TAAR1 Agonism: A Novel Approach to Schizophrenia Management

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Faculty Disclosures

- **Dr. Citrome:** Consultant—AbbVie/Allergan, Acadia, Adamas, Alkermes, Angelini, Astellas, Avanir, Axsome, BioXcel, Boehringer Ingelheim, Cadent Therapeutics, Eisai, Enteris BioPharma, HLS Therapeutics, Impel, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Lyndra, Medavante-ProPhase, Merck, Neurocrine, Novartis, Noven, Otsuka, Ovid, Relmada, Reviva, Sage, Sunovion, Supernus, Teva, University of Arizona, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; Speaker's Bureau—AbbVie/Allergan, Acadia, Alkermes, Angelini, Eisai, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Sage, Sunovion, Takeda, Teva, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and Universities and Professional Organizations/Societies; Stocks—Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer, Reviva [options]; Royalties— Wiley, UpToDate, Springer Healthcare, Elsevier

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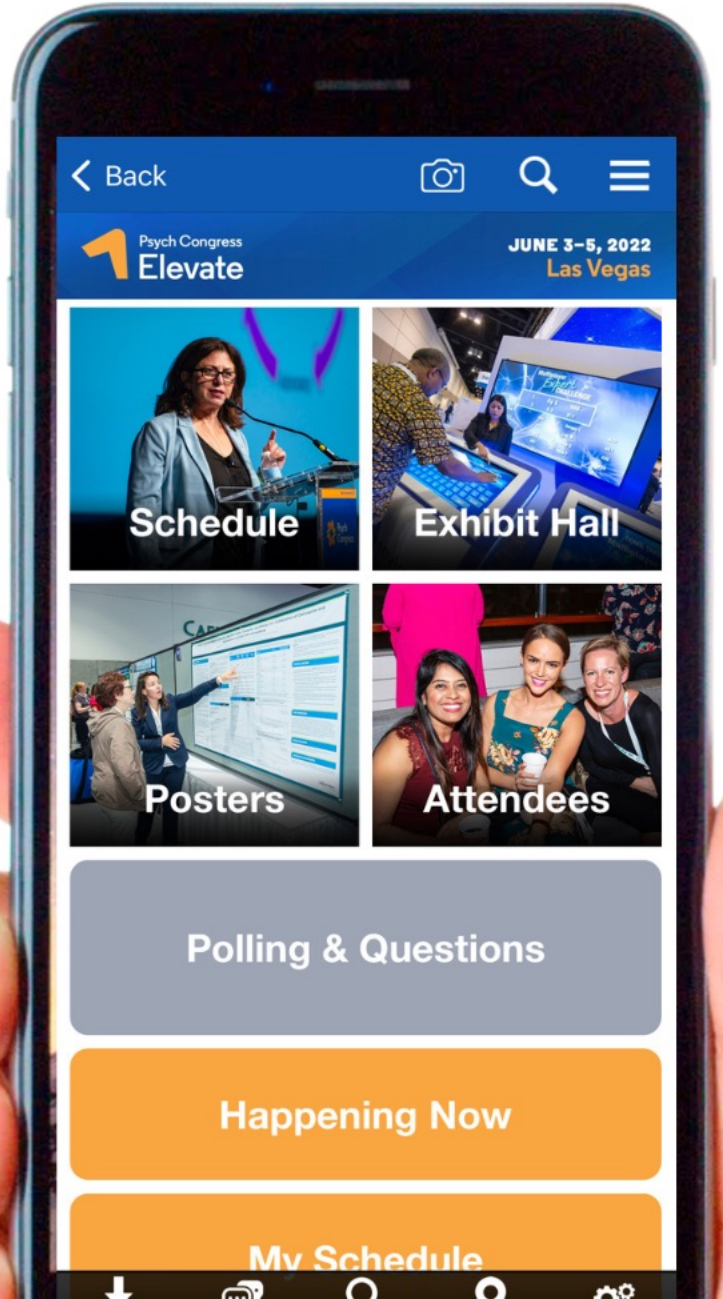
Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

Learning Objectives

- Assess the limitations associated with the current schizophrenia treatment landscape
- Evaluate the pharmacology, mechanisms of action, safety/efficacy data, and administration considerations associated with TAAR1 agonism in the management of schizophrenia
- Describe the clinical implications for TAAR1 agonists in schizophrenia management, including how to identify and educate patients to facilitate treatment selection and acceptance.



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Psych Congress Elevate

Schizophrenia Overview and Treatment Challenges

Rebecca Kraus, MSPAS, PA-C

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Diagnosis Overview

- 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

American Psychiatric Association. (2013). Neurodevelopmental disorders. In *Diagnostic and statistical manual of mental disorders* (5th ed.). Dedic, N, et al. Therapeutic Potential of TAAR1 Agonists in Schizophrenia: Evidence from Preclinical Models and Clinical Studies. *Int. J. Mol. Sci.* 2021;22(13185). Accessed May 25, 2022. https://doi.org/10.3390/ijms222413185. Stahl SM. (2021). Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications (5th ed). Cambridge, UK; New York: Cambridge University Press. p141-145.

Prevalence vs Burden

Prevalence

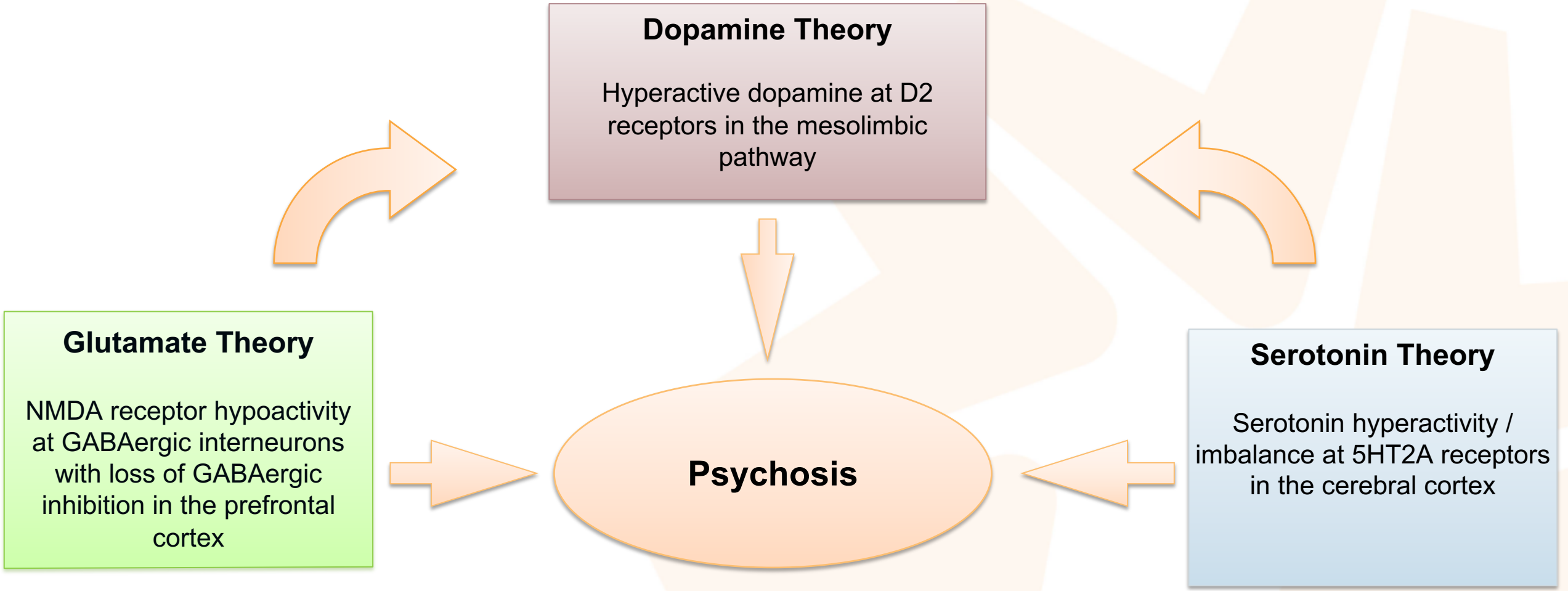
Schizophrenia affects approximately 1% of global population

Burden

- One of the top 15 leading causes of disability worldwide
  - affects ability of maintaining social relationships, maintaining employment, living independently
  - associated with higher rates homelessness and incarceration/arrest
- Mortality rates are 3-4x that of the general population
  - life expectancy reduced by 10-20 years
  - approximately 5% die by suicide
  - even more deaths associated with cardiovascular disease

National Institute of Mental Health, US Department of Health and Human Services. Schizophrenia. Accessed May 25, 2022. https://nimh.nih.gov/health/statistics/schizophrenia. Dedic N, et al. Therapeutic Potential of TAAR1 Agonists in Schizophrenia: Evidence from Practical Models and Clinical Studies. Int. J. Mol. Sci. 2021;22(13185). Accessed May 25, 2022. https://doi.org/10.3390/ijms222413185

Pathophysiology:
The Three Major Hypotheses of Psychosis



Stahl SM, (2021).Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications (5th ed). Cambridge, UK; New York: Cambridge University Press. p 141.

