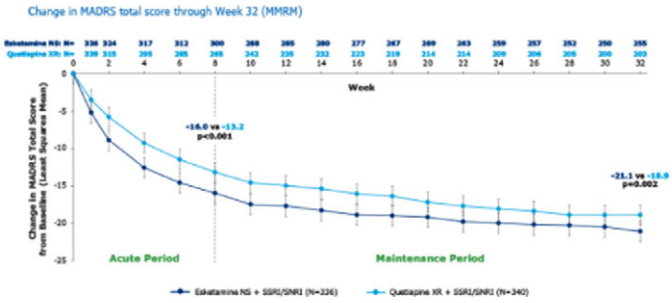
MADRS total score from baseline or MADRS≤10) rates were analysed over time using last observation carried forward. MADRS change from baseline was analysed using Mixed Models for Repeated Measures (MMRM). The most common adverse events (AEs) leading to discontinuation are reported for patients who received ≥1 dose of study medication.

Results: At baseline, 336 patients were randomised to esketamine NS and 340 to quetiapine XR. A significantly higher percentage of patients in the esketamine NS group achieved remission (at each visit from Wk6 [p=0.008] onward) and response (at each visit from Day 15 [p<0.001] onward) versus patients treated with quetiapine XR. Esketamine NS significantly improved MADRS score compared to quetiapine XR at each visit from Day 8 onwards, with an average difference over time in the least squares means total MADRS score change from baseline of -2.4 (**Figure**). The most common AEs leading to treatment discontinuation for esketamine NS were dizziness (n=2, 0.6%), dissociation (n=2, 0.6%) and vomiting (n=2, 0.6%), and for quetiapine XR were sedation (n=7, 2.1%), weight increased (n=6, 1.8%) and somnolence (n=5, 1.5%).

Image:



Conclusions: Esketamine NS increased the percentage of patients achieving response and remission and improved MADRS total score over time compared with quetiapine XR. Rates of discontinuation arising from the most common AEs were generally lower with esketamine NS than quetiapine XR.

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O0068

Improvement in Depression Symptoms Measured by Montgomery-Åsberg Depression Rating Scale and Quick Inventory of Depressive Symptomatology-Self Rated Items after Randomised Double-blind COMP360 Psilocybin Therapy for Treatment-resistant Depression

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Introduction: COMP360 is a synthetic, proprietary, purified form of psilocybin in development for treatment-resistant depression (TRD) with FDA Breakthrough Therapy designation. In a recent phase IIb study, COMP360 psilocybin 25mg was superior to 1mg on change from baseline (CFB) to Week 3 on the Montgomery-Åsberg Depression Rating Scale (MADRS) total score (primary efficacy endpoint), when administered alongside psychological support. Quick Inventory of Depressive Symptomatology-Self Rated ($QIDS\text{-}SR_{16}$) total score (exploratory efficacy endpoint) showed similar results.

Objectives: To analyse changes in specific depression symptoms after psilocybin treatment in the aforementioned study, as measured by individual item scores on the MADRS and $QIDS\text{-}SR_{16}$ (range 0-6 and 0-3).

Methods: Participants with TRD were randomised to single doses of psilocybin 25mg (n=79), 10mg (n=75), or 1mg (n=79). A remote, blinded rater assessed the MADRS at Baseline, Day 2 (the day post-psilocybin), and Weeks 1, 3, 6, 9, and 12. The $QIDS\text{-}SR_{16}$ was self-rated at Baseline, Day 1, Day 2, and Weeks 1, 2, 3, 6, 9, and 12. At each time point, descriptive statistics were calculated for each MADRS and $QIDS\text{-}SR_{16}$ individual item score.

Results: At Week 3, MADRS items with the largest differences in mean CFB in the 25mg arm were Inability to Feel, Apparent Sadness, Lassitude, and Reported Sadness. Greater improvement in the 25mg arm was apparent from Day 2 and remained to Week 12 (Lassitude remained to Week 6 only). On the $QIDS\text{-}SR_{16}$, the item with the largest difference in mean CFB at Week 3 in the 25mg arm was in Feeling Sad and remained evident to Week 12 (Table 1).

Table 1.

Item (mean CFB at Week 3 [standard deviation])	Psilocybin 25mg	Psilocybin 10mg	Psilocybin 1mg
MADRS - Inability to Feel	-1.8 [1.81]	-0.9 [1.54]	-0.8 [1.61]
MADRS - Apparent Sadness	-1.7 [1.94]	-1.1 [1.60]	-0.9 [1.62]
MADRS - Lassitude	-1.6 [1.81]	-1.2 [1.83]	-0.8 [1.58]
MADRS - Reported Sadness	-1.6 [1.95]	-1.0 [1.52]	-0.6 [1.53]
QIDS-SR$_{16}$ - Feeling Sad	-1.1 [1.08]	-0.8 [1.07]	-0.4 [0.91]

Conclusions: A single administration of COMP360 psilocybin therapy rapidly and dose-relatedly improved symptoms of depressed mood and anhedonia – the two key symptoms of depression. As anhedonia is predictive of poorer treatment response, and improvements in anhedonia correlate with improvements in functioning, it is important to understand the impact of treatments on this symptom.

