SEP-363856, a Novel Psychotropic Agent With a Non-D_2 Mechanism of Action, for the Treatment of Schizophrenia

Kenneth Koblan, Ph.D. on behalf of Sunovion Pharmaceuticals Inc.

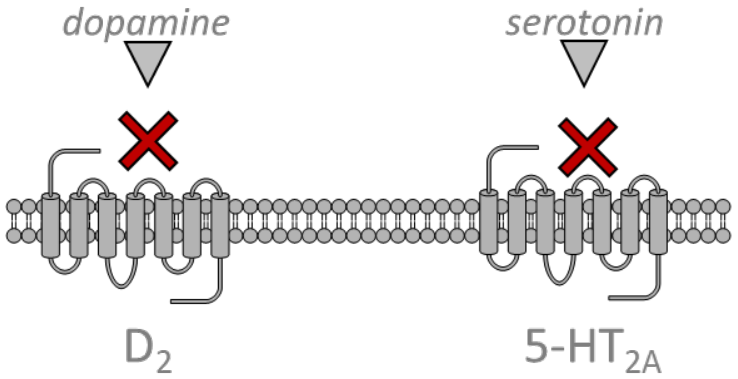
Sunovion discovered SEP-363856 in collaboration with PsychoGenics based in part on a mechanism-independent approach using the in vivo phenotypic SmartCube® platform and associated artificial intelligence algorithms.

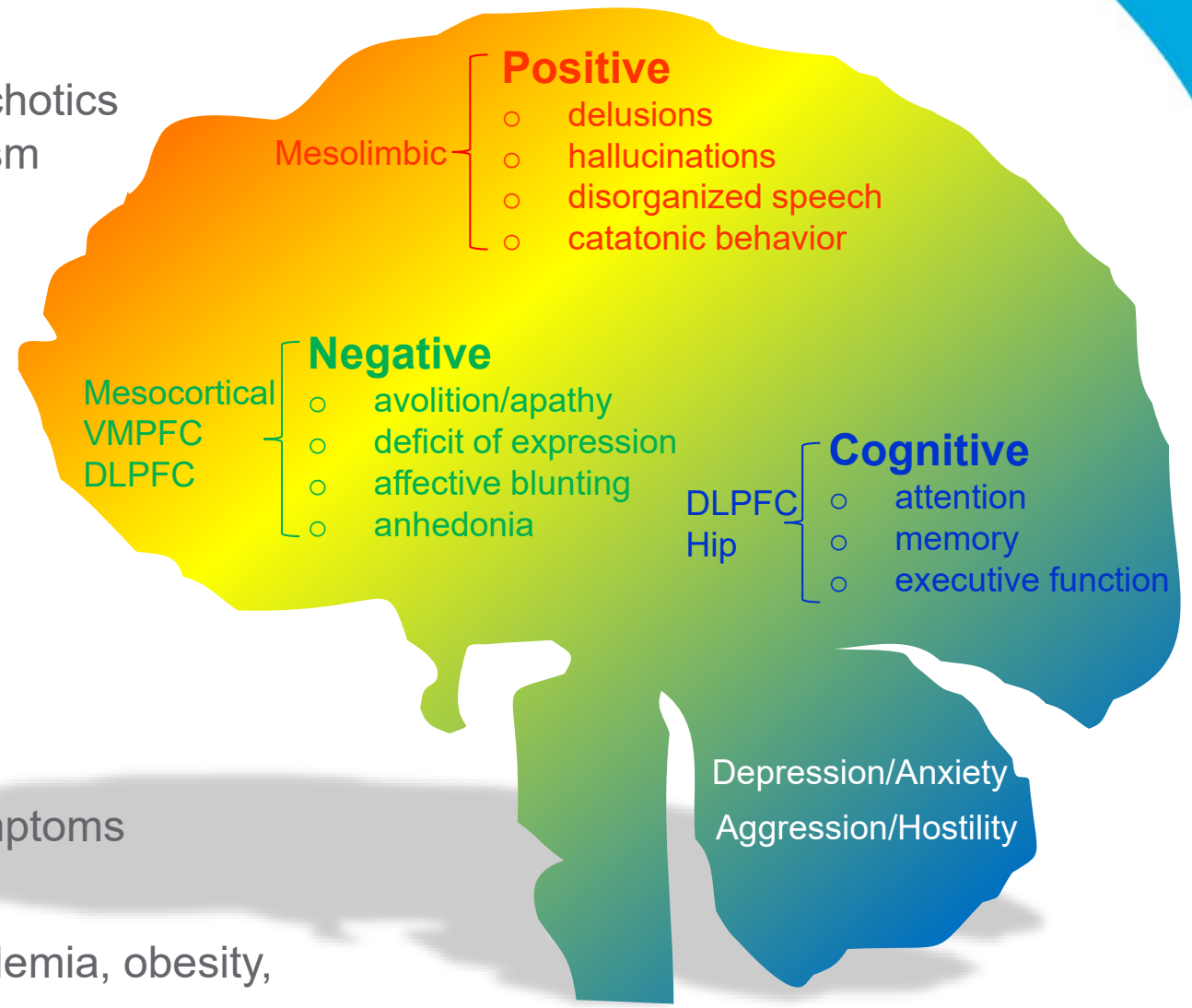
How can we improve schizophrenia treatment?

