Understanding the Role of TAAR1 Agonism in Schizophrenia:

Framing the Story Around the Whole Patient

schizophrenia360

Psych Congress MasterClass

Supported by an independent educational grant from
Sumitomo Pharma America, Inc and Otsuka America Pharmaceutical, Inc.

Examining TAAR1 Agonists

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All current treatments for schizophrenia involve direct binding to the D_2 receptor, and this lack of diversity has led to stagnation of both efficacy and tolerability.

Limitations of Current Standard of Care[1-6]

Unequal efficacy on core symptoms
Much lower efficacy for negative and cognitive symptoms, although their burden may be higher

Psychiatric comorbidities
Inadequately addressing common comorbidities (substance use disorder [SUD], depression, anxiety) can worsen outcomes

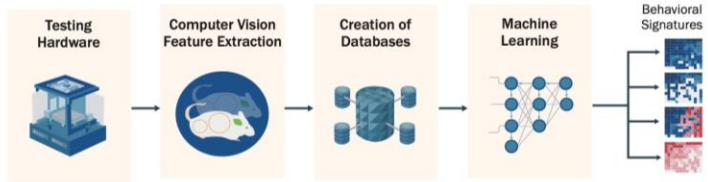
Medical comorbidities
May exacerbate preexisting risk of hyperglycemia (20%), dyslipidemia (40%), obesity (50%)

Adverse effects of medications
Patient perception of adverse effects (AEs) can reduce adherence, and first episode psychosis (FEP) patients are more susceptible to AEs

- One of the top 15 leading causes of disability worldwide
- More than 5% of people with schizophrenia die by suicide
- More excess cardiovascular deaths than from suicide
- Overall life expectancy reduced 10-20 years

- ~30% are resistant to treatment with D_2 antagonists
- ~30%-60% have a partial response or intolerability to medications
- ~10% achieve recovery[7-9]

A large body of preclinical evidence supports that TAAR1 agonists may reduce presynaptic synthesis and release of dopamine as well as have other potentially beneficial effects on symptoms commonly seen in serious mental illness.



A machine learning algorithm was trained to recognize the behavioral signatures of mice given known antipsychotics, antidepressants, and anxiolytics.

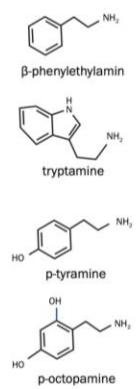
Artificial intelligence identified what, if any, psychotropic effects novel compounds had when given to mice in susequent trials.[10]

This occurs without regard to the receptor pharmacology of the compounds, eliminating the bias of favoring compounds with known mechanisms.

Thousands of compounds were screened—excluding any with D_2 or 5-HT_{2A} binding.

A compound displaying antipsychotic, anxiolytic, antidepressant, and wake-promoting properties was discovered.[10]

Trace Amines[11]



Monoamines[11]

The existence of trace amines has been known for a century, but they were thought to be incidental metabolites of monoamines.

Structurally related to classic monoamine neurotransmitters, but found in concentrations many-fold lower in the brain.

TAARs (trace amine-associated receptors) were only discovered in 2001, in part because of their predominantly intracellular nature.

TAARs modulate neurotransmission of monoaminergic neurons.

Humans express 6 of the 26 known TAAR receptors, but TAAR1 is believed to be the most important in neuropsychiatric disease.[11-14]

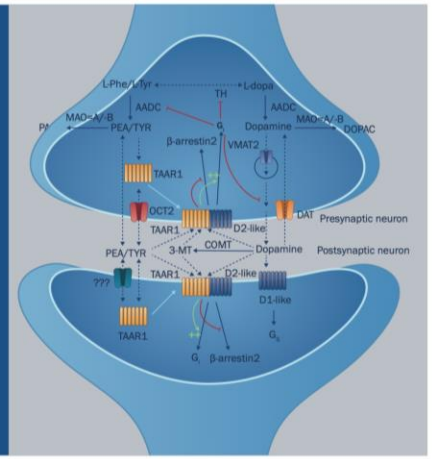
A novel approach to drug discovery brought renewed interest in the trace amine system.

TAAR1 Agonists Exert Antipsychotic Effects via Pre- and Postsynaptic activity[15]

TAAR1 receptors form heterodimers with D_2 receptors on presynaptic and postsynaptic neurons.

TAAR1 **agonists** decrease the firing rate in midbrain ventral tegmental dopamine neurons, while **antagonists** increase dopamine release.

TAAR1 **agonists** act postsynaptically via the Akt/β arrestin2/GSK3β pathway to reduce dopamine-driven behaviors.



Summary of Preclinical Data on TAAR1 Agonists[16]

Antipsychotic: Blocks the behavioral effects of stimulants (eg, cocaine, amphetamine), and NMDA glutamate antagonists.

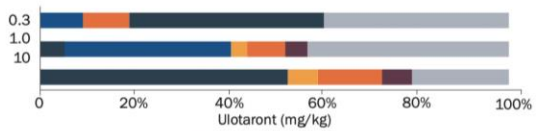
Potentiates the effects of antipsychotics (eg, olanzapine) on amphetamine-induced hyperactivity, but does not induce catalepsy and reduces the catalepsy from haloperidol.

Antidepressant: Based on behavioral response in forced swim test and behavioral reinforcement in primates.

Procognitive: Improves attentional set shifting in rodents and object retrieval in primates.

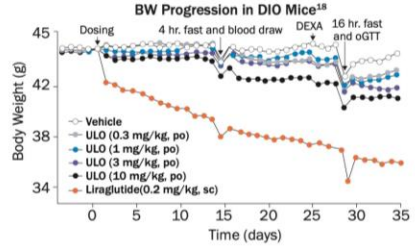
Metabolic: Prevents olanzapine-related weight gain and fat accumulation in mice.

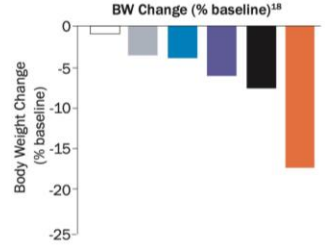
There Are Candidate Antipsychotic Molecules with TAAR1 Angonist Properties[10]



Novel TAAR1 agonists include ulotaront and ralmitaront

Ulotaront is an investigational compound that shows preclinical evidence of efficacy across a broad range of neuropsychiatric symptoms and reduced body weight in rodent models of obesity.





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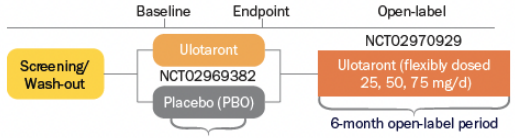
Ulotaront Efficacy Data

Authors – Craig Chepke, MD, DFAPA, Rakesh Jain, MD, MPH

Phase 2b Study Design

Dosing

Started with 50 mg each night at bedtime (QHS) days 1–3, and could be increased to 75 mg QHS on day 4 (or at weekly intervals through week 3) based on investigator judgment, with option of reduction to 50 mg for judgment reasons.



Double-blind, placebo controlled, 4-week, phase 2 inpatient trial

Patient characteristics

Characteristic	Ulotaront (N=120)	Placebo (N=125)
Age—yr	30.0 ± 5.8	30.6 ± 6.1
Sex—no. (%)		
Male	43 (35.8%)	46 (36.8%)
Female	77 (64.2%)	79 (63.2%)
Race—no. (%)		
White	19 (15.8%)	20 (16.0 %)
Black	5 (4.2%)	1 (0.8 %)
Other	96 (80.0%)	104 (83.2%)
Hispanic ethnic group—no. (%)	5 (4.2 %)	6 (4.8 %)

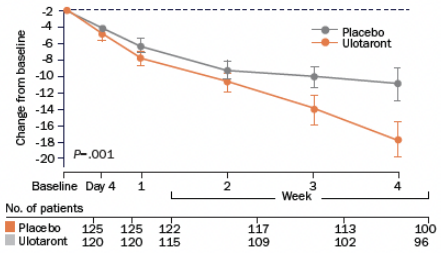
Characteristic	Ulotaront (N=120)	Placebo (N=125)
PANSS score		
Total	101.4 ± 8.4	99.7 ± 7.8
Positive subscale	25.8 ± 3.3	25.4 ± 3.1
Negative subscale	24.7 ± 3.9	24.9 ± 4.0
Clinical Global Impression-Severity (CGI-S) scale score	5.0 ± 0.4	4.9 ± 0.5
BNSS total score	37.2 ± 11.5	37.4 ± 11.0
Body mass index	25.0 ± 4.3	24.7 ± 3.7
Years since initial onset of schizophrenia	5.3 ± 4.8	5.5 ± 4.8
No. of prior psychiatric hospitalizations	1.3 ± 0.7	1.2 ± 0.7

Efficacy based on positive and negative syndrome scale (PANSS) total score

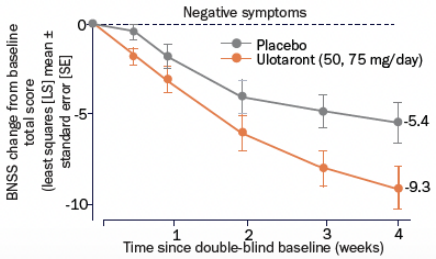
PANSS reduction:

Placebo: 9.7 ± 1.6 pts

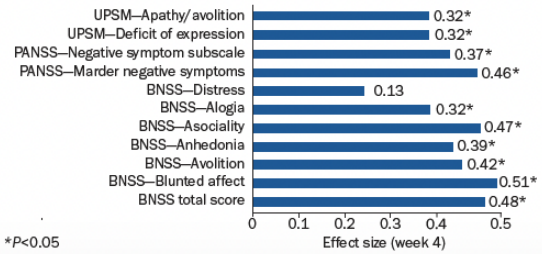
Ulotaront: 17.2 ± 1.7 pts
(*P* =0.001; effect size: 0.45)



Efficacy based on the brief negative symptom scale (BNSS)



Effect sizes of negative symptom measures at week 4 (ulotaront vs placebo)



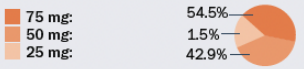
*P<0.05

6-month open-label extension

Method
Participants who completed the 4-week trial could enroll. All were started on 50 mg for 3 days, with flexible dosing in the range of 25–75 mg.

