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ORIGINAL ARTICLE

The role of placebo response in the efficacy outcome assessment in viloxazine extended-release pivotal trials in paediatric subjects with attention-deficit/hyperactivity disorder

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Aims: Four Phase 3 studies evaluated efficacy and safety of viloxazine extended-release in the treatment of attention-deficit/hyperactivity disorder (ADHD). The primary efficacy objective—change from baseline in ADHD Rating Scale-5 (ADHD-RS-5) Total score at end of study (EOS)—was not met in one of the studies (812P304). A band-pass analysis was performed to evaluate the impact of placebo response on the results.

Methods: The distribution of placebo response at EOS of each trial was evaluated. The 2.5th and 97.5th percentiles of the distribution of ADHD-RS-5 Total score were used as boundaries for the band-pass analysis. An independent mixed model for repeated measures analysis was conducted for each trial using all eligible data (active and placebo) from the total and band-pass filtered populations.

Results: The 2.5th and 97.5th percentiles at EOS were 3.5 and 53.5, respectively. Application of the band-pass filter (filtering out all subjects [active, $n = 305$ (32.1%) and placebo, $n = 134$ (33.5%)] of clinical sites with placebo scores <3.5 or >53.5) revealed statistically significant improvement at the primary endpoint (600-mg/d viloxazine ER *vs.* placebo) in Study 812P304 (mean [confidence interval] = 4.9537 [0.5405–9.3669]), previously masked by a high placebo response (mean [confidence interval] = 3.5756 [−0.3332–7.4844]). The outcome of the analysis indicated that the impact of the band-pass adjustment is greater when placebo response is higher.

Conclusion: This analysis indicated that a higher placebo response in Study 812P304 confounded the assessment of treatment effect. Application of the band-pass methodology confirmed the positive results of the 3 prior studies and the signal detection confounder in the fourth study.

The authors confirm that the Principal Investigator for this paper is Azmi Nasser and that he had direct clinical responsibility for patients.

KEYWORDS
ADHD, ADHD-RS-5, attention-deficit/hyperactivity disorder, band-pass analysis, placebo response, treatment effect, viloxazine extended-release

1 | INTRODUCTION

The development of new effective, safe and tolerable medications for the treatment of psychiatric disorders presents unique challenges. This is evident from the higher frequency of failed randomized clinical trials (RCTs) compared to other disease areas. For instance, >50% of placebo-controlled RCTs evaluating medications for major depressive disorder have failed to show statistically significant superiority over placebo.[1,2] Contributing to this phenomenon are nonspecific factors that are unrelated to the actual study medication, including, but not limited to, higher expectations of improvement, flaws in the study design, changes in the patient referral patterns and early drop-out rates.[3] These factors may exacerbate the placebo response, potentially reducing the likelihood to detect a statistically significant effect of a psychiatric medication in a placebo-controlled RCT.[4–7]

Placebo response was recently investigated in a randomized, double-blind, placebo-controlled, crossover clinical trial assessing efficacy/safety of methylphenidate in 540 children (age 6–12 y) with attention-deficit/hyperactivity disorder (ADHD). The results of this study identified a significant placebo response in the primary outcome as assessed by parents or teachers.[8] In a retrospective study, based on the data collected from medical files of 236 children who underwent a crossover study of methylphenidate and placebo, a 30% or higher placebo response in at least 1 of the Conners' Teacher Rating Scale subscales (effect size between 0.36 and 0.5) was observed in 18.8% of the participants.[9] In a pooled analysis of 731 paediatric ADHD patients treated with placebo across 10 placebo-controlled RCTs of ADHD, the placebo response rate varied between 17 and 40%, and a higher placebo response rate was observed in multisite trials and trials in adolescents and adults compared to single-site trials and trials in children, respectively.[10]

Several mediators and moderators of the placebo response have been identified (e.g., diagnostic misclassification, issues concerning inclusion/exclusion criteria, measurement errors, waxing and waning of the natural course of illness, regression toward the mean phenomenon, prior therapeutic experiences, patient and clinician expectations about the trial, study design issues, nonspecific therapeutic effects, high attrition, the natural course of central nervous system illness, inappropriate subject selection, and inadvertent supportive therapy).[7,11–13] Various strategies have been employed to reduce placebo response in clinical trials.[11] These strategies include increasing the sample size as an accommodation to yield greater power, innovative study designs to identify and exclude placebo responders (e.g., staggered, blinded placebo run-in phases or sequential parallel comparison design methods), rater training and inter-rater reliability programmes to enhance consistency across raters, surveillance of in-study data to identify measurement error, site-independent subject selection to minimize site biases, site-independent interviews to verify subject diagnosis and appropriateness (e.g., SAFER), and prestudy education of study participants (e.g., clinical patient *vs*. clinical trial participant) to minimize expectancy effects.[11,14–16] These placebo response mitigation efforts have been met with mixed success.[11]

What is already known about this subject

- Phase 3 placebo-controlled trials evaluated efficacy and safety of viloxazine ER in paediatric patients with ADHD: 3 studies evaluating 100-, 200- and 400-mg/d viloxazine ER met primary efficacy objective, while 1 study evaluating 400- and 600-mg/d viloxazine ER did not, possibly due to high placebo response.
- Band-pass filter analysis is a novel methodology based on predictive statistical models that is used to reassess the treatment effect in placebo-controlled clinical trials where excessively high/low placebo response rates are suspected.
- We used this method to evaluate whether a high placebo response confounded the assessment of the treatment effect in the Phase 3 clinical trial of viloxazine ER that did not meet the primary efficacy objective.