Approved pharmacological treatments

1st generation antipsychotics
- D_2 antagonism
- Chlorpromazine 1951/1952

2nd generation antipsychotics
- D_2/5-HT_{2A} antagonism
- Clozapine 1959



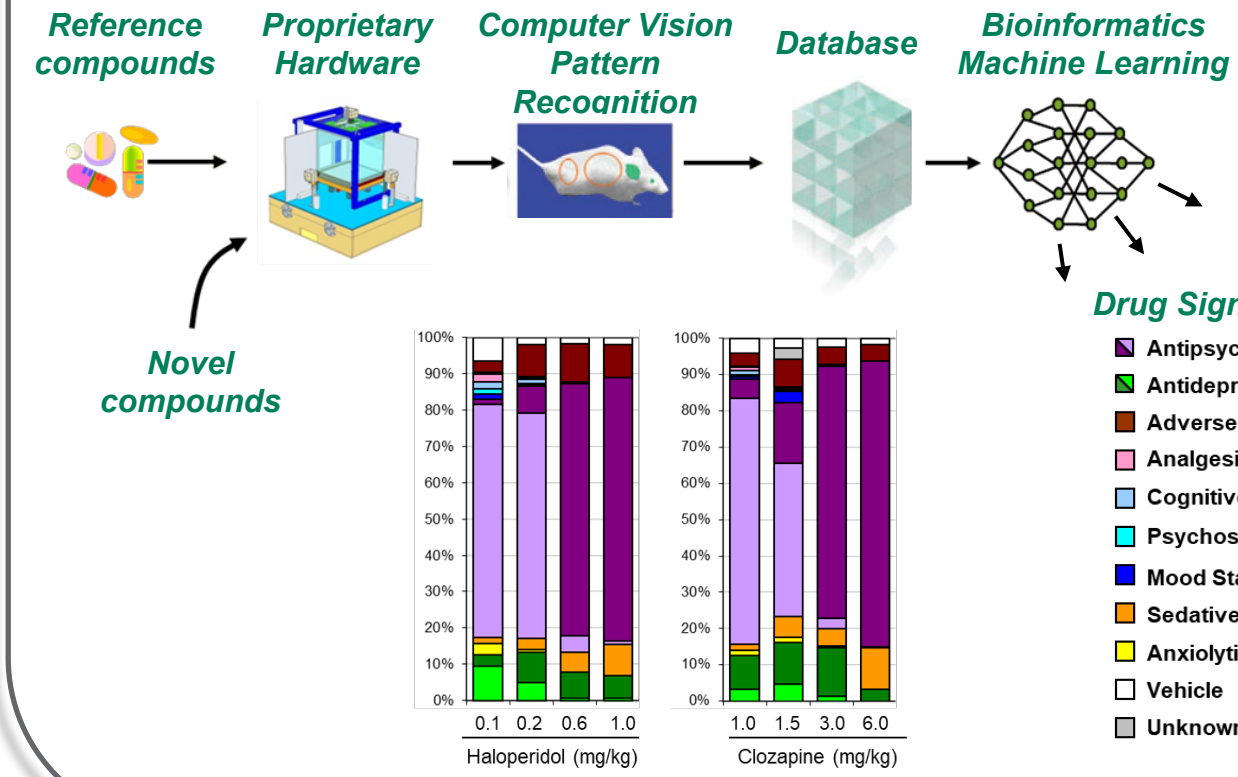


- ~30 % of patients do not respond
- Limited to no effect on negative and cognitive symptoms
- Extrapyramidal side effects
- Metabolic disturbances (hyperglycemia, hyperlipidemia, obesity, diabetes)

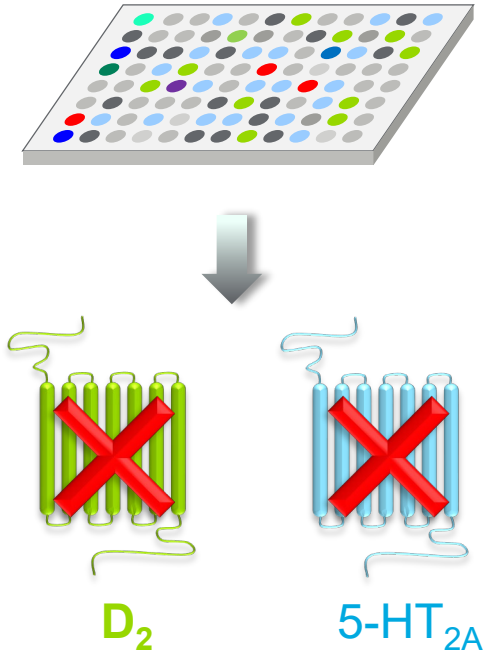
Development criteria for SEP-856

A non D_2/5-HT_{2A} compound with antipsychotic-like properties in rodents

In vivo phenotypic screening (SmartCube®)



