CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

DATE OF MEETING: DECEMBER 15, 1997

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SLIDES

Pulmonary Allergy Drugs Advisory Committee Meeting

15 December 1997

Cafcit™ (Caffeine Citrate)

NDA No. 20-793

O.P.R. Development, L.P.

Agenda

Sponsor's Presentation

December 15, 1997

Introduction:

Sean Alan Reade, M.A.

Director, Regulatory Affairs
Roxane Laboratories

History of Caffeine Development:

Kirk V. Shepard, M.D.

Sr. V.P., Marketing/Medical Affairs and Product Development
Roxane Laboratories

Apnea of Prematurity:

Allen Erenberg, M.D.

Medical Director
Kern Medical Center
Bakersfield, CA

Agenda

Sponsor's Presentation
December 15, 1997

Literature Overview:
Efficacy / Safety

Kristen Mosdell, PharmD
Consultant

Clinical Data Presentation:

Beverley A. Wynne, Ph.D.
Medical Director, Medical Affairs
Roxane Laboratories

Dennis G. Haack, Ph.D.
Consultant Biostatistian
International Pharmaceutical
Industry
Lexington, KY

Chronology

20 September 1988	Orphan Drug Designation
3 September 1991	Ownership
23 February 1993	Ownership

Chronology

28 December 1996	Roxane Laboratories, Inc.
6 January 1997	CMC presubmission submitted
22 August 1997	NDA No. 20-793 submitted
15 December 1997	Pulmonary-Allergy Drugs Advisory Committee Meeting

History of Caffeine Development

Kirk V. Shepard, M.D.

Senior Vice President of Marketing / Medical Affairs
and Product Development
Roxane Laboratories

History

- In 1985, the FDA contracted the University of Iowa to review literature of selected drugs used to treat newborns
- Caffeine was 1 of 7 drugs selected
- FDA Contract Report indicated that caffeine was being used to treat apnea of prematurity, and concluded that the literature provided persuasive evidence of effectiveness

History (cont'd)

Report also cited that theophylline was used, but indicated that caffeine was the drug of choice to treat apnea of prematurity because of:

- Larger therapeutic index
- Once daily administration
- Smaller fluctuations in plasma concentrates due to a longer half-life
- Penetration into CSF
- More potent central respirogenic effect
- Fewer adverse effects

History (cont'd)

- FDA contract report concluded it would be in the interest of public health to encourage an NDA for caffeine for the tx of apnea of prematurity
- Caffeine was designated as an orphan drug
- Caffeine citrate injection development was initiated: 10 mg of caffeine base/mL
- FDA agreed that only one double-blind, placebo-controlled study was required based on extensive literature reports

Apnea of Prematurity

Allen Erenberg, M.D.
Medical Director
Kern Medical Center

Apnea of Prematurity

- Definition
  - Respiratory pauses varying between 10 and 20 seconds in duration associated with bradycardia (< 80 beats per minute)
  - Short respiratory pauses are associated with startles, movement, defecation or swallowing during feeding, but are self-limiting and not associated with bradycardia

Apnea of Prematurity

- Must distinguish apnea from periodic breathing
- Three types of apnea
  - Central
  - Obstructive
  - Mixed
- The more preterm the infant, the more frequent its occurrence

Apnea of Prematurity

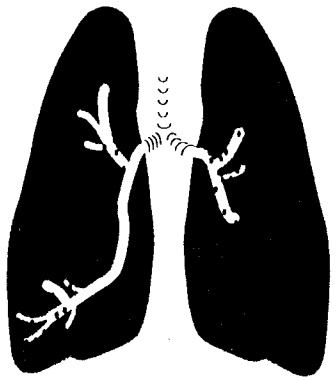
- Physiologic consequence of apnea
- Reflex effects of apnea
- Relation to sleep state

Proposed Actions of Methylxanthines

- Decrease frequency or elimination of apneic attacks
- Normalize respiratory patterns
- Alter the sensitivity of the medullary respiratory center to carbon dioxide

Apnea of Prematurity

- Evaluation of the apneic infant
  - History
  - Physical examination
  - Laboratory (if clinically indicated)



Apnea of Prematurity

- Treatment of Apnea of Prematurity
  - CPAP
  - Stimulation
  - Pharmacologic stimulation
    - Caffeine
    - Theophylline / Aminophylline

Caffeine Citrate for the Treatment of Apnea of Prematurity

Summary of Efficacy and Safety Data
From the Published Literature

Kristen Mosdell, PharmD

Consultant

Efficacy Studies Published in the Literature*

Types of Studies	Total No. of Studies	Caffeine-Treated Infants	Theophylline/ Aminophylline Treated Infants	Untreated Controls	Historical Controls
Total	22	387	177	31	19
Caffeine vs. Theophylline/ Aminophylline	7	158	160	---	---
Historically Controlled	2	47	---	---	19
Untreated Controls	2	28	17	31	---
Uncontrolled	11	154	---	---	---

*No randomized double-blind, placebo-controlled studies published

Demographic Data and Study Duration From Published Literature

- Wide range of infants studied
- Mean gestational age: 24 to 33 weeks
- Mean birth weight: 0.7 kg to 1.89 kg
- Duration of studies ranged from 24 hours to over 3 months

Summary of Results From Published Studies

- Equal efficacy of caffeine and theophylline
- Significant decrease in
  - total number of apnea attacks
  - apnea density
  - apnea index
  - number of episodes of bradycardia
  - oxygen desaturation
  - pCO_2
  - periodic breathing and percent periodic breathing
- Significant increase in respiratory rate
- Normalization of pneumocardiograms

Summary of Conclusions from Published Efficacy Studies

- Caffeine and theophylline demonstrated similar efficacy
- Significant improvement noted in caffeine-treated infants as compared to untreated infants, or historical controls
- Reports from uncontrolled trials indicated that caffeine was efficacious

Studies From the Published Literature Providing Safety Data

Type of Study	No. of Studies	No. of Pts. Treated With Caffeine
Active-Controlled	6	155
Untreated/Historically Controlled	4	81
Uncontrolled	5	70
Clinical Pharmacology	1	7
Pharmacokinetic	2	91
Safety	23	483
TOTAL	41	887

