

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **21-259**

STATISTICAL REVIEW(S)

Statistical Review & Evaluation

NDA #: 21-259
Sponsor: Medeva Pharmaceuticals, Inc.
Drug: Capsules, 20 mg
Indication: Attention Deficit Hyperactivity Disorder (ADHD)
Date received: April 4, 2000

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1. Background

Attention Deficit Hyperactivity Disorder (ADHD) is the most prevalent psychiatric disorder of childhood. Three to six percent of school-aged children in the United States are diagnosed with ADHD. Stimulant medications such as Bensedrine®, Dexedrine®, and methylphenidate (Ritalin®) have been used for over 55 years to treat ADHD children. Positive effects on behavior and academic productivity are well established for stimulant medication such as methylphenidate. It is a fast-acting drug. The serum blood level and the primary behavioral effect of methylphenidate have a similar time course: both reach a maximum between one and two hours after oral administration and have a half-life of about three hours. One of the primary drawbacks is its short behavioral half-time, which requires multiple doses per day to maintain efficacy. A primary problem with two or three times daily dosing is that administration of medication is required at school.

The overall purpose of the _____ program was to develop a formulation of methylphenidate that would produce a therapeutic benefit of sufficient duration to eliminate the need for a midday dose.

2. Protocol MAI 1001-04

2.1 Study title, objective and design

The study title is "A Double-Blind, Placebo-Controlled Study of Modified-Release (MR) Methylphenidate in Children with ADHD."

The primary objective of this study was to compare the efficacy, safety and tolerability of a once daily (early morning), modified-release (MR) formulation of methylphenidate (MPH) (containing both immediate-release (IR) and extended-release (ER) beads in a ratio of 30:70, respectively) to placebo in children with a confirmed diagnosis of attention deficit hyperactivity disorder (ADHD). The secondary objective of this study was to compare separately the morning and afternoon therapeutic response of the MPH MR formulation over placebo.

This was a randomized, double-blind, parallel-group, placebo-controlled, multi-center study, comprising a one-week single-blind placebo run-in and a three-week double-blind period of randomized treatment, comparing MPH MR (given in individually titrated dosages of 20, 40 or 60 mg daily) to matching placebo in ADHD subjects.

This trial consisted of 32 centers in the US. The first subject signed the informed consent on 4 January 1999 and the last subject completed the study on 15 December 1999. A total of 300 subjects were to be randomized based on statistical assumptions; 321 were randomized and 276 completed the trial.

Subjects were eligible for the study if they met DSM-IV criteria for a primary diagnosis of ADHD (code 314.01), either the combined or predominantly hyperactive-impulsive subtype, demonstrated a need for methylphenidate treatment, were 6 years of age or older

of either gender and in a school setting in which one teacher spent sufficient time with them to make valid morning and afternoon assessments of their behavior and had no comorbid psychiatric diagnosis or other symptomatic manifestations that, in the opinion of the investigator, would contraindicate methylphenidate treatment or confound efficacy or safety assessments.

A total of six visits were scheduled over a four to five-week period, one to screen candidate patients (Screening Visit), one to dispense single-blind placebo (Orientation Visit), one to obtain the baseline assessment on placebo and give the first double-blind treatment (Baseline Visit), and three to evaluate double-blind treatment (Evaluation Visits).

Patients who are eligible will be dispensed single-blind placebo at the Orientation Visit for a one week washout. Following the placebo washout week, at the Baseline Visit, qualified patients will be randomized to either methylphenidate MR or to Placebo and will receive the first week of double-blind treatment consisting of a daily morning dose.

For the first week of double-blind treatment, the dosage of methylphenidate MR will be 20 mg/day or matching placebo. For the second week of double-blind treatment, the dosage may be increased to 40 mg/day or kept at 20 mg/day as deemed appropriate by the investigator. For the third week of double-blind treatment, the dosage may be kept constant (at 20 or 40 mg/day), increased by 20 mg/day to either 40 or 60 mg/day, or reduced from 40 mg/day to 20 mg/day- depending on the investigator's assessment. Patients receiving double-blind placebo will have their dosages adjusted accordingly.

