U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number	22,331 (Supplement 001, SD-15; Supplement 002, SD-16) ; SN-0019
Drug Name:	CLONICEL® (clonidine HCI modified release)
Indication(s):	ADHD (Attention Deficit Hyperactivity Disorder)
Applicant:	Shionogi (initially, Addrenex)
Dates:	Received Date: September 30, 2009, PDUFA Due Date: July 30, 2010.
Review Priority:	Standard
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Keywords: Clinical studies; NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations[1]

The efficacy assessments based on the primary efficacy analysis of data from the submitted phase III studies, CLON-301 and CLON-302, have shown evidence to support the sponsor's efficacy claim of a new treatment, CLONICEL (clonidine HCI modified release), in children and adolescents (6 to 17 years old) with ADHD. The sponsor's phase III studies, CLON-301 and CLON-302, provided statistical evidence that CLONICEL is efficacious, as a monotherapy and as an add-on to a psychostimulant, in the treatment of subjects (6-17 years-old) with ADHD.

1.2 Brief Overview of Clinical Studies

The sponsor submitted two phase III studies, CLON-301 and CLON-302, to support the efficacy of two dosing regimens of CLONICEL(CLON), CLON 0.2 mg/day and CLON 0.4 mg/day, in children and adolescents (6 to 17 years) who meet DSM-IV criteria for ADHD.

Study CLON-301 was an 8-week (56 days), multi-center (US alone), parallel-group, randomized, double-blind, placebo-controlled study. A total of 236 male and female subjects were randomly assigned in a 1:1:1 ratio to CLONICEL treatment, CLON 0.2 mg/day (N=78) or CLON 0.4 mg/day (N=80), or placebo (N=78). The majority of subjects (60.6%) completed the treatment phase. 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, from Week 4 through Week 5, before being gradually tapered down to 0.1 mg/day at the last week of treatment. The primary efficacy assessment was conducted based on the primary efficacy measure, the ADHDRS-IV total score obtained at Week 5.

Study CLON-302 was an 8-week (56 days), multi-center (US alone), parallel-group, randomized, double-blind, placebo-controlled study. A total of 198 male and female subjects were randomly assigned in a 1:1 ratio to one of the two groups: CLONICEL as an add-on to psychostimulant (CLON+STM) (N=102) or PLACEBO and a psychostimulant (CLON +STM) (N=96). The majority of subjects (83.3%) completed the treatment phase. Patients 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 alpha adrenergic agonist as evidenced by a lack of adequate response to this stable regimen of stimulant medication. The CLON dose (or matching placebo) will be 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 will be maintained at this level for a period of 2 weeks, from Week 4 through Week 5, before being gradually tapered to 0.1 mg/day at the last week of treatment. The primary efficacy assessment was conducted based on the primary efficacy measure, the ADHDRS-IV total score obtained at Week 5.

[1] Refer to Section 5.2

1.3 Statistical Issues and Findings[2]

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 CLONICEL treatment against the placebo, both as a monotherapy and as an add-on to a psychostimulant.

The sponsor established statistical evidence to support the claim for the efficacy of CLONICEL, based on results from the pre-specified analysis LOCF ANCOVA (last observation carried forward analysis of covariance) as well as the pre-specified sensitivity analysis ANCOVA on Observed Cases. The dropout rates were around 40% and 17% respectively in these two studies. In order to explore the impact of the dropouts on efficacy findings, this reviewer performed a MMRM-based sensitivity analysis, which requires a milder assumption for the missing data mechanism. It was found that the result led to the same conclusion in supporting efficacy.

In the subgroup analysis, this reviewer observed differences in estimates of change from baseline scores among races in Study CLON-302, but not in Study CLON-301. In addition, this reviewer observed that the age groups (6-12 year-old and >12 year-old) did not show similar efficacy estimates in Study CLON-301, but in Study CLON-302. These differences, however, may be due to a chance or the fact that subgroups but the white had too small a sample size to statistically assess the estimated differences. Despite some apparent discrepancies in efficacy estimates for subgroups, overall evidence is strong to support the efficacy of the clonicel treatment.

[2] Refer to Section 5.1

2. INTRODUCTION

2.1 Overview

This review provides a statistical evaluation of CLONICEL (clonidine HCI modified release) as a monotherapy and as an add-on to a psychostimulant, indicated for children and adolescents (6 to 17 years old) with ADHD. The evaluation was based on the submitted data from two phase III studies: Studies CLON-301 and CLON-302.

CLONICELis a patented oral dose, modified release formulation of the widely available generic drug clonidine hydrochloride USP. Clonidine HCl is a mesomeric imidazoline derivative, chemically described as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride. The modified release formulation is achieved by combining clonidine (b) (4) (b) (4) The modified release period is targeted for a minimum of 12 hours to result in a twice daily dose regimen.

Clonidine is a centrally acting alpha2 adrenergic agonist that has been used effectively since the early 70s to treat mild to moderate hypertension. Because it has a different mechanism of action than most other antihypertensive agents, it can be used alone or in combination therapy with other agents. Clonidine is currently approved in the US in 3 formulations: immediate release oral, transdermal patch, and epidural injection.

Several studies have documented the effectiveness and safety of orally administered clonidine in the treatment of hypertension. Positive data on safety and efficacy led Boehringer Ingelheim, the original maker of the clonidine brand Catapres, to file a new drug application (NDA) with FDA for hypertension in 1973. In its review, the FDA relied on 7 studies, 6 of which were deemed adequate and well controlled trials, usually randomizing patients to Catapres vs. Aldomet (methyldopa), another well established antihypertensive at the time.

In addition to hypertension, clonidine has been evaluated and used extensively for several other indications, including attention deficit hyperactivity disorder (ADHD), alcohol withdrawal, atrial fibrillation, tic disorders, menopausal flushing, smoking cessation, and ulcerative colitis. Clonidine became widely accepted in the early 1990s as a drug for treating a variety of symptoms and disorders related to ADHD in children and adults.

Two important clinical studies have recently been performed, both 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). 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).

The second NIH-funded study, 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. Clonidine was not found to improve ADHD symptoms; however, subjects treated with clonidine had greater improvements on the Conner's Abbreviated Symptom Questionnaire for Parents and Children's Global Assessment.

The sponsor's discussions with clinicians who have used clonidine to treat ADHD were consistent in showing that while clonidine has been a useful medication for ADHD. However, significant problems with the traditionally available preparations (oral tablets and transdermal patches) have greatly limited its use. These problems have mostly involved the ease of administration and the control of side effects. The beneficial effects of a dose of oral clonidine appear to last only 3-4 hours in children with ADHD. This necessitates frequent dosing and causes roller coaster effects characterized by "peak" side effects of sedation and "trough" side effects of rebound hyper arousal. Clinical benefits from clonidine appear suddenly as it is rapidly absorbed, peaking sharply at about 45 to 60 minutes after ingestion. Effects fall off rapidly at about 4-5 hours after ingestion with a characteristic period of rebound hyper arousal. Children often report transient periods of drowsiness about 45 minutes to one hour after taking a dose, and may even fall asleep and nap for 10-15 minutes until the sedation passes. A rebound period can often be observed four to five hours after a dose characterized by hyperactivity, hyper emotionality, anxiety, aggressive behavior or emotional outbursts. This can occur in the middle of the night resulting in nightmares and insomnia.

An easy to administer clonidine formulation is needed that retains the efficacy of the current oral formulation in ADHD but has an improved safety profile similar to the patch formulation minus the dermatologic AEs and the poor adhesion. The CLONICEL clinical development program investigated the safety and efficacy of clonidine delivered from the modified release formulation of CLONICEL over a dose range that is commonly used in the treatment of ADHD.

2.2 Data Sources

Initially, Addrenex submitted the NDA on Novermber 15, 2009. The submission is located at the CDER's electronic document room: \\fdswa150\NONECTD\N22331\S_001\2009-11-05.

Due to a change in sponsorship to Shionogi, this new submission storage was created at the CDER's electronic document room: \\Cdsesub1\evsprod\NDA022331\0019\m5\datasets.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY CLON-301

Study title:

The title of Study CLON-301 is given as "A phase III, dose response evaluation of the efficacy and safety of CLONICEL (clonidine HCl sustained release) vs. placebo in the treatment of children and adolescents with attention deficit hyperactivity disorder (ADHD)".