Current Treatment Landscape

First Generation Antipsychotic Medications aka "Conventional", "Typicals," "Neuroleptics"

- Discovered in the 1950s
- High affinity D2 receptor blockade (= higher potency?)
- High rates of hyperprolactinemia and "EPS"

Second Generation Antipsychotic Medications aka "Atypicals"

- Introduced in the 1990s
- To improve the efficacy and tolerability of the FGAs (avoiding unnecessarily high D2 occupancy)
- Combines D2 antagonism with 5HT2A antagonism
- Less risk hyperprolactemia and "EPS"
- Metabolic issues (variable among atypicals)

Psychosocial supports

Options for Treatment Resistance?

Clozapine

EPS = Extrapyramidal Symptoms.

Dedic N, et al. Therapeutic Potential of TAAR1 Agonists in Schizophrenia: Evidence from Preclinical Models and Clinical Studies. International journal of molecular sciences. 2021;22(24),13185. Accessed My25, 2022. https://doi.org/10.3390/ijms222413185. Leucht S, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013 Sep 14;382(9896):951-62. Accessed May 25, 2022. doi: 10.1016/S0140-6736(13)60733-3. Epub 2013 Jun 27. Erratum in: Lancet. 2013 Sep 14;382(9896):940. PMID: 23810019. Kern RS, et al. Psychosocial Treatments to Promote Functional Recovery in Schizophrenia, Schizophrenia Bulletin. 2009;35(2):347–361. Accessed May 25, 2022.https://doi.org/10.1093/schbul/sbn177.

Limitations of Current Treatment Landscape

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. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005 Sep 22;353(12):1209-23. Epub 2005 Sep 19. Erratum in: N Engl J Med. 2010 Sep 9;363(11):1092-3. Dedic N, et al. Therapeutic Potential of TAAR1 Agonists in Schizophrenia: Evidence from Preclinical Models and Clinical Studies. *Int. J. Mol. Sci.* 2021;22(13185). Accessed May 25, 2022. https://doi.org/10.3390/ijms222413185. Yeomans D, et al. (2010). Resolution and remission in schizophrenia: Getting well and staying well. *Advances in Psychiatric Treatment*. 2020;16(2):86-95. Accessed May 25, 2022. doi:10.1192/apt.bp.108.006411

Adverse Effects and Treatment Challenges

Motor

- parkinsonism
- tardive dyskinesia
- dystonia
- akathisia
- NMS

Metabolic

- weight gain/obesity
- insulin resistance/diabetes
- dyslipidemia

Hyperprolactinemia

- gynecomastia/galactorrhea
- sexual dysfunction
- amenorrhea
- osteoporosis

"Other"

- hypotension
- anticholinergic effects
- agranulocytosis
- somnolence/sedation
- cardiac arrhythmias
- seizures

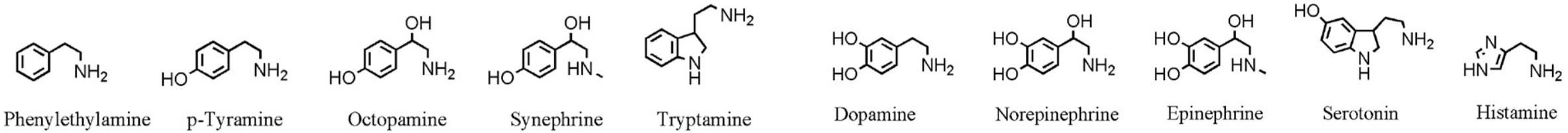
NMS = Neuroleptic Malignant Syndrome

Stahl SM. (2021). Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications (5th ed). Cambridge, UK; New York: Cambridge University Press. Chapter 5. Day JC, et al. Attitudes toward antipsychotic medication: the impact of clinical variables and relationships with health professionals. *Arch Gen Psychiatry*. 2005 Jul;62(7):717-24. Accessed May 25, 2022. doi: 10.1001/archpsyc.62.7.717. PMID: 15997012.

Introduction to TAAR1

Mechanism of Action Video

What Are Trace Amines?

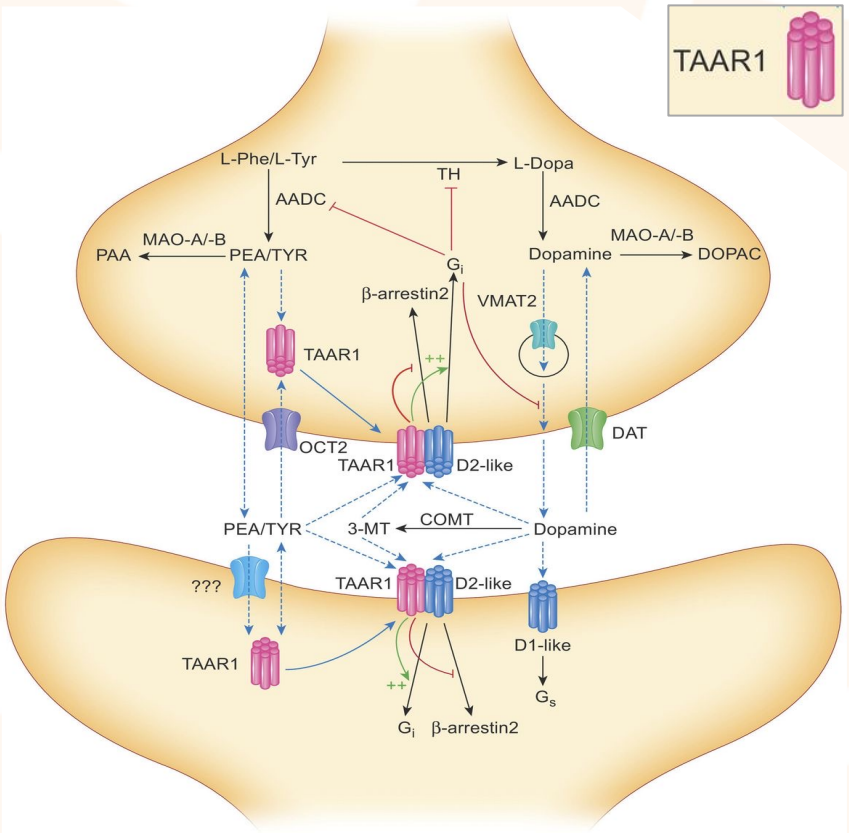


- Small and lipophylic substances
- Trace amines include β-phenylethylamine, tyramine, tryptamine and octopamine
- Sympathomimetic compounds known for more than 100 years
- Termed as “false neurotransmitters” – in vertebrates they are not released into the synapse through synaptic vesicles upon an action potential
  - In invertebrates, tyramine and octopamine are major neurotransmitters
- Present in food (seafood, cured meats, wine, cheese and chocolate in significant amounts)
- Involved in toxic action of MAO inhibitors and ergot poisoning
- Produced by human microbiota

Gainetdinov RR, et al. *Pharmacological Reviews*. 2018:70:549-620.

What Are Trace Amine Receptors? TAAR1?

- Trace amine-associated receptors (TAARs) are predominantly intracellular receptors that modulate neurotransmission in monoaminergic neurons
- Pre- and post-synaptic effects are possible
- Crosstalk between the dopamine and TAAR1 systems is complex and is not fully understood



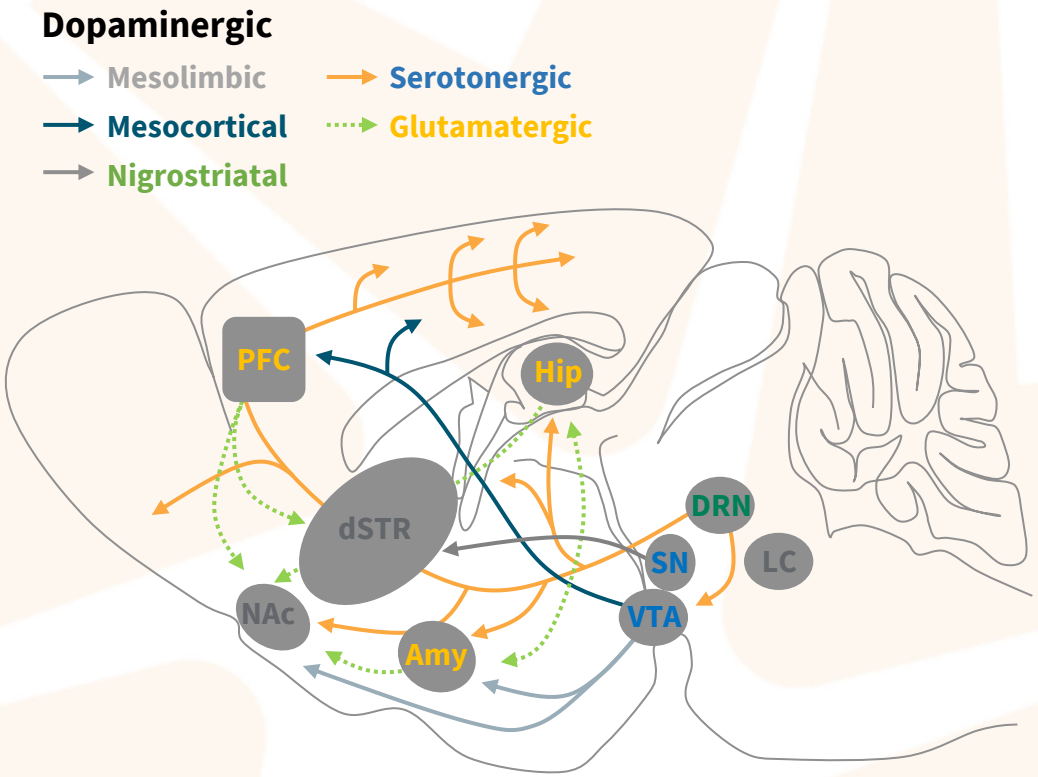
AADC, aromatic L-amino acid decarboxylase; 3-MT, 3-methoxytyramine; COMT, catechol-*o*-methyltransferase; D_2R, D_2-like dopamine receptor; DAT, dopamine transporter; DOPAC, 3,4-dihydroxyphenylacetic acid; MAO A/B, monoamine oxidase; L-Phe, l-phenylalanine; l-Tyr, l-tyrosine; OCT2, organic cation transporter; PAA, phenylacetic acid/4-hydroxyphenylacetic acid; PEA, β-phenylethylamine; TH, tyrosine hydroxylase; TYR, *p*-tyramine; VMAT2, vesicular monoamine transporter.

