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Dasotraline for the Treatment of Attention-Deficit/Hyperactivity Disorder: A Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Trial in Adults

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and impulsivity associated with clinically significant impairment in functioning. ADHD has an early onset, but frequently persists, with a prevalence estimate of 4% in adults. Dasotraline is a novel compound that is a potent inhibitor of dopamine and norepinephrine transporters that achieves stable plasma concentrations with once-daily dosing. In this study, adult outpatients meeting DSM-IV-TR criteria for ADHD were randomized to 4 weeks of double-blind, once-daily treatment with dasotraline 4 and 8 mg/day or placebo. The primary efficacy end point was change from baseline at week 4 in the ADHD Rating Scale, Version IV (ADHD RS-IV) total score. Secondary efficacy end points included the Clinical Global Impression, Severity (CGI-S) scale, modified for ADHD symptoms. Least squares (LS) mean improvements at week 4 in ADHD RS-IV total score were significantly greater for dasotraline 8 mg/day vs placebo (−13.9 vs −9.7; P = 0.019), and nonsignificantly greater for 4 mg/day (−12.4; P = 0.076). The LS mean improvements in modified CGI-S were significantly greater at week 4 for dasotraline 8 mg/day vs placebo (−1.1 vs −0.7; P = 0.013), and for 4 mg/day vs placebo (−1.1 vs −0.7; P = 0.021). The most frequent adverse events reported were insomnia, decreased appetite, nausea, and dry mouth. Discontinuations due to treatment-emergent adverse events were 10.3% and 27.8% of patients in 4 and 8 mg/day treatment groups, respectively. This study provides preliminary evidence that once-daily dosing with dasotraline, a long-acting, dual monoamine reuptake inhibitor, may be a safe and efficacious treatment for adult ADHD.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by persistent symptoms of hyperactivity (eg, restlessness, impulsiveness) and inattention (eg, distractibility, forgetfulness) associated with clinically significant impairment in social, academic, and occupational functioning (American Psychiatric Association, 2013). ADHD affects 5–7% of children (based on DSM-IV-TR criteria; Polanczyk et al, 2014), and frequently persists into adulthood, with prevalence estimates of 4% in adults (Faraone and Biederman, 2005; Kessler et al, 2006).

Dopamine (DA) and norepinephrine (NE) have been implicated in the pathophysiology of ADHD, and drugs that increase DA and NE neurotransmission are clinically useful in ADHD symptom management (Faraone et al, 2005).

Several classes of drugs have demonstrated efficacy in the treatment of ADHD, including short- and long-acting stimulant medications (eg, methylphenidate, amphetamine), and nonstimulant medications (eg, atomoxetine, clonidine, guanfacine; Faraone and Glatt, 2010; McDonagh et al, 2011). Currently available treatments for ADHD tend to produce high rates of adverse CNS and cardiovascular and gastrointestinal effects, with abuse liability a risk for the stimulant class of medications. Therefore, there is a need for additional treatment options that may offer reduced abuse liability and a different tolerability profile.

Dasotraline [(1R,4S)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-amine] is a novel compound with DNRI pharmacology. Dasotraline acts as a potent inhibitor of human DA transporters (DAT; dopamine uptake IC_{50} 3 nM) and NE transporters (NET; norepinephrine uptake IC_{50} 4 nM), and a weaker inhibitor of human serotonin transporters (SERT; serotonin uptake IC_{50} 15 nM) (Data on file, Sunovion, 2014).

In a behavioral paradigm of ADHD in rats (delay discounting test), administration of dasotraline significantly increased percent choice of delayed reward, a measure of

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impulsive choice (Data on file, Sunovion, 2014). The effects were similar to those observed with a methylphenidate control.

In humans, dasotraline has a t_{max} of 10–12 h, a $t_{\frac{1}{2}}$ of 47–77 h, achieves steady-state plasma concentration by 2 weeks of daily dosing, and is metabolized by oxidative pathways (Data on file, Sunovion, 2014).

The pharmacokinetic and pharmacodynamic characteristics of dasotraline suggest that it may have a favorable pharmacologic profile for the treatment of ADHD, including sustained treatment effects throughout a once-per-day 24 h dosing interval, and a reduced risk for abuse and diversion, thus providing an enhanced treatment approach for patients with ADHD (Minzenberg (2012)).

The primary objective of this study was to evaluate the efficacy of dasotraline for the treatment of adult patients with ADHD. Secondary objectives were to evaluate the safety and tolerability of dasotraline, and to assess the relationship between the plasma concentrations of dasotraline, improvement in efficacy measures, and plasma concentrations of 3,4-dihydroxyphenylglycol (DHPG).

