Review of the Trace Amine-Associated Receptor 1 (TAAR1) Agonist Ulotaront: Part II—Summary of Initial Clinical Efficacy/Safety Results

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Abstract

Introduction. Ulotaront is a trace amine-associated receptor 1 (TAAR1) agonist with serotonin 5-HT1A agonist activity that has received FDA Breakthrough Therapy Designation for the treatment of schizophrenia. Here we summarize ongoing clinical research characterizing the efficacy and safety of ulotaront as a member of the novel trace amine-associated receptor 1 (TAAR1) agonist class.

Methods. Summarized are results from a double-blind, placebo-controlled study to evaluate the efficacy and safety of ulotaront (50 mg or 75 mg) in an acute exacerbation of schizophrenia, and a 6-month, open-label follow-up study. Also summarized are post-hoc analyses evaluating negative symptom efficacy, and key safety and adverse event (AE) outcomes.

Results. In the short-term study, treatment with ulotaront was associated with significant (p<0.001) endpoint improvement in the PANSS total score (effect size [ES]: 0.45), the CGI-Severity score (ES: 0.52) and the Brief Negative Symptom Scale total score (ES: 0.48). The incidence of any AE was lower on ulotaront versus placebo (45.8% vs. 50.4%), and the number needed to harm (NNH) for individual AEs on ulotaront were all >40. Ulotaront was associated with lower risk for antipsychotic class-related AEs (extrapyramidal symptoms, akathisia, somnolence, nausea/vomiting, increased weight/metabolic labs, prolactinemia). The 6-month study demonstrated further improvement, with a completion rate (67%) that was higher than reported for current dopamine D2 antipsychotics.

Conclusions. The emerging profile of ulotaront is characterized by significant improvement in positive and negative symptoms of schizophrenia. The safety and tolerability profile of ulotaront is markedly different with respect to antipsychotic class-related AEs. The benefit-risk profile of ulotaront, as a member of a novel TAAR1 agonist class, is distinguished from antipsychotics by lack of AEs related to D2 and serotonin 5-HT2A receptor blockade.

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Review of the TAAR1 Agonist Ulotaront: Part I—From Discovery to Clinic

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Abstract

Introduction. Trace amine-associated receptors (TAARs) are a family of G-protein-coupled receptors (GPCRs) first identified in 2001. TAAR1 has emerged as a promising therapeutic target due to its ability to modulate monoaminergic and glutamatergic neurotransmission. Ulotaront is a trace amine-associated receptor 1 (TAAR1) agonist with serotonin 5-HT1A agonist activity that has received FDA Breakthrough Therapy Designation for the treatment of schizophrenia. Here we provide a brief review of the discovery of ulotaront and preclinical research suggesting efficacy in schizophrenia, leading to the first clinical trial of ulotaront resulting in FDA Breakthrough Therapy Designation.

Methods. Ulotaront was discovered through a target-agnostic approach optimized to identify drug candidates that demonstrate an antipsychotic-like profile in vivo but lack D2 and 5-HT2A receptor antagonism. Ulotaront was further characterized by in vitro pharmacology, electrophysiology, behavioral, and imaging studies.

Results. Ulotaront demonstrated an antipsychotic-like profile in a high-throughput, phenotypic behavior screening platform, as well as efficacy in preclinical models of schizophrenia, including phencyclidine (PCP)-induced hyperactivity, prepulse inhibition of acoustic startle, and subchronic PCP-induced deficits in social interaction. Although not fully elucidated, ulotaront's mechanism of action appears to be mediated by agonism at trace amine-associated 1 (TAAR1) and 5-HT1A receptors. This was further corroborated with whole cell patch clamp recordings, demonstrating inhibition of dorsal raphe nucleus (DRN) and ventral tegmental area (VTA) neuronal firing via 5-HT1A and TAAR1 receptors. Furthermore, ulotaront attenuated the ketamine-induced increase in striatal dopamine synthesis capacity, suggesting that it may modulate presynaptic dopamine dysfunction which is hypothesized to contribute to the pathophysiology of schizophrenia.

Conclusions. Preclinical studies have identified ulotaront as a TAAR1 agonist with antipsychotic-like activity. Ulotaront's unique receptor profile led to its designation as a member of the new "-taront" class of TAAR1 agonists, distinct in pharmacology from the D2/5-HT2A class of antipsychotics. A companion poster will summarize the efficacy and safety of ulotaront based on initial clinical trials in schizophrenia.

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