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LETTER TO THE EDITOR

Authors' Reply to Singh and Balasundaram: Comment on "A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Assessing the Efficacy and Safety of Viloxazine Extended-Release Capsules in Adults with Attention-Deficit/Hyperactivity Disorder"

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Dear Editor,

We are pleased that Singh and Balasundaram holds our recently published study, "*A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial Assessing the Efficacy and Safety of Viloxazine Extended-Release Capsules in Adults with Attention-Deficit/Hyperactivity Disorder*" [1] in high regard.

Below, we address the points raised by Singh and Balasundaram regarding the findings from our study [2].

In the series of pediatric clinical trials of viloxazine, somnolence was the most common adverse effect. Surprisingly, in the adult population, somnolence was almost nil.

Treatment-emergent adverse events (TEAE), which are summarized in the individual pediatric [3–6] and adult [1] phase III trials, are reported by the patients and recorded by the site investigator. In four pediatric 6- to 8-week, fixed-dose (100–400 mg) trials (N = 1289),16% of pediatric subjects treated with viloxazine ER (N = 826) reported a TEAE of *somnolence* (combined terms: somnolence, lethargy and sedation) compared with 4% of placebo-treated patients (N = 463) [7]. In the adult 6-week flexible-dose viloxazine ER (200–600 mg) trial (N = 372), 6% of adult subjects treated with viloxazine ER (N = 189) reported a TEAE of *somnolence*, compared with 2% of placebo-controlled patients (N = 183) [7].

The reason(s) for the difference observed in the percentage of patients reporting somnolence between pediatric and adult populations may be related to multiple factors. There were no covariate analyses performed to identify some of these factors. However, one possible explanation may be due to the age-related differences in the daily amount of caffeine consumption (e.g., children and adolescents do not have access to or consume as much caffeine-containing products as adults). In the adult trial, > 85% of subjects reported that they had consumed caffeine during treatment [1]. Although the caffeine consumption in the pediatric trials is unknown, it is reported that children and adolescents tend to consume less caffeine relative to adults [8]. This is perhaps a reasonable assumption since the reported TEAE of *insomnia* (combined terms: initial insomnia, insomnia, middle insomnia, poor quality sleep, sleep disorder, and terminal insomnia) was higher in adults (23%) compared with pediatric patients (4%) [7].

Similarly, in the pediatric population the responders (i.e. number of participants showing 50% or more improvement in ADHD-Rating Scale-5 and achieving a CGI-I score of 1 or 2) were significantly higher than placebo and this was also not observed in adults.

In each of the four pediatric short-term (6–8 weeks), double-blind, phase III trials, all viloxazine ER dose groups exhibited a higher percentage of responders at end of study (EOS) compared with placebo for the 50% ADHD Rating Scale–5 (ADHD-RS-5) responder rate (range: viloxazine ER, 34.2–48.2%; placebo, 19.8–32.9%) and Clinical Global Impression—Improvement (CGI-I) responder rate (range: viloxazine ER, 45.0–60.6%; placebo, 29.5–35.5%) [3–6]. In addition, the difference in responder rate between viloxazine

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ER and placebo was statistically significant for most, but not all dose groups for the 50% ADHD-RS-5 responder rate (e.g., 200 mg, children [5]; 600 mg, adolescents [4]) and the CGI-I responder rate (e.g., 200 and 400 mg, children [5]; 600 mg, adolescents [4]).

In the adult double-blind phase III trial, viloxazine ER-treated subjects also exhibited a higher 50% Adult ADHD Investigator Symptoms Rating Scale (AISRS) responder rate and CGI-I responder rate at end of study compared with placebo [1]. The 50% AISRS responder rate (39.2%) and CGI-I responder rate (48.5%) in adult viloxazine ER-treated subjects fall within the range (but nearer to the minimum) of the ADHD-RS-5 and CGI-I responder rate of viloxazine ER-treated dose groups in the four pediatric trials. However, the 50% AISRS responder rate (32.9%) and CGI-I responder rate (37.8%) in the adult placebo group fall above the upper range of the ADHD-RS-5 and CGI-I responder rate placebo groups in the four pediatric trials.