Primary objective:

- To evaluate the efficacy of two dosing regimens of CLONICEL: 0.2 and 0.4 mg/day compared to placebo in the treatment of children and adolescents with ADHD
- To evaluate the safety of these dosing regimens compared to placebo in the treatment of children and adolescents with ADHD

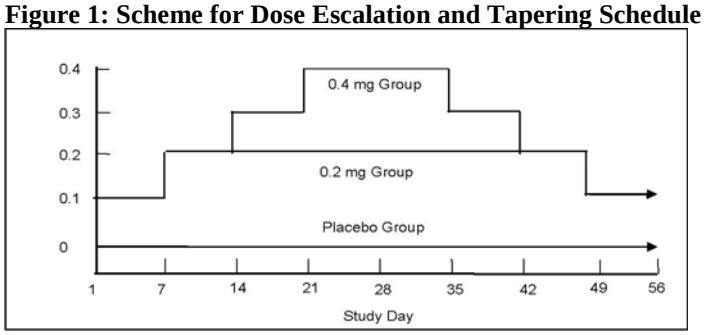
Secondary objective:

- To evaluate the efficacy of these dosing regimens in alleviating symptoms of sleep disturbance in this patient population
- To evaluate the efficacy of these dosing regimens in alleviating symptoms of aggression in this patient population
- To evaluate the population pharmacokinetics in children and adolescents receiving CLONICEL at these dosing regimens
- To correlate measures of efficacy and safety with genetic or other biologic markers

3.1.1.1 Study Design

This was an 8-week (56 days), multi-center, parallel-group, randomized, double-blind, placebo-controlled study of the efficacy and safety of two dosing regimens of CLONICEL in children and adolescents (6 to 17 years) who meet DSM-IV criteria for ADHD. 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. Figure 1 shows the dose escalation and dose tapering schedule for the three treatment groups.

Figure 1: Scheme for Dose Escalation and Tapering Schedule (CLON-301)



[Source: Figure 1. of CLON 301 CSR (page 39)]

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.

Sample size calculation:
The sample size calculation was based on comparing each active group to placebo on mean changes in ADHDRS-IV total scores from Baseline to the Week 5 (or last available) measure. The following assumptions were made:

Difference between active and placebo mean change scores = 8 points
Pooled standard deviation = 15
Alpha = 0.05
Power = 90%
Ratio of active/placebo = 1

Sample size calculations indicated that 75 patients per treatment group would be required to achieve statistical significance given the above assumptions.

3.1.1.2 Statistical Method and Analysis

Definition of study population in primary analysis:

The study population will consist of 225 children and adolescents (6 to 17 years) who meet DSM-IV criteria for ADHD of the hyperactive or combined inattentive/hyperactive subtypes will be enrolled, 75 per treatment group. The Intent to Treat (ITT) population was defined as all subjects who are randomized, took at least one dose of study drug, and provided at least one efficacy assessment post Baseline.

Primary endpoint and analyses:

The primary endpoint was the change from Baseline to Week 5 in the ADHDRS-IV scale total score. All primary statistical summaries and analyses were conducted using the ITT population. The primary analysis was based on ANCOVAs that model the change from baseline as a function of the baseline ADHDRS-IV total score, the study site, and the treatment group. Missing data was imputed by the Last Observation Carried Forward (LOCF) approach.

For study sites with fewer than 10 total subjects, the study sites were pooled. The pooling algorithm will match the largest site with fewer than 10 subjects with the smallest site until a pooled site with 10 or more subjects is obtained. The process continued with the remaining sites until all sites for analysis purposes included 10 or more subjects.

Confidence bounds presented will show two-sided 95% confidence limits for the average ADHDRS-IV total score difference between the two dosing regimens. A p-value of less than or

equal to 0.05 was deemed statistically significant. Any confidence bounds presented two-sided 95% confidence limits.

When comparing a given dose with placebo, the sponsor excluded the other dose group from the ANCOVA model. Since there were two comparisons (high dose vs. placebo and low dose vs. placebo), the sponsor referred to their primary analysis as "two independent ANCOVA's". However, they did not consider multiplicity adjustment for these two comparisons and declared a statistical significance for a nominal p-value of less than or equal to 0.05. This reviewer noted that in an email communication of statistical comments, dated on August 27, 2008, the sponsor was advised to prospectively propose a method for dealing with multiple comparisons due to the multiple doses, but apparently the sponsor did not address this.

The sponsor proposed to conduct two sensitivity analyses to investigate the sensitivity of the study results to other analysis methods and assumptions than the primary analysis method:
1) ANCOVA model with a covariate of baseline ADHDRS-IV total score, factors of treatment, study site, and the treatment × site interaction term, based on LOCF data.
2) The same ANCOVA model as in the primary analysis based on completed scores at Week 5 (observed cases) without LOCF imputation.

Secondary endpoints and analyses:

Secondary measurements 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). No key secondary endpoint was pre-specified.

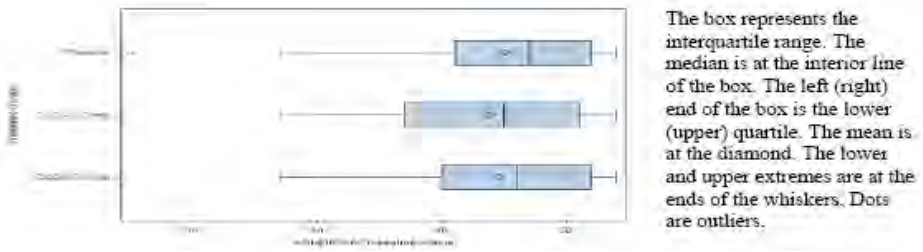
3.1.1.3 Efficacy Results

3.1.1.3.1 Subject Disposition and Baseline Demographic Characteristics

Baseline distributions of the treatment groups:

Figure 2 displays box plots of baseline ADHDRS-IV total scores of each treatment group. A visual inspection of this figure along with Table 1 suggest that the Baseline ADHDRS-IV total scores for the clonicel 0.2-mg treatment group appeared slightly smaller than the other groups, but the difference may not be clinically relevant.

Figure 2: Box-Whisker Plots: Baseline ADHDRS-IV total scores by treatment (CLON-301)



[Source: Reviewer's analysis]

Table 1: Baseline ADHDRS-IV total scores by treatment groups (CLON-301)

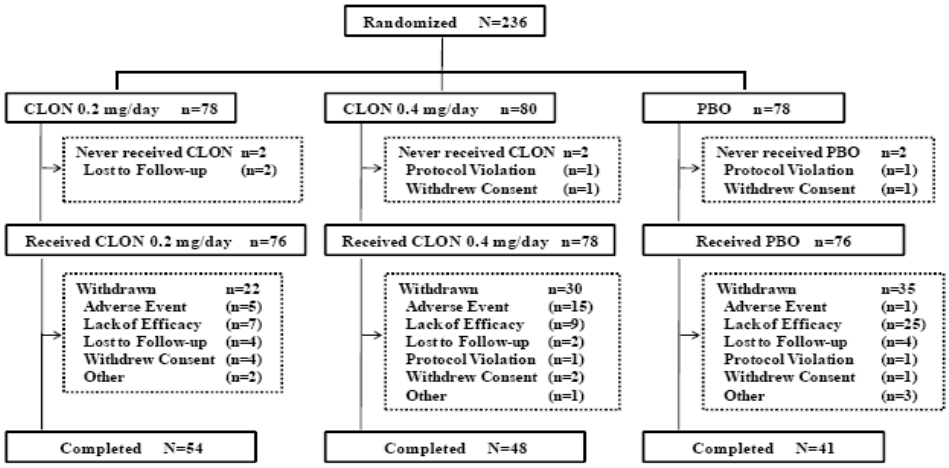
Treatment	N	Mean	SD	Median
CLON 0.2 mg	74	43.8	7.47	45.0
CLON 0.4 mg	78	44.6	7.73	46.0
Placebo	76	45.0	8.53	47.0

[Source: Reviewer's analysis]

Subject disposition:

A total of 236 male and female subjects were randomly assigned in a 1:1:1 ratio to CLONICEL treatment, CLON 0.2 mg/day (N=78) or CLON 0.4 mg/day (N=80), or placebo (N=78). As shown in Table 2, the majority of subjects (60.6%) completed the treatment phase. Figure 3 and Table 2 provide all the details of subject dispositions.

