Functional and Sexual Disability, and Quality of Life After One Dose of MM120 (Lysergide) in Adults With Generalized Anxiety Disorder

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Introduction

GAD is one of the most common psychiatric disorders, with a prevalence of approximately 10% among adults in the United States.[1] GAD is a chronic condition that is associated with reduced health-related quality of life (HRQoL), impaired psychosocial functioning, and decreased work productivity.[2-4] Patients experience persistent, excessive anxiety and worry, along with a range of other symptoms including fatigue, muscle tension, irritability, and sleep disturbances, which can result in long-term disability.[5,6]

There are current treatment options for patients with GAD; antidepressants, a currently approved pharmacotherapy for GAD, may not be effective in alleviating symptoms that affect patient HRQoL and functioning. In addition, antidepressants can have persistent side effects, such as sexual dysfunction, and are a common reason for treatment discontinuation.[7,8] To date, research has not focused on identifying novel treatment options that improve HRQoL and well-being in patients with GAD.

MM120, a pharmaceutically optimized formulation of lysergic acid diethylamide (LSD), is a semisynthetic ergoline belonging to the group of classic serotonergic psychedelics that is being studied as a potential therapy for neuropsychiatric disorders.[9-11] Prior studies with LSD have demonstrated its ability to reduce anxiety and improve HRQoL in anxiety patients with and without life-threatening disease.[12,13]

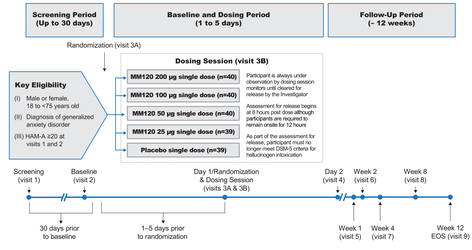
Objective

This study evaluated if single-dose MM120 results in improvements in functional disability, sexual dysfunction, and HRQoL in participants with GAD.

Methods

This phase 2b (NCT05407064) multicenter, randomized, double-blind, placebo-controlled, dose-finding study evaluated the effect of MM120 on functional disability, HRQoL, sleep quality, and sexual dysfunction in participants diagnosed with GAD. Eligible participants, as defined in **Figure 1**, were randomized equally across 5 arms to receive a single administration of MM120 at a dose of 25, 50, 100, or 200 µg; or placebo.

Figure 1: Study Design



Participants were **excluded** if they had contraindicated medical or psychiatric conditions or were taking concomitant medications, supplements, or other therapeutics that were contraindicated (eg, due to drug-drug interaction potential or anxiolytic or antidepressant function) and could not be paused.

Outcome Measures: All measures were assessed at baseline and at weeks 1, 2, 4, 8, and 12; the Pittsburgh Sleep Quality Index (PSQI) was not assessed at weeks 1 and 2.

- Functional disability was measured by the Sheehan Disability Scale (SDS). SDS is a self-rated scale that assesses the extent to which 3 domains in the participant's life (work, social life/leisure activities, and family life/home responsibilities) are functionally impaired by psychiatric or medical symptoms[14]
- HRQoL was measured by the EuroQoL 5-Dimension 5-Level (EQ-5D-5L). The EQ-5D-5L is used to evaluate health outcomes over a wide range of health conditions and treatments. It consists of a descriptive system that comprises 5 dimensions of health status, and a separate visual analog scale (VAS) of overall health status[15]
- Sleep quality was measured by the PSQI that assesses sleep quality and disturbances over the preceding month[16]
- Sexual dysfunction was measured by the Arizona Sexual Experience Scale (ASEX). The ASEX is a 5-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm over the past 7 days[17]

Statistical Analyses: The outcomes were measured as change from baseline. Results were summarized using means, mean differences vs placebo, and their associated confidence intervals. Categorical data were summarized using the relevant number of observations and percentages.

Results

A total of 554 participants were screened for eligibility between August 24, 2022, and August 30, 2023. Of these, 198 participants were randomized to receive a single administration of MM120 25 (n=39), 50 (n=40), 100 (n=40), or 200 µg (n=40); or placebo (n=39) constituting the randomized set. The full analysis set included all randomized participants with a valid baseline Hamilton Anxiety Rating Scale (HAM-A) assessment and at least one post-baseline HAM-A assessment.

