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The use of the scopolamine-induced cognitive impairment model to translate on-target activity for ABT-894 from rodents/monkeys to humans: Preclinical evidences

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Demonstrating the successful translation of a pharmacodynamic signal from preclinical species to humans has become an active focus of drug discovery research as a means to facilitate decision making early in the drug development process. Scopolamine-induced cognitive impairment has been proposed to be a useful tool to demonstrate the pharmacodynamic effect across species for multiple mechanisms such as acetylcholinesterase inhibitors, neuronal nicotinic receptor (NNR) ligands, stimulants and glycine analogs. The present preclinical study investigated whether this model could be used to advance the NNR α4ß2 agonist ABT-894 more rapidly to key PhII efficacy trials in the target patient population by providing a means to establish proof of pharmacological activity in humans. Scopolamine was used to induce deficits in the rat two-platform water maze (WM) assay of spatial reference memory (0.3 mg/kg, i.p.), in the rat T-maze assay of working memory (0.3 mg/kg, i.p.), in the rat passive avoidance response (PAR) assay of memory consolidation (0.1 mg/kg, s.c.) and in the monkey delayed matching-to-sample (DMTS) assay of short term/working memory (0.02 mg/kg, i.m.). ABT-894 was given 10-15 minutes prior to scopolamine, and the behavioral testing occurred 15–20 min after scopolamine administration. ABT-894 dose-dependently blocked scopolamine-induced deficits in WM (0.0062, 0.019 and 0.19 μmol/kg, i.p.). In T-maze, ABT-894 (0.019 μmol/kg, i.p.) significantly attenuated scopolamine-induced deficits at the short delay only. ABT-894 dose-dependently attenuated scopolamine-induced deficits in PAR, reaching significance at the dose of 0.03 μmol/kg, i.p.. Finally in DMTS, ABT-894 attenuated scopolamine-induced deficits at the dose of 0.03 but not at 0.01 or 0.1 μmol/kg, i.m.. Together, these data suggest that ABT-894 can attenuate scopolamine-induced deficits across multiple cognitive domains in preclinical species. As such, the translational model may be of use to demonstrate proof of pharmacological activity in humans and thereby allow more rapid advancement into the key PhII clinical efficacy trials. This hypothesis is being tested in human studies using the scopolamine-induced cognitive impairment model.

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A randomized, double-blind, placebo-controlled Phase 2 study of α4β2 agonist ABT-894 in adults with ADHD

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ABT-894 is a novel α4β2 neuronal nicotinic acetylcholine receptor agonist that displays consistent and robust activity in preclinical models of cognition and is generally well tolerated in healthy adults. Attention-deficit/hyperactivity disorder (ADHD) is characterized by core symptoms of hyperactivity, inattentiveness, and impulsivity, with 15–65% of diagnosed children continuing to experience symptoms into adulthood. There is a need for novel treatments that address the unmet medical need associated with ADHD. A randomized, double-blind, placebo-controlled, 2 period, crossover Phase 2 study was designed to determine the safety and efficacy of ABT-894 and atomoxetine in adults with ADHD. For each dose group, subjects received, in random order, placebo treatment and ABT-894 (1 mg, 2 mg, 4 mg PO QD, or 4 mg PO BID) or active comparator atomoxetine (40 mg PO BID) treatment for 28 days. The washout period between treatment periods was approximately 2 weeks. Subjects were assessed weekly and the primary efficacy variable was the Conners' Adult ADHD Rating Scale – Investigator Rated (CAARS:Inv) Total score at the final evaluation of each 4-week treatment period. Data were analyzed by analysis of covariance with baseline score from each period as a covariate. An expanded period by period analysis examined the consistency of ABT-894 effects. A total of 238 subjects were assessed for safety endpoints, 236 patients included in the intent-to-treat (ITT) dataset, and 196 included in the completers dataset, which was the pre-specified, primary dataset for efficacy. Administration of 4 mg BID ABT-894 resulted in a significant improvement compared with placebo in CAARS:Inv Total score (LS mean ± SE = −6.69 ± 2.30, $p = 0.003$). This effect was similar to atomoxetine treatment (−7.98 ± 2.65, $p = 0.002$). Results from secondary outcome measures were similar to those for the primary outcome measure. In analysis of Period 1, the response on the CAARS:Inv Total score to 4 mg BID ABT-894 was significantly improved vs placebo ($p = 0.041$). For subjects who received placebo in Period 1 and 4 mg BID ABT-894 or atomoxetine in Period 2, the change in CAARS:Inv total score for 4 mg BID ABT-894 was equivalent to that of atomoxetine in Period 2. Overall, ABT-894 was well tolerated at all dose levels, and the 4 mg BID dose was found to be efficacious compared with placebo and generally well tolerated in this Phase 2 trial in adults with ADHD. Evidence of efficacy for this dose was observed during both periods of this crossover study, suggesting that the results were not biased by carryover effects of the crossover design. A better efficacy and adverse event profile was observed for 4 mg BID vs 4 mg QD ABT-894, suggesting that consistently higher plasma levels of ABT-894 could improve its therapeutic potential. Further investigation of ABT-894, including doses higher than those tested in the current study, would be needed to determine its potential as a safe and effective treatment for adults with ADHD.

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