Figure 3: Subjects Dispositions in CLON-301



[Source: Figure 2 of CLON 301 CSR (page 63)]

Table 2: Subject Dispositions in CLON-301

	Treatment Group			
Summary	Clonicel 0.2 mg	Clonicel 0.4 mg	Placebo	All Subjects
Study Population				
All Randomized [1]	78	80	78	236
Intent-to-Treat (ITT) [2]	74	78	78	228
Safety	76	78	76	230
Subjects Completed Treatment Phase				
Yes	54 (69.2%)	48 (60.0%)	41 (52.6%)	143 (60.6%)
No	24 (30.8%)	32 (40.0%)	37 (47.4%)	93 (39.4%)
Reason for not Completing Treatment Phase				
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%)
Subjects Completed Follow-up Visit				
Yes	66 (84.6%)	68 (85.0%)	64 (82.1%)	198 (83.9%)
No	12 (15.4%)	12 (15.0%)	14 (17.9%)	38 (16.1%)
Reason for not Completing Follow-Up				
Withdrew Consent	4 (5.1%)	3 (3.8%)	2 (2.6%)	9 (3.8%)
Adverse Event	0	2 (2.5%)	1 (1.3%)	3 (1.3%)
Lack of Efficacy	0	0	0	0
Lost to Follow-Up	6 (7.7%)	3 (3.8%)	8 (10.3%)	17 (7.2%)
Protocol Violation	0	0	0	0
Other	2 (2.6%)	4 (5.0%)	3 (3.8%)	9 (3.8%)

[Source: Table 14.1.1 of CLON 301 CSR (page 105)]

Demographic characteristics:

As shown in Table 3, for all randomized subjects, the majority were male (72.4%) and White (59.2%). The mean subject age was 9.4 years (median 9.0 years), and most subjects were 6-12 years of age (82.5%). The mean body weight was 41.1 kg.

Table 3: Subgroup (Gender, Age, Age group, Race, Weight) in CLON-301

Summary	Treatment Group			All Subjects
	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%)
Female	16 (21.6%)	23 (29.5%)	24 (31.6%)	63 (27.6%)
Age (years)				
N	74	78	76	228
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%)
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
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

[Source: Table 14.1.3 of CLON 301 CSR (page 110)]

3.1.1.3.2 Sponsor's Efficacy Analysis Results

Results from the primary variable:

Table 4 displays the sponsor's primary analysis results, summarizing the change scores from Baseline for ADHDRS-IV comparing each dosing group to placebo. The least-squares mean difference in each of the comparisons was statistically significantly different from zero at the 2-sided, 5% nominal significance level, in favor of the corresponding clonicel dosing group.

Table 4: Sponsor Primary Efficacy Analysis in CLON-301

Primary analysis	**Treatment Group**	**N**	**LS Means Model Estimate for Difference (Clonicel-Placebo) in Week 5 ADHDRS-IV Total Score**	
			Difference* (95% CI)	**p-value****
ANCOVA (LOCF)	Clonicel 0.2 mg	74	-8.49 (-12.05, -4.93)	< .0001
	Clonicel 0.4 mg	78	-8.99 (-12.66, -5.32)	< .0001
	Placebo	76	--	--

* Treatment difference adjusted for study site and baseline ADHDRS-IV Total score based on ANCOVA

** p-values were obtained by "two independent ANCOVA's" (No multiplicity adjustment was performed).

[Source: Table 14.2.2 of CLON 301 CSR (page 117)]

The sponsor performed two sensitivity analyses. The analysis results can be found in Table 5 and Table 6. The results are consistent with those found in the primary analysis, and support the sponsor's efficacy claim. This reviewer confirmed the results.

Table 5: Sponsor sensitivity analysis: using observed cases - ANCOVA (OC) CLON-301

Sponsor sensitivity analysis: Using observed cases	**Treatment Group**	**N**	**LS Means Model Estimate for Difference (Clonicel-Placebo) in Week 5 ADHDRS-IV Total Score**	
			Difference* (95% CI)	**p-value****
ANCOVA (OC)	Clonicel 0.2 mg	58	-8.78 (-12.53, -5.04)	< .0001
	Clonicel 0.4 mg	52	-12.23 (-16.44, -8.01)	< .0001
	Placebo	59	--	--

* Treatment difference adjusted for study site and baseline ADHDRS-IV Total score based on ANCOVA
** p-values were obtained by "two independent ANCOVA's" (No multiplicity adjustment was performed).
[Source: Table 14.2.2 of CLON 301 CSR (page 117)]

Table 6: Sponsor sensitivity analysis: Inclusion of an interaction of study site and treatment - ANCOVA (LOCF) in CLON-301

Sponsor sensitivity analysis: Inclusion of an interaction of study site and treatment	**Treatment Group**	**N**	**LS Means Model Estimate for Difference (Clonicel-Placebo) in Week 5 ADHDRS-IV Total Score**	
			Difference* (95% CI)	**p-value****
ANCOVA (LOCF)	Clonicel 0.2 mg	74	-7.58 (-11.37, -3.80)	< .0001
	Clonicel 0.4 mg	78	-8.19 (-12.12, -4.26)	< .0001
	Placebo	76	--	--

* Treatment difference adjusted for study site and baseline ADHDRS-IV Total score based on ANCOVA
** p-values were obtained by "two independent ANCOVA's" (No multiplicity adjustment was performed).
[Source: Table 14.2.2 of CLON 301 CSR (page 117)]

Results of subscales of the ADHDRS-IV scale:

The ADHDRS-IV scale, where the primary endpoint was derived, consists of two subscales: Inattention and Hyperactivity. The sponsor concluded statistically significant improvements favoring the CLONICEL treatment groups for both subscales. (See Table 7)

Table 7: Change Scores for Subscales of the ADHDRS-IV Scale at Week 5 (LOCF) – CLON-301

	TREATMENT GROUP		
	CLON 0.2 mg/day	**CLON 0.4 mg/day**	**PBO**
Inattention Subscale, N	74	78	76
Baseline, Mean (SD)	22.9 (3.87)	23.1 (3.81)	23.4 (4.32)
Change Score at Week 5, Mean (SD)	-7.7 (6.88)	-7.7 (7.10)	-3.4 (5.13)
p-value[1]	p<0.0001	p<0.0001	--
Hyperactivity/Impulsivity, N	74	78	76
Baseline, Mean (SD)	20.9 (5.31)	21.5 (5.04)	21.6 (5.59)
Change Score at Week 5, Mean (SD)	-7.9 (6.96)	-8.8 (7.26)	-4.1 (5.04)
p-value[1]	p<0.0001	p<0.0001	--

1 Versus placebo p-value; obtained from the treatment parameters in an ANCOVA modeling change from Baseline as a function of Baseline, treatment, and pooled study site.
[Source: Synopsis Table 3 of CLON 301 CSR (page 9)]

Results of secondary endpoints:

The sponsor concluded that the results of the secondary endpoints supported those of the primary endpoint and achieved statistical significance (p-value at least <0.05). Statistical significance was found in pre-specified secondary endpoints, except for SSR-CF total score or derived subscales. This reviewer confirmed these results.

Sponsor's conclusion on efficacy:

Both dosing regimens of CLONICEL, 0.2 mg/day and 0.4 mg/day (in divided AM and PM doses), were efficacious in alleviating the symptoms of ADHD in pediatric patients and well-tolerated for up to 8 weeks of treatment.

Reviewer's Note:

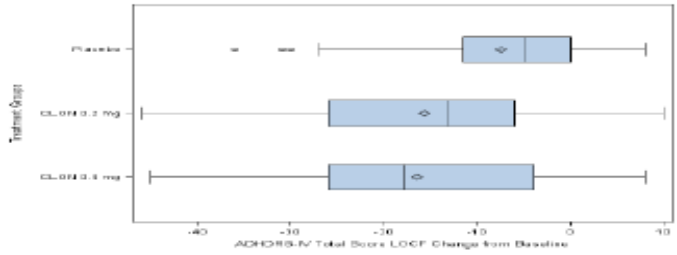
[1] The sponsor did not consider multiplicity adjustment for the two doses compared with placebo. However, since the p-values were nearly zero, any reasonable multiple testing procedure would lead to the same conclusion.
[2] The sponsor performed the primary analysis and the sensitivity analysis by excluding the irrelevant dose group from the ANCOVA model for each comparison. Typically, when comparing a given dose with placebo, all dose groups are included in the model. This approach takes more information into account and allows for implementation of multiple testing procedures (such as Dunnett's) that require correlation between comparisons. Since the p-values were very close to zero, the results were consistent whether excluding the irrelevant dose group from the model or not.