Summary of Safety Results From Published Literature

Safety Parameter	Total No. of Studies	Total No. Infants Evaluated
Overall	41	887
CNS Stimulation	13	268
Neurological Development	3	158
Seizures	1	2
Cardiovascular Events (LVO, HR, SV)	17	323
Cerebral Blood Flow	3	46

Summary of Safety Results From Published Literature (cont'd)

Safety Parameter	Total No. of Studies	Total No. Infants Evaluated
Gastrointestinal Effects	14	294
Renal Function	7	125
Thyroid Function	2	114
Laboratory Abnormalities (Glucose, Bilirubin)	8	174
Growth Parameters	5	92
Overdosage	4	7

Central Nervous System Adverse Events Reported in Published Literature

- Central nervous system stimulation (i.e., irritability, restlessness, jitteriness)
- Seizures only reported following overdosage, or use in treatment of near sudden infant death syndrome (SIDS)
- Data suggest that tolerance to these effects may develop
- Central nervous system adverse effects not observed in some studies

Cardiovascular Adverse Events Reported in Published Literature

- Effects variable, and generally less than those observed with theophylline (i.e., tachycardia)
- Increased left ventricular output and stroke volume observed in some studies
- No effect on cerebral blood flow; theophylline shown to decrease cerebral blood flow

Gastrointestinal Adverse Events Reported in Published Literature

- Both caffeine and theophylline increased gastroesophageal reflux in infants at risk for SIDS
- Median gastric aspirate was significantly higher with theophylline compared to caffeine in one study
- Gastrointestinal intolerance less frequent with caffeine compared to theophylline
- No reports of necrotizing enterocolitis (NEC) associated with caffeine; NEC associated with theophylline described

Long-Term Follow-Up Studies

- Neurological development not adversely affected in studies following infants for up to 40 months following caffeine administration
- Growth parameters not adversely affected in studies following infants for up to 12 months following caffeine administration

Safety of Caffeine Citrate From Published Literature

- Most adverse events were mild-to-moderate in severity
- Only one death reported due to cytomegalic inclusion disease, 30 days after last caffeine dose
- No long-term sequelae observed
- Large margin of safety; caffeine levels up to 346 mg/L observed following overdose without reports of neurological sequelae or death

Efficacy and Safety Advantages of Caffeine Versus Theophylline in Published Literature

- Faster increase in respiratory rate shown in one study
- Less cardiovascular, central nervous system, and gastrointestinal adverse events
- Less variability in plasma caffeine concentrations compared to plasma theophylline concentrations

There is a large body of evidence in the literature that can support the efficacy and safety of caffeine for the treatment of apnea of prematurity.

Caffeine Citrate Solution for the Treatment of Apnea of Prematurity, O.P.R. Study, 001

NDA No. 20-793

Beverley A. Wynne, Ph.D.
Medical Director, Medical Affairs
Roxane Laboratories

Dennis G. Haack, Ph.D.
Consultant Biostatician
International Pharmaceutical Industry - Lexington, KY

Study Design / Population

- Multicenter, randomized, double-blind, placebo-controlled, parallel study with an open-label rescue phase

- Population: preterm infants, age 28-32 weeks post-conception at time of study, with apnea of prematurity

Study Objectives

Primary Objective

Determine efficacy of caffeine citrate in treatment of apnea of prematurity by comparing the rate of apnea episodes in patients treated with caffeine citrate or placebo

Secondary Objectives

a) Determine safety of caffeine citrate compared to placebo in patients with apnea of prematurity

b) Obtain plasma concentrations of caffeine citrate in premature infants treated for up to 12 days

Inclusion Criteria

Patients who met the following criteria could be enrolled:

- At least 6 episodes of apnea in 24 hours or less. Apnea, defined as cessation of breathing for greater than 20 seconds, had to be clinically observed and documented in the Neonatal Intensive Care Unit
- Postconceptual age between 28 weeks, 0 days, and 32 weeks, 6 days, and >24 hours after birth
- Signed written informed consent from parent(s) or legal guardian(s)

Exclusion Criteria

Apnea with any of the following identifiable etiologies:

- CNS disorders: e.g., seizures, meningitis
- Primary lung disease: e.g., active respiratory distress syndrome
- Generalized disturbances: e.g., untreated sepsis / shock
- Metabolic disturbances: e.g., arterial blood pH < 7.2 on two consecutive determinations
- Cardiovascular abnormalities: e.g., untreated congestive heart failure
- Abnormal temperature: e.g., rectal temperature >38.5^{o} C on two consecutive readings
- Obstructive apnea defined as visual observation of chest wall movement with presence of bradycardia, cyanosis with respiratory effort, and/or airway obstruction

Exclusion Criteria (cont'd)

- Blood urea nitrogen > 20mg/dL, serum creatinine > 1.5mg/dL and, after the first 48 hours of life, urine output < 1mL/kg/hr
- AST & ALT > 3 times the upper limit of normal
- Requirement of mechanically-assisted ventilation
- Previous treatment with methylxanthines within 7 days prior to study enrollment
- Previous treatment with H_2 antagonists (i.e., cimetidine or ranitidine) for regurgitation within 7 days prior to study enrollment
- Receiving or experiencing the effects of CNS-active medication at the time of enrollment

Loading Dose and Maintenance Doses of Caffeine Citrate or Placebo (Double-Blind Phase)

	Dose	Route	Frequency
Loading Dose	10mg/kg - caffeine base (1 mL/kg of caffeine citrate solution) or placebo	IV* (over 30 minutes)	x 1
Maintenance Dose	2.5mg/kg - caffeine base (0.25 mL/kg of caffeine citrate solution) or placebo	IV* (over 10 minutes)	every 24 hours**
		PO	

*Using a syringe infusion pump.
**Beginning 24 hours after the loading dose

Loading Dose and Maintenance Doses of Caffeine Citrate or Placebo (Open-Label Phase)

	Dose	Route	Frequency
Loading Dose	10mg/kg - caffeine base (1 mL/kg of caffeine citrate solution) or placebo	IV* (over 30 minutes)	x 1
Maintenance Dose	3.0 mg/kg - caffeine base (0.30 mL/kg of caffeine solution) or placebo	IV* (over 10 minutes)	every 24 hours**
		PO	

*Using a syringe infusion pump.
**Beginning 24 hours after the loading dose

Efficacy Endpoints During the 10 Day* Treatment Period

- Success: At least a 50% reduction in the number of apnea episodes from baseline on Days 2 through 10*

- Success: Elimination of apnea on Days 2 through 10*

* Four patients received 11-13 days of therapy, but are included in the 10-day evaluation.