MATERIALS AND METHODS

Patients

The trial enrolled adult outpatients, ages 18–55 years, inclusive, with a primary diagnosis of ADHD based on DSM-IV-TR criteria, and confirmed by Conners' Adult ADHD Diagnostic Interview (CAADID; Epstein et al, 2001) Part 2. In addition, patients were required to have been prescribed at least one previous trial of medication (stimulant or non-stimulant). Patients were also required to have a minimum ADHD RS-IV (with adult prompts) total score of ≥ 26 at Screen (if receiving no current treatment) and Baseline, or ≥ 22 (if currently being treated for ADHD); an ADHD RS-IV total score of ≥ 26 at Baseline for all patients; and a Clinical Global Impression, Severity (CGI-S; modified to evaluate overall severity of ADHD symptoms) score of ≥ 4 at Screen and Baseline (moderate-or-greater symptom severity). Reasons for exclusion included the following: any active medical condition or any clinically significant abnormality on physical examination, laboratory testing, or ECG that could interfere with appropriate participation in the study; any history (based on DSM-IV-TR criteria using the Mini International Neuropsychiatric Interview; Sheehan et al, 1998), of bipolar disorder, schizophrenia, or other psychotic disorder; current Axis II personality disorder; history in the past 12 months of substance abuse or dependence, or positive breath alcohol test or urine drug screen at the Screen visit. Potential patients were also excluded if they had received treatment in the previous 6 months with lithium, or anticonvulsant or antipsychotic medication; or were currently being treated with any antidepressant, stimulant, sedating antihistamine medication, or an α-2 adrenergic receptor agonist (including clonidine and guanfacine).

The study was approved by an institutional review board at each investigational site and was conducted in accordance with the International Conference on Harmonisation Good Clinical Practices guidelines and with the ethical principles of the Declaration of Helsinki. Before study entry, all patients reviewed and signed an informed consent document explaining study procedures and potential risks. An independent data and safety monitoring board reviewed and monitored patient data throughout the study.

Study Design

This multicenter, randomized, double-blind, placebo-controlled, parallel-group study of dasotraline in adults with ADHD was conducted between December 2012 and November 2013 at 30 sites in the United States. The study consisted of 3 periods, a screening period of no more than 27 days, a double-blind 4-week treatment period, and a 2 week washout period. During the screening period, psychiatric, medical, and laboratory screening tests were completed, and any current medication for ADHD was discontinued (for a minimum of 5 half-lives, or 3 days, before randomization, whichever was longer). Patients who continued to meet all study inclusion and exclusion criteria at baseline were randomized in a 1 : 1 : 1 ratio via an interactive response system (IXRS) to receive 4 weeks of double-blind treatment with dasotraline in a fixed daily dose of either 4 or 8 mg or placebo. Study medication was provided in blister packs of either dasotraline 2 mg, or identically matched placebo capsules, and was taken once daily at approximately the same time in the evening, without regard to meals. At the end of 4 weeks of double-blind treatment, study medication was abruptly discontinued, and patients returned for weekly assessment visits during a 2-week washout period.

Dose Selection

Dasotraline at 4 and 8 mg/day were selected to target steady-state plasma concentrations of 8 and 18 ng/ml, and were estimated to correspond with DAT receptor occupancies of 56% and 71%, respectively, based on the results of a previous PET study with dasotraline (DeLorenzo et al, 2011). DAT receptor occupancies above 50% have been associated with clinically therapeutic effects for methylphenidate (Hannestad et al, 2010) and atomoxetine (Ding et al, 2014).

Concomitant Medications

Concomitant use of zolpidem, zaleplon, and eszopiclone were permitted on ≤ 3 nights per week during the study for the management of treatment-emergent insomnia, but not prophylactically, and not within 8 h of any psychiatric assessment. Patients treated for hypertension with stable doses of β-adrenergic receptor antagonists were permitted to continued treatment.

Efficacy Assessments

The primary efficacy measure was the ADHD Rating Scale, Version IV (ADHD RS-IV, with adult prompts; Adler et al, 2008), an 18-item scale based on DSM-IV-TR criteria that consists of a total score, and Hyperactivity/Impulsivity and Inattentiveness subscale scores. Additional efficacy measures included the Clinical Global Impression-Severity of Illness that was modified to evaluate the overall severity of ADHD symptoms (National Institute of Mental Health (NIMH), 1985), the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS; Marchant et al, 2013)

that measures the severity of ADHD symptoms in adults, and the 24-item Brief Psychiatric Rating Scale that assesses the presence and severity of psychotic symptoms (Guy, 1976). Efficacy assessments were obtained at baseline and weekly intervals.

