CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-331
Priority or Standard	S
Submit Date(s)	09-30-2009
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Division / Office	Division of Psychiatry Products
Reviewer Name(s)	Maju Mathews, MD
Review Completion Date	07/15/2010
Established Name	Clonidine hydrochloride
(Proposed) Trade Name	(b) (4) Clonicel
Therapeutic Class	Alpha-2-adrenergic agonist
Applicant	Shinoga
Formulation(s)	0.1 mg & 0.2 mg
Dosing Regimen	BID
Indication(s)	ADHD
Intended Population(s)	Children and Adolescents

Template Version: March 6, 2009

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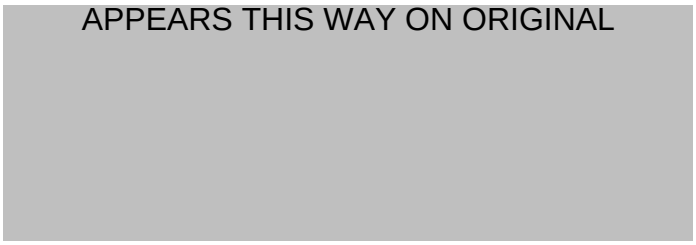
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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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Clonidine in the treatment of Attention Deficit-Hyperactivity Disorder (ADHD) in children and adolescents (ages 6-17 years-old). Studies CLON-301 and 302 were adequate and well-controlled trials that demonstrated the efficacy of Clonidine, as measured by the change in mean Attention Deficit-Hyperactivity Disorder Rating Scale- IV (ADHD-RS-IV) scores. There was a statistically and clinically significant difference in the treatment effect of Clonidine compared to placebo in both trials.

In my opinion, treatment with Clonidine was reasonably safe and well tolerated in the trials.

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1.2 Risk Benefit Assessment

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

The safety profile of TRADENAME is comparable to clonidine, a marketed oral formulation for hypertension. No new safety concerns were identified during the review. Risk Evaluation and Mitigation Strategies are not required at this time.

The sponsor should conduct a dedicated, thorough QT study of clonidine in healthy adult subjects.

1.4 Recommendations for Postmarket Requirements and Commitments

The sponsor has studied the safety and efficacy of Clonidine in the treatment of ADHD in two short term studies. However, ADHD is a chronic condition and patients are on medications for long periods of time, running into years.
The sponsor should conduct a placebo-controlled maintenance trial to assess the long term efficacy and safety of Clonidine in children and adolescents with ADHD. This should probably be a placebo-controlled randomized withdrawal study.

2 Introduction and Regulatory Background

2.1 Product Information

Clonidine is a centrally acting alpha2 adrenergic agonist and has been used effectively to treat mild to moderate hypertension. Clonidine is currently approved in the US in 3 formulations: immediate release, transdermal patch, and epidural injection. Clonidine was approved for the treatment of hypertension as Jenloga on September 29 2009. Jenloga is a patented oral dose, modified release formulation of clonidine hydrochloride. The modified release formulation is achieved by (b) (4) (b) (4)

In addition to hypertension, clonidine has been evaluated and used extensively off label for several other indications including attention deficit hyperactivity disorder (ADHD), alcohol withdrawal, atrial fibrillation, tic disorders, menopausal flushing, smoking cessation and ulcerative colitis.

The mechanism of action of clonidine in ADHD is thought to be related to a reduction of norepinephrine turnover in the central nervous system. A dysfunction of the adrenergic system may lead to a disruption of the inhibitory control functions of the prefrontal cortex

which could lead to the deficit in behavioral inhibition characteristic of ADHD. Clonidine may restore inhibitory control by regulating noradrenergic function.

2.2 Currently Available Treatments for Proposed Indications

The mainstays of approved treatment for ADHD have been the stimulants, methylphenidate and amphetamines. Included in this category are dexmethylphenidate, dextroamphetamine, methamphetamine, and amphetamine single and mixed salts. As listed below, there are numerous immediate-release and extended-release formulations of stimulants available for the treatment of ADHD. Atomoxetine (Strattera) is a non-stimulant drug approved for the treatment of ADHD. It is a selective norepinephrine reuptake inhibitor. Guanfacine, like clonidine is is an α_{2A}-adrenergic receptor agonist.

Available Treatments for ADHD

- Adderall (mixed salts of a single entity amphetamine product) Tablets
- Adderall XR (mixed salts of a single entity amphetamine product) Extended-Release Capsules
- Concerta (methylphenidate hydrochloride) Extended-Release Tablets
- Daytrana (methylphenidate) Transdermal System
- Desoxyn (methamphetamine HCl) Tablets
- Focalin (dexmethylphenidate hydrochloride) Tablets
- Focalin XR (dexmethylphenidate hydrochloride) Extended-Release Capsules
- Metadate CD (methylphenidate hydrochloride) Extended-Release Capsules
- Methylin (methylphenidate hydrochloride) Oral Solution
- Methylin (methylphenidate hydrochloride) Chewable Tablets
- Ritalin (methylphenidate hydrochloride) Tablets
- Ritalin SR (methylphenidate hydrochloride) Sustained-Release Tablets
- Ritalin LA (methylphenidate hydrochloride) Extended-Release Capsules
- Strattera (atomoxetine HCl) Capsules
- Vyvanase (lisdexamfetamine: a pro-drug of amphetamine)
- Intuniv (guanfacine)

Although not approved for the indication, several other drugs that are thought to be

effective in treating some patients with ADHD. These include (b) (4)

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2.3 Availability of Proposed Active Ingredient in the United States

Clonidine is an approved drug to treat hypertension. The active ingredients for this drug are available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

The most important safety issue related to this study drug is symptomatic sinus Bradycardia and hypotension. Other safety issues include somnolence, headache, fatigue, and dizziness.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The sponsor had a Pre-IND meeting with the FDA on January 16, 2007. It was agreed that a 505(b)(2) application could be submitted for this application. It was also conveyed to the sponsor that two positive studies in ADHD would be needed. In addition, it was also conveyed that it would be necessary to have some open-label safety experience under conditions of usual use, which may include combination with stimulants.
On March 9, 2009, the sponsor had a Pre-NDA meeting with the Agency. At this meeting, it was agreed that the studies conducted by the sponsor were adequate to file for an NDA.

2.6 Other Relevant Background Information

No other relevant background information is available.

3 Ethics and Good Clinical Practice

3.1 Submission Quality and Integrity

The quality of submission was adequate.

A clinical inspection summary was provided by Dr Anthony Orencia, MD on April 30, 2009. The conclusions of the inspection are as follows:

Four U.S. clinical investigator sites, two per study protocol, were inspected in support of this application, for Protocols CLON-301 (monotherapy indication) and CLON-302 (addon therapy indication), respectively, with the proposed indication of symptomatic treatment of adolescents with Attention Deficit/Hyperactivity Disorder. No discrepancies were noted with the data listings provided in the NDA and source documents. Inspection findings documented general adherence to Good Clinical Practices regulations governing the conduct of clinical investigations. Data appear acceptable for the proposed indication.

DSI also sent a note to the review division dated 5/18/10, signed by Branch Chief Tejashri Purohit-Sheth, M.D, which stated that

Research sub-investigators, not listed on the Form FDA Form 1572 "Statement of Investigator" conducted research investigations. Another inspectional finding was the lack of dose titration (e.g., up titration, or static drug dosing) for the investigational drug by patient's responsible guardian, per protocol dose schedules. This was an isolated occurrence, and noted in only one subject.

It was concluded these non-critical regulatory deficiencies were considered unlikely to impact patient welfare and safety, and data integrity. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3.2 Compliance with Good Clinical Practices

The sponsor states that the studies were conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines (ICH) and all applicable regulations. Compliance with these regulations and guidelines also constituted compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study was also carried out in accordance with local legal requirements. The study protocol, all protocol amendments, and the Informed Consent Form (ICF) were reviewed and approved by the central Institutional Review Board (IRB) prior to study initiation.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

A review done by Clinical Pharmacology concluded that clonidine is associated with a higher incidence of somnolence but there was no dose response relation due to titration design. Decreases in blood pressure were also noted. Combination therapy resulted in a 44% increase in clonidine exposure with amphetamines and 11% decrease with methylphenidate. Children greater than 50 kg showed less response to clonidine because of larger placebo effect.

4.1 Chemistry Manufacturing and Controls

Please see review.

4.2 Clinical Microbiology

None

4.3 Preclinical Pharmacology/Toxicology

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4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Clonidine is a centrally acting alpha2 adrenergic agonist that has been used effectively to treat mild to moderate hypertension. Clonidine is not a central nervous system stimulant.It has a different mechanism of action than most other antihypertensive agents.

Clonidine has been evaluated and used extensively off label for several other indications, including attention deficit hyperactivity disorder (ADHD). The mechanism of action of clonidine in ADHD is thought to be related to a reduction of norepinephrine turnover in the central nervous system. A dysfunction of the adrenergic system may lead to a disruption of the inhibitory control functions of the prefrontal cortex which could lead to the deficit in behavioral inhibition characteristic of ADHD. By regulating noradrenergic function, clonidine may restore inhibitory control and possibly improve attention and learning.

4.4.2 Pharmacodynamics

With immediate-release clonidine, blood pressure declines within 30 to 60 minutes after an oral dose with the maximum decrease occurring within 2 to 4 hours. Renal blood flow and glomerular filtration rate remain essentially unchanged. Normal postural reflexes

are intact; therefore, orthostatic symptoms are mild and infrequent. There is also a reduction (15% to 20%) of cardiac output in the supine position with no change in the peripheral resistance. During long-term therapy, cardiac output tends to return to control values, while peripheral resistance remains decreased. Slowing of the pulse rate has been observed in most patients given clonidine, but the drug does not alter normal hemodynamic response to exercise.

Studies in patients taking immediate-release clonidine have provided evidence of a reduction in plasma renin activity and in the excretion of aldosterone and catecholamines. The exact relationship of these pharmacologic actions to the antihypertensive effect of clonidine has not been fully elucidated.

Clonidine acutely stimulates growth hormone release in both children and adults, but does not produce a chronic elevation of growth hormone with long-term use.

4.4.3 Pharmacokinetics

Following oral administration of TRADENAME, peak clonidine levels are reached in 4 to 7 hours, and the plasma half-life averages 13 hours. The absorption of clonidine from TRADENAME is not affected by food. Following oral administration of the immediate-release formulation, about 40-60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours and about 50% of the absorbed dose is metabolized in the liver.

The half-life of clonidine from the immediate-release formulation increases up to 41 hours in patients with severe impairment of renal function. Although studies of the effect of renal impairment and studies of clonidine excretion have not been performed with TRADENAME, results are likely to be similar to those of the immediate-release formulation.

The peak to trough ratio (Cmax/Cmin) of clonidine, following repeat dosing with TRADENAME ranges from 1.4 to 1.5. The plasma concentrations of clonidine increased proportionately with increase in dose over 0.1 mg – 0.6 mg twice daily.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1: Table of Studies Conducted

CLON-301	A phase III, dose response evaluation of the efficacy and safety of TRADENAME® (clonidine HCl sustained release) vs. placebo in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD)
CLON-302	A phase III evaluation of the efficacy and safety of TRADENAME® (clonidine HCl sustained release) as add-on to psychostimulant medication vs. psychostimulant medication alone in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD)
CLON-303	An open-label, chronic exposure evaluation of the safety of TRADENAME® (clonidine HCl sustained release) in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD)

5.2 Review Strategy

For efficacy, studies CLON-301 and CLON-302 were reviewed. To evaluate safety, CLON-301, 302, and 303 were reviewed. Data from the studies were not pooled as the design of the studies were different and this reviewer did not feel that it was appropriate to pool these studies.

A listing of items examined during the course of this review is provided in the table below.

Table 2: Listing of Items reviewed

Submission date	Items Reviewed
09/30/2009	• Clinical Study Reports CLON-301,

	CLON-302, CLON-303 • Application Summary • Proposed Labeling • Financial Disclosure Information • Case Report Forms

5.3 Discussion of Individual Studies/Clinical Trials

A detailed discussion of each individual study is under the review of efficacy.

6 Review of Efficacy

A. STUDIES PERTINENT TO ADHD CLAIM

Rationale for Selection of Studies for Review

The sponsor has submitted results of two studies to support efficacy. Both of them will be reviewed under this section:

Study Summaries

Study 1: CLON-301: A phase III, dose response evaluation of the efficacy and safety of Clonidine vs. placebo in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD).

The study was conducted from 22nd October 2007 to 6th August 2008 in 15 centres across the United States. A total of 19 investigators participated in the study.

Methods/Study Design/Analysis Plan: This is a 5-week (8-week total, including taper down period), multicenter, parallel-group, randomized, double-blind, placebo controlled

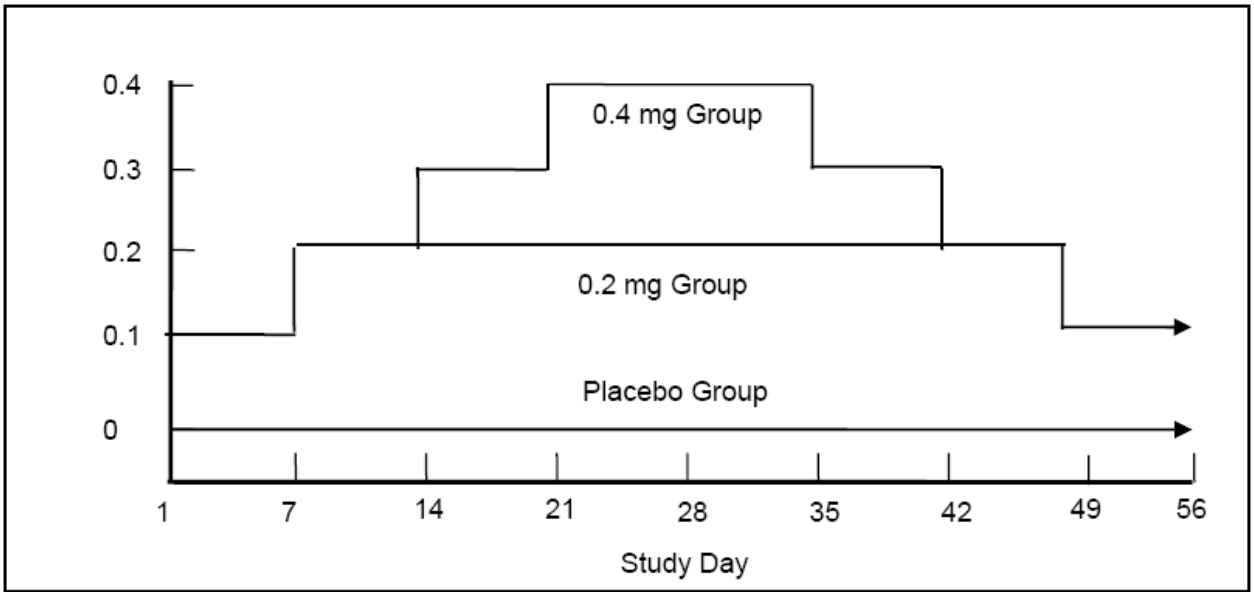
study of the efficacy and safety of two dosing regimens of clonidine in children and adolescents (6 to 17 years) who meet DSM-IV criteria for ADHD.