Study Patients

No. Pts. Enrolled:

87 (caffeine citrate = 46; placebo = 41)

No. Pts. Evaluable For Safety:

85* (caffeine citrate = 46; placebo = 39)

No. Pts. Evaluable For Efficacy:

82+ (caffeine citrate = 45; placebo = 37)

* 2 placebo pts. were randomized and never dosed.

+ 3 pts. (1 caffeine and 2 placebo) were excluded from efficacy because they had fewer than 6 apnea events at baseline, and were discontinued from the study.

Baseline Characteristics

	Caffeine (n=45)	Placebo (n=37)	p-value
Sex: (%) Male Female	 25 (55.6) 20 (44.4)	 26 (70.3) 11 (29.7)	(0.1715)+
Race: (%) Caucasian Non-Caucasian	 16 (35.6) 29 (64.4)	 20 (54.1) 17 (45.9)	(0.0930)+
Mean Gestational Age (weeks)	29.8	29.9	(0.7770)*
Mean Post-Conceptual Age (weeks)	30.6	30.6	(0.9957)*
Mean Baseline Apnea Episodes /24 hr Period	9.6	9.8	(0.8398)*
Mean Baseline Weight (grams)	1247.6	1203.4	(0.4763)*

87 patients enrolled; 2 never received drug, 3 not included in efficacy analysis because they had < 6 apnea episodes at baseline--a protocol requirement.

+ p-values calculated using ANOVA

* p-values calculated using chi-square test

Patient Disposition

	Double-Blind Treatment	
	Caffeine (n=45)	Placebo (n=37)
No. Pts. Completing 10 Days of Double-Blind Therapy	20	11
No. Pts. Transferred to Open-Label	14	16
No. Pts. Permanently Discontinued From Double-Blind Therapy Prior to Day 10	10	9
Other*	1	1

* Patients 304 (placebo, Day 7) and 523 (caffeine, Day 8) did not complete 10 days on DB treatment; these are not considered as "withdrawals" since they were withdrawn per hospital protocol (not as a result of treatment failure).

Patient Disposition (cont'd)

	Double-Blind Treatment	
	Caffeine (n=45)	**Placebo (n=37)**
Reasons for Patients Permanently Discontinued From Double-Blind Therapy Prior to Day 10:		
Adverse Event	2	1
Apnea Recurrence	5	6
Investigator Discretion	2	2
Transferred to Referring Hospital	1	0
TOTAL	**10**	**9**

Patients Transferred to Open-Label Caffeine (cont'd)

Day	Double-Blind Caffeine			Double-Blind Placebo		
	No. Pts.	≥ 50% Reduction* in Apnea Events		No. Pts.	≥ 50% Reduction* in Apnea Events	
		Yes	No		Yes	No
1	2	1	1	5	--	5
2	11	5	6	9	2	7
3	1	--	1	0	--	--
4	0	--	--	0	--	--
5	0	--	--	1	--	1
6	0	--	--	1	1	--
7-13	0	--	--	0	--	--
Total (%)	**14**	**6 (42.9)**	**8 (57.1)**	**16**	**3 (18.8)**	**13 (81.2)**

*No pts. transferred to open-label caffeine had elimination of apnea on day of transfer

Double-Blind Exposure By Treatment

	Caffeine n = 45	Placebo n = 37
Total Exposure (Days)	276	187
Mean Exposure* (Days)	6.13	5.05

