

CADTH Horizon Scan

Trace Amine-Associated Receptor 1 Agonists for Schizophrenia

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ISSN: 2563-6596

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Key Messages

This Horizon Scan summarizes the available information regarding trace amine-associated receptor 1 (TAAR1) agonists, an emerging technology for the treatment of patients with schizophrenia.

- TAAR1 agonists are an emerging drug class in the treatment of schizophrenia as they may offer a novel mechanism of action for symptom management without blocking dopamine D2 receptors, unlike currently available antipsychotic medications that act primarily via D2 binding.
- Two TAAR1 agonists are currently in clinical development for schizophrenia. The first is ulotaront, a TAAR1 full agonist with 5-hydroxytryptamine 1A agonist activity that is administered orally once daily, and the other is ralmitaront, a TAAR1 partial agonist that is also administered orally once daily.
- The published clinical trial evidence on TAAR1 agonists currently only pertains to ulotaront, which includes a 4-week, phase II, placebo-controlled randomized trial on patients with acute exacerbation of schizophrenia and a 26-week, open-label extension study of this same trial. These studies demonstrated improvements across disease-specific and global impression scales following treatment with ulotaront, with statistically significant differences compared to placebo, and no increased risk of the side effects (extrapyramidal symptoms and metabolic changes) associated with traditional D2-binding antipsychotic therapies.
- There is currently no cost information available for TAAR1 agonists.
- Ulotaront is currently undergoing phase III trials and, though it is not currently approved in any country and the date of Health Canada licensing and marketing in Canada is not yet known, it is expected to be the first TAAR1 agonist for schizophrenia in the Canadian market. Ulotaront received Breakthrough Therapy designation from the FDA in 2019 to expedite its development and the drug's manufacturer is planning to file a New Drug Application with the FDA in 2023. Ralmitaront is currently in phase II trials, which are expected to be completed in 2023.

Purpose

The purpose of this Horizon Scan is to present health care stakeholders in Canada with an overview of information related to an emerging drug class, trace amine-associated receptor 1 (TAAR1) agonists, for the treatment of patients with schizophrenia.

This report is not a systematic review and does not involve critical appraisal or include a detailed summary of study findings. It is not intended to provide recommendations for or against the use of the technology.

This Horizon Scan includes a background of the disease area and current details on the drugs in development for this emerging technology, including their regulatory status, a summary of the published clinical trial evidence and ongoing clinical trials, and considerations for future uptake of these drugs. This report is intended to inform health care stakeholders of this emerging drug class as these medications will potentially have a place in therapy in the treatment of patients with schizophrenia in Canada. As a result, health care providers,

decision-makers, and drug plan payers should be aware of their development in anticipation of their future entry into the Canadian drug market.

Methods

Literature Search Strategy

A limited literature search was conducted by an information specialist on key resources including Medline, Embase, PsycInfo, the Cochrane Library, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were trace amine-associated receptor 1 (TAAR1) agonists and schizophrenia. No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents published between January 1, 2017, and January 22, 2022. Updated searches were conducted up until March 14, 2022.

Study Selection

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention was TAAR1 agonists in the treatment of schizophrenia. Conference abstracts and grey literature were included when they provided additional information to that available in the published studies.

Peer Review

A draft version of this bulletin was reviewed by 1 clinical expert. The manufacturers were also given the opportunity to comment on an earlier draft; 1 drug manufacturer (Sunovion Pharmaceuticals Inc.) provided feedback.

Background

Schizophrenia is a chronic and, at-times, debilitating psychiatric disorder, characterized by emotional, behavioural, and cognitive disturbances; patients with this condition have a high risk of relapse.^{1,2} It is 1 of the top 20 causes of disability worldwide and associated with early mortality, with a life expectancy that is approximately 20 years less than that of the general population.³⁻⁵ Schizophrenia develops in early adulthood in most patients, with a peak age of onset in women in their early 30s or younger and men in their early 20s.^{2,6,7} The Canadian Chronic Disease Surveillance System shows that though incident cases of schizophrenia have decreased, its prevalence has increased over time; in 2016, among Canadians 10 years or older, the incidence of schizophrenia was approximately 50 per 100,000 people and its prevalence was approximately 1% of the population.⁸