Cognitive function was evaluated at baseline, week 2, and week 4 using a computerized cognitive assessment battery (Cognitive Drug Research (CDR); Wesnes, 2005) that measured attention, working memory, and episodic memory.

Safety Assessments

Safety and tolerability were assessed by physical examinations, 12-lead ECGs, vital signs, hematology, chemistry, urinalysis, and monitoring of adverse events. The severity of insomnia and insomnia-related interference with daytime functioning was assessed using the 7-item Insomnia Severity Index (ISI; Bastien *et al*, 2001); risk of drug withdrawal was evaluated using the 20-item Physician Withdrawal Checklist (PWC; Rickels *et al*, 2008); an Abuse Potential Monitoring Plan was implemented that included monitoring of sentinel adverse events and medication handling irregularities. Potential treatment-emergent suicidal ideation was monitored using the Columbia Suicide Severity Rating Scale (C-SSRS; Posner *et al*, 2011). Acute subjective response to study drug (drug liking) was monitored weekly using the 3-item Drug Effects Questionnaire (DEQ; Morean *et al*, 2013).

Blood draws for dasotraline plasma concentrations and DHPG/NE plasma levels were collected weekly. Plasma concentrations for dasotraline, DHPG, and NE were determined using a validated bioanalytical method via HPLC with MS/MS detection. Interassay coefficient of variation ranged from 2.0 to 2.7%; lower limit of quantitation (LLOQ) was 10.0 pg/ml.

Statistical Analysis

The primary efficacy variable was the change from baseline in ADHD RS-IV total score at week 4 in the dasotraline 4 and 8 mg groups compared with placebo. A mixed model for repeated measures (MMRM) was employed using the modified intent-to-treat (ITT) population. The MMRM model included treatment, visit (as a categorical variable), pooled center, baseline ADHD RS-IV total score, and treatment-by-visit interaction. An unstructured covariance matrix was used for the within-subject correlation. The Kenward–Roger approximation was used to estimate denominator degrees of freedom. The primary efficacy comparisons of only dasotraline 4 and 8 mg *vs* placebo at end point (week 4) were adjusted using the Hochberg procedure. Missing values were not imputed for this MMRM analysis. The MMRM assumed that data were missing at random (MAR). A random effects pattern mixture model with two patterns (completers and dropouts) demonstrated that MAR was a reasonable assumption for the primary efficacy end point. Secondary efficacy variables (change from baseline at each study week in the CGI-S, WRAADDS, ADHD RS-IV Inattentiveness, and Hyperactivity/Impulsivity subscale scores) were analyzed using the same MMRM method.

Analysis of responder rates (defined as ≥ 30% reduction in ADHD RS-IV-total score) was performed using a logistic

regression model that included baseline ADHD RS-IV total score, pooled center, and treatment, and was done for both observed case (OC) and last observation carried forward (LOCF) values at week 4.

Based on a clinically relevant improvement in the ADHD RS-IV total score reported in a meta-analysis of acute clinical trials (McGough and Faraone, 2009), it was estimated that a sample size of 85 patients per treatment group would be needed to provide 83% power for significant comparisons of both dasotraline dosages (*vs* placebo), or 94% power for at least one significant comparison. A prespecified upward sample-size adjustment was based on an estimated study attrition of 15%; the sample size was further increased to 112 per treatment group based on discontinuations observed during the course of the study.

Pharmacokinetic analyses. Observed values of plasma concentrations for dasotraline and DHPG were summarized descriptively at each visit by treatment group in both the PK and PD populations. The relationship between selected efficacy variables and dasotraline plasma concentrations and DHPG concentrations was analyzed using population PK/PD methods and will be reported separately.

RESULTS

Patients and Disposition

A total of 341 patients were randomized to 4-week double-blind treatment (Figure 1); 337 received at least one dose of study medication (safety population), and 331 had both baseline and at least one postbaseline efficacy assessment (modified ITT population). Baseline demographic and clinical characteristics were similar across the three treatment groups (Table 1). The majority of patients were male (59%), with a mean age of 34 years.