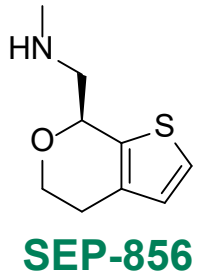
In vitro "anti-target" screening



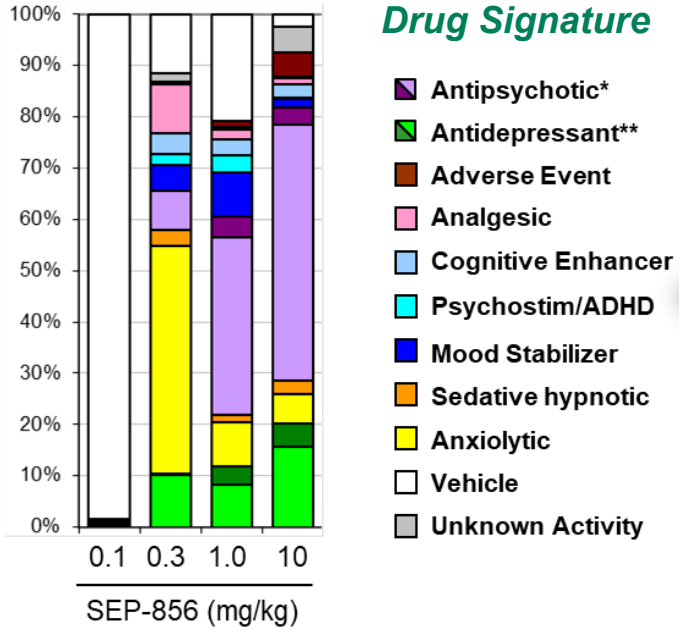
Roberds et al., 2011; Alexandrov et al., 2015; Shao et al., 2016; Leahy 2019; Dedic, Jones et al., 2019

SEP-856 does not exert its antipsychotic-like behavioral effects through D_2 or 5-HT_{2A} receptor blockade

Antipsychotic-like behavioral profile in mice



SEP-856



Drug Signature

- Antipsychotic*
- Antidepressant**
- Adverse Event
- Analgesic
- Cognitive Enhancer
- Psychostim/ADHD
- Mood Stabilizer
- Sedative hypnotic
- Anxiolytic
- Vehicle
- Unknown Activity

In vitro pharmacology (anti-target screen)

Antagonism		
	IC_{50} (μM)	% Inhibition
D_2	> 100 μM	< 35 % at 100 μM
5-HT_{2A}	> 30 μM	< 30 % at 30 μM

Dedic, Jones et al., JPET 2010

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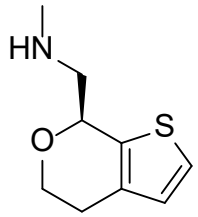
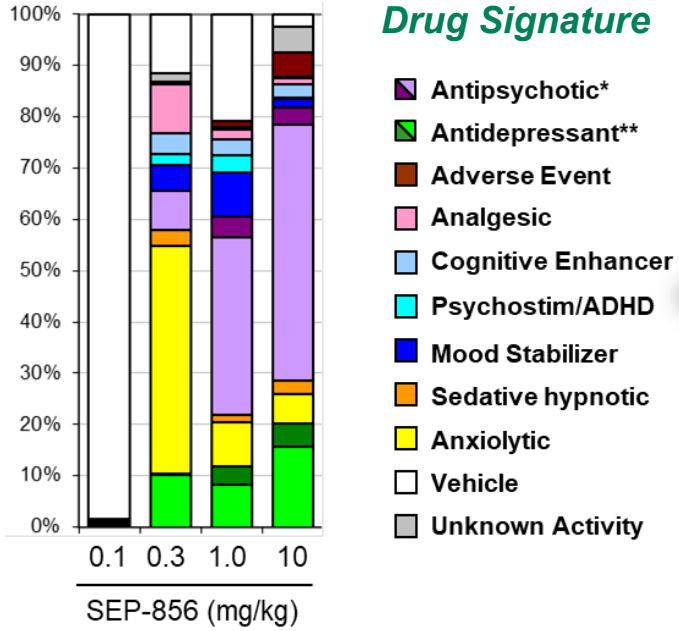
Antipsychotic-like behavioral profile in mice



