein the lubricant is a pharmaceutically acceptable salt of a saturated fatty acid.

18. The dosage form of any one of claims 7-17, wherein the dosage form comprises magnesium stearate.

19. The dosage form of any one of claims 7-18, w

20. The dosage form of any one of claims 7-19, wherein the dosage form is an oral dosage form.

21. The dosage form of claim 20, wherein the dosage form is a capsule.

22. The dosage form of claim 20, wherein the dosage form is a tablet.

23. A method of treating a subject in need thereof, comprising administering to the subject the dosage form of any one of claims 7-22.

24. The method of claim 23, wherein the method comprises treating post-traumatic stress disorder (PTSD) in the subject.

25. The method of any one of claims 23-24, wherein the dosage form comprises one or more individual dosage units.

26. The method of any one of claims 23-25, wherein the individual dosage units are administered during a single psychotherapy session.

27. The method of any one of claims 23-26, wherein the dosage form comprises three individual dosage units.

28. The method of claim 27, wherein the first and second of the individual dosage units are administered at the same time; and the third individual dosage unit is administered after the first and second individual dosage units during the psychotherapy session.

29. The method of claim 28, wherein the third individual dosage unit is administered about 1.5 hours to about 2 hours after the first and second individual dosage units.

ABSTRACT

This disclosure describes particles comprising 3,4-methylenedioxymethamphetamine (MDMA) or a pharmaceutically acceptable salt and/or solvate thereof, dose forms comprising same, and uses thereof, for example, for treating a disorder in a subject in need of such treatment.

FIG. 1

FIG. 2

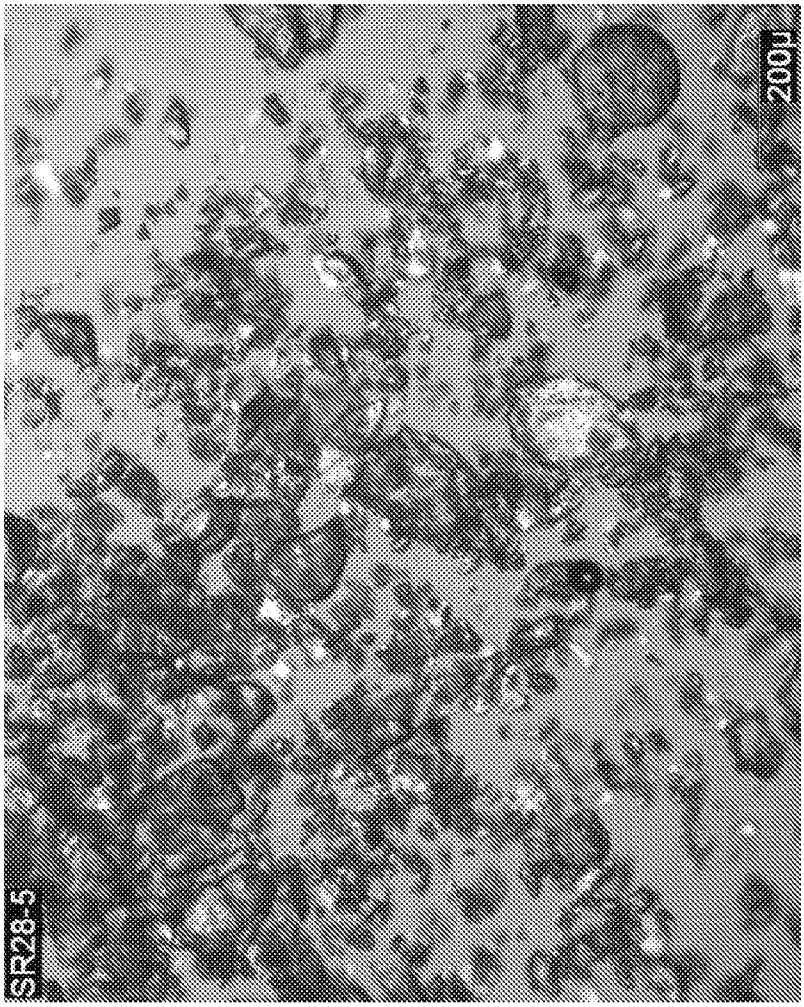
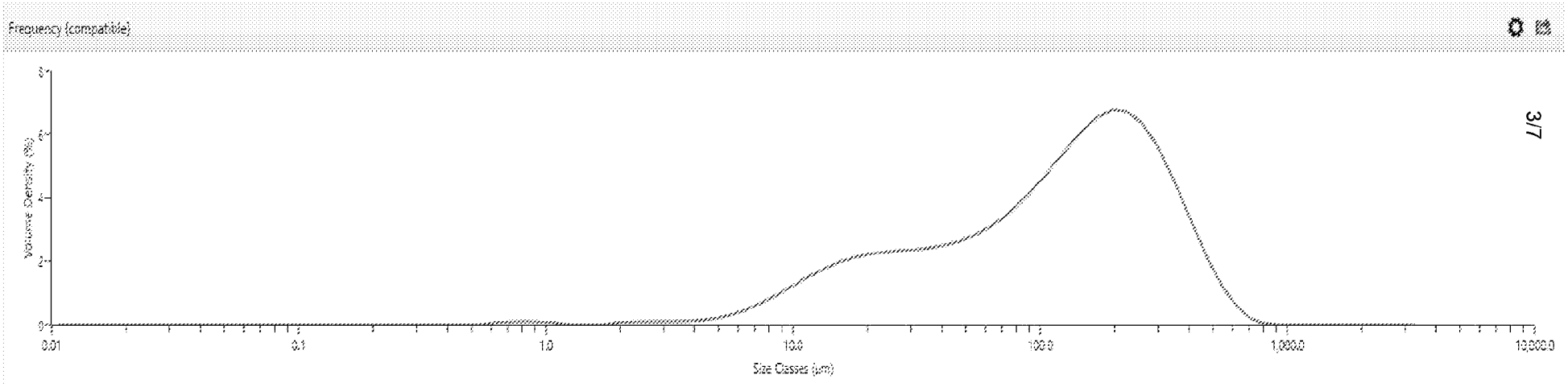