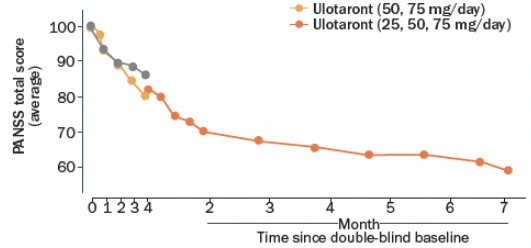
Disposition
N=156, with 66.9% completing. Causes of dropout:

Endpoint dosing



Safety
No significant change in metabolic parameters or prolactin, and 0.3 kg weight loss.

Note: A further 22.6-point improvement in total PANSS occured during the (OLE) phase



Phase 3 Clinical Trials

Study Element	DIAMOND[1] Schizophrenia Study SEP361-301 (Acute Study)	DIAMOND[2] Schizophrenia Study SEP361-302 (Acute Study)	DIAMOND[3] Schizophrenia Study SEP361-303 (Open-Label Extension)	DIAMOND[4] Schizophrenia Study SEP361-304 (Long-Term Safety Study)	DIAMOND[5] Schizophrenia Study SEP-363856 (Acute Study)
Clinicaltrials.gov identifier	NCT04072354	NCT04092686	NCT04109950	NCT04115319	NCT04825860
Study duration	6 weeks	6 weeks	52 weeks	52 weeks	6 weeks
Setting	Inpatient	Inpatient	Outpatient	Outpatient	Inpatient
Dosing type	Fixed	Fixed	Flexible	Flexible	Fixed
Ulotaront dosing	50 mg 75 mg	75 mg 100 mg	25–100 mg	50–100 mg	50 mg 75 mg
Comparators	Placebo	Placebo	None (open-label)	Quetiapine XR 400–800 mg	Placebo
Population	Acutely psychotic	Acutely psychotic	Rollover patients from 301 & 302	Stable patients	Acutely psychotic
Age	13–65 years	18–65 years		18–65 years	18–65 years
Randomization ratio	1:1:1	1:1:1		2:1 (Ulotaront:QXR)	1:1:1
Sample size	525	462	555	300	480
LS Mean PANSS CFB Placebo	–19.3	–14.3	In progress	In progress	In progress
LS Mean PANSS CFB Ulotaront	50 mg = –16.9 75 mg = –19.6	75 mg = –16.4 100 mg = –18.1			
Ulotaront-Placebo difference (*p*)	50 mg = +2.4 (ns) 75 mg = –0.3 (ns)	75 mg = –2.1 (ns) 100 mg = –3.8 (ns)			

CONCLUSIONS: Ulotaront showed acute efficacy vs placebo in a 4-week phase 2b trial on the PANSS total score. There was also notable efficacy on a variety of secondary measures on negative symptoms.

1. Kohlan KS, et al. N Engl J Med. 2020;382(16):1497-1506. 2. Hopkins SC, et al. Effects of SEP-363856 on negative symtoms in schizophrenia: analysis of an acute, placebo-controlled trial of a novel psychotropic agent with no dopamine-D2/5-HT2A antagonist activity. Presented at: 2019 ACNP Annual Meeting; December 8–11, 2019; Orlando, FL. 3. Hopkins SC, et al. Presented at: Psych Congress; Sept 17-20, 2022; New Orleans, Louisiana.
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Ulotaront Safety and Tolerability

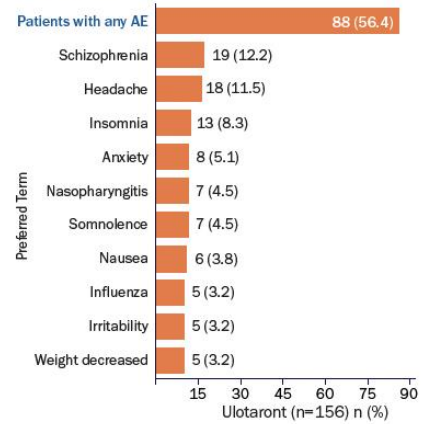
Authors – Craig Chepke, MD, DFAPA, Rakesh Jain, MD, MPH

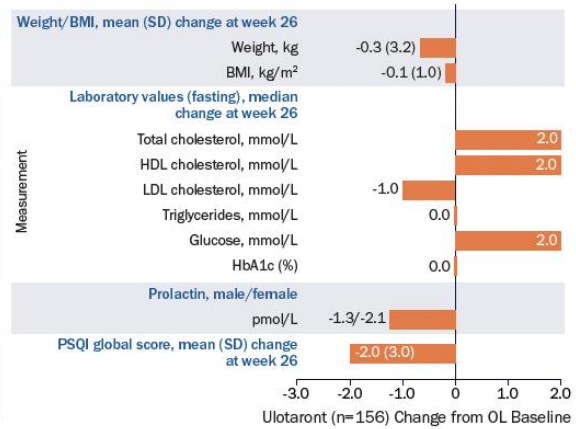
4-Week Phase 2b Acute Efficacy Trial

Variable	Ulotaront 50 mg or 75 mg	Placebo
Adverse events—no./total no. (%)		
Any adverse event	55 / 120 (45.8)	63 / 125 (50.4)
Somnolence	8 / 120 (6.7)	6 / 125 (4.8)
Agitation	6 / 120 (5.0)	6 / 125 (4.8)
Nausea	6 / 120 (5.0)	4 / 125 (3.2)
Diarrhea	3 / 120 (2.5)	1 / 125 (0.8)
Dyspepsia	3 / 120 (2.5)	
Serious adverse events—no./total no. (%)		
Worsening of schizophrenia	0.3 ± 1.9	3/125 (2.4)
Sudden cardiac death	0.3 ± 1.9	0/125
Suicide attempt	0/120	1/125 (0.8)
Changes from baseline in body weight and body mass index at week 4		
Body weight—kg	0.3 ± 1.9	-0.1 ± 2.3
Body mass index	0.1 ± 0.6	0.0 ± 0.8
Median changes from baseline in fasting metabolic laboratory values at week 4		
Total cholesterol—mmol/liter	-0.2	0.0
Low-density lipoprotein (LDL) cholesterol—mmol/liter	-0.1	0.0
Triglycerides—mmol/liter	0.0	0.1
Glucose—mmol/liter	0.0	-0.1
Glycated hemoglobin—%	0.0	0.0
Median change from baseline in prolactin level at week 4, male/female—mmol/liter	-0.037 / -0.175	-0.036 / -0.101
Discontinuation	22%	21%
Extrapyramidal effects (EPS) (akathisia, restlessness, musculoskeletal or joint stiffness, tremor, and nuchal rigidity)	3.3%	3.2%

Discontinuation due to AEs: ulotaront = 8.3% vs placebo = 6.4%; NNH = 52 (ns)

26-Week Open Label Extension





- Ulotaront is an oral compound that does not bind to D_2 receptors.
- It acts as an agonist at TAAR1 and 5-HT_{1A} receptors.
- It may represent a new class of psychotropic agents for the treatment of the full spectrum of symptoms of schizophrenia.

CONCLUSIONS: In both 4-week acute and 6-month long-term phase 2b studies, ulotaront showed minimal to no side effects characteristic of D_2 binding treatments for schizophrenia such as:

Weight gain | Metabolic disturbances | Drug-induced movement disorders

Ulotaront was described as being 'generally safe and well-tolerated' in the completed phase 3 trials by the studies' sponsors, but specific data is forthcoming.

Ulotaront remains a promising potential treatment for schizophrenia and other neuropsychiatric conditions.

1. Kobian KS, et al. *N Engl J Med.* 2020;382(16):1497-1506. 2. Correll, Christoph U., et al. "Safety and effectiveness of ulotaront (SEP-363856) in schizophrenia: results of a 6-month, open-label extension study." *NPJ Schizophrenia* 7.1 (2021): 63. 3. Hopkins, SC, et al. Poster Presented at: Psych Congress; New Orleans; Sept 17-20, 2022 4. Dedic N, et al. Presented at: Psych Congress; Sept 17-20, 2022; New Orleans, Louisiana.

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Faculty Disclosures

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- This activity has been independently reviewed for balance.

