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Food and Drug Administration
Center For Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

May 14, 2014

RE: IND 101,825; Serial No. 0011

Annual report for LSD-Assisted Psychotherapy for Anxiety associated with advanced-stage life threatening diseases

Attention: Ann Sohn, Pharm.D. LT USPHS, Regulatory Project Manager

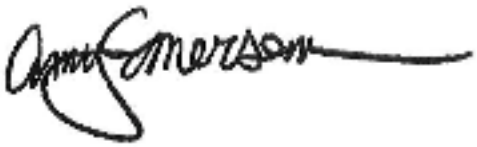
Dear CDER Staff:

Enclosed is the annual report for U.S. IND 101,825, LSD-Assisted Psychotherapy for anxiety associated with advanced-stage life threatening diseases. This report contains a brief summary of the clinical, nonclinical, and CMC issues that have occurred during the reporting period of February 28, 2013 to February 28, 2014.

This clinical trial is now complete, and the Final Report was submitted to FDA in September 2013.

Please do not hesitate to call me if you have questions or need additional information. Thank you very much for your assistance.

Sincerely,



Amy Emerson
Director of Clinical Research
MAPS

Enclosures:
Annual report, dated May 14, 2014

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Multidisciplinary Association for Psychedelic Studies (MAPS)

d-lysergic acid diethylamide (LSD)

U.S IND 101,825

Serial Number: 0011

ANNUAL REPORT

February 28, 2013 through February 28, 2014

May 14, 2014

MAPS

1215 Mission St.
Santa Cruz, CA 95060
USA

ANNUAL REPORT

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1. SUMMARY

This is the sixth annual report submitted by the Multidisciplinary Association for Psychedelic Studies (MAPS), a research and educational organization, sponsoring research into LSD-assisted psychotherapy to reduce anxiety in people confronting life-threatening illnesses under IND 101,825.

Lysergic acid diethylamide is an ergoline that was first synthezied by Hofmann in 1943. It is one of the first classic psychedelic (hallucinogenic) compounds studied in humans, producing changes in perception, emotion and cognition, including sometimes strong changes in perception of self and the self in relation to the external world. It acts on multiple serotonin receptors, with psychoactive effects likely due to activity at serotonin 5HT2A receptors.

The sponsor has completed an exploratory pilot study of LSD in combination with psychotherapy to treat anxiety at end of life, comparing anxiety before and after experimental sessions with 200 vresus 20 mcg LSD. Findings from this report are promising, suggesting that LSD-assisted psychotherapy reduced anxiety two months after the second of the two experimental sessions.

2. INDIVIDUAL STUDY INFORMATION

This annual report covers the period from February 28, 2013 through February 28, 2014. The following is a cumulative listing of all studies using LSD under US-IND. There were no MAPS studies for LSD conducted that were not under US-IND.

Protocol, Study Title, Phase, Country, Subject Population, Number of Subject Planned/Entered Treatment/Completed Treatment/Dropped Treatment, Relevant Product and Status during Reporting Period can be found in the Table 1.1 Summary of Clinical Trials.

Table 1.1: Summary of Clinical Trials

Protocol	Study Title	Phase	Subject Population	No. of Subjects	Relevant Product	Status During Reporting Period
LDA-1	LSD – assisted psychotherapy in persons suffering from anxiety associated with advanced-stage life-threatening diseases: A Phase-2, double-blind, placebo-controlled dose-response pilot study	2	Women and men 18 or older diagnosed with the advanced stage of an illness with a substantially reduced life expectancy	12 planned 12 entered treatment 12 completed treatment 0 dropped treatment 10 entered follow-up 1 dropped follow-up 9 completed follow-up	4 Subjects at 20 µg LSD, followed by open label extension at 200 µg LSD and 8 subjects at 200 µg LSD	Completed

3.2 Protocol LDA-1

Title: LSD – assisted psychotherapy in persons suffering from anxiety associated with advanced-stage life-threatening diseases: A Phase 2, double-blind, placebo-controlled dose-response pilot study.

Purpose: To develop a treatment method for LSD-assisted psychotherapy for people confronting anxiety relating to advanced-stage illnesses and to gather preliminary evidence on the safety and efficacy of this treatment in this population using current scientific standards.

Amendments During the Reporting Period: There have been no amendments during the reporting period.

Subject Population: Males and females suffering from anxiety associated with advanced-stage life-threatening diseases 18 years of age or older. The number of subjects reported below is the cumulative number for the reporting period.

