Phase 3 trial design and methodology: treatment with DT120 (lysergide) in Major Depressive Disorder (MDD)

Todd Solomon[1], Paula Jacobsen[1], Sarah Karas[1], Keisha Novak[1], Craig Conant[1], Jamileh Jemison[1], Kara Curry[1], Robert Barrow[1], Daniel Karlin[1]

[1]Definium Therapeutics, Inc., New York, NY, USA

Background

- Psychedelic clinical trials present distinct methodological challenges including functional unblinding, expectancy effects, safety monitoring during dosing sessions, and evaluation of the durability of treatment effects.
- Emerge and Ascend are complementary Phase 3 MDD trials designed in alignment with FDA recommendations[1] to translate contemporary psychedelic-trial methodology into a registrational program.

Methodological Issue being Addressed

We focus on key design considerations including participant selection, mitigation strategies for functional unblinding, selection of comparators, safety monitoring, and long-term follow-up. Here we describe the rationale for these decisions and illustrate how regulatory guidance was translated into a registrational psychedelic development program for adults with MDD.

Introduction

- The Phase 3 DT120 MDD program was designed to enhance interpretability of efficacy and safety findings and address challenges unique to psychedelic clinical trials.
- A two-part study structure was designed chosen: Part A evaluates acute efficacy and safety after a single administration; Part B prospectively evaluates durability of response, recurrence of symptoms, and retreatment patterns over 40 weeks.
- Additional design features include independent eligibility confirmation, centralized efficacy assessments, prospective assessment of expectancy, evaluation of perceived treatment assignment, and standardized non-directive support from trained Dosing Session Monitors (DSMs)

Methods

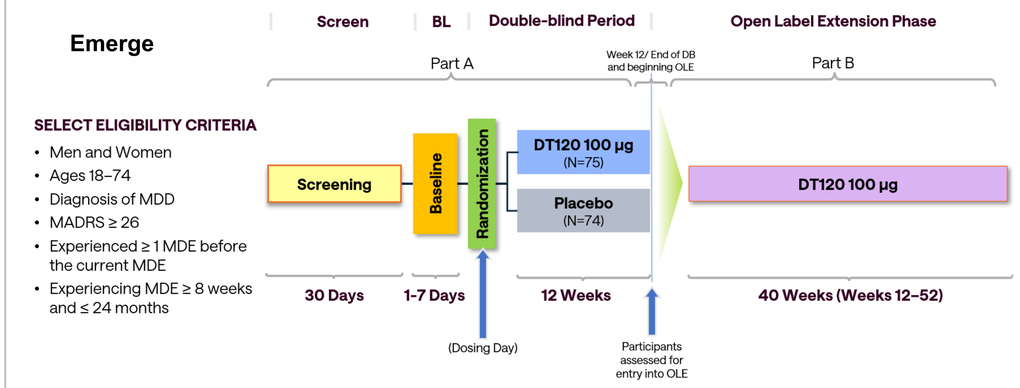
Table 1. Key Methodological Features

Feature		Why it matters
Eligibility framework	Site assessment plus central Montgomery–Åsberg Depression Rating Scale (MADRS) interview; final independent diagnostic confirmation before dosing.	Enhanced diagnostic accuracy and consistency reduced site-level variability.
Randomization and Masking	Site-stratified randomization; central raters blinded to treatment, visit number and dosing. Site blinded from primary endpoint scores	Minimizes allocation rater and site bias.
Expectancy and functional unblinding	Expectancy assessed at baseline; perceived treatment assignment assessed post-dose; Ascend includes 50ug comparator to better preserve blinding.	Allows quantification and mitigation of expectancy and functional unblinding effects.
Dosing-session procedures	Non-directive support from trained DSMs; no psychotherapy; monitored by 2 qualified DSMs with 3 trained DSMs onsite; observation for minimum of 8 hours	Promotes participant safety and standardization while isolating the pharmacologic treatment effect.
End-of-session readiness	End of Session Checklist (EOSC) beginning at 5 hours and repeated hourly until criteria are met.	Ensures participant stability before discharge; enhances safety monitoring
Durability and retreatment	Biweekly PHQ-9 in Part B; central MADRS assessment confirms symptom recurrence; retreatment criteria: PHQ-9 ≥ 10, MADRS ≥ 20, no safety concerns, >4 weeks since prior dose, maximum 4 Part B doses.	Prospective, standardized framework for durability assessment and retreatment decisions.
Statistical framework	Part A primary endpoint analyzed using mixed models for repeated measures (MMRM) in ITT population; primary comparison is 100 ug versus placebo, key secondary endpoint is CGI-S.	Appropriate handling of repeated measures and multiplicity maintains statistical integrity.

