Official Title: University of Alabama at Birmingham (UAB) Adult CBD Program

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Statistical Analysis Plan

The UAB Adult CBD Program enrolled 80 treatment resistant epileptic participants ages 18 years of age and older. All study participants received Epidiolex drug (Cannabidiol; CBD) as an add-on to their previously stable anticonvulsive treatment after baseline assessment. Participants received a starting dose was 5 mg/kg/day in twice daily dosing and titrated by 5 mg/kg/2 weeks, with a maximum dose of 50 mg/kg/day. Seizure frequency, severity, and adverse events together, with other clinical participant measures, were assessed at baseline and bi-weekly for the duration of study.

The first 12-months (1-year) of follow-up data were analyzed as follows:

1. The Primary Outcome Measures included:

    a. Severe adverse events (increase in seizure frequency by more than 100% leading   to emergency room visit or hospitalization),

    b. Change in resting blood pressure or heart rate by 25% if considered significant by managing neurologist,

    c. Any change in, CBC, CMP, Liver function tests (LFTs), Urinary Analysis or Antiepileptic drug (AED) levels considered by managing neurologists as clinically significant. Clinically significant will be determined by using the Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03. Adverse events (AEs) categorized as a grade 3 or above will be considered clinically significant. Adverse events graded 4 or above will be considered severe adverse events (SAEs).

The analysis plan is focused on safety. The information on safety will be tabulated as the percent of participants with each safety outcome AE and SAE, or others reported as meaningful as well as the number of occurrences of each AE and SAE. This enables an event rate calculation per exposure time as well as the average number of occurrences per participant with an AE or SAE.

2. The secondary analysis assessed the frequency and severity of seizure outcome measures to include:

    a. Change in seizure frequency as measured in total number of seizures per month.

    b. Change in seizure severity as measured by the Chalfont Seizure Severity Scale (Duncan & Sander, 1991, JNNP).

The analysis plan for frequency and severity of seizures (secondary outcome measures) assessed the pattern of change over time relative to baseline. The non-parametric Friedman's test was used since seizure frequency and severity outcome measures were not normally distributed. Wilcoxon's signed rank test with Bonferroni's multiple comparison correction was utilized as a post-hoc analysis for pairwise comparisons between baseline and each post-baseline time point.

Further parametric analysis used the generalized least squares statistical techniques for modeling longitudinal data, an extension of mixed effects models that accommodates heteroscedacity and correlation within group errors (Pinheiro and Bates, 2000), after normality of outcome measures were achieved through log-transformations methods. The longitudinal analysis included each month following baseline up to the 12-month endpoint, with a log transformation of seizure measures regressed on time (months), gender, and several identified baseline clinical variables including number of AEDs, number of AEDs tried, and history of epileptic surgery. A cubic spline with 4 knots (carefully chosen with AIC and BIC) was put on time to capture the non-linear trend in seizure outcome measures. AIC and BIC also aided in the choice of the specified correlation structure for this analysis.

Effectiveness of CBD exposure on the population of interest was established using estimated proportion of seizure frequency reduction at each post-baseline time point relative to baseline which were obtained after reported geometric least squares means were subtracted from 1. This analysis was also repeated for Chalfont seizure severity score measures instead of seizure frequency.

Parametric and non-parametric methods described above were also repeated using last observation carried forward (LOCF) principle on the data instead of complete cases of the data. An alpha level of 5% was used to achieve statistical significance.