Number of Subjects Planned	12
Number of Subjects Enrolled	12
Number of Subjects Dropped	0
Number of Subjects Completed Experimental Sessions	12
Number of Subjects Entered Follow-Up Extension	10
Number of Subjects Dropped Follow-Up Extension	1
Number of Subjects Completed Follow-Up Extension	9

Demographics: See Appendix A for summary of subject enrollment by demographic factors based on final Sponsor database listings from the study.

Status: The study has been completed and the Final Report was submitted in September,

3. SUMMARY INFORMATION

3.3 Clinical Safety

3.1.1. Summary of Serious Adverse Events (SAEs)

No SAEs occurred during the reporting period.

See Appendix B for cumulative final Sponsor database listings on SAEs reported to MAPS from studies conducted under US-IND.

3.1.2. Summary of Adverse Events

No severe adverse events occurred during the reporting period.

See Appendix C for cumulative final Sponsor database listings on severe Adverse Events reported to MAPS from studies conducted under US-IND.

3.1.3. Summary of IND Safety Reports

There have been no IND Safety Reports during the reporting period.

3.1.4. Summary of Deaths

There have been no deaths during the reporting period.

See Appendix D cumulative final Sponsor database listings on deaths reported to MAPS from studies conducted under US-IND.

3.1.5. Summary of Dropouts

No subjects dropped out during the reporting period.

3.1.6. Brief Description of Findings

Shortly after the reporting period, a research report containing findings from the study described above appeared electronically in the Journal of Nervous and Mental Disorrders, and it will appear in print subsequent to electronic publication. No SAEs related to drug administration or withdrawals caused by AEs occurred during the study. Sixteen severe related AEs were collected during the study, with 15 recorded during 200µg LSD sessions and one recorded during a 20µg LSD session. All severe related AEs were self-limiting, with only 3 AEs persisting until the day after treatment (2 Feeling Cold, 1 Feeling Abnormal). All related AEs returned to baseline by two days after the intervention, and none required treatment. Five severe AEs unrelated to drug administration were collected during the study, and all but one was caused by the qualifying life-threatening illness. One subject received notice from their oncologist that the qualifying cancer had been cured during the study prior to the final outcome assessment. The subject received this news 4.5 years ago and remains cancer-free to this day. Due to the rare event of a cancer cure, and the influence of this on the subject's diagnosis of Reactive Anxiety, this subject was excluded from final analysis.

After adjusting for multiplicity, reductions in state anxiety two months after LSD-assisted psychotherapy with 200µg LSD as compared with active placebo were statistically significant in this small sample. The effect size of the comparison was 1.2 on state anxiety, indicating a large effect. Reductions in trait anxiety at the same assessment were trending towards significance after the multiplicity adjustment. The effect size of the comparison was 1.1 on trait anxiety, which also indicates a large effect. However, only two of eight participants scored below the cut-off of 40 on state and trait anxiety at the two-month follow-up. Gains made in anxiety reduction seen two months after the final treatment were still present an average of 16.4 ± 4.3 months later. Consistent with the literature, subjects who received 200µg LSD experienced greater acute changes in consciousness than active placebo, and neither dose of LSD produced major changes in heart rate or blood pressure on average. The results of this small exploratory pilot study are promising and suggest that continued research into LSD-assisted psychotherapy for people facing anxiety associated with potentially life-threatening illnesses in larger studies is warranted.

3.2. Nonclinical Data

No new nonclinical studies were performed during the reporting period.

3.3. Chemistry, Manufacturing, and Controls

The final LSD treatment session took place on May 26, 2011, and the remaining study drug has been returned to the manufacturer, Lipomed AG, Arlesheim, Switzerland.

4. SAFETY FINDINGS FROM NON-INTERVENTIONAL STUDIES

No new safety information was obtained from non-interventional studies during the reporting period.

5. OTHER CLINICAL TRIAL/STUDY SAFETY INFORMATION

No new safety information was obtained from randomized clinical trials not supported by the sponsor during the reporting period

6. SAFETY FINDINGS FROM MARKETING EXPERIENCE

The investigational product has not been approved for marketing in any country.

7. LITERATURE

No new safety findings were published during the reporting period.

8. OTHER ANNUAL REPORTS

No other annual reports about MDMA were submitted by the sponsor during the reporting period.