Learning Objectives

- Summarize the persistent unmet needs and burdens associated with schizophrenia with regards to disability, morbidity, mortality, and quality of life
- Assess the treatment limitations associated with conventional antipsychotics for schizophrenia that directly alter postsynaptic D_2, including adverse effects, nonresponse, and nonadherence
- Describe the pathophysiologic role of TAAR1 in schizophrenia and the pharmacodynamics of novel TAAR1 agonists in comparison to current D_2 antagonists
- Evaluate the most recent efficacy, tolerability, and safety data associated with novel TAAR1 agonists and the clinical potential of these emerging agents

D_2=dopamine D_2 receptor; TAAR1 = trace amine-associated receptor 1.

What is Schizophrenia?

Schizophrenia

- Schizophrenia is a severe, chronic, disabling psychotic disorder, characterized by symptoms grouped into ***positive***, ***negative***, and ***cognitive*** domains

- First episode of psychosis typically occurs in late adolescence or early adulthood, frequently preceded by ***prodromal phase*** with cognitive and social deficits

Positive Symptoms

- Represent an ***excess*** of or distortion of normal functioning
  - delusions, hallucinations, disorganized behavior
- Typically occur in a ***relapsing***/***remitting*** fashion
- Most often ***dramatic***, drawing attention of family members, medical professionals, law enforcement

Negative symptoms

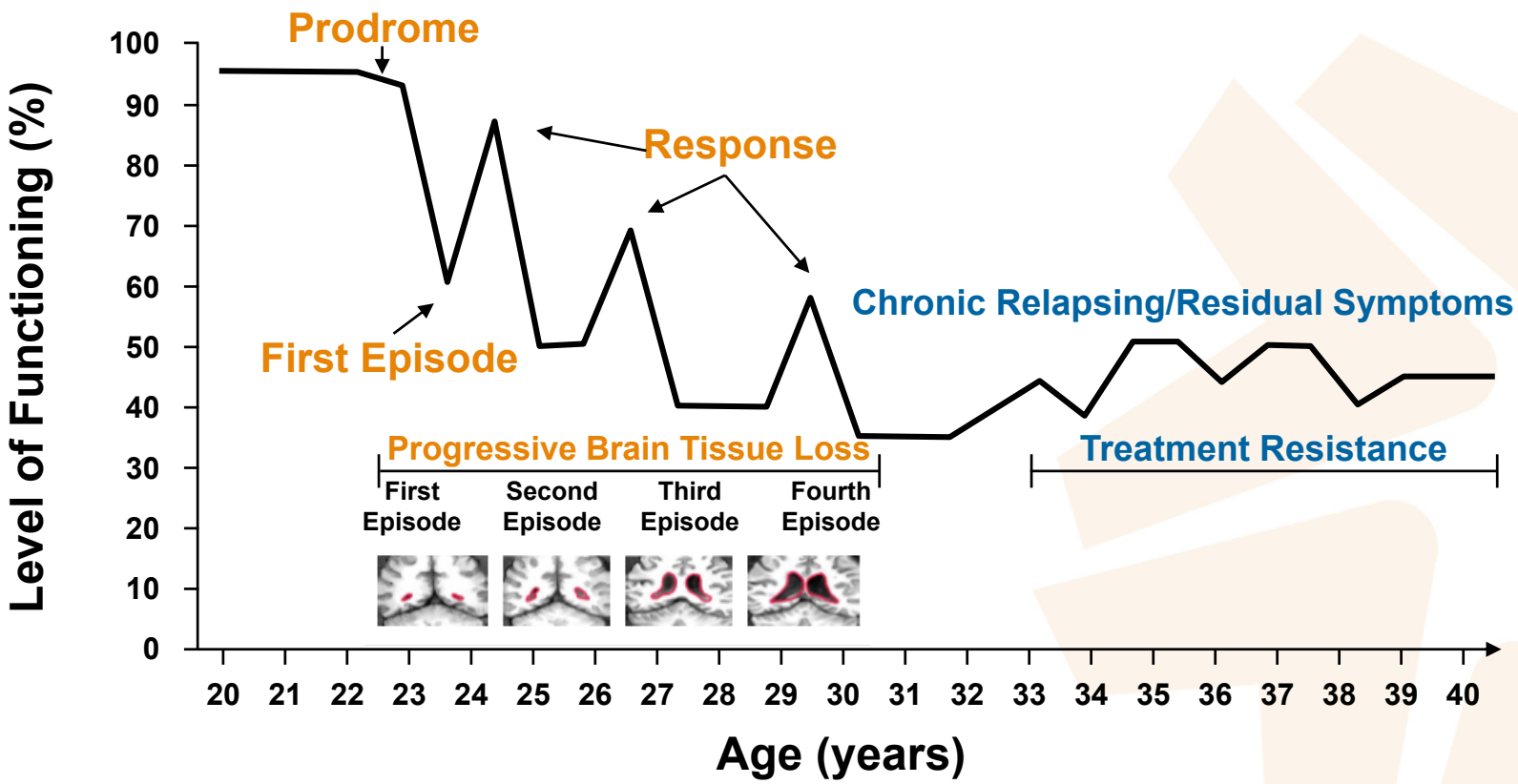
- Represent a ***deficit*** from normal behavior and functioning
  - anhedonia, alogia, blunting, avolition
- Tend to ***persist*** between psychotic episodes, having greater impact on social/occupational functioning
- Can be part of the prodrome before full onset and thus, particularly important to identify

Cognitive symptoms

- ***Deficits*** in working memory, attention and processing, executive functioning
- Deficits ***present before*** first episode of psychosis
  - manifesting as lower IQ scores as compared to general population
- Tend to be ***chronic*** and ***persisting*** between psychotic episodes, thus having greater functional impact

Faden J, et al. *Med Clin North Am.* 2023;107(1):61-72. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Text Revision. American Psychiatric Association Publishing; 2022.

Relapses Increase Risk of Treatment Resistance



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Physical Comorbidities

Infectious

- HIV
- Hepatitis B/C

Cardiovascular

- Hypertension
- Stroke

Respiratory

- Chronic obstructive pulmonary disease
- Asthma

Metabolic

- Diabetes
- Obesity
- Metabolic syndrome

These physical illnesses and disease categories were consistently reported to be more common compared with the general population.

De Hert M, et al. *World Psychiatry*. 2011;10(1):52-77. Bahorik AL, et al. *J Psychosom Res*. 2017;100:35-45. Carney CP, et al. *J Gen Intern Med*. 2006;21(11):1133-1137. Beyer J, et al. *Neuropsychopharmacology.* 2005;30(2):401-404. Carney CP, et al. *Psychosom Med*. 2006;68(5):684-691.

Mortality Risk

2.52×
risk of mortality

Meta-analysis of 135 studies

↓10-25 years

A 2014 fact sheet from the World Health Organization suggested there is a 10- to 25-year life expectancy reduction in patients with severe mental disorders.

Correll CU, et al. *World Psychiatry*. 2022;21(2):248-271. World Health Organization [www.who.int]. Last updated June 8, 2022. Accessed March 16, 2023. https://www.who.int/news-room/fact-sheets/detail/mental-disorders.

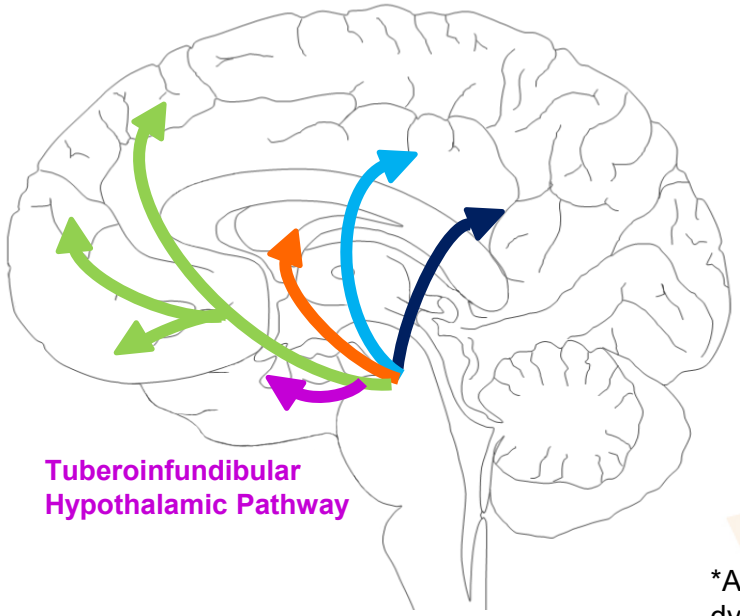
Current Antipsychotic Treatment Options In Schizophrenia

Disruptions of DA Pathways in Schizophrenia Lead to Changes in Other Circuits[1,2]

Mesolimbic Pathway*
(Limbic Striatum)
- Negative symptoms

Nigrostriatal Pathway 1
(Associative Striatum)
- Psychosis

Mesocortical Pathway
- Negative symptoms
- Cognitive symptoms
- Depression



Tuberoinfundibular Hypothalamic Pathway

Nigrostriatal Pathway 2
(Sensorimotor Striatum)
- Dystonia
- Akinesia
- Rigidity
- Tremor
- Dyskinesia

- Negative symptoms: **underactivity** in the **mesolimbic** and **mesocortical** pathways
- Cognitive dysfunction: **underactivity** in the **mesocortical** pathway
- Positive symptoms: **overactivity** in the **nigrostriatal** pathway 1

*Advances in neuroimaging techniques found that DA dysfunction in schizophrenia is highest within nigrostriatal pathways, indicating the dorsal striatum is involved in the illness. DA overactivity in the circuit from the dorsomedial substantia nigra to the associative and adjacent sensorimotor striatum is linked to positive symptoms.[2]

DA=dopamine.