The 4-week treatment completion rates were 90.9% for the placebo group, 82.8% for dasotraline 4 mg/day group, and 51.3% for dasotraline 8 mg/day group (Figure 1). The discontinuation rates due to adverse events were 10.3% for the dasotraline 4 mg/day group, 27.8% for the 8 mg/day group, and 1.8% for the placebo group.

Efficacy

The least squares (LS) mean improvement from baseline to week 4 in the ADHD RS-IV total score (the primary end point) was significantly greater for the dasotraline 8 mg/day group *vs* the placebo group (−13.9 *vs* − 9.7; *P* = 0.019; effect size = 0.41), and nonsignificantly greater for the 4 mg/day group (−12.4; *P* = 0.076, effect size = 0.25; Table 2). Both the 4 and 8 mg/day doses showed numerical advantages compared with placebo beginning at week 2 (Figure 2).

Improvement from baseline in both the ADHD RS-IV Hyperactivity/Impulsivity and Inattentiveness subscale scores were significantly greater for the dasotraline 8 mg/day group, and nonsignificantly greater for the 4 mg/day group (Table 2).

Treatment with 8 mg/day dasotraline was associated with significantly greater week 4 responder rates (≥30% reduction in ADHD RS-IV total score; LOCF) *vs* the placebo group (52.3% *vs* 38.2%; *P* = 0.029; NNT = 8). Treatment with
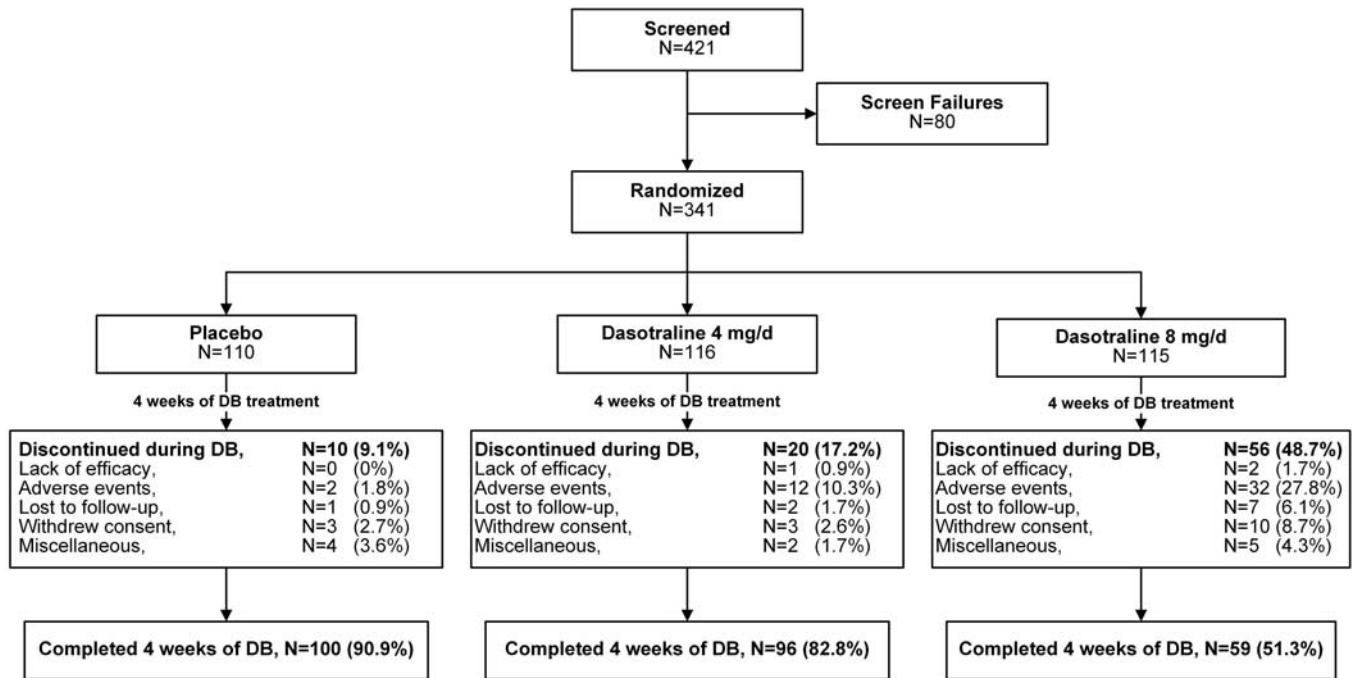
Figure I Patient disposition.