SEP-856



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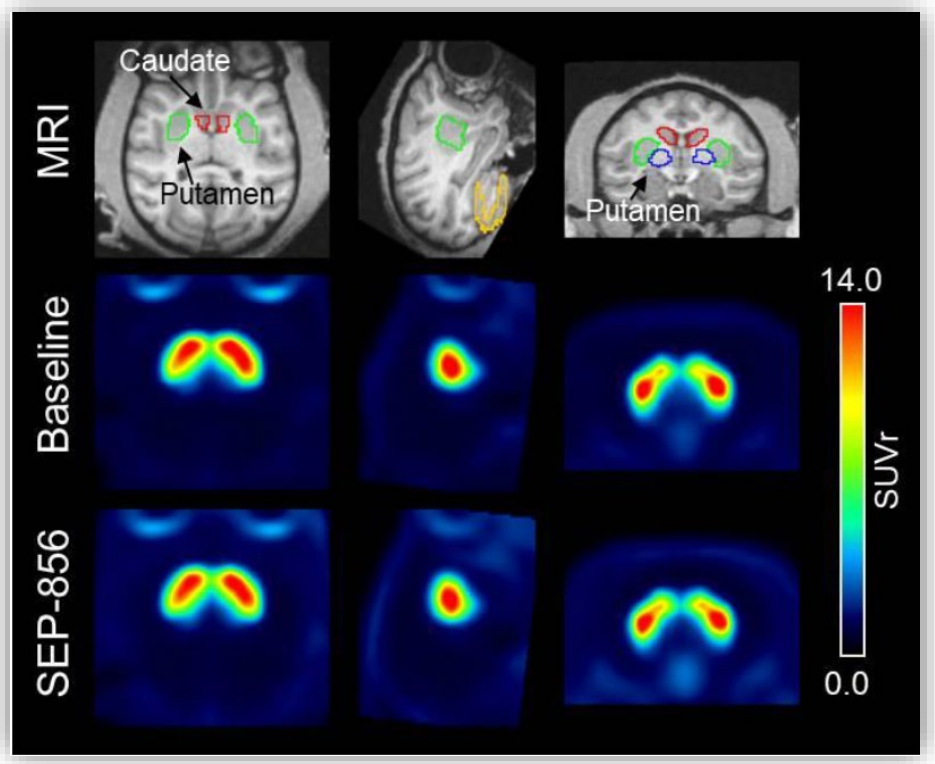
Lack of D_2 occupancy in NHP

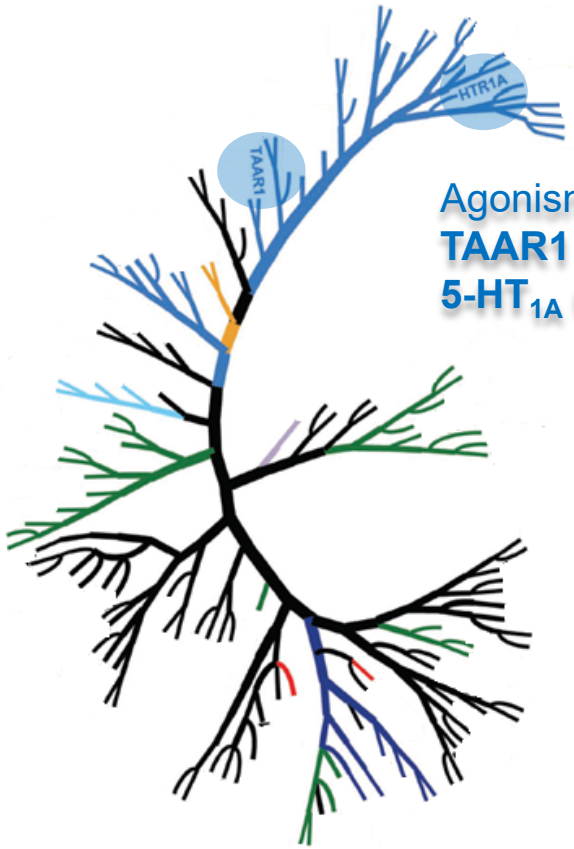


in vivo PET imaging of [^{18}F]-fallypride binding to D_2 receptors in non-human primates at 20x effective clinical concentrations of SEP-856 (consistent with observations in rodents)

Dedic, Jones et al., JPET 2019

Through which molecular targets does SEP-856 exerts it effects?

Broad screen of 182 receptor/ion channel/enzymes



Agonism at
TAAR1 (EC_{50} = 0.14 nM) and
5-HT_{1A} (K_i = 0.28 µM; EC_{50} = 2.3 µM)

Endogenous ligands

- bioamines
- melatonins
- lipids
- peptides
- purinergics
- adenosines
- orphans
- retinal

Dendogram of human GPCRs based on sequence similarity in binding sites. Lin et al., Nature Methods 2013

Trace amine receptor 1 (TAAR1)

