

OFFICE of CLINICAL PHARMACOLOGY
Efficacy Supplement
Pharmacometrics review

PRODUCT (Generic Name): Clonidine HCL

PRODUCT (Brand Name): (b) (4)

DOSAGE FORM: Tablets

DOSAGE STRENGTH: 0.1 mg tablet

NDA: 22331

NDA TYPE: 505(b)(2) Submission

SUBMISSION DATE: September 29, 2009

SPONSOR: Addrenex Pharmaceuticals

REVIEWER Andre Jackson

REVIEW OF CLONIDINE HCL TABLET FOR ADHD

| | | |
|-------|--------------------------------------|---|
| 1 | Summary of Findings..... | 2 |
| 1.1 | Key Review Questions..... | 2 |
| 1.1.1 | | 2 |
| 1.2 | Recommendations..... | 7 |
| 1.3 | Label Statements..... | 7 |
| 2 | Pertinent regulatory background..... | 8 |

| | | |
|-------|---|----|
| 2.1 | Sponsors' Analysis..... | 9 |
| 2.2 | Summary of Firm's Data Related to Label | 9 |
| 3 | Reviewer's Analysis | 15 |
| 3.1 | Introduction..... | 15 |
| 3.2 | Objectives | 15 |
| 3.3 | Methods..... | 16 |
| 3.3.1 | Data Sets | 16 |
| 3.3.2 | Software | 17 |
| 3.3.3 | Models..... | 17 |
| 3.4 | Results..... | 17 |
| 4 | Listing of Analyses Codes and Output Files..... | 17 |

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1. Do the firm's data (b) (4) somnolence appeared to be independent of clonidine dose or concentration?

2. To assess if the blood pressure measurements indicate the occurrence of hypotension in the subjects since the primary indication for clonidine is that of an antihypertensive agent?

3. Do the firm's data (b) (4) clonidine drug interactions with psycho-stimulants?

4. Does exposure response help to explain the lack of efficacy in adolescents when compared to younger children?

1.1.1

1. Does the firm's data (b) (4) that somnolence appeared to be independent of clonidine dose or concentration?

Data submitted by the firm clearly show clonidine is associated with higher incidence of somnolence compared to placebo although there was no clear relationship to dose. The lack of a clear dose response may be due to the titration design. Most of the somnolence

in the high dose group (0.4 mg/day) happened around 2 weeks when the patients were taking 0.2 mg day during the titration phase.

2. To assess if the blood pressure measurements indicate the occurrence of hypotension in the subjects since the primary indication for clonidine is that of an antihypertensive agent?

The firm conducted two studies, a fixed dose study 301 and adjunctive therapy study 302 which was variable doses of clonidine added to subjects previously receiving the stimulants methylphenidate or amphetamine.

Analysis of the systolic and diastolic changes in blood pressure from baseline from weeks 2-5 during the fixed dose phase of dosing of Study 301 indicated larger reduction in blood pressure with larger exposure. The reductions were less than those observed in the previous adult study in mild and moderate hypertensives, i.e., Study 201.

Figure 1 presents the regression of change in systolic blood pressure vs concentration for weeks 2-5 during fixed dosing and Figure 2 for diastolic blood pressure weeks 2-5. Table 1 presents the observed reductions in blood pressure for adult study 201 and the current study 301.

Figure 1. Significant Exposure-Response Relationship for Systolic Blood Pressure for fixed dose study 301