9. NEW GENERAL INVESTIGATIONAL PLAN

The rationale for LSD research is to re-evaluate the therapeutic potential of LSD-assisted psychotherapy and to develop a method that is safe and efficacious for patients with anxiety associated with an advanced-stage life-threatening illness. Based on the findings and estimates of effect size obtained from this study, future pilot studies may be planned to further optimize the double-blind and number of sessions of LSD-assisted psychotherapy.

10. REVISED INVESTIGATOR'S BROCHURE

The most recent version of the Investigator's Brochure has been submitted to FDA.

11. SIGNIFICANT PROTOCOL MODIFICATIONS

There have been no significant protocol modifications during the reporting period.

12. SUMMARY OF SIGNIFICANT FOREIGN MARKETING DEVELOPMENTS

LSD is not currently approved for marketing authorization elsewhere in the world.
There were no foreign marketing developments during the reporting period.

13. LOG OF ANY OUTSTANDING BUSINESS

None.

14. CONCLUSION

MAPS is interested in developing LSD-assisted psychotherapy as an approved treatment for anxiety when facing a life-threatening illness. Findings from the exploratory study, LDA1, are promising. No drug-related serious adverse events occurred during the study, and severe, expected drug-related adverse events were transient. MAPS may pursue future investigations into the safety and efficacy of this treatment.

Appendix A: All Studies Demographics*

Study	Subject No.	Age	Sex	Height/ cm	Weight /Kg	Ethnicity	Treatment Group	Diagnosis
LDA1	101	43	M	189	79	White European	200µg	Gastric Carcinoma, non metastatic
LDA1	102	43	M	170	61	White European	20µg	Renal Carcinoma, non metastatic
LDA1	103	46	M	180	68	White European	20µg	Very severe Migraine Disease**
LDA1	104	57	M	173	57	White European	200µg	Gastric Carcinoma, metastatic
LDA1	105	62	F	175	69	White European	20µg	Breast Cancer
LDA1	106	46	M	180	65	White European	200µg	Gastric Cancer
LDA1	107	62	F	168	57	White European	200µg	Breast Cancer
LDA1	108	39	F	174	92	White European	200µg	Breast Cancer
LDA1	109	64	M	173	81	White European	20µg	Non-Hodgkin Lymphoma
LDA1	110	60	M	178	69	White European	200µg	Parkinson's Disease
LDA1	111	43	F	173	69	White European	200µg	Breast Cancer
LDA1	112	47	M	174	58	White European	200µg	Bechterew's Disease

** Based on final CRFs collected from sites and analyzed from the sponsor database listings*
***This subject was enrolled as a protocol deviation based on previous history of suicidality caused by severe chronic pain in the form of cluster headaches. The severity of the migraine was such that a return to suicidal thinking was possible, although the subject was not suicidal at the time of enrollment. The investigator indicated that Swissmedic did not criticize enrollment of this subject and that since he was conducting a pilot study, it was appropriate to interpret life-threatening as either mental or physical.*

Appendix B: All Studies Cumulative Serious Adverse Events*

Study	Subject No.	Dose	Adverse Event Diagnosis	Date of last LSD Admin.	Onset date	Resolution date	Severity	Frequency	Action taken for Study	Action taken-treatment	Action Taken Other Specify	Outcome	Relationship to Drug
LDA1	104	200µg	Metastatic esophageal cancer	29-Jan-09	Before dosing	26-Oct-09	Severe	Continuous	None	None	Hospitalization	Death	None
LDA1	105	20µg	Inflammation of renal basin	1-Oct-09	26-Feb-10-	Ongoing	Severe	Continuous	None	Prescription Medication	Hospitalization	Persists, diminishing	None

* *Based on final CRFs collected from sites and analyzed from the sponsor database listings.*

Appendix C: All Studies Cumulative Severe Unrelated Adverse Events*

Study	Subject No.	Dose	Adverse Event Diagnosis	Serious	Date of last LSD Admin.	Onset date	Resolution date	Frequency	Action taken for Study	Action taken-treatment	Action Taken Other Specify	Outcome	Relationship to Drug
LDA1	104	200µg	Pneumonia	N	29-Jan-09	UNK-Feb-09	UNK-Mar-09	Single/Intermittent	None	Hospitalization	None	Full Recovery	None
LDA1	104	200µg	Metastatic esophageal cancer	Y	29-Jan-09	Before dosing	26-Oct-09	Continuous	None	None	None	Death	None
LDA1	105	20µg	Inflammation of renal basin	Y	1-Oct-09	26-Feb-10-	Ongoing	Continuous	None	Procedure, Prescription Medication	None	Persists, diminishing	None
LDA1	109	20µg	Skin lesion	N	8-Jul-10	26-Aug-10	Ongoing	Continuous	None	None	None	Persists, worsening	None
LDA1	111	200µg	Tumor progression	N	2-Dec-10	UNK-Jan-11	Ongoing	Continuous	Delayed treatment	Procedure, Prescription Medication	None	Persists, worsening	None