Krogmann A et al. *CNS Spectr.* 2019;24(S1):38-96. Gainetdinov RR et al. *Pharmacol Rev*. 2018;70(3):549-620.

TAAR1 is Expressed in Key Regions of the CNS That are Important for Schizophrenia

TAAR1 is being investigated as a drug target for the treatment of schizophrenia, as well as multiple other CNS conditions[2]

- Since its discovery in 2001, TAAR1 has been a target of interest for the treatment of psychiatric illnesses[1]
- Knockout mice studies indicate that TAAR1 is **heterogeneously distributed throughout the CNS**[2]
  - Key brain regions include prefrontal cortex (PFC), dorsal striatum (dSTR), amygdala (Amy), nucleus accumbens (NAc), ventral tegmental area (VTA)[3]
  - Localization of TAAR1 suggests that it **influences the monoamine system through downstream effects**[4]
- TAAR1 expression in these regions **may modulate dopaminergic** (VTA, SN), **glutamatergic** (cortex, Amy, subiculum), and **serotonergic** (dorsal raphe nucleus [DRN], VTA) **neurons**[2]
- Therefore, TAAR1 may play an **important role regulating reward circuits, cognitive processes, and mood states**[2]



Adapted from Dedic N, et al.[1] ©2021, the authors, under CC by 4.0.

Hip = hippocampus; LC = locus ceruleus; SN = substantia nigra.

1. Dedic N, et al. *Int J Mol Sci*. 2021;22(24):13185. Accessed May 25,2022. doi:10.3390/ijms222413185. 2. Nair PC, et al. *Mol Psychiatry*. August 10, 2021. Accessed May 25, 2022. doi:10.1038/s41380-021-01250-7. 3. Kantrowitz JT, et al. *CNS Drugs*. 2021;35(11):1153-1161. 4. Dodd S, et al. *Neurosci Biobehav Rev*. 2021;120:537-541.

TAAR1 Agonists in Phase 2/3 of Clinical Development: The Suffix/Stem "-taront" Connotes Membership in This Drug Class

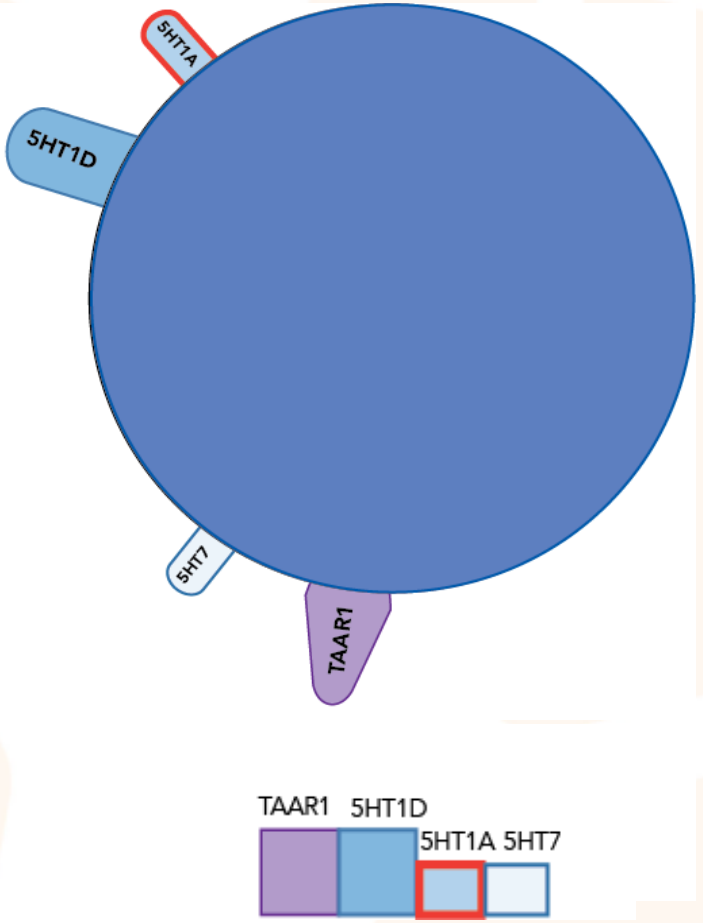
- **Ulotaront** (SEP-363856, Sunovion)- TAAR1 agonist with 5-HT_{1A} agonist activity
  - Phase 2 studies complete
    - In a 4-week study, demonstrated significant improvement in PANSS total score and secondary endpoints vs. placebo and was generally safe and well tolerated
    - In an open-label extension study, there were no new safety concerns and ulotaront continued to show improvement across secondary efficacy endpoints
  - Currently in Phase 3 development for the treatment of schizophrenia
- **Ralmitaront** (RO6889450, Roche)- TAAR1 Partial Agonist
  - Currently in Phase 2 trials for the treatment of patients with and acute exacerbation of schizophrenia or schizoaffective disorder
    - Two active Phase 2 studies (recruiting)

PANSS = Positive and Negative Syndrome Scale.

More About Ulotaront

Agonist at TAAR1 receptors; it also shows binding affinity for $5HT_{1D}$, $5HT_{1A}$, and $5HT_7$ receptors

- Main serotonergic activity through 5-HT_{1A} receptors
- Lacks activity at D_2 and 5-HT_{2A} receptors
- Phase 2 study demonstrated safety and efficacy in a 4-week study in patients with an acute exacerbation of schizophrenia
- Phase 2 study demonstrated no new safety concerns and continued effectiveness in a 26-week open-label extension study
- Currently in Phase 3 development for the treatment of adults and adolescents (ages 13-17) with schizophrenia



Stahl SM. Stahl's Essential Psychopharmacology. 5th ed. 2021.

Ulotaront Has Effects in Preclinical Models

Positive symptoms modeled by[1]:

- Prepulse inhibition (PPI)
- Phencyclidine (PCP) induced hyperactivity

Negative symptoms modeled by[1]:

- Social withdrawal induced by subchronic PCP treatment:
  - All doses of Ulotaront (1, 3, and 10 mg/kg, po) and clozapine (2.5 mg/kg, ip) significantly ($p < .05$) attenuated social interaction deficits

Depression symptoms modeled by[1]:

- Forced swim immobility time:
  - Doses of Ulotaront (1, 3, and 10 mg/kg, p.o.) significantly ($p<0.05$) reduced immobility time, though of a smaller magnitude than sertraline (20 mg/kg, i.p.)

Extrapyramidal symptoms modeled by[1]:

- Catalepsy bar test:
  - Haloperidol (1 mg/kg, i.p.) significantly ($p<0.05$) increased cataleptic time, whereas a 30-fold higher than the efficacious dose of Ulotaront (100 mg/kg, p.o.) did not increase cataleptic time

Vigilance/wakefulness modeled by[1,2]:

- Rapid eye movement (REM) sleep assessment:
  - Ulotaront dose-dependently decreased REM sleep, increased latency to REM sleep, and increased wake time without increasing locomotion

i.p. = intraperitoneal; PCP = phencyclidine; p.o. = by mouth; REM = rapid eye movement.

1. Dedic N, et al. *J Pharm Exp Ther*. 2019;371:1-14. 2. Dedic N, et al. *J Pharm Exp Ther*. 2019;371(Suppl):1-38.

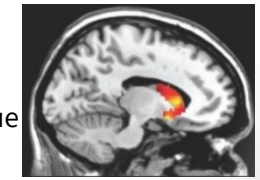
Summary of Proposed Ulotaront Mechanism of Action

Lacks D_2 blockade

Postsynaptic block induces disruption in basal ganglia motor outputs

Ameliorates presynaptic dopamine dysfunction

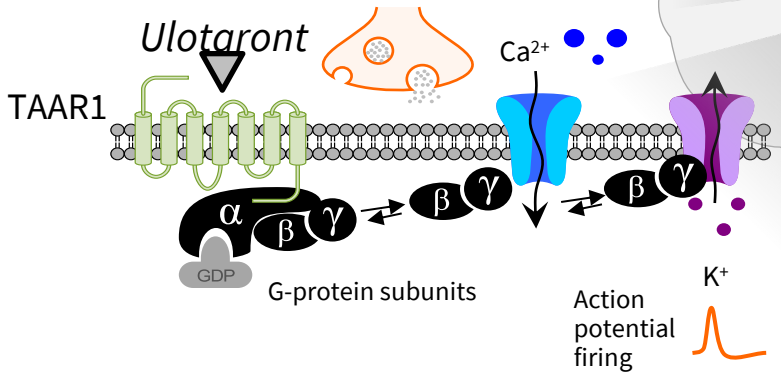
^{18}F-DOPA index of presynaptic dopamine synthesis capacity suggests psychosis is due to excessive dopamine signaling

