

# Clonidine Extended-Release Tablets for the Treatment of ADHD in Children and Adolescents With Inadequate Response to Stimulants

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## INTRODUCTION

- Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric and neurobehavioral disorder in children that may impair social and academic functioning<sup>2</sup>
- In 2007, the American Academy of Child and Adolescent Psychiatry Work Group recommended treatment of ADHD with stimulants (ie, agents in the methylphenidate and amphetamine classes) and atomoxetine,<sup>1</sup> but some patients may have an inadequate response or intolerability to these medications<sup>1,3</sup>
- Addition of an alpha<sub>2</sub>-adrenergic agonist nonstimulant to a stimulant regimen may improve response and tolerability<sup>1,4,5</sup>
- For many years, immediate-release clonidine has been the predominant alpha<sub>2</sub>-adrenergic agonist used alone or in combination with stimulants for the treatment of ADHD in children and adolescents<sup>1,4</sup>; however, its pharmacokinetic properties (ie, large peak-and-trough fluctuations in plasma concentration) deterred its widespread use
- Clonidine hydrochloride extended-release tablets (CLON-XR; Shionogi Inc, Florham Park, NJ) were developed to modify the absorption of the active drug by reducing the peak plasma concentration and prolonging the time to reach maximum plasma concentration<sup>6,7</sup>
- CLON-XR was approved recently by the US Food and Drug Administration as monotherapy or as combination therapy with stimulants for the treatment of core ADHD symptoms<sup>8</sup>
- We present results from the phase 3 clinical development study of CLON-XR used in combination with stimulants for the treatment of children and adolescents with combined- or hyperactive-type ADHD who had an inadequate response to stimulant therapy

## OBJECTIVE

- To evaluate the efficacy and safety of flexible-dose CLON-XR 0.1 to 0.4 mg/d as adjunctive therapy to a stable regimen of stimulant medication compared with stimulant medication alone for the treatment of children and adolescents with ADHD

## METHODS

- Patients aged 6 to 17 years with a diagnosis of ADHD received flexible-dose CLON-XR (0.1-0.4 mg/d; doses >0.1 mg/d administered twice daily) or placebo in combination with marketed stimulants (ie, medications in the methylphenidate or amphetamine classes) without regard to food consumption for 8 weeks
  - Patients were required to have had an inadequate response to stimulant medication as measured by the ADHD Rating Scale-IV (ADHD-RS-IV; total score ≥26) after a minimum of 4 weeks on a stable stimulant regimen
  - Patients were excluded from participation in the study if they had a current diagnosis or history of a psychiatric disorder that required psychotropic medication; severe comorbid mental, learning, or personality disorders; or a history of conduct disorder, syncopal episodes, or nonfebrile seizures
- CLON-XR and stimulant doses could be titrated (ie, flexible dosing) to achieve an optimal efficacy and safety profile for each patient
  - When necessary to achieve optimal efficacy, CLON-XR was escalated by 0.1 mg/d/wk
- CLON-XR was flexibly dosed by 0.1 mg/d/wk to produce an optimal efficacy and safety profile for each patient, as determined by the investigator
  - Dose was optimized during weeks 1 through 3, maintained during weeks 4 and 5, and tapered by 0.1 mg/d/wk after week 5 if necessary to achieve a 0.1-mg/d dose at week 8

- The primary efficacy endpoint was mean change in ADHD-RS-IV total score from baseline to week 5 versus stimulant alone using the last observation carried forward method for patients who discontinued early
- Secondary efficacy endpoints included improvement in scores from baseline to week 5 on the investigator-completed ADHD-RS-IV inattention and hyperactivity/impulsivity subscales, the Conners' Parent Rating Scale-Revised: Long Form (CPRS-R) total score and hyperactivity and oppositional subscales, the Parent Global Assessment (PGA) scale, and the investigator-rated Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) scales
- Effect size was calculated post hoc based on the observed mean differences between the groups and the observed standard deviations using the unbiased version of Hedges' *g*
- Safety data (eg, adverse events, vital signs, and electrocardiograms) were collected at baseline and throughout the study (ie, through week 8, including the 3-week, dose-tapering phase) from the defined safety population (ie, all patients who received ≥1 dose of study medication)

## RESULTS

### Patient disposition

- Of 243 patients evaluated for inclusion in the study, 198 were randomized to receive CLON-XR plus stimulant (CLON-XR + STM; n=102) or placebo plus stimulant (PBO + STM; n=96)
  - One patient in the PBO + STM group for whom there were no postbaseline assessments was not included in the intention-to-treat population
- Demographics were similar among patients in both treatment groups (Table 1)
  - Most enrollees (77%) were pediatric patients between the ages of 6 and 12 years
  - The majority of patients (68%) received CLON-XR 0.3 mg/d at week 5

