Evaluating Viloxazine ER (Qelbree®) Administered with Psychostimulants for Pediatric ADHD: Analysis of a Phase IV Safety Trial

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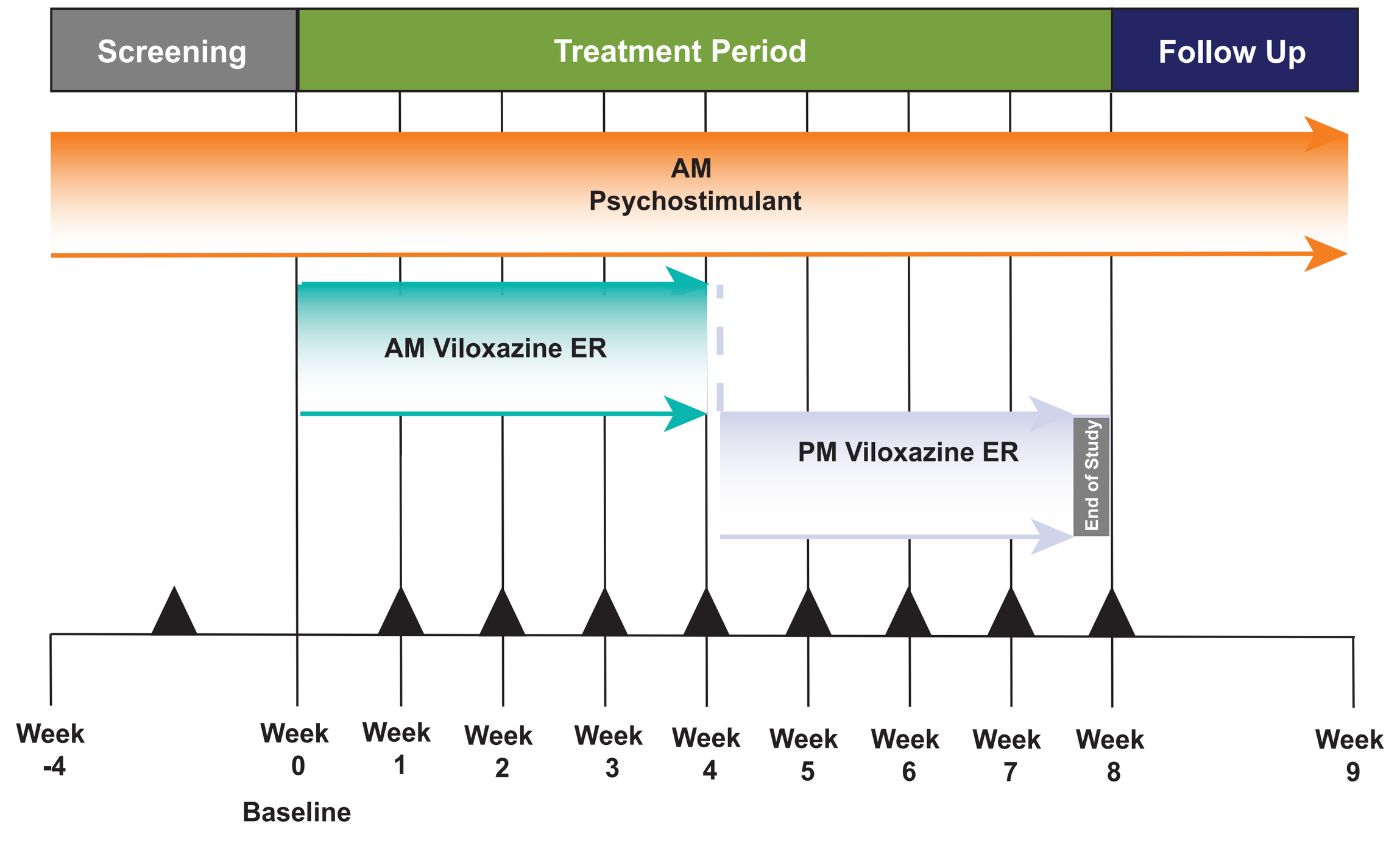
Introduction