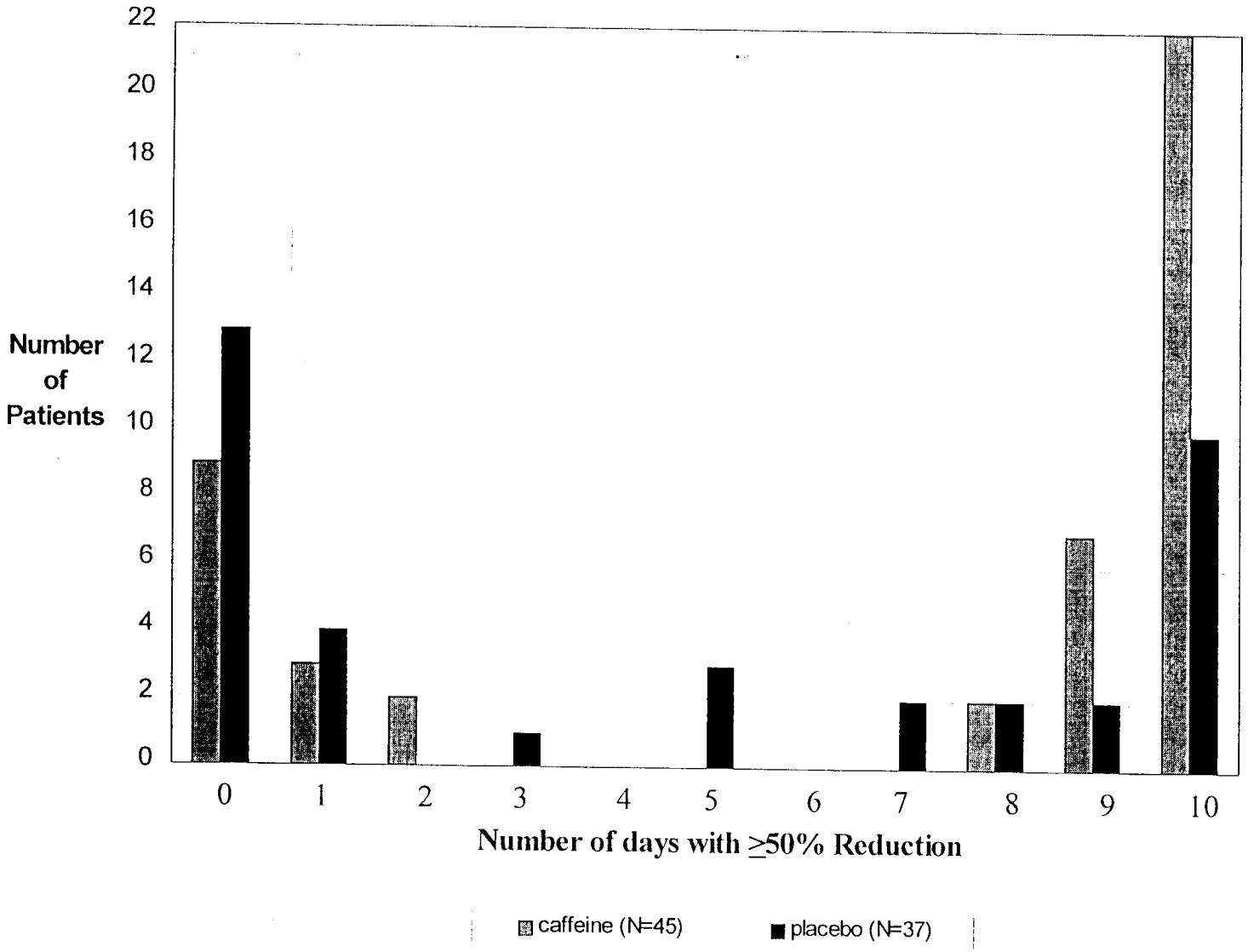
*p-value > 0.05

Success: Percent of Patients with ≥ 50% Reduction in Apnea Events

(Scaled To 24 Hours, Last-Value-Carried-Forward)

Day	Caffeine (n=45)	Placebo (n=37)	Chi-Squared p -value
1	62.2	48.7	0.2178
2	75.6	56.8	0.0715
3	66.7	48.6	0.0993
4	66.7	43.2	**0.0334**
5	66.7	43.2	**0.0334**
6	68.9	48.7	0.0629
7	68.9	46.0	**0.0359**
8	68.9	40.5	**0.0101**
9	66.7	40.5	**0.0180**
10	68.9	43.2	**0.0195**

Number of Patients with ≥50% Reduction in Apnea Events For 0 - 10 Days



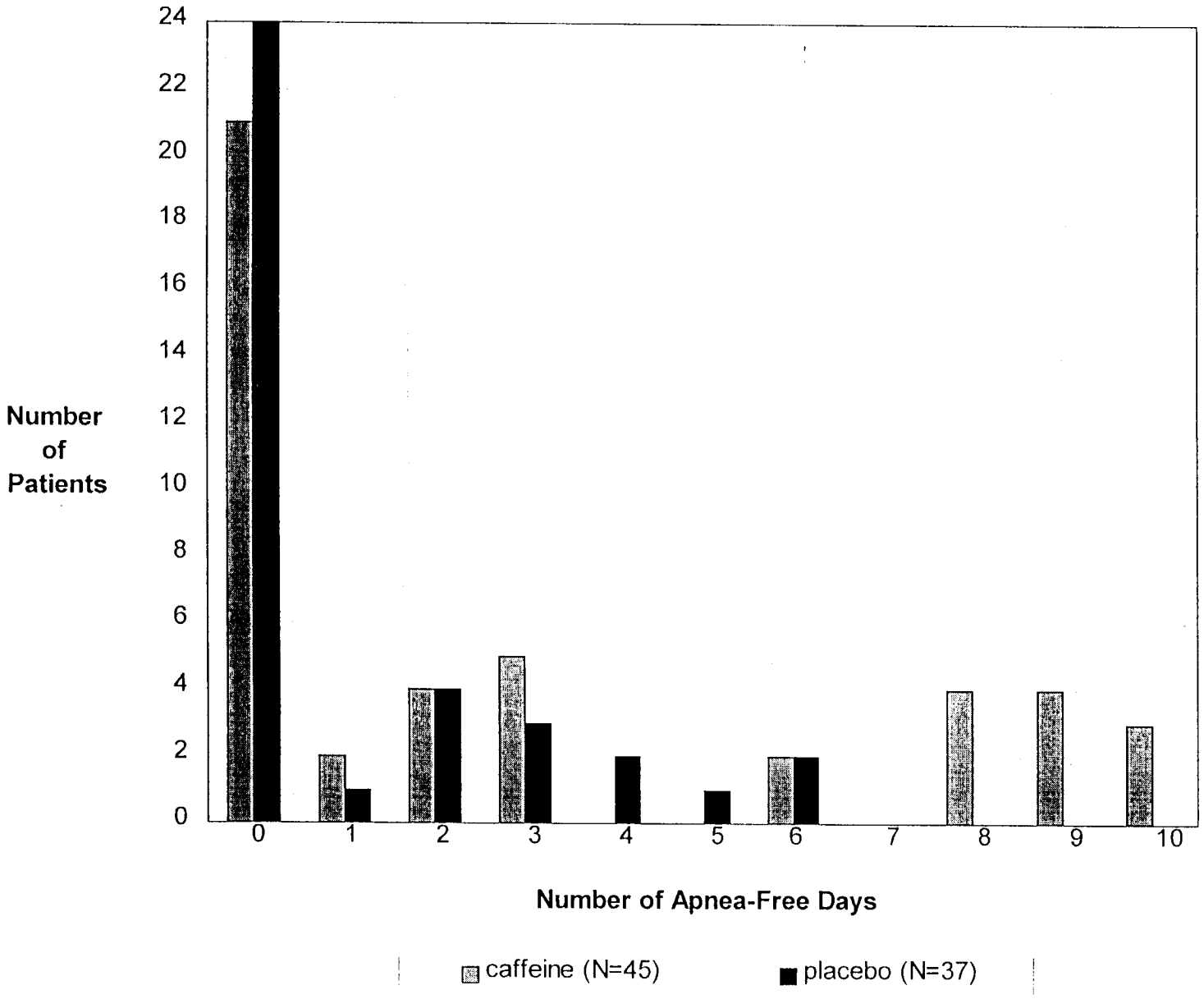
p=0.0256 (T-test analysis)
p=0.0253 (Cochran's chi-square test for trend)

Success: Percent of Patients with Elimination of Apnea Events

(Scaled To 24 Hours, Last-Value-Carried-Forward)