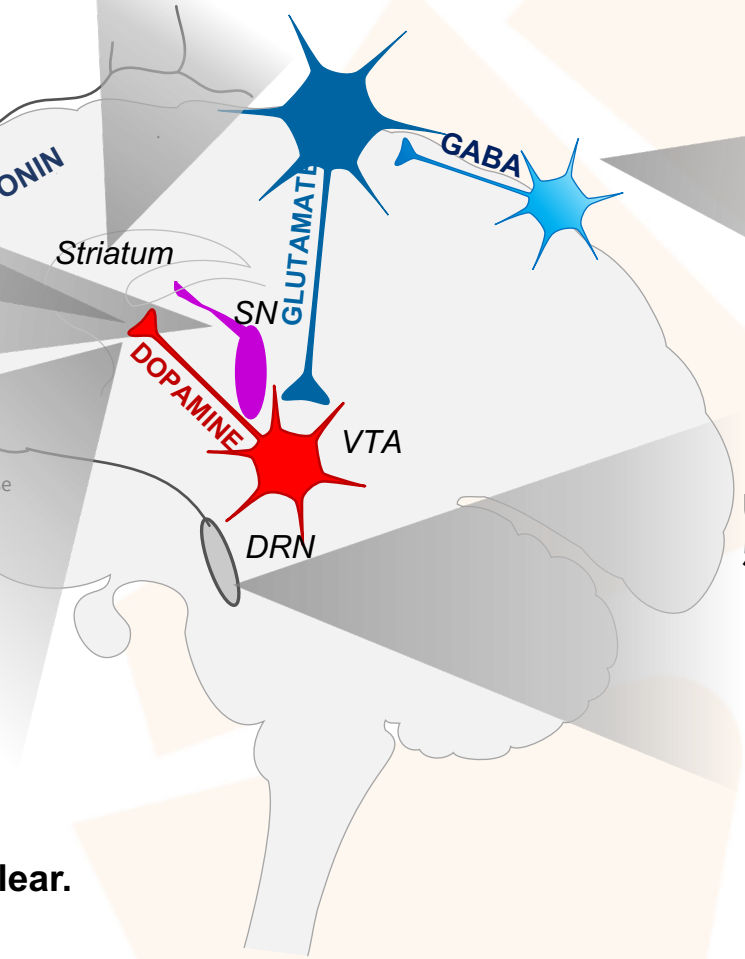


Reverses glutamate hypofunction

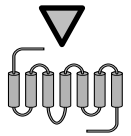
NMDA receptor antagonism by ketamine or PCP induces psychosis-like states in animals and humans by loss of cortical inhibition of midbrain dopamine neuronal circuits

Ulotaront activates TAAR1 receptors





Ulotaront activates 5-HT_{1A} receptors



The precise mechanism of action of ulotaront is unclear.

^{18}F-DOPA = fluorodeoxyphenylalanine; SN = substantia nigra.

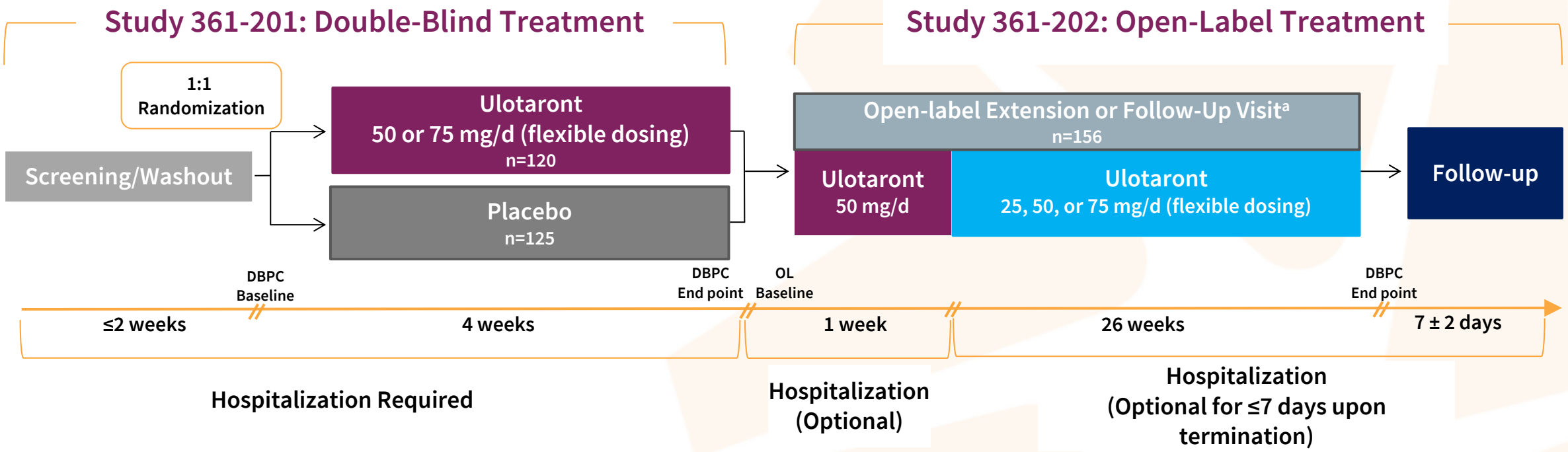
This is a Paradigm Shift, but the "Proof of the Pudding is in the Tasting"

- The concept that we can treat symptoms of schizophrenia without any direct blockade of postsynaptic D_2 receptors in the striatum is a profound **paradigm shift**
- TAARs provide an avenue to modulate dopamine and other monoamines, and **TAAR1 agonism** has been identified as a potential therapeutic target
- Molecules acting at TAAR1 have demonstrated activity in a wide-range of **animal models** suggestive of antipsychotic, antidepressant, precognitive, and anticataleptic effects
- However, **the proof of the pudding is in the tasting,** and direct-testing of this treatment approach in people with schizophrenia will inform us if this approach is indeed viable, and perhaps advantageous over older therapies

Gainetdinov RR, et al. *Pharmacol Rev.* 2018;70:549-620. Berry MD, et al. *Pharmacol Ther*. 2017;180:161-180.

Ulotaront Phase 2 Clinical Trial in Schizophrenia: 4-week RCT Followed by 26-week Extension

Studies 361-2011 and 361-2022



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

Study 201 Key Inclusion and Exclusion Criteria

KEY INCLUSION CRITERIA

- Male and female, 18-40 years of age
- Meets DSM-5 criteria for schizophrenia using SCID-CT (≥6 months duration)
- An acute exacerbation of psychotic symptoms having a duration ≤2 months
- Screening and baseline CGI-S score of ≥4
- Screening and baseline PANSS total score ≥80

KEY EXCLUSION CRITERIA

- Had been hospitalized for treatment of an acute exacerbation of schizophrenia ≥3 times
- Were being treated with depot neuroleptic agents within 30 days of screening

CGI-S = clinical global impression-severity scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; SCID-CT, structured clinical interview for DSM-5, clinical trials version.

Koblan KS, et al. *N Engl J Med*. 2020;382:1497-1506.

Primary, Secondary, and Safety Endpoints

Primary Endpoint
(BSLN to Week 4)
PANSS Total Score Change

Secondary Endpoints
(BSLN to Week 4)

- CGI-S Scale
- PANSS subscale scores (positive, negative, general psychopathology)
- BNSS total score
- MADRS total score
- Proportion of PANSS responders (≥20% decrease in PANSS total score)
- Change from baseline in the UPSM-transformed PANSS factor severity scores

Safety/Tolerability
(BSLN to Week 4)

- Adverse events
- Serious adverse events
  - Suicidality (C-SSRS)
- EPS assessments
  - AIMS, BARS, SAS
- Vital signs (including electrocardiography)
- Weight and clinical laboratory tests (e.g., glucose and lipid profiles)
- Sleep Quality (PSQI)

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; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; SAS = Simpson Angus Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; PSQI = Pittsburgh Sleep Quality Index.

Koblan KS, et al. *N Engl J Med*. 2020;382:1497-1506.

