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Supplementary Material

Article Title: Efficacy and Safety of Dasotraline in Adults With Binge-Eating Disorder: A Rndomized, Placebo-Controlled, Flexible-Dose Clinical Trial

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List of Supplementary Material for the article

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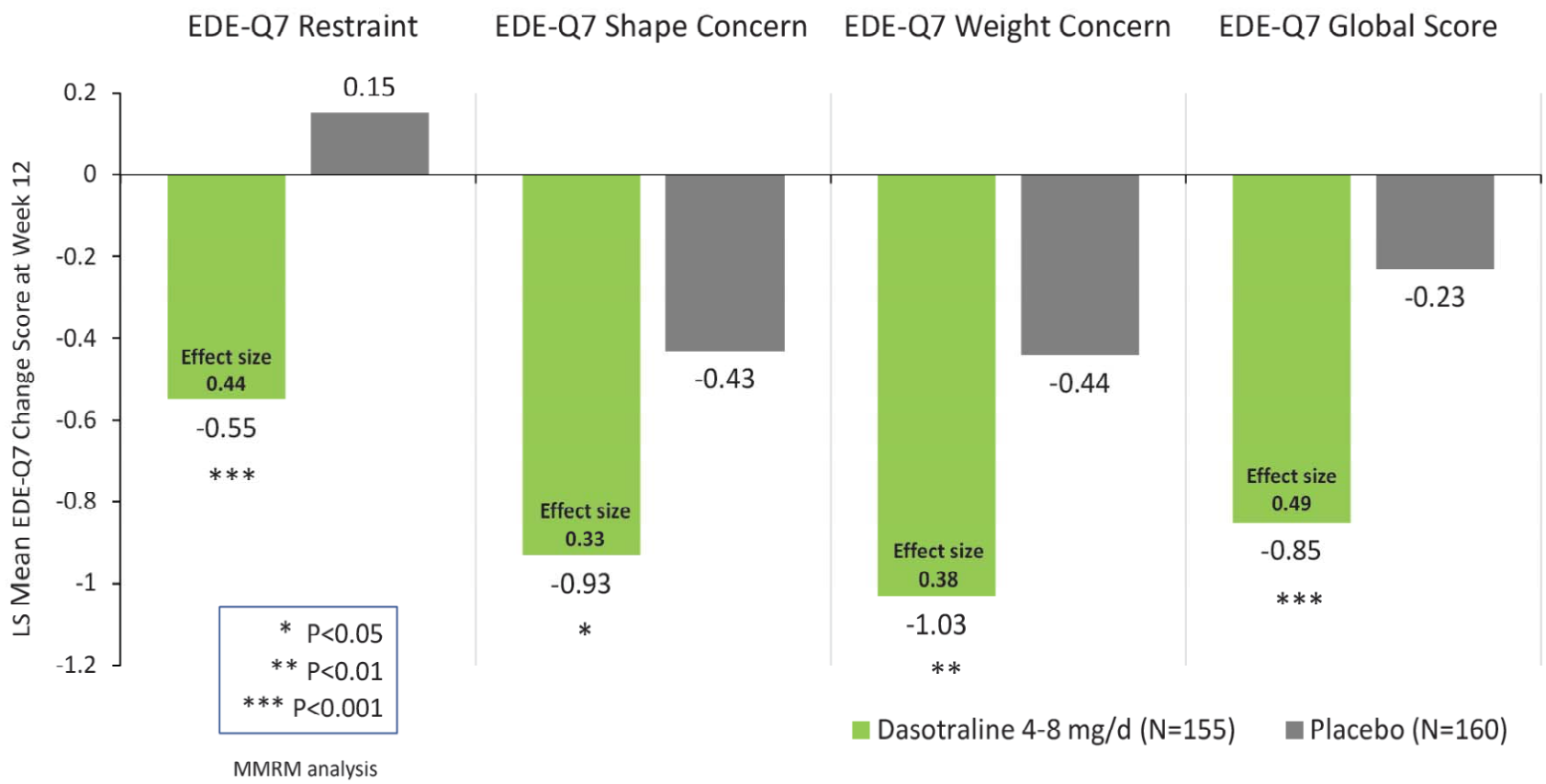
Supplementary Figure 1. LS Mean Change From Baseline in EDE-Q7 Global and Subscale Scores



Supplementary Table 1. Sensitivity Analyses, Change from Baseline-to-Week-12 in Binge-eating Days per Week