** Based on final CRFs collected from sites and analyzed from the sponsor database listings.*

Appendix C: All Studies Cumulative Severe Related Adverse Events*

Study	Subject No.	Dose	Stage	Diagnosis	Date Last Drug Admin.	Onset Date	Date stopped being severe	Resolution Date	Serious	Frequency	Action Taken for Study	Action Taken-Treatment	Outcome
LDA1	102	20µg	1	Anxiety	18-Sep-08	18-Sep-08	18-Sep-08	18-Sep-08	N	Continuous	None	None	Return to Baseline
LDA1	104	200µg	1	Illusion	8-Jan-09	8-Jan-09	8-Jan-09	8-Jan-09	N	Continuous	None	None	Return to Baseline
LDA1	106	200µg	1	Anxiety	12-Mar-10	12-Mar-10	12-Mar-10	12-Mar-10	N	Continuous	None	None	Return to Baseline
LDA1	106	200µg	1	Derealisation	12-Mar-10	12-Mar-10	12-Mar-10	12-Mar-10	N	Continuous	None	None	Return to Baseline
LDA1	108	200µg	1	Mydriasis	16-Sep-10	16-Sep-10	16-Sep-10	16-Sep-10	N	Continuous	None	None	Return to Baseline
LDA1	110	200µg	1	Feeling Abnormal	9-Dec-10	9-Dec-10	9-Dec-10	9-Dec-10	N	Continuous	None	None	Return to Baseline
LDA1	104	200µg	1	Illusion	29-Jan-09	29-Jan-09	29-Jan-09	29-Jan-09	N	Continuous	None	None	Return to Baseline
LDA1	106	200µg	1	Anxiety	26-Mar-10	26-Mar-10	26-Mar-10	26-Mar-10	N	Continuous	None	None	Return to Baseline
LDA1	106	200µg	1	Illusion	26-Mar-10	26-Mar-10	26-Mar-10	26-Mar-10	N	Continuous	None	None	Return to Baseline
LDA1	106	200µg	1	Feeling Abnormal	26-Mar-10	26-Mar-10	26-Mar-10	26-Mar-10	N	Continuous	None	None	Return to Baseline
LDA1	108	200µg	1	Affect Liability	23-Dec-10	23-Dec-10	23-Dec-10	23-Dec-10	N	Continuous	None	None	Return to Baseline
LDA1	112	200µg	1	Feeling Cold	17-Feb-11	17-Feb-11	18-Feb-11	18-Feb-11	N	Continuous	None	None	Return to Baseline
LDA1	103	200µg	2	Feeling abnormal	18-Dec-08	18-Dec-08	19-Dec-08	19-Dec-08	N	Continuous	None	None	Return to Baseline
LDA1	103	200µg	2	Illusion	18-Dec-08	18-Dec-08	18-Dec-08	18-Dec-08	N	Continuous	None	None	Return to Baseline
LDA1	105	200µg	2	Feeling Cold	18-Feb-10	18-Feb-10	19-Feb-10	19-Feb-10	N	Continuous	None	None	Return to Baseline
LDA1	105	200µg	2	Feeling Cold	18-Mar-10	18-Mar-10	18-Mar-10	18-Mar-10	N	Continuous	None	None	Return to Baseline

** Based on final CRFs collected from sites and analyzed from the sponsor database listings*

Appendix D: All Studies Cumulative Deaths*

Study	Subject No.	Dose	Adverse Event Diagnosis	Serious	Date of last LSD Admin.	Onset date	Resolution date	Frequency	Action taken for Study	Action taken-treatment	Outcome	Relationship to Drug
LDA1	104	200µg	Metastatic esophageal cancer	Y	29-Jan-09	Before dosing	26-Oct-09	Continuous	None	None	Death	None

** Based on final CRFs collected from sites and analyzed from the sponsor database listings.*