Study 201 Patient Demographics and Baseline Characteristics

Characteristic	Ulotaront, 50 or 75 mg/day (n=120)	Placebo (n=125)
Age, y, mean (SD)	30.0 (5.8)	30.6 (6.1)
Male, n (%)	77 (64.2)	79 (63.2)
Race, n (%)[a]		
• White	96 (80.0)	104 (83.2)
• Black	19 (15.8)	20 (16.0)
• Other	5 (4.2)	1 (0.8)
Hispanic ethnicity, n (%)[a]	5 (4.2)	6 (4.8)
BMI, kg/m^2, mean (SD)	25.0 (4.3)	24.7 (3.7)

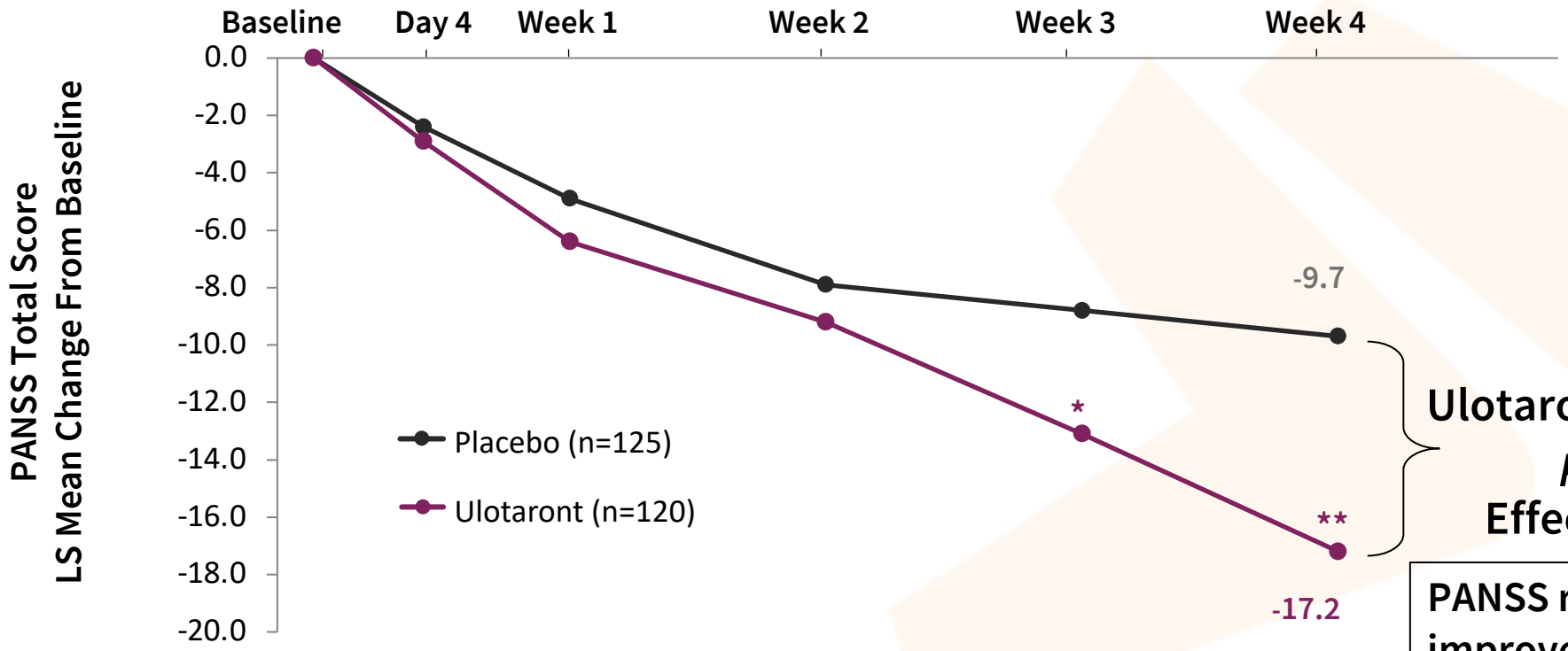
[a]Patient's reported personal race and Hispanic ethnicity.
BMI = body mass index; SD = standard deviation.
Koblan KS, et al. *N Engl J Med*. 2020;382:1497-1506.

Study 201 Patient Demographics and Baseline Characteristics (Cont'd)

Characteristic	Ulotaront, 50 or 75 mg/day (n=120)	Placebo (n=125)
PANSS total score, mean (SD)	101.4 (8.4)	99.7 (7.8)
PANSS positive subscale score, mean (SD)	25.8 (3.3)	25.4 (3.1)
PANSS negative subscale score, mean (SD)	24.7 (3.9)	24.9 (4.0)
CGI-S score, mean (SD)	5.0 (0.4)	4.9 (0.5)
BNSS total score, mean (SD)	37.2 (11.5)	37.4 (12.0)
MADRS total score, mean (SD)	13.1 (7.2)	12.6 (7.1)
Disease history		
• Years since initial onset of schizophrenia, mean (SD)	5.3 (4.8)	5.5 (4.8)
• Number of prior psychiatric hospitalizations, mean (SD)	1.3 (0.7)	1.2 (0.7)

Koblan KS, et al. *N Engl J Med*. 2020;382:1497-1506.

Study 201 Primary Endpoint: PANSS Total Score

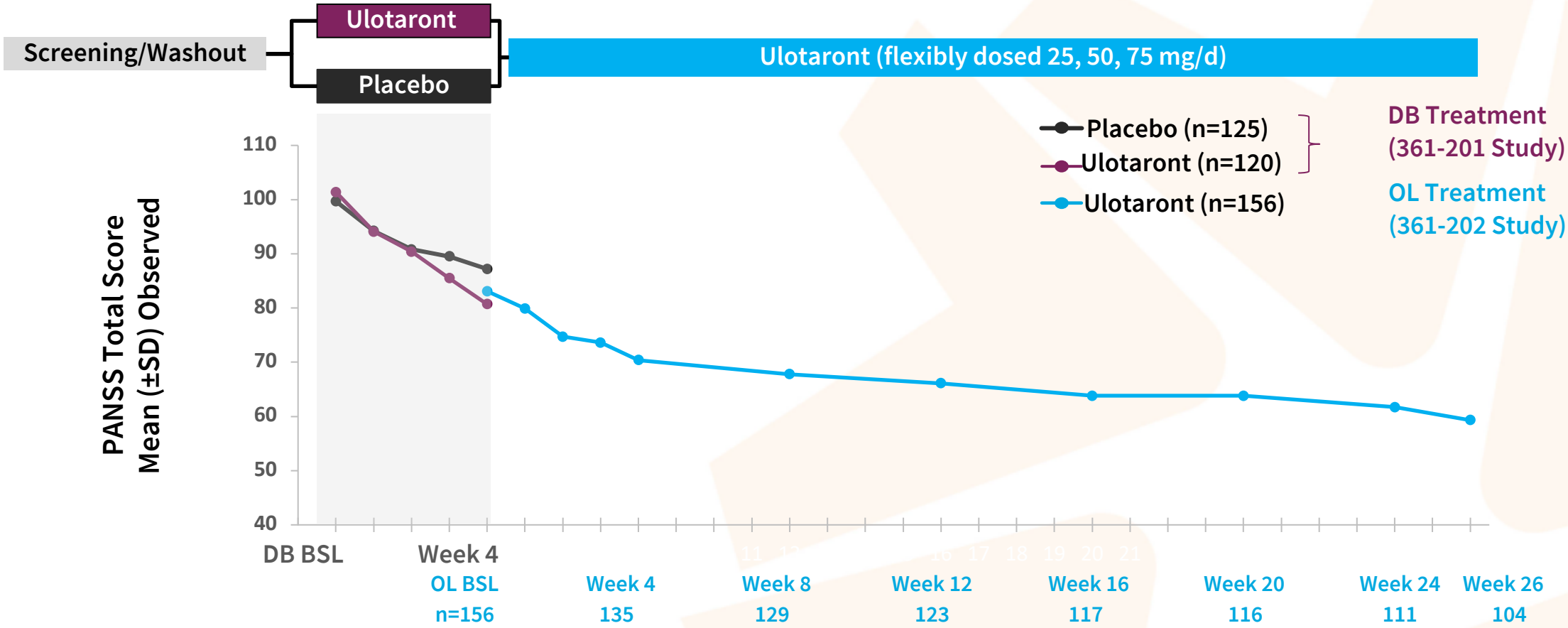


Ulotaront vs. Placebo
***p*= 0.001**
Effect Size=0.45

PANSS response (defined as an improvement of ≥20% in the total score on the PANSS) = 64.6% vs 44.0%, NNT = 5 (95% CI 3-12)

***P* < 0 .05; ****P* < 0.01.**
LS = least squares.
Koblan KS, et al. *N Engl J Med*. 2020;382:1497-1506. NNT calculations done by Citrome (unpublished).

Long-Term Effectiveness of Ulotaront in 202 Study (PANSS Total Score)

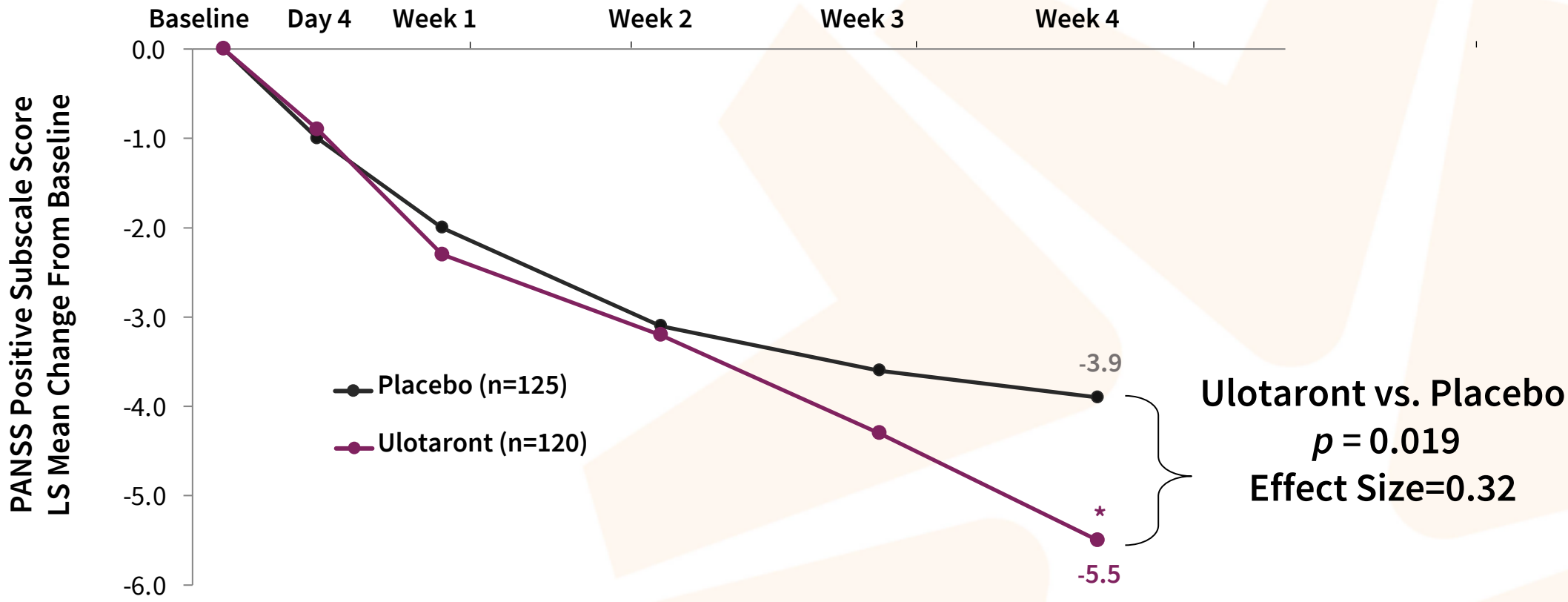


All PANSS subscale scores (e.g., positive, negative), as well as the CGI-S and BNSS followed a similar trend

BL = baseline.