What this study adds

- This analysis confirmed that the viloxazine ER Phase 3 clinical trial that did not meet primary efficacy objective (812P304) had a higher placebo response compared to the other 3 Phase 3 viloxazine ER trials that fulfilled the primary efficacy objective.
- The application of the band-pass methodology was able to confirm that the high placebo response observed with the fourth study contributed to its negative results; the analyses of the 3 other studies were positive in separating from placebo, which is in agreement with the original predefined statistical analyses.
- Our findings further confirm that the band-pass filter analysis is an effective *posthoc* enrichment methodology to improve the signal-to-noise ratio and optimize signal detection in placebo-controlled psychiatric clinical trials.

As an alternative, a novel methodology based on predictive statistical models has been proposed to enhance signal detection.[17,18] This analytic technique, called band-pass filter analysis, can reduce the interference of confounding signals such as excessively high or excessively low placebo response rates.[18–21] Based on signal detection theory, the band-pass filter strategy directly addresses nonplausible placebo response rates by identifying clinical study sites whose study participants exhibit excessively low or high placebo response and removing these sites (both placebo and active treatment groups) from the analysis.[18] This methodology optimizes the signal-to-noise ratio by identifying the cut-off values at the high/low ends of the placebo response distribution curve and subsequently filtering-out the values that fall outside of these boundaries. *Posthoc* filter rules are developed to exclude from the analysis all the data from the trial sites that fall outside the established mean placebo response boundaries, which are estimated based on historically reasonable rates found in the specific study population.[18,20]

The current analysis aims to use the band-pass filter methodology to evaluate the signal detection and the role of placebo response in the assessment of the efficacy outcome in pivotal clinical trials of viloxazine extended-release capsules (viloxazine ER; Qelbree).

In 4 pivotal Phase 3 clinical trials, once-daily 100- to 600-mg doses of viloxazine ER, which has demonstrated activity on norepinephrine and serotonin,[22] were tested in paediatric (age 6–17 y) patients with ADHD. All doses of viloxazine ER (100- to 600-mg/d) were generally safe and well tolerated (discontinuation rate due to adverse events was <5% within and across all 4 trials). The primary endpoint was the change from baseline (CFB) in the ADHD Rating Scale-5 (ADHD-RS-5) Total score at end of study (EOS). Statistically significant improvements (reduction in CFB in ADHD-RS-5 Total score at EOS) *vs*. placebo were demonstrated in 2 trials in children (age 6–11 y) with 100- and 200-mg/d viloxazine ER (Study 812P301[23]) and 200- and 400-mg/d viloxazine ER (Study 812P303[24]) and in 1 trial in adolescents (age 12–17 y) with 200- and 400-mg/d viloxazine ER (Study 812P302[25]). In the second Phase 3 trial in adolescents evaluating 400- and 600-mg/d viloxazine ER for the treatment of ADHD (Study 812P304[26]), statistically significant improvement was observed with the 400-, but not the 600-mg/d dose of viloxazine ER. As such, Study 812P304 was considered a negative study, given that 600 mg/d viloxazine ER did not reach statistical significance on the predefined primary endpoint. Considering that the reduction observed in the primary outcome measure in the 600-mg/d treatment arm (least square [LS] mean −16.7) was within the range of the active treatment groups in the other 3 trials (LS mean −16.0 to −17.7),[23–25] it was hypothesized that the lack of a statistically significant separation between 600 mg/d and placebo in the 812P304 study may be due to an excessively high placebo response (−13.2 *vs*. −16.7 as the CFB at EOS [LS mean] in ADHD-RS-5 Total score for placebo *vs*. 600 mg/d viloxazine ER, $P = .0712$).[26] To test this hypothesis and investigate the impact of the nonplausible high placebo response on the primary endpoint, a band-pass filter analysis was used to identify study sites with excessively high placebo response rates and then reanalyse the primary endpoint in these 4 studies with those study sites omitted.

2 | METHODS

2.1 | Study designs and populations

The data from the multicentre, Phase 3, randomized, placebo-controlled, double-blind, 3-arm clinical trials evaluating the efficacy and safety of viloxazine ER—812P301, 812P302, 812P303 and 812P304—were included in this analysis (Table 1).[23–25]

In each study, screening began with informed consent (and participant assent, if applicable). Eligibility was determined by predefined inclusion/exclusion criteria. Specifically, subjects were eligible to participate if they met the following criteria: diagnosis of ADHD based on Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), ADHD-RS-5 Total score ≥28, and Clinical Global Impression–Severity of Illness score ≥4.[23] Key exclusion criteria were: major psychiatric disorder or neurological disorder (excluding oppositional defiant disorder or major depressive disorder if the participant was free of major depressive episodes within the 6 months prior to screening), a history of allergic reaction to viloxazine or its excipients, any food allergy or intolerance that contraindicated trial participation, suicidal ideation, history of seizures, or significant systemic disease.[23] Children and adolescents had to weigh ≥20 kg and ≥35 kg, respectively, and have body mass index (BMI) ≤ 95th percentile for the appropriate age and sex. After a screening period of up to 28 days, eligible participants were randomized in a 1:1:1 ratio to receive either placebo or 1 of the 2 doses of viloxazine ER per the specific study protocol (Table 1).

Participants were instructed to take the study medication once-daily by mouth in the morning (the placebo capsules were identical in appearance), with or without food, throughout the treatment period.[23] If necessary, the capsules could be opened and sprinkled over a spoonful of soft food (e.g., apple sauce). The protocol required that participants refrain from taking medications prohibited by the study protocol starting 1 week prior to randomization until EOS (this included other Food and Drug Administration-approved medications for the treatment of ADHD). Baseline efficacy and safety assessments were conducted on the day of, but prior to, randomization and the administration of the first dose of study medication.

