Phase 3 Trial Design and Methodology: Treatment With DT120 (Lysergide) in Generalized Anxiety Disorder (GAD) & Major Depressive Disorder (MDD)

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Background

- Globally, an estimated 1.1 billion people live with a mental health disorder[1]
- Psychedelic treatments have received growing interest for the treatment of mental health disorders such as generalized anxiety disorder (GAD) and major depressive disorder (MDD)[2]
- Clinical trials of psychedelic treatments present unique methodological challenges, including functional unblinding, evaluation of durability, expectancy effects, and safety monitoring[3,4]
  - In 2026, the US Food and Drug Administration (FDA) issued final guidance for clinical investigations of psychedelic treatments[3]
- 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 is currently under development for the treatment of GAD and MDD
  - The phase 3 clinical trials Voyage and Panorama in GAD and Emerge and Ascend in MDD were designed to **operationalize FDA guidance** and address the methodological challenges associated with clinical trials of psychedelic treatments

FDA Guidance for Psychedelic Treatments

- ☑ Study design
- ☑ Retreatment patterns and durability of response
- ☑ Eligibility criteria
- ☑ Centralized raters
- ☑ Dosing session monitors
- ☑ Psychotherapy
- ☑ Expectancy and functional unblinding evaluation
- ☑ Adverse events

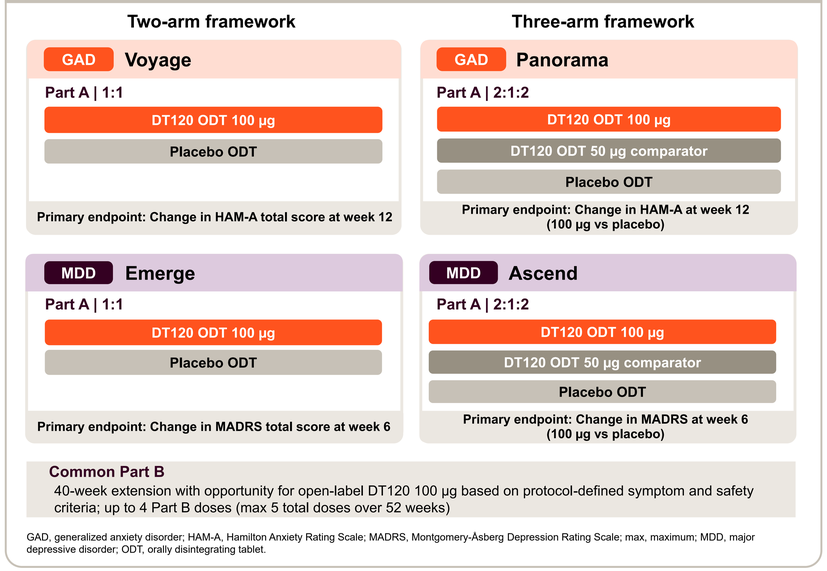
Objective

- To highlight key methodological aspects of the 4 DT120 phase 3 clinical trials and illustrate how FDA guidance was translated into a registrational psychedelic development program

Study Design

- Voyage, Panorama, Emerge, and Ascend are phase 3, randomized, **double-blind**, placebo-controlled trials (Part A), each with an open-label extension period (Part B; **Figure 1**)
  - Part A evaluated acute efficacy and safety over **12 weeks** following a single administration of DT120
  - Part B evaluated the maintenance of efficacy and safety and retreatment patterns over an **additional 40 weeks**
- Voyage and Emerge established a 2-arm framework of DT120 100 µg versus placebo to characterize target dose efficacy and safety. Panorama and Ascend added **DT120 50 µg as a low-dose comparator**, thereby creating a 3-arm framework to evaluate efficacy and safety as well as **mitigate functional unblinding** (**Figure 1**)

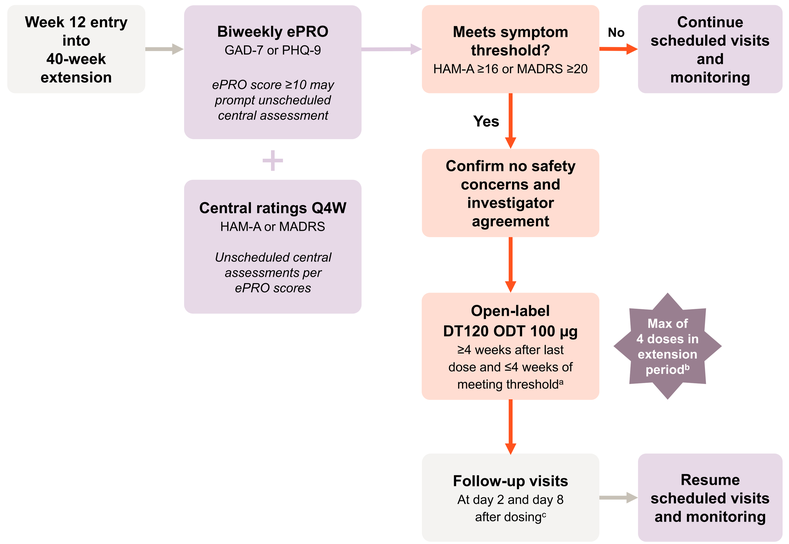
Figure 1. Phase 3 Clinical Trial Program



GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; max, maximum; MDD, major depressive disorder; ODT, orally disintegrating tablet.