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

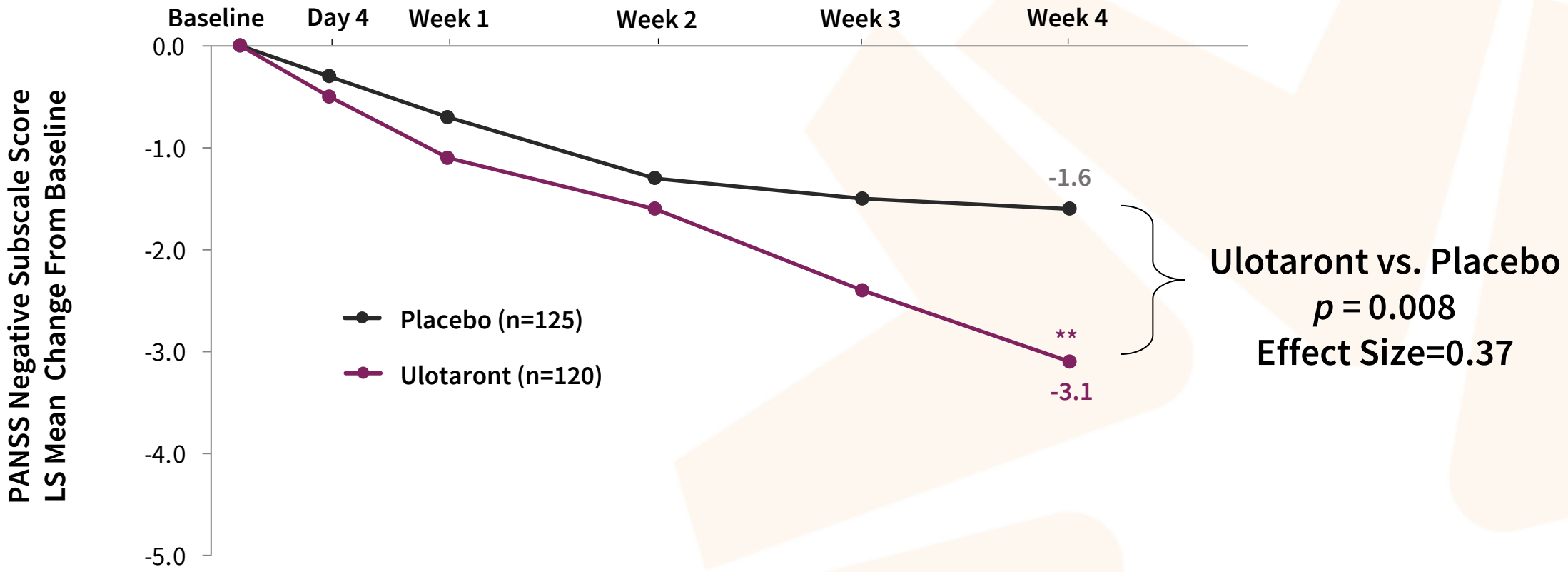
Study 201 Secondary Endpoint: PANSS Positive Subscale Score



*$p < 0.05$.

Koblan KS, et al. *N Engl J Med*. 2020;382:1497-1506.

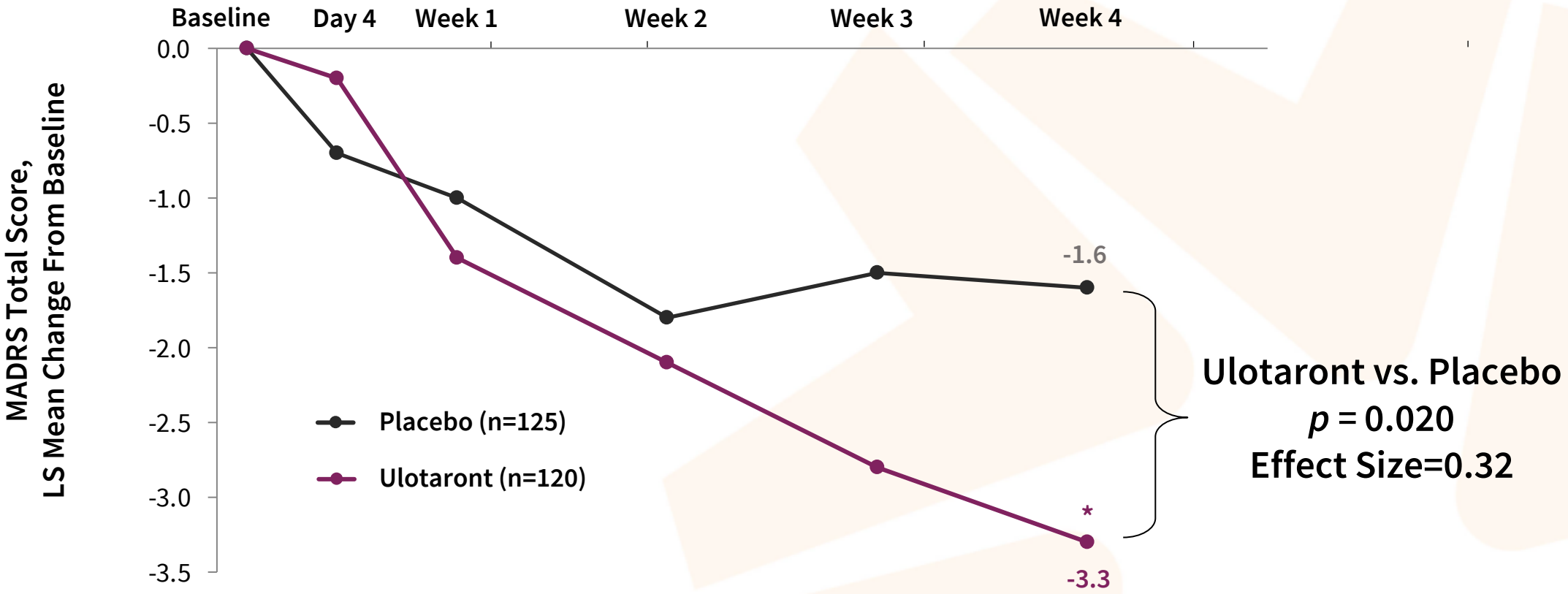
Study 201 Secondary Endpoint: PANSS Negative Subscale Score



**$p < 0.01$.

Koblan KS, et al. *N Engl J Med*. 2020;382:1497-1506.

Study 201 Secondary Endpoint: MADRS Total Score



*$p < .05$.

Koblan KS, et al. *N Engl J Med*. 2020;382:1497-1506.

Study 201: Adverse Events

	Ulotaront, 50 or 75 mg/day (n=120)	Placebo (n=125)	NNH (all ns)
Patients with any AE, n (%)[a]	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[b]			
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

[a]Indicates any event with a reported frequency ≥2% and more frequent in the Ulotaront group compared to placebo group. [b]Adverse events that occurred during the 4-week study and 7-day follow-up periods. AE, adverse event; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; EPS, extrapyramidal symptoms; SAS, Simpson-Angus Scale.

- Discontinuation for the study because of an AE = 8.3% vs 6.4%, NNH = 52 (ns)
- There were no significant differences observed in potential movement disorders between ulotaront and placebo patients, as measured by SAS, BARS, and AIMS[1]
  - Percentage of patients experiencing any EPS (including akathisia, restlessness, musculoskeletal/joint stiffness, tremor, or nuchal rigidity) was low for both ulotaront (3.3%) and placebo (3.2%), NNH = 750 (ns)

Koblan KS, et al. *N Engl J Med*. 2020;382:1497-1506. NNH calculations done by Citrome (unpublished).

