SHORTENING THE DURATION OF ACUTE SCHIZOPHRENIA REGISTRATION TRIALS IS A POSSIBILITY

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Background: Pivotal registration trials for acute schizophrenia are placebo controlled and typically of 6 week duration with mean change from baseline in Positive and negative symptom score (PANSS) as the primary end point. The objective of the analysis was to evaluate the feasibility of conducting a 3 or 4-week registration trial for demonstration of efficacy and safety.

Methods: The master database (32 trials, 14219 subjects) consisted of efficacy and safety information from eight new drug applications submitted to FDA between 2001 and 2015. The baseline adjusted mean change from baseline in PANSS at 3 and 4 weeks was estimated using a mixed model repeated measure analysis and compared with the original pre-specified analysis (6-week duration). Concordance and discordance rates with the 6-week trial results, implication of a shorter trial on the sample size requirements and proportion of important adverse events associated with atypical antipsychotics evident at early endpoints were assessed.

Results: The mean change from baseline in PANSS demonstrated consistent separation of placebo and drug effect as early as 2 weeks. The concordance and discordance rates for week 3 and week 4 endpoints compared with the pre-specified 6-week endpoint were 83% & 17% and 93% & 7%, respectively. A concordance rate of at least 90% was evident for seven of the eight drugs at four weeks. Adequate occurrence (at least 2%) of adverse events such as akathisia, somnolence, extra-pyramidal symptoms was evident as early as 2 weeks. For a 4-week endpoint, 32% higher sample size will be required as compared to 6-week endpoint, however the dropout rates at week 4 were 30% lower than week 6.

Conclusions: The comprehensive analysis based on the largest database of randomized controlled trial of atypical anti-psychotics suggested that the shorter, four-week trial can adequately provide evidence of efficacy and safety similar to a six-week trial and is a feasible option.