FIG. 3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Volume Density (%)
0
2
4
6
8
0.01
0.1
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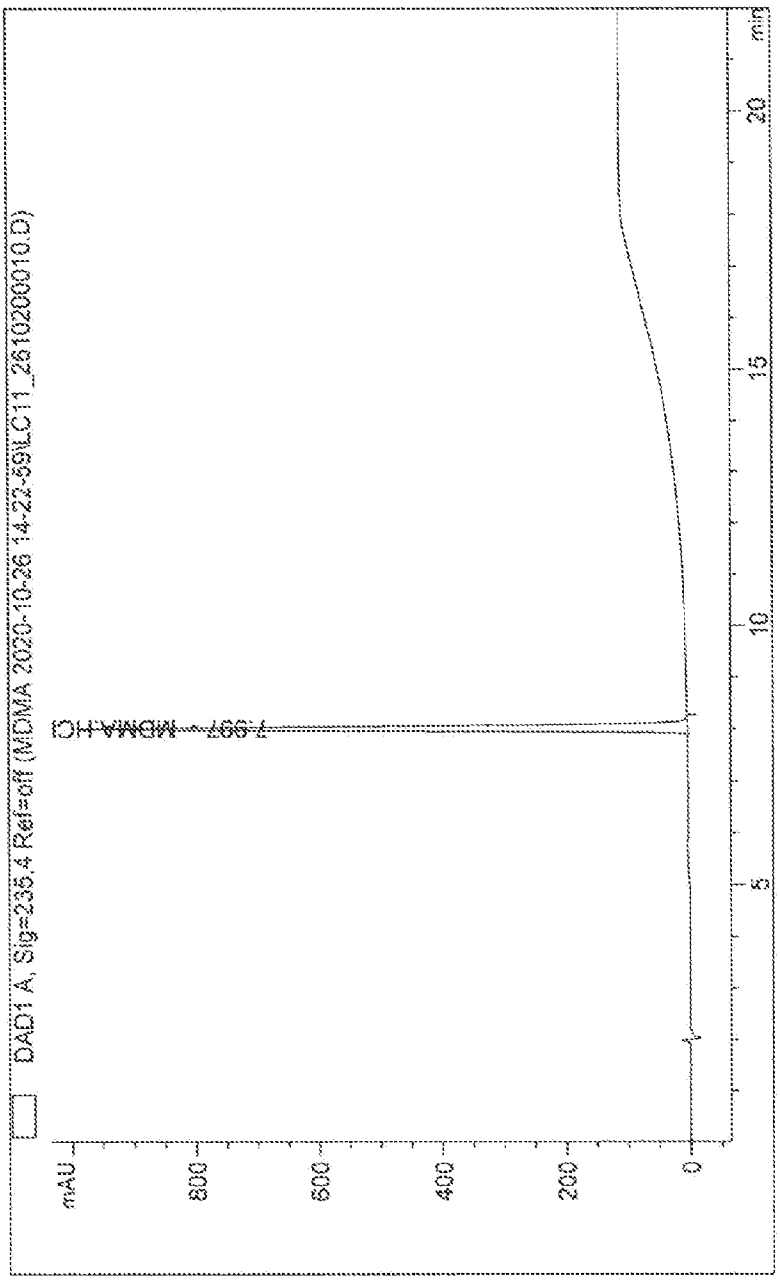
10.0
100.0
1,000.0
10,000.0
Size Classes (µm)