Table 2.1: Schedule of Evaluation by Visit

	Screening	Orientation	Baseline	Double-Blind Treatment		
Preceding week number	["a" to -1]	[-1]	0	1	2	3
Visit:	Vs	V0	Vb	V1	V2	V3
Study Activity						
Consent Form	X					
Physical Exam	X	X				
Psychiatric evaluation	X					
Dispense single-blind placebo		X				
Dispense double-blind Medication						
Clinical Global Impression		X	X	X	X	X
10-item Conners' Global Index		X	X	X	X	X
Adverse events			X	X	X	X

2.2 Primary efficacy variable

The protocol defined single primary efficacy measure was the overall mean of the change from baseline of the daily combined (mean of morning and afternoon) ratings of the Teacher total scores for the Conners' Global Index (TCGI) scale for the last week of double-blind treatment. The table below explains the 10-item TCGI measurements.

Table 2.2: 10-Item Conners' Global Index Scale- Teacher's version

	Never, Seldom	Occasionally	Often, Quite a Bit	Very Often, Very Frequent
1. Temper outbursts; explosive, unpredictable behavior	0	1	2	3
2. Excitable, impulsive	0	1	2	3
3. Restless or overactive	0	1	2	3
4. Cries often and easily	0	1	2	3
5. Inattentive, easily distracted	0	1	2	3
6. Fidgeting	0	1	2	3
7. Disturbs other children	0	1	2	3
8. Demands must be met immediately- easily frustrated	0	1	2	3
9. Fails to finish things he/she starts	0	1	2	3
10. Mood changes quickly and drastically	0	1	2	3

2.3 Secondary Efficacy Variables

1. One of the secondary efficacy variable was the parent's version of the Conners' Global Index (PCGI) scale. They are weekly average totals for the 10-item Conners' Global Index Scale completed by the parents three times on Saturday or Sunday of each treatment week. The changes from baseline were analyzed using analysis of variance.
2. Baseline severity of illness was recorded at 7 levels: 0 = Not assessed; 1 = Normal, not at all ill; 2 = Borderline mentally ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; 7 = Extremely ill. Related secondary efficacy measures was the Global Improvement score based on the Clinical Global Impression ratings completed by the Investigators (CGII) during the last week of the double-blind therapy. These ratings refer to the question: "Compared to his/her condition at admission to the project, how much has the patient changed?" There were seven possible response levels: 0 = Not assessed; 1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; 7 = Very much worse.

3. Sponsor's analyses and conclusions

The primary efficacy parameter, change from baseline in overall TCGI for the last week of double-blind therapy was highly significant (p-value < 0.001). Improvement in the symptoms scores of the methylphenidate subjects was statistically significantly greater than in the placebo subjects. According to the Last Observation Carried Forward (LOCF)

analysis mean changes for MPH MR and placebo are 7.9 and 1.2, respectively. These results are presented in a tabular form by the sponsor as follows.

Table 3.1: Endpoint LS Mean Change from baseline in Teacher Conners' Global Index Scale scores, by treatment (ITT)

	MPH MR (N=155)	Placebo (N=159)	p-value
Endpoint LS Mean ^a	7.9	1.2	< 0.001
ANOVA SE	0.51	0.51	
^a LS mean = mean derived from ANOVA			

When the morning and afternoon ratings of TCGI scale were examined separately, the degree of improvement over placebo in controlling the symptoms for methylphenidate-treated subjects was as good as in the afternoon as it was in the morning. An overview of the results are as shown in Table 3.2 below.

Table 3.2 : Changes in mean scores from baseline in TCGI Scale ITT, morning/afternoon groups, by week

Week	Time	MPH MR	Placebo	p-value
1	AM	5.7	0.8	<0.001
	PM	5.1	0.2	<0.001
2	AM	7.3	1.0	<0.001
	PM	7.0	0.4	<0.001
3	AM	8.3	1.6	<0.001
	PM	7.7	1.1	<0.001

There were also highly significant differences between the treatment groups that favored the MPH MR group, in terms of the following secondary efficacy endpoints:

- Change from baseline in the 10-item Conners' Global Index Scale completed by the parent three times during the Saturday or Sunday of the last week of double-blind therapy (p-value < 0.001).
- Clinical Global Impressions (CGII) Scale completed by the Investigator at the last week of double-blind therapy (p-value < 0.001).
- Parent's global assessment of efficacy (p-value < 0.001).