1. Correll CU et al. *J Clin Psychiatry.* 2022;83(1):SU21204IP1.
2. McCutcheon RA et al. *Trends Neurosci.* 2019;42(3):205–220.

D_2 Receptor Blockade Reduces Transmission in all Dopaminergic Pathways

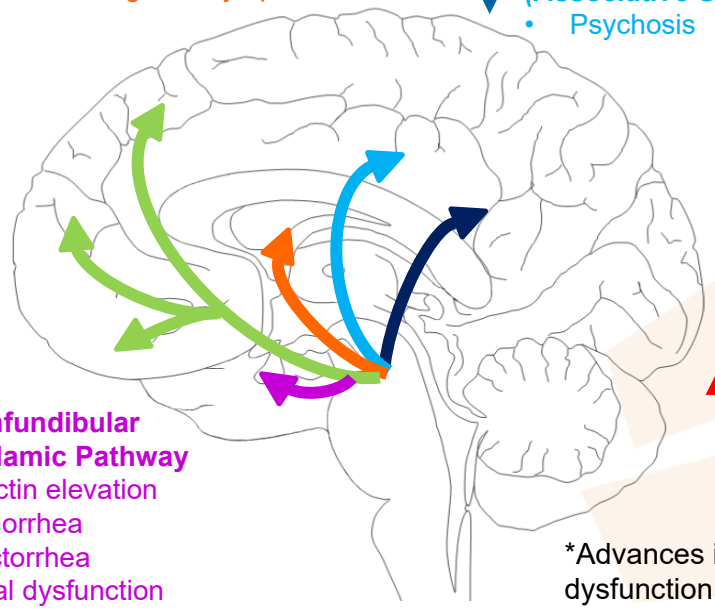
↑ Underactivity of these circuits is associated with schizophrenia; the goal is to increase the activity

↓ Overactivity of this circuit is associated with schizophrenia; the goal is to reduce the hyperactivity

↑ Mesolimbic Pathway* ***(Limbic Striatum)***
- Negative symptoms

↓ Nigrostriatal Pathway ***(Associative Striatum)***
- Psychosis

↑ Mesocortical Pathway
- Negative symptoms
- Cognitive symptoms
- Depression



↑ Nigrostriatal Pathway ***(Sensorimotor Striatum)***
- Dystonia
- Akinesia
- Rigidity
- Tremor
- Dyskinesia

↑ Tuberoinfundibular Hypothalamic Pathway
- Prolactin elevation
- Amenorrhea
- Galactorrhea
- Sexual dysfunction

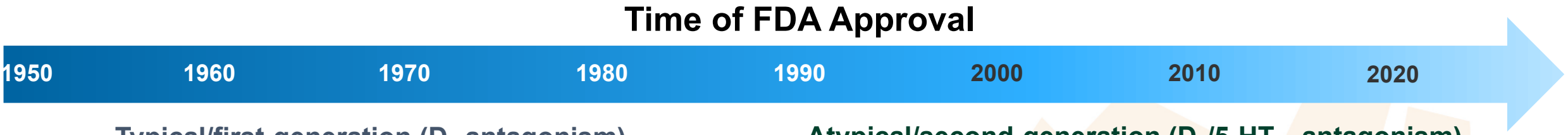
*Advances in neuroimaging techniques found that DA dysfunction in schizophrenia is highest within nigrostriatal pathways, indicating the dorsal striatum is involved in the illness. DA overactivity in the circuit from the dorsomedial substantia nigra to the associative and adjacent sensorimotor striatum is linked to positive symptoms.[2]

DA=dopamine.

1. Correll CU et al. J Clin Psychiatry. 2022;83(1):SU21204IP1.

2. McCutcheon RA et al. Trends Neurosci. 2019;42(3):205–220.

70 Years of Similar Treatments



Typical/first-generation (D_2 antagonism)

Atypical/second-generation (D_2/5-HT_{2a} antagonism)

Dopamine partial agonists

Despite the large number of available AP treatments:

All APs work via essentially the same mechanism

1 out of every 3 patients do not respond

Negative and cognitive symptoms may persist

Residual symptoms

Varying levels of side effects and long-term risks may contribute to negative outcomes and poor adherence

5-HT2A = serotonin 2A receptor; D_2 = dopamine D_2 receptor; FDA = US Food and Drug Administration.

Correll CU, et al. *J Clin Psychiatry*. 2022;83(1):SU21204IP1. Kane JM. *J Clin Psychiatry*. 2022;42(5 Suppl 1):S1-S13. Schultz SH, et al. *Am Fam Physician*. 2007;75(12):1821-1829. CLOZARIL® (clozapine) [prescribing information]. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/019758s101lbl.pdf. Faden J, et al. *Med Clin North Am*. 2023;107(1):61-72. Howes OD, et al. *Am J Psychiatry*. 2017;174(3):216-229. DiBonaventura M, et al. *BMC Psychiatry*. 2012;12:20.

Limitations of Current Treatment

Treatment Resistance

- ~30% of patients with schizophrenia are resistant to D2 antagonism
- 30-60% have a partial response or intolerability to medications used for treatment
- ~14% achieve recovery (long-term remission + good functional outcome)

Negative & Cognitive Symptoms

- Lower efficacy for addressing negative and cognitive symptoms, though their burden on quality of life may be higher
- Up to 60% of patients have been categorized as having prominent or predominant negative symptoms

Comorbidities

- Current treatments can exacerbate preexisting medical comorbidities
- Current treatments may inadequately address psychiatric comorbidities and greater than 50% of patients have psychiatric comorbidity

Adverse Effects of Medications

- Discontinuation rates in the CATIE trial due to side effects varied from 10-31%
- Side effects can contribute to reduced life expectancy and stigma
- Contributes to treatment noncompliance

Lieberman JA, et al. *N Engl J Med*. 2005;353(12):1209-1223; Dedic N, et al. *Int. J. Mol. Sci.* 2021;22(13185); Yeomans D, et al. *Advances in Psychiatric Treatment*. 2010;16(2):86-95.

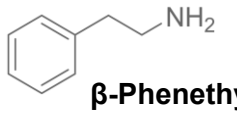
Key Learning Points

- **Negative** and **cognitive** symptoms are most strongly associated with impairments to patients' daily lives
- Approximately **30%** of patients are resistant to D2 antagonist antipsychotic treatment
- All conventional antipsychotic agents work via what is essentially the same mechanism

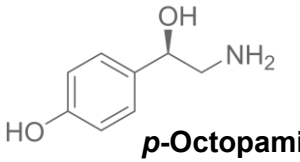
Emerging Treatment Options In Schizophrenia: TAAR1 Agonists

Trace Amines and TAARs

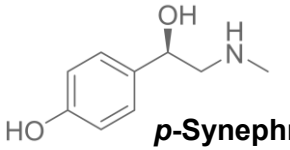
Traditional TAs



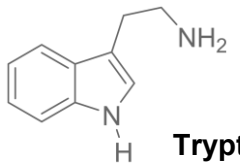
β-Phenethylamine



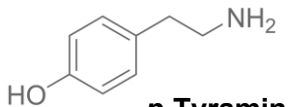
***p*-Octopamine**



***p*-Synephrine**

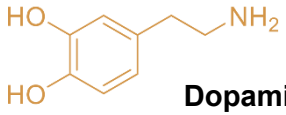


Tryptamine

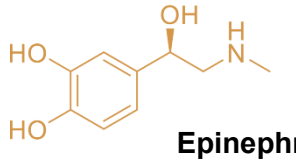


***p*-Tyramine**

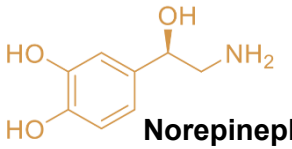
Monoamine Neurotransmitters



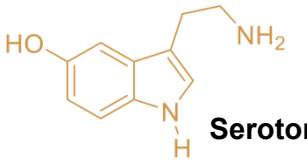
Dopamine



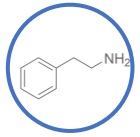
Epinephrine



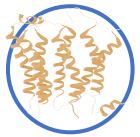
Norepinephrine



Serotonin



- Trace amines (TAs)
  - Endogenous chemical messengers
  - Structurally similar to monoamine neurotransmitters, DA, NE, and 5-HT
  - Expressed at levels at least 100-fold lower than corresponding neurotransmitters