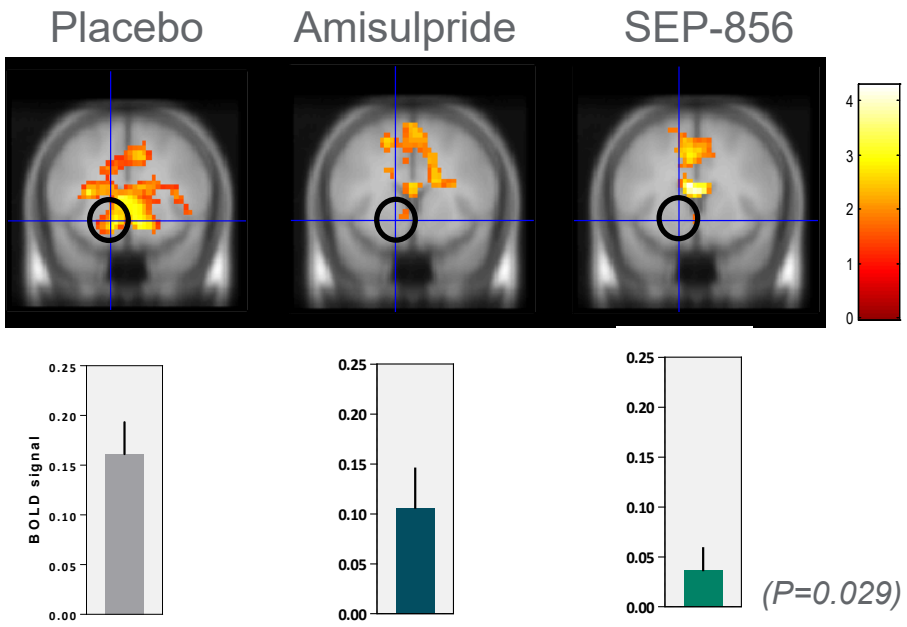
- Member of the GPCR trace amine family (TAAR 1-9)
- Expressed in the VTA, SN, DRN, cortex & limbic areas
- Physiologically activated by low “trace” level endogenous biogenic amines (phenylethylamine, tyramine, tryptamine, octopamine)
- Inhibits DA and 5-HT neuron firing
- Human receptor genes located in schizophrenia, BP locus (q23.1)
- Increased PEA levels in schizophrenia; depression associated with low levels
- Selective agonists demonstrate antipsychotic-, anxiolytic-, and antidepressant-like effects

5-HT_{1A} receptors

- Expressed in limbic areas, raphe nuclei, cortex, hypothalamus, thalamus, basal ganglia
- Presynaptic autoreceptors and postsynaptic receptors
- Modulate serotonergic signaling
- Clinically validated target implicated in various CNS disorders (e.g., depression, anxiety, Parkinson’s, schizophrenia, sleep-wake cycling)

Utilizing fMRI in a surrogate population to probe effects of SEP-856 on neural network modulation during early clinical development

Monetary Incentive Delay Task

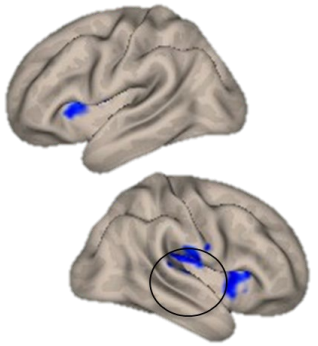


(Anticipation phase, Loss vs Neutral, left striatum)

SEP-856 and amisulpride (D_2 antagonist) reduced striatal activation during the anticipation phase of the MID task

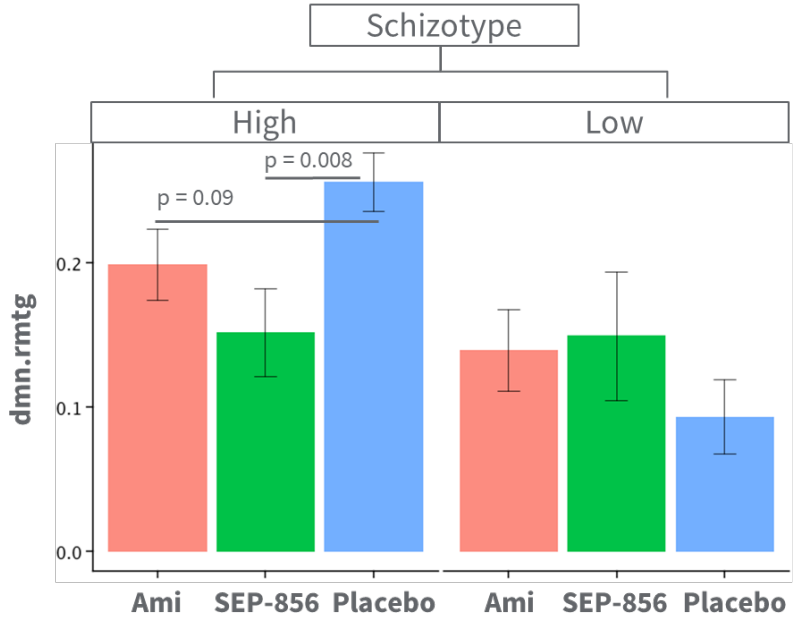
Bill Deakin, Gerry Dawson, Catherine Harmer
(University of Manchester, P1Vital, University of Oxford)

