Safety, Pharmacokinetics, and Pharmacodynamics of ABP-700: a Novel Intravenous Anesthetic

Objective: The objective of this Phase 1 study is to determine the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of a single bolus dose of ABP-700, a second-generation metabolically labile etomidate analogue.

Background: ABP-700 is a novel, potent, positive allosteric modulator of the $GABA_A$ receptor currently being developed for monitored anesthesia care (MAC) and/or general anesthesia. ABP-700 contains an ester bond that is precisely designed to undergo rapid hydrolysis in the body by nonspecific tissue esterases in order to produce an inactive carboxylic acid metabolite. The pre-clinical pharmacology of ABP-700 has been previously published and it shows the desirable properties of etomidate including minimal hemodynamic and respiratory depression, but augmented by faster emergence from anesthesia and no adrenocortical suppression.

Methods: A Phase 1, first-in-human, double-blind, randomized, placebo-controlled trial was performed in 60 healthy volunteers. Eight (8) cohorts of 6 subjects (5:1 active to placebo) received a single bolus dose of either placebo, or 0.03, 0.10, 0.175, 0.25, 0.35, 0.50, 0.75 or 1.00 mg/kg ABP-700. Two (2) cohorts of 6 subjects (5:1 active to placebo) received 1 µg/kg fentanyl as a pre-medication followed by 0.25 or 0.35 mg/kg ABP-700. Safety assessments included clinical laboratory evaluations, hemodynamic and respiratory stability and adverse event monitoring. Adrenocortical function was assessed using the ACTH stimulation test. PD effect was measured using the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S) and the BIS monitor (Aspect Medical Systems, Inc.)

Results: ABP-700 was safe and well tolerated. For the study overall, 105 of 112 (94%) of adverse events were reported as mild. Adverse events of moderate intensity were reported by 1 of 5 subjects (20%) and 2 of 5 subjects (40%) in the 0.75 and 1.00 mg/kg dose groups and in none of the other groups. PK was linear; peak venous serum concentration (T_{max}) ranged from 1.6-3.6 minutes, and the venous terminal elimination half-life ($T_{1/2}$) ranged from 10.5-18.7 minutes. PD effects as measured by MOAA/S and BIS were dose dependent and rapidly reversible. There was no effect on adrenal function at any of the doses tested.

Conclusions: ABP-700 was safe and well-tolerated following single bolus injections of up to a maximum dose of 1.0 mg/kg. The dose dependent differences in both type and frequency of adverse events are consistent with the mechanism of action of ABP-700 and its structurally related analog, etomidate. Consistent with pre-clinical observation, the PD effect of ABP-700 appears to be highly dose dependent with no adrenal suppression and context-insensitive rapid reversibility at all doses tested. The exposure and other PK parameters are also linear

and dose-proportional. Based on these data, further exploration of ABP-700 as a potential anesthetic is warranted.