- Psychostimulants are often used as first-line treatments for attention-deficit/hyperactivity disorder (ADHD);[1-4] however, some patients do not experience an adequate response or may not tolerate doses sufficient for efficacy.[5-8]
- Nonstimulants may also be used as first-line monotherapy or may be combined with stimulants to add to stimulant response.
- Viloxazine ER (viloxazine extended-release capsules; Qelbree®) is a nonstimulant medication, FDA-approved to treat ADHD in adults and children (≥6 years).[9]
- Approval for pediatric ADHD was based on the results of four pivotal Phase 3 clinical trials (two trials in children 6-11 years and two trials in adolescents 12- 17 years).[10-13]
- Pharmacokinetic studies of viloxazine ER and psychostimulants (methylphenidate and lisdexamphetamine) have not demonstrated any clinically important drug interactions in adults. However, to date, no clinical trials have evaluated the safety and efficacy of viloxazine ER used as an adjunctive therapy to stimulants.
- Therefore, the following Phase IV study was undertaken with dual objectives:
  - Evaluate the safety, tolerability, and efficacy of viloxazine ER use with psychostimulants.
  - Evaluate the safety, tolerability, and efficacy of AM vs. PM administration of viloxazine ER.

Methods

- **Design:** Phase IV, open-label, flexible-dose, study of viloxazine ER in pediatric patients diagnosed with ADHD and experiencing inadequate efficacy to psychostimulant therapy defined by an IR-ADHD-RS-5 score ≥24 and a CGI-S score ≥3 (mildly ill or worse) at Screening & Baseline (**Figure 1**).

Figure 1: Study design



- **Viloxazine ER:** Flexible dosing
  - Children: 100 mg/day Wk 1; optimized (100 mg/day/wk) to 100-400 mg/day.
  - Adolescents: 200 mg/day Wk 1; optimized (100 or 200 mg/day/wk) to 200-600* mg/day.

  *current FDA approved maximum dose of viloxazine ER for adolescents is 400 mg/day
- **Psychostimulant:** methylphenidate or amphetamine at least 5 days per week in the morning throughout study. Psychostimulant dose could be reduced once if needed, but not increased.
- **Primary Outcome:** Evaluate the safety and tolerability of viloxazine ER administered with psychostimulants.
- **Secondary Outcomes:**
  - Evaluate the safety and tolerability of AM versus PM dosing of viloxazine ER.
  - Evaluate the efficacy of viloxazine ER administered with psychostimulants.
  - Evaluate the efficacy of AM versus PM dosing of viloxazine ER.
  - Efficacy measures included:
    - ◊ Investigator-rated ADHD-RS-5 (IR-ADHD-RS-5)
    - ◊ Clinical Global Impression-Severity of Illness (CGI-S) scale
    - ◊ Clinical Global Impression-Improvement (CGI-I) scale
    - ◊ Sleep Disturbance Scale for Children (SDSC)
    - ◊ Weekly Parent Rating of Evening and Morning Behavior-Revised (WPREMB-R)
    - ◊ Morning Parent-Rated ADHD-RS-5 (PR-ADHD-RS-5)
    - ◊ Evening Parent-Rated ADHD-RS-5 (PR-ADHD-RS-5)

Viloxazine ER added to ongoing stimulant treatment appeared safe, well tolerated, and provided further efficacy to children and adolescents with ADHD.

Following viloxazine ER addition to psychostimulant therapy, ADHD symptoms (ADHD-RS-5) significantly improved relative to Baseline, starting at Week 1