Table 1: Baseline Characteristics and Demographics

Participant Characteristics	MM120 Dose				Placebo
	25 µg (n=39)	50 µg (n=36)	100 µg (n=40)	200 µg (n=40)	(n=39)
Mean age, years (SD)	38.0 (12.1)	45.3 (14.2)	42.7 (14.8)	42.1 (13.5)	38.7 (12.7)
Sex, n (%)					
Female	20 (51.3)	20 (55.6)	16 (40)	28 (70)	26 (66.7)
Male	19 (48.7)	16 (44.4)	24 (60)	12 (30)	13 (33.3)
HAM-A score, mean (SD)	30.2 (6.1)	30.3 (5.7)	29.3 (6.4)	31.0 (7.0)	30.3 (6.6)
SDS total score, mean (SD)	18.7 (5.1)	17.6 (5.6)	19.2 (5.3)	19.9 (5.4)	18.9 (4.1)
EQ-5D-5L index value, mean (SD)	0.59 (0.2)	0.60 (0.25)	0.63 (0.2)	0.61 (0.2)	0.67 (0.2)
EQ VAS score, mean (SD)	65.9 (18.6)	65.3 (19.8)	67.4 (15.6)	65.7 (18.6)	66.0 (16.0)
PSQI score, mean (SD)	10.7 (3.4)	11.1 (3.4)	11.0 (3.5)	10.1 (3.3)	10.9 (4.2)

Figure 2: Mean Change in SDS Total Score – Baseline to Week 12

MM120 100 and 200 µg demonstrated consistent improvement in functional disability from weeks 1 through 12. As part of this study, we found that 100 µg had the optimal level of clinical activity on the HAM-A (data presented in poster titled P3039: Rapid and Durable Response to a Single Dose of MM120 (Lysergide) in Generalized Anxiety Disorder: A Dose-Optimization Study).

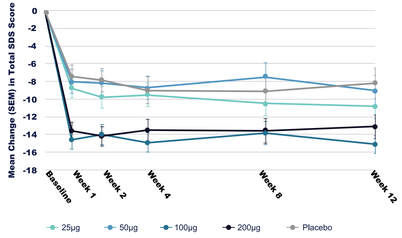


Table 2: Change From Baseline in SDS Total Score

		MM120 Dose		Placebo
		100 µg (n=40)	200 µg (n=40)	(n=39)
Week 1	Mean change	-14.6	-13.6	-7.4
	Mean difference*	-7.2	-6.2	
Week 2	Mean change	-14.0	-14.2	-7.8
	Mean difference*	-6.1	-6.4	
Week 4	Mean change	-14.9	-13.5	-9.0
	Mean difference*	-6.0	-4.5	
Week 8	Mean change	-13.8	-13.6	-9.1
	Mean difference*	-4.7	-4.4	
Week 12	Mean change	-15.1	-13.1	-8.2
	Mean difference*	-6.9	-4.9	

- The improvements in functional disability with 100 and 200 µg were evident as early as week 1 after dosing
- At week 12, the mean SDS total score with 100 and 200 µg were 3.4 and 6.3, respectively, vs 10.1 with placebo†

*Difference in mean change from baseline between MM120 and placebo.
†Higher scores indicate increased functional impairment.

Results (cont)

Figure 3: Mean Change in EQ VAS Score – Baseline to Week 12

MM120 100 and 200 µg demonstrated consistent improvement in the EQ VAS score from weeks 1 through 12.

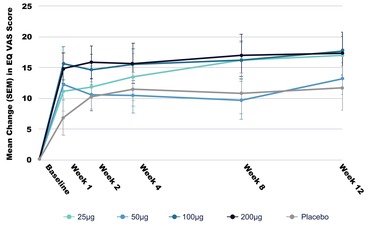


Table 3: Change From Baseline in EQ VAS Score

		MM120 Dose		Placebo
		100 µg (n=40)	200 µg (n=40)	(n=39)
Week 1	Mean change	15.7	14.9	6.9
	Mean difference*	8.8	8.0	
Week 2	Mean change	14.7	15.9	10.3
	Mean difference*	4.4	5.6	
Week 4	Mean change	15.5	14.9	11.5
	Mean difference*	4.0	4.2	
Week 8	Mean change	16.2	17.0	10.8
	Mean difference*	5.4	6.2	
Week 12	Mean change	17.7	17.3	11.7
	Mean difference*	6.0	5.6	

- At week 12, the mean EQ VAS scores with 100 and 200 µg were 85.2 and 86.3, respectively, vs 73.7 with placebo†

*Difference in mean change from baseline between MM120 and placebo.
†In the EQ VAS, scores range from 0=worst health you can imagine, to 100=best health you can imagine.

Figure 4: Mean Change in EQ-5D-5L Index Score – Baseline to Week 12

MM120 100 and 200 µg demonstrated consistent improvement in the EQ-5D-5L index score from weeks 1 through 12.