A total of 236 male and female subjects were randomly assigned to one of the following three treatment groups: clonidine (CLON) 0.2 mg/day (N=78), CLON 0.4 mg/day (N=80), or placebo (N=78). Dosing for the CLON groups started at 0.1 mg/day and a proper titration schedule was used to escalate subjects to their respective fixed dose. Subjects were maintained at their dose level for a minimum period of 2 weeks before being gradually tapered down to 0.1 mg/day at the last week of treatment. Treatment was discontinued for subjects who could not tolerate their assigned dose.

Prior to initiating the 8-week treatment period, subjects completed a screening period of up to 2 weeks during which all screening assessments were performed and any current ADHD treatments discontinued. During the treatment period, subjects returned to the investigative site weekly to complete efficacy and safety assessments. Subjects discontinued study medication at the Week 8 visit but returned for a closeout safety visit one week later.

Subjects who could benefit from continued treatment with clonidine and desired to do so were offered participation in an open-label follow-on study designed to gather additional efficacy and safety data on clonidine.

Figure 1: Study Design of CLON-301



Important Inclusion Criteria:

- Male or female between 6 and 17 years of age, inclusive
- Diagnosis of ADHD of the hyperactive or combined inattentive/hyperactive subtypes according to DSM-IV criteria
- Minimum score of 26 on the ADHDRS-IV questionnaire at Baseline
- General good health as judged by the Principal Investigator
- Body mass index ≥ 5th percentile of the subject's age group according to the CDC growth chart. BMI was calculated using the formula: weight (kg) / [height (m)]$_2$
- Ability to swallow tablets
- General IQ ≥ 80 as judged by the Principal Investigator
- Subject as well as parent/guardian able to sign informed assent or consent form.

Important Exclusion Criteria

- Females who were pregnant or lactating or who did not agree to use an acceptable form of birth control.
- Presence of clinically significant illness or abnormality on physical examination or clinical laboratory investigations or ECG's.
- History or presence of concomitant psychiatric disorder, conduct disorder, seizures, syncopal episodes, presence of drug or alcohol abuse or positive drug screen with the exception of ADHD drugs.

Efficacy:

The primary efficacy variable was the comparison between treatment groups on change in scores from Baseline to the Week 5 measure (or discontinuation measure if earlier than Week 5) of the Attention Deficit Hperactivity Disorder rating Scale (ADHDRS-IV) scale total score using a "Last Observation Carried Forward (LOCF)" analysis.

Secondary efficacy variables included:

• Conners' Parent Rating Scale Revised: Long Form (CPRS-L)
• Sleep Self Report questionnaire – Child's Form (SSR-CF)
• Horacek Adrenergic Dysregulation Scale (HADS)
• Clinical Global Impressions-Severity (CGI-S)
• Clinical Global Impressions-Improvement (CGI-I)
• Parent Global Assessment (PGA)

None of the above endpoints was prespecified as a key secondary endpoint.

Results

Demographics

The demographic characteristics were similar across the three treatment groups. No significant differences between the groups were noted. The majority were male (72.4%)

and white (59.2%). Mean subject age was 9 years and most subjects were 6-12 years of age. Mean body weight was 41.1 kg.

Table 3: Demographic characteristics-ITT subjects

Summary	Treatment Group			All Subjects	P-Value [1]
	Clonicel 0.2 mg	Clonicel 0.4 mg	Placebo		
ITT Subjects	74	78	76	228	
Gender					
Male	58 (78.4%)	55 (70.5%)	52 (68.4%)	165 (72.4%)	0.3589
Female	16 (21.6%)	23 (29.5%)	24 (31.6%)	63 (27.6%)	
Age (years)					
N	74	78	76	228	0.8988
Mean (Std)	9.6 (2.94)	9.4 (2.89)	9.4 (2.86)	9.4 (2.89)	
Median	9.0	9.0	8.5	9.0	
Min, Max	6.0, 17.0	6.0, 17.0	6.0, 16.0	6.0, 17.0	
Age					
6-12 Years	61 (82.4%)	65 (83.3%)	62 (81.6%)	188 (82.5%)	
>12-17 Years	13 (17.6%)	13 (16.7%)	14 (18.4%)	40 (17.5%)	
Race					
White	45 (60.8%)	46 (59.0%)	44 (57.9%)	135 (59.2%)	0.9889
Black/African American	19 (25.7%)	20 (25.6%)	23 (30.3%)	62 (27.2%)	
Hispanic or Latino	6 (8.1%)	7 (9.0%)	6 (7.9%)	19 (8.3%)	
Other	4 (5.4%)	5 (6.4%)	3 (3.9%)	12 (5.3%)	
Weight (kg)					
N	74	78	76	228	0.5202
Mean (Std)	40.8 (20.59)	40.1 (18.33)	42.3 (17.83)	41.1 (18.87)	
Median	33.7	34.4	36.9	34.8	
Min, Max	20.8, 128.7	17.0, 106.1	20.4, 90.9	17.0, 128.7	

Reviewer's Comments: As can be seen from the table above, the sex distribution was unequal, with over 2/3rd of the study subjects being males. The age group was also unequally distributed, with there being over four times the number of subjects in the 6-12 years age group compared to those in the 12-17 year group. This is not surprising as ADHD is more commonly diagnosed in younger boys. This reviewer feels that the sex and age distribution reflects the population distribution of patients who suffer from this condition. I do not believe that this affects the generalizability of the results of the study.

Patient Disposition

A total of 292 subjects were screened. Of these, 236 were randomly assigned to the study treatments. Six of the 236 randomized were withdrawn from the study shortly after randomization before taking the study medication; therefore, a total of 230 subjects were included in the safety population (76 in 0.2 mg/day, 78 in the 0.4 mg/day and 76 in

the placebo group). Two of the 230 subjects received at least one dose of the study drug but had no post-baseline measurements (One of them withdrew consent and one was lost to follow up).

Overall, the majority of subjects (60.6%) completed the treatment phase. A larger proportion of subjects completed the treatment phase in the CLON 0.2 mg/day group (69.2%) compared with the CLON 0.4 mg/day (60%) and placebo (52.6%).

Table 4: Patient Disposition in Study CLON-301

	CLON 0.2 mg	CLON 0.4 mg	Placebo	Total
All Randomized	78	80	78	236
Safety Population	76	78	76	230[1]
ITT for Efficacy	74	78	76	228[2]
Completed Treatment Phase	54 (69.2%)	48 (60.0%)	41 (52.6%)	143 (60.6%)
Withdrawn	24 (30.8%)	32 (40.0%)	37 (47.4%)	93 (39.4%)
Withdrew Consent	4 (5.1%)	3 (3.8%)	2 (2.6%)	9 (3.8%)
Adverse Event	5 (6.4%)	15 (18.8%)	1 (1.3%)	21 (8.9%)
Lack of Efficacy	7 (9.0%)	9 (11.3%)	25 (32.1%)	41 (17.4%)
Lost to Follow-Up	6 (7.7%)	2 (2.5%)	4 (5.1%)	12 (5.1%)
Protocol Violation	0	2 (2.5%)	2 (2.6%)	4 (1.7%)
Other	2 (2.6%)	1 (1.3%)	3 (3.8%)	6 (2.5%)
Completed Safety Follow-up	66 (84.6%)	68 (85.0%)	64 (82.1%)	198 (83.9%)

Concomitant Medication Use

During Clon-301, 27 subjects received a concomitant medication that was restricted in the protocol. Of these, 18 received a sedating antihistamine, 8 received bronchodilators, 4 received psychotropics and 2 got oral steroids.

Of the four subjects who received psychotropics, 1 received Lortab, 2 received phenergan and 1 received methylphenidate while tapering off study medication.

Reviewer's Comments: I do not think this affected study results…..

Important Protocol Violations

Entry Criteria Violations

Three subjects in the placebo group and two subjects in the CLON 0.2 mg/day group did not meet all entry criteria and were granted an exception by the sponsor for study enrollment.

Study Drug Dispensing error

One subject in the Clon 0.4 mg/day treatment group received an extra week of treatment due to a dispensing error.

Other protocol deviations

At one site during the study, the ADHDRDS-IV rating scale was mistakenly completed by a parent rather than the PI at the screening, baseline, and week 1 visits for subjects 0701, 0702, 0703 and 0704. This deviation was noted and documented in the CRF comment log.

Measurement of Treatment Compliance

Treatment compliance for each subject was determined by counting the number of pills taken from the blister packs in conjunction with patient report of dosing compliance; this was conducted at every scheduled visit. Treatment compliance was similar across the three treatment groups. Based on pill counts in conjunction with patient report of dosing, compliance ranged from 93.5% to 94.6% across the three treatment groups and was 94.0% for the overall study population.

Compliance with regard to completion of study visits was similar across the three treatment groups through Week 4. Greater than 83% of subjects in each of the three treatment groups completed study visits through Week 4, and greater than 66% of subjects in each of the three treatment groups completed study visits through Week 5. Approximately 63% of all subjects completed study visits through Week 8. The highest compliance was observed in the CLON 0.2 mg/day treatment group, having 71.6% of subjects complete through Week 8 compared with 62.8% in the CLON 0.4 mg/day and 53.9% in the placebo treatment groups.

Dosing

The 0.2 and 0.4 mg/day doses chosen for this study were based upon product labels for the immediate release clonidine tablets (Catapres®) and transdermal clonidine patch (Catapres TTS®) supplemented by a review of literature of doses used in clinical trials for ADHD. Upon completion of all baseline assessments, subjects who satisfied all entry criteria at the baseline visit were randomly assigned to one of the three treatment groups.

In the treatment phase, dose escalation began in a double blind fashion using a mix of active and placebo tablets in the dispensed blister pack. Each dose consisted of 2 tablets total. Subjects were instructed to take the morning doses at 8 am (± 2 h) and the evening doses at 8 pm (± 2 h). The timing of dose ingestion relative to mealtimes was at the parent/guardian or subject's discretion. Each subject started the treatment period with dosing on the morning of Day 1. The subject was dispensed the Week 1 blister pack and instructed to take the morning dose (2 tablets total) at 8 am (± 2 h) the next day. At the end of each week, subjects returned to the clinic with the previous week's blister pack(s) and received a new blister pack for the subsequent dosing week until completion of study treatment dosing on Day 56 of the study. The last dose of study medication was scheduled for the evening (8 am ± 2 h) of Day 56.

Efficacy Findings

The primary efficacy variable was the mean change from Baseline in the Investigator completed ADHDRS-IV scale total score at Week 5, or discontinuation measure if earlier than Week 5 based on an LOCF analysis. At Baseline, the mean total score was similar across the three treatment groups (range 43.8 to 45.0). At Week 5, the mean change from Baseline in ADHDRS-IV in the CLON 0.2 mg/day and CLON 0.4 mg/day treatment groups was -15.6 and -16.6, respectively, and was statistically significantly greater than in the placebo group (-7.5; $p<0.0001$). The result of the observed case (OC) analysis for completers was similar to the LOCF analysis, although the magnitude of the change was slightly higher in each treatment group (-16.5, -19.4, and -8.0, $p<0.0001$, for the CLON 0.2 mg, 0.4 mg and PBO groups respectively).

Table 5: Change from baseline to week 5 in the ADHDRS IV total score (ITT Population, LOCF & OC Analyses)

	TREATMENT GROUP								
	CLON 0.2 mg/day			CLON 0.4 mg/day			PBO		
ADHDRS-IV TOTAL SCORE	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	74	43.8	7.47	78	44.6	7.73	76	45.0	8.53
Week 5 (LOCF)	74	28.2	14.06	78	28.1	14.10	76	37.6	11.97
Change from Baseline (LOCF)[1]	74	-15.6	12.96	78	-16.5	13.54	76	-7.5	9.41
p-value (vs. PBO)[2]		<0.0001			<0.0001			--	
Week 5 (OC)	58	26.9	12.77	52	25.1	13.50	59	37.6	12.05
Change from Baseline (OC)	58	-16.5	12.08	52	-19.4	12.75	59	-8.0	9.16
p-value (vs. PBO)[2]		<0.0001			<0.0001			--	

[1] Primary efficacy analysis.

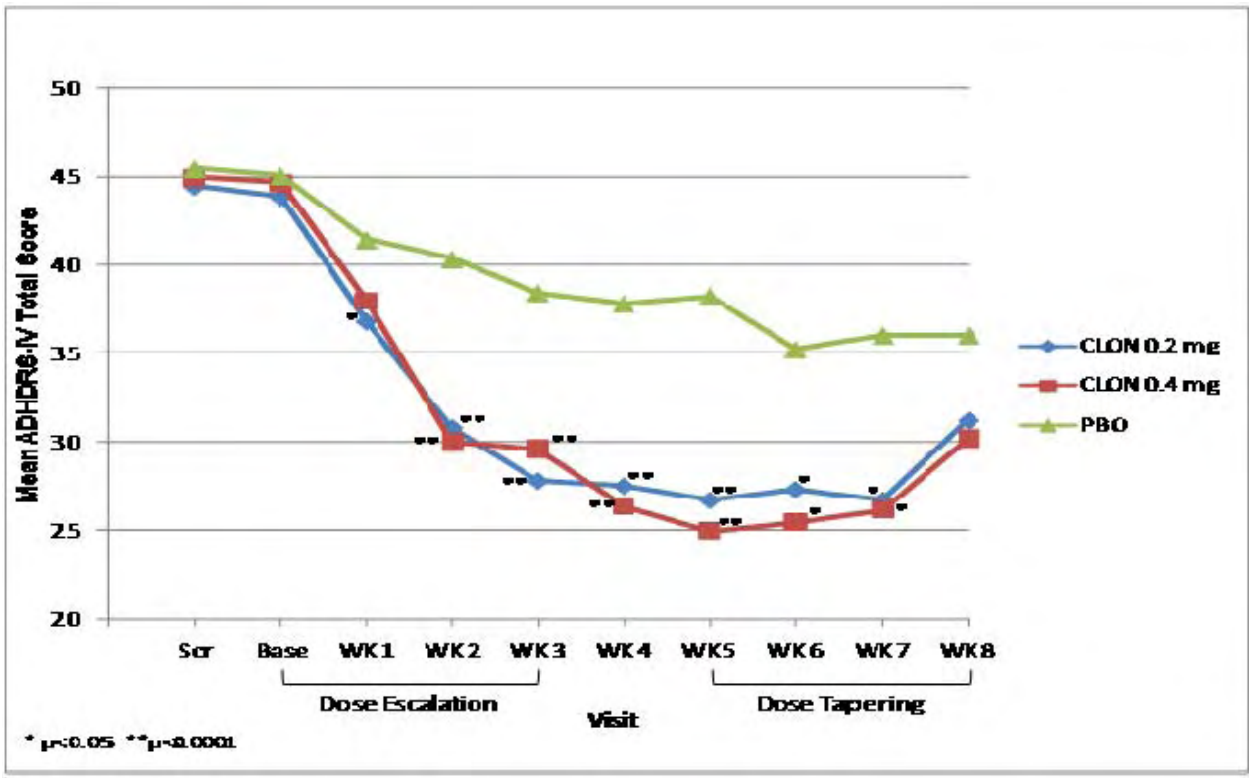
[2] Versus placebo p value; obtained from the treatment parameter in an ANCOVA modeling change from Baseline as a function of Baseline, treatment, and pooled study site.

