Phase 3 Topline Results of DT120 (Lysergide) in Major Depressive Disorder

Poster 115

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Background

- Major depressive disorder (MDD) is a complex condition that is associated with significant impairment of psychosocial functioning and quality of life.[1] MDD is episodic; however, the likelihood of recurrence is high, and almost 80% of patients experience at least 1 additional episode during their lifetime[2]
- Despite numerous treatment options for MDD, many patients do not experience a complete resolution of symptoms with standard-of-care treatments, which can often take several weeks to produce clinically meaningful effects and can be associated with significant side effects[2-4]
- DT120 orally disintegrating tablet (ODT) is an ergoline derivative belonging to the group of classic serotonergic psychedelics, which acts as a partial agonist at serotonin-2A (5-HT2A) receptors. DT120 ODT is currently under development for the treatment of MDD
- The observed efficacy findings are consistent with the proposed mechanism of action of DT120 100 µg and are aligned with findings from prior clinical development results[5]

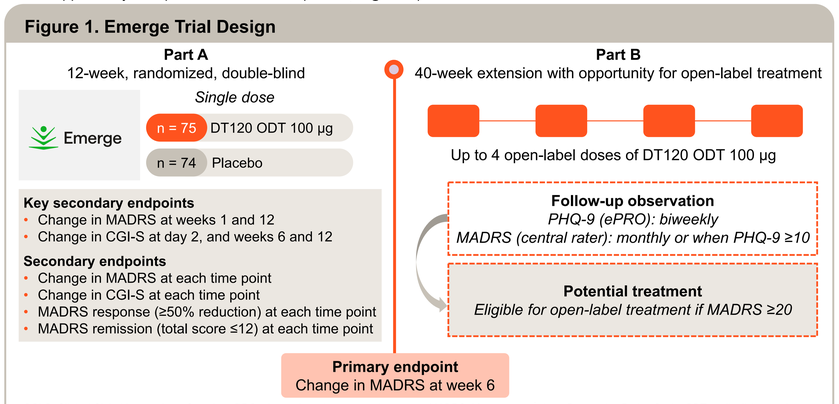
Objective

- To report topline efficacy and safety results from Emerge (NCT06941844), a phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluating a single 100-µg dose of DT120 in adults with MDD

Methods

- Participants between 18 and 74 years of age with a primary diagnosis of MDD were enrolled. Eligible participants had a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of ≥26, had a Clinical Global Impressions–Severity (CGI-S) score of ≥4, and were experiencing a major depressive episode of ≥8 weeks and ≤24 months in duration
- Participants were excluded if they had medical or psychiatric conditions that were contraindicated, or if they were taking concomitant medications, supplements, or other therapeutics with potential drug–drug interactions or anxiolytic or antidepressant effects and could not be discontinued
- The study consisted of a 12-week, randomized, double-blind, single-dose administration period in which participants were randomized 1:1 to DT120 or placebo (Part A), followed by a 40-week extension phase where participants had the opportunity for open-label treatment (Part B, **Figure 1**)

Figure 1. Emerge Trial Design



CGI-S, Clinical Global Impressions–Severity; ePRO, electronic patient-reported outcome; MADRS, Montgomery-Åsberg Depression Rating Scale; ODT, orally disintegrating tablet; PHQ-9, Patient Health Questionnaire-9.