Efficacy and safety assessments were conducted weekly until EOS or early termination. The ADHD-RS-5 was administered by a trained investigator at screening, baseline and each weekly post-baseline study visit until EOS/early termination. The primary efficacy endpoint was the CFB in the ADHD-RS-5 Total score at EOS. A key secondary endpoint in each trial was the Clinical Global Impression–Improvement score at EOS.

The statistical analyses plans were similar across 4 RCTs.[23–26] Sample size calculations indicated that 72 subjects per treatment

TABLE 1 Overview of Phase 3 randomized controlled trials providing data

Age group	Children (6–11 y)		Adolescents (12–17 y)	
Study	**812P301**	**812P303**	**812P302**	**812P304**
CT.Gov identifier	NCT03247530	NCT03247543	NCT03247517	NCT03247556
Study sites (USA)	34	28	33	27
Viloxazine ER doses	100 mg/200 mg	200 mg/400 mg	200 mg/400 mg	400 mg/600 mg
Weeks, T + M	6 (1 + 5)	8 (3 + 5)	6 (1 + 5)	7 (2 + 5)
Randomized (*n*)	477	313	310	297
Safety population (*n*)	474	310	308	296
ITT population (*n* total)	460	301	301	292
ITT population (*n* per group)	100 mg viloxazine ER/200 mg viloxazine ER/placebo: 147/158/155	200 mg viloxazine ER/400 mg viloxazine ER/placebo: 107/97/97	200 mg viloxazine ER/400 mg viloxazine ER/placebo: 94/103/104	400 mg viloxazine ER/600 mg viloxazine ER/placebo: 99/97/96

ER, extended-release; ITT, intent-to-treat; M, maintenance; T, titration.

group in the intent-to-treat (ITT) population would yield 90% power across treatment groups at a significance level of 0.05 (2-sided) using a 2-sample *t*-test, based on an effect size of 0.547 obtained in a previous Phase 2b trial for ADHD-RS-5 Total score at viloxazine ER dose of 200 mg *vs.* placebo.[27] The primary efficacy endpoint was analysed using a mixed model for repeated measures (MMRM), which assumes missing data are missing at random. The model included fixed-effect terms for baseline ADHD-RS-5 Total score, age group, treatment, visit and with treatment-by-visit interaction as the independent variables. Due to multiple treatment comparisons, the statistical analysis of the primary endpoint included a sequential testing procedure with a fixed testing method of the null hypotheses, first comparing viloxazine ER higher dose to placebo, and, if significant, then comparing viloxazine ER lower dose to placebo to control the overall Type I error rate at 0.05.

Advarra Institutional Review Board approved the study protocol. These studies were conducted in accordance with the Helsinki Declaration and the International Council for Harmonisation Note for Guidance on Good Clinical Practice. All versions of the informed consent form were reviewed and approved by the Institutional Review Board.

2.2 | Band-pass filter statistical analysis

The band-pass filter statistical analysis optimizes the signal-to-noise ratio by identifying the cutoff values located at the high and low ends of the placebo response distribution curve; subsequently, this approach excludes those sites that fall outside those boundaries from the analysis.[18,21] In the context of the present assessment, the 2.5th and the 97.5th percentiles of the distribution of the ADHD-RS-5 Total scores at EOS in the placebo arms were used to identify the excessively low and high placebo response. These limits assume that placebo scores falling outside these boundaries are extreme values. The presence of excessively high/low placebo response was considered as an indicator of a poor ability of that site to detect a possible treatment effect (TE). The reason for there being no exclusion of sites in which extreme values of active treatment were observed was that we did not dispose of any data indicating a response that could be a real TE. Therefore, and to avoid bias, only site-specific data (active and placebo) were excluded. Thus, the clinical sites with the placebo scores lower than the 2.5th or higher than the 97.5th percentile values, classified as excessively low and excessively high, were excluded (both placebo and active arms) from the reanalysis of the primary endpoint.

An independent analysis was conducted for each trial: the first analysis included the total trial population (reference), and the reanalysis included the population resulting from the application of the band-pass filter. The same band-pass boundaries were used for each study.

In each trial, an MMRM was used to assess the longitudinal CFB in ADHD-RS-5 Total score,[23] including terms for treatment, time, baseline, treatment by time interaction and baseline by time interaction. A significance level of $\alpha = 0.05$ was used to establish the significance of the TE (change *vs.* placebo), which was determined using the LS means.

The independent MMRM analyses were conducted using the PROC MIXED procedure in SAS (version 9.4 for Windows, SAS Institute, Cary, NC, USA).

3 | RESULTS

Of the 1354 subjects (ITT population), a total of 1350 subjects were eligible for band-pass analysis since they participated at a site that had at least 1 subject assigned to placebo, termed the reference population: 450 in the placebo group, 147 in the 100-mg/d viloxazine ER group, 359 in the 200-mg/d viloxazine ER group, 296 in the 400-mg/d viloxazine ER group, and 96 in the 600-mg/d viloxazine ER group. The descriptive statistics of the distribution of

the ADHD-RS-5 Total scores at EOS in the placebo groups are shown in Table 2.

Figure 1A shows the distribution of the ADHD-RS-5 Total scores at EOS in the placebo groups by study. The distributions of placebo response were similar in Studies 812P301, 812P302 and 812P303. Study 812P304 appeared to have an excessively high placebo response, indicating a potential issue for the estimation of the TE.

The median placebo response (the ADHD-RS-5 Total scores at EOS) and the 2.5 and 97.5 percentiles of the distribution of the placebo response at EOS in the pooled placebo sample (n = 450) were 31, 3.5 and 53.5, respectively (Figure 1B). Thus, the clinical sites with the mean ADHD-RS-5 Total placebo scores at EOS below 3.5 or above 53.5 were excluded from the reanalysis. Distribution of the ADHD-RS-5 Total score change from baseline at EOS in the total population for studies 812P301, 812P302, 812P303 and 812P304 by treatment group is shown for subjects included in the band pass analysis in Figure S1 and for subjects excluded from this analysis in Figure S2.