3.1.1.3.3 Reviewer's Assessments

Confirmation of sponsor's results of the primary analysis:

This reviewer confirmed the sponsor's primary analysis results. As displayed in Figure 4, the box plots of the change from baseline in ADHDRS-IV total scores suggest a distributional separation of each treatment group from the placebo group. The distribution in the placebo group appears narrower than the other two clonicel treatment groups. Given the robustness of ANCOVA analysis, however the distributions of the change from baseline in ADHDRS-IV total scores seem to be fairly acceptable for an ANCOVA analysis. This reviewer created normal QQ plots of residual errors after model fitting, and did not find apparent indications of a violation of the distributional assumption, so the ANCOVA model appears fairly robust.

Figure 4: Box-Whisker plots: Change from baseline in ADHDRS-IV total score by treatment (CLON-301)



The box represents the interquartile range. The median is at the interior line of the box. The left (right) end of the box is the lower (upper) quartile. The mean is at the diamond. The lower and upper extremes are at the ends of the whiskers. Dots are outliers.

[Source: Reviewer's analysis]

Reviewer's sensitivity analysis

This reviewer conducted a mixed model for repeated measures (MMRM) analysis as a sensitivity analysis, in order to look into the robustness of the sponsor's efficacy analysis result based on the LOCF ANCOVA. As in the sponsor's LOCF ANCOVA primary analysis, the MMRM model included baseline ADHDRS-IV total score as a fixed covariate, treatment group, study site, week and the treatment by week interaction as fixed factors. The method of estimation was restricted maximum likelihood (REML). The within subject covariance matrix was unstructured. The degree of freedom of the denominator was approximated by the Kenward-Roger's method. The results in Table 8 and Table 9 support the primary analysis results based on the LOCF ANCOVA analysis.

Table 8: Sensitivity Analysis by MMRM (CLON 0.2 mg vs. Placebo) – CLON-301

	Placebo		Clonicel 0.2 mg		Clonicel 0.2 mg vs. Placebo	
Visit	**N**	**MEAN**	**N**	**MEAN**	**LS Mean**	**P-value***
Week 1	75	-3.9	72	-7.0	-3.2	0.016
Week 2	74	-4.5	72	-13.1	-8.3	< 0.0001
Week 3	70	-6.9	68	-15.7	-8.1	< 0.0001
Week 4	67	-6.9	62	-16.2	-8.7	< 0.0001
Week 5	59	-8.0	58	-16.5	-8.2	< 0.0001

*No adjustment for multiplicity across visits was performed.
[Source: Reviewer's analysis]

Table 9: Sensitivity Analysis by MMRM (CLON 0.4 mg vs. Placebo) – CLON-301

	Placebo		Clonicel 0.4 mg		Clonicel 0.4 mg vs. Placebo	
Visit	**N**	**MEAN**	**N**	**MEAN**	**LS Mean**	**P-value***
Week 1	75	-3.9	77	-6.5	-2.5	0.053
Week 2	74	-4.5	65	-14.2	-9.5	< 0.0001
Week 3	70	-6.9	69	-16.0	-8.4	< 0.0001
Week 4	67	-6.9	57	-17.9	-10.7	< 0.0001
Week 5	59	-8.0	52	-19.4	-11.1	< 0.0001

*No adjustment for multiplicity across visits was performed.
[Source: Reviewer's analysis]

3.1.2 STUDY CLON-302

Study Title:

The title of Study CLON-301 is given as "A phase III evaluation of the efficacy and safety of CLONICEL (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)."

Primary Objective:

- To evaluate the efficacy of CLONICEL administered as a flexible dose of 0.1 to 0.4 mg/day as add-on to a stable regimen of psychostimulant medication compared to

psychostimulant medication alone in the treatment of children and adolescents with ADHD

- To evaluate the safety of this dosing regimen as add-on to psychostimulant medication compared to psychostimulant medication alone in the treatment of children and adolescents with ADHD

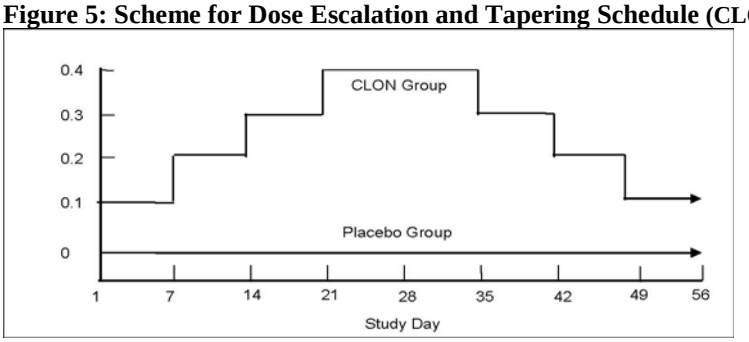
Secondary Objective:

- To evaluate the efficacy of the add-on therapy in alleviating symptoms of sleep disturbance in this patient population
- To evaluate the efficacy of the add-on therapy in alleviating symptoms of adrenergic dysregulation in this patient population
- To evaluate the population pharmacokinetics in children and adolescents receiving CLONICEL at this dosing regimen
- To correlate measures of efficacy and safety with genetic or other biologic markers

3.1.2.1 Study Design

This was an 8-week (56 days), multi-center, parallel-group, randomized, double-blind, placebo-controlled study of the efficacy and safety of a flexible dose of CLONICEL in children and adolescents (6 to 17 years) who met DSM-IV criteria for ADHD. Subjects were randomly assigned to one of two groups: CLONICEL as add-on to a psychostimulant (CLON+STM) or a psychostimulant and Placebo (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. 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. Figure 5 shows the dose escalation and dose tapering schedule for the two treatment groups.

Figure 5: Scheme for Dose Escalation and Tapering Schedule (CLON-302)



[Source: Figure 1. of CLON 302 CSR (page 41)]

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 medication at the Week 8 visit but returned for a closeout safety visit one week later.

Sample size calculation:
The sample size calculation was based on comparing the two treatment on mean changes in ADHDRS-IV scores from Baseline to the Week 5 (or last available) measure. The following assumptions were made:

Difference between active and placebo mean change scores = 7 points
Pooled standard deviation = 15
Alpha = 0.05
Power = 90%
Ratio of active/placebo = 1

Sample size calculations indicated that 100 patients per treatment group would be required to achieve statistical significance given the above assumptions.

3.1.2.2 Statistical Method and Analysis

Definition of study population in primary analysis:

The study population will consist of 200 children and adolescents (6 to 17 years) who meet DSM-IV criteria for ADHD of the hyperactive or combined inattentive/hyperactive subtypes will be enrolled, 100 per treatment group. The Intent to Treat (ITT) population was defined as all subjects who are randomized, took at least one dose of study drug, and provided at least one efficacy assessment post Baseline.

Primary endpoint and analyses:

The primary endpoint was the change from Baseline to Week 5 in the ADHDRS-IV scale total score. All primary statistical summaries and analyses were conducted using the ITT population. The primary analysis was based on ANCOVAs that model the change from baseline as a function of the baseline ADHDRS-IV total score, the study site, and the treatment group. Missing data was imputed by the Last Observation Carried Forward (LOCF) approach.

For study sites with fewer than 10 total subjects, the study sites were pooled. The pooling algorithm will match the largest site with fewer than 10 subjects with the smallest site until a pooled site with 10 or more subjects is obtained. The process continued with the remaining sites until all sites for analysis purposes included 10 or more subjects.

Confidence bounds presented will show two-sided 95% confidence limits for the average ADHDRS-IV total score difference between the two dosing regimens. A p-value of less than or

equal to 0.05 was deemed statistically significant. Any confidence bounds presented two-sided 95% confidence limits.
The sponsor proposed to conduct two sensitivity analyses to investigate the sensitivity of the study results to other analysis methods and assumptions than the primary analysis method:
1) ANCOVA model with a covariate of baseline ADHDRS-IV total score, factors of treatment, study site, and the treatment × site interaction term, based on LOCF data.
2) The same ANCOVA model as in the primary analysis based on completed scores at Week 5 (observed cases) without LOCF imputation.

Secondary efficacy endpoints and analyses:

Secondary measurements 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). No key secondary endpoint was pre-specified.