Results

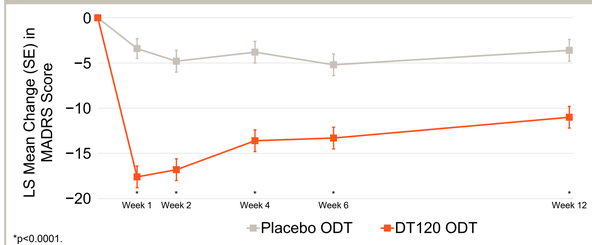
- A total of 423 participants were screened for eligibility. Of these, 149 participants were randomized 1:1 to receive a single administration of 100 µg of DT120 (n = 75) or placebo (n = 74; **Table 1**)
- DT120 met the primary endpoint, demonstrating a significant 8.1-point placebo-adjusted improvement in MADRS at week 6 (p<0.0001)
- Significant improvements were observed as early as week 1 and were maintained through week 12, with a 7.3-point placebo-adjusted improvement at the end of the double-blind period (p<0.0001; **Figure 2**)
- Key secondary endpoints were met with a 17.6-point improvement in MADRS from baseline at week 1 (p<0.0001), and 1.0-point, 1.2-point, and 1.0-point improvements from baseline in Clinical Global Impressions–Severity (CGI-S) at day 2, week 6, and week 12, respectively (p<0.0001). Secondary endpoints were also met, including significant improvements in CGI-S scores at all time points (**Figure 3**)
- Participants who received DT120 demonstrated significantly higher response and remission rates at week 6 compared with those who received placebo, supporting the clinical relevance of the observed effects (**Figure 4**)
- The treatment effect was maintained across key subgroups, including in participants with ≥2 failed prior lines of treatment (**Figure 5**)
- DT120 was generally well tolerated. No serious adverse events (AEs), suicidal behavior, or self-injurious behavior were reported during the study
- The AE profile was consistent with prior studies of DT120.[5] Most (99%) AEs reported for DT120 ODT were mild to moderate in severity. No treatment-emergent AEs (TEAEs) led to study withdrawal (**Table 2**). The most common TEAEs were illusion, euphoric mood, and nausea. The majority of TEAEs occurred on the dosing day. The most common TEAE reported after the dosing day was headache
- Average time to End-of-Session Checklist (EoSC) clearance was 5.8 hours. Over half of participants met EoSC criteria at hour 5, and all participants met EoSC by hour 8 (**Figure 6**)

Table 1. Demographics and Baseline Characteristics[a]

Participant characteristics	DT120 ODT n = 75	Placebo ODT n = 74	Overall N = 149
Age, mean (range), years	45 (20–73)	42 (22–70)	44 (20–73)
Sex, n (%)			
Female	37 (49)	31 (42)	68 (46)
Male	38 (51)	43 (58)	81 (54)
Race, n (%)			
American Indian or Alaska Native	0	1 (1)	1 (1)
Asian	8 (11)	5 (7)	13 (9)
Black or African American	14 (19)	8 (11)	22 (15)
Native Hawaiian or Other Pacific Islander	0	0	0
White	48 (64)	51 (69)	99 (66)
Not reported	1 (1)	3 (4)	4 (3)
Unknown	0	1 (1)	1 (1)
Multiple	4 (5)	5 (7)	9 (6)
Baseline MADRS score, mean (SD)[b]	35.0 (5.0)	34.0 (3.7)	34.5 (4.4)
MDD severity based on MADRS score, n (%)			
Moderate (20–30)	15 (20)	10 (14)	25 (17)
Severe (≥31)	60 (80)	64 (86)	124 (83)
Baseline CGI-S score, mean (SD)[c]	4.7 (0.6)	4.8 (0.6)	4.8 (0.6)
Past psychedelic use, n (%)			
Any psychedelic[d]	13 (17)	10 (14)	23 (15)
LSD	3 (4)	3 (4)	6 (4)
Length of current depressive episode			
Mean months (SD)	8.8 (5.0)	8.9 (5.8)	8.9 (5.4)
<1 year, n (%)	60 (80)	52 (70)	112 (75)
1–2 years, n (%)	15 (20)	22 (30)	37 (25)
>2 years, n (%)	0	0	0
Number of lifetime depressive episodes			
Mean (SD)	5.5 (3.5)	6.2 (5.4)	5.8 (4.6)
1–2, n (%)	24 (32)	25 (34)	49 (33)
3–4, n (%)	26 (35)	21 (28)	47 (32)
≥5, n (%)	25 (33)	28 (38)	53 (36)
Number of past antidepressants prescribed, n (%)			
0	18 (24)	23 (31)	41 (28)
1	16 (21)	13 (18)	29 (19)
≥2	41 (55)	38 (51)	79 (53)