Change=1.7252-0.0052*conc p<0.0001

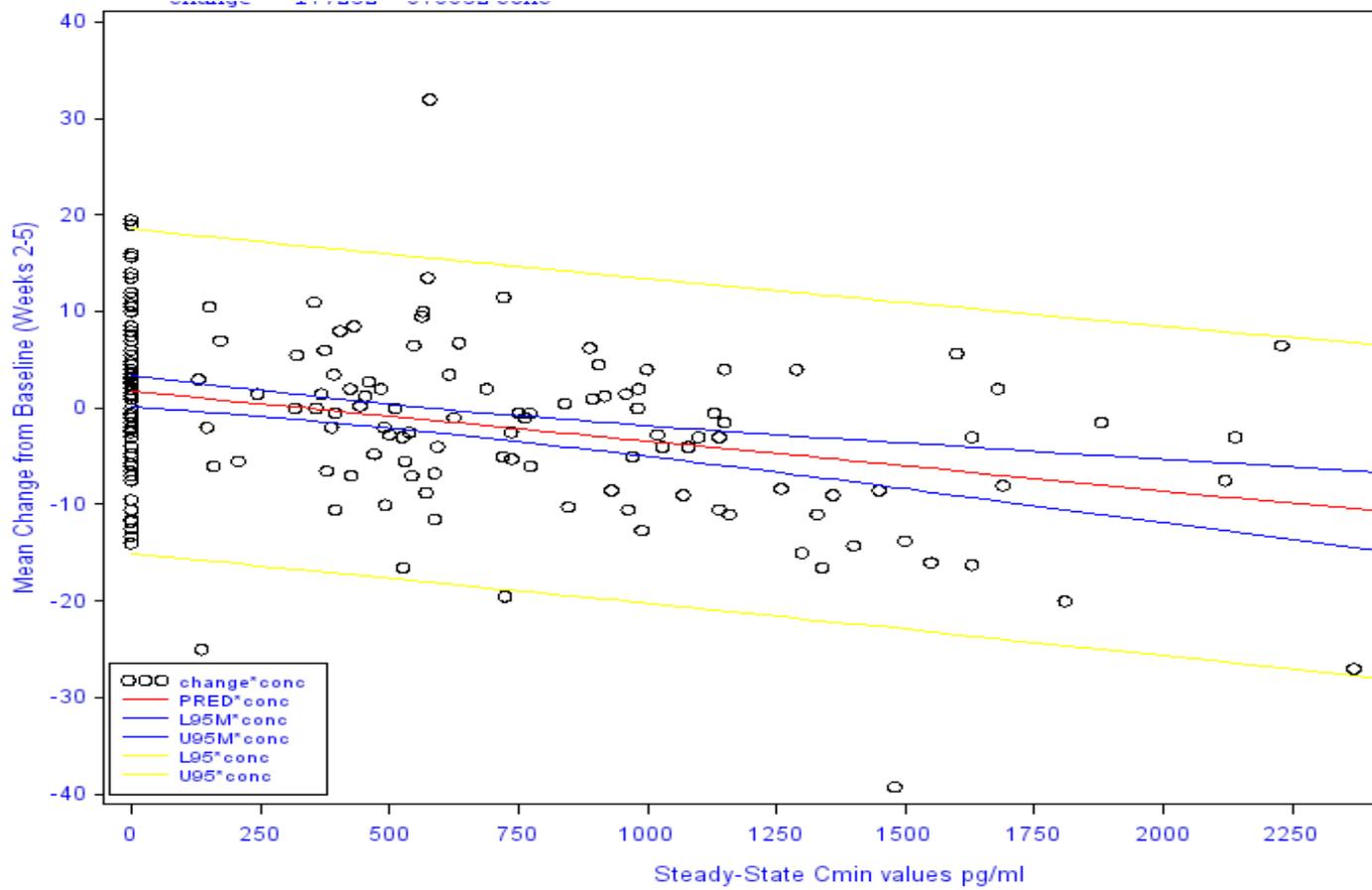


Figure 2. Significant Exposure-Response Relationship for Diastolic Blood Pressure for fixed dose study 301

