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Trace amine-associated receptor 1 (TAAR1) agonists

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Schizophrenia is a severe, chronic, and often disabling psychiatric disorder affecting nearly 20 million people worldwide [1]. Schizophrenia persists to be one of the hardest diseases to treat nowadays. Reasons can be found in the heterogeneity within the disease and regards to the treatment response. In general, the first episode occurs in late adolescence and is usually foregone by a prodromal phase characterized by social and cognitive deficits. Positive symptoms tend to appear in a relapsing-remitting fashion, while cognitive and negative symptomatology has a more chronic trajectory and impacts social functioning [2].

Despite the complexity of the disease, current pharmacological treatment primarily relies on dopamine receptor (D_2) blockade. First generation antipsychotics predominantly deploy their action through D_2 receptor blockade. Second-generation antipsychotics exert additional antagonism at other receptors such as those of the serotonin system, such as 5-HT_{2A}. Several antipsychotics also demonstrate additional activity at adrenergic, cholinergic, histaminergic and other serotonergic receptors. Although these additional targets may allocate therapeutic effects, they also contribute to the side effect profile. Currently available antipsychotic agents are effective in treating the positive symptoms of schizophrenia, but they largely leave the negative and cognitive symptom domains uninfluenced [3]. All that being said, there is ample room for improvement and that is the reason new possible psychopharmacologic targets are being evaluated constantly. One of the more promising candidates seems to be the trace amine-associated receptor 1 (TAAR1), due to its potential of modulating monoaminergic and glutamatergic neurotransmission. According to newly published research, TAAR1 agonist compounds show potential for future treatment of schizophrenia and other psychoses.

Trace amines are a group of endogenous chemical messengers which are closely related to the biogenic amine neurotransmitters dopamine, serotonin and norepinephrine. Trace amine concentrations in the central nervous system are low, about several hundred-fold lower than those of classical monoamine neurotransmitters [4]. Since the discovery of the first vertebrate trace amine-associated receptor - TAAR1, there has been an increasing interest in this G-protein coupled receptor as a novel target for the pharmacotherapy of various disorders including psychiatric illness [5].

TAAR1 mRNA and protein expression in rodents has been reported in the ventral tegmental area, substantia nigra, dorsal raphe

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nucleus, amygdala, basal ganglia and the PFC which positions TAAR1 optimally to modulate dopaminergic, serotonergic and glutamatergic neurotransmission and consequently regulate aspects of reward-processing, cognition and mood relevant to schizophrenia and other mental disorders. Presumably, in consequence, development of small-molecule agonists revealed antipsychotic-like, anxiolytic-like, antidepressant-like and pro-cognitive properties of TAAR 1 activation in rodents and non-human primates. All in all, the current preclinical data proposes that TAAR1 agonists have the potential to improve several symptom domains of schizophrenia along with lack of causing adverse effects such as motor impairments or weight gain [5-8].

The only TAAR1 agonist that has currently progressed to Phase 3 clinical trials is ulotaront, which was granted breakthrough therapy designation from the U.S. Food and Drug Administration for the treatment of schizophrenia. The aforementioned molecule was uncovered through a distinctive approach that was optimized to find candidates that lack D_2 and $5HT_2$ receptor antagonism while retaining an antipsychotic-like profile. Although the ulotaront's mechanism of action has not been totally explained, in vitro and in vivo studies demonstrated that full agonism at TAAR1 and partial agonism at 5-HT_{1A} receptors are essential to its efficacy [9]. Additionally, ulotaront demonstrates partial agonism at 5-HT_{1D} and weak functional activity at 5-HT_7 receptors. Pharmacokinetic studies in humans have discovered that at dose levels ranging from 10-100 mg ulotaront is well absorbed and exhibits linear PK dose-proportionality with a median T_{max} of 2.8 hours and an effective half-life of 7 hours [10]. The ongoing Phase 3 studies include two double-blind, placebo-controlled studies, one that enrolled patients aged 12-65 and the other 18-65, which each aim to evaluate the efficacy and safety of fixed doses of ulotaront in patients with an acute exacerbation of schizophrenia [11]. A 52-week, open-label, flexible-dose extension study and an another 52-week study which assessed ulotaront

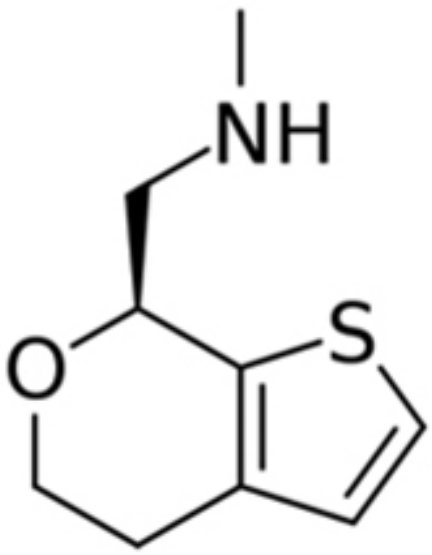

Figure 1. Chemical structure of ulotaront

compared to quetiapine XR in patients with stable schizophrenia [12,13]. Ralmitaront, another TAAR 1 agonist, is currently in Phase 2 development with two double-blind, placebo controlled clinical studies examining the efficacy and safety of ralmitaront in patients with schizophrenia. One study is designed to evaluate two doses of ralmitaront in patients aged 18 to 45 with an acute exacerbation of schizophrenia or schizoaffective disorder over 4 and 12 weeks, while the other aims to assess one dose of ralmitaront over 12 weeks in patients aged 18 to 55 with negative symptoms of schizophrenia as both a monotherapy and as adjunctive therapy to D_2 antagonists or $D_2/5HT_{2A}$ dual antagonists [14,15].

Taken together, preclinical research and recent clinical evidence demonstrates that TAAR1 agonists are a promising novel drug class for the treatment of schizophrenia. Also, we would point out that past work suggests a principally well-tolerated safety profile and potential of negative symptoms treatment for TAAR1 agonists such as ulotaront and ralmitaront which would additionally support this novel mechanism of action.

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