Day	Caffeine (n=45)	Placebo (n=37)	Chi-Squared p-value
1	20.0	10.81	0.2569
2	26.7	8.1	**0.0305**
3	31.1	13.5	0.0602
4	31.1	5.41	**0.0035**
5	31.1	16.22	0.1181
6	28.9	13.51	0.0942
7	33.3	10.8	**0.0162**
8	33.3	10.8	**0.0162**
9	33.3	10.8	**0.0162**
10	31.1	16.2	0.1181

Number of Patients With Zero Apnea Events for 0 - 10 Days



$p = 0.0050$ (T-test analysis)
$p = 0.0081$ (Cochran's chi-square test for trend)

Success (%) For 7 - 10 Days of Treatment

	Caffeine (n - 45)*	Placebo (n = 37)*
≥ 50% Reduction in Apnea Episodes[+]	69%	43%
Elimination of Apnea[+]	24%	0%

* 87 Patients enrolled; 2 never received drug, 3 not included in efficacy analysis because they had < 6 apnea episodes at baseline - a protocol requirement

[+]$p < 0.05$

Mean Serum Concentrations Related to ≥ 50% Decrease, or Elimination of Apnea Events in Patients Who Received Double-Blind Caffeine

No consistent pattern was observed between mean serum concentration(s) and response (≥ 50% reduction, or elimination of apnea events) for any of the 10 treatment days

Analysis of Pharmacokinetic Data Obtained During the Clinical Evaluation of Sterile Caffeine Citrate Solution in the Treatment of Apnea of Prematurity*

Report Conclusions:

- Caffeine pharmacokinetic data support the use of weight-adjusted loading and maintenance doses for neonates and young infants
- Clearance may be higher in patients with high baseline frequency of apnea episodes
- Hispanic patients may have a larger volume of distribution; needs to be confirmed by further clinical observation or studies

*Analyzed and written by Thomas M. Ludden, Ph.D. Professor and Chair, Department of Pharmaceutical Services, College of Pharmacy, University of Nebraska Medical Center.

Safety Evaluation
(Double-Blind)

Vital Signs:
(Mean Daily Temperature Respiratory Rate, Pulse, Systolic/Diastolic Blood Pressure Evaluations)

No Clinically Significant Differences Between Caffeine and Placebo Groups

Weight:
(Mean Daily Evaluations)

No Clinically Significant Differences Between Caffeine and Placebo Groups

Laboratory Parameters:
(Mean Glucose, Hct, BUN, Creat, Na, K, Cl, CO_2, AST, ALT, GGTP, Ca, Baseline and End-Of-Tx Evaluations)

No Clinically Significant Differences Between Caffeine and Placebo Groups

Adverse Effects Overall, and by Body System, in Patients Treated With Caffeine Citrate or Placebo in DB Phase

AEs (Body System - COSTART)	Caffeine n=46(%)	Placebo n=36(%)	p-values*
At Least one AE	25 (54.3)	24 (61.5)	0.519
Body as a Whole	10 (21.7)	7 (17.9)	0.788
Cardiovascular System	2 (4.3)	2 (5.1)	1.000
Digestive System	12 (26.10)	12 (30.8)	0.639
Hemic and Lymphatic System	4 (8.7)	7 (17.9)	0.331
Metabolic and Nutritive Disorders	2 (4.3)	2 (5.1)	1.000

*p-values calculated using Fisher's Exact Test

Adverse Effects Overall, and by Body System, in Patients Treated With Caffeine Citrate or Placebo in DB Phase

(cont'd)

AEs (Body System - COSTART)	Caffeine n=46(%)	Placebo n=36(%)	p-values*
Nervous System	1 (2.2)	0 (0.0)	1.000
Respiratory System	2 (4.3)	1 (2.6)	1.000
Skin & Appendages	6 (13.0)	4 (10.3)	0.748
Special Senses	2 (4.3)	1 (2.6)	1.000
Urogenital System	1 (2.2)	2 (5.1)	0.591

*p-values calculated using Fisher's Exact Test

Caffeine Citrate - Associated AEs*

Attribution to Drug	AE	Severity	No. Pts.
Definitely Drug Related	Drug Level Increased (31.4μg/mL)	Moderate	1+
Possibly Drug Related	Enterocolitis	Severe	1+
	GI Disorder	Moderate	1
	Feeding Disorder	Mild	1+
	Tachycardia	Mild	1+

*10 AEs in 8 patients

+ Occurred during open-label caffeine Tx

Caffeine Citrate - Associated AEs*

Attribution to Drug	AE	Severity	No. Pts.
Remotely Drug Related	Injection Site Inflammation	Moderate	1
	Hyponatremia	Severe	1[+]
	Lung Edema and Anemia	Mild	1

*10 AEs in 8 patients

[+] Occurred during open-label caffeine Tx

Necrotizing Enterocolitis (NEC)

- NEC is worldwide problem in preterm infants and second most common cause of neonatal death; pathogenesis remains enigmatic
- NEC is characterized by GI and systemic s/s, feeding intolerance, abdominal distention, poor perfusion; advanced cases: acidosis, shock, bacteremia
- Incidence inversely proportional to birth wt. and degree of immaturity
- Incidence up to 10.1%*
- Incidence in OPR-001 study: Caffeine 4/45 (8.9%) -- 2 deaths

  Placebo 2/39 (5.1%) -- 1 death‡

*Uauy RD, Farnaroff AA, Korones SB, Phillips AA, Phillips JB, Wright LL. Necrotizing enterocolitis in very low birth weight infants: biodemographic and clinical correlates. J. Pediatr 1991; 119: 630-8.

‡Infant was transferred to open-label caffeine; on Day 1 of open-label caffeine a small bowel resection was performed secondary to ileal perforation. Died 18 days after drug discontinued.

Three Serious Adverse Events Submitted to FDA

- One infant, 30 weeks GA, received 5 days of double-blind caffeine, then was transferred to referring hospital. He was readmitted 3 days later for a bowel resection (NEC) and PDA ligation and died of related complications and prematurity.

- One infant, 30 weeks GA, received 3 days of double-blind caffeine, followed by "house caffeine," for an additional 6 days. The infant developed NEC and died the next day.