$$\text{Change} = 1.325 - 0.0046 * \text{conc} \quad p < 0.0001$$

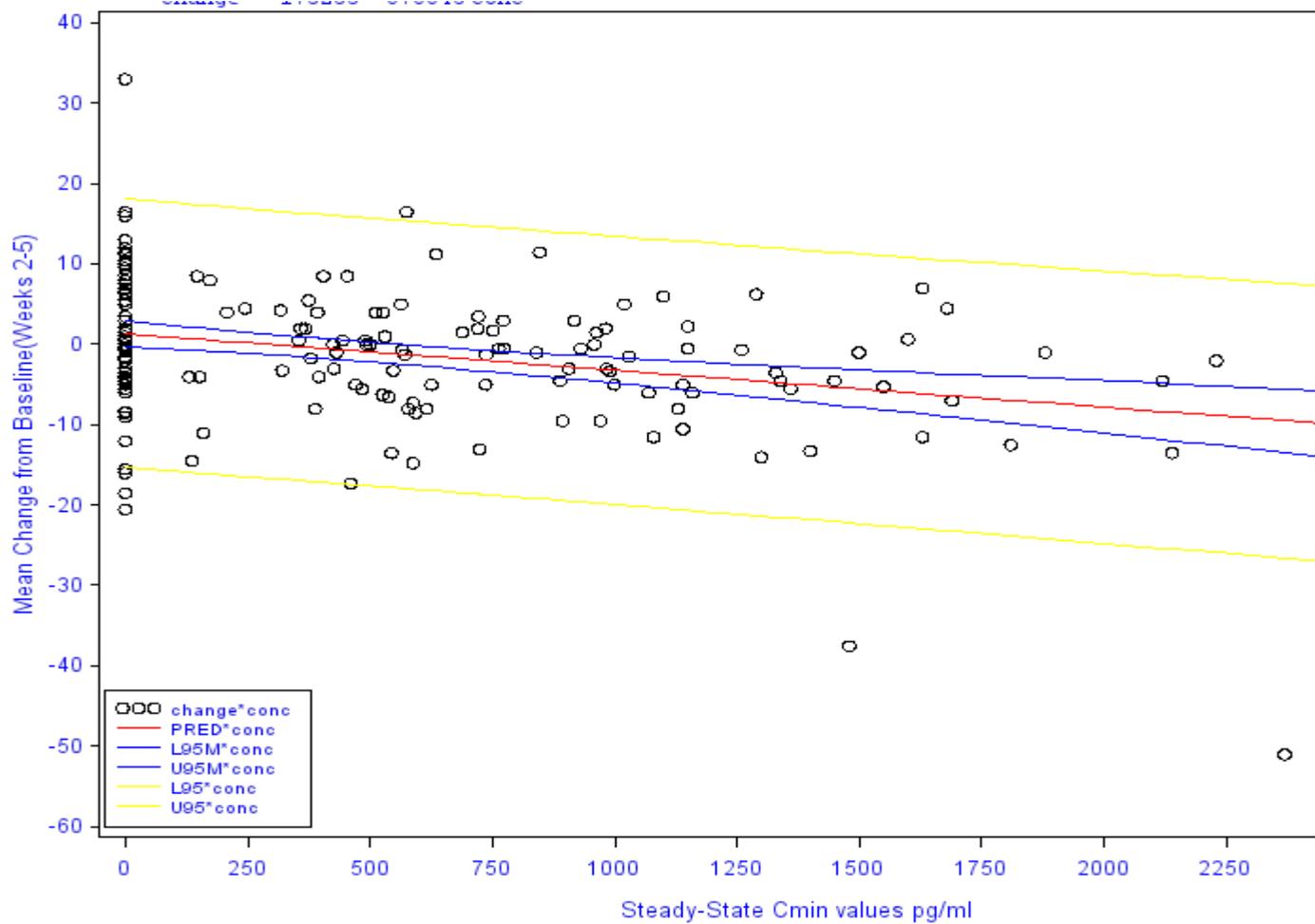


Table 1. Change in Blood Pressure from baseline in adult study 201 with mild to moderate hypertensive patients compared to normal adolescents and children in Study 301. Doses are bid for both studies.

| Study 201-Day 26-Hour 11 | | | Study 301-Weeks 2-5 | | |
|---|--------|--------|---|--------|-----|
| Reduction from Baseline Systolic BP (mmHg) | | | Reduction from Baseline Systolic BP (mmHg) | | |
| 0.2 mg | 0.4 mg | 0.6 mg | 0.2 mg | 0.4 mg | --- |
| 10.8 | 21.3 | 19.6 | 1-1.5 | 5-6 | |
| Reduction from Baseline Diastolic BP (mmHg) | | | Reduction from Baseline Diastolic BP (mmHg) | | |
| 0.2 mg | 0.4 mg | 0.6 mg | 0.2 mg | 0.4 mg | --- |
| 6.3 | 10.6 | 17 | 2 | 4-5 | |

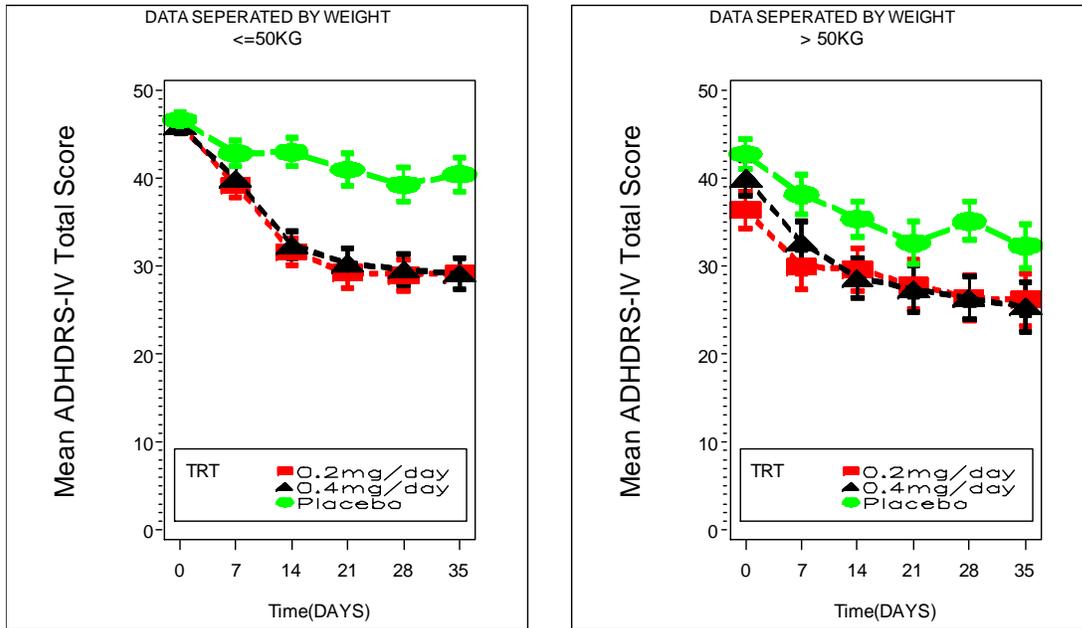
3. Do the firm's data (b) (4) clonidine drug interactions with psycho-stimulants?