Resting state functional connectivity



Seed: 4 DMN ROIs

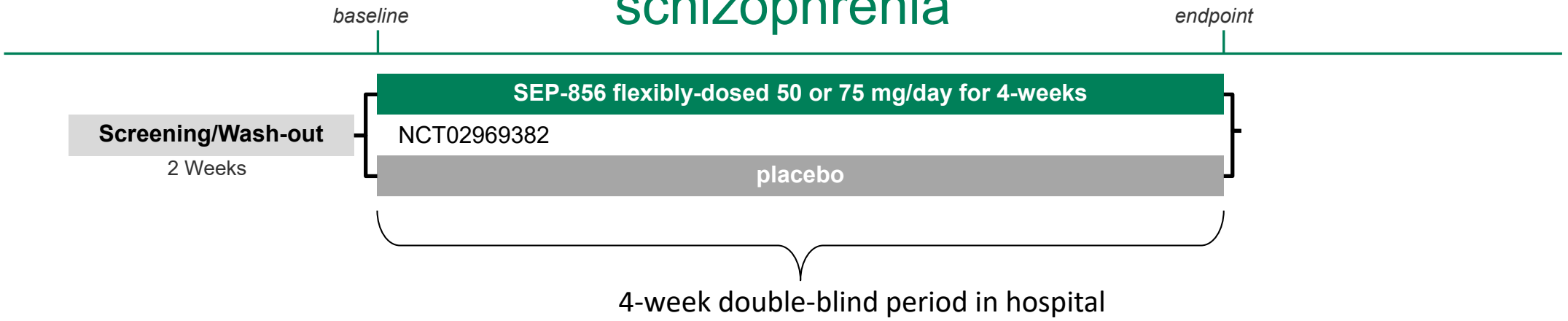
Voxel-level p < 0.001, cluster-level FDR-corrected p < 0.05



SEP-856 alleviates hyper-connectivity between DMN and auditory cortex in high schizotypes

Susan Whitfield-Gabrieli & Zhenghan Qi
(MIT & Northeastern University)

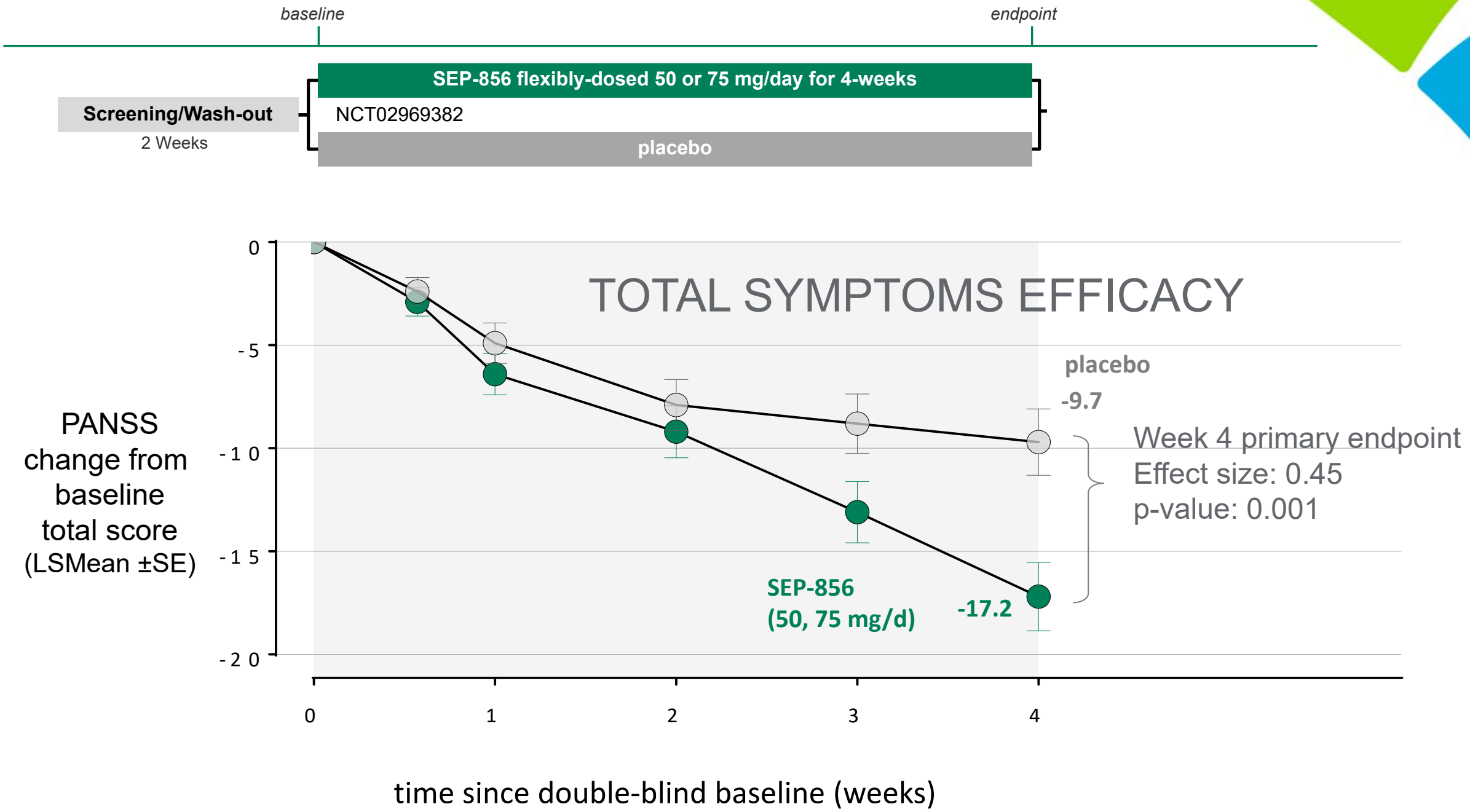
Efficacy and safety of SEP-856 in a Phase 2, randomized, controlled trial for the treatment of schizophrenia