Symptoms of schizophrenia are classified as positive (e.g., delusions and hallucinations), negative (e.g., lack of motivation and social withdraw), and cognitive (e.g., impaired memory, attention, and problem-solving), and the presence and severity of these symptoms varies

between patients.⁹⁻¹² As symptoms typically appear in early adulthood and there is currently no cure for this disease, many patients require lifelong management.¹³⁻¹⁵ Accordingly, the economic burden of schizophrenia is high.^{4,13,14} The Canadian Institute for Health Information reported that, in 2020, Canadian public drug plans spent \$342 million (or 2.3% of total spending) on antipsychotic drugs for schizophrenia and bipolar disorder.¹⁶ As schizophrenia also results in significant morbidity and early mortality, the productivity loss associated with this disease is also substantial.¹⁷⁻¹⁹ The socioeconomic impact of schizophrenia also worsens with disease progression, as greater disease severity is associated with increased hospitalizations, relapse, unemployment, and caregiver burden, as well as with lower quality of life,^{20,21} highlighting the importance of early and effective treatment.

The goals of treating a patient with schizophrenia are to control their acute symptoms, improve their function, and reduce their risk of relapse and hospitalization.^{13,15} As the societal costs of schizophrenia are attributed to both direct health care costs and productivity loss, achieving these treatment goals would decrease its overall financial burden.¹⁷⁻¹⁹ A major challenge is that schizophrenia represents a heterogeneous population, where patients differ in terms of presentation, course, treatment response, and outcomes.²² Additionally, symptoms of schizophrenia can fluctuate over time, which is influenced by factors such as response to treatment and side effects.²²

Current antipsychotic therapies act on dopamine D2 receptors, which produces a clinical response in patients with schizophrenia but also results in metabolic and motor side effects, namely increased prolactin levels, weight gain, and extrapyramidal symptoms (EPSs).^{9,10,12,23,24} Second-generation, or atypical, antipsychotic drugs also have activity at 5-hydroxytryptamine 2A receptors, which also contributes to weight gain and metabolic changes.^{23,25} Treatment-related side effects are risk factors for poor medication adherence and early death in this patient population, as they may cause patients to experience negative feelings of themselves or lead to the development of comorbid conditions such as diabetes or cardiovascular disease.^{3,25,26} Nonadherence to medication is also a risk factor for relapse and hospitalization.^{12,22} Additionally, currently available antipsychotic medications are effective in the management of positive symptoms, but there is still an unmet need for treatment options that can improve the negative and cognitive symptoms of schizophrenia.^{9-11,25} Antipsychotic therapies are effective for positive symptoms in about 70% of patients, the remainder have treatment-resistant disorder.²² Given these factors, there is a place in therapy for new interventions that do not produce the same side effects associated with current D2-receptor binding drugs and that can also treat the negative and cognitive symptoms of schizophrenia.^{7,9,10,27}

The Technology

In recent years, there have been considerable medical advances made with respect to TAAR1, a guanine nucleotide-binding protein-coupled receptor, and its potential role in treating schizophrenia and other psychiatric disorders.^{9,15,28-30} TAAR1 is found throughout the central nervous system as well as in peripheral tissues, and its expression in key areas of the brain makes it an attractive target for a number of neurologic disorders.^{28,29,31} TAAR1 agonists represent a novel drug class for treating schizophrenia as they do not block D2 receptors.^{10,12,23,25} TAAR1 agonism has been shown to help inhibit firing of a subset of neurons in the ventral tegmental area of the midbrain and play a role in regulating dopamine

and glutamate activity.^{10,23,28,32,33} More specifically, it modulates midbrain dopaminergic hyperactivity and cortical glutamatergic hypoactivity.^{9,28,30,31} Additionally, TAAR1 agonism has demonstrated the potential to treat a wider range of schizophrenia symptoms due to its effect on prefrontal cortical activity, and has shown no increased risk of the metabolic and motor side effects associated with the traditional first-line antipsychotic drugs currently available for schizophrenia.^{27,28,31} Preclinical studies have demonstrated the potential of TAAR1 agonism in the improvement of positive, negative, and cognitive symptoms of schizophrenia, as well as a possible role in the management of mood and anxiety-related behaviours.⁹

Two TAAR1 agonists are currently in clinical development for the treatment of schizophrenia (Table 1).^{9,28,31,34-36} Ulotaront is both a TAAR1 and 5-hydroxytryptamine 1A receptor agonist (5-hydroxytryptamine 1A receptor agonists also have a potential role in schizophrenia treatment), with no activity at 5-hydroxytryptamine 2A, and is administered orally once daily.^{9,10,23-25,37} Animal research demonstrated that ulotaront does not produce significant D2 receptor occupancy at clinically relevant doses, suggesting that its therapeutic effect is not dependent on this mechanism of action.^{10,38} Ralmitaront is another TAAR1 agonist and is also administered orally once daily.^{9,11,31,35,36} These 2 drugs differ in that ralmitaront is a TAAR1 partial agonist, whereas ulotaront is a TAAR1 full agonist.^{31,38}