The study was designed for subjects entering the study to 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. The aim was to determine if these subjects could potentially benefit from the addition of an alpha2 adrenergic agonist as evidenced by a lack of adequate response to the stable regimen of stimulant medication.

The clonidine 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. Since the drug was titrated the concern for a drug-drug interaction was minimized and if observed the dose could be tapered. The administered dose was maintained at a level for a period of 2 weeks before being gradually tapered to 0.1 mg/day at the last week of treatment. This tapering could be done if a drug-drug interaction was observed.

4. Does exposure response help to explain the lack of efficacy in adolescents when compared to younger children?

Figure 3. Change in the primary Clinical endpoint ‘Mean ADHDRS IV Total Score’ as a function of time for subjects separated by weight.



The results show that the children above 50 kg in weight have a much lower response to Clonidine as determined by the ADHDRS-IV (attention deficit hyperactivity disorder rating scale) score than lighter children. The lack of response is mainly due to a larger placebo effect in the heavier children.

1.2 Recommendations

All children and adolescents should only receive the 0.2 mg/day dose unless they fail to respond.

1.3 Label Statements

Firm's Proposed Label



(b) (4)

2 PERTINENT REGULATORY BACKGROUND REGULATORY BACKGROUND

The effectiveness and safety of orally administered clonidine in the treatment of hypertension has been documented and approved by the FDA in NDA 22331 for mild and moderate hypertensive adults. Despite the usefulness of clonidine in the treatment of hypertension, the regimen of administration required by the pharmacokinetic profile of the drug resulted in quite wide fluctuations in plasma concentrations for the IR formulation bid regimen, even at steady state. It has been established that many of the AEs observed during oral clonidine administration were related to its high peak plasma concentrations. The pharmacokinetic profile and relationship between plasma levels and AEs necessitated frequent dosing and resulted in a “roller coaster” effect characterized by “peak” AE of sedation and “trough” AE of rebound hypertension.

In addition to hypertension, clonidine has been evaluated and used extensively for several other indications, including attention deficit hyperactivity disorder (ADHD), (b) (4)

The current submission is a 505b(2) submission. All of the relevant

pharmacokinetic studies were conducted and submitted for review to the Division of Cardioresenal drug products. The main focus of this submission will be safety and effectiveness of clonidine in adolescents at two fixed bid doses of 0.2 mg and 0.4 mg.

For this submission the firm has conducted two studies relevant to OCP:

1. Study 301-dose response evaluation of the efficacy and safety of CLONICEL® (clonidine HCl) vs. placebo in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD)
2. Study 302- A phase III evaluation of the efficacy and safety of CLONICEL® (clonidine HCl) as add-on to psychostimulant medication vs. psychostimulant medication alone in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD).

2.1 Sponsors' Analysis

[\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Clonidine NDA22331S1 AJ\Sponsor Data and Reports](#)

Document: Results of Sponsor.doc-OCP Review of Sponsors Data

2.2 Summary of Firm's Data (b) (4)

The major assumption related to all the pharmacokinetic data was that based upon study (CLON-201)-study in adults with hypertension, the fluctuation index for Cloniceal is relatively low, averaging 34%. Since the same mg dose was given to adults, adolescents and children, the lower body weights in children resulted in higher doses on a µg/kg basis. As shown in Table 2, the mean daily doses in children were 5.66 and 5.86 µg/kg for the 0.2 mg dose, and 10.74 and 12.22 µg/kg for the 0.4 mg dose.