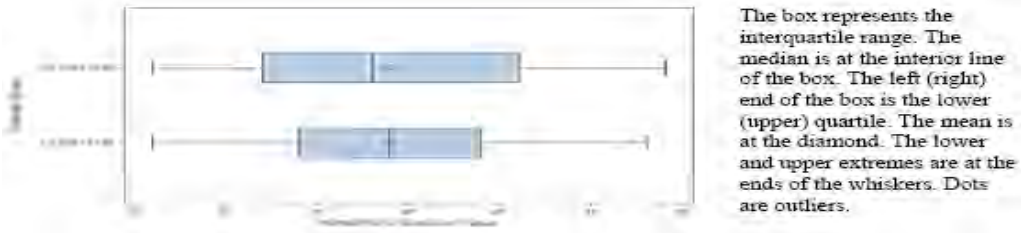
3.1.2.3 Efficacy Results

3.1.2.3.1 Subject Disposition and Baseline Demographic Characteristics

Baseline distributions of the treatment groups:

Figure 6 displays box plots of baseline ADHDRS-IV total scores of each treatment group. A visual inspection of this figure along with Table 10 suggests that the distribution of Baseline ADHDRS-IV total scores for PBO +STM group is wider than that of the CLON +STM group, but their means and medians are similar. The difference in the distribution may not be clinically relevant.

Figure 6: Box-Whisker Plots: Baseline ADHDRS-IV total scores by treatment (CLON-302)



[Source: Reviewer's analysis]

Table 10: Baseline ADHDRS-IV total scores by treatment groups (CLON-302)

Treatment	N	Mean	SD	Median
CLON +STM	102	38.9	6.95	39.0
Placebo +STM	95	39.0	7.68	38.0

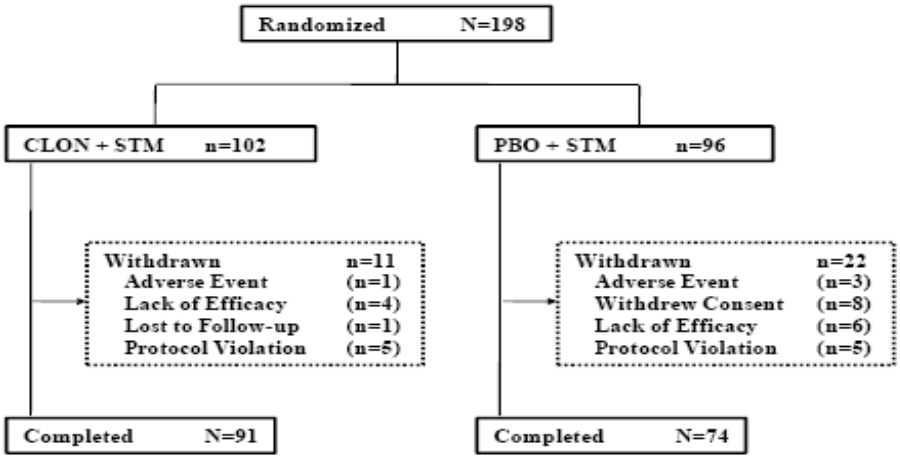
[Source: Reviewer's analysis]

Subject disposition:

A total of 200 subjects were planned for enrollment. Of the 243 subjects screened, 198 subjects were randomly assigned to 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 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. Figure 7 and Table 11 provide all the details of subject dispositions.

Figure 7: Subjects Dispositions in CLON-302



[Source: Figure 2 of CLON 302 CSR (page 61)]

Table 11: Subject Dispositions in CLON-302

Summary	Treatment Group		All Subjects
	Clonicel + STM	Placebo + STM	
Study Population			
All Randomized	102	96	198
Intent-to-Treat (ITT) [1]	102	95	197
Safety	102	96	198
Subjects Completed Treatment Phase			
Yes	91 (89.2%)	74 (77.1%)	165 (83.3%)
No	11 (10.8%)	22 (22.9%)	33 (16.7%)
Reason for not Completing Treatment Phase			
Withdrew Consent	0	8 (8.3%)	8 (4.0%)
Adverse Event	1 (1.0%)	3 (3.1%)	4 (2.0%)
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%)
Other	0	0	0
Subjects Completed Follow-up Visit			
Yes	95 (93.1%)	77 (80.2%)	172 (86.9%)
No	7 (6.9%)	19 (19.8%)	26 (13.1%)
Reason for not Completing Follow-Up			
Withdrew Consent	2 (2.0%)	16 (16.7%)	18 (9.1%)
Adverse Event	0	1 (1.0%)	1 (0.5%)
Lack of Efficacy	0	0	0
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%)

[Source: Table 14.1.1 of CLON 302 CSR (page 108)]

Demographic characteristics:

As shown in Table 12, for all randomized subjects, the majority were male (73.6%) and White (53.8%). The mean subject age was 10.5 years (median 10.0 years), and most subjects were 6-12 years of age (77.2%). The mean body weight was 39.6 kg.

Table 12: Subgroup (Gender, Age, Age group, Race, Weight) in CLON-302

Summary	Treatment Group		All Subjects
	Clonicel + STM	Placebo + STM	
ITT Subjects	102	95	197
Gender			
Male	79 (77.5%)	66 (69.5%)	145 (73.6%)
Female	23 (22.5%)	29 (30.5%)	52 (26.4%)
Age (years)			
N	102	95	197
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%)
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
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

[Source: Table 14.1.3 of CLON 302 CSR (page 115)]

3.1.2.3.2 Sponsor's Efficacy Analysis Results

Results from the primary variable:

Table 13 displays the sponsor's primary analysis results, summarizing the change scores from Baseline for ADHDRS-IV comparing the CLON+STM to the PBO+STM treatment group. The least-squares mean difference in the comparison was statistically significantly different from zero at the 2-sided, 5% nominal significance level, in favor of the CLON+STM treatment group.

Table 13: Sponsor Primary Efficacy Analysis in CLON-302

Primary analysis	**Treatment Group**	**N**	**LS Means Estimate of Difference (CLON+STM – PBO+STM) in Week 5 ADHDRS-IV Total Score**	
			Difference* (95% CI)	**p-value**
ANCOVA (LOCF)	Clonicel +STM	102	-4.48 (-7.83, -1.13)	0.0091
	Placebo +STM	95	--	--

* Treatment difference adjusted for study site and baseline ADHDRS-IV Total score based on ANCOVA
[Source: Table 14.2.2 of CLON 302 CSR (page 129)]

Table 14: Sponsor sensitivity analysis: using observed cases - ANCOVA (OC) in CLON-302

Sponsor sensitivity analysis: Using observed cases	**Treatment Group**	**N**	**LS Means Model Estimate for Difference (Clonicel+STM – Placebo+STM) in Week 5 ADHDRS-IV Total Score**	
			Difference* (95% CI)	**p-value**
ANCOVA (OC)	Clonicel +STM	92	-4.12 (-7.77, -0.47)	0.0273
	Placebo +STM	75	--	--

* Treatment difference adjusted for study site and baseline ADHDRS-IV Total score based on ANCOVA
[Source: Table 14.2.2 of CLON 302 CSR (page 129)]

The sponsor performed two sensitivity analyses. The analysis results can be found in Table 14 and Table 15. The results are consistent with those found in the primary analysis, and support the sponsor's efficacy claim. This reviewer confirmed the results.