Phase 3 Program Overview

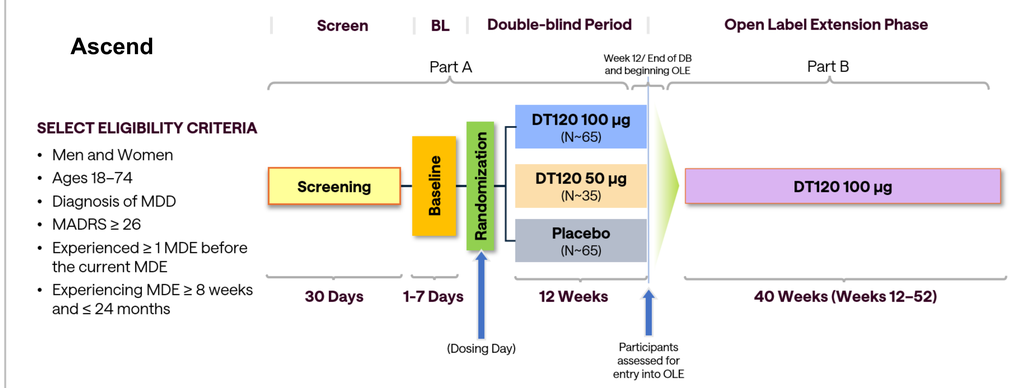
- Both studies enroll adults aged 18-74 with MDD, MADRS ≥26 and CGI-S ≥4 at screening and baseline.
- Emerge and Ascend share a 12-week double-blind Part A and a 40-week extension Part B.

Figure 1. Emerge Study Design



BL, baseline; DB, double-blind; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; N, number of subjects; OLE, open label extension.

Figure 2. Ascend Study Design



BL, baseline; DB, double-blind; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; N, number of subjects; OLE, open label extension.

Table 2. Comparative Design and Methodology

Characteristic	Emerge (DT120-310)	Ascend (DT120-311)
Population	Adults 18-74 years with DSM-5 MDD; MADRS ≥26; CGI-S ≥4	Adults 18-74 years with DSM-5 MDD; MADRS ≥26; CGI-S ≥4
Planned randomized N	149	~165
Randomization	1:1	2:1:2
Part A treatment groups	DT120 100 µg or placebo	DT120 100 µg, DT120 50 µg, or placebo
Primary endpoint	Change from baseline to week 6 in MADRS total score	Change from baseline to week 6 in MADRS total score
Key secondary endpoint	Change from baseline to week 6 in CGI-S score	Change from baseline to week 6 in CGI-S score
Central assessment	Blinded central raters for MADRS; SAFER interview during screening	Blinded central raters for MADRS; SAFER interview during screening
Masking strategy	Placebo-controlled	Placebo-controlled plus 50 µg comparator
Part B design	40-week extension with symptom monitoring and possible open-label retreatment	40-week extension with symptom monitoring and possible open-label retreatment
Distinguishing feature	---	50 µg methodological comparator to address functional unblinding

Results

These studies address a central challenge in psychedelic drug development; generating interpretable confirmatory evidence when treatment effects may be accompanied by recognizable acute subjective effects. The combination of centralized assessment, structured eligibility confirmation, expectancy measurement, and comparator strategy is intended to strengthen internal validity without altering the episodic-treatment model. This approach seeks to balance methodological rigor with clinical reality.

Table 3. Operational Feasibility

Metric	Emerge (DT120-310)	Ascend (DT120-311)
Independent eligibility confirmation and standardized DSM training	Successfully implemented across sites.	
Collection of expectancy assessments and perceived treatment assignment	97%	---
Mean DEA submission-to-approval time	45.4 days (27 sites)	16.2 days (21 sites)
Mean site-selection-to-activation time	35.7 weeks	14.6 weeks

Key Takeaways

- Contemporary psychedelic confirmatory trials require bias-mitigation strategies that extend beyond conventional placebo control.
- Independent eligibility confirmation helps ensure appropriate participants and may reduce site-level variability.
- Inclusion of a lower-dose comparator and blinded central outcome assessment may help quantify and mitigate functional unblinding[1,2].
- Standardized non-directive support and explicit separation from psychotherapy help isolate pharmacologic treatment effect.
- Longitudinal Part B follow-up provides a prospective framework for evaluating durability, symptom recurrence, and retreatment needs.
- These approaches may help improve reproducibility and interpretability across future registrational psychedelic programs.

Conclusions

Successful operationalization of contemporary psychedelic trial methodology required coordinated planning across study sites, trial partners, and federal agencies, as well as novel training, procedures, and data collection strategies.

- Emerge and Ascend use complementary controls and standardized procedures to address participant selection, masking, expectancy, dosing-session safety, and outcome assessment.
- Implementation across large multicenter studies required coordinated planning among sites, trial partners, sponsor teams, and federal agencies.
- These practical approaches illustrate solutions that may support standardization of future confirmatory psychedelic trials and improve reproducibility and interpretability.

References

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Disclosures

TS, PJ, SK, KN, CC, JJ, KC, RB, and DK are employees of Definium Therapeutics, Inc.

Contact email: medaffairs@definiumtx.com