Table 2. Dosing Information Summary for the PK Populations for CLON-301 and CLON-302

| Statistic | | CLON-301 | | CLON-302 | | | |
|-----------------|---------|----------|--------|----------|--------|--------|--------|
| | | 0.2 mg | 0.4 mg | 0.1 mg | 0.2 mg | 0.3 mg | 0.4 mg |
| Subjects | N | 57 | 51 | 1 | 7 | 20 | 52 |
| Average | Mean | 0.20 | 0.38 | 0.10 | 0.19 | 0.31 | 0.39 |
| Daily Dose (mg) | SD | 0.00 | 0.04 | NC | 0.02 | 0.02 | 0.01 |
| | Minimum | 0.20 | 0.20 | 0.10 | 0.16 | 0.27 | 0.36 |
| | Median | 0.20 | 0.40 | 0.10 | 0.20 | 0.30 | 0.39 |
| | Maximum | 0.20 | 0.40 | 0.10 | 0.20 | 0.34 | 0.40 |
| Weight | Mean | 5.66 | 10.74 | 2.51 | 5.86 | 8.25 | 12.22 |
| Normalized | SD | 2.25 | 4.50 | NC | 2.93 | 3.66 | 3.55 |
| Dose (µg/kg) | Minimum | 1.53 | 3.28 | 2.51 | 2.31 | 2.72 | 3.64 |
| | Median | 5.83 | 10.26 | 2.51 | 6.69 | 7.94 | 12.46 |
| | Maximum | 9.57 | 19.90 | 2.51 | 8.81 | 15.08 | 20.00 |

In contrast, the mean weight normalized doses in adults were substantially lower, averaging 1.20, 2.24, and 3.36 $\mu\text{g}/\text{kg}$ for the 0.2 mg, 0.4 mg, and 0.6 mg doses, respectively.

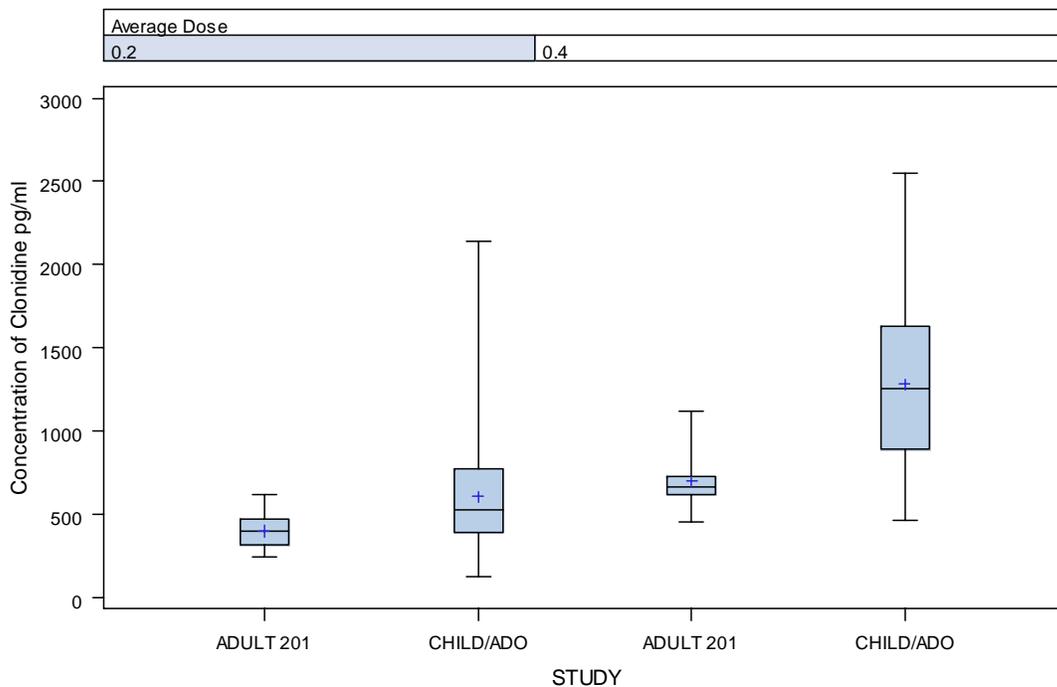
The OCP review for adult study 201 can be found at the following location.

<http://darrts.fda.gov:7777/darrts/ViewDocument?documentId=090140af8013545a>

The observed clonidine C_{MIN} concentrations for the doses studied in children and adolescents (i.e., 0.2 mg and 0.4 mg-Study 301) resulted in larger clonidine C_{min} values than those observed at the same 0.2mg and 0.4 mg doses in mild and moderate hypertensive adults, as shown in Figure 4.

