SAFETY AND EFFECTIVENESS OF SEP-363856 IN SCHIZOPHRENIA: RESULTS OF A 6-MONTH, OPEN-LABEL EXTENSION STUDY

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ABSTRACT

Background: SEP-363856 is a novel non-D2 receptor antagonist, and preclinical data suggest that agonism at trace amine associated receptor 1 (TAAR1) and the serotonin 5-H1A receptor contributes to its efficacy. In a previous double-blind (DB), placebo-controlled study, SEP-363856 demonstrated significant efficacy in the treatment of an acute exacerbation of schizophrenia (Koblan et al, NEJM 2020; 82:1497-1506). The aim of this extension study was to evaluate the safety and effectiveness of longer-term treatment with SEP-363856.
Method: Patients who completed the 4-week, DB, placebo-controlled study of SEP-363856 were treated for 26 weeks with open-label (OL) SEP-363856 (25/50/75 mg/d). The primary outcomes were safety measures; effectiveness outcomes were secondary and included the PANSS total score.
Results: Altogether, 156 patients were treated in this extension study and 66.9% were 26-week completers. Reasons for discontinuation consisted of adverse event (11.5%), withdrawal of consent (10.2%), lack of efficacy (5.1%), and other (6.4%). Individual AEs with an incidence ≥5% were schizophrenia (12.2%), headache (11.5%), insomnia (8.3%), and anxiety (5.1%). No clinically meaningful changes were observed on movement scales. Mean month 6 change from DB baseline in weight was -0.3 kg. No clinically meaningful changes were observed at week 26 in metabolic laboratory parameters, or prolactin levels. Continued improvement from OL baseline to week 26 was observed on the PANSS total score (mean: -19.8).
Conclusion: Up to 26 weeks of treatment with SEP-363856 had minimal effects on weight, metabolic parameters, prolactin, or extrapyramidal symptoms. SEP-363856 was associated with continued improvement from open-label baseline in the PANSS total score.

ClinicalTrials.gov Identifier: **NCT02970929**

INTRODUCTION

- SEP-363856 is a new class of compound without dopamine D_2 receptor occupancy that has demonstrated efficacy in animal models of psychosis. SEP-363856 is an agonist at trace amine receptor 1 (TAAR1). SEP-363856 also activates serotonin 5-HT_{1A} receptors. SEP-363856 does not bind to any dopaminergic, serotonergic (other than 5-HT_{1A}), glutamatergic, or other neuroreceptors thought to mediate the effects of currently available antipsychotics
- In nonclinical models, activation of TAAR1 has been shown to downregulate dopaminergic neurotransmission; and TAAR1 agonists, and mixed 5-HT_{1A}/TAAR1 agonists, have demonstrated antipsychotic-like activity in prepulse inhibition models, and cocaine and PCP-induced hyperactivity models of schizophrenia
- In a previous double-blind, placebo-controlled study, SEP-363856 (in flexible doses of 50 or 75 mg/d) demonstrated efficacy in the treatment of an acute exacerbation of schizophrenia

OBJECTIVE

- The aim of this 6-month extension study was to evaluate the safety and effectiveness of longer-term treatment with SEP-363856

METHODS

- Patients with an acute exacerbation of schizophrenia who completed a 4-week, double-blind, placebo-controlled, flexible-dose (50 or 75 mg) study of SEP-363856 were given the option to enroll in an extension study in which they were treated, open-label, with flexible doses (25/50/75 mg/d) of SEP-363856 for 26-week
- To maintain the blind in the initial placebo-controlled trial, patients enrolled in the extension study were started on a SEP-363856 dose of 50 mg/d for 3 days, regardless of initial treatment assignment
- The primary (safety) outcome measures were overall incidence of adverse events, adverse events leading to discontinuation, and serious adverse events. Secondary safety outcomes included change in weight, BMI, laboratory tests, ECG, and measures of extrapyramidal symptoms (EPS). Suicidality was assessed using the Columbia – Suicide Severity Rating Scale (C-SSRS). The Pittsburgh Sleep Quality Index (PSQI) was obtained

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METHODS (cont.)