Regulatory Status

According to the drug’s manufacturer, the expected date of Health Canada licensing and marketing of ulotaront in Canada is not yet known, and it is not currently approved in any country. The manufacturer is planning to file a New Drug Application for ulotaront with the FDA in 2023 and additional filings in other countries will occur thereafter. Ulotaront is currently undergoing phase III trials for schizophrenia and received Breakthrough Therapy designation from the FDA in May 2019 to expedite its development.^{9,15,25,34,36}

Ralmitaront is currently in phase II trials for schizophrenia, which are expected to be completed by 2023.^{6,9,31,35} No additional details regarding the regulatory status of ralmitaront were provided by the drug’s manufacturer.

Cost

There is no cost information currently available for TAAR1 agonists in schizophrenia.

Table 1: TAAR1 Agonists in Development for Schizophrenia

Drug	Development name	Sponsor
Ralmitaront	RG-7906; RO-6889450	F. Hoffmann-La Roche Ltd
Ulotaront	SEP-363856; SEP-856	Sunovion Pharmaceuticals Inc. (co-development with Otsuka Pharmaceutical Co., Ltd.)

TAAR1 = trace amine-associated receptor 1.

Target Population

The population targeted for the use of the emerging drugs described in this report is patients with schizophrenia, which represents more than 300,000 people in Canada.⁸ Ulotaront is being trialled in schizophrenia, but ralmitaront is being trialled in schizophrenia and schizoaffective disorder; the prevalence of schizoaffective disorder in Canada is unknown, though it has been estimated to be approximately one-third that of schizophrenia.^{39,40}

Current Practice

Antipsychotic medications targeting D2 receptors, broadly categorized as first- and second-generation antipsychotic drugs, are the current standard of care for treating patients with schizophrenia globally.^{4,9,10,22,31} There has been no evidence to suggest differences in clinical efficacy between first- and second-generation antipsychotic drugs, except in the case of treatment-resistant disorders where clozapine has demonstrated greater improvement in symptoms.^{9,11,41}

The most recent Canadian Schizophrenia Guidelines for the pharmacotherapy of schizophrenia in adults were published in 2017 and offer recommendations for 6 areas of schizophrenia treatment: (1) first-episode, (2) acute exacerbation, (3) relapse prevention and maintenance, (4) treatment-resistant, (5) clozapine-resistant, and (6) specific symptom domains.²² Across all of these 6 areas, treatment with an antipsychotic medication is recommended, with no specific drug being preferred over another except in the case of treatment-resistant schizophrenia, where only clozapine is recommended; otherwise, treatment decisions are guided by side effect profiles, which differ between medications.²² The American Psychiatric Association Guidelines inform the Canadian Schizophrenia Guidelines and were updated in 2020.⁴ The updated American Psychiatric Association Guidelines did not include any new or contrary guidance relative to the current Canadian Schizophrenia Guidelines in terms of antipsychotic therapies in the treatment of patients with schizophrenia.

Summary of the Evidence

The published phase II or higher clinical trial evidence on TAAR1 agonists in schizophrenia currently only pertains to 2 studies that evaluated the efficacy and safety of ulotaront ([Table 2](#)).^{23,42} Studies investigating ralmitaront in this patient population are currently still ongoing (refer to Ongoing Developments).

Study Design

The efficacy and safety of ulotaront was investigated in a phase II, 4-week, double-blind, placebo-controlled, randomized trial (SEP 361-201; NCT02969382) by Koblan et al. (2020) in adults with an acute exacerbation of schizophrenia.²³ The study by Correll et al. (2021) was a 26-week, open-label extension study (SEP 361-202; NCT02970929) of the SEP 361-201 trial.⁴²

Population

All published trials included adult patients with an acute exacerbation of schizophrenia.^{23,42}

Intervention

Patients who received ulotaront in the SEP 361-201 trial were administered a 50 mg or 75 mg dose of the drug once daily orally.²³ In the SEP 361-202 trial, patients were treated with a 25 mg, 50 mg, or 75 mg once daily oral dose of ulotaront.⁴²

Comparator(s)

The comparator in the SEP 361-201 trial was a matching placebo, while all patients enrolled in the open-label extension study by Correll et al. (2021) received ulotaront as there was no comparator treatment group in this study.^{23,42}

Outcomes

The main efficacy outcomes included in the published trials were the Positive and Negative Syndrome Scale (PANSS), Brief Negative Symptom Scale (BNSS), and Clinical Global Impression (CGI)-Severity. Besides adverse events (AEs), specific safety outcomes included EPSs and changes in metabolic parameters (i.e., body weight, body mass index, fasting metabolic laboratory values, and prolactin levels).