Figure 2: ADHD-RS-5 Results

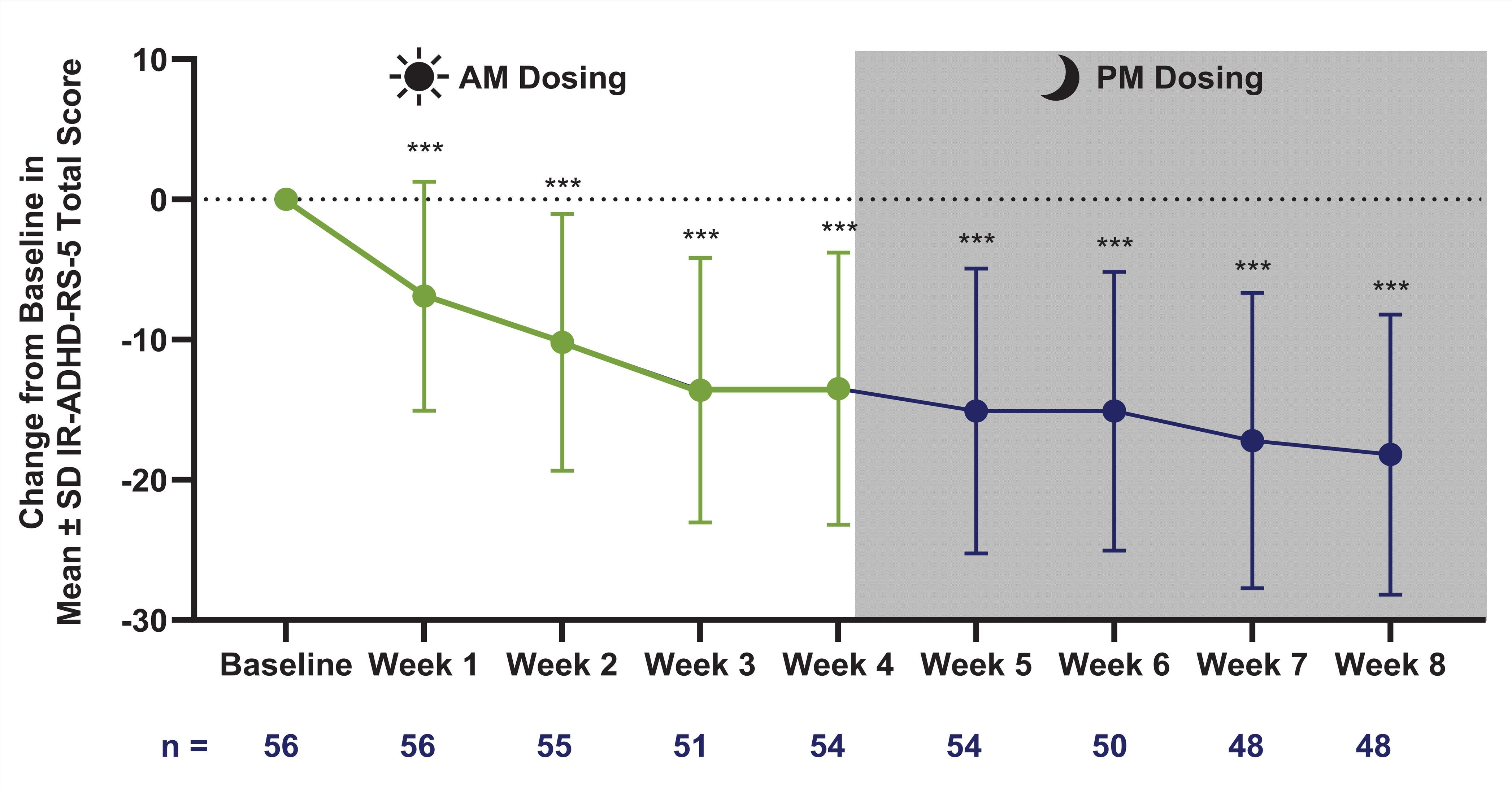


Figure 3: CGI-I Responders (score of 1 or 2, much or very much improved)

