Single-Dose COMP360 Psilocybin for Post-Traumatic Stress Disorder

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Abstract Purpose and content
Post-traumatic stress disorder (PTSD) is a severely debilitating psychiatric disorder for which there are few efficacious treatments. Results are presented from a phase 2 open-label clinical trial which examined the safety and tolerability of COMP360, Compass Pathfinder Limited's proprietary synthesized psilocybin formulation, in PTSD.

Methodology
This was a 12-week, open-label, nonrandomized trial. The primary outcome of this trial was the safety and tolerability of a single 25 mg dose of COMP360 psilocybin, administered with psychological support, in participants with PTSD. Secondary outcomes were change in PTSD symptoms (Clinician-Administered PTSD Scale for DSM-5 [CAPS-5]; and PTSD Checklist for DSM-5 [PCL-5]), functional impairment (Sheehan Disability Scale; SDS) and quality of life (EQ-5D-5L index score). Treatment-emergent adverse events (TEAEs), serious adverse events (TESAEs) and the PCL-5 were assessed at all visits. The CAPS-5, SDS and EQ-5D-5L were assessed at Baseline, Week 4 and Week 12. Spearman rank correlations (rs) between subjective psychedelic experience (5D-ASC) on Day 1, and CAPS-5 change from Baseline at Week 4 and Week 12 were also examined.

Results
Amongst the 22 participants enrolled (63.6% female; mean [SD] age, 39.0 [7.91] years), there was a total of 117 treatment-emergent adverse events (TEAEs); 70 (59.8%) were reported on administration day, of which 64/70 (91.4%) resolved by the end of the next day. TEAEs commonly included headache (n=11; 50.0%), nausea (n=8; 36.4%), crying (n=6; 27.3%), and fatigue (n=6; 27.3%). There were no TESAEs observed or TEAEs that led to study withdrawal. There were two TEAEs of suicidal ideation; both resolved during the study. Treatment was associated with a reduction in mean (standard deviation [SD]) CAPS-5 scores from Baseline to Week 4 (-29.9 [14.06]) and Week 12 (-29.5 [15.43]). This translated to an 81.8% response rate and a 63.6% remission rate at Week 4. Response and remission rates at Week 12 were 77.3% and 54.5%, respectively. Mean

[SD] PCL-5 score reduction was rapid, notable by Day 2 (-33.5 [14.32]) and sustained until Week 12 (-34.3 [18.13]). Participants showed an improvement in functional impairment over the 12 weeks of the study; from a mean SDS total score of 22.7 [5.38] at Baseline, there was a -11.7 [8.41] point reduction at Week 4 and a -14.4 [8.21] reduction at Week 12. Quality of life scores improved throughout the study, indicated by an EQ-5D-5L index score of 0.51 [0.287] at Baseline increasing to 0.73 [0.272] at Week 4 and 0.78 [0.269] at Week 12. The 5D-ASC dimension Oceanic Boundlessness on Day 1 was associated with a greater change from Baseline on the CAPS-5 at Week 4 (rs=-0.442) and Week 12 (rs=-0.394).

Importance
Single-dose 25 mg COMP360 psilocybin, delivered with psychological support, was generally well-tolerated and was not associated with any TESAEs. Participants experienced a clinically meaningful and durable reduction in clinician-rated PTSD symptoms, and rapid self-reported improvement by Day 2. Treatment was associated with improvements to functioning and quality of life across the 12-week study period. The intensity of participants' subjective positive psychedelic experience on dosing day was associated with better treatment response at Week 4 and Week 12, suggesting that this measure may be informative for predicting treatment response in PTSD. Results should be interpreted within the context of the modest sample size and the open-label design with no control comparator. Whilst the results are promising, larger well-controlled studies are required to inform the viability of COMP360 psilocybin as a potential efficacious treatment for PTSD.

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