Study 202: Adverse Events

- Overall, 56% of patients treated with ulotaront in the 26-week open-label extension study experienced an AE
  - Headache, schizophrenia (worsening or exacerbation of schizophrenia), insomnia, and anxiety occurred at an incidence greater than 5%
- Rate of serious AEs in patients treated with ulotaront was low (5.1%), with the only severe AE observed in more than 1 patient being schizophrenia
- Overall incidence of EPS-related adverse effects (parkinsonism, dyskinesia, tremor, and restlessness) was low (3.2%)
- Over the 26 weeks, rate of AEs leading to discontinuation was 11.5% in patients treated with ulotaront
- **Study completion rates were 66.9%**

	Ulotaront (n =156)
Patients with any AEs, n (%)[a]	88 (56.5)
Headache	18 (11.5)
Schizophrenia	19 (12.2)
Insomnia	13 (8.3)
Anxiety	8 (5.1)
Somnolence	7 (4.5)
Irritability	5 (3.2)
Nausea	6 (3.8)
Nasopharyngitis	7 (4.5)
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)

[a]Indicates any event with a reported frequency >2.

BMI, body mass index; HbA1c, glycolated hemoglobin A1c; LDL, low-density lipoprotein; PSQI, Pittsburgh Sleep Quality Index; SE, standard error.

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

Study 201: Change in Weight, BMI, Metabolic Laboratory Values, Vital Signs, and Sleep Quality (Safety Population)

- Treatment with ulotaront resulted in minimal changes in weight, lipids, and glycemic measures
- The effect of ulotaront on prolactin levels was minimal and comparable to placebo at Week 4
- Improvement noted in sleep quality

	Ulotaront, 50 or 75 mg/day (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)

[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;382:1497-1506.

Study 202: Change in Weight, BMI, Metabolic Laboratory Values, Vital Signs, and Sleep Quality (Safety Population)

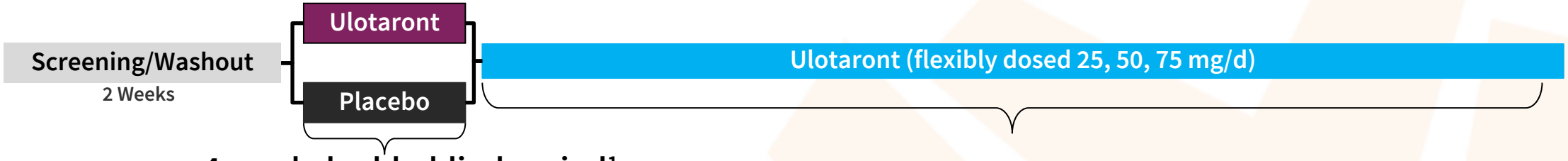
- Overall, the metabolic profile of ulotaront following up to 26 weeks of treatment was similar to OL baseline and not clinically notable
- Effect of ulotaront on prolactin levels was negligible at Week 26
- Improvement noted in sleep quality

Measurement	Ulotaront (n=156) Change From OL Baseline
Weight/BMI, mean (SD) change at week 26	
Weight, kg	–0.3 (3.20)
BMI, kg/m^2	–0.1 (1.03)
Laboratory values (fasting), median change at week 26	
Total cholesterol, mmol/L	2.00
HDL cholesterol, mmol/L	2.00
LDL cholesterol, mmol/L	–1.00
Triglycerides, mmol/L	0.00
Glucose, mmol/L	2.00
HbA1c (%)	0.00
Prolactin, male/female pmol/L	–1.26/–2.10
PSQI global score, mean (SD) change at week 26	–2.0 (2.97)

BMI, body mass index; HbA1c, glycolated hemoglobin A1c; LDL, low-density lipoprotein; PSQI, Pittsburgh Sleep Quality Index; SE, standard error.

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

Ulotaront: Rates of Extrapyramidal Symptoms



4-week double-blind period[1]

Preferred Term	Placebo (n=125)	Ulotaront (n=120)
Patients With Any EPS	4 (3.2)	4 (3.3)
Akathisia	1 (0.8)	2 (1.7)
Restlessness	1 (0.8)	0
Joint stiffness	1 (0.8)	0
Musculoskeletal stiffness	2 (1.6)	1 (0.8)
Nuchal rigidity	1 (0.8)	0
Postural tremor	0	1 (0.8)
Tremor	2 (1.6)	0

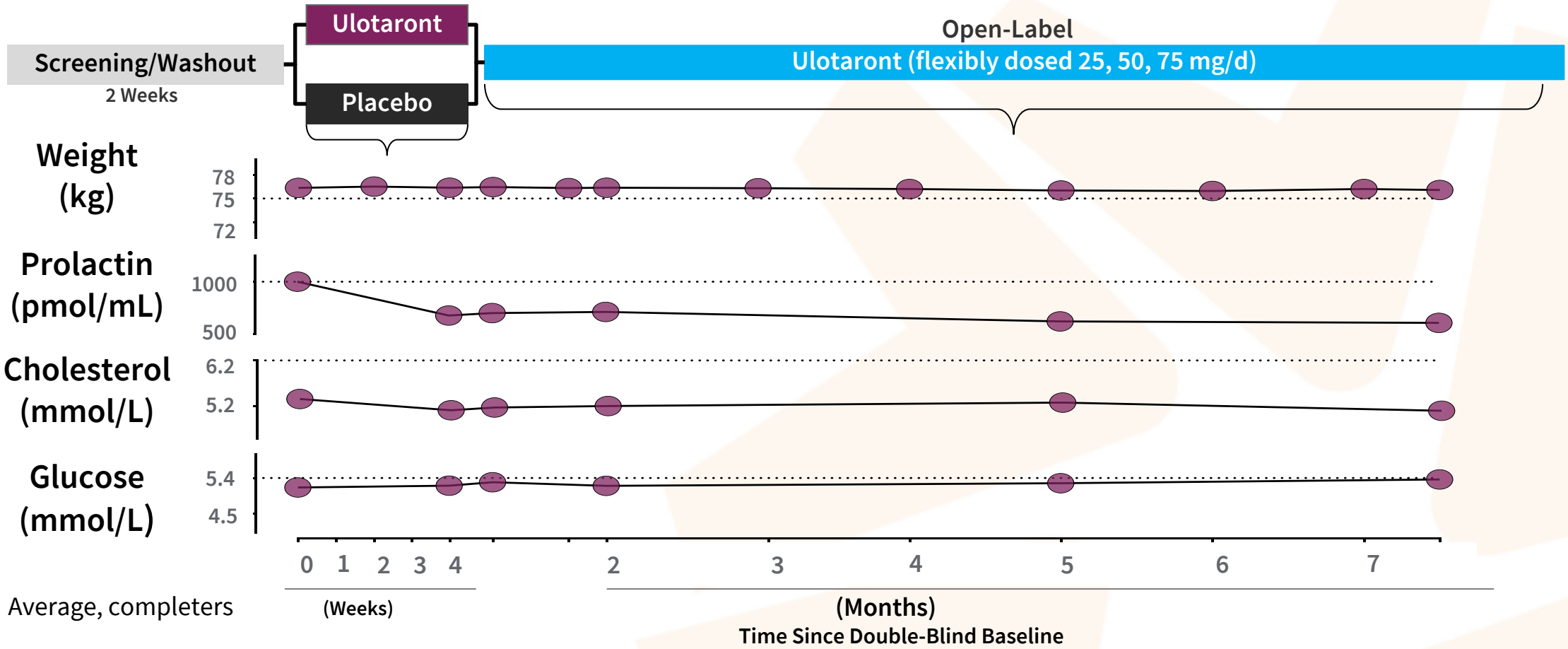
6-month open-label extension[2]

Preferred Term	Total (n=156)
Patients With Any EPS	5 (3.2)
Parkinsonism	2 (1.3)
Dyskinesia	1 (0.6)
Tremor	1 (0.6)
Restlessness	1 (0.6)

EPS, extrapyramidal symptom.

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

Ulotaront: Changes in Laboratory Values



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

Summary of Ulotaront Clinical Development in Schizophrenia

Clinical efficacy

- Effective in treating both positive and negative symptoms of schizophrenia (Study 201)
- Statistically significant improvement over 4 weeks in all secondary efficacy measures (Study 201)
- Effectiveness sustained over 6 months (Study 202)

Clinical safety and tolerability

- AE profile dissimilar from traditional first- and second-generation antipsychotics – minimal or no impact on motor function, weight/metabolic indices, or prolactin
- Discontinuation for the study because of an AE was 8.3% for ulotaront vs 6.4% for placebo

Based on results from Studies 201 and 202, ulotaront received Breakthrough Therapy Designation from the FDA for the treatment of schizophrenia, and is in Phase 3 of clinical development

- Two 6-week Phase 3 trials evaluating efficacy and safety of ulotaront in participants ages 13-65 with an acute exacerbation of schizophrenia
- Open-label extension study in adults and adolescents (52 weeks, patients rolled over from acute trials)
- Long-term safety study vs. quetiapine XR (52 weeks)

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

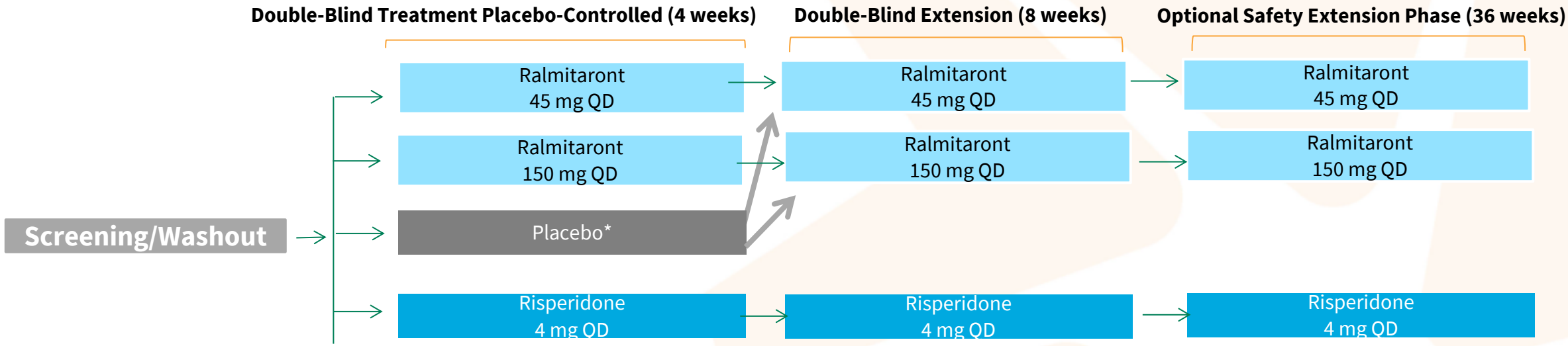
Ralmitaront (RO6889450) (Roche)

- Partial TAAR1 agonist
- Phase 2 randomized multicenter double blind parallel group placebo-controlled trials are currently underway
    - Acute Exacerbation of Schizophrenia or Schizoaffective Disorder: 4-week PANSS Total outcome
    - Schizophrenia or Schizoaffective Disorder, 12-week Brief Negative Symptoms Scale (BNSS) Avolition/Apathy Subscore outcome

Clinicaltrials.gov ; NCT04512066- Phase 2.