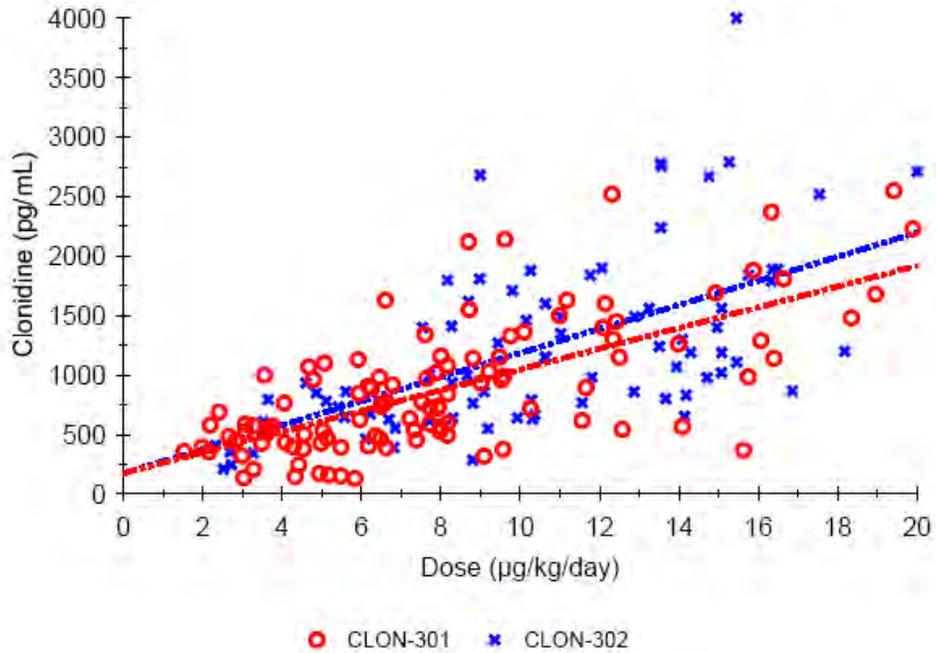
Figure 4. Clonidine C_{min} Concentrations by Study and Treatment for CLON-301-Children and adolescents fixed dose, and CLON-201-Adults with hypertension

Comparison of Trough Plasma Levels Adults vs Adolescents and Children
Doses of 0.2 0.4 mg



The plasma levels increased with dose for studies 301 and 302 as seen in Figure 5.

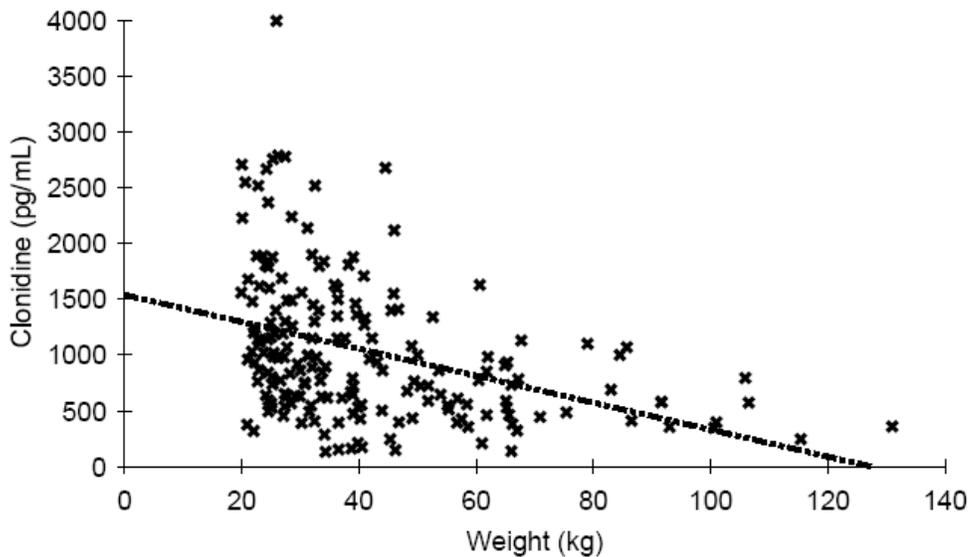
Figure 5. Plasma Clonidine Concentration vs Dose for CLON-301 and CLON-302



The results indicate that the plasma clonidine concentrations were proportional to dose.

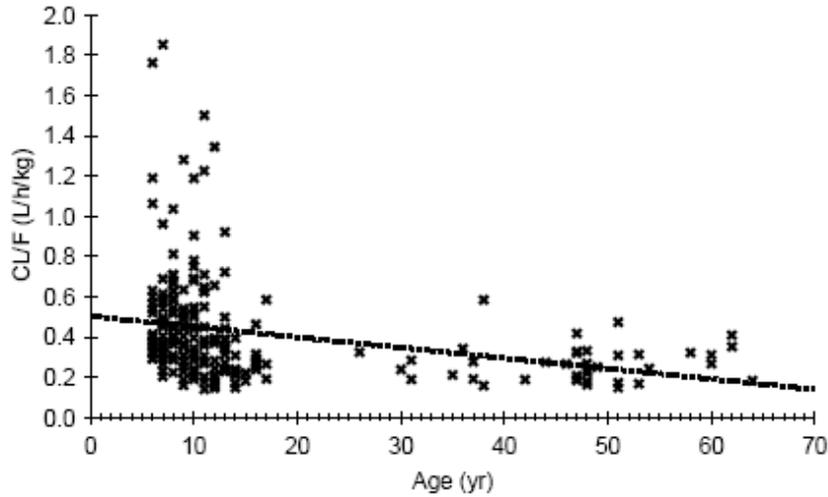
Weight was an important covariate with the fixed dose used in these studies, therefore one observes much larger exposure for lighter subjects, Figure 6.