Abbreviations: LOCF=last observation carried forward; OC=observed cases

Mean ADHDRS-IV Total Scores over Time

The difference between each active treatment group and placebo was statistically significant ($p<0.05$) in both the LOCF and OC analyses. Statistical separation from placebo was achieved as early as Week 1 in the CLON 0.2 mg/day treatment group and Week 2 in the CLON 0.4 mg/day treatment group even as the dose was being escalated to target. This treatment difference was maintained throughout the treatment phase, through Week 8 for the LOCF analysis and Week 7 for the OC analysis.

Figure 2: Mean of the ADHDRS-IV score by treatment and visit (ITT population, Observed Cases)



Conclusions

Both dosing regimens of clonidine were efficacious in alleviating symptoms in children and adolescents with ADHD.

At Baseline, for the primary efficacy variable, the investigator-rated ADHDRS-IV total score was similar across the three treatment groups (range 43.8 to 45.0). Treatment with clonidine resulted in a significantly greater mean change from Baseline in the ADHDRS-IV total score at Week 5, based on an LOCF analysis, in both the CLON 0.2 mg/day and CLON 0.4 mg/day treatment groups (-15.6 and -16.6, respectively) than treatment with placebo (-7.5; $p<0.0001$).

Two additional sensitivity analyses, including the observed case (OC) analysis for

completers, confirmed the results of the primary analysis that the difference between placebo and the CLON 0.2 mg/day or CLON 0.4 mg/day treatment groups was highly significant ($p<0.0001$ for each active treatment group in each model). The magnitude of the change was slightly higher in each treatment group (-16.5, -19.6, and -8.1, respectively) for the OC analysis. Moreover, the treatment difference was achieved as early as Week 1 in the CLON 0.2 mg/day treatment group and Week 2 in the CLON 0.4 mg/day treatment group and maintained throughout the treatment phase, through Week 8 for the LOCF analysis and Week 7 for the OC analysis ($p<0.05$ each analysis).

Study 2: CLON-302: A phase III evaluation of the efficacy and safety of clonidine as add-on to psychostimulant medication vs. psychostimulant medication alone in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD)

Methods/Study Design/Analysis Plan:

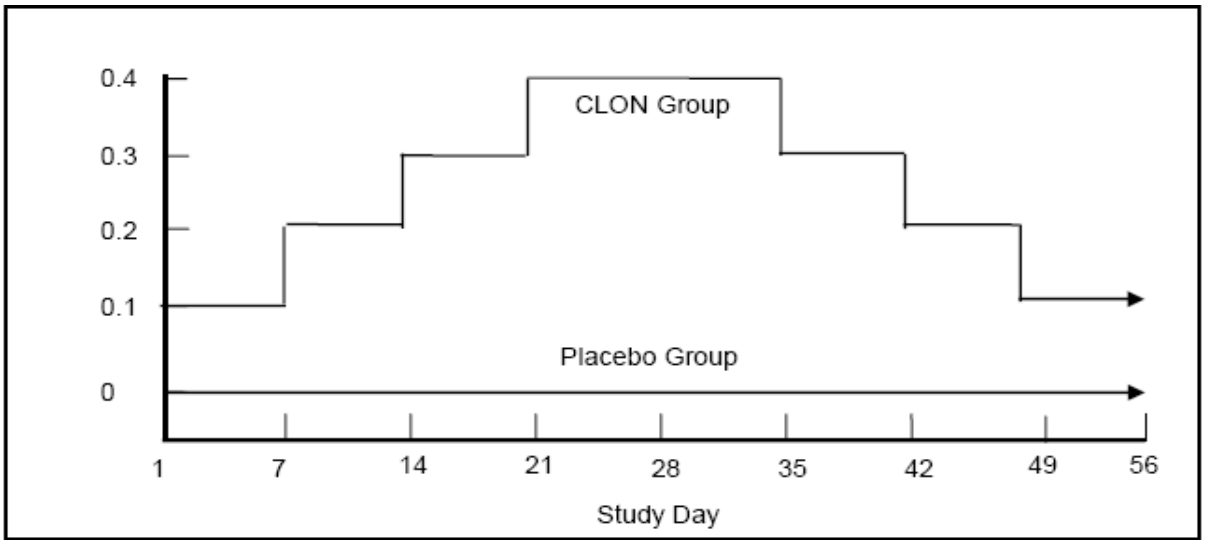
This was an 5-week (8-week including taper down period), multi-center, parallel-group, randomized, double-blind, placebo-controlled study (with clonidine or placebo as add-on therapy in patients who were on stimulants) of the efficacy and safety of a flexible dose of clonidine in children and adolescents (6 to 17 years) who met DSM-IV criteria for ADHD, hyperactive and combined inattentive hyperactive subtype.

Subjects were randomly assigned to one of two groups: clonidine as add-on to a psychostimulant (CLON+STM) or placebo as add-on to a psychostimulant (PBO+STM). Subjects entering the study should have been on a stable regimen of approved stimulant medication of either methylphenidate or amphetamine (or their derivatives) for a minimum period of 4 weeks and could potentially benefit from the addition of an alpha2 adrenergic agonist as evidenced by a lack of adequate response to this stable regimen of stimulant medication (score on ADHDRS-IV>26). The CLON dose (or matching placebo) was initiated at 0.1 mg/day and titrated up to a 0.4 mg/day (administered as 0.2 mg q12h) over a 3-week period. The dose was maintained at this

level for a period of 2 weeks before being gradually tapered to 0.1 mg/day at the last week of treatment. The investigator could elect to keep a subject on a CLON dose lower than 0.4 mg/day or taper the dose earlier than scheduled in the case of adverse events.

The investigator could also elect to change the dose of stimulant medication based on the profile of safety and efficacy observed, but changing the category of stimulant medication was not allowed. Subjects who could not tolerate a minimum CLON dose of 0.1 mg/day were discontinued. Prior to initiating the 8-week treatment period, subjects completed a screening period (1 to 2 weeks) during which all screening assessments were performed including performance while on the current stimulant treatment regimen. During the treatment period, subjects returned to the investigative site weekly to complete efficacy and safety assessments. Subjects discontinued study treatment at the Week 8 visit and returned for a safety assessment at Week 9. Subjects who might benefit from continued treatment with clonidine and desired to do so were offered participation in an open-label follow-on study designed to gather additional efficacy and safety data on TRADENAME.

Figure 3: Study Design CLON-302



Inclusion Criteria

- Male or female between 6 and 17 years of age, inclusive

- Diagnosis of ADHD of the hyperactive or combined inattentive/hyperactive subtypes according to DSM-IV criteria
- Stable regimen of approved stimulant medication of either methylphenidate or amphetamine (or derivatives) for a minimum period of 4 weeks prior to Baseline
- Lack of adequate response to the stable regimen of stimulants evidenced by a minimum score of 26 on the ADHDRS-IV questionnaire at Baseline
- Body mass index ≥ 5th percentile of the subject's age group according to the CDC growth chart. BMI was calculated using the formula: weight (kg) / [height (m)]$_2$

Important Exclusion Criteria

- If female of child-bearing potential, pregnant or lactating or did not agree to use a medically acceptable form of birth control
- Females who were pregnant or lactationg or who did not agree to use an acceptable form of birth control.
- Presence of clinically significant illness or abnormality on physical examination or clinical laboratory investigations or ECG's.
- History or presence of concomitant psychiatric disorder, conduct disorder, seizures, syncopal episodes, presence of drug or alcohol abuse or positive drug screen with the exception of ADHD drugs.

Efficacy: Primary Efficacy Variable was the comparison between treatment groups on change scores from Baseline to the Week 5 measure (or discontinuation measure if earlier than Week 5) of the Investigator-completed ADHDRS-IV scale total score.

Secondary efficacy variables included the comparison between treatment groups on change scores from Baseline to the Week 5 measure (or discontinuation measure if earlier than Week 5) of:

Investigator-completed ADHDRS-IV subscales (inattention, hyperactivity, and impulsivity) CGI-S, parent-completed CPRS-L and HADS scales child-completed SSR-CF The CGI-I and PGA rating scores at each weekly post-baseline visit were also secondary efficacy variables.

No key secondary endpoint was prespecified

Results

Demographics

The demographic characteristics across the two treatment groups, CLON+STM and PBO+STM, were similar without significant differences. For all randomized subjects, the majority were male (73.6%) and White (53.8%). Mean subject age was 10.5 years (median 10.0 years), and most subjects were 6-12 years of age (77.2%). Mean body weight was 39.6 kg (median 35.9 kg).

Table 6: Demographic characteristics: CLON-302

Summary	Treatment Group		All Subjects	P-Value [1]
	Clonicel + STM	Placebo + STM		
ITT Subjects	102	95	197	
Gender				
Male	79 (77.5%)	66 (69.5%)	145 (73.6%)	0.2576
Female	23 (22.5%)	29 (30.5%)	52 (26.4%)	
Age (years)				
N	102	95	197	0.9038
Mean (Std)	10.4 (2.50)	10.5 (2.53)	10.5 (2.50)	
Median	10.0	10.0	10.0	
Min, Max	6.0, 17.0	6.0, 16.0	6.0, 17.0	
Age				
6-12 Years	77 (75.5%)	75 (78.9%)	152 (77.2%)	
>12-17 Years	25 (24.5%)	20 (21.1%)	45 (22.8%)	
Race				
White	49 (48.0%)	57 (60.0%)	106 (53.8%)	0.1547
Black/African American	35 (34.3%)	19 (20.0%)	54 (27.4%)	
Hispanic or Latino	11 (10.8%)	11 (11.6%)	22 (11.2%)	
Other	7 (6.9%)	8 (8.4%)	15 (7.6%)	
Weight (kg)				
N	100	93	193	0.7945
Mean (Std)	40.2 (18.57)	38.9 (13.57)	39.6 (16.33)	
Median	36.4	35.7	35.9	
Min, Max	18.8, 112.6	20.0, 76.8	18.8, 112.6	

Baseline Characteristics

Patient Disposition

A total of 243 unique subjects were screened. Of those screened, 198 subjects were

randomly assigned to the study treatments (All Randomized population). All 198 subjects were included in the Safety population (102 subjects in the CLON+STM and 96 in the PBO+STM treatment groups).

One of the 198 subjects in the Safety population (Subject 3302, assigned to the placebo group) received at least one dose of study drug but had no post-baseline measurements. The remaining 197 subjects provided evaluable efficacy data and were included in the ITT population.

Overall, the majority of subjects (83.3%) completed the treatment phase. Most subjects (86.9%) completed the follow-up visit. One subject did not complete the follow-up visit due to an AE, and the remaining subjects did not return for the follow-up visit for other reasons shown in the table below.

Table 7: Subject disposition in Study CLON-302

	CLON+STM N (%)	Placebo + STM N (%)	Total N (%)
All Randomized	102	96	198
Safety Population	102	96	198
ITT for Efficacy	102	95[1]	197
Completed Treatment Phase	91 (89.2)	74 (77.1)	165 (83.3)
Withdrawn	11 (10.8)	22 (22.9)	33 (16.7)
Adverse Event	1 (1.0)	3 (3.1)	4 (2.0)
Withdrew Consent	0	8 (8.3)	8 (4.0)
Lack of Efficacy	4 (3.9)	6 (6.3)	10 (5.1)
Lost to Follow-Up	1 (1.0)	0	1 (0.5)
Protocol Violation	5 (4.9)	5 (5.2)	10 (5.1)
Completed Safety Follow-up	95 (93.1)	77 (80.2)	172 (86.9)
Did not complete Safety Follow-up	7 (6.9)	19 (19.8)	26 (13.1)
Adverse Event	0	1 (1.0)	1 (0.5)
Withdrew Consent	2 (2.0)	16 (16.7)	18 (9.1)
Lost to Follow-Up	5 (4.9)	0	5 (2.5)
Protocol Violation	0	1 (1.0)	1 (0.5)
Other	0	1 (1.0)	1 (0.5)

Concomitant Medication Use

During CLON 302, 20 subjects received one or more of 23 concomitant medications that were restricted in the protocol. This included 15 subjects who received one or more sedating antihistamines (non sedating antihistamines were allowed), 5 subjects who received a bronchodilator (the protocol restricted chronic use greater than 3 times per week), 1 subject who received an oral steroid and 1 subject who received a

psychotropic (Medical Monitor agreed to PI request to add risperidone during the study follow-up period).

Important Protocol Violations

Entry Criteria Violations

Two subjects in the placebo group and four subjects in the CLON+STM group did not meet all entry criteria and except one, was discovered post-randomization. Three of the subjects marginally failed to meet inclusion criteria of BMI and were granted an exception by the sponsor to enroll in the study. One subject failed to meet inclusion criteria of minimum score of 26 on ADHD rating scale. This child was granted an exception and completed the study. One subject (2804, PBO+STM) met exclusion criteria of participating in a clinical trial using a topical gel for the treatment of acne. Investigator granted an exception for the subject to enroll 23 days after the last topical use of medication.
Subject 2502 (PBO+STM) was noted after beginning study drug that she had failed inclusion criteria of diagnosis of ADHD of hyperactive or combined inattentive/hyperactive subtypes, as the subject's diagnosis was ADHD of the inattentive subtype only. She was allowed to continue as she was doing well and tolerating study medication.

Subjects who received the wrong treatment or dose of study medication

Subjects 2205 and 2206 were siblings and it was suspected that they were taking medications from each other's study medication bottles. They were discontinued for noncompliance with study medication instructions.

Subject 2910 (PBO+STM) was inadvertently randomized to the wrong kit number. This deviation was reported and reassignment made.

Subject 2601 was mistakenly not instructed to taper the study medication dose from 0.4 mg/day to 0.3 mg/day following the week 5 visit, and the subject continued on 0.4 mg/day for six additional days. The sponsor was contacted and during the final 2 weeks, the dose was tapered down.

Other protocol deviations

Two subjects changed the class of psychostimulant medication they were taking during the treatment phase of the study. Both entered the study taking an amphetamine (Vyvanse). Subject 2607 switched to Concerta during the second week due to perceived side effect of emotional lability, which resolved one day after taking Concerta. The subject was discontinued after 7 days due to lack of efficacy. Subject 3704 was switched from Vyvanse to Daytrana during the fourth week due to restlessness, which resolved on the same day that the psychostimulant was changed. The subject went on to complete the study as planned.

Treatment Compliance

Compliance with study drug dosing was similar across the two treatment groups, 97.2% and 94.5% for the CLON+STM and PBO+STM groups, respectively. Compliance with regard to completion of study visits was similar across the two treatment groups through Week 4. Greater than 94% and 88% of subjects in the CLON+STM and PBO+STM treatment groups, respectively, completed study visits through Week 4; and greater than 90 and 82% of subjects, respectively, completed study visits through Week 5. Approximately 87% of all subjects completed study visits through Week 8. Higher compliance was observed in the CLON+STM treatment group, having 90.2% of subjects complete through Week 8 compared with 84.4% in the PBO+STM treatment group.

Dosing

Efficacy Findings

The primary efficacy variable was the mean change from Baseline in the Investigator-completed ADHDRS-IV scale total score at Week 5, or discontinuation measure if earlier than Week 5 based on an LOCF analysis. The primary analysis was a comparison of mean scores for the CLON+STM treatment group versus PBO+STM.