- Effectiveness outcomes included the PANSS total and subscale scores, CGI-Severity score, the Brief Negative Symptom Scale (BNSS) total score, and the PANSS Marder negative symptom factor score
- **Response criteria:** a priori response was assessed based on reduction from double-blind baseline in PANSS total score of ≥20% (OC and LOCF-endpoint)

RESULTS

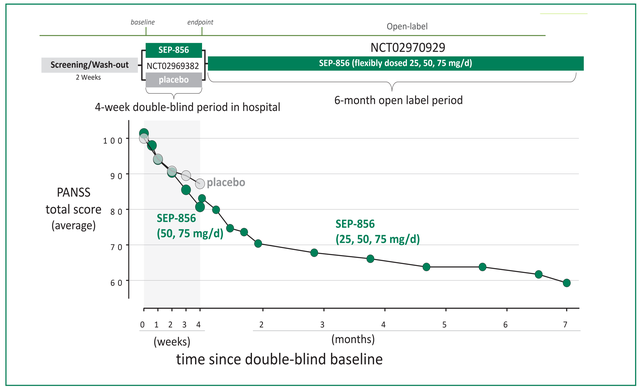
Table 1. Baseline Demographic and Clinical Characteristics (Safety Population)

	SEP-363856 (N=156)
Male, %	65.4
Age, yrs, mean	30.2
Race, %	
White	87.2
Black/African American	9.6
Other	3.2
Prior hospitalizations for schizophrenia, %	
None	18.6
One	39.7
Two	41.7
PANSS Total score, mean, DB / OL baselines	
SEP-363856	102.6/80.0
Placebo	100.4/86.3
CGI-Severity score, mean, DB / OL baselines	
SEP-363856	5.0/3.8
Placebo	4.9/4.2

DB: double-blind; OL: open-label

- **Patient disposition:** Study completers (66.9%); reasons for discontinuation consisted of adverse event (11.5%), withdrawal of consent (10.2%), lack of efficacy (5.1%), and other (6.4%)
- **Study treatment:** The modal daily dose of SEP-363856 was 25 mg/d in 1.9% of patients, 50 mg/d in 42.9%, and 75 mg/d in 54.5%

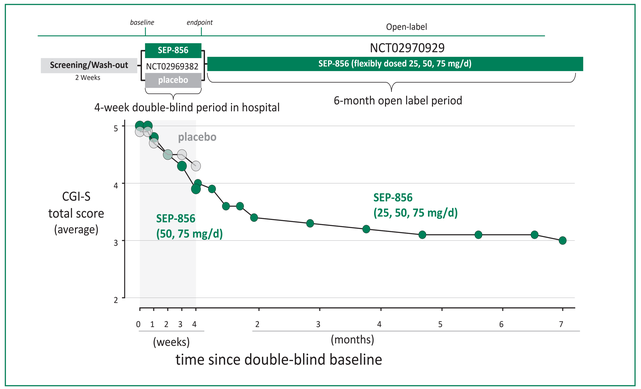
Figure 1. Mean PANSS Total Score During 6 Months of Open-label Treatment With SEP-363856



- Mean improvement at Week 26 in the PANSS total score was -41.8, with 22.6 points of the improvement occurring during 26 weeks of open-label treatment

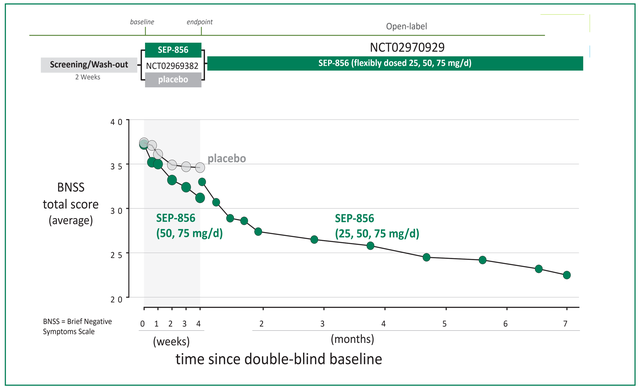
RESULTS

Figure 2. Mean CGI-Severity Score During 6 Months of Open-label Treatment With SEP-363856



- Mean change from DB Baseline in the CGI-S score at Week 26 was -2.0 (OC) and -1.5 (LOCF-endpoint)
- Mean change from DB Baseline in the PANSS subscale scores at LOCF-endpoint: Negative (-6.6), Positive (-10.4), General Psychopathology (-15.2)

Figure 3. Mean BNSS Total Score During 6 Months of Open-label Treatment With SEP-363856