TABLE 2 Descriptive statistics: distribution of the ADHD-RS-5 Total score at end of study for the placebo group of each study

Study	*n*	Mean	SD	Skewness	Min	Lower quartile	Median	Upper quartile	Max
812P301	132	31.9	13.64	−0.31	3	22	35	43	54
812P302	96	28.9	14.99	−0.28	0	16	31	40.5	54
812P303	86	31.6	13.24	−0.34	1	22	33	42	54
812P304	86	25	12.7	0.43	1	16	23	34	54

SD, standard deviation.

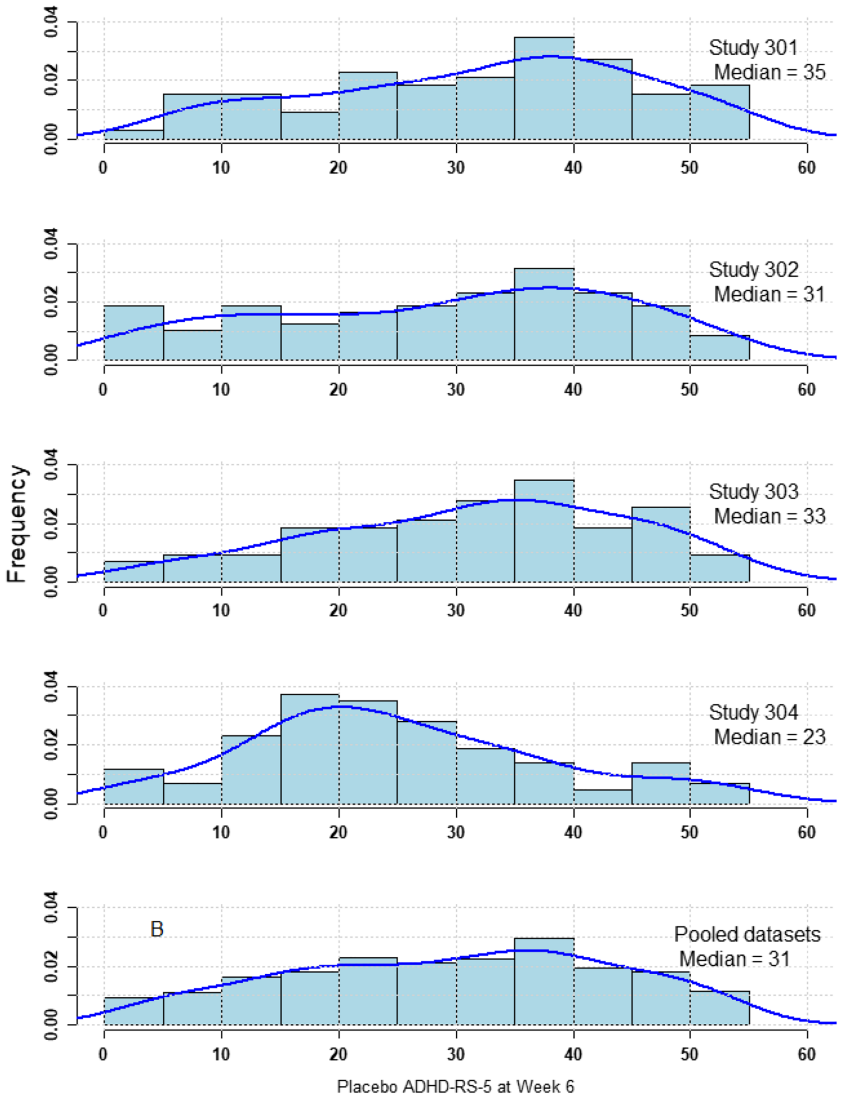

FIGURE 1 Distribution of ADHD-RS-5 Total score of subjects in the placebo arms in Studies 812P301, 812P302, 812P303 and 812P304

TABLE 3 Summary of the total number of sites and subjects (placebo and viloxazine extended-release [ER]) for each of 4 paediatric clinical trials before (*Reference population*) and after the application of the band-pass analysis; the *Included* population represents the subjects that were included in the band-pass reanalysis of treatment effect

		Children (6–11 y)		Adolescents (12–17 y)	
Category *treatment*	**Population**	**812P301**	**812P303**	**812P302**	**812P304**
Study sites	**Reference, *N***	32	24	28	28
	Excluded, *n* (%)	8 (25.0%)	7 (29.2%)	7 (25.0%)	8 (28.6%)
	Included, *n* (%)	24 (75.0%)	17 (70.8%)	21 (75.0%)	20 (71.4%)
Subjects *placebo*	**Reference, *N***	132	96	86	86
	Excluded, *n* (%)	38 (28.8%)	32 (33.3%)	33 (38.4%)	31 (36.0%)
	Included, *n* (%)	94 (71.2%)	64 (66.7%)	53 (61.6%)	55 (64.0%)
Subjects *viloxazine ER*	**Reference, *N***	326	205	215	204
	Excluded, *n* (%)	85 (26.1%)	83 (40.5%)	62 (28.8%)	75 (36.8%)
	Included, *n* (%)	241 (73.9%)	122 (59.5%)	153 (71.2%)	129 (63.2%)
Subjects *overall*	**Reference, *N***	458	301	301	290
	Excluded, *n* (%)	123 (26.9%)	115 (38.2%)	95 (31.6%)	106 (36.6%)
	Included, *n* (%)	335 (73.1%)	186 (61.8%)	206 (68.4%)	184 (63.4%)

Reference population includes only subjects from study sites in which at least 1 subject was assigned to placebo and had a baseline and at least 1 post-baseline ADHD-RS-5 assessment (ITT population); some sites provided data from more than 1 study. No sites (and consequently no subjects) were excluded because of values > 97.5%. All percentages are based on the number of subjects in reference population (i.e., *n*/*N*).