Figure 6. Plasma Clonidine Concentration vs Body Weight



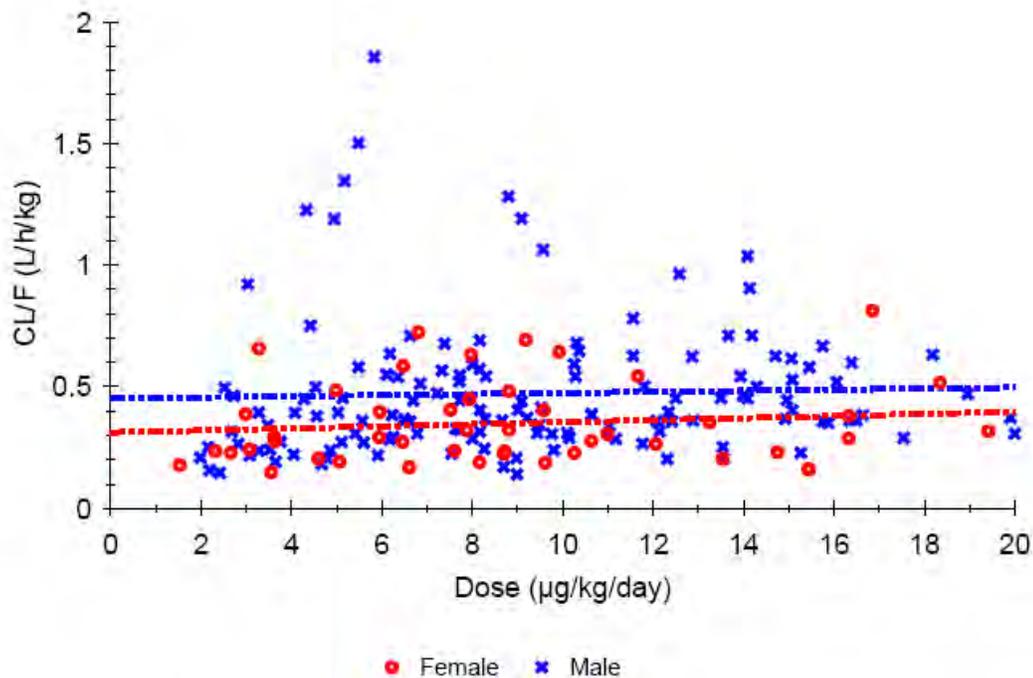
Further analysis of the CL/F vs age in Figure 7, showed a decrease with age which probably reflects the decrease in renal excretion related to age since the compound is primarily renally excreted.

Figure 7. Clonidine Weight Normalized CL/F vs Age for CLON-301, CLON-302 and CLON-201



The effects of gender on clonidine CL/F are displayed graphically in Figure 8.

Figure 8. Clonidine CL/F vs Dose by Gender for CLON-301 and CLON-302



The results seem to show a higher clearance in males than females. Overall, in both studies combined, the median CL/F was 0.393 L/h/kg for males and 0.294 L/h/kg for females, a 25% lower value for females.

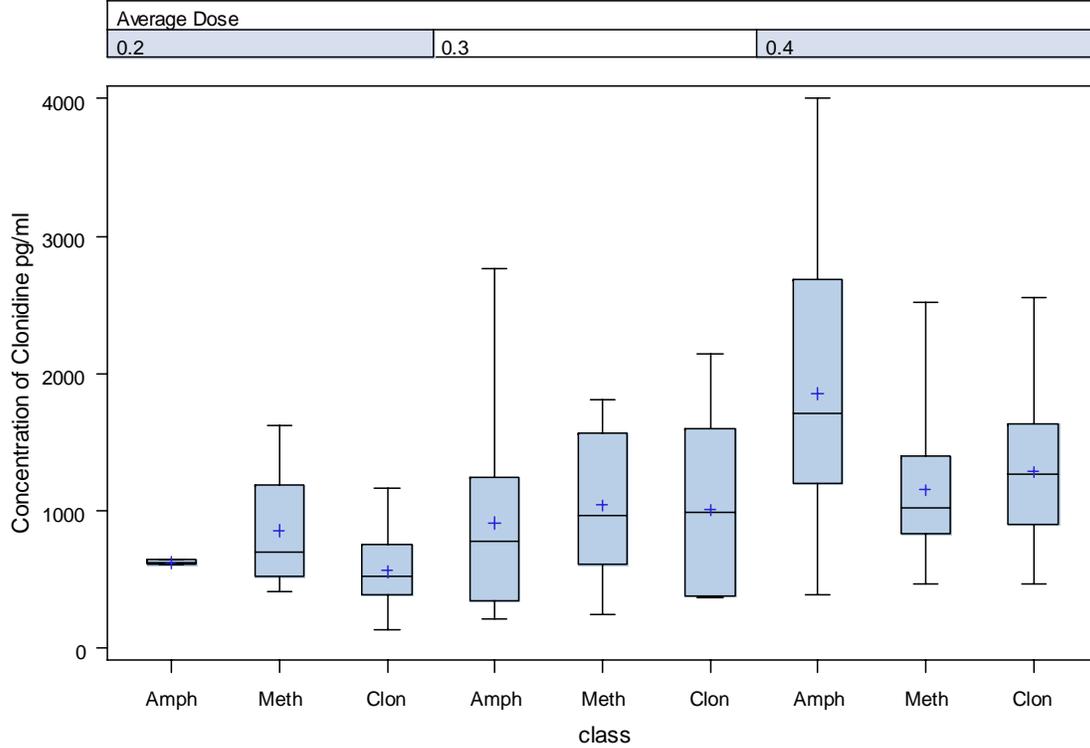
Effects of Concomitant Psychostimulant Therapy

