

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-793

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA #: 20-793

JAN 30 1998

Applicant: O.P.R. Development, L.P.

Name of Drug: CAFKIT (Caffeine Citrate Injection)

Indication: Treatment of Apnea of Prematurity

Documents Reviewed: Volumes 2.1 and 2.19-2.23 dated August 22, 1997

This review pertains to a clinical study comparing Caffeine citrate and placebo in premature infants.

The Medical officer for this review is L. Pina, M. D. HFD-570 with whom this review was discussed.

Background

Caffeine citrate is routinely used in hospitals to treat apnea of prematurity where each hospital makes its own preparation. The agency was interested in encouraging an NDA for caffeine citrate to assure that good manufacturing practices be used in the preparation of caffeine citrate if adequate evidence of efficacy could be established. Caffeine citrate was given orphan drug status on September 20, 1988. This review will refer to caffeine citrate as caffeine.

The agency has worked with the sponsor to develop the protocol for the current study. It was agreed that the results of one study, with adequate discussion of the literature on the use of caffeine for the treatment of apnea of prematurity, might be adequate for approval.

Study Description and Methods of Analyses

The study was a randomized, double-blind, parallel group, multi-center study comparing caffeine and placebo over up to 12 days of treatment in premature infants with apnea of prematurity. Patients were to have 6 or more apnea episodes within a 24-hour period to qualify for randomization into the study.

After randomization infants received a loading intravenous dose (1 mL/kg) of caffeine or placebo. This dose was followed by daily maintenance doses (0.25mL/kg) of intravenous or oral double-blind medication, caffeine or placebo. Treatment could be up to 12 days on double-blind medication. (The original protocol stated that there could be 10 days of double-blind treatment and only a few

patients were on more than 10 days of double-blind treatment.)

If the infant on Day 2 had an apnea rate greater than 50% of baseline apnea rate, the infant was considered a failure and was to be switched to open-label caffeine. The infant could also be switched to open-label caffeine if he/she had greater than 50% of the baseline apnea rate on Days 3 to 7. [Infants who failed to meet the 50% reduction from baseline apnea rate on a particular day were not always switched to open-label caffeine on that day in this study.] The infant was considered to be a failure at the day of switching. The open-label portion of this study will not be discussed in this review.

The protocol originally stated that the primary efficacy variable was the percentage of patients getting a 50% or greater reduction in their apnea episodes on Day 2 (between 24 and 48 hours). The sponsor's sample size estimate assumed a 70% success rate for caffeine and a 20% success rate for placebo.

The sponsor amended the protocol to make the primary analysis a covariance analysis on the Day 2 apnea rate with covariates baseline apnea rate and duration of baseline period. [The sponsor did not provide a reason for the change in analysis of the primary efficacy variable nor state how these covariates would be calculated (e.g. baseline apnea episodes scaled to 24 hours or not scaled).] The sponsor did not amend the protocol's sample size calculations using the new analysis. The sponsor did not present the results of the covariance analysis in the study report but did provide the results of analyses based on differences from baseline in apnea rates by day in study. The sponsor provided a covariance analysis to the medical officer upon her request using baseline apnea episodes not scaled to 24 hours.

The sponsor's study report treated the original variable, percentage of patients having a 50% or greater reduction of apnea rate, as the primary analysis. The sponsor provided this analysis for each day of double-blind treatment.

The sponsor stated in the protocol that the duration of apnea episodes was a secondary efficacy variable. The protocol stated that the average duration of apnea episodes on Day 2 would be analyzed by an analysis of variance with factors: treatment and center. Duration of apnea episodes was captured and coded with a score of 1 to 3, where 1 was 0-10 seconds, 2 was 10-30 seconds, and 3 was more than 30 seconds beyond the apnea alarm. The sponsor did not provide any analysis of duration. The sponsor did summarize the duration of the apnea episodes on each double-blind treatment day and each open-label caffeine day for each treatment group as randomized.

The infants could be withdrawn from the study or be put on open-label caffeine at any time at the investigator's discretion. Almost all analyses carried forward the last daily results at withdrawal or switch to open-label treatment. By the last-value-carried-forward convention, the last observed number of apnea events scaled to 24 hours, prior to withdrawal or movement to open-label was used for the number of apnea events for succeeding days.

Results

There were 87 patients entered at 9 centers into this study. Five patients were excluded from the efficacy analyses because they were never dosed (2 patients) or because they had too few apnea episodes at baseline and were prematurely discontinued from the study after this violation was discovered (3 patients). There were, therefore, 82 patients (45 caffeine and 37 placebo) in the efficacy analyses.