Table I Baseline Characteristics (Intent-to-Treat Population)

	Placebo (*N* = 110)	Dasotraline 4 mg/day (*N* = 114)	Dasotraline 8 mg/day (*N* = 107)
Male, %	60.0	56.1	59.8
Age, years, mean (SD)	33.9 (11.0)	34.2 (10.1)	34.5 (11.2)
Race, %			
White	85.5	80.7	81.3
Black/African American	10.9	13.2	10.3
Other	3.6	6.1	8.4
ADHD RS-IV, mean (SD)			
Total score	36.7 (6.8)	36.8 (6.9)	36.6 (7.2)
Hyperactivity/Impulsivity score	15.0 (5.2)	15.4 (5.6)	15.6 (5.5)
Inattentiveness score	21.7 (3.5)	21.4 (3.3)	21.0 (4.0)
WRAADS total score, mean (SD)	35.4 (7.6)	34.5 (8.0)	33.9 (7.6)
CGI-S, mean (SD)	4.5 (0.5)	4.6 (0.5)	4.4 (0.6)

4 mg/day dasotraline was associated with nonsignificantly higher week 4 responder rates *vs* the placebo group (49.1% *vs* 38.2%; $P = 0.109$; NNT = 10).

Improvement from baseline in the modified CGI-S scale was significantly greater at week 4 for both the dasotraline 4 and 8 mg/day dosage groups (Table 2). Improvement from baseline in the WRAADDS total score was nonsignificantly greater at week 4 for both the dasotraline 4 and 8 mg/day dosage groups (Table 2). On the WRAADDS attention difficulties subscore, LS mean improvement from baseline was significantly greater at week 4 for the dasotraline 8 mg/day group *vs* the placebo group (-1.3 *vs* -0.8; $P = 0.008$), and for the dasotraline 4 mg/day group *vs* the placebo group (-1.1 *vs* -0.8; $P = 0.025$). On the WRAADDS disorganization subscore, LS mean improvement from baseline was significantly greater at week 4 for the dasotraline 8 mg/day group *vs* the placebo group (-1.0 *vs* -0.8; $P = 0.037$); and was nonsignificantly greater for the dasotraline 4 mg/day group *vs* the placebo group (-1.0 *vs* -0.8; $P = 0.056$).

On the computerized cognitive assessment battery, no significant main effects for dasotraline were observed for measures of attention, working memory, or episodic memory.

Mean Brief Psychiatric Rating Scale (BPRS) scores were relatively low at baseline for all three study treatment groups (31.3–31.7), and did not worsen at week 4 in the dasotraline 4 mg/day (-1.3), 8 mg/day (-1.6), and placebo (-1.8) groups.
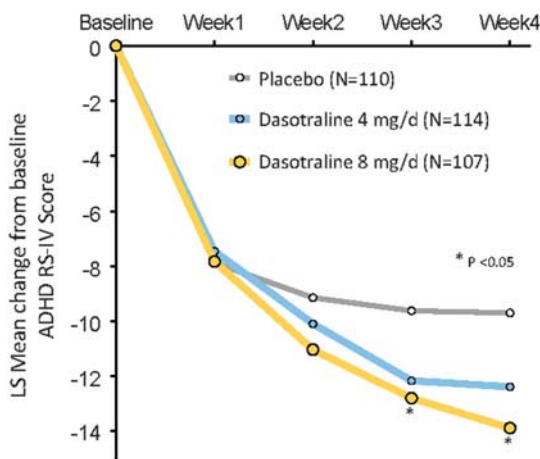
Safety

Treatment-emergent adverse events (TEAEs) are summarized in Table 3. The percentages of patients with TEAEs were similar between the 4 and 8 mg dasotraline groups (77.6% and 81.1%, respectively) and were higher than the percentage of TEAEs in the placebo group (59.1%). Insomnia, decreased appetite, and dry mouth were the most frequent adverse events. The majority of adverse events were rated as mild or moderate; the incidence of events rated as 'severe' was 13.5% in the dasotraline 8 mg/day group, 6.0% in the dasotraline 4 mg/day group, and 2.7% in the placebo group. The most

