DT120 for Major Depressive Disorder: Number Needed to Treat (NNT) and Number Needed to Harm (NNH)

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Background

- Major depressive disorder (MDD) is one of the most common psychiatric disorders, affecting an estimated 10.4% of adults annually in the United States[1]
- MDD is characterized by substantial physical and psychological symptoms, and approximately 90% of lifetime cases are classified as moderate to severe[1]
- 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
- Emerge (NCT06941844), a phase 3, multicenter, randomized, double-blind, placebo-controlled study (Part A), evaluated the efficacy and safety of DT120 in adults diagnosed with MDD[2]
- Number needed to treat (NNT) and number needed to harm (NNH) are measures of effect size often calculated to contextualize the clinical relevance of trial results[3]
  - NNT refers to the number of participants needed to identify an additional therapeutic benefit when compared with placebo[3]
  - Conversely, NNH indicates the number of participants needed before encountering an adverse outcome of interest[3]

Objective

- This post hoc analysis evaluated the clinical benefit-risk profile of a single 100-µg administration of DT120 in adults with MDD using NNT and NNH estimates derived from Emerge Part A study data

Methods

- Patients eligible for enrollment in the phase 3 study included adults aged 18 to 74 years with a primary diagnosis of MDD and a baseline Montgomery-Åsberg Depression Rating Scale (MADRS) total score of ≥26
- Participants received a single dose of DT120 100 µg or placebo. The study's primary outcome was the change in total MADRS score from baseline to week 6 with additional secondary endpoint measurements
- NNT (95% confidence interval [CI]) was calculated as the inverse of the absolute risk reduction for DT120 vs placebo for the following outcomes:
  - Clinical response (≥50% or ≥25% reduction in MADRS score from baseline)
  - Clinical improvement (Clinical Global Impression–Improvement [CGI-I] score of 1 or 2)
  - Clinical remission (MADRS score ≤12)
  - Mild or better symptoms (MADRS score <20)
- NNH (95% CI) was calculated as the inverse of the absolute risk increase for adverse event (AE) outcomes, including discontinuation due to treatment-emergent AEs (TEAEs; defined as AEs with onset after the dose or that were a consequence of a preexisting condition that worsened since baseline) and TEAEs by severity
- NNTs and NNHs were calculated to 1 decimal place (0.X) and subsequently rounded up to the next highest whole number[3]

Results

- A total of 149 patients were included in the Emerge study (DT120, n = 75; placebo, n = 74). Demographics and baseline characteristics are presented in **Table 1**
- NNT analyses used the intention-to-treat population (n = 149), defined as all randomly assigned participants; NNH analyses used the safety population (n = 149), defined as all patients who received study treatment

EFFICACY

- At week 6 (primary endpoint), the response rate for a ≥50% improvement in MADRS score from baseline was 34.9% (22/63) for DT120 vs 6.5% (4/62) for placebo (**Figure 1, Table 2**)
  - With a threshold of ≥25%, response rates increased to 60.3% (38/63) vs 27.4% (17/62)
- At week 6, 38.1% (24/63) of patients in the DT120 arm achieved CGI-I scores of 1 or 2 (corresponding to "much improved" or "very much improved"), compared with 5.1% (3/59) in the placebo arm (**Figure 1**)
- NNTs ranged between 2 and 4 for different definitions of response and improvement (**Table 2**)
- At week 6, remission (MADRS score ≤12) was achieved by 23.8% (15/63) of patients in the DT120 arm, compared with 3.2% (2/62) in the placebo arm. Rates of mild or better depression symptoms (MADRS score <20) were 41.3% (26/63) and 12.9% (8/62), respectively (**Figure 2**)
- NNTs ranged from 3 to 5 for remission and 2 to 4 for patients achieving mild or better symptoms (**Table 3**)

TOLERABILITY

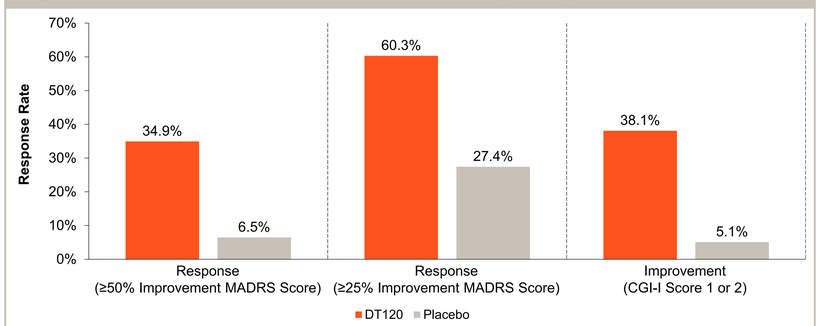
- Overall, no TEAEs led to study discontinuation in either arm; therefore, NNH for this outcome could not be calculated
- Most TEAEs were reported as mild, with NNHs corresponding to 6, 5, and 75 for mild, moderate, and severe, respectively
  - Almost all (99%) of AEs were mild to moderate in severity, with 1 severe AE reported as a recurrence of chronic back pain occurring approximately 6 weeks after dosing
  - Most TEAEs occurred and resolved on the dosing day
- No indication of increased suicidal ideation or suicide-related risk was noted as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)

Table 1. Patient Demographics and Baseline Characteristics[a]

Participant characteristics	DT120 n = 75	Placebo 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, 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]CGI-S is a clinician-rated outcome measure assessing overall severity of illness with a range of 1–7.
[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; SD, standard deviation.