- One infant, 29 weeks GA, received 2 days of double-blind placebo, and was transferred to open-label caffeine. On the day of transfer an ileal resection was performed. Caffeine was administered for 10 days. Infant expired 18 days later. NEC was diagnosed at autopsy.

Caffeine Citrate is Safe and Effective For Treatment of Apnea of Prematurity

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEETING

Food and Drug Administration
Center for Drug Evaluation and Research

Discussion of Caffeine Citrate Injection for Intravenous or Oral Use in the Treatment of Apnea of Prematurity

PADAC Primary Reviewer Summary
Stanley J. Szefler, M.D.

December 15, 1997

I. Clinical significance of apnea of prematurity

A. Incidence

1. Overall - occurs in approximately 25% of pre-term infants with a birth weight under 2500 grams

2. Relation to extent of prematurity - occurs in approximately 84% of those with a birth weight less than 1000 grams

B. Risk

1. Morbidity - can lead to irreversible neurological damage secondary to hypoxia and acidosis

2. Mortality - may lead to death if untreated, i.e. 23% in cases where no treatment administered or postponed due to mild apnea (34% required mechanical ventilation)

C. Available methods of management

1. Monitoring
2. Physical stimulation
3. Bagging
4. Theophylline - narrow therapeutic range, significant forms of toxicity with overdose, including mortality
5. Caffeine sodium benzoate - has benzoyl alcohol which can affect bilirubin distribution
6. Caffeine citrate extemporaneous formulation - poor stability and quality control, risk of overdose with documented reports of toxicity

II. Potential benefits of caffeine citrate preparation

A. FDA guidelines reinforce application of safety principles for the commercial preparation

B. FDA approved dosage guidelines facilitates uniform application of this medication in a patient population at risk for significant morbidity and mortality

C. Continued monitoring will improve application

D. Benefits over available preparations

1. long half-life facilitates once daily administration and reduces day to day and within day variability of serum caffeine concentrations
2. stability and quality control
3. caffeine is medication of choice based on communication with several opinion leaders
4. caffeine has no effect on cerebral blood flow as noted with theophylline

III. Information to support application

A. Extensive past literature in relevant patient population and long clinical experience.

B. No placebo controlled trials with caffeine in the past literature

C. Sponsor has followed FDA guidance

1. Orphan drug

2. Supportive literature analysis - extensive pharmacokinetic, pharmacodynamic and comparative studies with theophylline.

3. Single study - first randomized, double-blind, placebo-controlled study to confirm efficacy. Overall efficacy supports past literature.

D. Adverse effect profile - reasonable

1. Central nervous system - objective findings, for example irritability, jitteriness, restlessness. Tolerance to these adverse effects can develop.

2. No indication of long-term effects on growth and neurological development.

3. Seizures can occur with overdose.

4. No deaths reported.

E. Clinical experience - very good profile

1. Rapid onset of effect

2. Caffeine is the drug of choice at present

a. better safety profile than theophylline with equivalent efficacy

b. once daily administration

c. potential therapeutic advantages - i.e. CNS penetration

d. extemporaneous preparations used widely

IV. Areas of concern

A. Primary efficacy variable not met, but good results for secondary efficacy variables and open label efficacy component.

B. Risk of necrotizing enterocolitis -

1. Second most common cause of neonatal death
2. Concomitant disorder in this patient population - 10% incidence. At risk patient population with or without methylxanthines
3. Caffeine less risk than theophylline

C. Considerations for future application

1. Dosage guidelines -
   a. Appears adequate for target population
   b. Needs information on pharmacodynamics, i.e. onset of effect, time of maximum effect, offset of effect when discontinued.
   c. Need to indicate that there are responders and non-responders. Some are dramatic responders; some are non-responders; and some lose effect after initial response. Add methods to define adequate response. Also, product information could benefit from inclusion of methods to handle non-responders, i.e. increase dose or switch to alternative treatment, i.e. theophylline
   d. Discuss duration of treatment - when to consider stopping medication and how to do it, i.e. tapering

2. Precautions - limited study population

a. Absence of data in adults, i.e. potential application as respiratory stimulant. Could assess subjective adverse effects, i.e. gastrointestinal irritability, anxiety, etc. in adults.

b. Absence of data in premature newborns less than 28 weeks or <1000 grams - recent study may provide more information

c. Hispanic population has higher volume of distribution

d. Clearance is higher in patients with high baseline frequency of apnea

3. Application of serum caffeine concentration monitoring - once per week seems adequate

4. May require increase in dose if efficacy is diminished (tolerance).

5. Limited duration of evaluation - 12 days

D. Monitor extent of use

1. Information to date does not indicate long term adverse effects, but needs to be followed.

2. Limited use of this specific product to date, i.e. controlled studies.

3. Product would be used, if available, and would likely become preparation of choice for the management of apnea of prematurity. May be used in adults who require a respiratory stimulant.

3. Need to assess pharmacodynamic implications of patient subsets with varying pharmacokinetics.

4. Landmark initiative - fulfills intentions of new initiatives in better medication guidelines for children. Need to monitor outcomes of application for this medication and implications for other medications.

CAFCIT
(caffeine citrate injection)
NDA 20-793

Liza Miriam Pina, M.D.

Medical reviewer

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Cafcit
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Cafcit
FDA Presentation

- 1. Trial OPR-001
  - –Study design
  - –Results
- 2. Overview of the Literature
- 3. Summary

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Trial OPR-001

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Study Design

- OPR-001

Multicenter (9 centers), randomized, double-blind, placebo-controlled, parallel study with an open-label rescue phase.

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Study Design

- Population:
  - 28 to < 33 weeks GA
  - >24 hours after birth.
  - With at least 6 apnea episodes (>20 seconds) in a 24-hour period or less (baseline).

Cafcit
Study Design

- Dosage
  - Double blind phase
    - Loading dose: 10 mg/Kg, I.V.
    - Maintenance dose: 2.5 mg/Kg. I.V. or oral
  - Open label phase
    - Loading dose: 10 mg/Kg, I.V.
    - Maintenance dose: 3.0 mg/Kg. I.V. or oral

Cafcit
Study Design

- Primary efficacy endpoint
  - Original Protocol: Reduction in Apnea Events by at least 50% from baseline on Day 2.

vs.