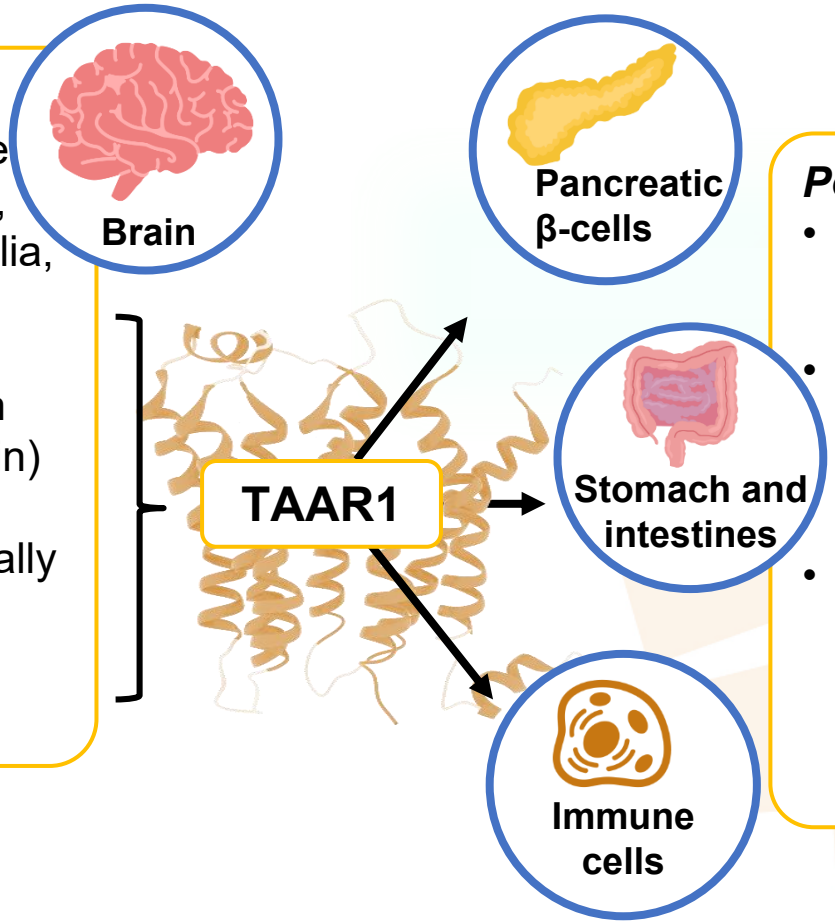
- Trace amine-associated receptors (TAARs)
  - In 2001, TAs were found to selectively activate a family of receptors called TAARs
  - Most studied is TAAR1 (the main TAAR in humans)

5-HT=serotonin; DA=dopamine; NE=norepinephrine; TA=trace amine; NH_2=azanide; OH/HO=hydroxide; N=nitrogen; H = hydrogen. Nair PC, et al. *Mol Psychiatry*. 2022;27(1):88-94. Gainetdinov RR, et al. *Pharmacol Rev*. 2018;70(3):549-620. Dedic N, et al. *Int J Mol Sci*. 2021;22(24):13185.

Where is TAAR1 Expressed?

Brain

- In rodent brains, expression has been reported in the VTA, SN, and DRN, limbic areas (eg, Amy), basal ganglia, and the PFC
- Predominantly intracellular, but can move to the membrane (and back in)
- Found both pre- and post-synaptically
- Can form heterodimers with other receptors



Periphery

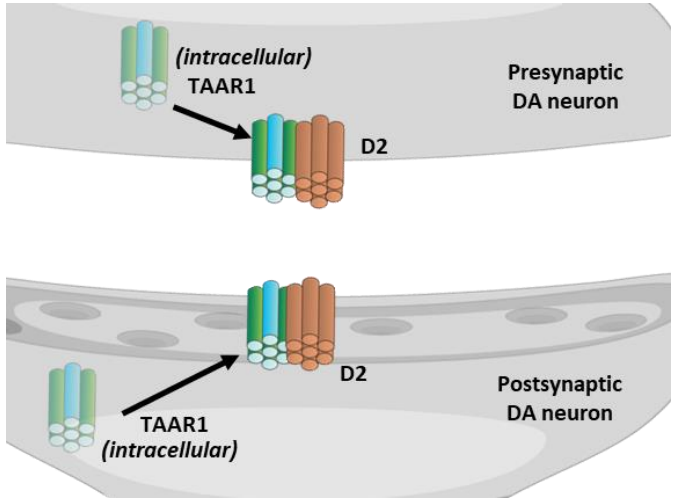
- Localized in the gut and tissues associated with energy metabolism
- Highest expression outside of the CNS in pancreatic β-cells, stomach and intestines, and leukoctyes
- Preclinical evidence for potential utility in regulation of glycemic control, immune response, fasting glucose, metabolic syndrome, and obesity

Amy=amygdala; DRN=dorsal raphe nucleus; PFC=prefrontal cortex; SN=ubstantia nigra; VTA=ventral tegmental area.

Dedic N, et al. *Int J Mol Sci*. 2021;22(24):13185. Nair PC, et al. *Mol Psychiatry*. 2022;27(1):88-94. Dodd S, et al. *Neurosci Biobehav Rev*. 2021;120:537-541.

What Does TAAR1 Agonism Do?

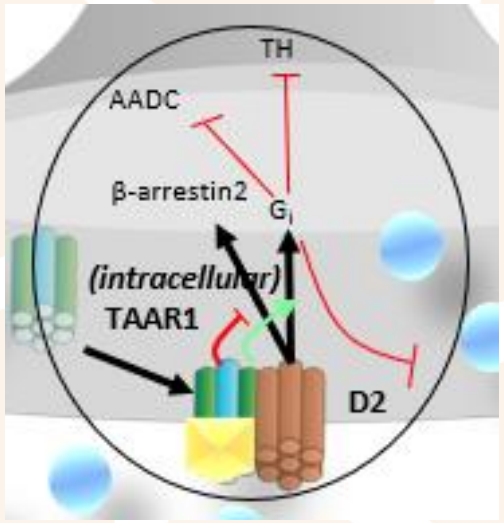
1. Can activate distinct signaling pathways depending on its cellular localization



2. Can adaptively modulate neurotransmitters suggesting a potential role in modulating systems involved in reward, cognition, mood, and other symptoms relevant to schizophrenia

- Modulation of DA Tone
- Regulation of Glu Circuits
- Modulation of 5-HT Activity

3. Can modulate the presynaptic DA dysfunction observed in psychosis without postsynaptic receptor blockade



= TAAR1 agonist

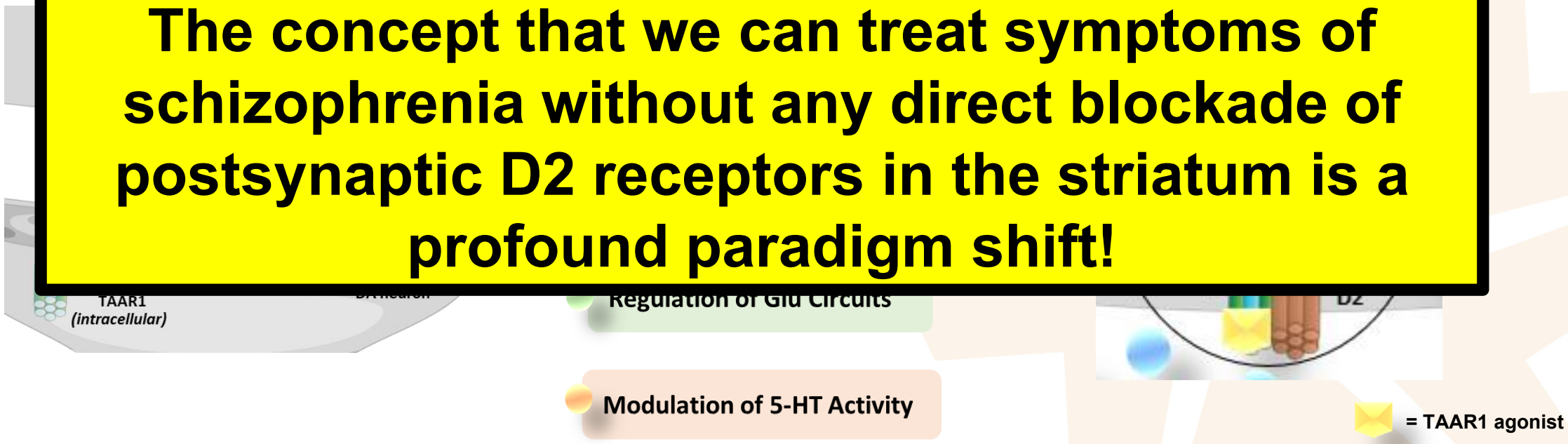
Glu=glutamate.

Gainetdinov RR, et al. *Pharmacol Rev.* 2018;70(3):549-620. Halff, EF et al. *Trends Neurosci*. 2023;46(1):60-74. Saarinen M, et al. *Neuropsychopharmacology*. 2022;47(13):2319-2329.

What Does TAAR1 Agonism Do?

1. Can activate distinct signaling pathways depending on its cellular localization
2. Can adaptively modulate neurotransmitters suggesting a potential role in modulating systems involved in
3. Can modulate the presynaptic DA dysfunction observed in psychosis without postsynaptic receptor blockade

The concept that we can treat symptoms of schizophrenia without any direct blockade of postsynaptic D2 receptors in the striatum is a profound paradigm shift!



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Investigational TAAR1 Agonists

One TAAR1 compound is in clinical development for the treatment of schizophrenia

- Ulotaront: TAAR1 agonist with 5-HT_{1A} agonist activity

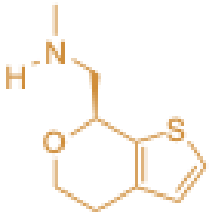
- Ralmitaront: A TAAR1 partial agonist was evaluated in two Phase 2 studies that were terminated because of inadequate efficacy
- TAAR1 antagonists have been studied preclinically, but none have reached clinical trials

Dedic N, et al. *J Pharmacol Exp Ther*. 2019;371(1):1-14. Dedic N, et al. *Int J Mol Sci*. 2021;22(24):13185.