TABLE 4 Studies 812P301 and 812P303 evaluating viloxazine extended-release in children (age 6–11 y) with attention-deficit/hyperactivity disorder— mixed model for repeated measures results in the reference and band-pass analyses

		Reference					Band-pass				
					CI					CI	
Day	**Dose (mg)**	**TE**	**SE**	**Significant**	**Lower**	**Upper**	**TE**	**SE**	**Significant**	**Lower**	**Upper**
A—812P301											
7	100	3.89	1.06	Yes	1.80	5.98	3.45	1.21	Yes	1.07	5.83
	200	2.32	1.03	Yes	0.28	4.35	2.01	1.16	No	−0.28	4.29
14	100	4.79	1.17	Yes	2.49	7.08	4.27	1.37	Yes	1.57	6.97
	200	4.28	1.13	Yes	2.05	6.51	3.98	1.31	Yes	1.40	6.56
21	100	5.44	1.32	Yes	2.84	8.03	5.15	1.55	Yes	2.10	8.21
	200	5.49	1.27	Yes	2.99	7.99	5.97	1.48	Yes	3.06	8.88
28	100	5.69	1.44	Yes	2.87	8.51	6.46	1.67	Yes	3.18	9.74
	200	6.13	1.38	Yes	3.41	8.84	6.26	1.59	Yes	3.14	9.39
35	100	5.08	1.56	Yes	2.02	8.15	5.43	1.74	Yes	2.01	8.85
	200	6.03	1.50	Yes	3.08	8.98	5.98	1.66	Yes	2.72	9.24
42	100	5.46	1.65	Yes	2.21	8.70	5.25	1.76	Yes	1.78	8.71
	200	6.32	1.59	Yes	3.19	9.45	6.46	1.68	Yes	3.16	9.77
B—812P303											
7	200	2.94	1.30	Yes	0.38	5.49	4.09	1.64	Yes	0.85	7.34
	400	1.67	1.33	No	−0.95	4.30	2.06	1.70	No	−1.30	5.41
14	200	3.33	1.54	Yes	0.29	6.36	4.24	1.89	Yes	0.51	7.97
	400	2.52	1.58	No	−0.59	5.63	3.46	1.96	No	−0.41	7.33
21	200	3.28	1.71	No	−0.08	6.64	4.60	2.12	Yes	0.42	8.77
	400	3.08	1.75	No	−0.37	6.52	5.54	2.20	Yes	1.20	9.89

(Continues)

TABLE 4 (Continued)

		Reference					Band-pass				
					CI					CI	
Day	Dose (mg)	TE	SE	Significant	Lower	Upper	TE	SE	Significant	Lower	Upper
28	200	3.10	1.84	No	−0.52	6.72	3.66	2.21	No	−0.71	8.03
	400	3.47	1.88	No	−0.23	7.17	5.03	2.30	Yes	0.49	9.58
35	200	6.24	1.89	Yes	2.52	9.96	7.42	2.30	Yes	2.89	11.95
	400	4.84	1.94	Yes	1.03	8.66	6.88	2.41	Yes	2.13	11.63
42	200	5.60	1.91	Yes	1.85	9.36	6.61	2.31	Yes	2.05	11.16
	400	5.37	1.96	Yes	1.52	9.22	6.80	2.42	Yes	2.03	11.57
49	200	6.00	2.00	Yes	2.07	9.94	6.79	2.32	Yes	2.21	11.37
	400	4.50	2.05	Yes	0.46	8.54	7.22	2.43	Yes	2.43	12.02
56	200	6.39	2.10	Yes	2.26	10.52	6.58	2.35	Yes	1.94	11.22
	400	5.99	2.16	Yes	1.75	10.24	7.65	2.46	Yes	2.79	12.52

TE = treatment effect; SE = standard error; CI = 95% confidence interval.

TABLE 5 Studies 812P302 and 812P304 evaluating viloxazine extended-release in adolescents (age 12–17 y) with attention-deficit/hyperactivity disorder— mixed model for repeated measures results in the reference and band-pass analyses

		Reference					Band-pass				
					CI					CI	
Day	Dose (mg)	TE	SE	Significant	Lower	Upper	TE	SE	Significant	Lower	Upper
A—812P302											
7	200	2.28	1.25	No	−0.17	4.74	2.05	1.50	No	−0.91	5.01
	400	3.20	1.21	Yes	0.82	5.57	2.86	1.43	Yes	0.03	5.69
14	200	2.92	1.39	Yes	0.18	5.66	3.01	1.75	Yes	−0.43	6.45
	400	4.01	1.35	Yes	1.35	6.67	3.56	1.68	Yes	0.26	6.87
21	200	3.68	1.49	Yes	0.74	6.62	4.46	1.77	Yes	0.96	7.95
	400	5.04	1.45	Yes	2.18	7.91	5.29	1.71	Yes	1.91	8.66
28	200	5.17	1.68	Yes	1.87	8.47	6.14	1.92	Yes	2.36	9.91
	400	5.92	1.63	Yes	2.71	9.13	6.28	1.85	Yes	2.63	9.93
35	200	5.32	1.92	Yes	1.53	9.10	6.63	2.16	Yes	2.37	10.90
	400	5.44	1.87	Yes	1.77	9.11	6.34	2.08	Yes	2.24	10.44
42	200	5.18	2.03	Yes	1.18	9.17	6.64	2.16	Yes	2.39	10.89
	400	5.83	1.97	Yes	1.95	9.70	6.54	2.07	Yes	2.45	10.62
B—812P304											
7	400	1.98	1.48	No	−0.94	4.91	1.96	1.79	No	−1.58	5.50
	600	2.89	1.49	No	−0.04	5.81	2.99	1.79	No	−0.55	6.52
14	400	4.38	1.58	Yes	1.27	7.50	5.81	1.81	Yes	2.25	9.38
	600	3.26	1.59	Yes	0.14	6.39	3.76	1.81	Yes	0.19	7.34
21	400	4.95	1.69	Yes	1.62	8.27	6.87	2.10	Yes	2.72	11.02
	600	4.01	1.70	Yes	0.66	7.35	5.02	2.11	Yes	0.86	9.18
28	400	4.09	1.78	Yes	0.59	7.60	6.65	2.27	Yes	2.16	11.13
	600	2.17	1.79	No	−1.36	5.70	3.38	2.28	No	−1.12	7.88
35	400	4.08	1.77	Yes	0.60	7.56	7.47	2.16	Yes	3.20	11.74
	600	2.36	1.79	No	−1.16	5.87	3.57	2.18	No	−0.72	7.87