  - Final Amendment: Apnea rate on Day 2.

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Study Design

- Secondary Analyses of Primary Endpoint
  - Reduction in Apnea Episodes by at least 50%
    - by Treatment Day (2 - 10)
    - % Of Patients Who Maintained Drug Effect
  - Zero Apnea events in 24 hours
    - By Treatment Day
    - By Total Number of Days

Cafcit
Study Design

- Secondary Efficacy Endpoints
  - Lowest Heart Rate Associated with Apnea, by treatment day
  - Lowest Oxygen Saturation (%) Associated with Apnea, by treatment day
  - Duration of Apnea Events

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Study Design

- Sample size
  - Calculated on the original primary endpoint
  - Assumed a success rate of 70% in the caffeine and 20% in the placebo groups
  - The difference in observed success rates was lower than the sponsor had predicted (actual study power was only 44%)

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Study Results

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Disposition of Patients

Study Day	Caffeine group Double-blind N (%)	Placebo group Double-blind N (%)
Baseline	45 (100)	37 (100)
1	41 (91)	32 (86)
2	28 (62)	19 (51)
3	26 (57)	18 (48)
4	24 (53)	16 (43)
5	23 (51)	15 (41)
6	22 (48)	14 (38)
7	21 (47)	12 (32)
8	20 (44)	11 (30)
9	20 (44)	11 (30)
10	20 (44)	11 (30)

N= number of patients who completed that study day.

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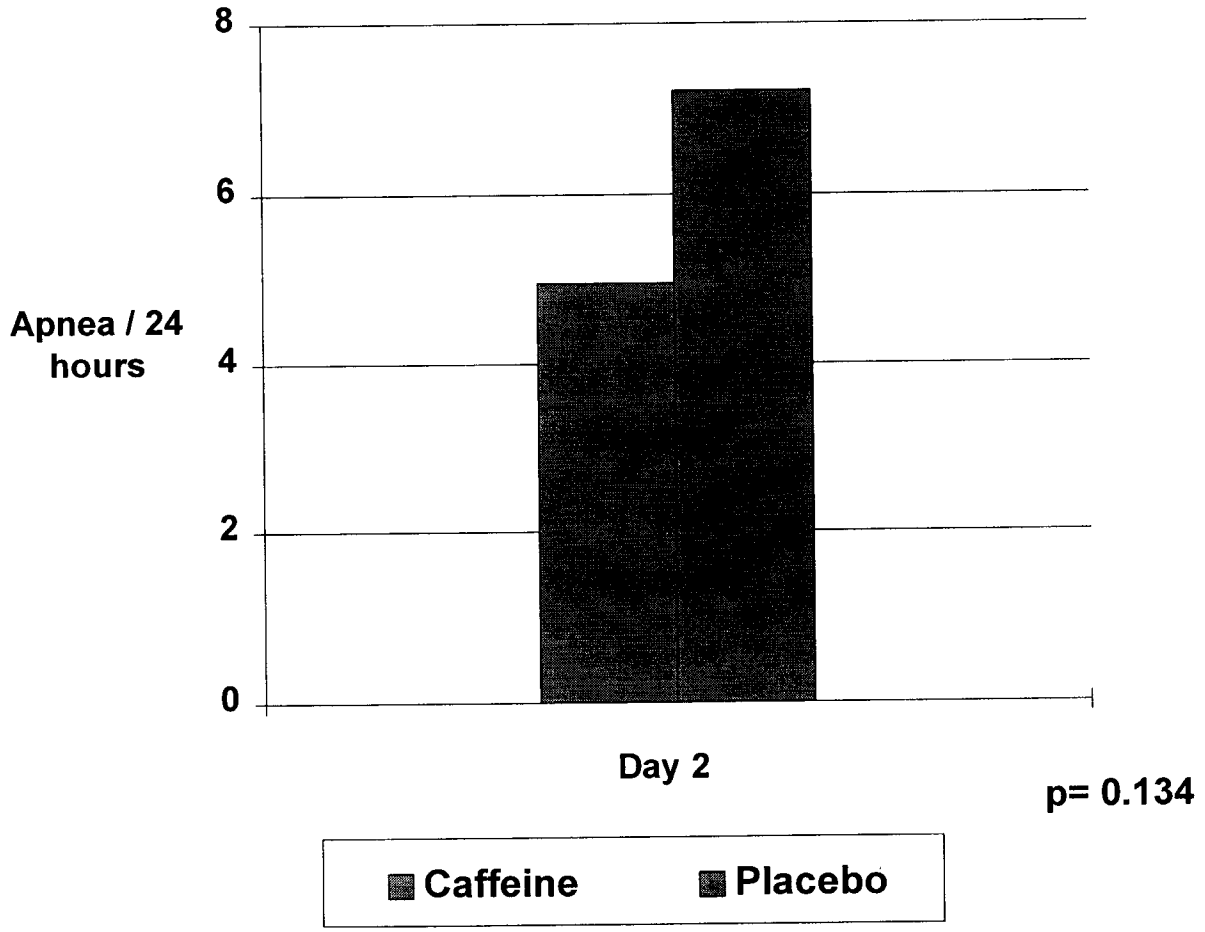
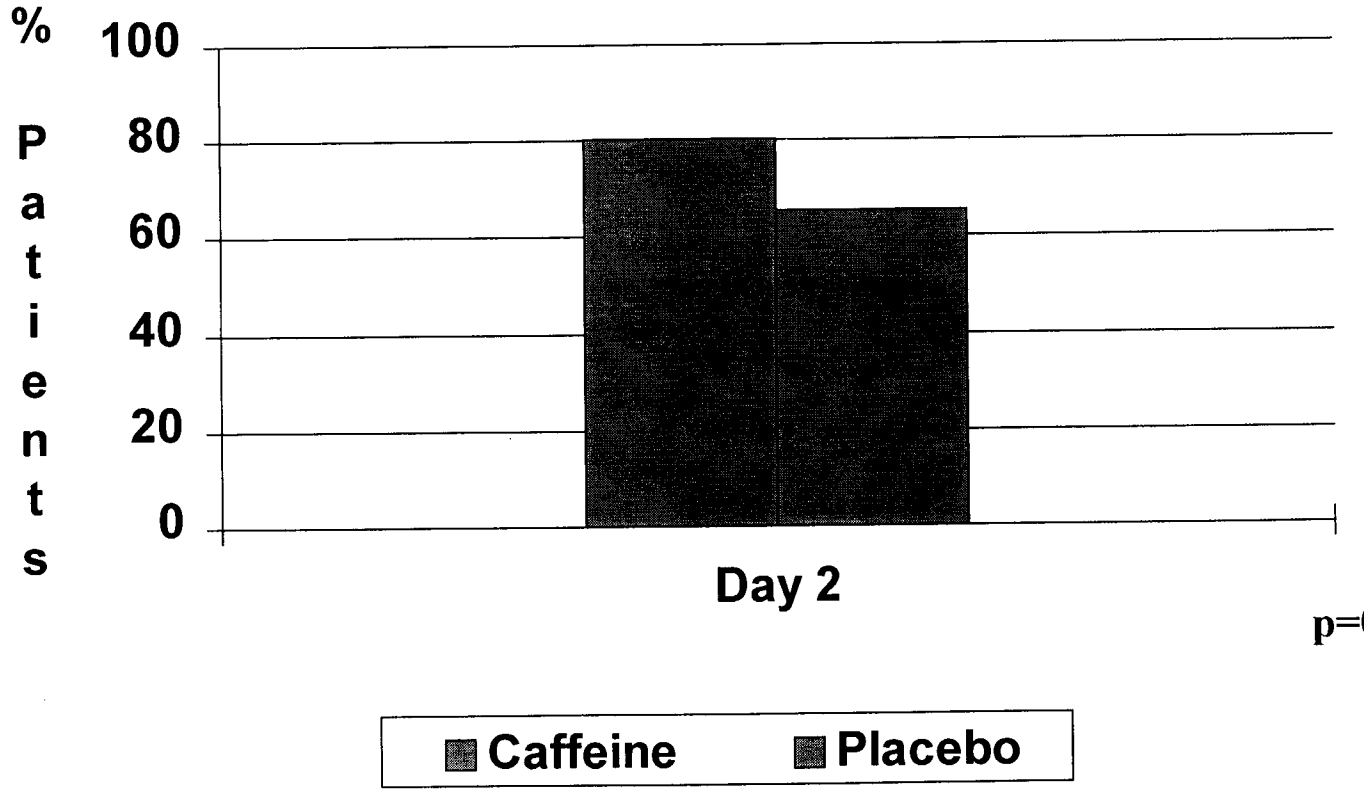
Primary Efficacy Endpoint
Apnea Rate, Day 2