Ralmitaront vs. Placebo in Patients with an Acute Exacerbation of Schizophrenia or Schizoaffective Disorder

NCT04512066- Phase 2
Currently recruiting patients age 18-45



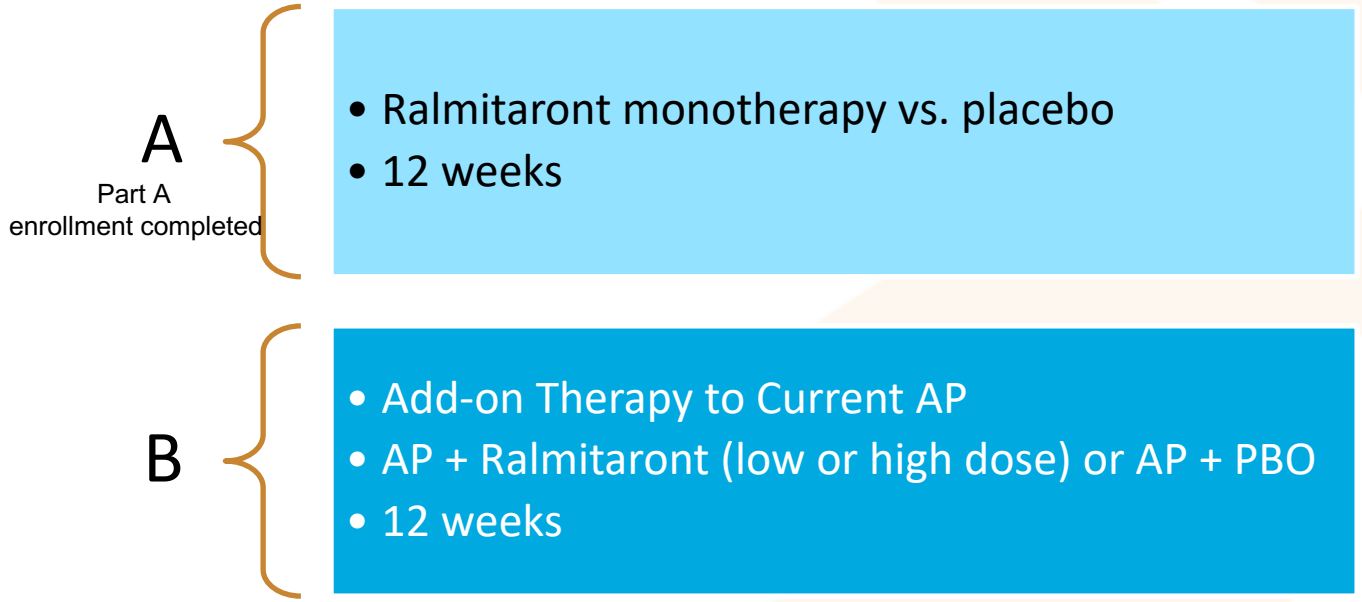
*Placebo randomized to Ralmitaront 45 or 150 mg QD at the end of 4 weeks

Primary Outcome Measure: Positive and Negative Syndrome Scale (PANSS) Total Score to Week 4
Estimated enrollment: 308 participants
Estimated primary completion date: July 31, 2022
Estimated completion date: April 23, 2023

Clinicaltrials.gov; NCT04512066- Phase 2.

Effects of Ralmitaront in Participants With Schizophrenia or Schizoaffective Disorder and Negative Symptoms

NCT03669640- Phase 2, Two Experimental Arms
Currently recruiting patients age 18-55



Primary Outcome Measure: Brief Negative Symptoms Scale (BNSS) Avolition/Apathy Subscore at Week 12
Estimated enrollment: 247 participants
Estimated completion date: May 6, 2023

Clinicaltrials.gov; NCT03669640- Phase 2

How All This May Fit

- Novel medications currently in development have demonstrated early promise as treatments for schizophrenia **without any direct blockade of postsynaptic dopamine D2 receptors** in the ventral striatum

- Preliminary evidence of these novel agents may suggest **positive tolerability and minimal negative effects** related to weight, metabolic indices, ECG changes, motoric adverse effects, or alterations in prolactin

- A TAAR1 and 5-HT_{1A} agonist **(ulotaront)** is in Phase 3 of clinical development and a TAAR1 partial agonist **(ralmitaront)** is in Phase 2 of clinical development

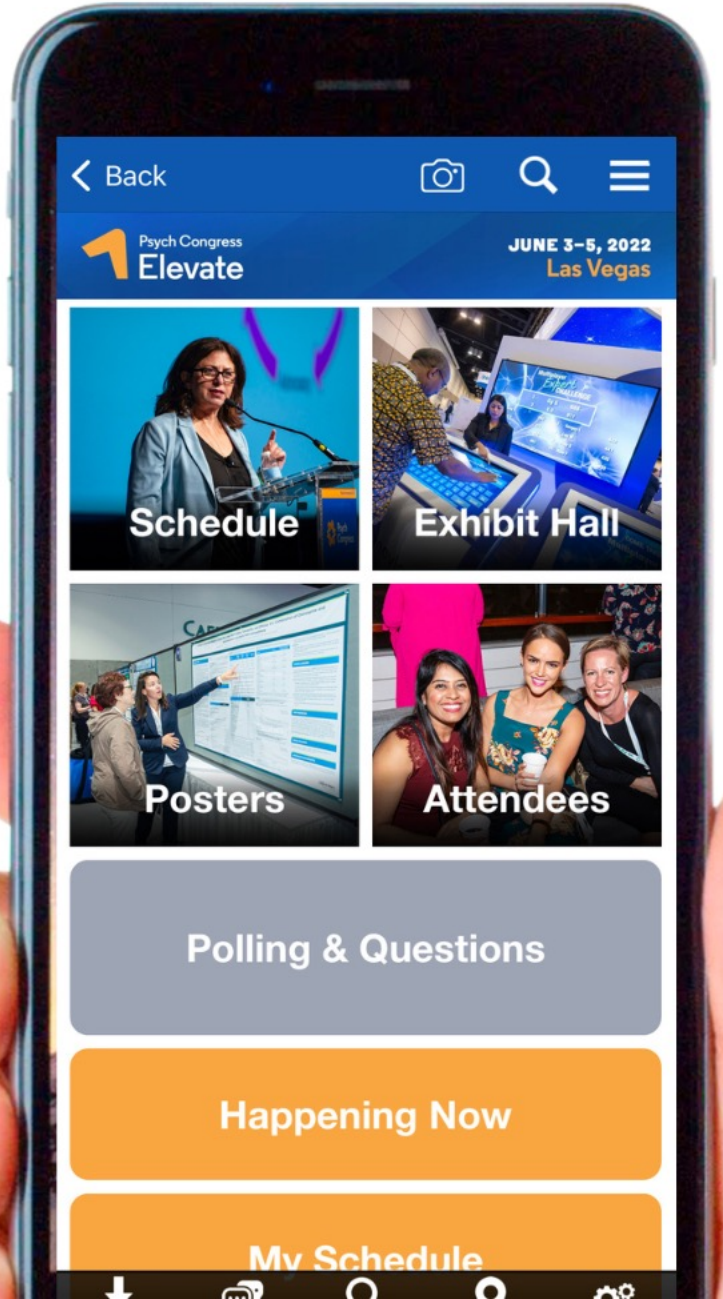
- Other novel mechanisms of action are also in Phase 3 of clinical development: M1/M4 muscarinic agonism (xanomeline-trospium combination) and GlyT1 inhibition (BI 425809)

Koblan KS, et al. *N Engl J Med.* 2020;382:1497-1506. Correll CU, et al. *NPJ Schizophr.* 2021;7(1):63. Brannan SK et al. *N Engl J Med.* 2021;384(8):717-26. Fleischhacker WW, et al. Lancet Psychiatry. 2021;8(3):191-201. Clinicaltrials.gov; NCT03669640- Phase 2.

Implications for Future Treatment Landscape

Successful Strategies for Patient-Provider Communication
Identifying Patient-Related Barriers to Novel Treatments

Meet Bethany



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