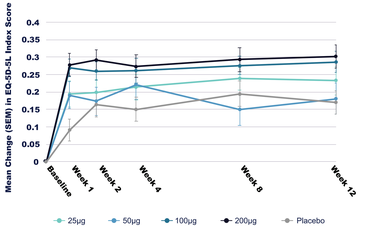


Table 4: Change From Baseline in EQ-5D-5L Index Score

		MM120 Dose		Placebo
		100 µg (n=40)	200 µg (n=40)	(n=39)
Week 1	Mean change	0.3	0.3	0.1
	Mean difference*	0.2	0.2	
Week 2	Mean change	0.3	0.3	0.2
	Mean difference*	0.1	0.1	
Week 4	Mean change	0.3	0.3	0.2
	Mean difference*	0.1	0.1	
Week 8	Mean change	0.3	0.3	0.2
	Mean difference*	0.1	0.1	
Week 12	Mean change	0.3	0.3	0.2
	Mean difference*	0.1	0.1	

- At week 12, the mean EQ-5D-5L index score was 0.9 with both 100 and 200 µg vs 0.8 with placebo

*Difference in mean change from baseline between MM120 and placebo.

Results (cont)

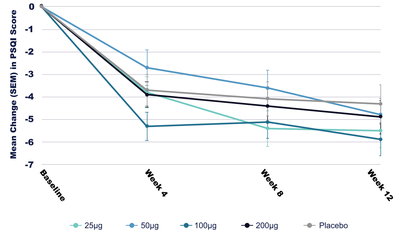
Table 5: Summary of EQ-5D-5L Responses by Dimension

EQ-5D-5L Dimension: Usual Activities	MM120 Dose		Placebo
	100 µg (n=40)	200 µg (n=40)	(n=39)
Baseline			
No problems	12	11	14
Slight problems	11	7	11
Moderate problems	12	15	11
Severe problems	5	5	3
Extreme problems	0	2	0
Week 12			
No problems	27	25	14
Slight problems	5	3	8
Moderate problems	1	2	4
Severe problems	0	1	0
Extreme problems	0	0	0
EQ-5D-5L Dimension: Pain/Discomfort	**MM120 Dose**		**Placebo**
	100 µg (n=40)	200 µg (n=40)	(n=39)
Baseline			
No problems	15	8	15
Slight problems	12	20	10
Moderate problems	11	11	13
Severe problems	2	1	1
Extreme problems	0	0	0
Week 12			
No problems	25	20	17
Slight problems	7	9	3
Moderate problems	1	2	6
Severe problems	0	0	0
Extreme problems	0	0	0
EQ-5D-5L Dimension: Anxiety/Depression	**MM120 Dose**		**Placebo**
	100 µg (n=40)	200 µg (n=40)	(n=39)
Baseline			
No problems	0	0	1
Slight problems	1	2	2
Moderate problems	21	17	19
Severe problems	12	14	17
Extreme problems	6	7	0
Week 12			
No problems	14	16	7
Slight problems	15	7	7
Moderate problems	4	6	9
Severe problems	0	1	2
Extreme problems	0	1	1

- More than twice the number of participants with 100 and 200 µg reported 'no problems' in usual activities at week 12 compared to baseline; there was no change with placebo
- There was a much larger increase from baseline in the number of participants reporting 'no problems' for pain/discomfort with 100 and 200 µg at week 12, compared with placebo
- There was an overall decrease in the number of participants reporting 'severe/extreme problems' in the anxiety/depression dimension with 100 and 200 µg from baseline to week 12; there was a similar decrease in the number of participants reporting 'severe problems' with placebo and an increase in those reporting 'extreme problems'

Figure 5: Mean Change in PSQI Score – Baseline to Week 12

Sleep quality scores improved with both MM120 and placebo from baseline to week 12.



Results (cont)

Table 6: Change From Baseline in PSQI Score

		MM120 Dose		Placebo
		100 µg (n=40)	200 µg (n=40)	(n=39)
Week 4	Mean change	-5.3	-3.9	-3.7
	Mean difference*	-1.6	-0.2	
Week 8	Mean change	-5.1	-4.4	-4.1
	Mean difference*	-1.0	-0.3	
Week 12	Mean change	-5.9	-4.9	-4.3
	Mean difference*	-1.6	-0.6	

- At week 12, the mean PSQI score with 100 and 200 µg was 4.9 and 5.1, respectively, vs 7.3 with placebo†

*Difference in mean change from baseline between MM120 and placebo.
†Higher scores indicate more severe difficulty in all areas.

Figure 6: ASEX Dysfunction Rates in Male Participants

The number of male participants who reported sexual dysfunction at week 12 compared to baseline decreased by more than 60% with 100 µg and 100% with 200 µg. The number of male participants in the placebo group who reported sexual dysfunction was similar at baseline and week 12. This decrease from baseline in the number of participants with sexual dysfunction in the MM120 high-dose groups is particularly relevant due to the much higher proportion of participants with sexual dysfunction who received 100 and 200 µg vs placebo at baseline. The differences at baseline are likely due to a low n number and because there was no stratification.