At Baseline, the mean total scores were similar, 38.9 and 39.0 in the CLON+STM and PBO+STM treatment groups, respectively. At Week 5, the mean change from Baseline in ADHDRS-IV in the CLON+STM treatment group was -15.7, and was statistically significantly greater than in the PBO+STM group (-11.5; p=0.0091 for treatment difference vs. placebo using an ANCOVA modeling the change from Baseline as a function of Baseline scores, treatment, and pooled study site).

Two additional sensitivity analyses, the primary efficacy model (LOCF) with the treatment by site interaction included and another model based on subjects who completed the study up to Week 5 confirmed the results of the primary analysis that the difference between PBO+STM and the CLON+STM treatment group was statistically significant (p=0.0045 for the model that includes treatment by site interaction; p=0.0273 for the observed case [OC] analysis). The result of the OC analysis for completers was similar to the LOCF analysis, although the magnitude of the change was slightly higher in each treatment group (-16.9 and -13.3, respectively). Placebo-subtracted least square mean differences between the two treatment groups ranged from 4 to 5 points, favoring the CLON+STM group.

Table 8: Change from Baseline to Week 5 in the ADHDRDS-IV Total Score (LOCF & OC Analyses)

	TREATMENT GROUP					
	CLON+STM			PBO+STM		
ADHDRS-IV TOTAL SCORE	N	Mean	SD	N	Mean	SD
Baseline	102	38.9	6.95	95	39.0	7.68
Week 5 (LOCF)	102	23.1	12.53	95	27.5	13.39
Change from Baseline (LOCF)[1]	102	-15.7	12.30	95	-11.5	12.22
p-value (vs. PBO)[2]	p=0.0091			--		
Week 5 (OC)	92	22.1	12.47	75	25.6	12.83
Change from Baseline (OC)	92	-16.9	12.22	75	-13.3	11.86
p-value (vs. PBO)[2]	p=0.0273			--		

[1] Primary efficacy analysis.

[2] Versus placebo p-value; obtained from the treatment parameter in an ANCOVA modeling change from Baseline as a function of Baseline, treatment, and pooled study site.

Conclusions

Overall, clonidine, as add-on therapy to ADHD psychostimulants, was efficacious in alleviating symptoms in children and adolescents with ADHD who lacked adequate response on a stable regimen of stimulant medication alone.

Treatment with clonidine for up to 8 weeks as add-on to stimulants in this patient population resulted in a significantly greater mean change from Baseline in the ADHDRS-IV total score at Week 5, based on the LOCF analysis, in the CLON+STM treatment group compared with PBO+STM (-15.7 and -11.5, respectively; p=0.0091). Results from most of the secondary efficacy analyses, supported the results of the primary efficacy analysis and achieved statistical significance (p-value at least <0.05).

Crosscutting Issues

Key Secondary Endpoints

There were no prespecified key secondary endpoints.

Overall, results of the secondary efficacy analyses, supported the results of the primary efficacy analysis and achieved statistical significance (p-value at least <0.05). Statistical

significance for a treatment difference between the active and placebo treatment groups was achieved for the investigator-rated scales, CGI-I, CGI-S and subscales of the ADHDRS-IV, and parent-rated scales, HADS, CPRS, derived subscales, and PGA, but not for the child rated sleep scale (SSR-CF) total score or derived subscales.

Patients were on average considered to be moderately to markedly ill at the beginning of the study and by Week 5 of treatment with clonidine, subjects were considered on average to be mildly to moderately ill and much improved with regard to symptoms of ADHD, compared to placebo subjects who showed little change in severity of disease and minimal improvement of symptoms. Parents on average considered subjects minimally improved following treatment with clonidine compared with placebo subjects who were considered to have no change in symptoms.

Table 9: Secondary Efficacy results for Study CLON-301

SECONDARY EFFICACY VARIABLE	TREATMENT GROUP								
	CLON 0.2 mg/day			CLON 0.4 mg/day			PBO		
Inattention Subscale of the ADHDRS-IV	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	74	22.9	3.87	78	23.1	3.81	76	23.4	4.32
Change from Baseline to Week 5 (LOCF)	74	-7.7	6.88	78	-7.7	7.10	76	-3.4	5.13
p-value (vs. PBO)[1]	<0.0001			<0.0001			--		
Hyperactivity/Impulsivity Subscale of the ADHDRS-IV	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	74	20.9	5.31	78	21.5	5.04	76	21.6	5.59
Change from Baseline to Week 5 (LOCF)	74	-7.9	6.96	78	-8.8	7.26	76	-4.1	5.04
p-value (vs. PBO)[1]	<0.0001			<0.0001			--		
CPRS Total Score	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	74	128.6	35.82	78	137.2	37.20	76	142.5	35.19
Change from Baseline to Week 5 (LOCF)	74	-40.7	39.01	78	-46.2	48.66	76	-23.3	31.33
p-value (vs. PBO)[1]	0.0002			0.0003			--		
CPRS Oppositional Subscale	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	74	16.8	7.56	78	18.1	7.91	76	18.4	7.08
Change from Baseline to Week 5 (LOCF)	74	-4.9	6.94	78	-5.5	8.29	76	-2.4	5.22
p-value (vs. PBO)[1]	0.0017			0.0027			--		
CPRS Hyperactivity Subscale	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	74	17.6	6.93	78	18.3	6.15	76	19.5	6.32
Change from Baseline to Week 5 (LOCF)	74	-6.4	6.95	78	-7.5	7.27	76	-3.8	5.18
p-value (vs. PBO)[1]	0.0004			<0.0001			--		
HADS	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	74	47.3	21.49	78	50.9	22.11	76	52.7	20.36
Change from Baseline to Week 5 (LOCF)	74	-15.3	18.22	78	-17.3	23.57	76	-8.8	16.72
p-value (vs. PBO)[1]	0.0032			0.0042			--		
Hyper-adrenergia Subscale	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	74	40.8	14.01	78	43.3	14.40	76	44.8	12.87
Change from Baseline to Week 5 (LOCF)	74	-12.6	13.75	78	-15.3	17.53	76	-7.9	12.26
p-value (vs. PBO)[1]	0.0065			0.0013			--		
SSR-CF Total Score	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	74	16.0	6.27	77	16.8	6.04	75	17.8	6.48
Change from Baseline to Week 5 (LOCF)	74	-1.9	5.20	77	-1.5	6.67	75	-3.4	5.83
p-value (vs. PBO)[1]	0.2946 (NS)			0.1838 (NS)			--		
SSR-CF Bedtime Subscale	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	74	8.1	3.91	77	9.1	3.80	75	9.5	4.25
Change from Baseline to Week 5 (LOCF)	74	-1.1	3.59	77	-1.1	3.62	75	-1.9	3.29
p-value (vs. PBO)[1]	0.6164 (NS)			0.2558 (NS)			--		
SSR-CF Sleep Behavior Subscale	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	74	4.5	2.47	77	4.2	2.24	75	4.3	2.40
Change from Baseline to Week 5 (LOCF)	74	-0.7	2.38	77	-0.1	3.29	75	-0.6	2.55
p-value (vs. PBO)[1]	0.9771 (NS)			0.4205 (NS)			--		
SSR-CF Daytime Sleepiness Subscale	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	74	3.4	1.82	77	3.5	1.85	75	4.1	1.83
Change from Baseline to Week 5 (LOCF)	74	-0.1	1.98	77	-0.2	2.10	75	-0.9	2.11
p-value (vs. PBO)[1]	0.2523 (NS)			0.5426 (NS)			--		
CGI-S	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	74	4.7	0.65	78	4.8	0.65	76	4.9	0.65
Change from Baseline to Week 5 (LOCF)	74	-1.2	1.02	78	-1.3	1.14	76	-0.5	0.82
p-value (vs. PBO)[1]	<0.0001			<0.0001			--		
CGI-I	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Week 5 (LOCF)	74	2.6	0.96	78	2.8	1.12	76	3.4	0.88
p-value (vs. PBO)[2]	<0.0001			0.0003			--		
PGA	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Week 5 (LOCF)	74	3.0	1.32	78	3.2	1.51	76	3.8	1.16
p-value (vs. PBO)[2]	0.0002			0.0043			--		

Secondary Efficacy Results for Study CLON-302

Results from most of the secondary efficacy analyses, supported the results of the primary efficacy analysis and achieved statistical significance (p-value at least <0.05). Statistically significant differences favoring the clonidine group were observed for the following secondary endpoints: Investigator-rated scales CGI-I and CGI-S; parent-rated scales, CPRS-L total score and the hyperactivity subscale, Hyper-adrenergia subscale, and PGA (p-value at least <0.05 for each analysis). Often the magnitude of the change was higher in the OC versus the LOCF analysis. The difference between the active treatment group and placebo was usually achieved early in the treatment phase and maintained through Week 7. No statistically significant differences were observed for the HADS, CPRS-L oppositional subscale, and SSR-CF scale total score and subscales.

Thus, clonidine as add-on to psychostimulant therapy was effective in alleviating symptoms of ADHD such as inattention, impulsivity, and hyperactivity. However, it was not effective in alleviating symptoms of sleep disturbance based on the child-rated sleep scale nor aggression based on the CPRS-L oppositional subscale in this population of ADHD patients who lacked adequate response on a stable regimen of stimulant medication alone. Investigators on average considered subjects to be moderately to markedly ill at the beginning of the study and by Week 5 of treatment with clonidine, subjects were considered on average to be mildly to moderately ill and much improved with regard to symptoms of ADHD, compared to placebo subjects who showed minimal improvement of symptoms. Parents on average considered subjects minimally to much improved following treatment with clonidine compared with placebo subjects who were considered to have minimal improvement in symptoms.

Table 10: Secondary Efficacy Results for Study CLON-302

	TREATMENT GROUP					
SECONDARY EFFICACY VARIABLE	CLON+STM			PBO+STM		
Inattention Subscale of the ADHDRS-IV	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	102	20.7	4.22	95	20.8	4.21
Change from Baseline to Week 5 (LOCF)	102	-7.8	6.81	95	-5.8	6.85
p-value (vs. PBO)[1]		0.0169			--	
Hyperactivity/Impulsivity Subscale of the ADHDRS-IV	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	102	18.2	4.94	95	18.2	5.14
Change from Baseline to Week 5 (LOCF)	102	-7.9	6.70	95	-5.8	6.32
p-value (vs. PBO)[1]		0.0143			--	
CPRS Total Score	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	102	118.2	37.58	95	120.5	39.57
Change from Baseline to Week 5 (LOCF)	102	-40.2	41.44	95	-27.1	38.25
p-value (vs. PBO)[1]		0.0166			--	
CPRS Oppositional Subscale	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	102	15.6	7.04	95	16.5	7.53
Change from Baseline to Week 5 (LOCF)	102	-5.1	6.61	95	-3.6	6.31
p-value (vs. PBO)[1]		0.0615	(NS)		--	
CPRS Hyperactivity Subscale	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	102	14.7	6.27	95	14.6	6.61
Change from Baseline to Week 5 (LOCF)	102	-5.8	6.49	95	-3.8	5.71
p-value (vs. PBO)[1]		0.0166			--	
HADS	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	102	45.3	20.73	95	47.8	20.79
Change from Baseline to Week 5 (LOCF)	102	-16.0	18.71	95	-13.3	18.84
p-value (vs. PBO)[1]		0.1741	(NS)		--	
Hyper-adrenergia Subscale	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	102	38.1	13.61	95	39.4	14.36
Change from Baseline to Week 5 (LOCF)	102	-14.1	13.74	95	-10.0	13.70
p-value (vs. PBO)[1]		0.0244			--	
SSR-CF Total Score	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	102	15.7	6.33	95	16.4	7.44
Change from Baseline to Week 5 (LOCF)	102	-1.9	5.34	95	-1.6	6.12
p-value (vs. PBO)[1]		0.3759	(NS)		--	
SSR-CF Bedtime Subscale	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	102	8.2	3.75	95	8.6	4.39
Change from Baseline to Week 5 (LOCF)	102	-1.1	3.32	95	-0.8	4.03
p-value (vs. PBO)[1]		0.2154	(NS)		--	
SSR-CF Sleep Behavior Subscale	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	102	4.0	2.38	95	4.4	2.83
Change from Baseline to Week 5 (LOCF)	102	-0.4	2.39	95	-0.8	2.58
p-value (vs. PBO)[1]		0.5646	(NS)		--	
SSR-CF Daytime Sleepiness Subscale	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	102	3.4	1.90	95	3.3	1.76
Change from Baseline to Week 5 (LOCF)	102	-0.4	1.82	95	-0.1	1.55
p-value (vs. PBO)[1]		0.2021	(NS)		--	
CGI-S	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	102	4.7	0.74	95	4.8	0.81
Change from Baseline to Week 5 (LOCF)	102	-1.5	1.23	95	-1.2	1.28
p-value (vs. PBO)[1]		0.0210			--	
CGI-I	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Week 5 (LOCF)	102	2.5	1.16	95	3.0	1.22
p-value (vs. PBO)[2]		0.0065			--	
PGA	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Week 5 (LOCF)	102	2.7	1.26	95	3.4	1.38
p-value (vs. PBO)[2]		0.0012			--	

Subgroup Analyses

The statistical reviewer and sponsor conducted an analysis of results by gender, race and age as potential predictors of response using the ITT Population.

In Study 301, an analysis of results by gender showed that the observed treatment effect appeared comparable between genders in both treatment comparisons, except that the female CLON 0.4 mg group had a numerically larger treatment effect.

In the analysis of race (White, Black/African American, Hispanic, Other), the overall treatment effect for clonidine relative to placebo was not affected by race.

The statistical review concluded that the 6-12 year-old subgroup was the contributor of the overall efficacy evidence, while the >12 year-old was not. This may have been due to the small number of subjects of this subgroup, and thus there is no information in the data to draw any conclusion on the efficacy of the >12 year-old subgroup.

In Study 302, the overall treatment effect for clonidine relative to placebo was not affected by gender, age or race.

Longterm Efficacy

There were no long-term efficacy studies done

Pediatric Development

This is a pediatric study

Efficacy Conclusions Regarding ADHD

The phase III studies, Study CLON-301 and Study CLON-302, established statistical evidence of a mean difference in the ADHDRS-IV total score at the study endpoint (Week 5) in favor of TRADENAME treatment against placebo, both as monotherapy and as an add-on to a psychostimulant.

7 Review of Safety

Safety Summary

7.1 Methods

The evaluation of the safety of clonidine consisted of two general approaches:

- Assessment of the more serious adverse events in the entire study population arising from all datasets; deaths, non-fatal serious adverse events, and adverse events that led to premature discontinuiation.

- Examination of the less serious adverse events. This examination encompasses common adverse events, laboratory findings, vital signs data, and ECG findings associated with exposure to Clonicel.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This review will focus on the safety data from trials CLON-301 and CLON-302.

7.1.2 Categorization of Adverse Events

Adverse events were categorized under the occurrence of deaths, non-fatal serious adverse events, and premature discontinuations due to adverse events. Additionally common adverse events, vital signs, laboratory test data, and ECG results were also analyzed.
All subjects receiving at least one dose of the study medication were evaluated for safety.
Adverse events were coded using the Coding Symbol for Thesaurus of Adverse Reaction Terms (COSTART) dictionary.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This NDA submission consisted of three trials, one was a placebo controlled study and the other was clonidine as add on therapy to patients currently receiving a stimulant. The third study was an open label long term study. Since they had different designs, this reviewer did not feel that it was appropriate to pool data from the different studies.