Analysis	Statistics	Placebo (N=160)	Dasotraline (N=155)
PMM with placebo-based multiple imputation result at Week 12	LS mean (SE)	-2.75 (0.128)	-3.59 (0.136)
	Difference from placebo		
	LS mean difference (SE)		-0.84 (0.184)
	LS mean difference 95% CI		(-1.20, -0.48)
	p-value		< 0.001
PMM with multiple imputation result at Week 12 by deflating 100% SD penalties of dasotraline group	Difference from placebo		
	LS mean difference (SE)		-0.76 (0.179)
	LS mean difference 95% CI		(-1.11, -0.41)
	p-value		< 0.001
GLMM to fit data over time based on binomial distribution at Week 12 [(a)]	LS mean (SE)	-2.82 (0.155)	-3.83 (0.136)
	Difference from placebo		
	LS mean difference (SE)		-1.00 (0.206)
	LS mean difference 95% CI		(-1.41, -0.60)
	p-value		<0.0001
Permutation test results at Week 12	Empirical p-value		< 0.0001
MMRM result	LS mean (SE)	-2.75 (0.117)	-3.74 (0.124)
	Difference from placebo		
	LS mean difference (SE)		-0.99 (0.172)
	LS mean difference 95% CI		(-1.33, -0.65)
	p-value		< 0.001

Abbreviations: CI = confidence interval; ITT = intent-to-treat; LS = least square; MMRM = mixed-effects model for repeated measures; PMM = pattern mixture model; SD = standard deviation; SE = standard error.

(a) LS means of change and differences of LS mean of change (dasotraline vs. placebo) were obtained from the GLMM model directly. SEs, 95% CIs, and p-values related to LS means of change and difference of LS mean of changes were derived using delta method.

Sensitivity Analyses: Methodology

To address early dropouts under the assumption of missing not at random, a pattern mixture model (PMM) using a placebo-based multiple imputation method and a PMM using multiple imputations with penalties (ie, tipping point analysis by deflating the individually estimated treatment effect size by known factors) were performed as sensitivity analyses to explore the robustness of the MMRM results for the primary analysis based on the ITT population.

The PMM, using a placebo-based multiple imputation method assuming that efficacy profiles of dropouts after discontinuation are similar to those of placebo subjects, was considered very conservative because this methodology tended to minimize the difference between the dasotraline and placebo groups. The PMM, using multiple imputations with penalties by deflating the individually estimated treatment-effect size by known factors, provided a way to assess plausible deviations from missing at random. The tipping point, defined as the value of the factor where statistical significance of treatment effect was lost, was evaluated. If the tipping point was unrealistically high, treatment effect was robust. This approach generated a serial of conservative estimates and provided the extent of robustness of primary efficacy results in a stepwise way.

In case of a deviation from the assumptions required for the primary analysis, to confirm the robustness of the primary analysis result, 2 additional sensitivity analyses, ie, permutation test and generalized linear mixed model (GLMM) analysis were performed. The permutation test was done to fit a large number of datasets (ie, 10,000) based on a same MMRM for the primary analysis with randomly assigning pseudo-treatment group designations. The empirical p-value was obtained from the permutation test. The nonparametric based permutation test provided a conservative way to assess the primary efficacy endpoint. The GLMM analysis was performed for count data over time (ie, number of binge-eating days among number of assessed days at each period) based on a binomial distribution. This approach may have better addressed the potential unequal variances assumption among subjects due to different number of assessed days (either because of assessment schedule, early dropout, or missing diary) among subjects and, therefore, was expected to better reflect the true distribution of the primary efficacy endpoint. Since the GLIMMIX procedure in SAS cannot provide statistical inferences directly (ie, standard error, 95% CI, and p-value) related to LS means of change from Baseline and difference of changes from Baseline between dasotraline group and placebo group, corresponding statistical inferences were derived using the delta method.

Supplementary Table 2. Adverse events of special interest in the dasotraline group (psychosis-related and OCD spectrum behaviors)

Patient #	Sex	Age, years	Dose, mg/d	Onset Study Day	Psychosis-related adverse event (severity)	Drug discontinued due to event?	Adverse event resolved?
Psychosis-related events							
0002-00001	Female	53	6	17	auditory hallucinations (moderate), paranoia (mild)	No	Resolved after dose was reduced to 4 mg
0012-00014	Female	30	6	63	delusion (moderate; intermittent paranoid thoughts that interfered with sleep)	No (entered extension study)	Ongoing (intermittent)
0018-00007	Female	24	4	69 (paranoia) 72 (hallucination)	paranoia (mild and intermittent), auditory hallucinations (mild and intermittent)	No (completed study but did not enter extension study)	Ongoing until end of study
0023-00002	Female	20	6	15	paranoia and visual hallucinations (severe); formication (moderate)	Yes	paranoia and visual hallucinations (resolved in 48 hrs); formication (resolved “same day”)
0026-00006	Female	49	8	64	visual hallucination (mild “visual illusions; awake for 48 hours working and seeing things move on the computer”)	No; and no change in dose. Study drug was later discontinued due to persistent severe insomnia	Event resolved the same day
OCD spectrum behaviors							
0026-00001	Female	41	4	20	trichotillomania (moderate)	No; and no change in dose. Study drug was later discontinued due to severe anxiety	Resolved 5 days after study drug was discontinued
0027-00015	Female	46	6	29	dermatillomania (moderate)	No; and no change in dose	Event resolved after 9 days