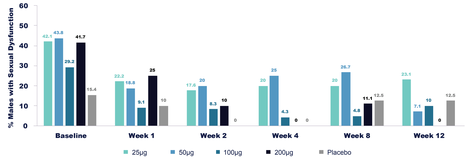
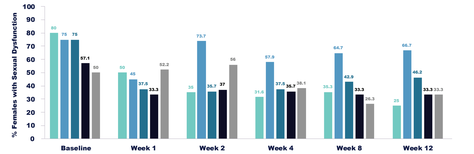


Figure 7: ASEX Dysfunction Rates in Female Participants

With 100 and 200 µg, there was a reduction of almost 40% in the number of female participants who reported sexual dysfunction at week 12 compared to baseline. A reduction of approximately 30% was observed with placebo. This decrease from baseline in the number of participants with sexual dysfunction with 100 µg is particularly relevant due to the much higher proportion of participants with sexual dysfunction who received 100 µg vs placebo at baseline.



Conclusions

In participants with moderate-to-severe GAD, a single dose of MM120 100 and 200 µg demonstrated clinically meaningful improvement in functional disability, HRQoL, and sexual dysfunction. Improvements in functional disability were evident as early as week 1 post dose and were sustained through the 12-week study period. The higher doses of MM120 were also associated with improvement in different domains of the EQ-5D-5L including usual activities and pain/discomfort that were not observed with placebo. In contrast with placebo, there was an improvement from baseline in the proportion of male participants with sexual dysfunction with 100 and 200 µg. For female participants, although there was an improvement from baseline in sexual dysfunction with 100 and 200 µg, a similar, but slightly lower improvement was also observed in the placebo group. Overall, this study demonstrates that a novel treatment, MM120, is associated with improvement in anxiety symptoms as well as overall HRQoL and functioning in persons with GAD.

References

1. Ringeisen H, et al. Mental and Substance Use Disorders Prevalence Study (MDPS): Findings Report. RTI International. 2023. https://www.rti.org/publication/mental-and-substance-use-disorders-prevalence-study/fulltext.pdf 2. Harnarn N et al. *Different Views of Anxiety Disorders*. 2011; 199-218 3. Locke AB, et al. *Am Fam Physician*. 2015;91(9):617-624. 4. Barrera TL, et al. *J Anxiety Dis*. 2009;23(8):1086-1090. 5. Patriquin MA, Mathew SJ. *Chronic Stress (Thousand Oaks)*. 2017;1:2470547017703593. 6. Henchiks SM, et al. *BMC Psychiatry*. 2016;16:248. 7. Gartlehner G, et al. *Ann Intern Med*. 2011;155(11):772-785. 8. Kavan MG, et al. *Am Fam Physician*. 2009;79(9):785-791. 9. Jastrzebiak MK, et al. *Molecules*. 2022; 27:7322. 10. Fuentes JJ, et al. *Front Psychiatry*. 2019;10:943. 11. Reiff CM, et al. *Am J Psychiatry*. 2020;177:5. 12. Gasser P, et al. *J Nerv Mental Dis*. 2014;212:513-520. 13. Holze F, et al. *Biol Psychiatry*. 2023;93:215-223. 14. Sheehan KH, Sheehan DV. *Int Clin Psychopharmacol*. 2008;23(2):70-83. 15. Herdman M, et al. *Qual Life Res*. 2011;20(10):1727-1736. 16. Buysse DJ, et al. *Psychiatry Res*. 1989;28(2):193-213. 17. McGahuey CA, et al. *J Sex Marital Ther*. 2000;26(1):25-40.

Abbreviations:
ASEX, Arizona Sexual Experience Scale; **EOS**, end of study; **DSM-V**, Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; **EQ-5D-5L**, EuroQoL-5 Dimension-5 Level; **EQ VAS**, EuroQoL Visual Analog Scale; **GAD**, generalized anxiety disorder; **HAM-A**, Hamilton Anxiety Rating Scale; **HRQoL**, health-related quality of life; **LSD**, lysergic acid diethylamide; **PSQI**, Pittsburgh Sleep Quality Index; **SD**, standard deviation; **SDS**, Sheehan Disability Scale; **SEM**, standard error of the mean; **VAS**, visual analog scale.

Disclosures:
JJ, RB, CC, JMF, PLJ, SMK, DRK, TMS, MHW are employees of Mind Medicine, Inc. RR is employed by Numinus and has stock ownership in Numinus.
EF has no conflicts of interest to disclose.

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