Table 2 LS Mean (SE) Change from Baseline to Week 4 in Efficacy Measures

	Placebo (N = 110)		Dasotraline 4 mg/day (N = 114)			Dasotraline 8 mg/day (N = 107)		
	LS mean change (SE)	95% CI	LS mean change (SE)	95% CI	P-value	LS mean change (SE)	95% CI	P-value
ADHD RS-IV								
Total score	−9.7 (1.1)	(−11.8, −7.6)	−12.4 (1.1)	(−14.5, −10.3)	0.076[a]	−13.9 (1.2)	(−16.3, −11.5)	0.019[a]
Hyperactivity/Impulsivity score	−4.1 (0.5)	(−5.2, −3.1)	−5.4 (0.5)	(−6.5, −4.3)	0.094	−5.9 (0.6)	(−7.2, −4.7)	0.027
Inattentiveness score	−5.6 (0.6)	(−6.9, −4.4)	−7.0 (0.6)	(−8.3, −5.7)	0.125	−8.0 (0.7)	(−9.4, −6.5)	0.016
CGI-Severity score	−0.7 (0.1)	(−1.0, −0.5)	−1.1 (0.1)	(−1.3, −0.9)	0.021	−1.1 (0.1)	(−1.4, −0.9)	0.013
WRAADDS total score	−9.0 (1.0)	(−10.9, −7.0)	11.0 (1.0)	(−13.0, −9.0)	0.147	−11.9 (1.2)	(−14.2, −9.6)	0.056

[a]P-value was adjusted for multiple comparisons using the Hochberg procedure.

Figure 2 LS mean change in ADHD RS-IV total scores (MMRM).

Table 3 Incidence of Treatment-Emergent Adverse Events, % (Safety Population; Incidence ≥ 3% and 2-Times Placebo)

	Placebo (N = 111)	Dasotraline 4 mg/day (N = 116)	Dasotraline 8 mg/day (N = 111)
Insomnia	15.5	34.5	45.0
Decreased appetite	2.7	10.3	22.5
Dry mouth	2.7	7.8	17.1
Anxiety	1.8	9.5	9.0
Nausea	2.7	6.0	9.9
Dizziness	0.9	6.9	8.1
Palpitations	0	5.2	2.7
Weight decreased	0.9	2.6	5.4
Tension headache	0	5.2	0
Panic attack	0.9	0	3.6
Any TEAE rated as 'severe'	2.7	6.0	13.5

Abbreviation: TEAE, treatment-emergent adverse event.

common adverse events leading to discontinuation (and occurring in ≥ 2 patients) in the dasotraline 4 and 8 mg/day and placebo groups, respectively, were insomnia (2.6, 10.8, and 0%), anxiety (2.6, 1.8, and 0%), and panic attack (0, 2.7, and 0%). Overall, discontinuations due to adverse events were 10.3%, 27.8%, and 1.8% in the dasotraline 4 and 8 mg/day and placebo groups respectively.

There were 5 serious TEAEs that occurred in 4 patients: 2 patients in the dasotraline 4 mg/day group (ectopic pregnancy and psychotic disorder) and 2 patients in the dasotraline 8 mg/day group (mediastinitis and bacteremia in one patient and adjustment disorder with depressed mood). The SAEs were reported as unrelated to study drug, except for psychotic disorder that was possibly related.

Insomnia severity index. Small LS mean changes were observed in the ISI total score for each dasotraline treatment group from week 1 (4 mg, +0.89; 8 mg, +2.17; placebo, −1.53) to week 4 (4 mg, +0.34; 8 mg, +0.99; placebo, −2.48).

Drug liking and withdrawal. No evidence of drug liking was observed on the DEQ, with mean item scores remaining within 5 mm of the 0 point at all assessment weeks. No evidence of drug misuse or diversion was detected through

the Abuse Potential Monitoring Plan. No signs or symptoms of withdrawal were observed upon discontinuation of study drug, with a mean maximum change on the PWC of − 1.3 in the dasotraline 4 mg/day group, − 0.5 in the dasotraline 8 mg/day group, and − 0.3 in the placebo group from week 4 to week 6.

Suicidal ideation. On the C-SSRS, three patients (one in each treatment group) reported mild, treatment-emergent suicidal ideation, but with no plan.

Weight. The mean change from baseline to week 4 in weight was − 1.07 kg for the 4 mg/day dasotraline group, − 2.90 kg for the 8 mg/day dasotraline group, and +0.24 kg for the placebo group.