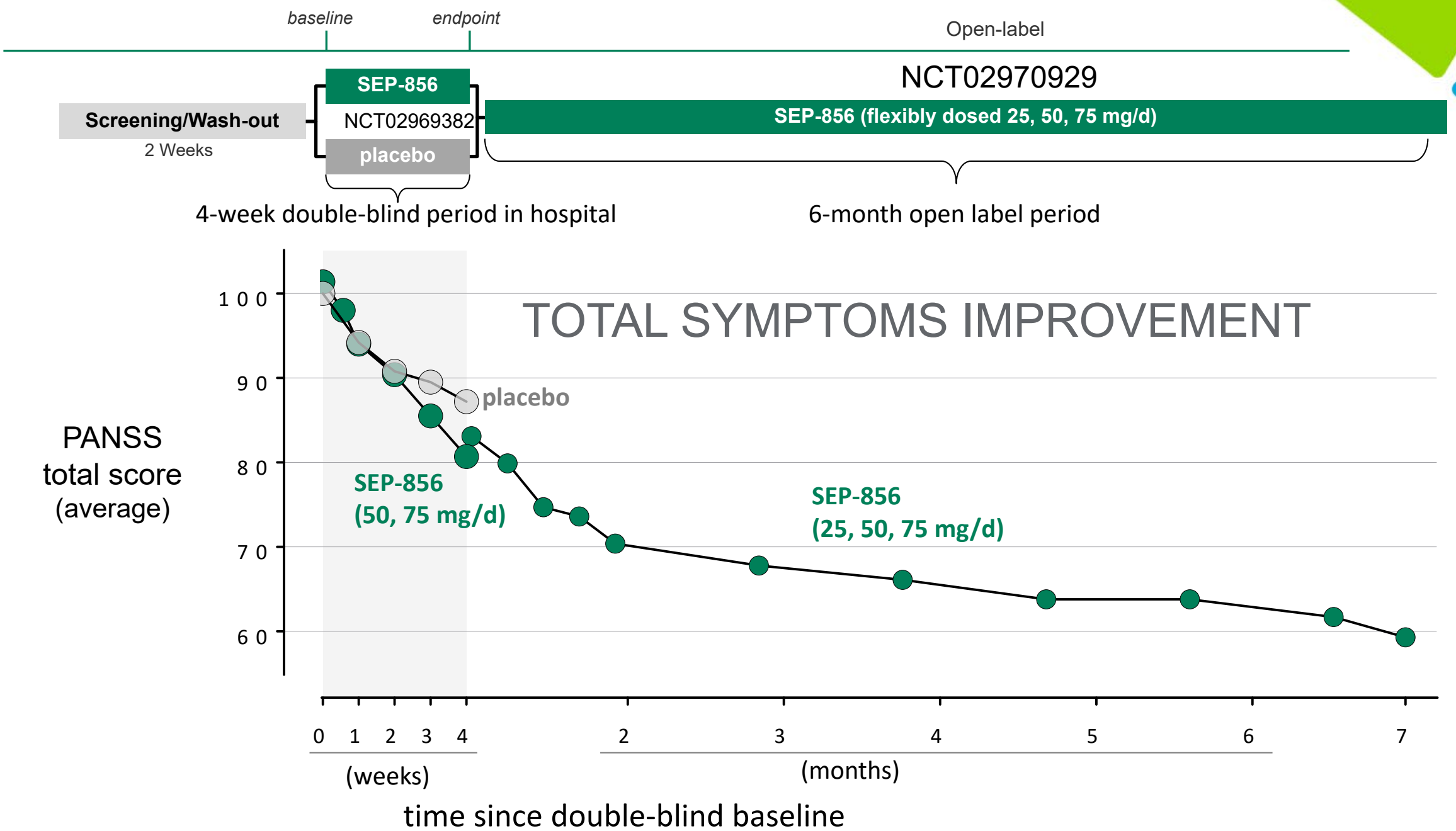


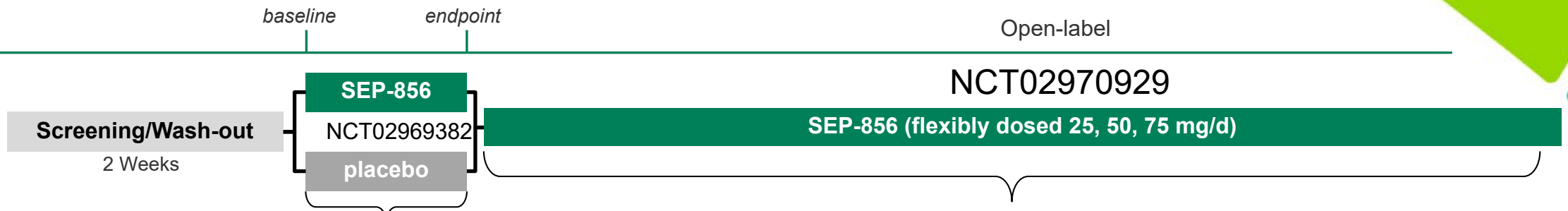
Key Entry Criteria

- Male and female, 18-40 years of age
- Meets DSM-5 criteria for schizophrenia using SCID-CT (≥6 months duration)
- Time since current acute exacerbation of psychotic symptoms ≤2 months
- ≤2 prior hospitalizations for treatment of acute exacerbation of schizophrenia
- Screening and Baseline PANSS total score ≥80 and PANSS item score ≥4 on two or more of:
  - Delusions (P1); Conceptual disorganization (P2); Hallucinatory behavior (P3); Unusual thought content (G9)
- Screening and Baseline CGI-S score ≥4

BASELINE CHARACTERISTICS	Placebo (N=125)	SEP-856 (N=120)
Age, years, mean (SD)	30.6 (6.07)	30.0 (5.76)
PANSS Total Score (SD)	99.7 (7.76)	101.4 (8.40)
Sex, n (%)		
Male	79 (63.2%)	77 (64.2%)
Race, n (%)		
White	104 (83.2%)	96 (80.0%)
Black	20 (16.0%)	19 (15.8%)
BMI, kg/m^2, mean (SD)	24.7 (3.73)	25.0 (4.24)







4-week double-blind period in hospital

6-month open label period

Preferred Term	Placebo (N = 125)	SEP-363856 (N = 120)
	n (%)	n (%)
Subjects with Any AE	**63 (50.4%)**	**55 (45.8%)**
Somnolence	6 (4.8%)	8 (6.7%)
Agitation	6 (4.8%)	6 (5.0%)
Nausea	4 (3.2%)	6 (5.0%)
Insomnia	13 (10.4%)	4 (3.3%)
Diarrhea	1 (0.8%)	3 (2.5%)
Dyspepsia	0	3 (2.5%)
Anxiety	9 (7.2%)	2 (1.7%)
Subjects 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

Preferred Term	Total (N = 156)
	n (%)
Subjects with Any AE	**88 (56.4%)**
