Definition and selection of generalized anxiety disorder (GAD) and major depressive disorder (MDD) patients for inclusion in Phase 3 pivotal trials

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Background

- Generalized anxiety disorder (GAD) and major depressive disorder (MDD) are diagnostically distinct but frequently co-occur (>50% co-occurrence)[1,2] and share symptom domains.
- This overlap can complicate participant selection for pivotal trials because the condition under study must be clearly defined while clinically meaningful comorbidity remains common in practice.
- Eligibility methods that are too broad may increase diagnostic heterogeneity, whereas methods that are too restrictive may limit generalizability.

Methodological Issue being Addressed

The DT120 Phase 3 program sought to confirm that the target disorder was primary, clinically active, and sufficiently severe; limit cross-indication symptoms likely to confound efficacy attribution; and apply consistent eligibility decisions across sites and studies. The central question is how to achieve diagnostic interpretability without creating populations that are disconnected from real-world psychiatric practice.

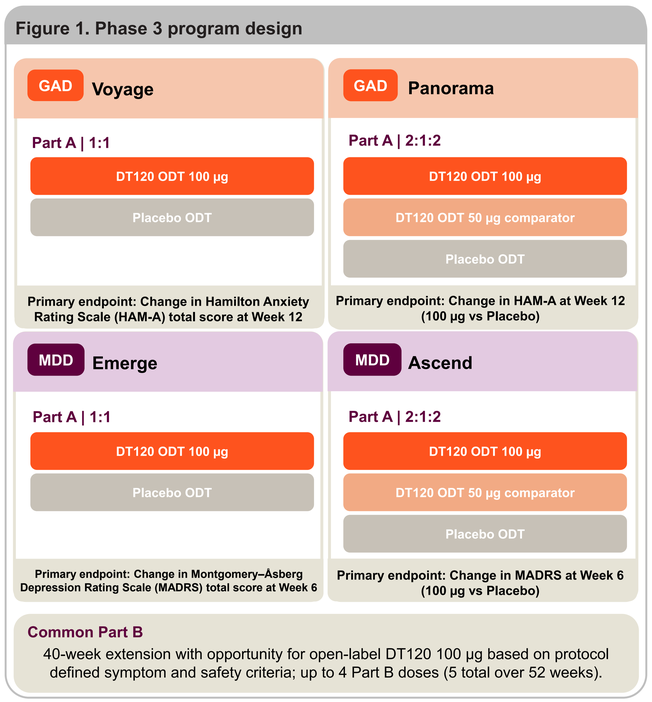
Objective

- To compare how participants were defined and selected across four Phase 3 DT120 trials, identify harmonized and indication-specific eligibility methods, and examine how these choices support diagnostic interpretability while affecting representation of real-world GAD—MDD Comorbidity.

Introduction

- The program includes 2 Phase 3 studies in GAD (Voyage and Panorama) and 2 Phase 3 studies in MDD (Emerge and Ascend).
- These studies used a common participant selection architecture with indication-specific criteria for GAD and MDD.