Table 2: Characteristics of Published TAAR1 Agonist Trials in Schizophrenia

Author (year), name of study or clinical trial number, countries	Study design, study duration, sample size	Population	Intervention and comparator	Outcomes
Koblan (2020) ²³ SEP 361-201/NCT02969382 Hungary, Romania, Russia, Ukraine, US	Phase II RCT 4 weeks N = 245	Adults who had an acute exacerbation of schizophrenia	Ulotaront: 50 mg or 75 mg once daily orally (n = 120) Matching placebo once daily orally (n = 125)	PANSS BNSS CGI-Severity Discontinuation AEs EPSs Metabolic changes
Correll (2021) ⁴² SEP 361-202/NCT02970929 Hungary, Romania, Russia, Ukraine, US	Phase II, open-label extension of RCT 26 weeks N = 157	Adults with schizophrenia who completed the SEP 361-201 trial	Ulotaront: 25 mg, 50 mg, or 75 mg once daily orally (n = 157 enrolled; 156 analyzed)	PANSS BNSS CGI-Severity Discontinuation AEs EPSs Metabolic changes

AE = adverse event; BMI = body mass index, BNSS = Brief Negative Symptom Scale, CGI = Clinical Global Impression, EPS = extrapyramidal symptom, PANSS = Positive and Negative Syndrome Scale, RCT = randomized controlled trial.

Results

PANSS

In the SEP 361-201 trial, patients treated with ulotaront exhibited a change from baseline in PANSS total score of -17.2 points at week 4, and the mean difference versus placebo was -7.5 points (95% confidence interval [CI], -11.9 to -3.0) in favour of ulotaront, with statistically significant differences between treatment groups across all PANSS subscales (i.e., positive symptoms, negative symptoms, and general psychopathology subscales).²³ In the open-label extension phase, patients treated with ulotaront exhibited a change from the open-label baseline in PANSS total score of -22.6 (95% CI, -25.6 to -19.6) after 26 weeks; reductions in scores were observed across all subscales in this study as well.⁴²

BNSS

In the SEP 361-201 trial, patients treated with ulotaront exhibited a change from baseline in BNSS total score of -7.1 points at week 4, and the mean difference versus placebo was -4.3 points (95% CI, -6.8 to -1.8) in favour of ulotaront.²³ In the open-label extension phase, patients treated with ulotaront exhibited a change from the open-label baseline in BNSS total score of -11.3 (95% CI, -13.2 to -9.3) after 26 weeks.⁴²

CGI-Severity

In the SEP 361-201 trial, patients treated with ulotaront exhibited a change from baseline in CGI-Severity score of -1.0 points at week 4, and the mean difference versus placebo was -0.5 points (95% CI, -0.7 to -0.2) in favour of ulotaront.²³ In the open-label extension phase, patients treated with ulotaront exhibited a change from the open-label baseline in CGI-Severity score of -1.0 (95% CI, -1.2 to -0.8) after 26 weeks.⁴²

Discontinuation and Safety

Discontinuation

Treatment discontinuation was similar between the ulotaront (26/120 or 21.7%) and placebo (26/125 or 20.8%) groups in the SEP 361-201 trial.²³ At the end of the 26-week open-label extension period, 33.1% (52/157) of patients treated with ulotaront had discontinued the study.⁴²

Adverse Events

In the SEP 361-201 trial, the incidence of AEs between the ulotaront and placebo groups was similar (55/120 or 45.8% versus 63/125 or 50.4%, respectively).²³ The most common AEs with ulotaront included somnolence (8/120 or 6.7% versus 6/125 or 4.8% with placebo) and gastrointestinal symptoms (nausea [6/120 or 5.0% versus 4/125 or 3.2% with placebo], diarrhea [3/120 or 2.5% versus 1/125 or 0.8% with placebo], and dyspepsia [3/120 or 2.5% versus 0/125 or 0% with placebo]). The incidence of insomnia was 3.3% (4/120) in the ulotaront group and 10.4% (13/125) in the placebo group. Severe AEs occurred in 7 out of 120 patients (5.8%) in the ulotaront group and 2 out of 125 patients (1.6%) in the placebo group. Two serious AEs that occurred in the ulotaront group were worsening of schizophrenia (1/120 or 0.8%) and an acute cardiovascular insufficiency that resulted in sudden death (1/120 or 0.8%). Four serious AEs occurred in the placebo group, which included 3 out of 125 patients (2.4%) with a worsening of schizophrenia and 1 out of 125 patients (0.8%) who attempted suicide.

