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DASOTRALINE EFFICACY THROUGHOUT THE DAY IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: RESULTS OF A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY IN A LABORATORY CLASSROOM SETTING

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DISCLOSURES

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ABSTRACT

Objectives: Once-daily dosing with dasotraline, a novel dopamine and norepinephrine reuptake inhibitor, achieves stable plasma concentrations over 24 hours. This study evaluated the efficacy and safety of dasotraline in children with attention deficit hyperactivity disorder (ADHD), in a laboratory classroom setting.

Methods: Children (6–12 years) meeting the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for ADHD were randomized to 2 weeks of dasotraline or placebo (dosed daily at home at ~8PM). Laboratory classroom evaluations took place at Baseline and Day 15. The primary endpoint was change from Baseline at Day 15 in ADHD symptoms, as measured by mean Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale – Combined Score (SKAMP-CS), derived from 7 assessments across the 12-hour laboratory classroom day (12–24 hours post-dose). Secondary endpoints included SKAMP scores at timepoints from 8AM through 8PM, and measures of safety.

Results: The intent-to-treat population comprised 112 patients. Mean age was 9.5 years; 68.8% were male; 91% completed the study. Dasotraline 4 mg/day significantly improved mean SKAMP-CS vs placebo ($p<0.001$, effect size 0.85) with significant effects persisting throughout the day. Mean SKAMP subscores improved significantly vs placebo (Attention $p<0.001$, effect size 0.81; Deportment $p<0.001$, effect size 0.70). Treatment-emergent adverse events (TEAEs) were mild or moderate in severity; most frequent were (dasotraline 4 mg/day; placebo): insomnia (19.6%; 3.6%, all terms combined), decreased appetite (10.7%; 3.6%), headache (10.7%; 8.9%), affect lability (8.9%; 7.1%), irritability (5.4%; 3.6%), orthostatic tachycardia (5.4%; 0%), and perceptual disturbances (5.4%; 0%).

Conclusions: In this laboratory classroom study in children with ADHD, dasotraline significantly improved ADHD symptoms compared with placebo and demonstrated sustained efficacy up to 24 hours post-dose. Most common TEAEs were insomnia, decreased appetite, and headache.

BACKGROUND

- Dopamine (DA) and norepinephrine (NE) have been implicated in the pathophysiology of attention deficit hyperactivity disorder (ADHD), and drugs that increase DA and NE neurotransmission are clinically effective in the management of ADHD symptoms[1]
- Limitations of currently available ADHD treatments include: inadequate duration of effect, pharmacokinetic (PK) drug concentration peaks and troughs within dosing intervals, and a risk of abuse liability for the stimulant class of ADHD medications. Hence, there is a need for additional treatment options, including non-stimulant alternatives
- Dasotraline is a novel oral medication currently being evaluated for the treatment of ADHD in children and adults, and binge-eating disorder in adults
- Dasotraline is a potent inhibitor of human DA transporters (DA uptake IC_{50} 3 nM) and NE transporters (NE uptake IC_{50} 4 nM)[2,3]
- In adults, dasotraline has a time-to-maximum concentration (t_{max}) of 10–12 hours, and a terminal elimination half-life ($t_{1/2}$) of 47–77 hours, resulting in steady-state plasma concentrations over 24 hours after 2 weeks of daily dosing,[4] with low potential for abuse demonstrated in recreational stimulant users.[5] The PK profiles in children and adolescents are similar to those reported in adults[6]
- Previous studies of dasotraline in adults[2] and in children with ADHD[7] have demonstrated efficacy, safety, and tolerability

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OBJECTIVE

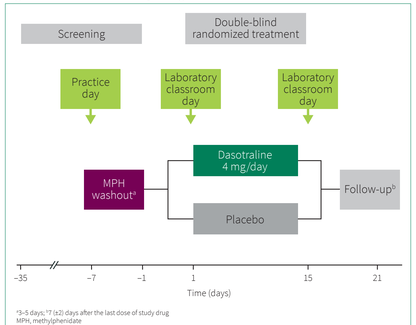
- To evaluate the efficacy, safety, and tolerability of 4 mg/day dasotraline compared with placebo in children (6–12 years) with ADHD throughout the day in a laboratory classroom setting[8] (NCT02734693; Study SEP360-305)

METHODS

Study design

- Children (6–12 years) meeting the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for ADHD were randomized to 2 weeks of dasotraline 4 mg/day or placebo (1:1; dosed daily at home at approximately 8PM, with or without food)
- The study consisted of a screening period (up to 35 days), a 3–5-day ADHD medication washout period prior to Day –1, and a treatment period (Day 1 to Day 14) followed by an End of Study visit (7 days after last dose) (**Figure 1**)
- Following an abbreviated practice day in the laboratory classroom setting and the washout period, evaluations took place over the course of 12 hours (8AM through 8PM), with assessments every 2 hours, at Baseline (Day 1) and Day 15
- The study contained a dasotraline 6 mg/day arm (with no titration). Shortly after initiation, the study protocol was amended to omit the 6 mg/day arm