Table 15: Sponsor sensitivity analysis: Inclusion of an interaction of study site and treatment - ANCOVA (LOCF) in CLON-302

Sponsor sensitivity analysis: Including an interaction of study site and treatment	Treatment Group	N	LS Means Model Estimate for Difference (Clonicel+STM vs. Placebo+STM) in Week 5 ADHDRS-IV Total Score	
			Difference* (95% CI)	p-value
ANCOVA (LOCF)	Clonicel +STM	102	-4.97 (-8.38, -1.56)	0.0045
	Placebo +STM	95	--	--

* Treatment difference adjusted for study site and baseline ADHDRS-IV Total score based on ANCOVA
[Source: Table 14.2.2 of CLON 302 CSR (page 129)]

Results of subscales of the ADHDRS-IV scale:

The ADHDRS-IV scale, where the primary endpoint was derived, consists of two subscales: Inattention and Hyperactivity. The sponsor concluded statistically significant improvements favoring the CLONICEL treatment groups for both subscales, Inattention and Hyperactivity, of the ADHDRS-IV scale. (See Table 16)

Table 16: Change Scores for Subscales of the ADHDRS-IV Scale at Week 5 (LOCF) – CLON-302

	TREATMENT GROUP	
	CLON+STM	PBO+STM
Inattention Subscale, N	102	95
Baseline, Mean (SD)	20.7 (4.22)	20.8 (4.21)
Change Score at Week 5, Mean (SD)	-7.8 (6.81)	-5.8 (6.85)
p-value[1]	p=0.0169	--
Hyperactivity/Impulsivity, N	102	95
Baseline, Mean (SD)	18.2 (4.94)	18.2 (5.14)
Change Score at Week 5, Mean (SD)	-7.9 (6.70)	-5.8 (6.32)
p-value[1]	p=0.0143	--

1 Versus placebo p-value; obtained from the treatment parameters in an ANCOVA modeling change from Baseline as a function of Baseline, treatment, and pooled study site.
[Source: Synopsis Table 3 of CLON 301 CSR (page 9)]

Results of secondary endpoints:

The sponsor concluded that most of the results of the secondary efficacy analyses supported those of the primary efficacy analysis and achieved statistical significance (p-value at least <0.05). Statistical significance was found in pre-specified secondary efficacy endpoint, except for the HADS, CPRS-L oppositional subscale, and SSR-CF scale total score and all subscales. This reviewer confirmed the results.

Sponsor's conclusion on efficacy:

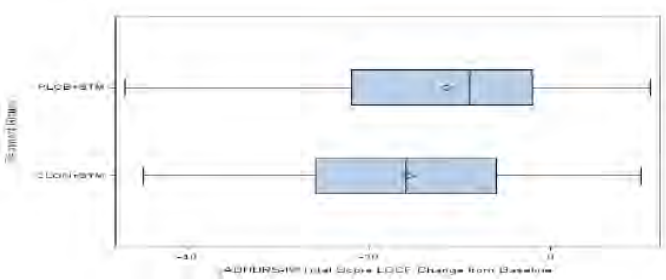
CLONICEL (clonidine HCl modified release), as add-on therapy to ADHD psychostimulants, was efficacious in alleviating symptoms in children and adolescents with ADHD who lacked adequate response on a stable regimen of stimulant medication alone.

3.1.2.3.3 Reviewer's Assessments

(b) (4)

. As displayed in Figure 8, in each of the two treatment groups, a box plot of the change from baseline ADHDRS-IV total scores suggests a distributional separation of the CLON +STM treatment group from the PBO +STM treatment group. Both the distributions of the change from baseline ADHDRS-IV total scores are determined to be fairly acceptable for an ANCOVA analysis. This reviewer created a normal QQ plot for each treatment group, and confirmed that there is no indication of a violation of the distributional assumption, considering that the ANCOVA model is fairly robust for the assumption of the normality of the distribution of the dependent variable.

Figure 8: Box-Whisker plots: Change from baseline in ADHDRS-IV total score by treatment (CLON-302)



The box represents the interquartile range. The median is at the interior line of the box. The left (right) end of the box is the lower (upper) quartile. The mean is at the diamond. The lower and upper extremes are at the ends of the whiskers. Dots are outliers.

[Source: Reviewer's analysis]

Reviewer's sensitivity analysis:

This reviewer conducted a mixed model for repeated measures (MMRM) analysis as a sensitivity analysis, in order to look into the robustness of the sponsor's efficacy analysis result based on the LOCF ANCOVA. As in the sponsor's LOCF ANCOVA primary analysis, the MMRM model included baseline ADHDRS-IV total score as a fixed covariate, treatment group, study site, week and the treatment by week interaction as fixed factors. The method of estimation was restricted maximum likelihood (REML). The within subject covariance matrix was unstructured. The degree of freedom of the denominator was approximated by the Kenward-Roger's method. The results in Table 17 support the primary analysis results based on the LOCF ANCOVA analysis.

Table 17: Sensitivity Analysis by MMRM (CLON+ STM vs. PBO+STM) – CLON 302

	Placebo + STM		Clonicel +STM		Clonicel +STM vs. Placebo + STM	
Visit	**N**	**Mean**	**N**	**Mean**	**LS Mean**	**P-value***
Week 1	93	-4.6	100	-4.3	0.3	0.7575
Week 2	85	-8.6	97	-11.5	-2.9	0.0563
Week 3	91	-10.4	96	-14.1	-3.7	0.0281
Week 4	81	-12.6	93	-17.2	-4.9	0.0048
Week 5	75	-13.3	92	-16.9	-3.9	0.0274

[Source: Reviewer's analysis]

3.2 Evaluation of Safety

(The evaluation of safety is deferred to the clinical team.)

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section all the subgroup analyses were exploratory for the purpose of assessing the consistency across subgroups.

4.1 Gender, Race and Age

4.1.1 STUDY CLON-301

4.1.1.1 Gender

The sponsor conducted an analysis on the ADHDRS-IV primary endpoint by including the factor of gender as a potential predictor of the response in the ANCOVA model. The ANCOVAs were fit modeling the change from baseline as a function of the baseline ADHDRS-IV total score, the treatment group, gender and the interaction of the treatment and gender. The sponsor's interpretations of this analysis are as follows:

> In the analysis of gender, the overall treatment effect for CLONICEL relative to placebo was not affected by gender, but there were statistically significant main effects for gender. As Table 14.2.17 shows, the effects do not relate to the overall treatment performance of CLONICEL relative to placebo which is substantial in both genders. However, as shown in the estimated mean response by gender and treatment in Table 14.2.17, the trend between the treatment arms is reversed for CLONICEL 0.2 mg and CLONICEL 0.4 mg between males and females.

Table 18: Gender subgroup analysis results in CLON-301

Gender	Variable	ADHDRS-IV Total score (Observed)						ADHDRS-IV Total score (LOCF)	
		Clon 0.2 mg		Clon 0.4 mg		Placebo		Clon 0.2 mg vs. Placebo	Clon 0.4 mg vs. Placebo
		N	MEAN (SD)	N	MEAN (SD)	N	MEAN (SD)	DIFFERENCE in LSMEAN of CFB	DIFFERENCE in LSMEAN of CFB
Female	Baseline	16	41.5 (7.28)	23	44.83 (8.04)	24	45.08 (7.58)	-9.48	-12.77
	CFB Mean from Placebo	16	-17.63 (13.52)	16	-21.69 (10.46)	19	-9.84 (11.14)		
Male	Baseline	58	44.48 (7.45)	55	44.49 (7.67)	52	45.02 (9.00)	-8.31	-7.64
	CFB Mean from Placebo	42	-16.02 (11.63)	36	-18.44 (13.66)	40	-7.10 (8.07)		
Overall	Baseline	74	43.8 (7.47)	78	44.6 (7.73)	76	45.0 (8.53)	-8.49	-9.13
	CFB Mean from Placebo	58	-16.5 (12.08)	52	-19.4 (12.75)	59	-8.0 (9.16)		

* All the LS Means were calculated based on the same ANCOVA model as in the primary efficacy analysis. CFB denotes change from baseline.

[Source: Reviewer's analysis]

This reviewer conducted a gender-based subgroup analysis for the primary analysis data. The analysis results appear in Table 18. The ANCOVA model with a covariate of the baseline ADHDRS-IV total score and a factor of the treatment group was fit on each of the subgroup (male and female). The observed treatment effects appeared comparable between genders in both the treatment comparisons (CLON 0.2-mg vs. Placebo and CLON 0.4-mg vs. Placebo), except that the female CLON 0.4-mg group had a numerically larger treatment effect (-12.77).

4.1.1.2 Race

The sponsor conducted a subgroup analysis on the ADHDRS-IV primary endpoint by including the factor of race as potential predictors of response in the endpoint with an ANCOVA model analogous to that for the gender subgroup analysis. The sponsor's interpretations of this analysis are as follows:

> In the analysis of race (White, Black/African American, Hispanic, Other), the overall treatment effect for CLONICEL relative to placebo was not affected by race; there were not statistically significant effects for race or a race by treatment interaction. As shown in the least square means model estimates for race and treatment in Table 14.2.17, the effects of CLONICEL relative to placebo was substantial in Whites compared with Black/African Americans and Other races.

There are not many patients in each subgroup except for the white. The observed treatment effects in the White appear similar to the overall treatment effects for each treatment group, as summarized in this reviewer's results (Table 19).