[a]Based on ITT population.
[b]MADRS is a 10-item clinician-rated outcome measure assessing various domains of depression with a range of 0–60. In Emerge, MADRS ratings were assessed by central raters blinded to both treatment assignment and visit number.
[c]The CGI-S is a clinician-rated outcome measure assessing overall severity of illness with a range of 1 to 7.
[d]Psychedelics include LSD, psilocybin, dimethyltryptamine, and other classic serotonergic psychedelics.
CGI-S, Clinical Global Impressions–Severity; ITT, intention-to-treat; LSD, lysergic acid diethylamide; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; ODT, orally disintegrating tablet; SD, standard deviation.

Figure 2. MADRS Change From Baseline Through Week 12[a,b]

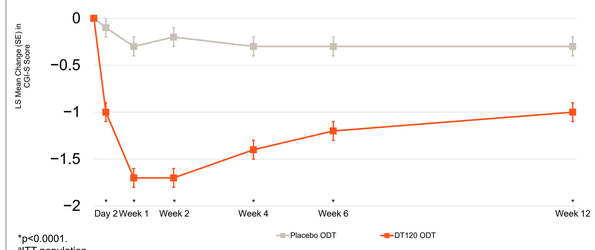


Change from baseline[b]
- Week 1: −17.6 points
- Week 4: −13.6 points
- Week 6: −13.3 points
- Week 12: −11.0 points

Improvement over placebo[b]
- Week 1: −14.2 points
- Week 4: −9.8 points
- Week 6: −8.1 points
- Week 12: −7.3 points

*p<0.0001.
[a]ITT population.
[b]Primary endpoint of the study was change from baseline in MADRS at week 6 using a mixed-effects model repeated-measures statistical analysis with reference-based imputation.
ITT, intention-to-treat; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; ODT, orally disintegrating tablet; SE, standard error.

Figure 3. CGI-S Change From Baseline Through Week 12[a,b]

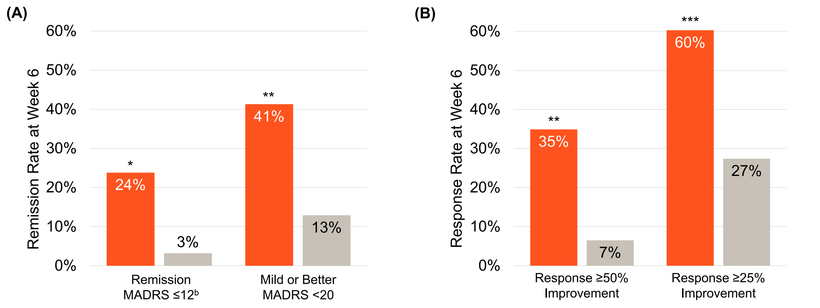


Change from baseline[b]
- Day 2: −1.0 points
- Week 1: −1.7 points
- Week 4: −1.4 points
- Week 6: −1.2 points
- Week 12: −1.0 points

Improvement over placebo[b]
- Day 2: −0.9 points
- Week 1: −1.4 points
- Week 4: −1.1 points
- Week 6: −0.9 points
- Week 12: −0.7 points

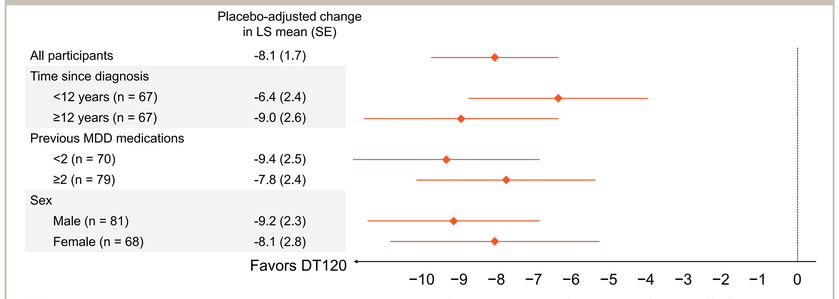
*p<0.0001.
[a]ITT population.
[b]Key secondary endpoint of the study was change in CGI-S at week 6 using a mixed-effects model repeated-measures statistical analysis with reference-based imputation.
CGI-S, Clinical Global Impressions–Severity; ITT, intention-to-treat; LS, least squares; ODT, orally disintegrating tablet; SE, standard error.