Figure 1. SEP360-305 study design



[a]3–5 days; [b]7 (±2) days after the last dose of study drug
MPH, methylphenidate

Key inclusion/exclusion criteria

- Children aged 6–12 years at the time of randomization and with a primary diagnosis of ADHD (DSM-5 criteria) were eligible. Diagnosis was confirmed using the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL)
  - Subjects were required to be taking a methylphenidate (MPH) formulation within the approved dose range for ADHD for ≥6 weeks prior to Day –7, with the same dose for ≥1 week immediately prior to Day –7, and confirmed as being well tolerated and effective
  - On Day –1, subjects had to show evidence of worsening of ADHD symptoms as measured by ADHD Rating Scale Version IV – Home Version (ADHD RS-IV HV) total score ≥26, and ≥30% worsening in ADHD RS-IV HV total score following a 3–5-day washout from MPH
- Key exclusion criteria included medical instability, failure of 2 adequate courses of stimulant or non-stimulant treatment for ADHD, or use of any antipsychotic medication within 6 months of screening

Efficacy and safety measures

- The primary endpoint was change from Baseline at Day 15 in ADHD symptoms as measured by the mean Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Scale – Combined Score (CS), obtained from an average of 7 assessments collected across the 12-hour laboratory classroom day (12–24 hours post-dose)
- Secondary efficacy endpoints included SKAMP-CS throughout Day 15 at individual timepoints from 8AM through 8PM (12–24 hours post-dose); change from Baseline at Day 15 in mean SKAMP-Attention subscale score and mean SKAMP-Deportment subscale score; and change from Baseline at Day 15 in Permanent Product Measure of Performance (PERMP) scores for Problems Attempted and Problems Correct at each of the assessment times. PERMP is a 10-minute math test that is tailored to the ability level of each child
  - An analysis of covariance (ANCOVA) model was used to evaluate treatment effect for the primary efficacy endpoint between the dasotraline 4 mg/day and placebo groups for the intent-to-treat (ITT) population. A similar ANCOVA model was used for the secondary efficacy endpoints for the ITT population. The safety population included all subjects
- Safety endpoints included physical and neurological examinations, 12-lead ECGs, vital signs, adverse event (AE) reports, and clinical laboratory results
- Safety data obtained from the 6 mg/day arm (prior to its discontinuation) are summarized

RESULTS

Patients

- 112 patients were randomized to dasotraline 4 mg/day or placebo, comprising the ITT population. Mean age was 9.5 years, 68.8% were male (**Table 1**)
- Overall, 91% of patients completed the study. AEs were the most common reason for discontinuation (4 mg/day: 5.4%; placebo: 1.8%; **Table 2**)

Efficacy

- In the ITT group, dasotraline 4 mg/day significantly improved mean SKAMP-CS vs placebo (**Figure 2**)

Table 1. Baseline characteristics

Characteristic		Dasotraline 4 mg/day (N = 56)	Placebo (N = 56)
Age, years	Mean	9.3	9.7
	≤9 years, n (%)	30 (53.6)	24 (42.9)
Male, n (%)		39 (69.6)	38 (67.9)
Race, n (%)	White	26 (46.4)	31 (55.4)
	Black	25 (44.6)	23 (41.1)
Weight, kg	Mean	35.1	37.7
SKAMP-CS score	Mean	21.8	21.0
PERMP-Problems Attempted	Mean	58.8	57.5
PERMP-Problems Correct	Mean	54.8	52.3

SKAMP-CS and PERMP mean scores were obtained from 7 assessments (evaluated at 2-hour intervals) across the day
PERMP, Permanent Product Measure of Performance; SKAMP-CS, Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale – Combined Score

Table 2. Patient disposition

Population, n (%)	Dasotraline 4 mg/day (N = 56)	Placebo (N = 56)
Randomized subjects	56	56
Completed	53 (94.6)	50 (89.3)
Discontinued	3 (5.4)	6 (10.7)
AE	3 (5.4)	1 (1.8)
Lost to follow-up	0	2 (3.6)
Lack of efficacy	0	1 (1.8)
Protocol violation	0	1 (1.8)
Withdrawal consent	0	1 (1.8)
Study drug non-compliance	0	0

AE, adverse event

- Mean SKAMP subscores improved significantly for Attention and Deportment (**Figure 3**)

Figure 2. Change from Baseline in SKAMP-CS scores over Day 1 and Day 15 in the dasotraline 4 mg/day and placebo groups, and treatment difference (ITT population)