Figure 1. Clinical Response Rates for DT120 vs Placebo (Week 6)



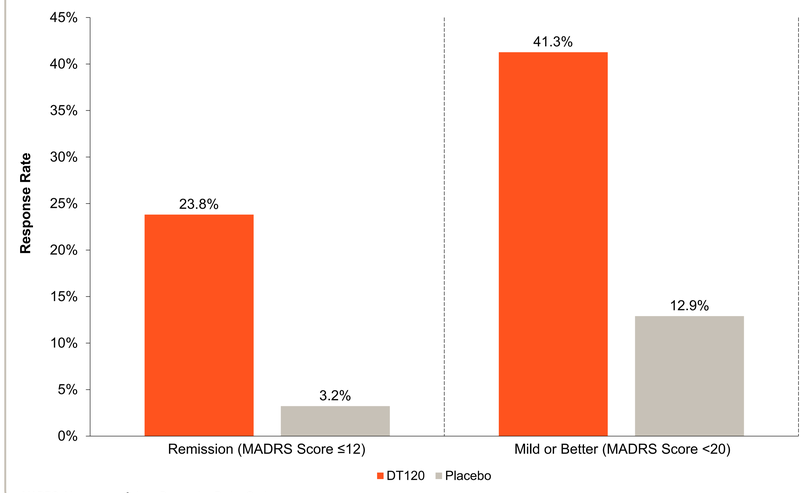
CGI-I, Clinical Global Impression–Improvement; MADRS, Montgomery-Åsberg Depression Rating Scale.

Table 2. Response Rates and NNTs for DT120 vs Placebo (Weeks 1–6)

	DT120 n/N (%)	Placebo n/N (%)	NNT (95% CI)
Response (≥50% improvement in MADRS score from baseline)[a]			
Week 1	39/67 (58)	2/61 (3)	**2 (2, 3)**
Week 6	22/63 (35)	4/62 (6)	**4 (3, 7)**
Response (≥25% improvement in MADRS score from baseline)			
Week 1	47/67 (70)	9/61 (15)	**2 (2, 3)**
Week 6	38/63 (60)	17/62 (27)	**3 (2, 7)**
Improvement (CGI-I score of 1 or 2)[b]			
Week 1	42/68 (62)	3/62 (5)	**2 (2, 3)**
Week 6	24/63 (38)	3/59 (5)	**3 (3, 6)**

[a]MADRS ranges from 0 to 60, where higher scores indicate greater severity of depressive symptoms.
[b]CGI-I ranges from 1 to 7 and measures the degree of improvement or worsening in a patient's condition relative to baseline at the start of treatment. Scores of 1 and 2 correspond to "very much improved" and "much improved," respectively.
CGI-I, Clinical Global Impressions–Improvement scale; CI, confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale; NNT, number needed to treat.

Figure 2. Remission Rates for DT120 vs Placebo (Week 6)



MADRS, Montgomery-Åsberg Depression Rating Scale.

Table 3. Clinical Remission Rates and NNTs for DT120 vs Placebo (Weeks 1–6)

	DT120 n/N (%)	Placebo n/N (%)	NNT (95% CI)
Remission (MADRS score ≤12)[a]			
Week 1	28/67 (42)	2/61 (3)	**3 (2, 4)**
Week 6	15/63 (24)	2/62 (3)	**5 (4, 11)**
Mild or better (MADRS score <20)[a]			
Week 1	41/67 (61)	3/61 (5)	**2 (2, 3)**
Week 6	26/63 (41)	8/62 (13)	**4 (3, 8)**

[a]MADRS ranges from 0 to 60, where higher scores indicate greater severity of depressive symptoms.
CI, confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale; NNT, number needed to treat.

Discussion

- In Emerge, the NNTs for a single 100-µg dose of DT120 (relative to placebo) ranged between 2 and 4 for clinical response (≥50% improvement in MADRS score) and 3 and 5 for clinical remission (MADRS score ≤12) through week 6 (primary endpoint)
- Although dependent on the outcome, typically a single-digit NNT (ie, NNT <10) and a double-digit NNH (ie, NNH ≥10) for a severe AE indicate a favorable treatment[3]
- A previously published Cochrane review, consisting of 14 studies, evaluated selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) vs placebo for the treatment of MDD[4]
  - Nearly all studies were of short duration, typically 6 to 8 weeks[4]
  - NNTs for reductions in depressive symptoms ranged from 7 to 8 (median, 7) for SSRIs and from 7 to 16 (median, 9) for TCAs. NNTs specific to remission were not reported[4]

Conclusions

- The low NNTs (ie, <10) for both response and remission are consistent with clinically relevant improvements in depressive symptoms
- Overall, the treatment was well tolerated, with most AEs being mild in severity and limited to the dosing day
- At week 6, for every 4 patients treated with DT120 instead of placebo, 1 additional patient achieved response, and for every 5 patients treated, 1 additional patient achieved remission
- These findings support DT120 as a highly effective, rapid-acting, oral treatment for adults with MDD that provides substantial clinical benefit following a single administration

References

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Acknowledgments

The study was funded by Definium Therapeutics, Inc. Medical writing and editorial support were provided by Jamie Maze, PharmD, MPH, of Red Nucleus and funded by Definium Therapeutics, Inc.

Disclosures

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