FIG. 4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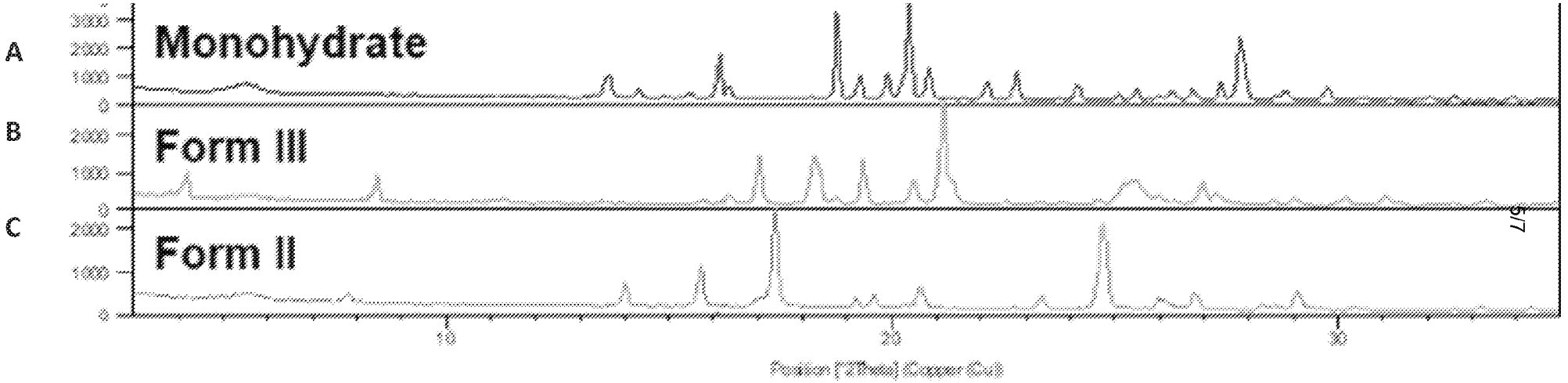
mAU
800
600
400
200
0
7.997 - MDMA-HCl
5
10
15
20
min