TABLE 5 (Continued)

		Reference					Band-pass				
					CI					CI	
Day	Dose (mg)	TE	SE	Significant	Lower	Upper	TE	SE	Significant	Lower	Upper
42	400	4.36	1.83	Yes	0.76	7.95	7.90	2.17	No	3.62	12.18
	600	3.34	1.84	No	−0.29	6.97	5.36	2.18	Yes	1.06	9.65
49	400	4.48	1.96	Yes	0.62	8.35	7.47	2.23	Yes	3.08	11.87
	600	3.58	1.99	No	−0.33	7.48	4.95	2.24	Yes	0.54	9.37

TE, treatment effect; SE, standard error; CI, 95% confidence interval.

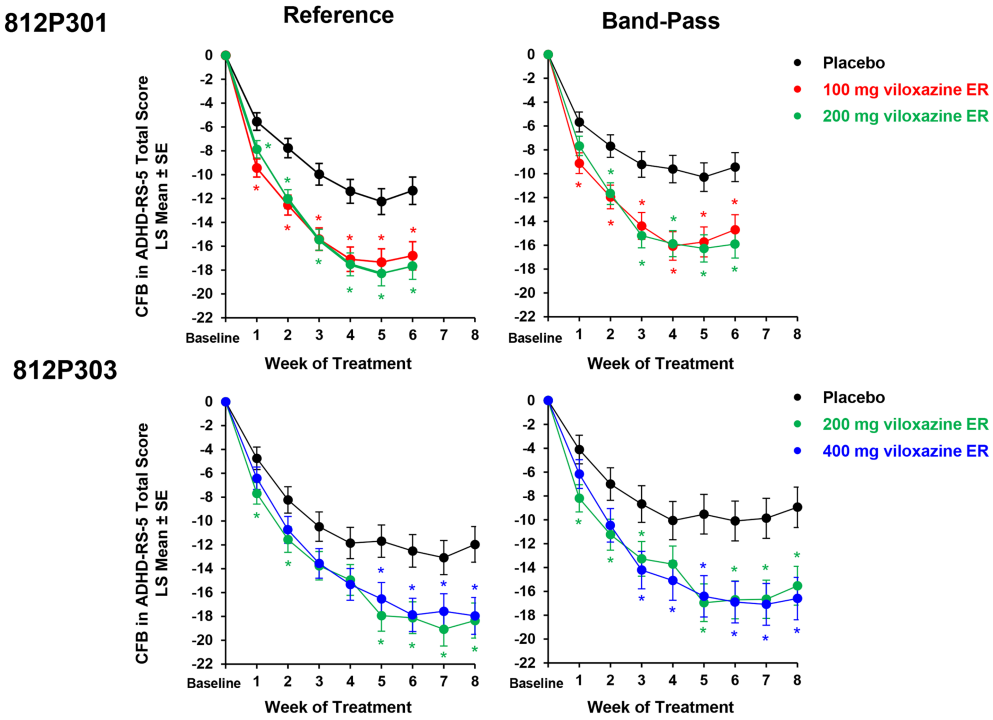

FIGURE 2 Studies 812P301 and 812P303. Time course of the change from baseline in the ADHD-RS-5 Total score in the reference population (left panel) and in the band-pass filtered population (right panel) by treatment group. *$P < .05$

Table 3 shows the total number of reference population subjects and sites included in the 4 clinical trials and the number/percentage of subjects and sites excluded/included from the reanalysis. The band-pass analysis identified 14 out of 58 recruitment sites with excessively high/low placebo response. After removing all subjects from these 14 sites from further analysis, the sample size was reduced from the full reference data set of 1350 patients to 911 patients (67%) in the band-pass population. The number of data points (patients) excluded in the placebo arm were 134 (33.5%) and the number included in the analysis were 266 (66.5%). Likewise, the number of data points excluded in the viloxazine ER arm were 305 (32.1%) and the number included in the analysis were 645 (67.9%).

The results (LS means, standard errors and 95% confidence intervals) of the first analyses, which included the total study population (reference) and the reanalysis, which included the population resulting from band-pass filtering for each clinical trial, are presented in Tables 4 and 5. The estimated TE and the associated *P* value for the comparison with placebo are shown by treatment day. In Study 812P301 (100- and 200-mg/d doses of viloxazine ER in children [age 6–11 y]; Table 4A), both doses demonstrated statistically significant TE at EOS (Week 6) *vs.* placebo in the reference ($P = .001$, $P < .0001$, respectively) and band-pass ($P = .0031$, $P = .0001$, respectively) populations. In Study 812P303 (200- and 400-mg/d doses of viloxazine ER in children [age 6–11 y]; Table 4B), both doses demonstrated statistically significant TE at EOS (Week 8) *vs.* placebo in the reference ($P = .0026$, $P = .0058$, respectively) and band-pass ($P = .0057$, $P = .0022$, respectively) populations.

