Study: #7662 “A randomized controlled trial of Lorcaserin for Cannabis Use Disorder”

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NCT# NCT03637842

SAP originally created: 11-07-2017 as part of grant submission.

SAP unchanged and approved 9/21/2018 when protocol approved.

Data Analysis:

Outcome measures: Primary Cannabis Outcomes: (1) Weekly average dollar value of cannabis use per day (continuous; longitudinal,); Secondary Cannabis Outcomes: (1) number of days of abstinence per week (continuous; longitudinal); (2) Weekly THC-COOH urine levels (continuous; longitudinal). Primary lmpulsivity Outcomes: (1) Premature responses on the 4-CSRTT (continuous, longitudinal); Secondary lmpulsivity Outcomes: (1) changes in calculated k values from the Monetary Choice Questionnaire (continuous, longitudinal); (2) number of beads drawn prior to decision for the Beads Task (continuous, longitudinal); (3) top Signal Reaction Time (SSRT) from the Stop Signal Task (continuous, longitudinal); (4) Total and subscale scores on the UPPS-P (continuous, longitudinal); (5) daily BIS-7 report through EMA (continuous, longitudinal). Exploratory Outcomes: Drop-out rates, time to discontinuation of study, FTND total scores, self-report of missed doses of medication, % response completed of EMA, and study visits attended. **Covariates**: Demographics (including age, gender) and baseline cannabis use measured by dollar amount of cannabis pen using day at baseline. **Sample size and randomization**: 60 participants will be randomly allocated (1 :1) to receive either lorcaserin or placebo, using random block sizes of 4, 6, and 8, stratified by baseline severity of cannabis use (dichotomized by dollars spent per day >$10) as we have previously done in CUD treatment trials. **Intent to Treat/Drop outs and missing data**: The primary analyses will be on the intent-to-treat (ITT) sample of all randomized participants. Those participants will be included in the ITT analysis of primary and secondary outcomes. **Significance testing and preliminary analyses**: Tests for main effects will be performed at a two-tailed significance a=0.05. We will examine all variables for outliers before performing analyses. The distributions for all continuous variables will be checked for normality, and transformations will be employed, if necessary, before applying specific parametric techniques. The distribution of demographic variables and measures of symptomatology at baseline will be examined and described in terms of means, standard deviations, proportions and 95% confidence intervals. We will examine the associations between key baseline variables (demographics, cannabis use severity) and the primary outcome measures. Baseline variables strongly associated with outcome will be included as covariates in models used to test the study hypotheses. We will also explore effect moderation; i.e., baseline covariate by treatment interactions.

Hypotheses:

Primary hypotheses:

Aim 1 hypothesis: Lorcaserin will show greater reductions in (1) dollars and (2) the number of abstinent days of cannabis use reported by TLFB and (3) reductions in THC-COOH urine levels as compared to placebo. The following longitudinal mixed effects model will be used:

(1) $Y_{ijt} = \beta_0 + \beta_1 I_i + \beta_2 t + \beta_3 t*I_i + \beta_4 U_{ii} + S_i + E_{ijt}$

where Y_{iit} is the daily amount of cannabis used (either (1) dollar value, (2) number of abstinent days, or (3) ifHC-COOH urine level averaged over a one-week period) by the i^{1h} subject in the treatment group j at week t (t=2, ... 13); Ui is the vector of covariates; Ii is the indicator variable for treatment with lorcaserin; si is a random intercept for subject i and Eiit is a random error term. Significant interaction t*Ii indicates that the effect of each treatment group is different over time (that corresponds to rejecting the null hypothesis that β_3=0). If so, the effect of time will be estimated for each group

separately and the groups will be compared (using contrast) at the last time point t=13. If the interaction term is not significant, we will refit the model without the interaction term and test the main effect of treatment.

Aim 2 hypothesis: During the medication lead-in (weeks 2-3), lorcaserin will significantly reduce action impulsivity (4-CSRTT premature responding and SSRT), choice impulsivity (MCQ calculated k values and# of beads drawn), and UPPS-P scores and self-report on BIS-7 through EMA as compared to placebo.

For all impulsivity measures collected at study visits, a similar model as used to test Aim 1 will be used.

Secondary hypothesis:

Reductions in impulsivity will mediate the effects of lorcaserin on cannabis use. If lorcaserin is shown to reduce different constructs of impulsivity, then these measures will be evaluated as potential mediators through the Baron and Kenny mediation framework for their effects on cannabis use outcomes.

Exploratory hypotheses: The effect of lorcarserin as compared to placebo on the proportion of participants who drop out will be explored using a Chi-square test. Time to discontinuation between treatment groups will be examined using survival analysis and Cox models. The effects of lorcaserin on treatment adherence and nicotine use will be examined using regression analysis and longitudinal mixed effects models, respectively.

Power: The primary purpose of this proposed study is to estimate effect size of lorcaserin on cannabis use. This will be done using 95% confidence interval methodology. The resulting 95% confidence interval provides considerably more information than testing a specific null hypothesis: it gives a range of plausible parameter estimates for the difference of cannabis use between the placebo and lorcaserin groups. Such range of plausible effect sizes can be used to estimate the potential effect size in larger clinical trials. The following power calculations are only in support of the study proposal and for the purpose of sample size calculation. With 30 participants per group the study prrovides 80% Rower to detect significant effect size = .74 or larger.