Each of the pediatric phase III trials was powered based solely on the ADHD-RS-5 total score. The statistical method used to perform the categorical analyses on the 50% ADHD-RS-5 and CGI-I responder rate was the same (Pearson's Chi-squared test); a comparison is generated at each study visit. Similarly, the adult phase III trial was powered based solely on AISRS total score. The statistical method used to perform the categorical analyses on the 50% ADHD-RS-5 and CGI-I responder rates was the same as that used in the pediatric trials (Pearson's Chi-squared test). However, for subjects who discontinued early (dropouts, e.g., Week 3 of treatment), the observation at the last available study visit was used to impute the missing value at the EOS for all pediatric trials, whereas the missing value at the EOS was not imputed in the adult trial. The sample size of the data analyzed at EOS in the pediatric trials was based on the total analysis population, whereas in the adult trial it was based on the number of subjects in the analysis population who completed the study. As a result, the manner in which dropouts were handled in the adult trial reduced the number of subjects included in the analysis at EOS. Therefore, the power to detect a significant difference between viloxazine ER and placebo in the adult trial was further reduced. For instance, compared with the responder rate results per the FDA-approved statistical analysis plan for the adult trial, the *p*-value is lower for both the 50% AISRS responder rate (0.2736 vs 0.1639) and CGI-I responder rate (0.0744 vs 0.0186) when the same method for handling missing data per the FDA-approved statistical analysis plan for the individual pediatric trials is used.

The authors applied the Kruskal Wallis test for baseline comparison of scores for primary and certain secondary endpoints, but in usual practice it is applied when there is a need to compare the mean ranks of more than two groups.

While Singh and Balasundaram is correct that the Kruskal Wallis is used to compare ranks, our analysis included a two-group t-test to perform the baseline comparability analysis. However, because the *p*-values from the *t*-test and the Kruskal–Wallis were similar, we neglected to update the table with the *t*-test *p*-values. It should be noted that the baseline comparability test is not important because subject randomization is generally enough to ensure sufficient baseline comparability between treatment groups.

Repetition of the same adverse events (hepatic enzymes and transaminases) twice in the summary of adverse events table could have been avoided.

This apparent repetition of adverse events (AEs) is due to the way that AEs were coded by the Medical Dictionary for Regulatory Activities (MedDRA) and then categorized by preferred term (PT). The site investigator records the AE. These two AEs occurred in subjects at different sites and thus by two different investigators using slightly different terms, which through the coding, generated the PTs. In the publications for both pediatric and adult trials, the "AEs leading to discontinuation" were listed strictly by preferred term as they were coded, and combined terms were not used to report any particular AE(s) (PTs).

Again, we are delighted that Singh and Balasundaram find our results regarding the efficacy and safety of viloxazine ER for the treatment of adult ADHD as promising.

Declarations

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Conflicts of interest AN, JTH, TL, NF, and JR are employees of Supernus Pharmaceuticals, Inc. AJC has received research support from Aevi Genomics, Akili Interactive, Arbor Pharmaceuticals, Ironshore Pharmaceuticals, Janssen, KemPharm, Lundbeck, Neos Therapeutics (now Aytu BioPharma), Neurovance, Noven, Otsuka, Purdue Canada, Rhodes Pharmaceuticals, Shire, Sunovion, Supernus Pharmaceuticals, Inc., Takeda, and Tris Pharma. He has received fees for consulting, advisory boards, and promotional speaking from Adlon Therapeutics, Aevi Genomics, Akili Interactive, Arbor Pharmaceuticals, Atentiv, Cingulate Therapeutics, Corium, Ironshore Pharmaceuticals, Janssen, Lundbeck, MedAvante-ProPhase, Neos Therapeutics (now Aytu BioPharma), NLS Pharmaceutics, Noven, Otsuka, Shire, Sunovion, Supernus Pharmaceuticals, Inc., Takeda, and Tris Pharma. He is an employee and board member of the Neuroscience Education Institute. AC has received research support from, served as a consultant or speaker for, or served on an advisory board for Allergan, Takeda (Shire), Emalex, Pearson, Akili, Arbor, Cingulate Therapeutics, Ironshore, Lumos, Aevi Genomic Medicine, Neos Therapeutics, Neurovance, Noven, Otsuka, Pfizer, Purdue, Adlon, Rhodes, Sunovion, Tris, KemPharm, Supernus Pharmaceuticals, Inc., the U.S. FDA, NLS Pharma, and Jazz.

Ethics approval Not applicable.

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Consent for publication Not applicable.

Availability of data and material The data are not available in a repository, but requests can be directed to anasser@supernus.com.

Code availability Not applicable.

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