The treatment groups were comparable at baseline in demographic variables and mean number of apnea episodes on the baseline day. Apnea episodes at baseline and on treatment were scaled to 24 hours (6 apnea episodes in 4 hours is more serious than 6 episodes in 24 hours).

Table 1 provides the observed cases sample sizes and percentage of patients having (50% reduction from baseline in apnea episodes in the double blind phase of the study. By Day 2, nine patients had dropped out of the double-blind phase and by Day 3, 35 patients had dropped out of this phase.

Table 2 contains the results of the analysis of success rates (at least 50% reduction in apnea episodes) using last observation carried forward convention for each day in the double-blind portion of the study. The p-value (unadjusted for multiple endpoints) is significant at Days 4, 5, 7, 8, 9, and 10. However, it is not significant at Day 2 ($p=0.0715$), pre-specified as the primary analysis time. The observed success rate for placebo (> 40%) was higher than the sponsor had assumed in designing the protocol. It should be mentioned that the Day 10 analysis, which is an endpoint analysis, was significant.

A higher percentage of patients had 7 to 10 days with at least a 50% reduction in apnea events in the caffeine group than in the placebo group: 31 of 45 caffeine patients, 68.9% (7 days=0, 8 days=2, 9 days=7, and 10 days=22), and for placebo 16 of 37, 43.2% (7 days=2, 8 days=2, 9 days=2, and 10 days=10). This difference in percentages is significant (P -value=0.019, chi-square test, reviewer's calculation.) The caffeine group had a mean number of days with (50% reduction in apnea episodes of 6.8 days compared to 4.6 days for the placebo group ($P=0.0256$, t-

test). [Note that these are also carried forward analyses. As table 1 shows, there were only 20 patients in the caffeine group at Day 10 but these analyses have 22 patients with 10 days of (50% reduction using the carried forward convention.)]

Apnea was reduced by at least 50% for all 10 days of treatment for 22 of 45 patients (48.9%) who received caffeine (double-blind) compared to 10 of 37 patients (27.0%) who received placebo. This difference in percentages is also significant (P-value = 0.04, chi-square test, reviewer's calculation.)

Table 2, also, contains the results of the sponsor's analysis of changes from baseline in apnea rates. This analysis was not significant for any day.

Table 3 contains the results of the sponsor's analysis of success rate on the double-blind days with success here defined as a 100% reduction in apnea episodes. The P-values, again unadjusted for multiple endpoints, are significant at Days 2, 4, 7, 8, and 9. Here the Day 10 analysis, which is an endpoint analysis, is not significant.

A higher percentage of caffeine patients had 7 to 10 days without apnea episodes than the placebo group; caffeine 11 of 45 patients, 24.4% (7 days=0, 8 days=4, 9 days=4, and 10 days=3); placebo 0 out of 37. This result is also significant (P-value=0.001, chi-square test, reviewer's calculation.) The caffeine group had a mean number of days without apnea of 3.0 days compared to 1.2 days for the placebo group (P=0.005, t-test).

Table 11 of the sponsor summarizes the duration of apnea episodes during the days of double-blind and open-label treatment. The results of double-blind Day 3 (the only day suggestive of a difference between placebo and caffeine) are very problematic. The proportion of caffeine episodes with duration of episodes between 0-10 seconds after the alarm was 84.9% on Day 3, whereas on the other days the percentage was always less than 63%. [In general, the summarization shows that there is not much effect of caffeine on duration of the apnea episodes.]

Reviewer's Comments

The sponsor sized the study to detect a difference of 50% in success rates (at least 50% reduction in apnea episodes). The sponsor chose Day 2 as the day for the primary analysis, because the sponsor thought that the placebo patients would seek open-label treatment with caffeine early. The difference in success rates was lower than the sponsor anticipated (success rates about 60-70% for caffeine and 40-50% for placebo). The study is estimated to have only 44% power to pick up the observed

difference in success rates. Thus the study is under-powered to detect differences of the magnitude observed in the study.

This reviewer performed the primary analysis that the sponsor did not provide in the study report. As the sponsor did not state how baseline apnea rate and baseline duration were going to enter the analysis, this reviewer scaled the baseline apnea rate to 24 hours (like apnea rates were treated on the treatment days) because this seems the most appropriate way to treat it. [This makes duration a less important variable. If duration is low (this would usually be caused by a lot of episodes early on), it means that there would be a lot of apnea episodes when the baseline apnea episodes are scaled to 24 hours. Other values of duration are determined by when the measurements were made. Once baseline apnea episodes scaled to 24 hours is in the analysis, duration is not important as will be shown by the discussion of the results of the covariance analysis.]