Figure 1. Phase 3 program design



Methods

Figure 2. Phase 3 trial eligibility architecture

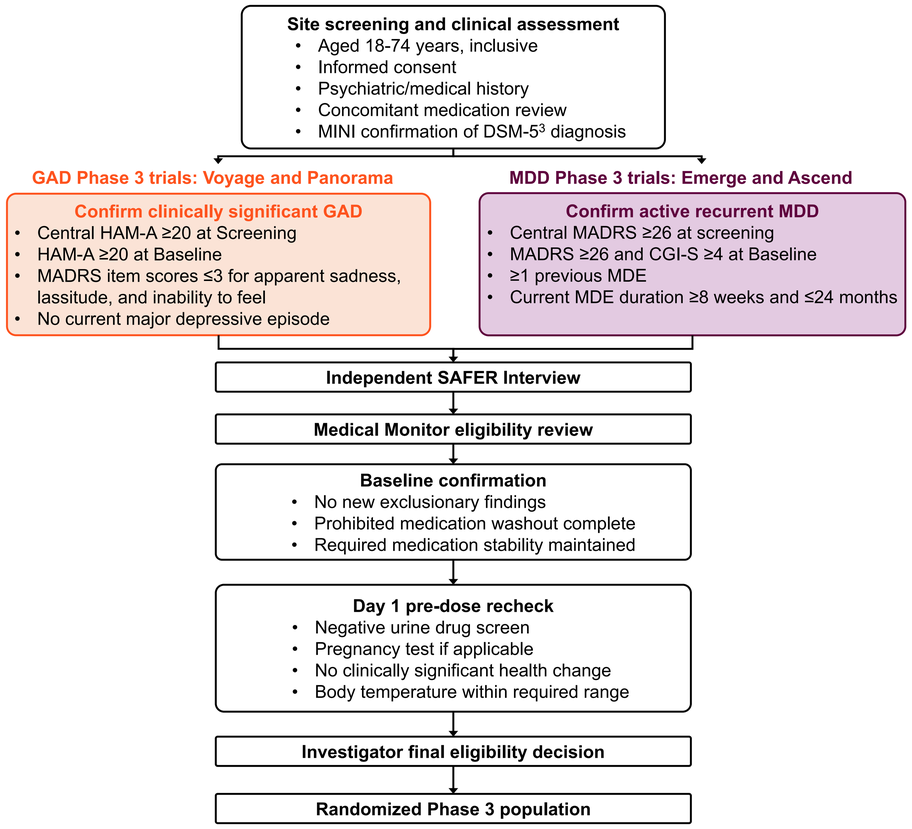


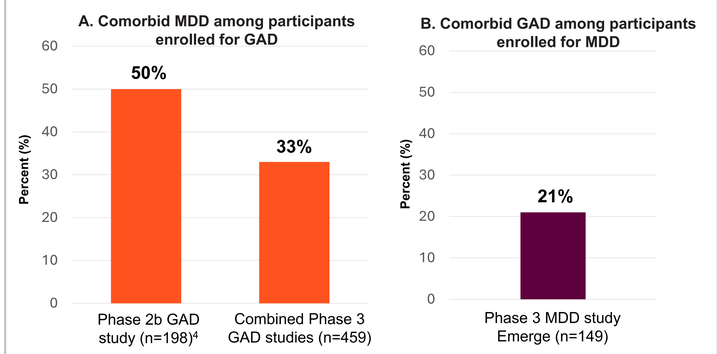
Table 1. Participant definition and eligibility framework across DT120 Phase 3 GAD and MDD program

Domain	Program-wide approach	Indication-specific implementation	Methodological interpretation
Target diagnosis	Clinical assessment plus DSM-5 diagnosis confirmed by MINI	GAD vs MDD by indication	Provides common categorical anchor
Condition-specific severity	Confirmed at screening and baseline	GAD = HAM-A ≥20; MDD = MADRS ≥26 and CGI-S ≥4	Establishes clinically active illness
Illness course	---	MDD required ≥1 previous MDE and current MDE 8 weeks-24 months; GAD had no separate episode-duration criterion	Reflects indication-specific temporal definition
Control of GAD-MDD overlap	Competing diagnosis could not be primary or sufficiently symptomatic to confound	GAD required limited depressive symptoms and no current MDE; MDD excluded other primary/confounding psychiatric illness, GAD was not categorically excluded	Limits cross-indication confounding
Independent eligibility confirmation	Site review plus central primary-scale assessment, SAFER interview, medical monitor review, and final investigator decision	Same across GAD and MDD studies	Improves consistency and separates eligibility from local enrollment pressure
Psychiatric safety and competing diagnosis	Shared exclusions for psychotic disorders, bipolar disorder, PTSD, personality disorder, significant suicidality, and clinically confounding psychiatric illness	Same Across GAD and MDD studies	Protects safety and interpretability
Treatment and medication stability	Prohibited psychiatric medications tapered or discontinued when medically appropriate; chronic medications stable; recent psychotherapy initiation restricted	Same across GAD and MDD studies	Reduces confounding
Final eligibility integrity	Screening, Baseline, and Day 1 review	Same across GAD and MDD studies	Reproducible final checkpoint before dosing

Results

A common eligibility scaffold was evident across all four Phase 3 studies. Participants were 18-74 years of age, had the DSM-5 target diagnosis confirmed by MINI, met indication-specific severity thresholds at Screening and Baseline, completed independent eligibility assessment, and underwent final pre-dose review. The GAD studies emphasized clinically significant anxiety while limiting active depressive symptomatology, whereas the MDD studies required recurrent, active moderate-to-severe depression and excluded competing psychiatric conditions when primary or sufficiently symptomatic to confound interpretation.

Figure 3. Preliminary GAD—MDD comorbidity in DT120 development cohorts



Interpretation of preliminary enrollment patterns

- The preliminary enrollment patterns are consistent with greater diagnostic differentiation in Phase 3 populations than was observed in the earlier Phase 2b GAD study, which used a different eligibility approach.
- The Phase 3 criteria did not eliminate psychiatric comorbidity. Rather, they were designed to establish the target disorder as the primary, clinically active condition and to limit competing symptomatology likely to confound efficacy assessment.
- This distinction may be particularly relevant in GAD and MDD, where symptoms and diagnoses frequently overlap.
- Evaluation of treatment effects across comorbidity-defined subgroups and in broader real-world populations will be important for understanding generalizability.

Conclusions

- Across four Phase 3 studies, participant selection was harmonized in structure but differentiated according to the target indication.
- The program combined structured diagnosis, severity thresholds, independent eligibility assessment, medical review, and final investigator adjudication to reduce GAD—MDD confounding.
- Preliminary enrollment patterns suggest more diagnostically differentiated populations while reinforcing the need to interpret pivotal-trial findings alongside broader real-world populations.
- The Phase 3 participant-selection approach aligns with the 2026 FDA psychedelic-drug guidance[5] by balancing diagnostic specificity needed for interpretable trials with the need for clinically representative study populations.

References

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Disclosures

PJ, EF, JM, TS, JH, RB, and DK are employees of Definium Therapeutics, Inc.

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