Ulotaront

TAAR1 agonist with 5-HT_{1A} agonist activity

Phase 2 complete; currently in Phase 3 Clinical Development for Schizophrenia



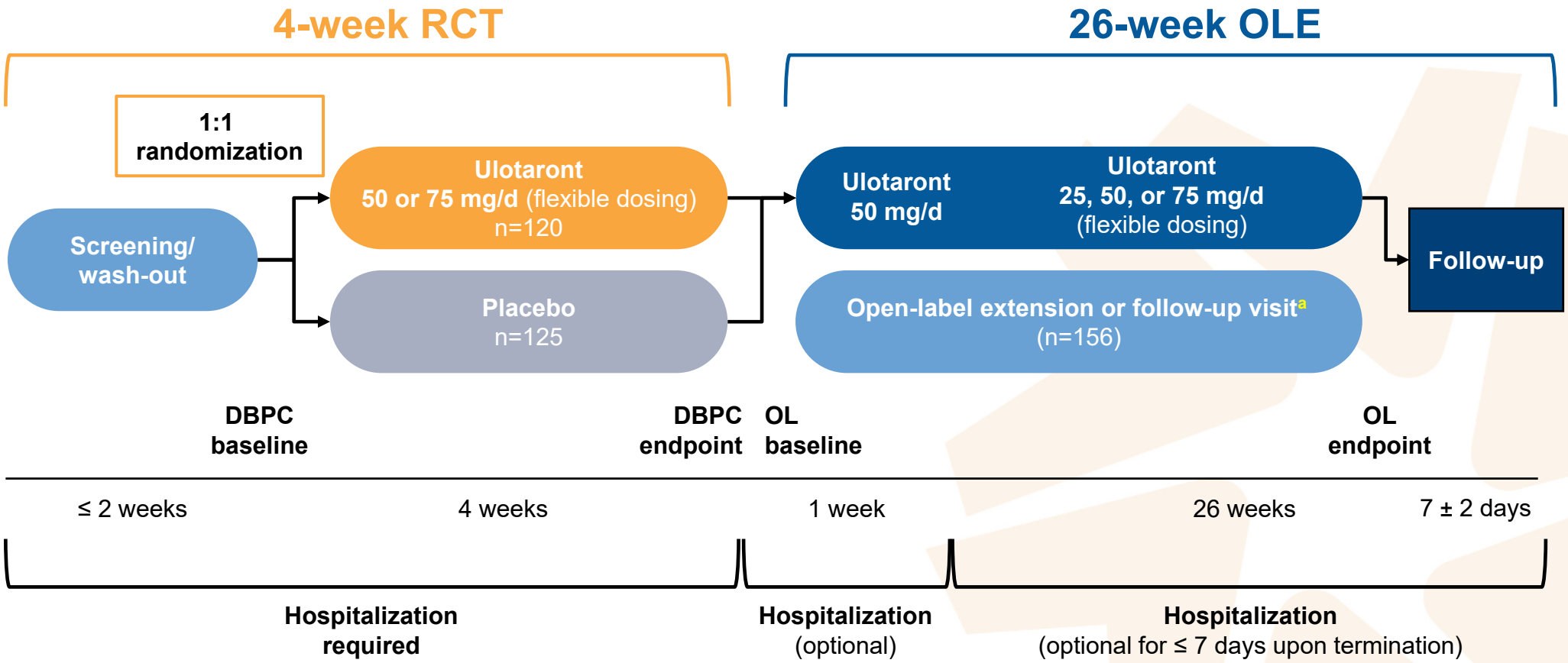
Ulotaront

STUDY ELEMENT	SEP361-301 (Acute Study)	SEP361-302 (Acute Study)	SEP361-303 (Open-Label Extension)	SEP361-304 (Long-Term Safety Study)
Clinicaltrials.gov identifier	NCT04072354	NCT04092686	NCT04109950	NCT04115319
Study duration	6 weeks	6 weeks	52 weeks	52 weeks
Setting	Inpatient	Inpatient	Outpatient	Outpatient
Population	Acutely psychotic	Acutely psychotic	Rollover patients from 301 & 302	Stable patients
Age	13-65 years	18-65 years		18-65 years
Randomization ratio	1:1:1	1:1:1		2:1 (ulotaront:QXR)
Sample size	525	462	555	300
Dosing type	Fixed	Fixed	Flexible	Flexible
Ulotaront dosing	50 mg 75 mg	75 mg 100 mg	25-100 mg	50-100 mg
Comparators	Placebo	Placebo	None (open-label)	Quetiapine XR 400-800 mg

OLE=open-label extension; QXR=quetiapine extended release.

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated April 12, 2023. https://clinicaltrials.gov/ct2/show/NCT04072354. ClinicalTrials.gov [www.clinicaltrials.gov]. March 21, 2023. https://clinicaltrials.gov/ct2/show/NCT04092686. ClinicalTrials.gov [www.clinicaltrials.gov]. February 28, 2023. https://clinicaltrials.gov/ct2/show/NCT04109950. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated February 17, 2023. https://clinicaltrials.gov/ct2/show/NCT04115319.

Ulotaront Phase 2



[a]Half not continuing into open-label extension, follow-up visit to occur 7 ± 2 days after last dose.
DBPC = double-blind, placebo-controlled; RCT = randomized clinical trial.
Koblan KS, et al. *N Engl J Med*. 2020;382(16):1497-1506. Correll CU, et al. *NPJ Schizophr*. 2021;7(1):63.

Ulotaront Phase 2: Key Info

KEY PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- Subjects were between 18-40 years old—mean age 30.6 (placebo), 30.0 (ulotaront)
- Mostly male (63.2% placebo, 64.2% ulotaront) and white (83.2% placebo, 80.0% ulotaront)
- PANSS total score at baseline 99.7 (placebo), 101.4 (ulotaront)

PRIMARY ENDPOINT
PANSS total score

SECONDARY ENDPOINTS
CGI-S scale; PANSS subscales; BNSS; MADRS; PANSS responders; UPSM-transformed PANSS factor severity scores

PRIMARY ENDPOINT
Safety

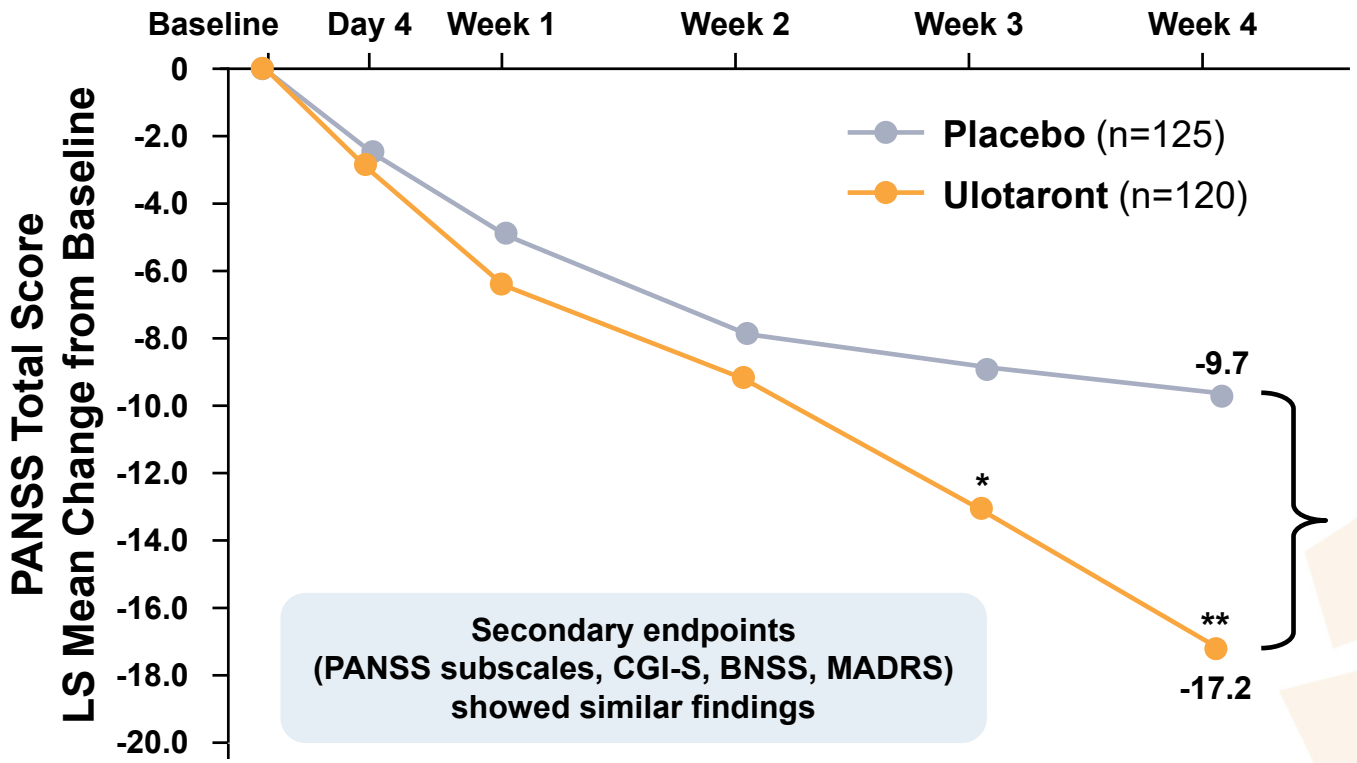
SECONDARY EFFICACY ENDPOINTS
Relapse, time to relapse, PANSS total and subscales,
CGI-S; BNSS total score; MADRS total score, PANSS responders

Not inclusive of all endpoints and analyses.