FIG. 5



See Nair, et al., ACS Omega 20022, 7, pp. 900-907

FIG. 6

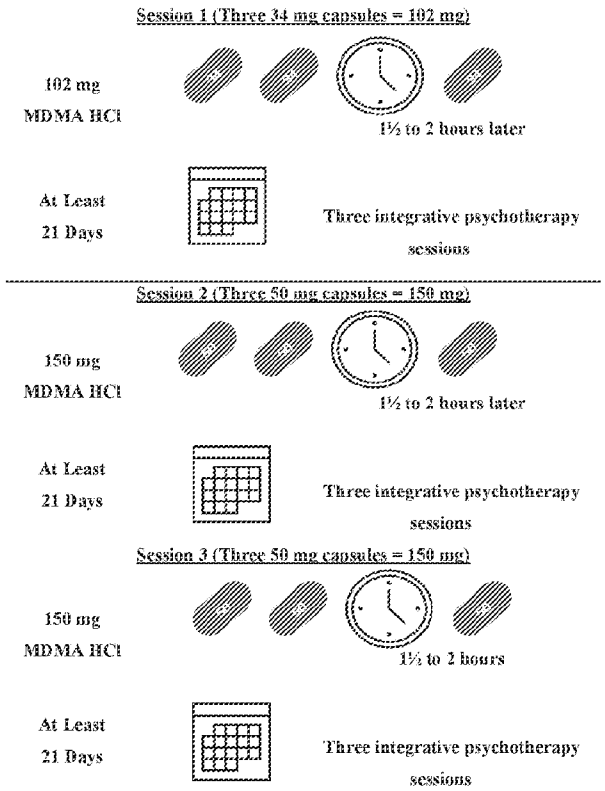
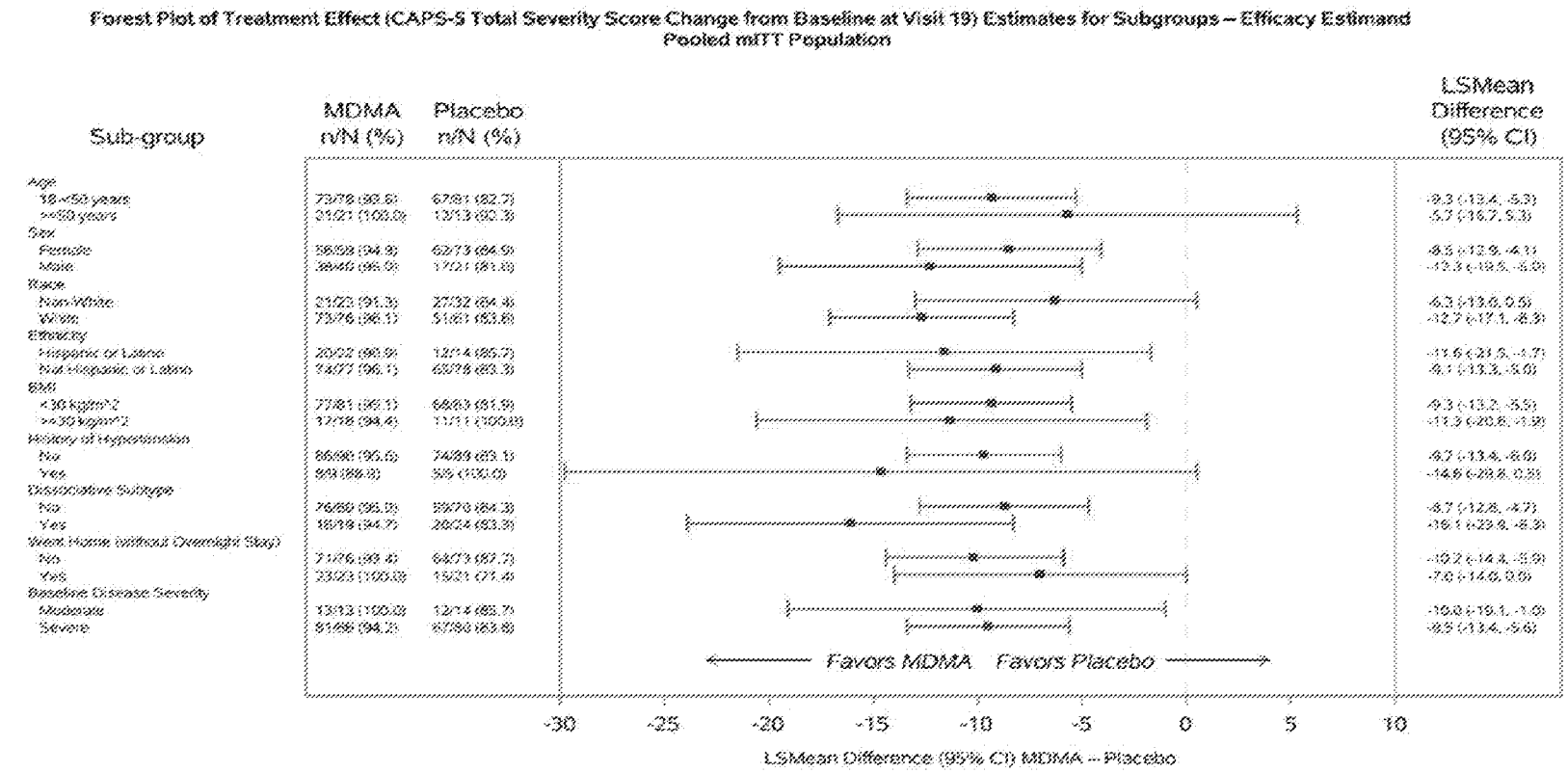