In the 26-week open-label extension study, the most frequently reported AEs following treatment with ulotaront were schizophrenia (19/156 or 12.2%), headache (18/156 or 11.5%), insomnia (13/156 or 8.3%), and anxiety (8/156 or 5.1%).⁴² The majority of AEs were either mild or moderate in severity, with 8 out of 156 patients (5.1%) reporting a severe AE. The only severe AE reported by more than 1 patient was schizophrenia in 5 out of 156 patients (3.2%). Fifteen patients (9.6%) reported a serious AE and no deaths occurred during the study.

Extrapyramidal Symptoms

In the SEP 361-201 trial, the incidence of EPSs was similar between the ulotaront (4/120 or 3.3%) and placebo (4/125 or 3.2%) groups.²³ Additionally, changes from baseline in the measured movement disorder scales (i.e., the Simpson-Angus Scale, Barnes Akathisia Scale, and Abnormal Involuntary Movement Scale) were similar between treatment groups. In the open-label extension phase, scores on movement disorder scales showed no clinically meaningful extrapyramidal effects in patients treated with ulotaront.⁴² Five patients (3.2%) had an AE associated with an EPS during the 26-week period.

Metabolic Changes

In the SEP 361-201 trial, changes in body weight, body mass index, fasting lipid levels (i.e., cholesterol and triglycerides), fasting glucose and glycated hemoglobin, and prolactin levels were similar between the ulotaront and placebo groups.²³ Patients treated with ulotaront in the open-label extension period exhibited minimal changes in these same parameters at the end of the study.

Ongoing Developments

Several international phase II and III clinical trials evaluating ralmitaront or ulotaront in patients with schizophrenia are ongoing ([Table 3](#)). Of these trials, 2 are phase II trials investigating the use of ralmitaront, in which 1 study is a placebo-controlled trial on adults with schizophrenia or schizoaffective disorder and negative symptoms, and the other study is on patients with acute exacerbation of schizophrenia or schizoaffective disorder where the investigational drug is being evaluated against an active comparator (risperidone). Six ongoing trials (DIAMOND 1 to 6) were identified investigating ulotaront. Two of these trials (DIAMOND 1 and 2) are 6-week, phase III, placebo-controlled randomized controlled trials (RCTs) in patients who have schizophrenia and are acutely psychotic; DIAMOND 1 includes both adolescents and adults while DIAMOND 2 includes adults only. DIAMOND 3 is a 52-week, open-label extension study on ulotaront in patients who complete DIAMOND 1 and 2. DIAMOND 4 is a 52-week, phase III RCT in clinically stable adults with schizophrenia and includes an active comparator (quetiapine). DIAMOND 5 is a 6-week, phase II-III, placebo-controlled RCT with a 12-week open-label extension phase in acutely psychotic adults with schizophrenia, and DIAMOND 6 is a 52-week open-label study in patients with schizophrenia treated with ulotaront; both of these studies are enrolling patients in Japan only.