BNSS=brief negative symptom scale; CGI-S=clinical global impression-severity scale; MADRS=The Montgomery-Åsberg Depression Rating Scale; PANSS=Positive and Negative Syndrome Scale; UPSM=uncorrelated PANSS score matrix.

Koblan KS, et al. *N Engl J Med*. 2020;382:1497-1506. Correll CU, et al. *NPJ Schizophr*. 2021;7(1):63.

Primary Endpoint: Phase 2 RCT



Response rate
(total PANSS improvement ≥20%):
64.6% ulotaront vs 44.0% placebo
NNT = 5 (95% CI 3-12)^

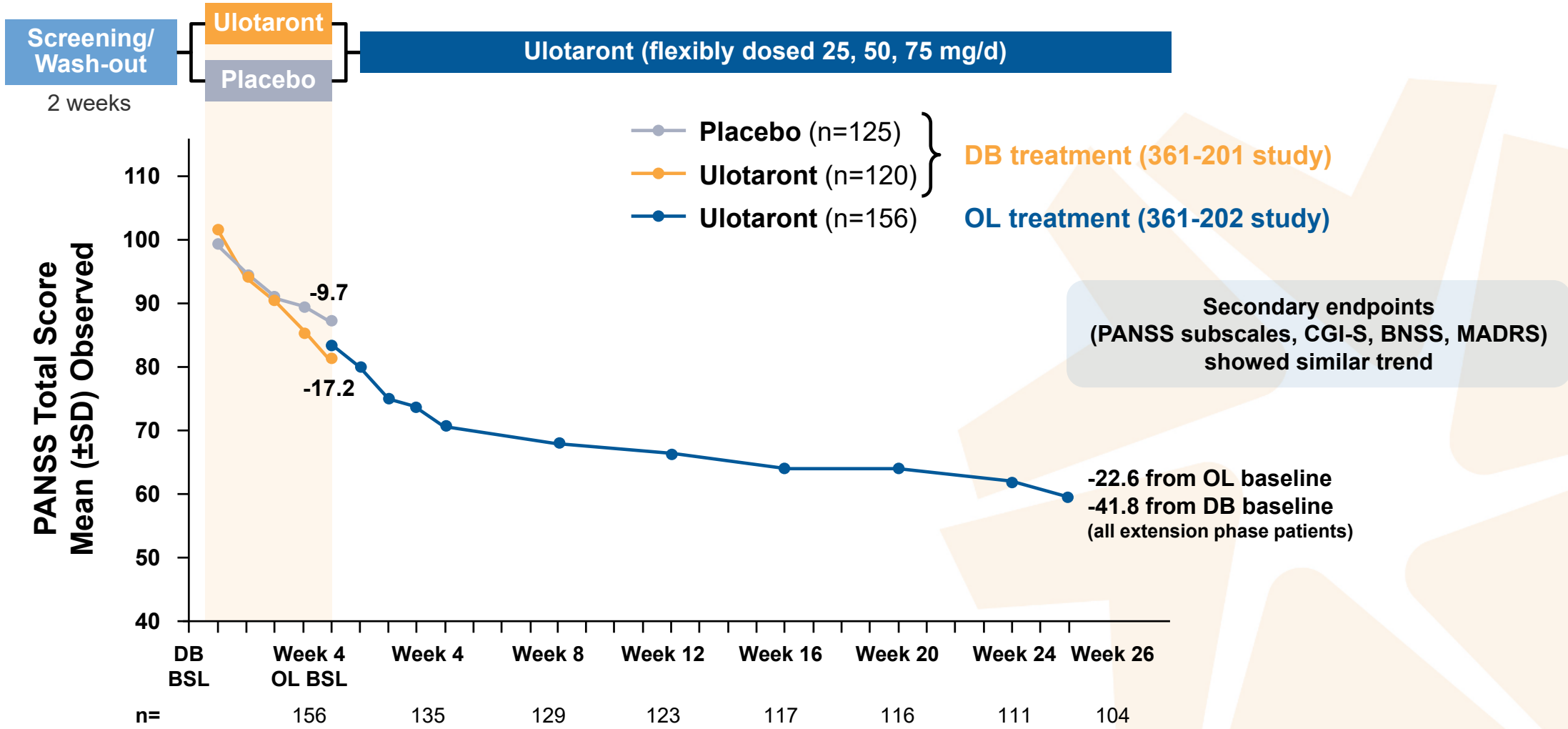
Ulotaront vs placebo
***P*=0.001**
Effect size=0.45

Secondary endpoints
(PANSS subscales, CGI-S, BNSS, MADRS)
showed similar findings

By the end of the flexible dosing period (week 3), 27.5% were on 50 mg and 72.5% on 75 mg

*** *P*<0.05. ** *P*<0.01. ^NNT calculations performed by Dr. Leslie Citrome.**
LS=least squares; NNT=number needed to treat.
Koblan KS, et al. *N Engl J Med*. 2020;382(16):1497-1506.

PANSS: Phase 2 OLE



BSL=baseline.

Koblan KS, et al. *N Engl J Med*. 2020;382(16):1497-1506. Correll CU, et al. *NPJ Schizophr*. 2021;7(1):63.

Adverse Events: Phase 2 RCT

- Table lists most common AEs vs placebo (≥ 2% and more frequent than placebo)
- Discontinuation due to an AE = 8.3% (ulotaront) vs 6.4% (placebo); NNH=52 (ns)
- No significant differences observed in potential movement disorders between ulotaront and placebo patients, as measured by SAS, BARS, and AIMS scales
  - Percentage of patients experiencing any EPS (including akathisia, restlessness, musculoskeletal/joint stiffness, tremor, or nuchal rigidity) was 3.3% for ulotaront and 3.2% for placebo; NNH = 750 (ns)

Frequency ≥ 2% in ulotaront group and > placebo group	**Ulotaront** (n=120)	**Placebo** (n=125)	**NNH** (all ns)
Patients with any AE, n (%)	55 (45.8)	63 (50.4)	-22
Somnolence	8 (6.7)	6 (4.8)	54
Agitation	6 (5.0)	6 (4.8)	500
Nausea	6 (5.0)	4 (3.2)	56
Diarrhea	3 (2.5)	1 (0.8)	59
Dyspepsia	3 (2.5)	0 (0.0)	40
Serious adverse events			
Worsening of schizophrenia	1 (0.8)	3 (2.4)	-64
Sudden cardiac death	1 (0.8)	0	120
Suicide attempt	0	1 (0.8)	-125

NNH calculations performed by Dr. Citrome
AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; EPS=extrapyramidal symptoms; NNH=number needed to harm; ns=not significant; SAS=Simpson-Angus Scale.
Koblan KS, et al. *N Engl J Med*. 2020;382(16):1497-1506.

Adverse Events: Phase 2 OLE

Safety parameter, n (%)[a]	Ulotaront (n =156)
At least one adverse event	88 (56.5)
Schizophrenia	19 (12.2)
Headache	18 (11.5)
Insomnia	13 (8.3)
Anxiety	8 (5.1)
Somnolence	7 (4.5)
Nasopharyngitis	7 (4.5)
Nausea	6 (3.8)
Irritability	5 (3.2)
Influenza	5 (3.2)
Weight decreased	5 (3.2)
Blood prolactin increased	4 (2.6)
Serious AE, n (%)	15 (9.6)
AEs leading to discontinuation, n(%)	18 (11.5)

- Overall, 56% of patients treated with ulotaront in the 26-week OLE experienced an AE
  - Schizophrenia (worsening or exacerbation of), headache, insomnia, and anxiety occurred at an incidence greater than 5%
- Rates of severe AEs in patients treated with ulotaront was 5.1%
  - The only severe AE observed in more than 1 patient was schizophrenia (n=5)
- Overall incidence of EPS-related AEs (parkinsonism, dyskinesia, tremor, and restlessness) was 3.2%
- Study completion rates were 66.9%
  - Over the 26 weeks, rate of AEs leading to discontinuation was 11.5% in patients treated with ulotaront

[a]Indicates any event with a reported frequency ≥ 2%

Correll CU, et al. *NPJ Schizophr*. 2021;7(1):63.