The sponsor concludes as follows.

1. Analyses of the primary efficacy measures strongly support the efficacy of MPH MR in the treatment of ADHD. The change in average totals from baseline in the TCGI for Week 3, combining morning and afternoon ratings, showed statistically significantly greater improvement in the MPH MR group than in the placebo group (p < 0.001). All the secondary efficacy parameters were consistent with the primary efficacy parameter in showing statistically significant differences between MPH MR and placebo, all favoring MPH MR.

2. *Of particular interest are the differences between MPH MR and placebo in changes from baseline of the morning and afternoon average totals of TCGI. Not only is the MPH MR statistically significantly superior to placebo in controlling the symptoms of ADHD both in the morning and the afternoon, the degree of improvement in the afternoon was as large as that in the morning in the MPH MR treated group, demonstrating that once-daily dosing in the morning with MPH MR can control symptoms of ADHD for the entire school day eliminating the need for a second midday dose.*

4. Reviewer’s analyses and comments

As mentioned earlier, the protocol defined single primary efficacy measure was the overall mean of the change from baseline of the daily (combined morning and afternoon) ratings of the Teacher total scores for the Conners’ Global Index (TCGI) scale for the Week 3 of the double-blind treatment. We denote this by CHANGE3, for convenience. That is, the primary efficacy variable is

$$\text{CHANGE3} = \text{BASELINE TCGI} - (\text{WK3AM TCGI} + \text{WK3PM TCGI}) / 2.$$

By definition, smaller TCGI score means *normal behavior* and therefore, large change from baseline means *improvement*. Analysis of variance (ANOVA) is the protocol defined statistical method for the primary efficacy variable CHANGE3 defined above.

The data indicate that the study was conducted on 31 SITES of which 4 SITES recruited less than 3 patients. The study included a total of 321 patients at the baseline: The Metadate™ MR group had 158 patients and placebo had 163. The LOCF population at Week 3 consisted of 155 patients in Metadate™ MR and 158 in placebo.

4.1 Demographic characteristics

The ITT population consisted of 254 (81%) boys and 59 (19%) girls. There were 229 (71%) Caucasians and 91 (29%) belonged to other races. Descriptive statistics for age and weight of subjects in the ITT population are as follows.

Table 4.1: Age and Weight (ITT Population)

Variable	N	Mean	Std. Dev.	Minimum	Maximum
AGE	313	9.11	1.86	5.3	14.5
WEIGHT	312	34.26	11.56	18.6	94.43

In the ITT population 199 patients had ADHD treatment earlier and 114 were naïve to ADHD treatment. In what follows “PRNAIVE = no” means that a patient was treated earlier for ADHD and “PRNAIVE = yes” means that the patient was not treated earlier.

4.2 Baseline comparison

The means of the baseline teacher’s version of the Conners’ Global Index Scale (TCGI) scales for placebo and Metadate™ RM were 11.51 and 12.68, respectively. One-way analysis of variance of TCGI indicated that the two treatment groups were not statistically

significantly different with respect to the baseline measurements on the TCGI scales (p-value = 0.2417). In addition, the baseline Clinical Global Impression (CGII) evaluated by Investigator had an average of 4.4 for placebo and 4.52 for Metadate™ MR. One-way analysis of variance of CGII indicated that the two treatment groups were not statistically significantly different (p-value = 0.248). Therefore, we can state that the two treatment groups were comparable.

4.3 Protocol defined primary endpoint

The change from baseline in Week 3 Teacher's version of Conners' Global Index scale (which is abbreviated as CHANGE3) is the protocol defined primary efficacy variable. Analysis of variance (ANOVA) of the LOCF data is the protocol specified statistical method. An exploratory analysis of variance of CHANGE3 with SITE, GENDER, RACE, PRNAIVE and TREATMENT as class variables indicated that all factors except TREATMENT are not statistically significant. Other details of this exploratory analysis are shown in Appendix 1. The exploratory analysis does not include the *interaction* terms as they were not statistically significant (p-value > 0.1).