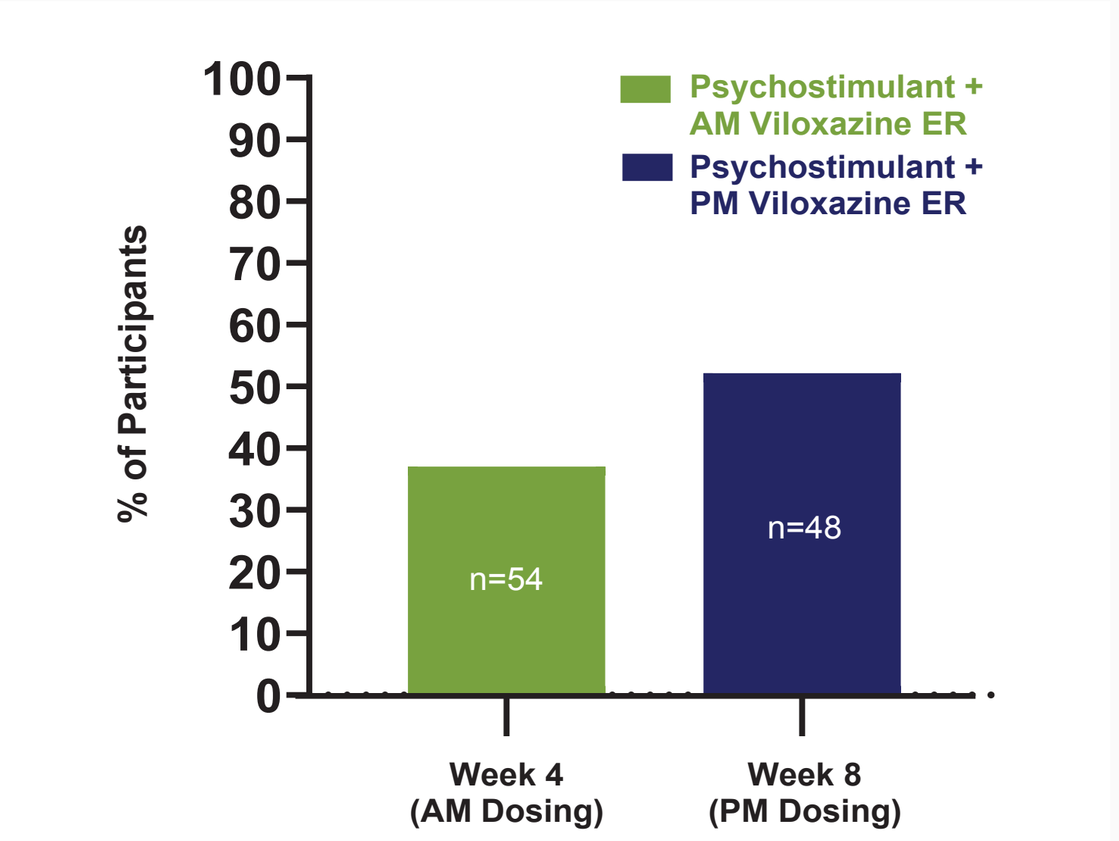


Figure 4: SDSC Total score

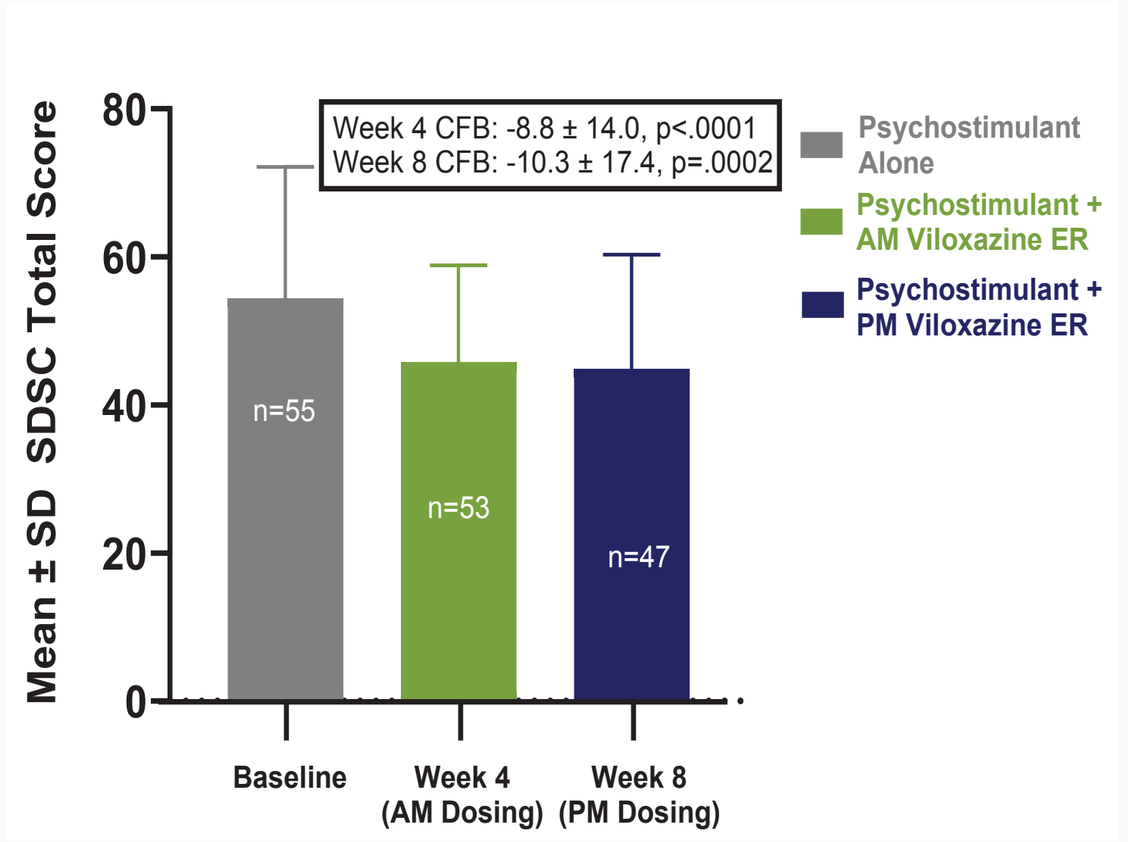


Figure 5: Parent Ratings: Morning Behavior WPREMB-R morning subscale score

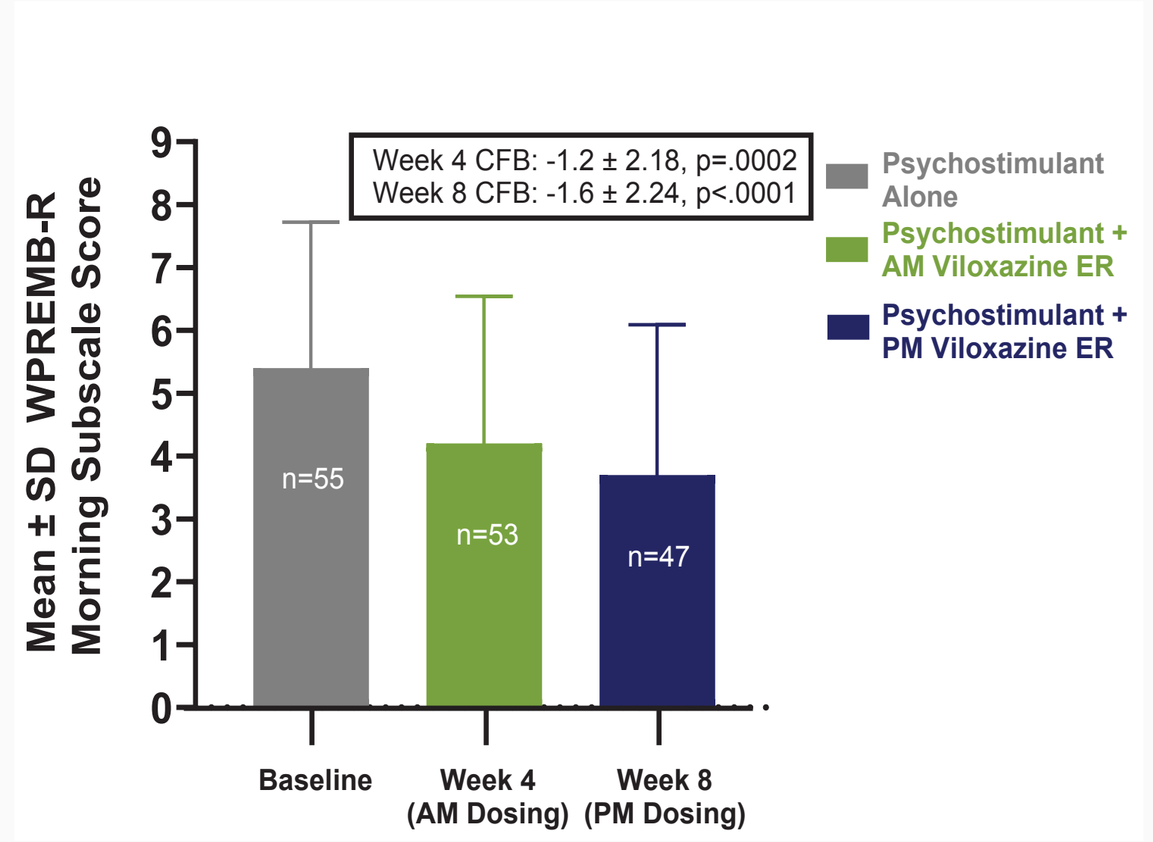
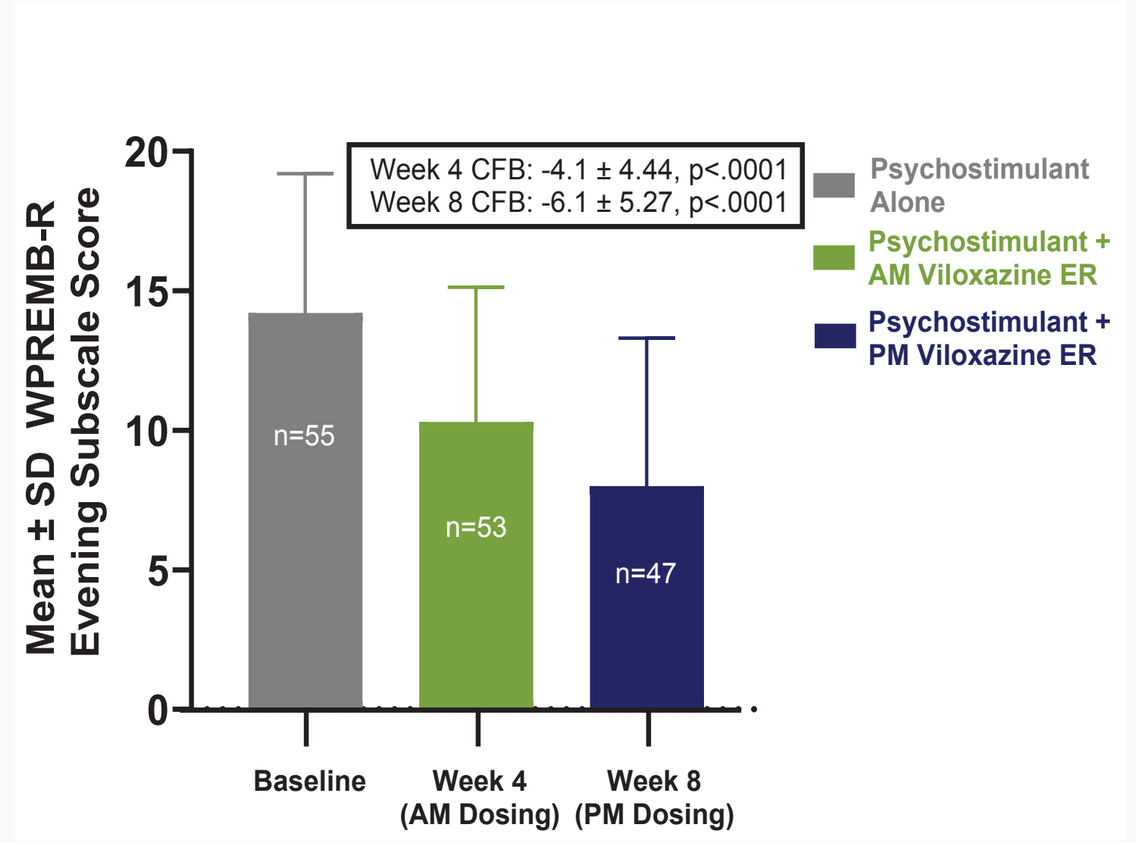


Figure 6: Parent Ratings: Evening Behavior WPREMB-R evening subscale score



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Results

- 56 participants received viloxazine ER. 48 (85.7%) completed the study.
  - 39 (69.6%) were male, 17 (30.4%) female.
  - Roughly half (46.4% vs. 53.6%) were children (6-11 years) and adolescents (12-17 years), respectively.
- Doses at end of study (Week 8) for participants maintained on optimized viloxazine ER for full protocol are shown below:

	Children (6-11 yrs) N=20	Adolescents (12-17 yrs) N=27	Overall N=47
100 mg	60.0%	3.7%	27.7%
200 mg	15.0%	55.6%	38.3%
300 mg	0%	3.7%	2.1%
400 mg	25.0%	14.8%	19.1%
500 mg	0%	0%	0%
600 mg	0%	22.2%	12.8%

Safety:

- Adverse events are shown in **Table 1**.
- BMI and vital signs (sitting position) were, mean ± SD:

	Baseline N=56	Week 8/ End of Study n=48	Change from BL n=48
BMI, kg/m²	19.0 ± 3.6	19.1 ± 3.5	-0.3 ± 0.9
Pulse, bpm	82 ± 11.4	87 ± 11.8	6 ± 11.6
Systolic BP, mmHg	110 ± 8.8	114 ± 9.7	3 ± 8.5
Diastolic BP, mmHg	69 ± 7.5	72 ± 8.5	3 ± 8.6

Table 1: Adverse events (% of participants)

	Weeks 1-4 n=56, (%) AM Dosing	Weeks 5-8 n=50, (%) PM Dosing	Overall n=56, (%)
Any treatment-emergent AE	50.0%	36.0%	55.4%
Any serious AE	0%	0%	0%
Maximum AE severity			
Mild	32.1%	24.0%	32.1%
Moderate	16.1%	12.0%	21.4%
Severe	1.8%	0%	1.8%
Relationship of AE to study medication			
Related	32.1%	16.0%	35.7%
Not Related	17.9%	20.0%	19.6%
AE leading to discontinuation	1.8%	2.0%	3.6%
Adverse Events (≥5% of participants)			
Headache	10.7%	8.0%	17.9%
Insomnia	3.6%	6.0%	8.9%
Upper Respiratory Tract Infection	7.1%	4.0%	10.7%
Nausea	5.4%	0%	5.4%
Decreased Appetite	12.5%	0%	12.5%
Irritability	5.4%	0%	5.4%
Fatigue	1.8%	4.0%	5.4%

AEs are shown based on time period of onset. AEs starting in Weeks 1-4 that persist into Weeks 5-8 are only shown counted in Weeks 1-4.

- Adverse events of tachycardia or blood pressure increase, reported by one patient each, were mild but considered treatment related.
- One patient reported weight decrease as an adverse event.

Efficacy:

- Significant improvement in mean ± SD IR-ADHD-RS-5 scores were seen over Baseline (mean ± SD: 37.2 ± 8.35, n= 56) at all study weeks (**Figure 2**). Scores at Week 8 (PM dosing) were significantly better than scores at Week 4 (AM dosing); however, the extent to which this resulted from time on treatment cannot be determined.
- At Baseline, mean CGI-S scores indicated subjects were moderately ill (mean ± SD: 4.4 ± 0.56, n= 56). At end of study (Week 8), over 50% of participants were rated much or very much improved on the CGI-I scale (**Figure 3**).
- Sleep disturbance scores on the SDSC improved from Baseline (mean ± SD: 54.4 ± 17.75, n= 55) at both Weeks 4 and 8 (**Figure 4**).
- There was a significant reduction in WPREMB-R score after viloxazine ER addition in the morning and evening compared to Baseline (morning mean ± SD: 32.6 ± 12.10, n= 50, evening 33.6 ± 10.50, n=47) (**Figures 5-6**). Differences in Baseline WPREMB-R scores may be due to stimulant effect.

Conclusions

- Use of viloxazine ER as adjunctive therapy with stimulant medications appeared safe and well-tolerated in this 8-week, open-label study of 56 children and adolescents with ADHD.
- Viloxazine ER dosing in combination with stimulants was seen in the full range of monotherapy dosing with 25% of children and 37% of adolescents receiving ≥400 mg/day.
- All parent- and clinician-rated efficacy outcomes (including assessments of morning and evening behaviors and sleep disturbance), showed significant improvement following viloxazine ER adjunctive use with stimulants, including assessments at Week 1.
- Viloxazine ER given once-daily in either AM or PM appeared safe and effective as adjunctive treatment to AM stimulant medication.
- Limitations include: no placebo control, open-label design, no wash-out period, one-way crossover of AM to PM dosing, no attempt to reduce stimulant after addition of viloxazine ER.

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- KH, KA, IY, JE, and JR are employees of Supernus Pharmaceuticals, Inc.
- AC has received research support from, served as a consultant or speaker for or 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., US Food and Drug Administration, NLS Pharma, and Jazz.

For questions about these data, contact Supernus Medical Affairs at medinfo.supernus@apcerls.com