Schizophrenia	19 (12.2%)
Headache	18 (11.5%)
Insomnia	13 (8.3%)
Anxiety	8 (5.1%)
Nasopharyngitis	7 (4.5%)
Somnolence	7 (4.5%)
Nausea	6 (3.8%)
Influenza	5 (3.2%)
Irritability	5 (3.2%)
Weight decreased	5 (3.2%)
Subjects with any EPS	**5 (3.2%)**
Parkinsonism	2 (1.3%)
Dyskinesia	1 (0.6%)
Tremor	1 (0.6%)
Restlessness	1 (0.6%)


The NEW ENGLAND JOURNAL of MEDICINE
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A Non–D2-Receptor-Binding Drug for the Treatment of Schizophrenia
Kenneth S. Koblan, Ph.D., Justine Kent, M.D., Seth C. Hopkins, Ph.D., John H. Krystal, M.D., Hailong Cheng, Ph.D., Robert Goldman, Ph.D., and Antony Loebel, M.D.

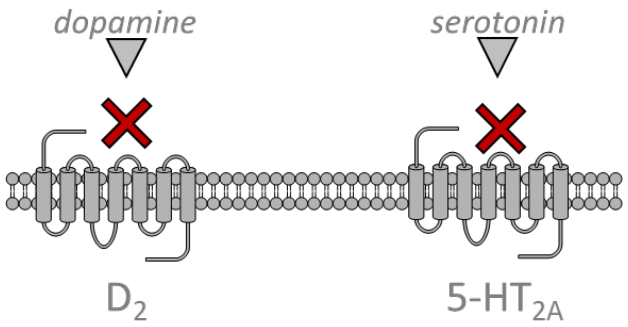
EPS = Extra Pyramidal Symptoms

SEP-856, a novel compound with a non-D_2 mechanism of action

- Discovered in combination with mouse phenotypic and in vitro (anti-target) screening
- Demonstrates antipsychotic-like efficacy across a broad range of animal models/assays
- Mechanism of action - TAAR1 and 5-HT_{1A} agonism
- May exert its efficacy through modulation of presynaptic dopamine synthesis capacity
- Clinically effective in reducing overall symptoms in schizophrenia patients without class-related side-effects of current atypical antipsychotics
- Phase 3 clinical trials for the treatment of schizophrenia ongoing

D_2/5-HT_{2A} antipsychotic class

monoamine receptor BLOCKADE



SEP-856

monaamine receptor ACTIVATION