Table 3: Ongoing TAAR1 Agonist Clinical Trials

Drug	Study name and clinical trial number	Study sponsor	Study design and estimated completion date	Study objective(s)	Primary end point
Ralmitaront	BP40283 NCT03669640; EudraCT 2020-004752-16	F. Hoffmann-La Roche Ltd	Phase II RCT (16 weeks) Adults with schizophrenia or schizoaffective disorder and negative symptoms N = 247 Japan, Spain, Ukraine, US May 2023	To compare the efficacy of once-daily ralmitaront vs. placebo	Change from baseline in the BNSS avolition-apathy subscale at 12 weeks
	NCT04512066	F. Hoffmann-La Roche Ltd	Phase II RCT (48 weeks) Acute exacerbation of schizophrenia or schizoaffective disorder N = 308 Japan, Russia, Ukraine, US April 2023	To compare the efficacy and safety of once-daily ralmitaront vs. placebo vs. risperidone	Change from baseline in PANSS total score at 4 weeks
Ulotaront	DIAMOND 1 or SEP361-301 NCT04072354; EudraCT 2019-000470-36	Sunovion Pharmaceuticals Inc.	Phase III RCT (6 weeks) Acutely psychotic patients (13 to 65 years) with schizophrenia N = 525 January 2023 Bulgaria, Russia, Serbia, Ukraine, US	To compare the efficacy and safety of 2 doses of once-daily ulotaront vs. placebo	Change from baseline in PANSS total score at 6 weeks
	DIAMOND 2 or SEP361-302 NCT04092686; EudraCT 2019-000697-37	Sunovion Pharmaceuticals Inc.	Phase III RCT (6 weeks) Acutely psychotic adult patients with schizophrenia N = 462 February 2023 Bulgaria, Latvia, Russia, Serbia, Ukraine, US	To compare the efficacy and safety of 2 doses of once-daily ulotaront vs. placebo	Change from baseline in PANSS total score at 6 weeks
	DIAMOND 3 or SEP361-303 NCT04109950; EudraCT 2019-000696-16	Sunovion Pharmaceuticals Inc.	Phase III, open-label extension study (52 weeks) on patients who completed DIAMOND 1 or DIAMOND 2 Patients between 13 and 65 years of age with schizophrenia	To evaluate the long-term safety and tolerability of ulotaront	The incidence of AEs, serious AEs, and AEs leading to discontinuation

Drug	Study name and clinical trial number	Study sponsor	Study design and estimated completion date	Study objective(s)	Primary end point
			N = 555 Bulgaria, Latvia, Russia, Serbia, Ukraine, US February 2024		
	DIAMOND 4 NCT04115319	Sunovion Pharmaceuticals Inc.	Phase III RCT (52 weeks) Clinically stable adults with schizophrenia N = 300 Romania, Russia, Ukraine, US January 2023	To evaluate the long-term safety and tolerability of ulotaront vs. quetiapine XR	The incidence of AEs, serious AEs, and AEs leading to discontinuation
	DIAMOND 5 NCT04825860; jRCT2071210003	Sumitomo Pharma Co., Ltd. (Sunovion Pharmaceuticals Inc. is a US subsidiary of Sumitomo Pharma Co., Ltd.)	Phase II-III RCT (6 weeks) with an open-label extension phase (12 weeks) Adult patients with schizophrenia who were acutely psychotic N = 480 Japan June 2025	To compare the efficacy and safety of 2 doses of once-daily ulotaront vs. placebo	Change from baseline in PANSS total score at 6 weeks
	DIAMOND 6 NCT05359081	Sunovion Pharmaceuticals Inc.	Phase III open-label study (52 weeks) Clinically stable adults with schizophrenia N = 220 Japan March 2025	To evaluate the long-term safety and tolerability of ulotaront	The incidence of AEs, serious AEs, and AEs leading to discontinuation

AE = adverse event; BNSS = Brief Negative Symptom Scale; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; vs. = versus; XR = extended release.

Additional Considerations

Uptake

TAAR1 agonists may have a future role in the management of schizophrenia given their potential to fill unmet needs for this patient population. These include the need for non-D2-receptor binding agents to reduce the occurrence of side effects associated with current antipsychotic therapies and the need for options that can treat the broader range of schizophrenia symptoms, not just the positive symptoms. Additional research is needed on this emerging drug class as the published evidence is currently limited to a 4-week, phase II, placebo-controlled trial with a 26-week, open-label extension period on ulotaront in adults with

acute exacerbation of schizophrenia. Additionally, neither of the 2 TAAR1 agonists currently in development have yet been approved in any country.

Future studies on these drugs should evaluate their long-term efficacy, safety, and treatment adherence; confirm their efficacy across the positive, negative, and cognitive symptoms of schizophrenia; and establish their relative effects compared to current antipsychotic medications. Given this heterogenous patient population and availability of both oral and long-acting injectable antipsychotic formulations,⁴³ such investigations will help identify which individuals will benefit most from the use of TAAR1 agonists and determine their place in therapy.

The cost of these therapies, when available, will also need to be considered. As there are a number of antipsychotic medications currently available for schizophrenia, comparative cost-effectiveness studies and budget impact analyses will also be needed to help inform public payer reimbursement of these emerging drugs. Given manufacturer timelines and the current status of ongoing trials, it is expected that ulotaront will be the first TAAR1 agonist for schizophrenia available in the Canadian market.

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