**Table 1. Patient Demographics and Characteristics (ITT Population)**

Parameter	Patients (N=197)	
	PBO + STM (n=95)	CLON-XR + STM (n=102)
Age, mean (range), y	10 (6-16)	10 (6-17)
Age category, n (%)		
6-12 y	75 (79)	77 (76)
>12-17 y	20 (21)	25 (24)
Gender, n (%)		
Male	66 (70)	79 (78)
Female	29 (30)	23 (22)
Weight, mean (range), kg	39 (20-77)	40 (19-113)
ADHD-RS-IV total score, mean (range)	39 (26-54)	39 (26-53)

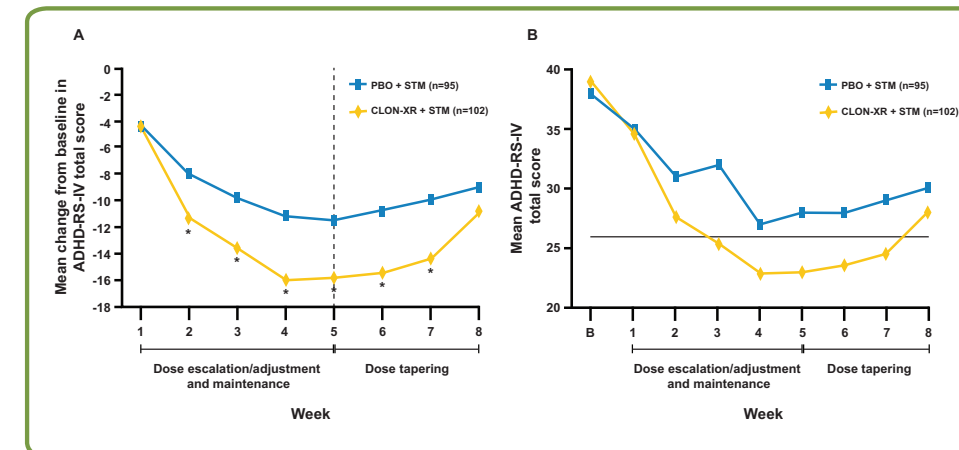
ADHD-RS-IV, Attention-Deficit/Hyperactivity Disorder Rating Scale-IV; CLON-XR, clonidine hydrochloride extended-release tablets; ITT, intention-to-treat; PBO, placebo; STM, stimulant.

- A greater percentage of patients receiving CLON-XR + STM (89%) completed the treatment and tapering phases of the study (ie, weeks 1-8) than patients receiving PBO + STM (77%)

### Efficacy

- At week 5 (ie, primary efficacy endpoint), CLON-XR + STM was associated with a statistically significant improvement from baseline in ADHD-RS-IV total score compared with PBO + STM (difference of -4.48 [95% confidence interval, -7.83 to -1.13]; *P*=0.009) (Figure A)
  - Statistically significant improvements in ADHD-RS-IV total score began at week 2 and continued through week 7 (Figure A)
  - Statistically significant improvements from baseline also were observed in the inattention (*P*=0.017) and hyperactivity/impulsivity (*P*=0.014) subscale scores of the ADHD-RS-IV scale

- Mean ADHD-RS-IV total score of <26 was achieved with CLON-XR + STM at weeks 3 through 7 but not with PBO + STM (Figure B)



**Figure.** Mean change in ADHD-RS-IV total score from baseline (A) and mean ADHD-RS-IV total score during the study (B) in the ITT population. ADHD-RS-IV, Attention-Deficit/Hyperactivity Disorder Rating Scale-IV; B, baseline; CLON-XR, clonidine hydrochloride extended-release tablets; ITT, intention-to-treat. PBO, placebo; STM, stimulant. \**P*<0.05. Dashed line indicates the primary efficacy endpoint. Solid black line indicates ADHD-RS-IV total score of 26.

- The overall effect size for CLON-XR + STM versus PBO + STM with respect to ADHD-RS-IV total score was 0.34
- Results of analyses of secondary efficacy endpoints are presented in Table 2

**Table 2. Improvement in Secondary Efficacy Endpoints From Baseline to Week 5 (ITT Population)**

Efficacy assessment	PBO + STM (n=95)	CLON-XR + STM (n=102)	<i>P</i> value
CPRS-R, mean (SD)			
Total score	-27.1 (38.2)	-40.2 (41.4)	0.017
Hyperactivity subscale	-3.8 (5.7)	-5.8 (6.5)	0.017
Oppositional subscale	-3.6 (6.3)	-5.1 (6.6)	0.062
CGI-S, mean (SD)	-1.2 (1.3)	-1.5 (1.2)	0.021
CGI-I, mean (SD)	3.0 (1.2)	2.5 (1.2)	0.006
PGA, mean (SD)	3.4 (1.4)	2.7 (1.3)	0.001

CGI-I, Clinical Global Impression of Improvement; CGI-S, Clinical Global Impression of Severity; CLON-XR, clonidine hydrochloride extended-release tablets; CPRS-R, Conners' Parent Rating Scale-Revised: Long Form; ITT, intention-to-treat; PBO, placebo; PGA, Parent Global Assessment; SD, standard deviation; STM, stimulant.