Table 19: Race subgroup analysis results in CLON-301

Race	Variable	ADHDRS-IV Total score (Observed)						ADHDRS-IV Total score (LOCF)	
		Clon 0.2 mg		Clon 0.4 mg		Placebo		Clon 0.2 mg vs. Placebo	Clon 0.4 mg vs. Placebo
		N	MEAN (SD)	N	MEAN (SD)	N	MEAN (SD)	DIFFERENCE in LSMEAN of CFB	DIFFERENCE in LSMEAN of CFB
Black	Baseline	19	44.9 (8.89)	20	47.0 (6.50)	23	46.9 (8.82)	-6.04	-8.48
	CFB Mean from Placebo	13	-14.9 (12.62)	14	-19.3 (11.54)	20	-9.3 (11.11)		
White	Baseline	45	43.1 (7.24)	46	43.3 (8.29)	44	45.2 (8.29)	-9.13	-9.20
	CFB Mean from Placebo	37	-16.0 (12.29)	32	-18.9 (13.33)	30	-7.3 (8.43)		
Hispanic	Baseline	6	46.3 (5.61)	7	45.7 (6.45)	6	42.5 (6.72)	-12.65	-13.11
	CFB Mean from Placebo	5	-20.2 (12.38)	4	-20.8 (17.08)	6	-7.8 (8.82)		
Other	Baseline	4	43.0 (5.89)	5	45.0 (7.97)	3	34.0 (6.24)	-11.28	-9.43
	CFB Mean from Placebo	3	-22.3 (8.50)	2	-26.0 (8.49)	3	-6.3 (3.05)		
Overall	Baseline	74	43.8 (7.47)	78	44.6 (7.73)	76	45.0 (8.53)	-8.49	-9.13
	CFB Mean from Placebo	58	-16.5 (12.08)	52	-19.4 (12.75)	59	-8.0 (9.16)		

* All the LS Means were calculated based on the same ANCOVA model as in the primary efficacy analysis. CFB denotes change from baseline.

[Source: Reviewer's analysis]

4.1.1.3 Age

The sponsor performed their subgroup analysis on the ADHDRS-IV primary endpoint by including the covariate of age as potential predictors of response, with an ANCOVA model analogous to that for their gender subgroup analysis. The sponsor's interpretations of this analysis are as follows:

Age was evaluated as a continuous variable. The main effects for treatment were greater than were observed in the primary efficacy model. The age by treatment interaction was a significant factor. CLONICEL group age slopes were positive while the placebo slope was slightly negative. For the mean overall age, 9.4 years, the mean for the groups was -15.9, -16.4, and -7.4 for CLONICEL 0.2 mg, CLONICEL 0.4 mg, and placebo, respectively.

According to the sponsor's report, the interaction of treatment and age was significant and concluded that the treatment effect might differ according to the age of the subject.

This reviewer explored the age impact by dichotomizing the age into two subgroups: 6-12 year-old, and >12 year-old. In each subgroup, the ANCOVA with a covariate of baseline score and a factor of treatment was applied. The results, as summarized in Table 20, suggest that the 6-12 year-old subgroup was the contributor of the overall efficacy evidence, while the >12 year-old was not. In both comparisons, the difference of the least-square means was much smaller for the >12 year-old subgroup than for the 6-12 year-old group. This, however, may be due to the small number of subjects of this subgroup, and thus there is no information in the data enough to draw any conclusion on the efficacy of the >12 year-old subgroup.

Table 20: Age subgroup analysis results in CLON-301

Age group	**Variable**	**ADHDRS-IV Total score (Observed)**						**ADHDRS-IV Total score (LOCF)**	
		Clon 0.2 mg		**Clon 0.4 mg**		**Placebo**		**Clon 0.2 mg vs. Placebo**	**Clon 0.4 mg vs. Placebo**
		N	**MEAN (SD)**	**N**	**MEAN (SD)**	**N**	**MEAN (SD)**	**DIFFERENCE in LSMEAN of CFB**	**DIFFERENCE in LSMEAN of CFB**
6-12 year-old	**Baseline**	61	45.1 (6.93)	65	45.9 (7.07)	62	46.2 (8.0)	-10.62	-10.80
	CFB Mean from Placebo	46	-18.0 (12.49)	40	-21.0 (12.52)	49	-6.8 (8.43)		
>12 year-old	**Baseline**	13	38.2 (7.54)	13	38.0 (7.74)	14	39.7 (9.06)	-1.53	-1.69
	CFB Mean from Placebo	12	-10.5 (8.32)	12	-14.3 (12.67)	10	-13.9 (10.74)		
Overall	**Baseline**	74	43.8 (7.47)	78	44.6 (7.73)	76	45.0 (8.53)	-8.49	-9.13
	CFB Mean from Placebo	58	-16.5 (12.08)	52	-19.4 (12.75)	59	-8.0 (9.16)		

* All the LS Means were calculated based on the same ANCOVA model as in the primary efficacy analysis. CFB denotes change from baseline.
[Source: Reviewer's analysis]

4.1.2 STUDY CLON-302

4.1.2.1 Gender

The sponsor conducted an analysis on the ADHDRS-IV primary endpoint by including the factor of gender as a potential predictor of the response in the endpoint. The ANCOVAs were fit modeling the change from baseline as a function of the baseline ADHDRS-IV total score, the treatment group, gender and the interaction of the treatment and gender. The sponsor's interpretations of this analysis are as follows:

In the analysis of gender, the overall treatment effect for CLONICEL relative to placebo was not affected by gender; there were no statistically significant effects for gender or a gender by treatment interaction. The least squares means for the treatments adjusted for gender were -16.4 and -11.2 for CLON+STM and PBO+STM, respectively, and the treatment difference was highly significant (p=0.0087).

The sponsor found that the gender and the interaction of gender and treatment were not statistically significant in the specified ANCOVA model, and concluded that the overall treatment effect for CLONICEL relative to placebo was not affected by gender.

This reviewer conducted a gender-based subgroup analysis for the primary analysis data. The ANCOVA model with a covariate of the baseline ADHDRS-IV total score and a factor of the treatment group was fit on each of the subgroup (male and female). The observed treatment effects appeared consistent in favoring the combination therapy. (See Table 21)

Table 21: Gender subgroup analysis in CLON-302

Gender	Variable	ADHDRS-IV Total score (Observed)				ADHDRS-IV Total score (LOCF)
		Clon +STM		Placebo +STM		Clon +STM vs. Placebo +STM
		N	MEAN (SD)	N	MEAN (SD)	DIFFERENCE in LSMEAN of CFB
Female	Baseline	23	38.9 (7.92)	29	37.6 (8.25)	-6.8
	CFB Mean from Placebo	22	-17.4 (14.55)	21	-12.2 (14.09)	
Male	Baseline	79	38.9 (6.70)	57	39.6 (7.39)	-3.1
	CFB Mean from Placebo	70	-16.8 (11.51)	44	-13.7 (10.98)	
Overall	Baseline	102	38.9 (6.95)	95	39.0 (7.68)	-4.5
	CFB Mean from Placebo	92	-15.7 (12.08)	75	-11.5 (12.75)	

* All the LS Means were calculated based on the same ANCOVA model as in the primary efficacy analysis. CFB denotes change from baseline.
[Source: Reviewer's analysis]

4.1.2.2 Race

The sponsor performed a subgroup analysis on the ADHDRS-IV primary endpoint by including the factor of race as potential predictors of response. The ANCOVAs were fit modeling the change from baseline as a function of the baseline ADHDRS-IV total score, the treatment group, race and the interaction of the treatment and race. The sponsor's interpretations of the analysis are as follows:

In the analysis of race, the ANOVA tests for homogeneity of race and race/treatment interaction were not significant. However, inspection of the least squares means and model estimates show that the effect of CLONICEL relative to placebo was most substantial in Whites compared to Other races (Hispanic/Latino and other) and Black/African American subjects. The overall least squares mean average treatment responses were -15.7 and -12.4 for CLON+STM and PBO+STM, respectively (p=0.0888). The pair-wise p-value for Whites was statistically significant on its own (p=0.0397) with estimated means of -17.1 and -10.2 for CLON+STM and PBO+STM, respectively. There was a reasonable number of Blacks/African Americans and Other Races in this study and the proportion of Whites in the CLON+STM group (48.0%) was actually lower than in the PBO+STM group (60.0%) primarily as a result of having more Blacks/African Americans in the CLON+STM group, though the test for overall homogeneity of the race distributions was not statistically significant (p=0.1547). This imbalance may explain the lack of statistical significance in the average pair-wise treatment comparison.