Weight, Labs, Sleep: Phase 2 RCT

	Ulotaront (n=120)	Placebo (n=125)
Weight/BMI, mean (SD) change at week 4[a]		
Weight, kg	+0.3 (1.9)	-0.1 (2.3)
BMI, (kg/m^2)	+0.1 (0.6)	0.0 (0.8)
Laboratory values (fasting), median change at week 4[b]		
Total cholesterol, mmol/L	-0.2	0.0
LDL cholesterol, mmol/L	-0.1	0.0
Triglycerides, mmol/L	0.0	-0.1
Glucose, mmol/L	0.0	+0.1
HbA1c (% change)	+0.04	-0.03
Prolactin, male/female[c] pmol/L	-37/-175	-36/-101
PSQI global score, LS mean (SE) change at week 4[d]	-2.5 (0.4)	-1.7 (0.4)

Endpoints were not controlled for multiplicity and were obtained as part of the safety evaluation

[a]n=120 for ulotaront and n=125 for placebo; [b]n=117 for ulotaront and n=124 for placebo; [c]n=74 (males) and n=40 (females) for ulotaront and n=71 (males) and n=42 (females) for placebo; [d]n=115 for ulotaront and n=113 for placebo.
BMI=body mass index; HbA1c=glycolated hemoglobin A1c; LDL=low-density lipoprotein; PSQI=Pittsburgh Sleep Quality Index; SE=standard error.
Koblan KS, et al. *N Engl J Med*. 2020;382(16):1497-1506.

Weight, Labs, Sleep: Phase 2 OLE

Parameter	Ulotaront (n =156)
Mean (SD)[a]	
Weight, kg	-0.3 (3.7)
BMI, kg/m^2	-0.1 (1.2)
Laboratory values, median	
Total cholesterol, mmol/L[b]	-2.0
HDL cholesterol, mmol/L[b]	0
LDL cholesterol, mmol/L[b]	-9.0
Triglycerides, mmol/L[b]	-5.0
Glucose, mmol/L[c]	+2.0
HbA1c (%)[c]	0.0
Prolactin, male/female (ng/mL)[d]	-2.7/-3.4
PSQI global score LS mean (SD)	-2.0 (3.0)

Endpoints were not controlled for multiplicity and were obtained as part of the safety evaluation

[a]n=104; [b]n=117 for ulotaront and n=111; [c]n=109; [d]n=73 (males) and n=39 (females).
Ulotaront data are shown for all extension phase patients.
Correll CU, et al. *NPJ Schizophr*. 2021;7(1):63.

Ulotaront Phase 2 Summary

Phase 2 Results

- Change from baseline in PANSS total score was -17.2 for ulotaront and -9.7 for placebo (*P*=0.001) at week 4
- Incidence of AEs for ulotaront was 45.8% and 50.4% for placebo with a difference of 2.5% or less for each event; discontinuation due to an AE was 8.3% for ulotaront and 6.4% for placebo

- 56.5% of patients experienced an AE; 66.9% of patients completed 26 weeks of open-label treatment with ulotaront
- On average, patients showed a mean PANSS total score reduction of -22.6 from open-label baseline to week 26

- FDA granted breakthrough therapy designation to ulotaront for the treatment of schizophrenia
- Ulotaront is currently in phase 3 clinical trials in patients with schizophrenia

Koblan KS, et al. *N Engl J Med*. 2020;382(16):1497-1506. Correll CU, et al. *NPJ Schizophr*. 2021;7(1):63. Sunovion [news.sunovion.com]. Last updated May 10, 2019. Accessed April 21, 2023. https://news.sunovion.com/press-releases/press-releases-details/2019/Sunovion-and-PsychoGenics-Announce-that-SEP-363856-Has-Received-FDA-Breakthrough-Therapy-Designation-for-the-Treatment-of-People-with-Schizophrenia/default.aspx.

Ulotaront Phase 3 DIAMOND 1 and 2 Trials: Top Line Results

- DIAMOND 1 study: multicenter, randomized, double-blind, parallel-group, fixed-dosed trial comparing **ulotaront 50 mg/d and 75 mg/d vs placebo** over 6 weeks in 435 acutely psychotic adults with schizophrenia.

- All three groups showed a reduction in the Positive and Negative Syndrome Scale (PANSS) total score over time, without either ulotaront treatment group being superior to placebo on PANSS total change at Week 6 (least squares [LS] mean:
  - **ulotaront 50 mg/day: -16.9; ulotaront 75 mg/day: -19.6; placebo: -19.3 points**

- DIAMOND 2 study: multicenter, randomized, double-blind, parallel-group, fixed-dosed trial comparing **ulotaront 75 mg/d and 100 mg/d vs. placebo over 6 weeks** in 464 acutely psychotic adults with schizophrenia

- All three groups showed a reduction in PANSS total score over time, without either ulotaront treatment group being superior to placebo on PANSS total change at Week 6 (least squares [LS] mean:
  - **ulotaront 75 mg/day: -16.4; ulotaront 100 mg/day: -18.1; placebo: -14.3 points**

- Ulotaront was generally safe and well-tolerated in both studies

https://otsuka-us.com/news/sumitomo-pharma-and-otsuka-announce-topline-results-phase-3-diamond-1-and-diamond-2-clinical

Key Learning Points

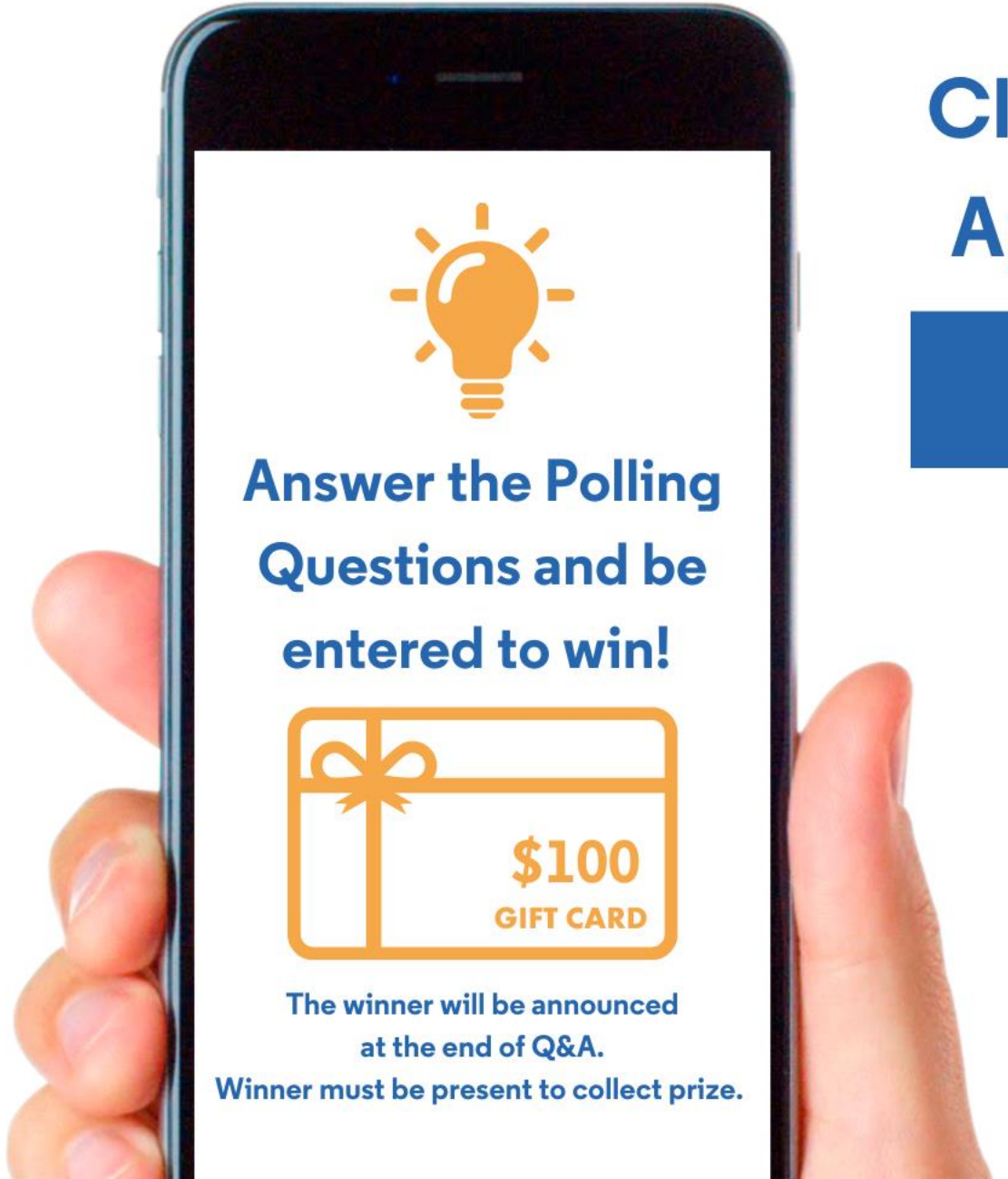
- Ulotaront's proposed mechanism of action is TAAR1 agonism and **5-HT1A agonism**
- TAAR1 agonists modulate presynaptic dopamine dysfunction observed in psychosis without postsynaptic receptor blockade
- **In the Phase 3 DIAMOND trials Ulotarant was overall well-tolerated and safe, but its efficacy was obscured by a high placebo response**

Now What?

Discussion Points

- TAAR1 agonists appear to be free of neuromotor adverse effects, do not adversely impact weight/metabolic variables, do not increase prolactin, do not prolong the ECG QTc interval, and are largely devoid of sedation
- Should they be proven to work in reducing symptoms, they will be a compelling choice
- Will they be used first-line? Later-line? Monotherapy? Combination therapy?
- How do we explain this new class of anti-schizophrenia medication?

ECG = electrocardiogram; Sx = symptoms.



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