Disclosure of Interest: G. Goodwin Shareolder of: COMPASS Pathways, P1Vital, and P1Vital products , Employee of: COMPASS Pathways, L. Marwood Shareolder of: COMPASS Pathways, Employee of: COMPASS Pathways, S. Mistry Employee of: COMPASS Pathways, A. Nowakowska Employee of: COMPASS Pathways, H. Simmons Employee of: COMPASS Pathways, J. Tsai Employee of: COMPASS Pathways, S. Williams Employee of: COMPASS Pathways, M. Young Shareolder of: COMPASS Pathways, Employee of: COMPASS Pathways, E. Malievskaia Employee of: COMPASS Pathways

O0069

Patient iPSC-derived neurons reveal mechanisms underlying antidepressant response: a potential diagnostic tool

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Introduction: Depression is a leading cause of disability worldwide despite dozens of approved antidepressants. There are currently no clear guidelines to assist the physician in their choice of drug, with existing tools limited to pharmacogenetics that have shown sub-optimal response prediction outcomes resulting in a subscription process that is largely a trial and error one. Consequently, the majority of depressed patients do not respond to their first prescribed antidepressant, with >30% not responding to subsequent drugs. We report here on molecular readouts from an in vitro-based platform that provides patient-specific information on antidepressant mechanisms using cortical neurons derived individually from each patient.

Objectives: To assess gene expression differences in prefrontal cortex neurons derived from responders and non-responders to two commonly used antidepressants, the selective serotonin reuptake inhibitor Citalopram and the atypical antidepressant Bupropion.

Methods: Patient-derived lymphoblastoid cell lines from the Sequenced Treatment Alternatives to Relieve Depression (STARD) study with known response to Citalopram or Bupropion were reprogrammed and then differentiated to cortical neurons. Differential gene expression analysis was preformed to identify genes that are differentially expressed between drug responders and non-responders.

Results: Significant differential expression was shown in 359 genes between Bupropion responders and non-responders (Fig1A) and 12 genes between Citalopram responders and non-responders (Fig1B). Clustering on the differentially expressed genes showed high agreement with the known response to both drugs (Fig1). Functional enrichment analysis revealed biologically relevant pathways that differ between responders and non-responders in Bupropion versus Citalopram.

Image:

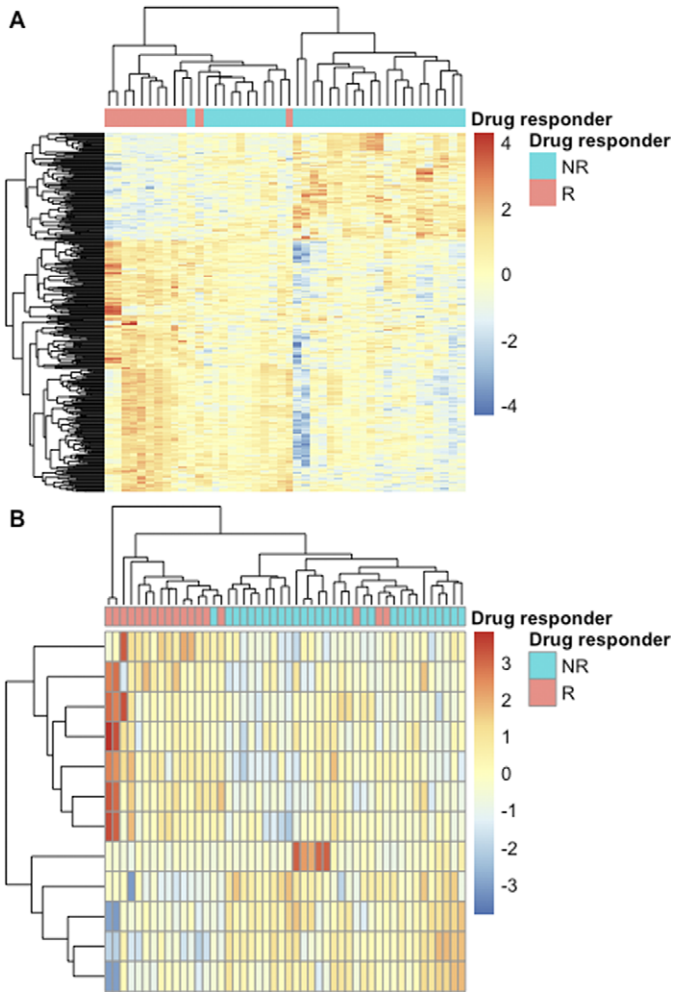

Figure 1. Heatmap of the expression of genes that show significant differential expression between neurons derived from Bupropion (A) and Citalopram (B) responders and non-responders. Color is the scaled gene expression; lines are genes and columns are samples. Column side colors represent the known response of the patient. Colum and line dendrograms are unsupervised hierarchical clustering.