Vital signs and ECG. Mean change from baseline to week 4 in supine heart rate was +5.7, +6.2, and − 1.2 b.p.m., respectively, for the dasotraline 4 and 8 mg/day groups and the placebo group. Mean change from baseline to week 4 in
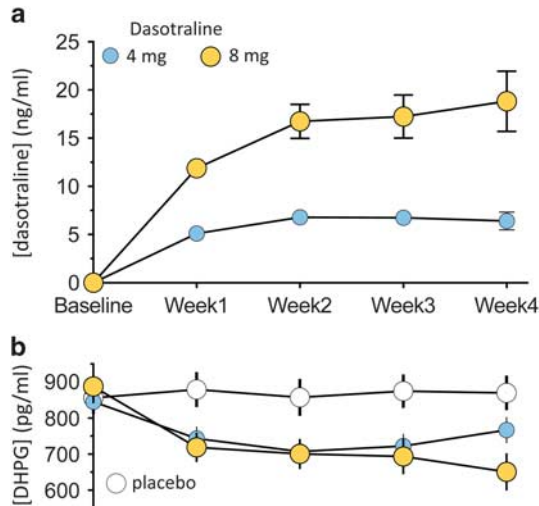
Figure 3 Mean (95% CI) plasma concentrations for dasotraline (a) and DHPG (b).

supine systolic/diastolic blood pressure was − 0.2/+0.3, +3.3/+2.5 mm Hg, and +0.4/ − 0.5 mm Hg, respectively, for the dasotraline 4 and 8 mg/day groups and the placebo group. On the ECG, minimal mean changes were observed at week 4 in QTcF of +1.1, +1.6, and − 0.2 ms, respectively, for the dasotraline 4 and 8 mg/day groups and the placebo group. No patients treated with dasotraline had clinically significant increases in QTcF duration (>60 ms).

Laboratory. Laboratory measures did not identify any safety concerns for dasotraline.

Plasma Concentrations of Dasotraline and DHPG

For the 4 and 8 mg/day doses, mean dasotraline plasma levels increased during the first 2 weeks of treatment, and then plateaued at weeks 3 and 4 (Figure 3a). Plasma concentrations of DHPG decreased in the first week of treatment for both the 4 and 8 mg/day doses of dasotraline, and then plateaued at subsequent weeks (Figure 3b).

DISCUSSION

We report here the first placebo-controlled efficacy trial of dasotraline in adult patients with ADHD. In this 4-week, fixed-dose study, 8 mg/day dasotraline significantly improved symptoms of ADHD assessed by the ADHD RS-IV total score (the primary efficacy end point), and the ADHD RS-IV hyperactivity/impulsivity and inattentiveness subscale scores. Dasotraline at 4 mg/day was associated with trend-significant improvement on the ADHD RS-IV total and subscale scores. Dasotraline significantly improved global ADHD symptom severity, assessed by the CGI-S scale (modified for ADHD), at both doses studied. Treatment response (at least 30% improvement on the ADHD RS-IV total score) favored dasotraline vs placebo with NNT values of 8–10.

For the 8 mg/day dose, a trend separation from placebo on the ADHD RS-IV total score was apparent by week 2; this

became significant at weeks 3 and 4. The dasotraline 4 mg/day dose showed a similar time course of response on the ADHD RS-IV total score, with numeric separation observed by week 2 and at all subsequent study visits. The effect sizes for the dasotraline 4 mg/day (0.25) and 8 mg/day (0.41) doses observed in this study at week 4 overlapped with the range and 95% confidence intervals of those reported in meta-analyses of the DAT/NET inhibitor methylphenidate (Faraone et al, 2004; Koesters et al, 2009), but were smaller than the effect sizes reported for amphetamine-based medications (Faraone and Glatt, 2010). Given the prolonged elimination half-life of dasotraline, requiring ∼ 2 weeks to achieve steady state, it is possible that a longer duration of study treatment (beyond 4 weeks) could have provided additional therapeutic benefit.

The pharmacokinetics and pharmacology of dasotraline differentiate it from other agents that have demonstrated efficacy for the treatment of ADHD. In contrast to the pharmacokinetics of amphetamine, methylphenidate, and atomoxetine, dasotraline has slow absorption and a long-elimination half-life resulting in stable plasma concentrations of over 24 h with once-daily dosing. Pharmacologically, dasotraline is a dual dopamine and norepinephrine reuptake inhibitor (DNRI), unlike psychostimulants such as amphetamine that facilitate the direct release of dopamine and norepinephrine (Rothman et al, 2001), and unlike atomoxetine, a nonstimulant that inhibits only norepinephrine transporters (Wong et al, 1982). In this study, dasotraline at 4 mg/day resulted in mean concentrations at steady state of 6 ng/ml. A prior human PET study demonstrated that dasotraline plasma concentrations of 4.5 ng/ml were associated with 50% DAT occupancy, with no significant serotonin transporter occupancy (DeLorenzo et al, 2011). Dasotraline at 4 and 8 mg/day also decreased circulating DHPG levels, indicative of central inhibition of norepinephrine transporters (Vincent et al, 2004).