7.2 Adequacy of Safety Assessments

Safety evaluations were done through adverse event monitoring, which were reported by the subject, as well as those noted by the Investigator. These were recorded in the source documents and on the CRF. AE collection began at the baseline visit prior to start of administration of study drug and continued till study completion.
The sponsor also collected laboratory parameters at screening and day 56 (week 8). If consent could be obtained, blood was collected for pharmacogenomic study. Additional safety assessments included vital signs, physical exams, medical history, ECG's and pregnancy testing.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In Study CLON-301, a total of 154 subjects received clonidine, of which 76 received 0.2 mg/day and 78 received 0.4 mg/day. The mean (94.9 AND 87.0) and median (109 AND 107) number of doses taken were similar across the two treatment groups. Treatment compliance was similar across the three treatment groups. The total amount of drug taken for the two clonidine treatment groups were on an average 8.2 mg in the CLON 0.2 mg/day and 10.6 mg in the CLON 0.4 mg/day group.

In Study CLON-302, A total of 102 subjects received clonidine. For the ITT Population, the mean number of doses taken (120.4) and median (132.5) in the CLON+STM group

was similar to the PBO+STM treatment group (mean 113.9, median 132.0). The total amounts of drug taken in milligrams for the CLONICEL treatment group was on average 12.0 mg (median 13.3 mg). Treatment compliance was similar across the two treatment groups (97.2% and 94.5%).

Study CLON-303 was an open-label, chronic exposure evaluation of the safety of clonidine in the treatment of children and adolescents with ADHD. For the 301 subjects included in the Study CLON-303 Safety Population, exposure was calculated by including time on active treatment in the prior double-blind study (CLON-301 or CLON-302). With prior double-blind exposure included, 215 subjects (74.1%) received clonidine for ≥24 weeks and 113 subjects (37.5%) received clonidine for ≥48 weeks .

7.2.2 Explorations for Dose Response

Formal explorations for dose response were not done. However, in study CLON-301, it was noticed that the AE's of constipation, nightmares, and tremors were more common in the CLON 0.4 mg group than the 0.2 mg group. The number of subjects who experienced headaches and somnolence were higher in the lower dose groups. No conclusions can be drawn from these numbers regarding causality.

7.2.3 Special Animal and/or In Vitro Testing

There was no special animal and/or in vitro testing done.

7.2.4 Routine Clinical Testing

7.2.5 Metabolic, Clearance, and Interaction Workup

None

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The other drug in the same class as clonidine is guanfacine (INTUNIV), which was approved by the FDA for the treatment of ADHD in 2009. Guanfacine is also a selective al[pha-adrenergic receptor agonist. Common adverse events seen with guanfacine include the potential for hypotension, bradycardia, syncope, sedation/somnolence, abdominal pain, dry mouth and constipation.

7.3 Major Safety Results

Study CLON-301

The overall incidence of AE's, irrespective of relationship to study medication was not higher in the active treatment groups and was not dose-related: approximately 83% of patients in each active group reported at least one AE, compared to 72% in the placebo group. The percentage of TEAEs judged by the investigator to be possibly or probably related to study drug were higher in the active treatment groups (62 to 70%) compared to the placebo treatment group (45%), but were not dose related.

Table 11: Overview of Adverse Events in CLON-301

	TREATMENT GROUP					
	CLON 0.2 mg N=76		CLON 0.4 mg N=78		PBO N=76	
AE CATEGORY[1,2]	Events	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)
TEAEs	240	63 (82.9)	230	65 (83.3)	138	55 (72.4)
Related[3] TEAEs (ADRs)	135	53 (69.7)	139	48 (61.5)	60	34 (44.7)
SAEs[4]	0	0 (0.0)	0	0 (0.0)	0	0 (0.0%)
AEs Leading to Discontinuation	5	5 (6.6)	15	15 (19.2)	1	1 (1.3)

1. Subjects may be counted in more than one AE category.
2. This includes all AEs for subjects who were randomized and received at least one dose of study medication.
3. Relationship was determined by the Investigator.
4. There were no SAEs, and therefore, no deaths reported in this study.

Study CLON-302

The overall incidence of AEs, irrespective of relationship to study medication, was only slightly higher in the group treated with CLON+STM than in the group treated with PBO+STM (68% and 64%, respectively, reported at least one TEAE). The incidence of TEAE considered by the investigator to be possibly or probably related to study Drug were somewhat higher in the CLON+STM group than in the PBO+STM group: 45% of patients in the CLON+STM group reported at least one of the 100 AE's reported by the group, and 41% of patients in the PBO+STM group reported at least one of the 78 AE's reported by that group.

Table 12: Overview of Adverse Events in Study 302

	TREATMENT GROUP			
	CLON+STM N=102		PBO+STM N=96	
AE CATEGORY[1,2]	Events	Subjects n (%)	Events	Subjects n (%)
TEAEs	224	69 (67.6)	174	61 (63.5%)
Related[3] TEAEs (ADRs)	100	46 (45.1%)	78	39 (40.6%)
SAEs[4]	1	1 (1.0)	2	2 (2.1)
AEs Leading to Discontinuation	1	1 (1.0%)	4	4 (4.2%)

7.3.1 Deaths

There were no deaths in Study CLON-301 or CLON-302.

7.3.2 Nonfatal Serious Adverse Events

In Study CLON-301, there were no serious adverse events.

In Study CLON-302 there were three Serious Adverse Events (SAE's).

Patient 2702 (CLON+STM)
13 year old Hispanic male receiving CLON 0.2 mg daily and Concerta 54 mg/day took 3 additional doses (0.5 mg) of the study drug in the second week of study following and argument with sibling and mother. The subject reported this to his mother and was taken to his Primary care Physician (PCP) and and was hospitalized. On interview following his discharge, it was determined that this behavior was consistent with previous behaviors and unrelated to study medication.

Patient 2907 (PBO+STM)
8 year old female on stable psychostimulant regimen of metadate hit another child with a board during week 4 of the study, while tapering off study medication because of lack of efficacy.

Patient 2908 (PBO+STM)
12 year old male on a stable psychostimulant regimen of Concerta 54mg/day and randomized to placebo who threatened his mother with a knife during week 2. The patient was hospitalized and discontinued from the study.

Reviewer's Comments: None of these events classed as SAE's can be attributed to the effects of study medication.

7.3.3 Dropouts and/or Discontinuations

Study CLON-301

In Study CLON-301, the number of patients who discontinued study due to an AE in the low dose (0.2 mg/day), high dose (0.4 mg/day) and placebo groups were 5(7%), 15 (19%), and 1(1%) respectively. In the 0.2 mg group, 3 (3.9%) subjects discontinued because of somnolence and 2(2.6%) discontinued because of fatigue. Among the 15 subjects who discontinued the study drug in the 0.4 mg group, the reasons were somnolence 5 (6.4%), formication 1 (1.3%), fatigue 4 (5.1), GI disorders (1 each of constipation and vomting), rash 1 (1.3%), Prolonged QT 1 (1.3%) and increased heart rate 1 (1.3%).

Table 13: Adverse Events Leading to Study Discontinuiation CLON-301

	TREATMENT GROUP		
	CLON 0.2 mg/day N=76	CLON 0.4 mg/day N=78	PBO N=76
PREFERRED TERM	Subjects n (%)	Subjects n (%)	Subjects n (%)
TEAEs leading to discontinuation	**5 (6.6)**	**15 (19.2)**	**1 (1.3)**
Somnolence	3 (3.9)	5 (6.4)	0
Fatigue	2 (2.6)	4 (5.1)	0
Formication	0	1 (1.3)	0
Constipation	0	1 (1.3)	0
Vomiting	0	1 (1.3)	0
Electrocardiogram QT Prolonged	0	1 (1.3)	0
Heart Rate Increased	0	1 (1.3)	0
Rash	0	1 (1.3)	0
Dizziness	0	0	1 (1.3)

Study CLON-302

Of the 198 subjects, 4 discontinued because of TEAE's. One subject in the CLON+STM group discontinued because of TEAE's.

Table 14: Adverse Events leading to Study Discontinuation: Study CLON-302

	TREATMENT GROUP	
	CLON+STM	PBO+STM
	N=102	N=96
PREFERRED TERM	Subjects n (%)	Subjects n (%)
Bradyphrenia	1 (1.0)	0
Aggression	0	2 (2.1)
Somnolence	0	1 (1.0)
Heart Rate Increased	0	1 (1.0)

Patient 2602 (CLON+STM) was a 16 year old white male on a stable psychostimulant regimen of Vyvanse 30 mg/day and randomized to the CLON+STM group and developed fatigue and slowed thinking during week 2 while on 0.2 mg CLON daily. He

also developed moderate dizziness on the first day of dosing with 0.3 mg daily of CLON during week 4. He reduced his dose and discontinued from further dosing, primarily because of slowed thinking. Symptoms resolved 5 days after discontinuing study drug.

Patient 2202 (PBO+STM) 13 year old white female experienced increase in heart rate while engaged in sports on her fourth day of dosing in the study.The event resolved on the same day, but she was discontinued from the study.

Patient 2908 (PBO+STM) 12 year old on Concerta who threatened his mother with a knife during week 2. Patient was hospitalized and treatment discontinued.

Patient 3203 (PBO+STM) 9-year old white male on stable psychostimulant regimen of Ritalin and Focalin, randomized to placebo who experienced moderate sleepiness, moderate hyperventilation, and moderate weakness in the knees on the third day of dosing. Each event resolved on the same day, but it was decided to discontinue the patient.

Reviewer's Comments: I reviewed the narratives of all patients who discontinued in both studies. In Study CLON-301, the most common reason for discontinuation were somnolence and fatigue. Both of these are recognized AE's seen in therapy with clonidine. This AE can be adequately managed by education by the clinician and appropriate labeling.

7.3.4 Significant Adverse Events

Study CLON-301

Special event adverse events were classed as 'somnolence' (drowsiness, sleepiness sedation) and fatigue (fatigue and lethargy). Somnolence and fatigue each occurred in 59 patients and 23 patients respectively. 53% of subjects taking 0.2 mg experienced one of these after a mean duration of 9.8 days. 43% of subjects in the 0.4 mg group experienced one of these after a mean duration of 8.3 days whereas only 7.9% of

subjects in the placebo group experienced somnolence or lethargy. The duration (onset of first such TEAE to termination of last such TEAE) of one of these TEAEs was 25 to 30 days for all three treatment groups.

Table 15: Special Event Adverse Event: Somlolence, sedation, fatigue and lethargy. **Safety population: CLON-301**

Summary	Treatment Group		
	Clonicel 0.2 mg	Clonicel 0.4 mg	Placebo
Total Safety Subjects	76	78	76
Total Subjects with at least one Special Interest Adverse Event [1]	40 (52.6%)	33 (42.3%)	6 (7.9%)
Onset of Special Interest Adverse Event (days)			
N	40	33	6
Mean (Std)	9.8 (9.45)	8.3 (6.62)	12.7 (15.62)
Median	8.0	7.0	7.5
Min, Max	0, 56	0, 28	0, 41
Duration of Special Interest Adverse Event (days)			
N	40	33	6
Mean (Std)	29.6 (16.68)	25.2 (19.60)	27.8 (29.16)
Median	26.5	21.0	23.5
Min, Max	5, 64	1, 74	0, 80

Study CLON-302

Somnolence occurred in 20 patients (20%) in the CLON+STM group and 8 patients (8%) in the PBO+STM group; fatigue occurred in 16% and 4% of these treatment groups, respectively. At least one of these two “Special Interest TEAEs” occurred in 33 patients (32%) in the CLON+STM group and in 11 (11.5 %) in the PBO +STM group. In the active group, the mean onset of either of these events was on Day 14, late in the second week of dose titration (when patients typically had been receiving 0.1mg b.i.d for at least several days). Mean onset of either of these TEAEs was on Day 9 for the placebo patients. The durations (onset of first such TEAE to termination of last such TEAE) of these TEAEs were 16 and 15 days, for the CLON+STM and PBO+STM groups, respectively. The incidence and occurrence of one of these events is not affected by choice of psychostimulant. The duration was longer in the PBO+MPH

subgroup than in the PBO+AMPH subgroup (18 days vs 9 days). However, the duration of the two CLON+STM subgroups are similar.

7.3.5 Submission Specific Primary Safety Concerns

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study CLON-301

Analyses of TEAEs by System Organ Class (SOC) revealed GI, Psychiatric and Nervous System disorders to be most common. TEAEs from one of these classes were reported by 36%, 33% and 30% of patients respectively. With the exception of constipation and dry mouth, GI disorders were not more common in the active treatment groups than in the placebo groups. Psychiatric disorders and nervous system disorders were more common in active groups than in placebo groups, but, overall, not dose-related. Somnolence occurred in 40%, 31%, and only 7% of patients in the 0.2 mg/day, 0.4 mg/day, and placebo groups respectively. Headache occurred in 30% of the 0.2 mg/day group, but in fewer patients in the 0.4 mg/day and placebo groups.

Table 16: TEAEs with 2% or greater incidence CLON-301

	TREATMENT GROUP		
	CLON 0.2 mg/day N=76	CLON 0.4 mg/day N=78	PBO N=76
SYSTEM ORGAN CLASS **Preferred Term**	**Subjects n (%)**	**Subjects n (%)**	**Subjects n (%)**
GASTROINTESTINAL DISORDERS			
Abdominal Pain Upper	15 (19.7)	13 (16.7)	14 (18.4)
Nausea	4 (5.3)	7 (9.0)	5 (6.6)
Vomiting	2 (2.6)	2 (2.6)	5 (6.6)
Diarrhoea	3 (3.9)	2 (2.6)	2 (2.6)
Constipation	1 (1.3)	5 (6.4)	0
Dry Mouth	0	4 (5.1)	1 (1.3)
NERVOUS SYSTEM DISORDERS			
Headache	23 (30.3)	16 (20.5)	15 (19.7)
Insomnia	4 (5.3)	5 (6.4)	1 (1.3)
Tremor	1 (1.3)	3 (3.8)	0
Abnormal Sleep-Related Event	2 (2.6)	1 (1.3)	0
PSYCHIATRIC DISORDERS			
Somnolence	30 (39.5)	24 (30.8)	5 (6.6)
Nightmare	3 (3.9)	7 (9.0)	0
Emotional Disorder	3 (3.9)	4 (5.1)	1 (1.3)
Aggression	2 (2.6)	1 (1.3)	1 (1.3)
Enuresis	0	3 (3.8)	0
Poor Quality Sleep	0	2 (2.6)	1 (1.3)
Tearfulness	1 (1.3)	2 (2.6)	0
Sleep Terror	2 (2.6)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Cough	2 (2.6)	4 (5.1)	11 (14.5)
Pharyngolaryngeal Pain	6 (7.9)	6 (7.7)	3 (3.9)
Nasal Congestion	2 (2.6)	4 (5.1)	2 (2.6)
Rhinorrhoea	2 (2.6)	0	2 (2.6)
Epistaxis	2 (2.6)	1 (1.3)	0
INFECTIONS AND INFESTATIONS			
Upper Respiratory Tract Infection	10 (13.2)	6 (7.7)	6 (7.9)
Gastroenteritis Viral	5 (6.6)	3 (3.8)	3 (3.9)
Nasopharyngitis	3 (3.9)	2 (2.6)	1 (1.3)
Lower Respiratory Tract Infection	2 (2.6)	1 (1.3)	1 (1.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue	12 (15.8)	10 (12.8)	1 (1.3)
Irritability	7 (9.2)	6 (7.7)	3 (3.9)
Influenza Like Illness	2 (2.6)	3 (3.8)	1 (1.3)
CARDIAC DISORDERS			
Dizziness	5 (6.6)	2 (2.6)	5 (6.6)
Bradycardia	0	3 (3.8)	0
INVESTIGATIONS			
Body Temperature Increased	4 (5.3)	2 (2.6)	2 (2.6)
Heart Rate Increased	0	3 (3.8)	0
METABOLISM AND NUTRITION DISORDERS			
Decreased Appetite	3 (3.9)	3 (3.8)	3 (3.9)
Thirst	1 (1.3)	2 (2.6)	0
EAR AND LABYRINTH DISORDERS			
Ear Pain	4 (5.3)	0	1 (1.3)
Otitis Media Acute	3 (3.9)	1 (1.3)	0
IMMUNE SYSTEM DISORDERS			
Asthma	2 (2.6)	1 (1.3)	1 (1.3)
Multiple Allergies	2 (2.6)	0	1 (1.3)
SKIN AND SUBCUTANEOUS TISSUE			

TEAEs with greater than 5% incidence or at least twice the incidence in placebo group is presented below in Table 17.

