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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SUBMISSION DETAILS

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What is the Methodological Issue Being Addressed? GAD and MDD are highly prevalent and comorbid conditions. Regulatory approval requires that pivotal studies clearly define the primary condition under study to avoid confounding results. Methodologies utilized to ensure that participants selected have primary GAD or MDD for inclusion in these registration studies may result in populations that are less comorbid than the overall patient population. Utilizing a methodology that includes a several step process with independent interviews confirming diagnoses and eligibility criteria restricting comorbid conditions and/or symptom severity of comorbidity, and additional third-party and sponsor review results in enrollment of a "purer" population.

Introduction GAD and MDD are independently prevalent yet highly comorbid conditions (>50% co-occurrence), sharing several overlapping diagnostic features that make it clinically challenging to distinguish the primary diagnosis. This challenge is compounded by current treatment options routinely used for both conditions, yet despite their shared use, most existing standard-of-care agents are not efficacious for both. This gap between real-world practice and clinical outcomes underscores the need for novel therapeutics prospectively evaluated across both conditions. For regulatory approval, sponsors must demonstrate that confounding symptomatology has been adequately mitigated; however, given the frequency and burden of comorbid GAD and MDD, development programs for innovative treatments should be designed to characterize efficacy in both disorders. The impact on the efficacy of comorbid population reflecting real-world compared to the "purer" clinical trial population must also be evaluated.

Methods The phase 3 clinical development program for DT120 (lysergide, formerly MM120) includes two GAD studies (VOYAGE, PANORAMA) and two MDD studies (EMERGE and ASCEND). Participant selection for the GAD studies needed to exclude individuals who were anxiously depressed, meaning they may have met inclusion criteria based on anxiety symptom severity, but were also experiencing a major depressive episode (MDE). For the GAD studies, the inclusion criteria required a Hamilton Anxiety Rating Scale (HAM-A)≥20 and Montgomery-Åsberg Depression Rating (MADRS) for core depression items 1, 7 and 8≤3. In addition, the patient could not have met criteria for an MDE, which was confirmed via independent rater assessment in addition to a stringent eligibility review process overseen by the sponsor.
Enrollment into the MDD studies required a MADRS≥26 and CGI-S≥4 and no other current diagnosis that would be considered the primary diagnosis requiring treatment. This was also confirmed via

an independent rater and eligibility review overseen by the sponsor.

Results Preliminary results indicate that these studies are enrolling fewer patients with overlapping comorbid GAD and MDD than current epidemiological data indicates. In one phase 3 MDD trial of 149 participants approximately 21% of those enrolled had comorbid GAD. In the current ongoing two phase 3 GAD trials, approximately one-third of the 459 participants enrolled have comorbid MDD. In contrast, our previously completed phase 2b study in 198 GAD patients, which utilized a different eligibility methodology, enrolled GAD patients with approximately 50% comorbid MDD, consistent with the overall population. Full descriptive results will be available for both GAD studies and one MDD study at the time of presentation. We will discuss the implications of strategies for selection of patients who have less overlapping comorbidity in order to support registration, including potential impacts on efficacy, in the context of real-world comorbidity of GAD and MDD.

Conclusion Clinical trial enrollment requires balancing two competing priorities: minimizing diagnostic confounding through strict inclusion criteria, and ensuring the study population reflects real-world comorbidity. Trials enrolling patients with clearly defined, non-overlapping diagnoses generate clean efficacy data but may underrepresent the substantial proportion of patients presenting with both conditions. Real-world analysis of the broader comorbid population is warranted.

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Guidelines I have read and understand the Poster Guidelines

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