Epigenetics and MDMA-Assisted Psychotherapy for PTSD

A substudy of “A Multi-Site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD” (ClinicalTrials.gov Identifier: NCT03537014).”

December 6, 2023

Study Protocol

For a detailed description of the planned data collection for the parent clinical trial see “A Multi-Site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD” (ClinicalTrials.gov Identifier: NCT03537014). The current substudy is concerned only with collecting additional salivary DNA samples from research participants in the main clinical trial that will be sent to the PI at USC for evaluation and co-registration with psychometric and clinical scale data on a subject-by-subject basis, for those subjects that volunteer to be included in this substudy. The parent study is 18 weeks in duration and involves 20 planned study visits.

For the current substudy, the site coordinators at participating sites in the multi-site clinical trial will collect saliva from research participants in the parent study at the following time points:

1) Collect saliva prior to first MDMA (vs placebo) treatment session at the Baseline Visit 3 or Visit 4 for the Phase 3 parent study, prior to the first MDMA (vs placebo) treatment session.

2) Collect saliva following final MDMA (vs placebo) treatment session at Primary Outcome Visit 19 or Visit 20 in the Phase 3 parent study, approximately 18 weeks after the first MDMA (vs placebo) treatment session.

3) Collect saliva at 1 year follow up time point (optional, for subjects in the MDMA group only)

4) Collect saliva at Integrative Session after last MDMA treatment session for subjects in the Placebo group

The collection of saliva will be accomplished using the Oragene DNA OG-500 salivary DNA kits (https://www.dnagenotek.com/ROW/products/collection-human/oragene-dna/500-series/OG-500.html).

The salivary samples take no more than 2-3 minutes to collect by passive drool into the salivary collection kit.

After capping, these salivary samples will be stored at room temperature and will then be sent back to the PI at USC for epigenetic analysis of gene methylation patterns.

Statistical considerations for the study

The statistical power calculations for the parent study were made by fitting a Mixed-Effect Model Repeated Measure (MMRM) model to CAPS-4 data from the MAPS Phase 2 study MP1 to obtain covariance parameter estimates. The previous Phase 2 MP1 study followed a similar design with outcomes measured by CAPS-4 outcome scores, which allowed for estimation of within-subject covariance parameters. With a sample size of 50 participants per treatment group in the modified Intent-to-Treat (mITT) population, this study has 90% power to detect a treatment effect, using a two-sided test with an alpha of 0.0499.

For the purposes of the current substudy analyzing the impact of the treatment on epigenetic regulation of candidate genes we have identified other studies in the literature showing significant effects with similar size population, demonstrating that we can expect treatment effects on epigenetic regulation with a large enough effect size to be discernible from this sample size.

In addition to standard statistical approaches with corrections for multiple comparisons to assess the methylation changes on the target genes and gene networks, a second level of statistical analysis to be accomplished will be the assessment of the correlations between the change from baseline in PTSD and Depression symptoms (and related psychometrics) and the change from baseline in the methylation patterns of the target genes/gene networks obtained.