Somnolence (31 to 40% of patients in active groups), fatigue (13 to 16%), irritability (8 to 9%), insomnia (5 to 6%), and emotional disorders (4 to 5%) appeared to occur at greater frequency in the active groups compared with placebo (1 to 7%), but did not appear to be dose-related. Three common, but less frequent TEAEs demonstrated possible dose-related effects: nightmares, constipation, and dry mouth.

Table 17: TEAEs with 5% or greater incidence in any active treatment group and at least twice the incidence of placebo.

	TREATMENT GROUP		
	CLON 0.2 mg/day N=76	CLON 0.4 mg/day N=78	PBO N=76
PREFERRED TERM	Subjects n (%)	Subjects n (%)	Subjects n (%)
Somnolence	30 (39.5)	24 (30.8)	5 (6.6)
Fatigue	12 (15.8)	10 (12.8)	1 (1.3)
Irritability	7 (9.2)	6 (7.7)	3 (3.9)
Pharyngolaryngeal pain	6 (7.9)	6 (7.7)	3 (3.9)
Body Temperature Increased	4 (5.3)	2 (2.6)	2 (2.6)
Insomnia	4 (5.3)	5 (6.4)	1 (1.3)
Ear Pain	4 (5.3)	0	1 (1.3)
Emotional Disorder	3 (3.9)	4 (5.1)	1 (1.3)`
Nightmare	3 (3.9)	7 (9.0)	0
Constipation	1 (1.3)	5 (6.4)	0
Dry Mouth	0	4 (5.1)	1 (1.3)

Study CLON-302

Headache was the most common AE in both treatment groups, occurring in 19 and 20 patients in the CLON+STM and the PBO+STM groups, (19% and 21%), respectively. Only four TEAEs met the criteria of an incidence of at least 5% in the CLON+STM group and at least twice the incidence of the PBO+STM group: somnolence, fatigue, increased body temperature and dizziness.

Somnolence occurred in 20 (20%) patients in the CLON+STM group and only 8 (8%) patients in the PBO+STM group. In this study, somnolence included all reports of sleepiness, drowsiness and similar verbatim terms as well as reports of “sedation”. Fatigue (which included reports of lethargy, malaise and similar terms), occurred in 16 patients (16%) in the CLON+STM group and in only 4 patients (4%) in the PBO+STM group. The other two TEAEs that met the above criteria were less frequent: increased body temperature and dizziness each occurred in 5 patients (5%) in the CLON+STM group and 2 patients (2%) in the PBO+STM group.

Dry mouth occurred in only 1 patient (1%) in the CLON+STM group and in 2 patients (2%) in the PBO+STM group. Vomiting occurred in 8 patients (8%) in the PBO+STM group but in no patient in the CLON+STM group.

Table 18: Treatment Emergent Adverse Events with 2% or Greater Incidence in Any Treatment Group by System Organ Class and Preferred Term (CLON 302 Safety Population)

	Treatment Group	
	CLON+STM N=102	PBO+STM N=96
SYSTEM ORGAN CLASS Preferred Term	Subjects n (%)	Subjects n (%)
NERVOUS SYSTEM DISORDERS		
Headache	19 (18.6)	20 (20.8)
Insomnia	5 (4.9)	3 (3.1)
Tension Headache	0	2 (2.1)
PSYCHIATRIC DISORDERS		
Somnolence[1]	20 (19.6)	8 (8.3)
Affect Lability	3 (2.9)	2 (2.1)
Aggression	2 (2.0)	5 (5.2)
Anxiety	2 (2.0)	1 (1.0)
Nightmare	2 (2.0)	1 (1.0)
Emotional Disorder	2 (2.0)	0
Enuresis	2 (2.0)	0
GASTROINTESTINAL DISORDERS		
Abdominal Pain Upper	12 (11.8)	8 (8.3)
Abdominal Pain	2 (2.0)	1 (1.0)
Diarrhoea	2 (2.0)	4 (4.2)
Nausea	1 (1.0)	3 (3.1)
Dry Mouth	1 (1.0)	2 (2.1)
Vomiting	0	8 (8.3)
Oral Pain	0	3 (3.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Nasal Congestion	9 (8.8)	6 (6.3)
Pharyngolaryngeal Pain	8 (7.8)	4 (4.2)
Cough	6 (5.9)	8 (8.3)
Epistaxis	3 (2.9)	1 (1.0)
Rhinorrhoea	3 (2.9)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue[1]	16 (15.7)	4 (4.2)
Irritability	5 (4.9)	9 (9.4)
INFECTIONS AND INFESTATIONS		
Upper Respiratory Tract Infection	4 (3.9)	4 (4.2)
Gastroenteritis Viral	3 (2.9)	0

SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	4 (3.9)	2 (2.1)
METABOLISM AND NUTRITION DISORDERS		
Decreased Appetite	6 (5.9)	4 (4.2)
Increased Appetite	0	2 (2.1)
INVESTIGATIONS		
Body Temperature Increased[1]	5 (4.9)	2 (2.1)
Heart Rate Increased	0	4 (4.2)
CARDIAC DISORDERS		
Dizziness[1]	5 (4.9)	2 (2.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Pain in Extremity	2 (2.0)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Joint Sprain	0	2 (2.1)

[1] AEs with a 5% or greater incidence in the CLON+STM treatment group and at least twice the incidence of PBO+STM

Treatment Emergent Adverse events by Dose

No analyses of TEAE vs dose was done.

TEAE by severity

Three patients in each study group had TEAEs rated by the investigator as severe: 6 TEAEs in the CLON+STM group and 4 TEAEs in the PBO+STM group.

TEAE by time

TEAE were classed by according to whether or not the event was present during any of the following three time periods: Day 0 to 21 (period of dose titration), Day 22-35 (stable dose regimen) and after Day 35 (period of down titration of study medication, generally through Day 56). The incidence of TEAEs was highest during the first time period and decreased during the last two periods for both treatment groups. In the CLON+STM group 51 of 102 patients (50%) reported a TEAE during the first time period and 32 of 102 (31%) and 25 of 95 (26%) reported TEAEs in the second and third time periods respectively. Similarly, for the PBO+STM group, 50%, 23% and 22% reported at least one TEAE in the first, second and third periods, respectively. In the CLON+STM group, somnolence decreased in the three time periods from 12% in the first period, to 8% in

the second period to 1% in the third period. The incidence of headache in this group (13%, 8% and 3%), fatigue (14%, 2% and 0%) and upper abdominal pain (8%, 4% and 0%) in these three periods, respectively, showed the same pattern. Similar patterns occurred in the frequency of reporting over time of the most common TEAEs in the PBO+STM group: headache (incidences of 12%, 9%, and 1% in the three time periods, respectively), upper abdominal pain (6%, 1%, and 1%) and somnolence (6%, 1% and 0).

Most Common Treatment Emergent Adverse Events by ADHD Psychostimulant Use

Fifty nine patients received CLON+MPH, 59 patients received PBO+MPH, 43 patients received CLON+AMPH, and 37 patients received PBO+AMPH. The patterns of TEAEs in the CLON subgroups appear unaffected by the choice of stimulant administered.

Table 19: Most Common (5% or Greater Incidence in a CLON+STM group) Treatment-Emergent Adverse Events by Concomitant ADHD Psychostimulant Use

PREFERRED TERM	AMPHETAMINE		METHYLPHENIDATE	
	CLON+STM	PBO+STM	CLON+STM	PBO+STM
	N=43	N=37	N=59	N=59
	Subjects n (%)	Subjects n (%)	Subjects n (%)	Subjects n (%)
Somnolence[1]	7 (16.3)	2 (5.4)	13 (22.0)	6 (10.2)
Headache	9 (20.9)	8 (21.6)	10 (16.9)	12 (20.3)
Fatigue[1]	9 (20.9)	2 (5.4)	7 (11.9)	2 (3.4)
Abdominal Pain Upper[1]	8 (18.6)	2 (5.4)	4 (6.8)	6 (10.2)
Nasal Congestion[1]	5 (11.6)	0	4 (6.8)	6 (10.2)
Pharyngolaryngeal Pain[1]	4 (9.3)	0	4 (6.8)	4 (6.8)
Cough	4 (9.3)	2 (5.4)	2 (3.4)	6 (10.2)
Decreased Appetite	3 (7.0)	2 (5.4)	3 (5.1)	2 (3.4)
Body Temperature Increased[1]	4 (9.3)	1 (2.7)	1 (1.7)	1 (1.7)
Irritability	4 (9.3)	3 (8.1)	1 (1.7)	6 (10.2)
Dizziness[1]	2 (4.7)	2 (5.4)	3 (5.1)	0
Insomnia	2 (4.7)	1 (2.7)	2 (3.4)	2 (3.4)
Rash	2 (4.7)	2 (5.4)	2 (3.4)	0
Upper Respiratory Tract Infection	1 (2.3)	2 (5.4)	3 (5.1)	2 (3.4)
Epistaxis [1]	2 (4.7)	0	1 (1.7)	1 (1.7)
Rhinorrhoea[1]	2 (4.7)	0	1 (1.7)	0
Gastroenteritis Viral[1]	2 (4.7)	0	1 (1.7)	0
Affect Lability	2 (4.7)	2 (5.4)	1 (1.7)	0
Abdominal Pain[1]	2 (4.7)	0	0	1 (1.7)

Laboratory Findings

Clinical Laboratory values were obtained at Screening and at Week 8 visit (last day of study drug administration) or discontinuation visit if the patient was discontinued prior to end of study. Laboratory parameters included Chemistry (glucose, urea, creatinine, sodium, potassium, chloride, CO2, bilirubin, alkaline phosphatase, uric acid, calcium, albumin, serum HCG, TSH), Hematology (CBC with differential, MCV, MCHC), Urinalysis (pH, blood, protein, glucose, ketones and bilirubin) and Urine drug screen.

Study CLON-301

Analyses of these results did not reveal significant abnormalities in any patient on active treatment or other evidence of a drug effect on these laboratory parameters. One patient (0717), in the placebo group, had elevated TSH values at Screening which rose during the study at Week 8 (6.46 uIU/mL at Screening and 9.37 uIU/mL at Week 8; upper limit of normal = 4.20 uIU/mL). Following review of the Week 8 laboratory results, the patient was referred to an endocrinologist for further evaluation and was subsequently diagnosed with hypothyroidism for which he began treatment.

One patient on CLON 0.2 mg had an elevation in TSH at Week 8 (3.66 uIU/mL at Screening compared to 6.05 uIU/mL at Week 8; upper limit of normal = 4.20 uIU/mL). The patient went on to enroll in the CLON-303 open-label continuation study and received 6 months of open label treatment. Five months after completing the open-label study, a repeat TSH level was obtained with a result of 4.27 uIU/mL.

CLON-302

Four patients receiving CLON+STM had possible clinically significant laboratory abnormalities.

Two children (3803 and 4301) had urinalyses results suggestive of urinary tract infections (UTIs). Neither child was symptomatic. Repeat urinalysis for both patients was later performed without UTI therapy and results were normal.

Patient 3604 had a small drop in hematocrit from a low normal value of 38.2% at Screening to a below-normal value of 36.8% at Week 8. Hemoglobin and red cell counts remained just within normal limits. Repeat complete blood count is planned. A TEAE of “anemia” was reported.

Patient 2308 had a Screening white blood cell (WBC) count of 5.0 x 10^9/L (normal) with a neutrophil count of 1.35 x 10^9/L (low). At Week 8 the WBC count was 3.3 x 10^9/L (low) but the differential was not performed; thus the neutrophil count was unknown. The Investigator requested that the subject return for a repeat CBC with differential; however, attempts to contact the subject were unsuccessful.

Reviewers Comments: These findings were confirmed by this reviewer on a detailed review of data submitted by the sponsor. There were no signals suggestive of a treatment related effect on any of the laboratory parameters. This reviewer is of the opinion that use of clonidine in this population did not show any effect on the laboratory parameters.

7.4.3 Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate and body temperature) were collected at Screening, Baseline prior to dosing, at weekly on-therapy visits and at closeout visits. Vital signs were measured with the subject in a sitting position and resting for at least two minutes prior to taking the measurement. The dominant arm was used for blood pressure and heart rate measurements.

7.4.3.1 Blood pressure

Study CLON-301

Changes from baseline in Systolic Blood pressure (SBP) were dose related. Mean Systolic BP decreased from baseline values by upto 1.5 mm Hg during weeks 2 through 5 in the 0.2 mg/day group and by upto 6 mm Hg during weeks 2 through 5 in the 0.4 mg/day group. The mean change from weeks 2 to 5 was -0.7 mmHg in the 0.2 mg/day group and -4.58 mmHg in the 0.4 mg/day group. The minimum and maximum observed SBP in the 0.2 mg/day group were 80 mm Hg and 139 mm Hg respectively. In the 0.4

mg/day group, the minimum and maximum observed SBP were 72 mm Hg and 143 mm Hg respectively. In the placebo group, the minimum and maximum observed values were 82 mm Hg and 147 mm Hg respectively.

Mean Diastolic Blood pressure (DBP) changed from Baseline values with increases of about 0.5 mm to decreases of about 2 mm during Weeks 2 through 5 in the 0.2 mg/day group. Mean DBP decreased about 4 to 5 mm Hg during Weeks 2 through 5 in the 0.4 mg/day group and increased about 0.5 to 1.5 mm Hg at most time points in the placebo group. The mean change from weeks 2 to 5 was -1 mm Hg for the 0.2 mg/day group and -4.38 mmHg for the 0.4 mg/day group. The minimum and maximum observed DBP in the 0.2 and 0.4 mg/day groups were 41 mm Hg and 84 mm Hg respectively. In the 0.4 mg/day group, the minimum and maximum observed values in the low and high dose groups were 40 and 89 respectively. In the placebo group, the minimum and maximum observed values were 48 mm Hg and 117 mm Hg respectively.
Overall, the placebo-subtracted mean changes in blood pressure ranged from -2.2 mmHg on Tradename 0.2 mg/day to -6 mmHg on Tradename 0.4 mg/day. The placebo subtracted mean change in diastolic pressure was -2 mmHg on Tradename 0.2 mg/day to -5.4 mmHg on Tradename 0.4 mg/day.