- Open-label treatment in Part B was based on **prespecified symptom severity**, which allowed for assessment of **retreatment patterns and durability of response** in a real-world fashion (**Figure 2**)
  - To maintain data integrity, participants who met retreatment thresholds and had no safety concerns were required to re-treat

Figure 2. Symptom-Triggered Open-Label Treatment



[a]If dosing day is >14 days from meeting the retreatment threshold, safety laboratory assessments, drug screen, and serum pregnancy test (if applicable) must be repeated.
[b]Total of up to 5 doses over 52-week period with final dose no later than week 50.
[c]Telephone follow-up at day 3 postdose.
ePRO, electronic patient-reported outcome; GAD-7, Generalized Anxiety Disorder 7-item; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; max, maximum; ODT, orally disintegrating tablet; PHQ-9, Patient Health Questionnaire-9; Q4W, every 4 weeks.

Eligibility Criteria

- **Eligibility criteria were reviewed independently** by site personnel, central raters, and medical monitors, thereby enhancing diagnostic accuracy and reducing site-level variability (**Table 1**)

Table 1. Key Inclusion and Exclusion Criteria

	Key inclusion criteria	Key exclusion criteria
Voyage and Panorama	• Age 18–74 years • GAD diagnosis based on *DSM-5* and confirmed by MINI • HAM-A total score ≥20 at screening and baseline • MADRS items 1, 7, and 8 score ≤3 at screening and baseline • Use of highly effective methods of contraception	• Contraindicated medical or psychiatric conditions • Systematic psychotherapy ≤4 weeks prior to screening or plans to initiate therapy • Use of prohibited concomitant medications, supplements, or other therapeutics • >10 instances of psychedelics use in the past 5 years and any use in the past 2 years[a]
Emerge and Ascend	• Age 18–74 years • MDD diagnosis based on *DSM-5* and confirmed by MINI • MADRS total score ≥26 at screening and baseline • ≥1 MDE before current MDE with current episode lasting ≥8 weeks and ≤24 months at screening • CGI-S ≥4 at screening and baseline • Use of highly effective methods of contraception	• Contraindicated medical or psychiatric conditions • Systematic psychotherapy ≤4 weeks prior to screening or plans to initiate therapy • Use of prohibited concomitant medications, supplements, or other therapeutics • >10 instances of psychedelics use in the past 5 years and any use in the past 2 years

[a]Exclusion criteria related to prior use of psychedelics was later amended to any lifetime use of psychedelics based on FDA feedback.
CGI-S, Clinical Global Impression–Severity; *DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*; FDA, Food and Drug Administration; GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; MINI, Mini International Neuropsychiatric Interview.

Shared Assessment Framework

- Each study included a shared assessment framework that strengthened interpretability of findings by combining blinded and independent efficacy ratings, separation of dosing and rating roles, standardized session management, and explicit measures of expectancy, perceived treatment, and safety (**Figure 3**)

Figure 3. Shared Assessment Framework

Blinding
Participants, DSMs, central raters, and dosing sites were blinded to treatment and primary endpoint data

Centralized ratings
HAM-A (GAD) or MADRS (MDD) **central raters** were independent from the dosing site and **blinded to treatment and visit number**

Rater oversight
Site raters could not serve as the DSM or HCP for the same participant after the screening or baseline assessments to **mitigate functional unblinding**

DSMs
Two qualified and trained DSMs monitored dosing, with the second DSM having the option to monitor remotely via video. A total of 3 DSMs were onsite, and a **licensed HCP** was available or on call ≤15 minutes from the site[a]

Standardized dosing sessions
Psychotherapy was prohibited during dosing sessions. Standardized EoSC was used to assess participant status and ability to end the dosing session

Expectancy and functional unblinding evaluation
Baseline **expectancy** was measured in participants, and **perceived treatment** was recorded for both participants and central raters

Safety
AE collection included **AESIs that may have been viewed as positive experiences**, such as euphoria, and PRO assessment of participant's experience and perception of drug effects

[a]If an onsite DSM was a licensed HCP, a separate HCP was not required.
AE, adverse event; AESI, adverse event of special interest; DSM, dosing session monitor; EoSC, End-of-Session Checklist; GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; HCP, health care provider; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; PRO, patient-reported outcome.

Conclusions

- The DT120 phase 3 clinical trial program provides an example of how FDA guidance can be translated into optimized trial design for psychedelic treatments; furthermore, the program addresses key methodological and regulatory challenges associated with psychedelic treatment development
- The 2- and 3-arm frameworks provide complementary evidence for efficacy, safety, and functional unblinding of DT120
- Symptom-triggered open-label treatment allows for assessment of retreatment patterns in a real-world fashion
- Independent eligibility confirmation, blinded central raters, standardized dosing sessions, explicit expectancy, perceived treatment, and safety measures all strengthen interpretability
- These practical approaches illustrate solutions that may support standardization of future confirmatory psychedelic clinical trials

References

1. World Health Organization. Accessed August 19, 2026. https://www.who.int/news-room/fact-sheets/detail/mental-disorders/
2. Acero VP, et al. *Front Pharmacol.* 2023;14:1240295. 3. US Food and Drug Administration. July 2026. Accessed August 19, 2026. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/psychedelic-drugs-considerations-clinical-investigations.
4. van Elk M, Fried EI. *Ther Adv Psychopharmacol.* 2023;14:1-20.

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Disclosures

All authors are employees of Definium Therapeutics, Inc.

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