Pharmacokinetic and Safety Comparison of MM120 (Lysergide) Capsules and Orally Disintegrating Tablets in Healthy Adults

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Abstract Introduction: Generalized anxiety disorder (GAD) and major depressive disorder (MDD) represent leading causes of disease burden, possess overlapping symptomatic and diagnostic profiles, and often exist as comorbid conditions. A phase 2b dose-finding study of a single treatment with MM120 (lysergide D-tartrate) suggests a rapid, safe, and durable dose-dependent response in participants with moderate-to-severe GAD. Considering the efficacy and safety profile observed in the phase 2b study, MM120 100µg (freebase-equivalent) is considered an acceptable therapeutic dose. This phase 1 study compared the pharmacokinetic (PK), subjective effect, and safety profiles of the phase 2b capsule formulation at 100µg with a new 100µg orally disintegrating tablet (ODT) formulation that was subsequently included in the phase 3 program.
Methods: This was a phase 1, multicenter (two sites), open-label, randomized, 2-period, 2-sequence, cross-over, within-subject study designed to compare the plasma PK profile of 2 MM120 formulations in healthy adults aged 18 to 55 years. All participants received a single dose of each formulation (capsules or ODT) in separate evaluation periods, separated by a 2-week washout period between dosing. Participants were randomized equally to receive either four 25-µg MM120 capsules followed by 100µg MM120 ODT or ODT followed by capsules. Plasma concentrations of MM120 were determined by validated bioanalytical method. The PK and analysis of relative bioavailability between the 2 formulations were performed using Phoenix WinNonlin. Subjective effects were assessed using the Visual Analogue Scales (VAS) and 5-Dimensional Altered States of Consciousness (5D-ASC) scale, and descriptive statistics were presented for each category. Adverse events (AEs) were summarized for each treatment group by system organ class and preferred term. Terms used to identify AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA v26.0).
Results: A total of 29 participants were randomized, and 24 participants received each MM120 formulation as a single dose. MM120 ODT showed a faster onset of plasma concentrations than MM120 capsules, retaining similar relative bioavailability for Cmax. For AUC, the GMR for MM120 ODT was 16% higher compared with MM120 capsules. Similar to PK profiles, the VAS scores showed an earlier onset of effects for MM120 ODT compared with capsules. Maximum drug effect VAS scores were reported at 3 and 4 hours post-dose for participants receiving MM120 ODT or capsules, respectively. In both formulations, the most frequently reported treatment-emergent adverse

events (TEAEs) were from the system organ class of psychiatric disorders. Twenty-three (79.3%) and 22 (75.9%) participants reported 69 and 65 TEAEs after receiving MM120 ODT and capsules, respectively. Of these, participants receiving MM120 ODT compared with capsules reported similar rates of visual hallucinations (58.6 vs 51.7%), euphoric mood (48.3 vs 41.4%), and illusion (20.7 vs 17.2%).
Conclusion: This is the first study to characterize the PK of 100µg MM120 in both capsules and ODT formulations. The ODT formulation had bioavailability similar to that of the capsule. ODT absorption occurred faster compared with capsules and there was a more rapid onset of acute drug effects in the ODT formulation. Most TEAEs were mild to moderate after a single dose of both formulations and were consistent with the expected acute effects of MM120. This study demonstrated that 100µg MM120 ODT was an acceptable formulation to take forward in clinical development. Phase 3 programs are underway to investigate MM120 100µg ODT as a potential treatment for GAD and are planned for MDD.

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