The essential part of the sponsor's interpretations is that no other race had a greater impact on the outcome of the primary efficacy analysis than the white.

Table 22: Race subgroup analysis in CLON-302

Race	Variable	ADHDRS-IV Total score (Observed)				ADHDRS-IV Total score (LOCF)
		Clon +STM		Placebo +STM		Clon +STM vs. Placebo +STM
		N	MEAN (SD)	N	MEAN (SD)	DIFFERENCE in LSMEAN of CFB
Black	Baseline	35	39.7 (6.04)	19	41.7 (7.22)	-0.3
	CFB Mean from Placebo	29	-15.3 (13.22)	14	-15.1 (11.57)	
White	Baseline	49	38.7 (7.39)	57	38.4 (7.52)	-7.0
	CFB Mean from Placebo	45	-18.3 (11.41)	44	-11.9 (10.94)	
Hispanic	Baseline	11	39.4 (7.92)	11	36.7 (9.43)	-0.6
	CFB Mean from Placebo	11	-13.9 (14,96)	9	-14.1 (11.48)	
Other	Baseline	7	35.6 (6.90)	8	40.0 (6.76)	-7.5
	CFB Mean from Placebo	7	-19.7 (8.24)	8	-16.8 (17.85)	
Overall	Baseline	102	38.9 (6.95)	95	39.0 (7.68)	-4.5
	CFB Mean from Placebo	92	-15.7 (12.08)	75	-11.5 (12.75)	

* All the LS Means were calculated based on the same ANCOVA model as in the primary efficacy analysis. CFB denotes change from baseline. [Source: Reviewer's analysis]

This reviewer applied the primary analysis to each subgroup of race: the white, the black, the Hispanic, and the other (see Table 22). The white accounts for the largest proportion of the race, and the observed treatment effect for this subgroup was in favor of the clonicel group. For the black, they appear similar between treatment groups. It is noted that the black in the placebo group seem to have numerically considerable improvement. The reason is unclear, but it might be explained by the effect contributed by the use of stimulant or the chance because of the sample size in this subgroup.

4.1.2.3 Age

The sponsor performed their subgroup analysis on the ADHDRS-IV primary endpoint by including the covariate of age as potential predictors of response. The ANCOVAs were fit modeling the change from baseline as a function of the baseline ADHDRS-IV total score, the treatment group, age and the interaction of the treatment and age. The sponsor's interpretations of this analysis are as follows:

> Age was evaluated as a continuous variable. Age and the age by treatment interaction were not significant factors. Slopes indicated that the PBO+STM improved with increasing age (slope = -0.41), while the overall slope for CLON+STM was close to zero (-0.03). There was a large difference in the intercepts with CLON+STM having a -8.29 difference relative to PBO+STM associated with the treatment parameter. As noted above, the p-value for the overall least squares mean treatment comparison adjusted for age was statistically significant (p=0.0143). For the mean overall age, 10.5 years, the means were -15.8 and -11.5 for CLON+STM and PBO+STM, respectively.

The sponsor found that the age and the interaction of age and treatment were not statistically significant in the specified ANCOVA model. This reviewer confirmed the analysis results and has no further comments to the sponsor's interpretations shown above.

This reviewer explored the age impact by dichotomizing the age into two subgroups: 6-12, and >12. In each subgroup, the ANCOVA with a covariate of baseline score and a factor of treatment was applied. The results, as summarized in Table 23, appear consistent between these two subgroups.

Table 23: Age subgroup analysis in CLON-302

Age group	Variable	ADHDRS-IV Total score (Observed)				ADHDRS-IV Total score (LOCF)
		Clon +STM		Placebo +STM		Clon +STM vs. Placebo +STM
		N	MEAN (SD)	N	MEAN (SD)	DIFFERENCE in LSMEAN of CFB
6-12 Years	Baseline	77	39.3 (6.85)	75	39.5 (7.69)	-3.8
	CFB Mean from Placebo	70	-16.51 (12.29)	62	-13.4 (12.27)	
>12 Years	Baseline	25	37.7 (7.2)	20	36.9 (7.47)	-5.8
	CFB Mean from Placebo	22	-18.2 (12.17)	13	-12.8 (10.26)	
Overall	Baseline	102	38.9 (6.95)	95	39.0 (7.68)	-4.5
	CFB Mean from Placebo	92	-15.7 (12.08)	75	-11.5 (12.75)	

* All the LS Means were calculated based on the same ANCOVA model as in the primary efficacy analysis. CFB denotes change from baseline.
[Source: Reviewer's analysis]

4.2 Other Special/Subgroup Populations

4.2.1 STUDY CLON-302: Psychostimulant subgroup

The sponsor conducted their subgroup analysis for the stimulant based subgroups (Amphetamine or Methylphenidate). The results are provided in Table 14.2.1.3 (observed data) and Table 14.2.1.4 (LOCF data) of the study report. Means and standard deviations of observed baseline scores and observed (and LOCF) changes from baseline in ADHDRS-IV total score at all the visits (Screening, Baseline, Week 1- Week5) are provided in these tables. The sponsor also conducted a model-based analysis; the same ANCOVA model as in the primary efficacy analysis, with an additional categorical variable of stimulants. These results are also provided in Table 14.2.1.3 (observed data) and Table 14.2.1.4 (LOCF data) of the study report.

The sponsor found that there were no statistically significant differences between the CLON+STM treatment group and PBO+STM treatment group at Week 5, but attributed this to the small sample sizes. This reviewer agrees. These corresponding results along with essential statistics are provided in Table 24. The small difference between the subgroups in magnitude of each of the LS mean estimates (-4.2 for Amphetamine and -3.4 for Methylphenidate) does not seem to suggest any inconsistency that may affect the interpretations of the overall primary efficacy result.

Table 24: Sponsor subgroup analysis by Psychostimulant (Amphetamine/Methylphenidate) in CLON-302

Stimulant group	Variable	ADHDRS-IV Total score (Observed)				ADHDRS-IV Total score (LOCF)
		Clon +STM		Placebo +STM		Clon +STM vs. Placebo +STM
		N	MEAN (SD)	N	MEAN (SD)	DIFFERENCE in LSMEAN of CFB
Amphetamine	**Baseline**	42	39.3 (6.60)	35	38.9 (6.67)	-4.2
	CFB Mean from Placebo	41	-18.6 (12.44)	30	-14.6 (10.88)	
Methylphenidate	**Baseline**	60	38.6 (7.22)	60	39.0 (8.26)	-3.4
	CFB Mean from Placebo	51	-15.6 (11.99)	45	-12.4 (12.50)	
Overall	**Baseline**	102	38.9 (6.95)	95	39.0 (7.68)	-4.5
	CFB Mean from Placebo	92	-15.7 (12.08)	75	-11.5 (12.75)	

* All the LS Means were calculated based on the same ANCOVA model as in the primary efficacy analysis. CFB denotes change from baseline.
[Source: Reviewer's analysis]

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

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 CLONICEL treatment against the placebo, both as a monotherapy and as an add-on to a psychostimulant.

The sponsor established statistical evidence to support the claim for the efficacy of CLONICEL, based on results from the pre-specified analysis LOCF ANCOVA (last observation carried forward analysis of covariance) as well as the pre-specified sensitivity analysis ANCOVA on Observed Cases. The dropout rates were around 40% and 17% respectively in these two studies. In order to explore the impact of the dropouts on efficacy findings, this reviewer performed a MMRM-based sensitivity analysis, which requires a milder assumption for the missing data mechanism. It was found that the result led to the same conclusion in supporting efficacy.

In the subgroup analysis, this reviewer observed differences in estimates of change from baseline scores among races in Study CLON-302, but not in Study CLON-301. In addition, this reviewer observed that the age groups (6-12 year-old and >12 year-old) did not show similar efficacy estimates in Study CLON-301. These differences, however, may be due to a chance or the fact that subgroups but the white had too small a sample size to statistically assess the estimated differences. Despite some apparent discrepancies in efficacy estimates for subgroups, overall evidence is strong to support the efficacy of the clonicel treatment.

5.2 Conclusions and Recommendations

The sponsor's phase III studies, CLON-301 and CLON-302, provided statistical evidence that CLONICEL is efficacious, as a monotherapy and as an add-on to a psychostimulant, in the treatment of subjects (6-17 years-old) with ADHD.

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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

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