Exposure-Response Analyses to Support Dosing Recommendations for RBP-6000 Buprenorphine Monthly Formulation in Subjects with Opioid Use Disorder

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Objectives: To characterize exposure-response relationships for RBP-6000 regarding illicit opioid use and opioid craving, and to assess dropout patterns in a pivotal Phase III efficacy study.

Methods: Longitudinal data for illicit opioid use (binary) and opioid craving (treated as ordinal) were obtained in 489 subjects with moderate or severe opioid use disorder, previously on sublingual (SL) buprenorphine/naloxone treatment who received subcutaneous (SC) injections of RBP-6000 (2 doses of 300mg followed by 4 doses of 100mg or 300mg) or placebo in a randomized double-blind Phase III efficacy and safety study. A 2-compartment pharmacokinetic model with first-order absorption for SL buprenorphine and a dual absorption submodel for RBP-6000 was used. Exposure-response relationships for illicit opioid use and craving were described by $E_{\text{max}}$ logistic regression models. Dropout data were modeled using time-to-event analysis.

Results: The time to dropout was described by a Gompertz hazard model. Opioid craving and race were significant predictors of dropout in all treatment groups: an opioid craving score $>20$ was associated with up to 3.0- and 3.6-fold higher dropout rates in active and placebo arms, respectively, compared to craving scores $\leq 5$. Age and disease severity were significant predictors of dropout in placebo subjects only. Baseline and maximum probability of being negative for illicit opioid use following buprenorphine treatment were 3.6% and 82.6%, respectively ($EC_{50}=1.2 \text{ ng/mL}$). Opioid use by injectable route at baseline (260% higher $EC_{50}$), TC and TT genotypes for rs678849 on delta-opioid receptor (71% and 94% lower $EC_{50}$, respectively), baseline employment status (43% higher $E_{\text{max}}$) and race (black) (31% lower $E_{\text{max}}$) were identified as clinically-relevant covariates. The only significant covariate for opioid craving was BMI which had no clinical relevance.

Conclusions: Data for illicit opioid use, opioid craving and dropout and their relationship to RBP-6000 plasma concentration were successfully modelled and used to justify final dosing recommendations of RBP-6000.