If the covariance analysis is run on the Day 2 apnea rates with baseline apnea rate and duration as covariates, a P-value of 0.1343 was obtained with duration being not significant ($P=0.22$). When duration was excluded from the covariance analysis, a P-value of 0.0790 was obtained. Therefore, the amended protocol defined primary efficacy analysis is not significant. The sponsor's analysis of covariance, provided to the medical officer, did not scale the baseline apnea episodes to 24 hours. This does not seem appropriate to this reviewer. The sponsor's covariance analysis was, also, not significant.

There were 6 significant results (Days) for the at least 50% reduction analysis and 5 significant results (Days) for the 100% reduction analysis. Since these are last observation carried forward analyses and highly correlated endpoints, no assessment can be made whether the multiple significance is any more significant than nearly significant results for percent of patients with reduction (50% of baseline at Day 2 or significant results for percent of patients with no apnea episodes at Day 2.

The summarization of the duration of apnea episodes indicates that caffeine does not have much effect on duration of the episodes.

The sponsor's analyses of success being "100% reduction in apnea episodes from baseline on a day" was a post-hoc analysis. The sponsor for unknown reasons failed to include this variable as a secondary efficacy variable in the protocol.

Although this reviewer calculated P-values for some additional analyses, it should be emphasized that these are also post-hoc analyses.

Overall Comments.

The sponsor has failed to show efficacy in the primary efficacy analysis of apnea episodes on Day 2 scaled to 24 hours (covariance analysis that was given in the amended protocol, $p=0.13$) or in the analysis of the percentage of patients having at least a 50% reduction in the number of apnea episodes on Day 2, $p=0.07$ (the original protocol defined primary efficacy variable). In addition the sponsor did not show efficacy with respect to the secondary variable, duration of apnea episodes on Day 2 (no analysis provided).

The study did show significant results favoring caffeine for percentage of patients showing no episodes of apnea on Days 2, 4, 7, 8 and 9 and for the percentages with at least 50% reduction in apnea episodes from baseline on Days 4, 5, 7, 8, 9 and 10. [The Day 10 analyses are endpoint analyses.] These post-hoc analyses are suggestive of efficacy for caffeine. The effectiveness of caffeine, if real, was less than the sponsor assumed and, therefore, the study was under-powered for the smaller difference observed between caffeine and placebo for the primary analyses on Day 2. [The effectiveness of placebo was underestimated.]

/S/

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This review contains 6 pages of text and 3 pages of tables.

cc:

Archival NDA 20-793

HFD-570

HFD-570/Dr. Pina

HFD-570/Mr. Cobbs

HFD-715/Div. File, Chron

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Table 1

Proportion of patients having (50% reduction in apnea episodes during the double-blind phase of the study.

	Caffeine		Placebo	
	N	%	N	%
Day 1	45	62.2	37	48.6
Day 2	41	80.5	32	65.6
Day 3	28	82.1	19	73.7
Day 4	26	88.5	18	66.7
Day 5	24	91.7	16	75.0
Day 6	23	95.7	15	93.3
Day 7	22	100.0	14	85.7
Day 8	21	100.0	12	75.0
Day 9	20	95.0	11	81.8
Day 10	20	100.0	11	90.9

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Table 2

Day	% Success ((50% reduction from baseline)			Difference from Baseline in Apnea Rates		
	Caffeine (N=45)	Placebo (N=37)	P-Value ¹	Caffeine (N=45)	Placebo (N=37)	P-value ²
1	62.22	48.65	.2178	-7.73	-5.08	.1824
2	75.56	56.76	.0715 ³	-8.29	-5.50	.1614
3	66.67	48.65	.0993	-6.59	-5.02	.4689
4	66.67	43.24	.0334	-6.45	-4.78	.4370
5	66.67	43.24	.0334	-6.70	-4.59	.3312
6	68.89	48.65	.0629	-6.58	-4.94	.4567
7	68.89	45.95	.0359	-6.53	-2.41	.1995
8	68.89	40.54	.0101	-6.55	-2.06	.1662
9	66.67	40.54	.0180	-6.55	-1.85	.1441
10	68.89	43.24	.0195	-6.71	-2.12	.1573

¹ P-value from Chi-square test

² P-value from t-test

³ Original protocol specified primary analysis
(Note that analyses are LOCF analyses.)