The LOCF data analysis of variance on the change from baseline in Week 3 Teacher's version of Conners' Global Index scale indicates that the Metadate™ MR is significantly different from placebo (p-value = 0.0001). The mean change is 7.89 for Metadate™ MR while it is 1.22 for placebo.

In addition, the SAS output for the analysis of covariance (ANCOVA) for the protocol defined primary efficacy variable with covariate WEIGHT are shown below in Appendix 2. The results indicate that the two treatment groups are statistically significantly different (0.0001). The means of CHANGE3 for placebo and Metadate™ MR are 1.25 and 7.89, respectively. That is, much larger improvement is seen in subjects receiving Metadate™ MR compared to placebo.

Similar analyses are performed for Week 1 and Week 2. The results are presented in Table 4.2 below. Data profile is found in Figure 1 on page 8.

Table 4.2: An overview of efficacy

	Change ^A : Least-Squares Means		p-value (TRT comparison)
	Placebo	Metadate™	
Week 1 ^B	0.503	5.08	0.0001
Week 2 ^C	0.714	6.867	0.0001
Week 3 ^C	1.251	7.89	0.0001
^A :	CHANGE = BASELINE TCGI – (AM TCGI + PM TCGI) / 2.		
^B :	Model CHANGE = PRNAIVE WEIGHT TREAT		
^C :	Model CHANGE = WEIGHT TREAT		

As mentioned earlier, the LOCF data also suggest that WEIGHT is a significant influential factor. The treatment effect seems to diminish along with increasing WEIGHT of a patient. However, Metadate™ MR remains superior to placebo for patients of all body weight. This is seen from Figure 2 on page 8.

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4.4 Subgroup analyses on the primary efficacy endpoint

Analysis of variance of change from baseline in Week 1 TCGI (morning and afternoon combined) indicated that significant difference between the groups- who had (PRNAIVE = no) and who did not (PRNAIVE = yes) have ADHD treatment earlier. However, similar LOCF data analyses for Week 2 and Week 3 did not indicate significant differences between these two groups.

Study was conducted on thirty-one sites. SITE 14, 15, 27, and, 30 recruited 1, 1, 1, and 2 subjects, respectively. This reviewer combines SITE 14, 15, 27 and 30. Exploratory analysis in Appendix 1 shows that there were no significant differences among SITES with respect to the protocol defined primary efficacy variable.

Gender is not a significant factor in the global analysis. That is, the mean CHANGE3 for boys and mean CHANGE3 for girls are equal. However, separate analyses for boys and girls indicate that the treatment groups are significantly different at each gender group. The means and p-values are presented in Table 4.2 below.

Table 4.2: Protocol defined Primary Efficacy Variable
Gender-wise analyses

	Placebo (Mean)	Metadate (Mean)	p-value
Boys	0.87	8.33	0.0001
Girls	2.63	5.93	0.0178

Race is not a significant factor in the global analysis. That is, means of CHANGE3 for Caucasians are not different. However, separate analyses for Caucasians and others indicate that the treatment groups are significantly different for Caucasians as well as for others. The means and p-values are presented in Table 4.3 below.

Table 4.3: Protocol defined Primary Efficacy Variable
Race-wise analyses

	Placebo (Mean)	Metadate (Mean)	p-value
Caucasians	1.51	7.41	0.0001
Others	0.56	9.23	0.0001

4.5 Morning vs. Afternoon: TCGI

The secondary objective of this study was to compare separately the morning and afternoon therapeutic response of the MPH MR formulation over placebo. The following refers to this secondary objective. The results in Table 4.4 below show that the TCGI in the afternoon is observed to be consistently higher than the morning TCGI in all three weeks and for both treatment groups.