Figure 4. MADRS (A) Remission and (B) Response Rates at Week 6[a]



*p<0.01; **p<0.001; ***p<0.0001.
[a]ITT population.
[b]Using a cutoff of MADRS ≤10, remission rates were 24% for DT120 ODT compared with 3% for placebo ODT.
ITT, intention-to-treat; MADRS, Montgomery-Åsberg Depression Rating Scale; ODT, orally disintegrating tablet.

Figure 5. Subgroup Analysis of Change in MADRS Score From Baseline at Week 6[a-c]



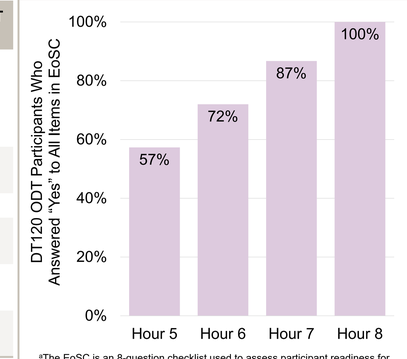
[a]ITT population.
[b]Data presented as LS mean ± SE.
[c]For each subgroup, the change from baseline in MADRS total score was analyzed using the same mixed-effects model repeated-measures model as the primary efficacy analysis. If the number of patients was small for a subgroup, the treatment difference is not stable as it is highly sensitive to outliers.
ITT, intention-to-treat; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; SE, standard error.

Table 2. Summary of AEs Reported During Part A of the Emerge Study

AE	DT120 ODT n = 75	Placebo ODT n = 74
Any TEAE, n (%)	74 (99)	42 (57)
Mild	45 (61)	31 (74)
Moderate	28 (38)	11 (26)
Severe	1 (1)[a]	0
Any study drug–related TEAE, n (%)	74 (99)	24 (32)
Any AESI, n (%)	71 (95)	15 (20)
Any treatment-emergent SAE, n (%)	0	0
Any TEAE leading to discontinuation, n (%)	0	0
Any TEAE leading to death, n (%)	0	0

[a]SAE was recurrence of chronic back pain occurring approximately 6 weeks after dosing.
AE, adverse event; AESI, AE of special interest; ODT, orally disintegrating tablet; SAE, serious AE; TEAE, treatment-emergent AE.

Figure 6. Time to EoSC Clearance[a]



[a]The EoSC is an 8-question checklist used to assess participant readiness for completion of monitoring after receiving DT120.
EoSC, End-of-Session Checklist; ODT, orally disintegrating tablet.

Conclusions

- Significant improvements in MADRS total score were observed by week 1 and sustained through week 12
- CGI-S scores significantly improved at all time points following dosing day
- DT120 demonstrated a favorable safety profile, with no serious AEs
- These findings following a single administration of DT120 support its continued development as a potential treatment option for patients with MDD

References

1. Christensen M, et al. *Front Psychiatry*. 2020;11:280. 2. Malhi G, et al. *Lancet*. 2018;392(10161):2299-312. 3. Fava M, et al. *Neuron*. 2000;28(2):335-41. 4. Machado-Vieira R, et al. *Pharmaceuticals*. 2010;3(1):19-41. 5. Robison R, et al. *JAMA*. 2025;334(15):1358-72.

Acknowledgments

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Disclosures

JGS is the owner of Uptown Research Institute. TMS, PLJ, JJ, SMK, JMF, CC, RB, and DRK are employees of Definium Therapeutics, Inc.

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