### Safety

- Rates of treatment-emergent adverse events (TEAEs) were similar between treatment groups (45% and 41% for CLON-XR + STM and PBO + STM; Table 3)
  - Median time to onset of somnolence and fatigue with CLON-XR + STM was during the first 2 weeks of therapy, and median duration of these symptoms was 19 days

**Table 3. Treatment-Emergent Adverse Events With ≥5% Incidence in the CLON-XR + STM Group and at Least Twice the Incidence of the PBO + STM Group (Safety Population)**

TEAE, n (%)	PBO + STM (n=96)	CLON-XR + STM (n=102)
Somnolence	8 (8)	20 (20)
Fatigue	4 (4)	16 (16)
Increased body temperature	2 (2)	5 (5)
Dizziness	2 (2)	5 (5)

CLON-XR, clonidine hydrochloride extended-release tablets; PBO, placebo; STM, stimulant; TEAE, treatment-emergent adverse event.

- At the end of treatment, 4 patients in the PBO + STM group had discontinued because of a TEAE (increased heart rate [n=1], aggression [n=2], and somnolence [n=1]), and 1 patient in the CLON-XR + STM group had discontinued because of a TEAE (bradycardia)
- Alterations in blood pressure and electrocardiographic parameters at week 4 or 5 are provided in Table 4

**Table 4. Mean Change from Baseline in Blood Pressure and ECG Parameters (Safety Population)**

Parameter	PBO + STM (n=96)	CLON-XR + STM (n=102)
Heart rate, bpm (range) <sup>a</sup>	0.9 (-33 to 38)	-4.9 (-40 to 22)
SBP, mm Hg (range) <sup>a</sup>	1.1 (-28 to 56)	-3.5 (-35 to 25)
DBP, mm Hg (range) <sup>a</sup>	1.2 (-24 to 28)	-0.9 (-33 to 21)
QTcF interval, msec (range) <sup>b</sup>	1.4 (-31.0 to 31.5)	3.2 (-39.0 to 58.5)

CLON-XR, clonidine hydrochloride extended-release tablets; DBP, diastolic blood pressure; ECG, electrocardiographic; PBO, placebo; QTcF, QT interval corrected using Fridericia's formula; SBP, systolic blood pressure; STM, stimulant. <sup>a</sup>At week 5. <sup>b</sup>At week 4.

## DISCUSSION AND CONCLUSIONS

- In this flexible-dose trial of children and adolescents with ADHD who had an inadequate response to stimulant monotherapy, CLON-XR (total daily dose of 0.1-0.4 mg/d; doses >0.1 mg/d administered twice daily) as adjunctive therapy to a stimulant regimen significantly improved core ADHD symptoms (ie, overall symptoms, inattention, and hyperactivity) compared with stimulant treatment alone
  - The improvement in ADHD-RS-IV total score and the effect size of CLON-XR + STM demonstrate an incremental benefit of combination therapy in pediatric patients with ADHD who have an inadequate response to stimulants
- During the majority of the study period (ie, weeks 3 through 7), more patients receiving CLON-XR + STM had an ADHD-RS-IV total score of <26 than patients receiving stimulants alone
- Safety data suggest that the addition of CLON-XR (0.1-0.4 mg/d) to a stimulant regimen is generally well tolerated
  - Overall completion rate was higher with CLON-XR than with placebo when administered with stimulants
  - Occurrence of TEAEs was lower with CLON-XR in combination with stimulants than with stimulants alone
  - Most common TEAEs with CLON-XR + STM were somnolence, fatigue, increased body temperature, and dizziness
- The occurrence of TEAEs with CLON-XR + STM was lower than that previously reported with CLON-XR monotherapy,<sup>8</sup> suggesting that combination therapy lessens the potential for TEAEs
- No patient discontinued CLON-XR + STM therapy because of somnolence or fatigue
  - Most incidences of somnolence and fatigue with CLON-XR + STM developed during dose titration and were of limited duration
- CLON-XR is an effective and well-tolerated adjunctive therapy that can be used to optimize response in pediatric patients with ADHD who have less-than-satisfactory improvement with stimulants

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