Table 3

Day	% Success (100% reduction from baseline)		
	Caffeine (N=45)	Placebo (N=37)	P-Value ¹
1	20.00	10.81	.2569
2	26.67	8.11	.0305
3	31.11	13.51	.0602
4	31.11	5.41	.0035
5	31.11	16.22	.1181
6	28.89	13.51	.0942
7	33.33	10.81	.0162
8	33.33	10.81	.0162
9	33.33	10.81	.0162
10	31.11	16.22	.1181

¹ P-value from Chi-square test
(Note that analyses are LOCF analyses.)

O.P.R. Development L.P.
 NDA 20-793 - Caffeine Citrate Injection, 10 mg/ml (Caffeine Base Equivalent)
 Protocol No. OPR-001

Table 11.0
 Duration (sec.) of Apnea Events
 by Day and Treatment Group

Day	Caffeine									Placebo								
	Double-Blind			Open-Label			Double-Blind			Open-Label								
	H	0 - 10 n (%)	10 - 30 n (%)	Over 30 n (%)	H	0 - 10 n (%)	10 - 30 n (%)	Over 30 n (%)	H	0 - 10 n (%)	10 - 30 n (%)	Over 30 n (%)	H	0 - 10 n (%)	10 - 30 n (%)	Over 30 n (%)		
Day 1	228	107 (46.9)	91 (39.9)	30 (13.2)	0	0 (0.0)	0 (0.0)	0 (0.0)	264	121 (45.8)	128 (48.5)	15 (5.7)	58	26 (44.8)	31 (53.4)	1 (1.7)		
Day 2	139	67 (48.2)	65 (46.8)	7 (5.0)	5	1 (20.0)	4 (80.0)	0 (0.0)	138	71 (51.4)	62 (44.9)	5 (3.6)	69	38 (55.1)	24 (34.8)	7 (10.1)		
Day 3	119	101 (84.9)	14 (11.8)	4 (3.4)	66	33 (50.0)	29 (43.9)	4 (6.1)	67	34 (50.7)	33 (49.3)	0 (0.0)	62	38 (61.3)	23 (37.1)	1 (1.6)		
Day 4	62	34 (54.8)	27 (43.5)	1 (1.6)	147	77 (52.4)	63 (42.9)	7 (4.8)	62	30 (48.4)	24 (38.7)	8 (12.9)	40	27 (67.5)	12 (30.0)	1 (2.5)		
Day 5	32	20 (62.5)	11 (34.4)	1 (3.1)	53	34 (64.2)	17 (32.1)	2 (3.8)	52	33 (63.5)	17 (32.7)	2 (3.8)	60	48 (80.0)	12 (20.0)	0 (0.0)		
Day 6	38	21 (55.3)	14 (36.8)	3 (7.9)	74	39 (52.7)	31 (41.9)	4 (5.4)	27	19 (70.4)	8 (29.6)	0 (0.0)	12	5 (41.7)	7 (58.3)	0 (0.0)		
Day 7	20	10 (50.0)	10 (50.0)	0 (0.0)	46	23 (50.0)	22 (47.8)	1 (2.2)	25	16 (64.0)	8 (32.0)	1 (4.0)	12	7 (58.3)	5 (41.7)	0 (0.0)		
Day 8	16	6 (37.5)	8 (50.0)	1 (6.3)	51	41 (80.4)	9 (17.6)	1 (2.0)	29	13 (44.8)	15 (51.7)	1 (3.4)	10	9 (90.0)	1 (10.0)	0 (0.0)		
Day 9	17	8 (47.1)	6 (35.3)	3 (17.6)	34	19 (55.9)	9 (26.5)	6 (17.6)	31	12 (38.7)	19 (61.3)	0 (0.0)	2	2 (100.0)	0 (0.0)	0 (0.0)		
Day 10	10	6 (60.0)	4 (40.0)	0 (0.0)	5	3 (60.0)	2 (40.0)	0 (0.0)	15	6 (40.0)	9 (60.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)		

NOTE: Patients 701 (randomized to caffeine), 305, 314, 319, and 702 (all randomized to placebo) are excluded from this analysis. Patients 305, 701, and 702 did not have 6 baseline attacks within 24 hours. Patients 314 and 319 were not given study drug.

Open-label Day 1 is defined as the day patients went on open-label for placebo patients, whereas open-label Day 1 and double-blind Day 1 are the same for caffeine patients.

H = Number of events at that day
 n = Number of events at given duration
 X = (n/H) * 100.

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