Session 1 (Three 34 mg capsules = 102 mg)
102 mg
MDMA HCl
1½ to 2 hours later
At Least
21 Days
Three integrative psychotherapy sessions
Session 2 (Three 50 mg capsules = 150 mg)
150 mg
MDMA HCl
1½ to 2 hours later
At Least
21 Days
Three integrative psychotherapy sessions
Session 3 (Three 50 mg capsules = 150 mg)
150 mg
MDMA HCl
1½ to 2 hours
At Least
21 Days
Three integrative psychotherapy sessions

FIG. 7



CAPS-5 = Clinician Administered PTSD Scale for DSM-5. Note: The Pooled mITT Population is all randomized subjects who received at least one dose of study treatment and have at least one post baseline CAPS-5 assessment. CAPS-5 Total Severity Scores range from 0 to 80; a change from baseline <0 indicates improvement. LS Mean difference <0 favors MDMA. Note: for the efficacy estimand, prior to summarizing data, all data collected after treatment discontinuation is set to missing.

LS Mean and SE are obtained from a Mixed Model for Repeated Measures (MMRM), with treatment group, visit, treatment group by visit interaction, site, study, and dissociative subtype (except for Dissociative Subtype subgroup) as fixed effects, subject as a random effect, and baseline CAPS-5 as a covariate. An unstructured covariance matrix is used.

Electronic Acknowledgement Receipt

EFS ID:	47931136
Application Number:	63463169
International Application Number:	
Confirmation Number:	8325
Title of Invention:	COMPOSITIONS COMPRISING MDMA AND METHODS OF USING SAME
First Named Inventor/Applicant Name:	. .
Customer Number:	26191
Filer:	William Turner Spencer III/Kristine McGuirk
Filer Authorized By:	William Turner Spencer III
Attorney Docket Number:	54925-0003P02
Receipt Date:	01-MAY-2023
Filing Date:	
Time Stamp:	15:48:26
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$120
RAM confirmation Number	E202351F49146722
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Provisional Cover Sheet (SB16)	54925_0003P02_Transmittal.pdf	134234 cc6dda36d613df29d9e50b4598cce7795c6e9b94	no	2
Warnings:					
This is not a USPTO supplied Provisional Cover Sheet SB16 form.					
Information:					
2	Application Data Sheet	54925_0003P02_ADS.pdf	2225638 4ff634adc9f3a5d44436cbaff9782b6fcda25c6f	no	8
Warnings:					
Information:					
Given Name of First Inventor is a mandatory data field in the Application Data Sheet (ADS) form and is incorrectly entered in the attached form. You may remove the form to add the required data in order to correct the Informational Message or if you chose not to, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. By default, the USPTO will use the data inputted in the Application Data web screen that was entered via the EFS Web interface and the ADS information will be manually reviewed and keyed into USPTO systems.					
3		54925_0003P02_Specification.pdf	537541 c35cda0f4ffe7089b66c1d0d786580e4d99bf50e	yes	100

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	96
Claims	97	99
Abstract	100	100

Warnings:					
Information:					
4	Drawings-other than black and white line drawings	54925_0003P02_Figs.pdf	1764386 614e90c3437fe37fe13f2645864e3e4db219e7b2	no	7
Warnings:					

Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	37408 56df343fdb576394f81fe18daf265ad262d19445	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	4699207	

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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