Table 4.4: Teacher's version of Conners' Global Index Scale
AM vs. PM

GROUP	BASE LINE	WEEK 1		WEEK 2		WEEK 3	
		AM	PM	AM	PM	AM	PM
Placebo	11.72	10.67	11.35	10.45	11.17	10.03	10.67
Metadate	12.69	7.01	7.50	5.72	5.85	4.52	5.04

In addition, repeated measures analysis for Week 3 morning and afternoon data suggests that the TCGI is higher in the afternoon compared to the morning (p-value = 0.0023). The details are found in the SAS output in Appendix 3.

4.6 Analyses of Secondary efficacy variables

One-way analysis of variance (ANOVA) of LOCF data on change from baseline in Parents' version of the Week 3 Conners' Global Index (PCGI) scale indicated that the two treatment groups were statistically significantly different (p-value = 0.0001). The mean change for placebo and MetadateTM MR are 2.58 and 5.92, respectively.

Frequency distributions of Clinical Global Impression by Investigator for placebo and MPH MR are shown below.

Table 4.6: Frequency Distributions of CGII

CGII	Placebo		Metadate TM MR	
	Frequency	Percentage	Frequency	Percentage
0	1	0.6	-	-
1	8	5.1	39	25.2
2	30	19.1	61	39.4
3	40	25.5	26	16.8
4	50	31.8	17	11.0
5	18	11.5	5	3.2
6	9	5.7	5	3.2
7	1	0.6	2	1.3
Total	157	100	155	100

The Wilcoxon rank-sum test for the data on Clinical Global Improvement scale completed by Investigator (CGII) during Week 3 indicated that the two treatment groups were significantly different (p-value 0.0001). The median CGII scores for placebo and MetadateTM MR are 3 and 2, respectively. The mean CGII scale for placebo and MetadateTM MR re 3.43 and 2.42, respectively.

4.7 MPH MR DOSE analyses

At the end of the double-blind phase 50 (16%) patients were on 20-mg, 64 (20.4%) were on 40-mg and 41 (13.1%) were on 60-mg of Metadate™ MR. A total of 158 remained in the placebo group. The analysis of covariance model

CHANGE3 = WEIGHT DOSE

for the protocol defined primary efficacy variable yields the following results:

General Linear Models Procedure						
Least Squares Means						
DOSE	CHANGE3 LSMEAN	Pr > T i/j	H0: LSMEAN(i)=LSMEAN(j)			
			1	2	3	4
METH20	6.65926526	1 .	0.2523	0.0575	0.0001	
METH40	8.01513500	2 0.2523	.	0.3521	0.0001	
METH60	9.17509944	3 0.0575	0.3521	.	0.0001	
PLAC	1.25418229	4 0.0001	0.0001	0.0001		.

That is, the change from baseline in Week 3 TCGI for placebo, Metadate™ MR at dose level 20-mg, 40-mg and 60-mg has mean equal to 1.25, 6.66, 8.02 and 9.17, respectively. The Metadate™ MR at each dose level is significantly different from placebo. However, there are no significant differences among the three levels of Metadate™ MR. As mentioned earlier, WEIGHT is a significant influential factor (p-value = 0.0015).

5. Overall conclusions

The data on the protocol defined primary efficacy endpoint provide sufficient evidence in support of the sponsor's claim that the average reduction from baseline in the teacher's version of Conner's Global Index scale under Metadate™ MR is significantly greater than the reduction expected under placebo. That is, the data on the primary efficacy variable support the efficacy of MPH MR in the treatment of ADHD.

The analyses of data on the change from baseline in the Parents' version of Conners' Global Index scale and the Clinical Global Improvement scale (completed by the Investigator) support these conclusions.

In addition, the sponsor's claim "*the degree of improvement in the afternoon was as large as that in the morning in the MPH MR treated group*" is not supported.