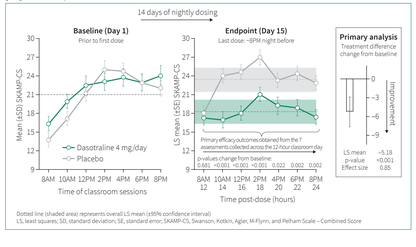
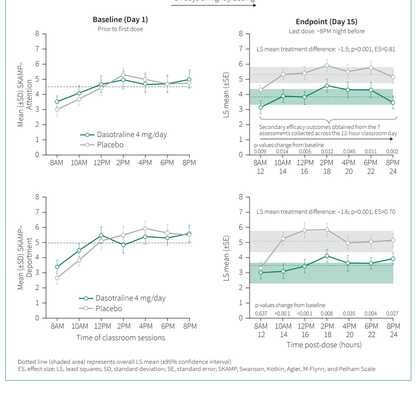


Figure 3. Change from Baseline to Day 15 in mean SKAMP-Attention and -Deportment subscale scores



- Similarly, least squares (LS) mean changes from Baseline to Day 15 in PERMP subscales significantly improved in the 4 mg/day dasotraline group compared with the placebo group (**Figure 4**):
  - Problems Attempted: LS mean treatment difference +23.7 (95% confidence interval [CI]: 8.99, 38.35)
  - Problems Correct: LS mean treatment difference +24.1 (95% CI: 9.38, 38.71)

Figure 4. Change from Baseline to Day 15 in mean PERMP subscale scores

Safety

- Treatment-emergent AEs (TEAEs) were more common in patients taking dasotraline compared with those taking placebo (**Table 3**):
  - TEAEs were generally mild or moderate in severity. Four patients in the dasotraline groups experienced severe TEAEs: 4 mg/day: 1 case of insomnia and 1 case of decreased appetite; 6 mg/day: 2 cases of insomnia
  - No serious AEs occurred in patients treated with dasotraline
  - TEAEs associated with discontinuation were hallucinations (2 cases in the 6 mg/day group, 1 case in the 4 mg/day group), insomnia (1 case in the 4 mg/day group), decreased appetite (1 case in the 6 mg/day group), and rash (1 case in the 4 mg/day group)

Table 3. TEAEs summary

TEAE, n (%)	Dasotraline 4 mg/day (N = 56)	Placebo (N = 56)
Any TEAE	29 (51.8)	19 (33.9)
Treatment-related TEAEs	24 (42.9)	13 (23.2)
Severe TEAEs	2 (3.6)	1 (1.8)
Serious TEAEs	0	1 (1.8)
TEAEs leading to discontinuation	3 (5.4)	1 (1.8)

TEAEs, treatment-emergent adverse events

- The most frequent TEAEs (≥2%) occurring in the dasotraline 4 mg/day vs placebo groups are presented in **Table 4**. In the dasotraline 6 mg/kg group (N = 20), the following AEs occurred in more than one patient: insomnia (n = 6; 30%); affect lability and decreased appetite (n = 4; 20% each); hallucinations (n = 3; 15%); and decreased weight, abdominal pain, vomiting (n = 2; 10% each)
- Mean change in supine heart rate from Baseline at Day 15 was (4 mg/day; 6 mg/day; placebo): +1.4, +3.4, –2.2 beats per minute

Table 4. Incidence of TEAEs ≥2% and greater than placebo

TEAE, n (%)	Dasotraline 4 mg/day (N = 56)	Placebo (N = 56)
Combined insomnia[a]	11 (19.6)	2 (3.6)
Headache	6 (10.7)	5 (8.9)
Decreased appetite	6 (10.7)	2 (3.6)
Affect lability	5 (8.9)	4 (7.1)
Irritability	3 (5.4)	2 (3.6)
Perceptual disturbances[b]	3 (5.4)	0
Orthostatic tachycardia	3 (5.4)	0
Increased appetite	2 (3.6)	0
Rash	2 (3.6)	0
Diarrhea	2 (3.6)	0

[a]Combined insomnia includes insomnia, initial insomnia, middle insomnia, and terminal insomnia; [b]Hallucinations (tactile, auditory, visual)

- Mean change in supine systolic blood pressure from Baseline at Day 15 was (4 mg/day; 6 mg/day; placebo): +0.3, +0.8, –0.6 mmHg
- Mean weight change from Baseline at Day 15 was (4 mg/day; 6 mg/day; placebo): –0.54, –1.09, +0.31 kg

DISCUSSION

- In this 2-week, randomized, double-blind, laboratory classroom study in children aged 6–12 years with ADHD, dasotraline 4 mg/day significantly improved ADHD symptoms, including attention and deportment, compared with placebo
- Improvements in SKAMP-CS (primary endpoint) and PERMP scores (secondary endpoint) were clinically relevant, with large effect sizes
- In this study, dasotraline demonstrated sustained efficacy throughout the day, up to 24 hours post-dose
- Dasotraline 4 mg/day was generally well tolerated, with the most common AEs being combined insomnia, decreased appetite, and headache

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