A Phase 1 Dose Optimization Study of ABP-700 with Opiates and/or Midazolam Targeting Induction of General Anesthesia (Preliminary Results)

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Background and Objective: ABP-700 is a positive allosteric modulator of the $GABA_A$ receptor in development for procedural sedation and induction of general anesthesia. The goal of this dose ranging study was to determine safety, pharmacokinetics (PK) and pharmacodynamics (PD) of ABP-700 given as an infusion either alone, after premedication with an opiate, benzodiazepine or their combination, or during co-administration with an opiate.

Method: An open label, Phase 1 healthy volunteer study was performed with ethics approval in accordance with the Declaration of Helsinki. Doses of ABP-700 were selected based on prior Phase I results demonstrating a safety, efficacy and tolerability profile consistent with clinical utility for induction of general anesthesia and refined with the use of compartmental PK/PD modeling. 120 subjects were enrolled in fifteen cohorts (8 subjects/cohort, 50% male, ages 18 to 54). Thirteen cohorts received a single stage infusion of ABP-700 at 100, 120, 140, or 160 µg/kg/min for 7 min and 2 cohorts received a 3 stage infusion as 140, 100, 90 µg/kg/min for 2, 2, 3 min. ABP-700 was given alone in 4 cohorts and the remaining 11 cohorts were dosed in combination with three premedication regimens: fentanyl (1 µg/kg), midazolam (30 µg/kg), midazolam-fentanyl (15 µg/kg-1 µg/kg) or as co-administration regimen: remifentanil as a 2 ng/ml effective site target controlled infusion. Safety assessments included clinical labs, hemodynamic, respiratory and adverse event (AE) monitoring. Clinical effect was assessed by MOAA/S scoring and BIS monitoring.

Results: ABP-700 produced a dose-dependent increase in the proportion of subjects achieving unconsciousness: within 5 minutes of dose initiation, 12.5%, 62.5% and 100% of subjects achieved a MOAA/S = 0 with 100, 120 or ≥140 µg/kg/min for 7 minutes, respectively. Clinical effect was not substantially affected by any of the pre- or co-medication regimens. Respiration was well preserved with apnea reported in 3 subjects, all of which were co-administered remifentanil.

The most common AEs (>20%) were involuntary muscle movements, sinus tachycardia and systolic hypertension. Premedication improved tolerability and decreased the frequency and extent of hemodynamic excursions and also incidence and intensity of any involuntary muscle movements.

Conclusion: ABP-700 as a 7 min infusion is safe and generally well tolerated. Infusion rates of 100 µg/kg/min and above are associated with drug-induced unconsciousness with good preservation of spontaneous breathing. When dosed with pre- and co- medications, ABP 700 given as a short infusion may be useful as an induction agent.