COMP005 and COMP006: Example Approaches to Challenges in Randomized-Controlled Clinical Trials with Psychedelics

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Abstract Background: There is great interest in the development of psychedelic treatments for a range of psychiatric conditions. Although many neuropsychiatric treatments have psychoactive effects, the acute effects of psychedelic compounds magnify challenges to the design and interpretation of clinical trials with these compounds. Recently completed and ongoing clinical studies with psychedelics and similar compounds can provide insight into these challenges and how they may be addressed in study design.

Methods: We describe some of the considerations in designing clinical trials with psilocybin and explore two ongoing Phase 3 registrational clinical trials with investigational COMP360 psilocybin for treatment-resistant depression (COMP 005 and COMP 006).

Results: Some of the considerations in the clinical development of psilocybin include: (1) potent psychoactive drug effects that could be functionally unblinding, (2) the inclusion of psychological support aimed at safeguarding patients during the drug administration, and (3) how to adequately inform a non-daily treatment regimen. Ongoing trials with investigational COMP360 psilocybin (COMP005 and COMP006) include several design elements to help address these considerations and align with FDA draft guidance on clinical trials with psychedelics. COMP005 and COMP006 are double-blind RCTs designed to assess safety and efficacy. In addition to assessing efficacy, COMP005 provides key safety data by comparing 25 mg COMP360 to inert placebo. COMP006 addresses some of the functional unblinding risks of an inert placebo-control by comparing the safety and efficacy of 25 mg COMP360 to a low active control dose of COMP360 (1 mg), while also including a moderately psychoactive active treatment arm (10 mg COMP360 psilocybin). In contrast to psychedelic-assisted psychotherapy, COMP360 psilocybin is administered with non-directive psychological support rather than directive psychotherapy. The Compass Psychological Support Model (CPSM) has been designed as a manualized standard of care in clinical research with COMP360 psilocybin, not to support efficacy, but to safeguard study participants and ensure consistency across multi-site trials. Lastly, both COMP005 and COMP006 are 52-week trials that

allow double-blind collection of data on the durability of effect as well as the safety and efficacy of repeat dosing over 26 weeks, longer than typical pivotal RCTs of antidepressants.

Conclusions: COMP005 and COMP006 take into consideration challenges confronted in the development of COMP360 psilocybin for treatment resistant depression. Outcomes from these trials may further inform future study design with psilocybin and other psychedelic treatments.

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