Study-CLON-302

Mean changes in blood pressure were modest in the active treatment group. Mean SBP decreased about 4 to 5 mm Hg from Baseline values during weeks 2 through 5 in the CLON+STM group and increased about 1 mm Hg during most time points in the PBO+STM group. The minimum and maximum observed values in the low and high dose groups in SBP were 64 and 145 respectively in the CLON+STM group and 59 and 147 in the PBO+STM group.

Mean DBP decreased about 1 to 4 mm Hg during Weeks 2 through 5 in the CLON+STM group compared with no change or 1 mm of Hg increase in the PBO+STM group at most time points. The minimum and maximum observed DBP in the 0.2 and 0.4 mg/day groups were 42 mm Hg and 108 mm Hg respectively. In the PBO+STM group, the minimum and maximum observed values in the low and high dose groups were 44 and 113 respectively.

7.4.3.2 Heart Rate

CLON-301

Mean heart rate generally decreased from Screening values by 3 to 4 beats per minute (bpm) during weeks 2 through 5 in the 0.2 mg/day group and decreased by about 5 to 6 bpm in the 0.4 mg/day dose group. The mean change in heart rate from weeks 2 to 5 was -2.5 bpm in the clonidine 0.2 mg/day and -5 bpm in the 0.4 mg/day groups The change in the placebo group was -0.76 bpm. The placebo-subtracted change in heart rate was -3.25 to -5.75 bpm in the 0.2 mg/day and 0.4 mg/day groups respectively. The minimum observed heart rate was 46 and the maximum rate was 117 bpm on 0.2 mg/day of clonidine. On 0.4 mg/day, the minimum and maximum rates were 47 and 120 respectively. In the placebo group, the minimum and maximum observed heart rates were 55 and 103 respectively.

CLON-302

Mean heart rate decreased from Baseline by 4 to 5 beats per minute (bpm) in the CLON+STM group compared with increases of 1 to 3 bpm at most time points in the PBO+STM group. The minimum and maximum heart rates in the CLON+STM treatment group was 50 and 125.

7.4.3.3 Body temperature

CLON-301

There were no meaningful changes in body temperatures between any of the three treatment groups.

However, 4 subjects in in the CLON 0.2 mg group, 2 subjects in the 0.4 mg/day group and 2 subjects in the placebo group developed increased body temperatures. All the readings returned to normal levels by the next visit and the increased temperatures were thought to be not related to study drug.

CLON-302

There were no meaningful changes in Body Temperature in either treatment group. Five patients in the CLON+STM group and 2 patients in the PBO+STM group had TEAEs of increased body temperature. None were considered possibly related to study drug. All but one report of increased temperature (in the PBO+STM group) were associated with a reported infection.

7.4.4 Electrocardiograms (ECGs)

Twelve-lead ECGs were obtained at the Screening visit and repeated 3 times at 10 minute intervals; an average reading was used for screening purposes. A single reading was obtained at the Baseline visit unless otherwise indicated. In addition, ECGs were collected at Days 7, 14, 28, 42, and 56 (Weeks 1, 2, 4, 6, and 8 visits) and at the Week 9 (Safety Follow- Up/Close-out) visit.

CLON-301

A total of 745 ECG readings were obtained from subjects in the CLON 0.2mg/day group, 773 from subjects in the CLON 0.4mg/day group, and 749 from subjects in the placebo group. ECGs were obtained three times at Screening and once at Baseline (from which four ECGs, the Screening/Baseline average values were obtained), one

time during each on-therapy visit at Weeks 1, 2, 4, 6 and 8, and one ECG on the week 9 closeout visit. Week 4 visits represent the ECG assessment visit at which maximum doses were given. Investigators were allowed to obtain additional ECGs at their discretion. I have separately analysed these findings under heart rate and QT intervals.

Heart Rate: Bradycardia was defined as a heart rate less than 55 bpm for ages 6 to 11 and less than 50 for ages 12 to 17. Tachycardia was defined as a heart rate more than 134 for children aged 6 to 11 or >119 for children aged 12 to 17.

At baseline/screening, the incidence of sinus bradycardia in the low dose, high dose and placebo groups were 12%, 4%, and 7% respectively; during therapy, these increased to 18%, 25% and 12% respectively.
Subject 0605 in the CLON 0.4 mg group had one reading of HR at 48 at week 4. This returned to normal by the next week.
Subject 0609 had one reading of HR at 53 and two subsequent readings at 52.
Subject 0707 had one reading of 55 at week 1.

None of these patients reported TEAE's of symptoms associated with symptomatic bradycardia. All of these were considered related to study medication.

At baseline/screening, the incidence of tachycardia was made in 4%, 1% and 3% of patients in the low, high and placebo groups respectively. During drug therapy, the incidences of this diagnosis were 4%, 5% and 3% respectively.

Three patients were reported to have sinus tachycardia.

Subject 0609 had a reading on HR at 115 at week 9.

Subject 0614 had three readings at week 1 which were 108, 104 and 109. Patients ECG's were also abnormal and hence study medications were stopped. However, patient received cardiology overread after patient had been off drug for 10 days. The readings were normal, but medical monitor felt that patient had been off drug for too long and was hence felt to be inappropriate to start him back on the study drug.

Subject 0647 in the 0.4 mg group had HR readings >115 with a maximum reading of 126 at week 8. Subject had a 'stomach virus'.

ECG changes- QTc Values

No patient had an on-therapy QTcB or QTcF result of 500 msec or greater.

There were no differences in incidence of increase of QTcB or QTcF of 30 msec or less between active and placebo groups. The incidence of increases in QTc of 30 msec to 60 msec were 17%, 20.5%, and 26% for QTcB and 9%, 17% and 9% for QTcF in the low dose, high dose and placebo groups, respectively.

Three patients had QTc values which increased from Screening/Baseline averages by at least 60 msec while on therapy with study medication.

Subject 0715 in the low dose group had average baseline/screening QTcF and QTcB of 399 and 409 msec respectively that rose while patient was on only 0.1 mg/day to 466 msec and 494 msec respectively. On 0.2 mg dose the next week, the values returned to baseline/screening levels. The patient was discontinued. However, the reason for discontinuiation was fatigue.

Patient 0618 had average baseline/screening QTcF and QTcB of 398.5 msec and 404 msec, which rose at week 4, while on 0.4 mg/day to 467 msec and 480 msec

respectively. The patient was discontinued. The reason for discontinuiation was the AE of prolonged QT.

Patient 0928 had baseline/screen QTcB mean reading of 403.8, which increased at week 6 to 468.0. QTcF at screen was 408.3 and increased at week 6 to 443. Both these had returned to baseline values by week 8.

Study CLON-302

A total of 1041 ECG readings were obtained from subjects in the CLON+STM group and 944 from subjects in the PBO+STM group. ECGs were obtained three times at Screening, once at Baseline (from which initial 4 ECGs the Screening/Baseline average values were obtained), one time during on-therapy Weeks 1, 2, 4, 6 and 8, and one ECG at the week 9 closeout visit. Week 4 visits represent the ECG assessment visit at which maximum doses could be given. Investigators were allowed to obtain additional ECGs at their discretion.

Heart rate decreases were consistent with the pharmacologic effect of clonidine. The mean Heart rate decreased by about 7 beats per minute (bpm) in the CLON+STM group compared to decreases of less than 1 bpm in the PBO+STM group. Corrected QT in the CLON+STM group showed small or no change from Screening/Baseline values when compared with changes in the PBO+STM group.

QTcB *decreased* by 2.5 msec and QTcF *increased* by 3 msec in the CLON+STM group compared with a 2 msec *increase* in QTcB and a 1 msec *increase* in QTcF in the PBO+STM groups. These small changes do not suggest an effect of active treatment on QTc. Changes in QRS and PR intervals were minimal. QRS intervals increased by less than 1 msec in both treatment groups and PR interval increased about 1 msec in both treatment groups.

No patient in the study had a QTcF of 450 msec or more, and no patient had a QTcB of 475 msec or more. For changes in either QTcB or QTcF, there were no suggested differences between the CLON+STM and PBO+STM groups in the incidence of individual increases from average Screening/Baseline to any on-therapy value of QTcB or QTcF of 30 msec or less, of more than 30 msec to 60 msec, or of greater than 60 msec.

One patient in the PBO+STM group had an increase of QTc of >60 msec. Subject 3806 in the PBO+STM group had QTcB screen value of 374.5 and QTcF of 366. At the week 2 ECG, the QTcB value was 445 msec, which is a shift of 70.5 msec. The QTcF value was 407, which was a shift of 41 msec. The shifts at week 4, 6, 8 and closeout on QTcB were 26.5, 35.5, 30.5 and 54.5 and on QTcF were 21, 20, 17 and 34 respectively. The patient completed the study.

Reviewer's Comments: This reviewer is of the opinion that monitoring done with regards to vital signs were adequate.In both the studies, changes in blood pressure were noted. Changes from baseline in Systolic Blood pressure (SBP) were dose related, with mean Systolic BP decreasing from baseline values by upto 1.8 mm Hg 0.2 mg/day group and by 5 to 6 mm Hg in the 0.4 mg/day group. Mean Diastolic Blood pressure (DBP) decreased about 4 to 5 mm Hg.
No subjects had QTc>500. Three subjects in the monotherapy group had an increase in QTc>60 msec while on therapy and one had to be discontinued from the trial. This reviewer discussed the case with the QT team who suggested that no further consult was warranted at this time.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were done.

7.4.6 Immunogenicity

No data on immunogenicity was submitted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Overall, the incidence of patients with a TEAE is higher in the active groups than placebo, although there is not a relationship with dose. The numbers and incidences of patients with TEAEs are 63 (83%), 65 (83%) and 55 (72%) in the low dose, high dose and placebo groups respectively. There were 240, 230 and 138 TEAEs in each of these groups, respectively.

7.5.2 Time Dependency for Adverse Events

Time dependency was evaluated by noting if the event was present during any of the following three time periods: Day 0 to 21 (period of upward dose titration, achieved on Day 7 for the low dose group, achieved on Day 21 for the high dose group), Day 22-35 (stable maximum dose) and after Day 35 (period of down titration, generally through Day 56).

Overall, the incidence of TEAEs was slightly higher during the first time period and similar during the last two periods. For all patients in the study, TEAEs occurred in 129 of 230 (56% of patients) during the first time period; in 102 of 223 (46% of patients) in the second time period, and in 98 of 211 (46% of patients) in the third time period. The pattern of relatively higher reporting of TEAEs during the first time period was strongest for the high dose group which reported TEAEs in 62%, 45% and 50% in the first, second and third time periods, respectively, and weakest for the placebo group which reported TEAEs in 42%, 37% and 35% of patients in these three time periods, respectively. In particular, the high dose group reported a much higher rate of

somnolence (24%) during the first period than during the later two periods, (11% and 3%, respectively). Headache also followed a strong pattern of decreasing frequency with time in the high dose group. The low dose group showed similar, but less striking reductions in somnolence and headache with time. The placebo group tended to report fewer headaches and more cough in the third time period than in earlier time periods.

7.5.3 Drug-Demographic Interactions

No such analyses was conducted.

7.5.4 Drug-Disease Interactions

No analyses conducted.

7.5.5 Drug-Drug Interactions

Adverse events related to interactions between clonidine and methylphenidate are of special interest as this is a commonly used regimen and the sponsor is seeking such an indication in this NDA. The label of methylphenidate contains the statement: "Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination has not been systematically evaluated."

(b) (4)

There have been concerns raised in the literature about the potential for interaction between clonidine and methylphenidate. These were from four reports of life-

threatening or fatal cases in children. This was published in a paper by Robert Fenichel in 1995. The four cases are described below:

In study CLON-302, the overall incidence of AE's was only slightly higher in the group treated with CLON+STM than in the group treated with PBO+STM (68% and 64% respectively).

There were no deaths and one serious or severe TEAE's leading to discontinuiation from the study in the CLON+STM group and 4 in the PBO+STM group.
The single serious TEAE in the CLON+STM group involved an intentional overdose of three tablets of study medication and was termed as 'attention-seeking behavior'. Study medication was restarted and the child completed the study without further events.
The severe TEAEs in the CLON+STM group included one child who developed three severe TEAEs during Week 7 of the study: "memory disorder" (a single 5-10 minute episode of "zoning out" with loss of memory), an episode of anger, and "movement disorder" (increased mouth noises for a day). One child in the CLON+STM group developed severe fatigue and severe "bradyphrenia" (slow thinking) associated with moderate dizziness. Another patient in this group reported a severe sore throat.

The one patient in the CLON+STM group who discontinued study drug because of a TEAE, was the patient with severe bradyphrenia and fatigue, noted in the preceding paragraph.

The Division of Psychiatry products also requested that the Division of Pharmacovigilance I (DPV I) search the Adverse Events reporting System (AERS) database for cases of death associated with combination. The review concluded that

(b) (4)

Reviewer's Comments: *In all of the three fatalities described in the literature, the presence of multiple contributing factors precludes attributing the deaths to clonidine, methylphenidate, or the combination. The one case of the 6-year old boy, can be explained by the fact that clonidine can lower blood pressure and heart rate, and not necessarily to the combination.*

Study CLON-302 did not find significant differences between the CLON+STM and PBO+STM groups in AE's except somnolence (18.6% vs 7.3%), fatigue (13.7% vs 4.2%) and dizziness (4.9% vs 1%). Of the subjects who experienced dizziness, the differences were in the group that was treated with clonidine+methylphenidate (3 subjects with dizziness compared to 0 in the PBO+STM group).
Treating patients with a combination of TRADENAME and stimulants has been shown to be well tolerated. (b) (4)
(b) (4)
(b) (4)
At this time, there is no reason to conclude that the combination of clonidine and methylphenidate has any additional safety concerns.

7.6 Additional Safety Evaluations

Study CLON-303

An open-label, chronic exposure evaluation of the safety of CLONICEL® (clonidine HCl sustained release) in the treatment of children and adolescents with ADHD.

This was a 12-month, multi-center, open-label study of the safety of a flexible dosing regimen of clonidine in children and adolescents (6 to 17 years) who met DSM-IV criteria for ADHD. Candidates for enrollment in this study were subjects who completed Study CLON-301 or Study CLON-302, were good candidates for continued treatment with clonidine in the opinion of the Principal Investigator, and expressed the desire to do so. Approximately 350 subjects were targeted for enrollment in this chronic dosing study, but the actual final number was dependant on the percent of patients in CLON 301 and CLON-302 who elected to continue treatment with clonidine. Dosing started at 0.1 mg/day (given in the evening) and a proper titration schedule was used to escalate

patients to a maximum of 0.4 mg/day, given as 0.2 mg b.i.d. Subjects were maintained at the maximum tolerated dose for up to 12 months when they were gradually tapered off treatment. Treatment was discontinued for subjects who could not tolerate a minimum of 0.1 mg/day. In addition to treatment with clonidine, patients could also receive treatment with other medications for their ADHD symptoms, including stimulants and/or antidepressants.

During the review cycle, the sponsor submitted the complete study report for this study.

Results: A sample size for enrollment was not determined; enrollment depended on the number of subjects from CLON-301 and CLON-302 who elected to continue treatment in CLON-303.