The results of this study support the concept that symptoms of ADHD may be improved by providing constant, steady-state inhibition of DA and NE reuptake. This pharmacologic profile suggests the potential for sustained treatment effects throughout the 24 h dosing interval, and contrasts with the peak and trough pattern of effects within the dosing interval induced by current ADHD medications, attributable to either their faster pharmacodynamics (methylphenidate medications) or their facilitated release of dopamine (amphetamine-based medications).

The most frequent adverse events reported for dasotraline in this study were insomnia, decreased appetite, and dry mouth, consistent with DNRI pharmacology. The majority of adverse events were transient, and mild to moderate in severity. Insomnia occurred in 35% of patients at the 4 mg/day dose, and in 45% of patients at the 8 mg/day dose. Insomnia led to study discontinuation in a smaller proportion of patients, 2.6% for the 4 mg/day dose and 10.8% for the 8 mg/day dose. The rates of insomnia at the 4 mg/day dose were comparable to rates observed for stimulant drugs such as methylphenidate (Peterson et al, 2008), whereas higher rates were observed for the 8 mg/day dose. Rates of insomnia were also higher for dasotraline compared with atomoxetine (Stattera US Prescribing Information (2015)), whereas rates of nausea were lower in this study on dasotraline (10% at 8 mg/day vs 30%; Stattera US

Prescribing Information (2015)). The pharmacokinetics of dasotraline, with slow onset to peak effect and prolonged elimination half-life, may have contributed to the reduced incidence of nausea, while increasing the incidence of insomnia. Future studies will investigate whether gradual titration to higher doses, and use of flexible dosing, will be associated with reduced rates of insomnia or other DNRI-related adverse events.

In this study, no evidence of drug liking was observed on the DEQ for either dose of dasotraline, nor was any drug misuse or diversion detected through the study Abuse Potential Monitoring Plan. In addition, no signs or symptoms of withdrawal were observed on the PWC for either dose of dasotraline. Delayed absorption and/or maintenance of steady plasma concentrations is known to reduce the abuse potential of stimulant drugs (Volkow et al, 1995; Kollins et al, 1998; Spencer et al, 2012). For example, tesofensine, a drug with slow absorption and elimination rates in humans, and substantial DAT occupancy (Appel et al, 2014), demonstrated low abuse potential comparable to atomoxetine and bupropion in a study of recreational stimulant users (Schoedel et al, 2010). Dasotraline has been evaluated at single doses of up to 36 mg in a randomized, double-blind, crossover study of recreational stimulant users, and was found to have abuse potential no greater than placebo and significantly less than that of methylphenidate (data on file). These findings are consistent with the delayed time to peak serum concentration and prolonged elimination half-life of dasotraline.

Monitoring of vital signs and laboratory parameters did not identify any clinically significant safety concerns for dasotraline. Small increases were noted in mean heart rate and, for the 8 mg/day dose only, in mean systolic and diastolic blood pressure. Dasotraline had no notable effect on QTc or other ECG parameters. No increased risk of suicidal ideation was noted on the C-SSRS for either dasotraline dose group compared with placebo.

The limitations of this study include, as noted above, the short (4 weeks) treatment period, the lack of titration in the higher dose treatment arm, and the requirement that all patients in the study have a history of medication treatment for ADHD. The latter requirement may have biased the treatment population by increasing recruitment of ADHD patients with higher levels of chronicity and/or current stimulant use. In fact, plasma samples collected during study treatment identified several patients with plasma concentrations of amphetamine or methylphenidate in the placebo treatment group ($n = 14$; 13.5%) and in the dasotraline treatment group (4 mg/day, $n = 7$, 6.1%; 8 mg/day, $n = 9$, 8.4%). All efficacy and safety data from these patients were included in the analyses and results reported here; exclusion of these subjects from the primary efficacy analysis did not change the results.

In conclusion, the results of this fixed-dose, placebo-controlled, proof-of-concept trial found once-daily dosing with dasotraline, a novel, long-acting dopamine and norepinephrine reuptake inhibitor, to be an efficacious treatment of ADHD in adults. Dasotraline was generally well tolerated. Higher rates of insomnia were observed at 8 mg/day compared with 4 mg/day in this fixed-dose study where patients were initiated at these doses without titration. Further evaluation of the clinical utility of dasotraline in ADHD is warranted.

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