- Negative symptoms continued to show improvement during 26 weeks of open-label treatment with SEP-363856 as assessed by the BNSS total score (see Figure, above), and by the Marder PANSS-negative symptom factor score (DB baseline: 38.4; OL baseline 33.0; Week 26-OC: 22.5)
- Week 26 responder rates rates (≥20% criterion) were 97% (observed case) and 81% (LOCF-endpoint)
- The mean PSQI Global Score at DB baseline was 6.8 (a score ≥6 is represents a criterion level for clinically significant insomnia). Insomnia continued to show improvement during 26 weeks of open-label treatment with SEP-363856 with mean PSQI Global Scores of 4.6 at OL baseline and 2.1 at Week 26-OC

Table 2. Change From Double-blind Baseline in Weight, BMI, Metabolic Parameters and Prolactin at Week 26

	SEP-363856 (N=156)
Weight, kg, mean change	-0.3
BMI, kg/m², mean change	-0.1
Total Cholesterol, mg/dL, median change	-2.0
LDL Cholesterol, mg/dL, median change	-9.0
HDL Cholesterol, mg/dL, median change	0.0
Triglycerides, mg/dL, median change	-5.0
Glucose, mg/dL, median change	+2.0
HbA1c, %, median change	0.0
Prolactin, ng/L, Overall / Male / Female, median change	-2.7 / -2.7 / -3.4

The sample size at Week 26 ranged from 104-111

- No clinically meaningful median changes were observed at week 26 in metabolic laboratory parameters or in prolactin levels
- No patient had an increase in QTcF ≥60 msec or a QTcF interval ≥480 msec

Table 3. Treatment-emergent Adverse Events, % (≥2%; Safety population)

Event, %	SEP-363856 (N=156)
Schizophrenia	12.2
Headache	11.5
Insomnia	8.3
Anxiety	5.1
Somnolence	4.5
Nasopharyngitis	4.5
Nausea	3.8
Irritability	3.2
Influenza	3.2
Weight decreased	3.2
Prolactin increased	2.6
Extrapyramidal adverse events	
Parkinsonism	1.3
Dyskinesia	0.6
Tremor	0.6
Restlessness	0.6
At least one adverse event	56.4
Adverse event rated as "severe"	5.1
Adverse event leading to study discontinuation	11.5

- A total of 15 patients (9.6%) experienced an SAE; schizophrenia was the only SAE to occur in more than one patient (n=7, DB placebo group; n=4, DB SEP-363856 group). One patient each reported an SAE of psychotic disorder and acute psychosis (DB SEP-363856). One patient each reported an SAE of uterine hemorrhage (DB SEP-363856 group) and suicidal ideation (DB placebo group)
- There were no deaths in the study. Suicidal ideation (assessed using the C-SSRS) was reported by 3 patients; 1 patient made an aborted attempt

DISCUSSION

- SEP-363856 is a new class of compound, without dopamine D_2 receptor occupancy, that is an agonist at TAAR1 and 5-HT_{1A} receptors. SEP-363856 has demonstrated significant efficacy in the treatment of schizophrenia in a previous short-term trial (Koblan et al., 2020;382:1497-1506)
- In this extension study, completers of the short-term trial received 6-months of open-label treatment with flexible doses of SEP-363856 (25-75 mg/d). Treatment with SEP-363856 was associated with notable continued improvement from OL-baseline in the PANSS total score (-19.2) and negative symptoms as measured by the BNSS total score (-10.5)
- The completion rate was 67% during the 6-month extension study. The most frequently reported TEAEs (≥ 5%) were schizophrenia, headache, insomnia and anxiety. Most SAEs, and adverse events leading to study discontinuation, were related to the worsening of schizophrenia. SEP-363856 had minimal effects on weight, lipids, glycemic indices, prolactin or risk of extrapyramidal symptom measures

DISCLOSURES

Dr. Correll has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Angelini, Boehringer-Ingelheim, Gedeon Richter, Gerson Lehrman Group, Indivior, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Merck, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Boehringer-Ingelheim, Lundbeck, Rovi, Supernus, and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a shareholder of LB Pharma. Drs. Koblan, Hopkins, Kent, Cheng, Goldman and Loebel are employees of Sunovion Pharmaceuticals Inc. Medical writing support was provided by Edward Schweizer, MD of Paladin Consulting Group, and was funded by Sunovion Pharmaceuticals Inc.
Note: 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.