A total of 303 subjects were enrolled in CLON-303 and their status is as follows:

Table 20: Disposition of Study Subjects in CLON-303

	CLONICEL[1]
Planned, N	350
Enrolled, N	303
Final Dataset, N	301
Efficacy Evaluable, N	290
Safety Population[1], N	301
Completed Original Protocol (6 months), n (%)	53 (17.6)
Completed Amendment 1 (12 months), n (%)	108 (35.9)
Discontinued Prematurely[2], n (%)	140 (46.5)
Withdrew Consent	45 (15.0)
Adverse Event	18 (6.0)
Lack of Efficacy	16 (5.3)
Lost to Follow-up	37 (12.3)
Protocol Violation	15 (5.0)
Other[2]	9 (3.0)

Exposure:

For the 301 subjects included in the Study CLON-303 Safety Population, exposure was calculated by including time on active treatment in the prior double-blind study (CLON-301 or CLON-302). With prior double-blind exposure included, 215 subjects (74.1%) received clonidine for ≥24 weeks and 113 subjects (37.5%) received clonidine for ≥48 weeks .

Table 21: Overview of Treatment-Emergent Adverse Events in Study CLON-303 (Safety Population)

Summary	All Subjects
Total Safety Population, n	301
Subjects with one or more TEAEs, n (%)	246 (81.7)
Total Number of TEAEs, n	954
Subjects with one or more Related[1] TEAEs (Adverse Drug Reactions), n (%)	178 (59.1)
Total Number of Related[1] TEAEs (Adverse Drug Reactions), n	438
Subjects with one or more Serious Adverse Events, n (%)	2 (0.7)
Total Number of Serious Adverse Events, n	2
Subjects with one or more Adverse Events Leading to Discontinuation[2], n (%)	17 (5.6)[2]

Deaths: There were no deaths in the program.

Serious Adverse Events: There were 2 serious adverse events in the 215 patients in the safety program. One was an episode of cellulitis associated wirg second-degree burns incurred in a motor bike accident that was unlikely due to a relationship with the study drug. The other was an event of suicidal behavior, which was not associated with clinical signs or symptoms of a large overdose.

Discontinuiations: Eighteen patients (5.6%) discontinued because of a TEAE. These included three patients with somnolence, two with headache and one each with anger, depressed mood, auditory hallucinations, self mutilation, fatigue, irritability, dizziness QT prolongation, sleep terror, abdominal pain, stomach discomfort and suicidal behavior (also an SAE).

Treatment Emergent Adverse Events: The most common TEAEs were expected adverse events of clonidine or common adverse events expected of the population.

Table 22: Common Treatment Emergent Adverse Events –Study CLON 303

Preferred Term, n (%)	All Subjects (N=301)
Somnolence	96 (31.9)
Headache	49 (16.3)
Upper Respiratory Tract Infection	39 (13.0)
Abdominal Pain Upper	37 (12.3)
Fatigue	37 (12.3)
Irritability	28 (9.3)
Insomnia	28 (9.3)
Cough	25 (8.3)
Decreased Appetite	25 (8.3)
Body Temperature Increased	22 (7.3)
Gastroenteritis Viral	20 (6.6)
Nasal Congestion	18 (6.0)
Vomiting	17 (5.6)
Pharyngolaryngeal Pain	16 (5.3)

There were no changes in chemistry or hematology values over time to suggest a drug effect. Vital sign assessments revealed that changes in blood pressure and heart rate appeared to be drug related and consistent with the known pharmacology of the drug.

During the course of the study, 4 subjects reported TEAEs consistent with hypotension, 4 reported TEAEs related to increases in heart rate, and 1 subject reported a TEAE related to dyspnea. None of these events were serious, severe, or resulted in discontinuation, and each event resolved.

ECG-recorded decreases in heart rate were consistent with the known pharmacology of clonidine. Heart rate decreased by a mean of 8-10 bpm at most time points.Mean weight increased during the study, probably reflecting the expected growth of children during the long-term study.

Mean body weights increased by 0.9 kg at the Month 2 visit, 2.1 kg at the Month 6 visit and 4.5 kg at the Month 12 visit.

There were 4 TEAEs that appeared to be related to ECG findings. All four patients, 0418, 0703, 0714 and 0721, were reported to have TEAEs of QT prolongation. All four TEAEs were considered mild and possibly related to study drug. One of these patients, 0418 was discontinued because of the TEAE. The other patients continued on therapy without dose adjustment.

Patient 0418 was a 7 year-old white female whose pre-dosing ECGs in both CLON-301 and CLON-303 demonstrated higher-than-normal QTcB/QTcF values (average of four assessments in CLON-301 = 462/458 msec and a single assessment in CLON-303 = 472/448 msec, compared with upper limits of 449/449 msec). The values remained little changed throughout CLON-301 and 4 months into CLON-303. Three weeks later, the values rose on repeated ECGs: QTcB values varied between

499 and 532 msec; QTcF values varied between 496-520 msec. There were no large changes in heart rate to explain these latest changes in QTc.

The PI contacted the Sponsor's Medical Monitor at that time, leading to the patient's discontinuation from the study. Five days later, the QTc values were similar to those throughout the study (but remained higher than normal age-related values).
The patient was referred to a cardiologist who confirmed post-study elevated QTc values of 460-480 msec (correction factor not provided), which he considered "borderline elevations". Exam and family history were not revealing, and the patient is being followed by the cardiologist without restrictions. The Investigator considered the event mild and possibly related to study drug.

Patient 0703 was a 10 year-old white male who experienced a one-time QTcB/QTcF elevation on the last day of dosing (Month 6).

The patient had completed CLON-301 study after randomization to the 0.4 mg daily dose group. In that study the average QTcB/QTcF on four pre-dosing ECGs were 424/412 msec (highest QTcB/QTcF were 443/427 msec). Heart rates were 65 to 74 bpm. The single Baseline QTcB/QTcF values in CLON-303 were considerably lower, 403/399 msec. The child was titrated up to 0.3 mg daily in CLON-303, and took this dose on most days of the trial.

There was little change in QTcB/QTcF values during the study until the patient's final Month 6 visit when he had been tapered down to 0.1 mg daily. ECG on that day demonstrated QTcB/QTcF values of 462/433. Heart rate, which had ranged between 53 to 79 bpm at prior visits, was higher (88 bpm) at Month 6, which may have contributed to the one-time increase in QTc.
A week after the last dose, ECG values (QTcB/QTcF and heart rate) were similar to those at Baseline.

The Investigator considered the event to be mild and possibly related to study drug.

Patient 0714 was a 9 year-old white female whose Month 6 ECG (the patient's scheduled final visit) showed an abnormal elevated QTcB/QTcF of 452/401 msec (normal range up to 449/449 msec). The patient had received 0.3 mg for the last 2 ½ months of treatment; she received 0.1 mg on the day of the 6 month visit. A TEAE of "Prolonged QT" was reported. The Investigator considered the event to be mild and possibly related to study drug. However, this value was similar to (even slightly less than) the abnormal CLON-303 Baseline values of 453/409 msec. QTcB/QTcF values a month after final dosing were normal. All other QTcB/QTcF values during the study were normal, as were all Baseline and on-therapy values obtained during the CLON-301 study (0.2 mg dosing group). Thus the event did not represent a true change from Baseline.

Patient 0721 was an 11 year-old white female who had an abnormal QTcB at Week 2 while receiving 0.2 mg per day of study drug. QTcB/QTcF values were 456/405 msec. Baseline values were similar: 443/412 msec. A TEAE of mild QT prolongation, possibly related to study drug, was reported. Week 3 and 4 QTcB/QTcF values (on 0.3 mg study drug daily) were 458/426 msec and 447/412 msec, respectively. The TEAE was considered resolved at Week 4.

The patient was discontinued for lack of efficacy a month later. A final ECG, obtained 2 weeks after final dosing demonstrated QTcB/QTcF values of 392/371 msec.

In the CLON-301 study, the patient had been randomized to the 0.2 mg/day dosing group. All QTcB/QTcF values in that study were normal, without evidence of drug related effects.

Comments: The exposure to clonidine in this study satisfies the ICH recommendations. The results from CLON-303 are consistent with the known pharmacology of the drug and its mechanism of action. The safety profile is similar to results obtained from the controlled trials. There are no new safety signals identified.

7.6.1 Human Carcinogenicity

No data on carcinogenicity was submitted

7.6.2 Human Reproduction and Pregnancy Data

No reproduction or pregnancy data was submitted

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessment of effects on growth was conducted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were two cases of overdose in the clinical program. One of them was in study CLON-302 and the other was in study CLON-303.

Overdose in Study CLON-302

Patient 2702: A 13 year old Hispanic male receiving 0.2 mg CLON daily (0.1 mg b.i.d) and Concerta (methylphenidate) 54 mg/day took 3 additional doses of the study drug during the second week (receiving a total of 0.5 mg), after an argument with sibling and mother. He reported this event to his mother the following morning and was taken to his primary care physician, complaining of a stomach ache and feeling anxious since taking the extra medication. He was admitted to the hospital for a suspected suicide attempt. Study medication was temporarily held, although he was continued on Concerta 54

mg/day and received clonidine immediate release 0.2 mg daily on two of his three days in the hospital.

The Investigator met with the child and mother on the day of hospital discharge, and after the interview and review of hospital and prior records, was convinced that the event “did not appear premeditated, related to depression, or sincere desire to do himself harm.” The Investigator noted that the child had a documented history of impulsive behavior and he strongly believed that the event was “attention-seeking behavior”, consistent with previous behaviors and unrelated to study medication. Study medication was restarted that day at 0.1 mg daily and was eventually titrated to 0.4 mg daily. The child completed the study without further adverse events.

Overdose in Study CLON-303

Patient 1105: A 14-year old white male who was diagnosed with ADHD, combined type, had completed study CLON-301 (0.2 mg daily dose group) and was enrolled in CLON-303 a week later. He was titrated up to 0.2 mg twice daily with good response to treatment with much improved ADHD symptoms.

At the Month 3 visit, 140 tablets (0.1 mg tabs) of study medication were dispensed. That same evening, the patient reported that he had ingested all 140 tablets (a potential 14 mg dose in this 65 kg child). Empty study drug containers were found at home. The event apparently occurred following a disagreement with the patient’s girlfriend. He was evaluated that evening in the emergency room and admitted to the hospital intensive care unit (ICU) for psychiatric observation.

The child was given charcoal in the ambulance but it was not known whether pill fragments were recovered. On subsequent stomach lavage, no pill fragments were found. The child experienced no clinical sequale and vital signs were stable and no intervention was required for blood pressure or heart rate.There was some skepticism

by hospital personnel regarding the reported amount of drug ingested, given the lack of signs or symptoms of a large overdose. According to the child's father the child had remained awake following the overdose until 1:15am and then fell asleep, and experienced drowsiness during the two days following the overdose but was oriented to date and time.

The child was transferred to a psychiatric facility, and was reported to have been started on Prozac, and was initially very hyperactive, but calmed down. The child was physically stable and was doing well six weeks after the event.

Thus, important details regarding whether an actual overdose occurred, the state of mind of the subject at the time of the event, diagnoses and follow up care remain unknown. The event was considered by the Investigator to be moderate in severity and probably not related to study medication.

Abuse potential wasn't studied.

7.7 Additional Submissions / Safety Issues

None

8 Postmarketing Experience

JENLOGA has not been marketed since approval.

9 Appendices

9.1 Literature Review/References

The sponsor has submitted a review of the literature in support of the efficacy of clonidine in treating symptoms of ADHD. An review of the literature from 1980 to 1999 (Connor et al., 1999) revealed 39 publications that reported on clonidine's efficacy and side effects for symptoms of ADHD and coexisting conditions in children. Of these, 11 studies provided sufficient information to be included in a meta-analysis.
A total of 150 patients received clonidine in these 11 studies. The mean ages in the studies ranged from 8 to 16 years. The dose of clonidine averaged 0.18 mg/day with a range of 0.10 to 0.24 mg/day. The average duration of treatment was 11 weeks with a range of 3 to 51 weeks. Using the most conservative approach of determining effect sizes, the authors found that clonidine demonstrated positive treatment effects on symptoms of ADHD in all 11 studies, with parents reporting more benefits than teachers or clinicians, probably due to clonidine's main effects on behavior, more so than on attention or cognition. The most frequent side effects of clonidine included sedation, irritability, dry mouth, hypotension, dizziness, and sleep disturbance (generally awakening in the middle of the night). Skin irritation and erythema were a common problem reported by patients using the clonidine transdermal patch.

Connor et al. (2000) randomly assigned 24 children with ADHD to receive, in blinded fashion, clonidine alone, methylphenidate (MPH) alone or the combination of both agents for 3 months. Only the clonidine monotherapy group showed significantly decreased fine motor speed. Total adverse events were similar in the three groups with a 'trend for the combination clonidine and MPH group to have lower mean severity of side effects." The only specific adverse event noted in the report was of drowsiness and sleepiness which were rated on a check list and found to be of similar severity in all three groups.

Two important clinical studies were funded by the National Institutes of Health (NIH). The first was a randomized double-blind placebo-controlled parallel-group study of 16 weeks treatment with clonidine, methylphenidate (MPH) or the combination of both treatments in 136 children with Tourette's Syndrome and comorbid ADHD (TACT Study, Tourette Syndrome Study Group 2002). Although underpowered to show differences between any two of the four groups, the two groups receiving clonidine (clonidine alone and clonidine plus MPH) showed statistically better improvement in the primary endpoint, the Conners' Abbreviated Symptom Questionnaire for Teachers (CASQ-Teacher) than the two groups not receiving clonidine (MPH alone and placebo). Similarly, the groups receiving MPH (MPH alone and MPH plus clonidine) showed statistically significantly better improvement in the ASQ-Teacher score than the two groups not receiving MPH (clonidine alone and placebo). While improvements of each of the single drug groups for this primary endpoint were virtually identical and only marginally significant, the combination of clonidine and MPH showed larger treatment effects which were statistically significant vs. placebo ($p < 0.0001$).

The second study funded by NIH, the Clonidine in ADHD Trial (CAT Study, Palumbo et al., 2008), which was performed by a subset of investigators of the first study, evaluated 122 patients with ADHD without chronic tic disorder using a study design very similar to that of the TACT study. This study evaluated the efficacy, safety, and tolerability of clonidine used alone or with methylphenidate in children with any subtype of ADHD, randomly assigned to clonidine, methylphenidate, clonidine in combination with methylphenidate, or placebo according to a 2 x 2 factorial design, Treatment duration was 16 weeks with doses flexibly titrated up to 0.6 mg/day for clonidine and 60 mg/day for methylphenidate. Clonidine was not found to improve ADHD symptoms, whereas subjects treated with methylphenidate showed significant improvement compared to those not treated with methylphenidate on the primary outcome measure, ASQ Teacher Questionnaire. One explanation might be a relatively small sample size; another

explanation might be that the analysis collapsed both clonidine groups (clonidine, clonidine + methylphenidate) and both non-clonidine groups.
However, subjects treated with clonidine had greater improvements on the Conner's Abbreviated Symptom Questionnaire for Parents and Children's Global Assessment.

Comments: The literature review provides additional evidence for the safety and efficacy of clonidine for the treatment of ADHD.

(b) (4)

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9.3 Advisory Committee Meeting

Not applicable.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAJU MATHEWS
07/16/2010

JING ZHANG
07/16/2010