CLON-302 required that subjects be on a stable regimen of a stimulant drug for treatment of their ADHD. Of the total of 80 subjects in CLON-302, 35 were receiving amphetamine and 45 were being treated with methylphenidate as stimulant therapy for ADHD. The box plot in Figure 9 shows, the median steady-state clonidine concentration alone for clonidine and when co-administered with amphetamine and when administered with methylphenidate. Compared to clonidine alone there was a 44% increase in exposure for amphetamine (Clonidine-1284 pg/ml; Clonidine+amphetamine-1857 pg/ml; Clonidine + methylphenidate-1151 pg/ml) and an 11% decrease in exposure for methylphenidate.

Figure 9. Effect of Concomitant Stimulant Administration on Steady-state Clonidine Concentrations

COMPARISON OF TROUGH PLASMA LEVELS

DOSES OF 0.2 0.3 0.4 MG



Two of the most common adverse events in both studies, with a notably higher incidence in the active treatment groups versus placebo were the “sedation-like” adverse events of somnolence (which includes sedation), and fatigue (which includes lethargy).

Table 3. Treatment Emergent Adverse Events with 5% or Greater Incidence in any active Treatment Group and at least Twice the Incidence of Placebo (Safety Population) Relationship Between AE Incidence and Clonidine Dose and Concentration for 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 (%) |
| 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) |
| Data Source: Table 14.3.1.2 | | | |

Reviewer's Comments:

(b) (4)
 In addition, exposure response related to adverse events and efficacy will be explored by the reviewer.

3 REVIEWER'S ANALYSIS

3.1 Introduction

The reviewer's analysis is being done to further delineate exposure response for blood pressure and somnolence in the children. In addition the impact of weight on efficacy will be investigated since large weight led to lower exposure for clonidine.

3.2 Objectives

Analysis objectives are:

1. To determine if the data presented by the firm support that somnolence appeared to be independent of clonidine dose or concentration.
2. To assess if the blood pressure measurements indicate the occurrence of hypotension in the children and adolescents since the approved indication for clonidine is that of an antihypertensive agent.
3. To evaluate if the firm's data (b) (4) related to clonidine drug interactions with psycho-stimulants.

4. To determine if exposure response helps to explain the lack of efficacy in adolescents when compared to younger children.

3.3 Methods

3.3.1 Data Sets



(b) (4)

3.3.2 Software

SAS 9.2 was used for statistical and graphical analysis of the data.

3.3.3 Models

No PK models were used to analyze this data.

3.4 Results

Figures 1- Figure 2 in Section 1.1.1 clearly show an exposure response for blood pressure reduction for the fixed dose Study 301.

Figure 3 in section 1.1.1 shows that effect was based upon weight with children < 50 kg having a lower ADHD Rating Scale (Attention Deficit Hyperactivity Disorder) compared to placebo.



Conclusions:

Submission Number

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1. Clonidine is associated with a higher incidence of somnolence but there is a lack of dose response due to the titration design.
2. There was a decrease in blood pressure in children and adolescents taking 0.1 mg or 0.2 mg of Clonidine bid.
3. There appeared to be a 44% increase in clonidine exposure with amphetamines and an 11% decrease in exposure for clonidine with methylphenidate in children and adolescents taking clonidine as adjunctive therapy compared to the presence of no interacting drug.
4. Children greater than 50kg showed less response to clonidine because of a larger placebo effect in this patient group.

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

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