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

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What is the Methodological Issue Being Addressed? Clinical trial design of psychedelic drugs presents unique methodological challenges, including functional unblinding, expectancy effects, safety monitoring during dosing sessions, and evaluation of the durability of treatment effects. To address these challenges, we describe two complementary Phase III Major Depressive Disorder (MDD) trials (EMERGE and ASCEND) designed in alignment with FDA recommendations. Key design considerations included 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 III DT120 MDD program was designed to address methodological challenges unique to psychedelic clinical trials. Building on the DT120 Phase 2b GAD study and evolving FDA recommendations, EMERGE and ASCEND incorporate several design features intended to enhance the interpretability of efficacy and safety findings.

A key component is the two-part study structure, with Part A evaluating acute efficacy and safety following a single administration of DT120, and Part B prospectively evaluating durability of response, recurrence of depressive symptoms, and retreatment patterns over 40 weeks. Additional 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 EMERGE and ASCEND are randomized, double-blind (DBL), placebo-controlled studies evaluating DT120 in adults aged 18 to 74 years with MDD. Key eligibility criteria included MADRS ≥26 and CGI-S ≥4 confirmed through independent rater interviews. Both studies include a 30-day screening period, 3-to-7 day interval between Baseline and randomization, a 12-week DBL treatment phase and a 40-week extension phase. The primary endpoint is change from baseline to Week 6 in MADRS total score, assessed by blinded central raters.

ASCEND further expands upon the EMERGE design through inclusion of a 50 µg DT120 comparator arm alongside the 100 µg dose, and placebo. This approach mitigates functional unblinding by providing a lower dose comparator that may better preserve blinding than a traditional placebo-only design. Advantages include enhanced assessment of blinding integrity, improved characterization of treatment durability and retreatment needs, and alignment with emerging

regulatory expectations. Potential limitations include increased operational complexity.

All dosing sessions are supported by trained DSMs (two lead, one secondary). Participant expectancy is assessed at Baseline, while perceived treatment effect is assessed repeatedly post-dose. Psychotherapy is not provided during dosing sessions.

Results Independent eligibility confirmation and standardized DSM training was successfully implemented across all sites in both programs. In EMERGE, collection of both expectancy assessments and perceived treatment assignment were 97%. Average time from DEA submission to approval in EMERGE was 45.4 days (27 sites), and 16.2 days (21 sites) in ASCEND. Time from site selection to site activation required an average of 35.7 weeks in EMERGE, and 14.6 weeks in ASCEND, reflecting additional training and oversight required to operationalize FDA-recommended methodological procedures. These findings demonstrate the feasibility of implementing contemporary psychedelic trial methodology within large multicenter Phase III studies.

Conclusion The successful operationalization of contemporary psychedelic trial methodology required coordinated planning across study sites, trial partners, and federal agencies, as well as the creation and implementation of novel training, study procedures, and data collection strategies. The successful execution of these programs highlight practical challenges and potential solutions that can help standardize future confirmatory psychedelic trials and improve the reproducibility and interpretability of their findings.

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Keywords

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Clinical Trial Methodology
Functional Unblinding
Psychedelic Clinical Trials
Major Depressive Disorder

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Disclosures This work was supported by Definium Therapeutics. One or more authors report potential conflicts, which are described in the program. Relevant financial relationships have been reviewed and mitigated to ensure the content is evidence-based and unbiased.

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