In Study 812P302 (200- and 400-mg/d doses of viloxazine ER in adolescents [age 12–17 y]; Table 5A), both doses demonstrated statistically significant TE at EOS (Week 6) *vs.* placebo in the reference ($P = .0113$, $P = .0033$, respectively) and band-pass ($P = .0024$, $P = .0019$, respectively) populations. In Study 812P304 (400- and

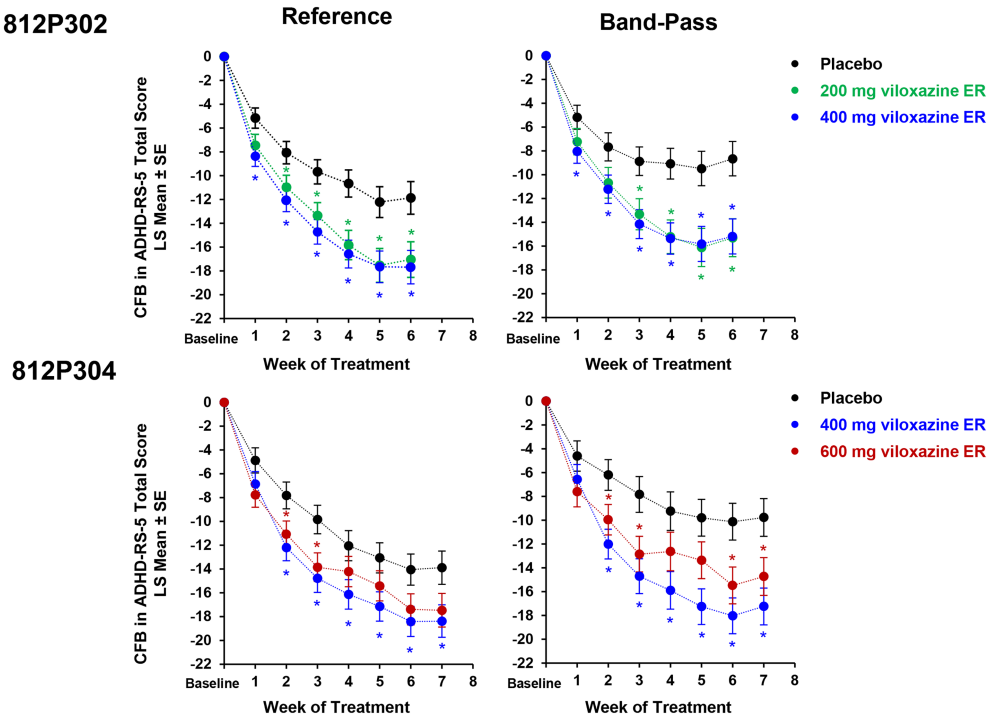

FIGURE 3 Studies 812P302 and 812P304. Time course of the change from baseline in the ADHD-RS-5 Total score in the reference population (left panel) and in the band-pass filtered population (right panel) by treatment group. *$P < .05$

600-mg/d doses of viloxazine ER in adolescents [age 12–17 y]; Table 5B), the 400-mg/d dose demonstrated statistically significant TE at EOS (Week 7) *vs.* placebo in the reference ($P = .0232$) and band-pass ($P = .001$) populations. For the 600-mg/d dose, the TE at EOS was not statistically significant in the reference population ($P = .0728$). When the band-pass filter was applied to Study 812P304, a statistically significant TE of the 600-mg/d dose was observed ($P = .028$). The time courses of the CFB in ADHD-RS-5 Total score (LS mean ± standard error) in the reference and band-pass populations for each trial are presented in Figures 2 and 3.

4 | DISCUSSION

The results of 3 Phase 3 clinical trials of viloxazine ER have demonstrated consistent efficacy outcome with 100-, 200- and 400-mg/d doses in paediatric subjects with ADHD (Studies 812P301, 812P302 and 812P303). In the Phase 3 Study 812P304, however, the higher than usual placebo response confounded the results of the highest dose (600-mg/d viloxazine ER).

Based on the distribution of the ADHD-RS-5 Total score at EOS in the placebo groups, the placebo response in Study 812P304 was 44, 73 and 62% higher than in the 812P301, 812P302 and 812P303 studies, respectively.

The band-pass analysis identified 14 (24.1%) out of 58 recruitment sites with excessively high/low placebo response. This was despite the rating clinicians at all sites being blinded to the treatment assignment, completing a rater training session and being certified prior to rating subjects in the trial. The proportion of sites with excessively high/low placebo response identified in this study was lower than the typical fraction of uninformative sites (40%) reported in previous studies.[21]

The application of a band-pass filter (to avoid bias, all data from subjects enrolled in the study sites with excessively high/low placebo response were excluded from the analysis, not only placebo groups) revealed a statistically significant TE of 600-mg/d dose at EOS (Week 8; $P = .028$), previously masked by high placebo response.