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Mathematical Statistician

Concur:

Dr. Kun Jin

Dr. George Chi

CC:

Arch. NDA 21-259

HFD-120

HFD-120 / Dr. Russell Katz

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HFD-710 / Chron

Appendix 1
Exploratory analysis

SAS OUTPUT

General Linear Models Procedure

Dependent Variable: CHANGE3

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	33	4787.5147	145.0762	3.64	0.0001
Error	278	11076.2462	39.8426		
Corrected Total	311	15863.7609			

R-Square C.V. Root MSE CHANGE3 Mean
0.301789 139.9342 6.3121 4.5108

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	27	1291.3929	47.8294	1.20	0.2316
PRNAIVE	1	14.4805	14.4805	0.36	0.5471
GENDER	1	11.7740	11.7740	0.30	0.5871
RACE	3	293.7748	97.9249	2.46	0.0632
TREAT	1	3176.0923	3176.0923	79.72	0.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	27	1220.9408	45.2200	1.13	0.2985
PRNAIVE	1	26.2240	26.2240	0.66	0.4179
GENDER	1	2.4207	2.4207	0.06	0.8055
RACE	3	171.6441	57.2147	1.44	0.2325
TREAT	1	3176.0923	3176.0923	79.72	0.0001

Appendix 2

ANCOVA of the protocol defined primary efficacy variable

SAS OUTPUT

General Linear Models Procedure

Dependent Variable: CHANGE

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	3792.2949	1896.1475	48.75	0.0001
Error	308	11980.7205	38.8984		
Corrected Total	310	15773.0154			

R-Square	C.V.	Root MSE	CHANGE Mean
0.240429	137.3351	6.2369	4.5413

Source	DF	Type I SS	Mean Square	F Value	Pr > F
WEIGHT	1	366.4147	366.4147	9.42	0.0023
TREAT	1	3425.8802	3425.8802	88.07	0.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
WEIGHT	1	368.1319	368.1319	9.46	0.0023
TREAT	1	3425.8802	3425.8802	88.07	0.0001

General Linear Models Procedure
Least Squares Means

TREAT	CHANGE LSMEAN	Pr > T H0: LSMEAN1=LSMEAN2
METH	7.89250762	0.0001
PLAC	1.25421758	

Appendix 3

Repeated measures analysis: Week 3 Morning vs. Afternoon

SAS OUTPUT

General Linear Models Procedure

Dependent Variable: TCGI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	316	32153.057611	101.750182	23.28	0.0001
Error	311	1359.176481	4.370342		
Corrected Total	627	33512.234092			

R-Square	C.V.	Root MSE	TCGI Mean
0.959442	46.54613	2.0905364	4.4913217

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TREAT	1	6992.839819	6992.839819	1600.07	0.0001
SUBJ_ID(TREAT)	314	25088.973950	79.901191	18.28	0.0001
TIME	1	41.205325	41.205325	9.43	0.0023

General Linear Models Procedure

Source	Type III Expected Mean Square
TREAT	Var(Error) + 1.975 Var(SUBJ_ID(TREAT)) + Q(TREAT)
SUBJ_ID(TREAT)	Var(Error) + 1.9873 Var(SUBJ_ID(TREAT))
TIME	Var(Error) + Q(TIME)

General Linear Models Procedure

Dependent Variable: TCGI

Tests of Hypotheses using the Type III MS for SUBJ_ID(TREAT) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TREAT	1	6992.8398191	6992.8398191	87.52	0.0001

To Roberta

The interaction term in the model

$$\text{CHANGE3} = \text{WEIGHT DOSE WEIGHT*DOSE}$$

is marginally significant (p-value = 0.0543). The median weight is 31.4. To gain some insight, divide the patients into two groups: small (<31.4 lbs) and large (over 31.4 lbs). The mean CHANGE3 is cross-classified in the following table.

Table: Change from baseline in Week 3 TCGI
CHANGE3

	WEIGHT	
	Less than 31.4*	All others
PLAC	1.32	1.11
METH20	7.51	5.96
METH40	9.56	6.2
METH60	9.72	8.6

November 27, 2000

Table: Raw Means of Change from baseline in TCGI

WEEK	NAIVE TO ADHD TREATMENT		COMMENTS
	NO	YES	
WEEK 1	3.423	2.145	Significant*
WEEK 2	3.76	3.85	Not significant
WEEK 3	4.38	4.74	Not significant

* p-value < 0.05

/s/

Kallappa Koti
12/14/00 11:55:59 AM
BIOMETRICS

Kun Jin
12/14/00 12:52:43 PM
UNKNOWN

George Chi
12/14/00 01:02:44 PM
BIOMETRICS