The Entactogen, EMP-01, Represents a Novel Approach to the Treatment of Social Anxiety Disorder with its Pharmacological Selectivity and Distinct Subjective Effects Supportive of Safety and Therapeutic Utility

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Abstract Background: Social anxiety disorder (SAD) is among the most common psychiatric disorders, with an estimated lifetime prevalence of 12.1% and has one of the lowest remission rates in psychiatry (~35%) (Keller, 2006; Ruscio et al., 2008). Untreated SAD can be associated with debilitating avoidant behaviors due to fear-based beliefs and leads to chronic health problems and co-morbid psychiatric disorders (Vriends et al., 2014). Entactogens, including racemic MDMA, have been shown to be effective in treating SAD in autistic adults, post-traumatic stress disorder (PTSD), anxiety, and by facilitating improvements in affect, empathy, introspection, openness to new ideas and prosocial behaviors, while reducing social anxiety and increasing emotional disclosure and trust (Bedi et al., 2010; Danforth et al., 2018; Fluyau et al., 2024; Hysek et al. 2014; Mithoefer et al., 2011). EMP-01, the R-enantiomer of MDMA, is an entactogen with subjective effects indicative of therapeutic utility in SAD and has a favorable safety profile.

Methods: The pharmacology of EMP-01 was characterized using in vitro assays of receptor and transporter interactions and functional activity. SAD translational in vivo, disease-relevant effects of EMP-01 were determined in the mouse fear extinction assay. Following full characterization of the nonclinical safety and tolerability of EMP-01, a first-in-human (FiH) Phase 1 single-ascending dose study characterized the safety, tolerability, pharmacokinetic (PK), and PD effects of EMP-01 in healthy adult volunteers.

Results: EMP-01 selectively activates known targets of entactogen potential with selectivity toward beneficial serotonergic activity and low activity at catecholaminergic targets (receptors and reuptake transporters). In mice, EMP-01 facilitated fear extinction, an SAD-relevant translational assay. EMP-01 presented no significant concerns in rat and dog absorption, distribution, metabolism, and excretion (ADME), safety pharmacology and toxicology studies, with the potential for a good therapeutic window across species. In the FiH study with EMP-01, 32 adults received a

single dose of EMP-01 at a dose level of 75mg, 125mg, 175mg, 225mg or placebo. EMP-01 was found to be safe and well-tolerated at all dose levels up to 225 mg, with no serious adverse events (SAEs). There were no early study or drug discontinuations. No clinically significant abnormalities were found in vital signs, laboratory parameters, or ECG in any cohort. Treatment emergent AEs (TEAEs) were mild or moderate and generally dose-dependent; the most common were nausea and headache. EMP-01 was associated with dose-related increases in emotional breakthrough experiences, greater introspective awareness, increased self-compassion scores, and it produced subjective experiences and altered states that were more like those of classic serotonergic psychedelics.

Conclusions: There is substantial nonclinical and clinical data to support the development of an entactogen to treat SAD. The entactogen EMP-01 was found to be safe and well-tolerated in healthy adults. EMP-01 has a distinct pharmacology leading to differentiated subjective effects and a favorable safety profile and is being developed as a novel treatment for SAD. A Phase 2a, randomized, placebo-controlled trial of EMP-01 with SAD patients is currently underway.

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