For the past few decades, researchers have assessed contributing factors of increased placebo responses in clinical drug trials for psychiatric disorders. Many factors for this phenomenon have been identified, including diagnostic misclassification, lack of sensitivity of the outcome measures, measurement errors, poor quality of data, fluctuations of the natural course of illness, regression toward the mean phenomenon, patient and clinician expectations about the trial and study design issues.[11] In the clinical trials evaluating the efficacy of the medications for ADHD, it has been noted that a high placebo response has been associated with patient and site-specific factors rather than factors related to study design.[10] For instance, adolescent and adult clinical trials had higher placebo response rates compared to clinical trials conducted in children, and multicentre trials had a higher placebo response *vs.* single-centre trials.[10] The clinical trial of viloxazine ER, in which high placebo response was observed, was conducted in adolescents; however, it is unlikely that the age of the subjects in this study contributed substantially to high placebo response, because another Phase 3 trial of viloxazine ER in adolescents with ADHD was positive.[25]

In the context of multicentre trials, such as the clinical trials of viloxazine ER reported here, each site may select subjects differently and may manage expectations for treatment outcome differently. This may result in a varying performance of the site. In some sites, this may

also lead to an inflated measure of the study outcome (for both placebo and active treatment).[21] The typical way to address this issue is to select sites on the basis of their track record and provide awareness sessions and good clinical practice training to the investigators at the beginning of every multicentre RCT. Despite these efforts, heterogeneity among the performance levels of the centres remains relevant to the degree of the placebo response. In addition, the centre's performance may become increasingly inconsistent over time, again potentially impacting the placebo response.[18]

As illustrated here, another approach to evaluate the degree to which the placebo response affects the outcome of the trial is the band-pass filter analysis, which can be considered a *posthoc* enrichment methodology to improve the signal-to-noise ratio and optimize signal detection. Like any enrichment approach, a criticism of this method is that it can lead to the involuntary introduction of an estimation bias associated with a potential inflation of the Type I error. To address this criticism, a trial simulation study was conducted, and it was found that the band-pass methodology preserves the Type I error without the introduction of any bias in the assessment of the TE.[20] It is important to note that the band-pass filter analysis is not intended to adjust the primary results reported in the ITT population, but to explain the high placebo response observed in the clinical trials.

The present assessment used the 2.5th and the 97.5th percentiles of the distribution of the ADHD-RS-5 Total scores at EOS of the placebo arms from 4 trials to identify the excessively low and high placebo response. The reason for selecting the cutoff boundary was to evaluate how the exclusion of no more than 5% of the data could affect the signal detection. The ADHD-RS-5 total score (sum of 18 items) can range from 0 (no symptoms) to 54 (severe). Subjects with an ADHD-RS-5 Total score ≥28 at baseline were eligible to participate in the Phase 3 clinical trial. The selected boundaries of 2.5% and 97.5% in the placebo group are equivalent to ADHD total scores <1.35 to >52.65, respectively.

The band-pass filter analysis has previously been used to reassess the TE of other medications used for psychiatric disorders. For instance, it has been applied to reanalyse the data from a negative trial evaluating CX157 (a reversible and selective monoamine oxidase inhibitor-A) *vs*. placebo for the treatment of depression (the development of CX157 was terminated in 2013 due to the lack of efficacy).[28] The application of band-pass filters to the mean change of the total Montgomery–Asberg Depression Rating Scale scores in this study increased the separation of active drug from placebo and reversed the direction of the original trial outcome (MMRM; $P = .58$) by generating a nonsignificant trend in a positive direction ($P = .13$ and 0.16). The present study is the first to use band-pass filter methodology to reassess the efficacy outcome of a medication being developed for ADHD. Taken together, these findings support the Merlo-Pich *et al*. hypothesis,[18,21] which states that *posthoc* elimination of data from clinical trial sites that generate excessively high or excessively low placebo response rates can enhance signal detection.

Other approaches used in previous studies to reduce the impact of nonplausible placebo responses have involved the independent validation of the appropriateness of the inclusion of subjects through more effective interview methodologies.[15,16,29] Our data also highlight the importance of ratings precision at individual clinical trial sites and support the use of site-independent surveillance strategies to pre-emptively minimize inappropriate subject selection. The availability and use of the band-pass technique should not, however, reduce the efforts to determine the role of placebo response and other confounders in efficacy assessments in clinical trials. It is also important to note that this analysis was conducted to examine the role of excessively high placebo response in 1 of the clinical trials of viloxazine ER and not to evaluate the effectiveness of the drug, which has been evaluated and approved for treatment of ADHD in children and adolescents (ages 6–17 years) by the Food and Drug Administration based on the data from 3 Phase 3 RCTs.

To conclude, this analysis confirms the positive results of the 3 Phase 3 studies (812P301, 812P302 and 812P303) and the signal detection confounder (high placebo response) in the fourth negative study (812P304) of viloxazine ER. Band-pass methodology was able to mitigate the excessively high placebo response in Study 812P304 and show that all doses of viloxazine ER (100- to 600-mg/d) tested in the 4 paediatric Phase 3 clinical trials assessing viloxazine ER for the treatment of ADHD provided a statistically significant benefit compared to placebo when the level of placebo response was factored into the assessment of the efficacy outcome.

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COMPETING INTERESTS

A.N., Z.W., J.T.H., G.D.B., Z.M., W.O. and J.R. are or were formerly employees of Supernus Pharmaceuticals, Inc. R.G. was a paid consultant to Ironshore Pharmaceuticals; Sunovion Pharmaceuticals; Supernus Pharmaceuticals; Teva; Biomedical Science Institutes; Nanomi BVs; Laboratorios Liconsa; Massachusetts General Hospital; UCB; Recordati Rare Diseases; Indivior; Tris Pharma; and F. Hoffmann-La Roche. For the list of M.F.'s lifetime disclosures, please see https://mghcme.org/app/uploads/2020/10/MF-Disclosures-Lifetime-updated-October-2020.pdf.

CONTRIBUTORS

A.N. conceptualized and designed this study. A.N., R.G., Z.W. and J.T.H. participated in statistical analysis. A.N., R.G., Z.W., J.T.H. and M.F. participated in data interpretation. G.D.B. and Z.M. drafted and revised the manuscript. A.N., R.G., Z.W., J.T.H., G.D.B., Z.M., M.F., W.O. and J.R. reviewed the manuscript.

DATA AVAILABILITY STATEMENT

Authors elect to not share data.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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