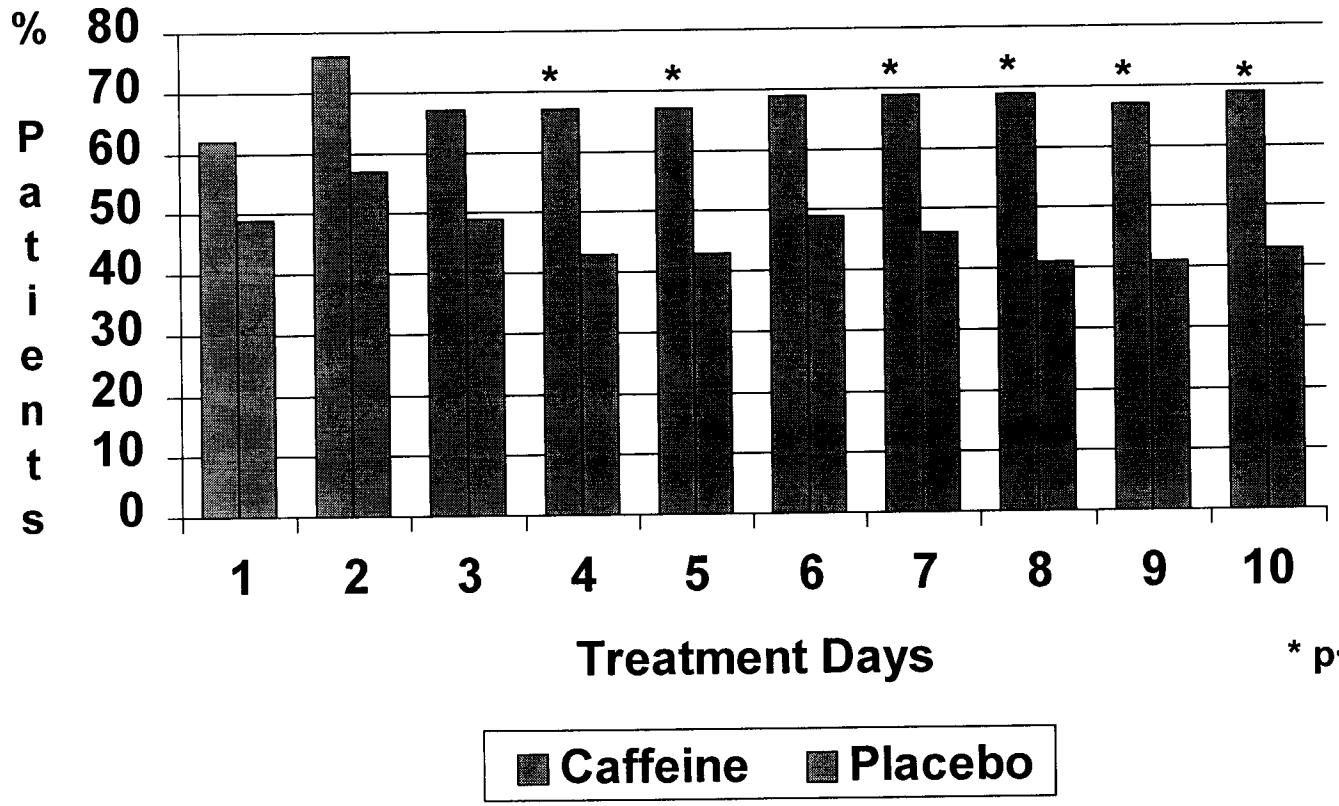


Cafcit
50% Reduction of Apnea Events, Day 2

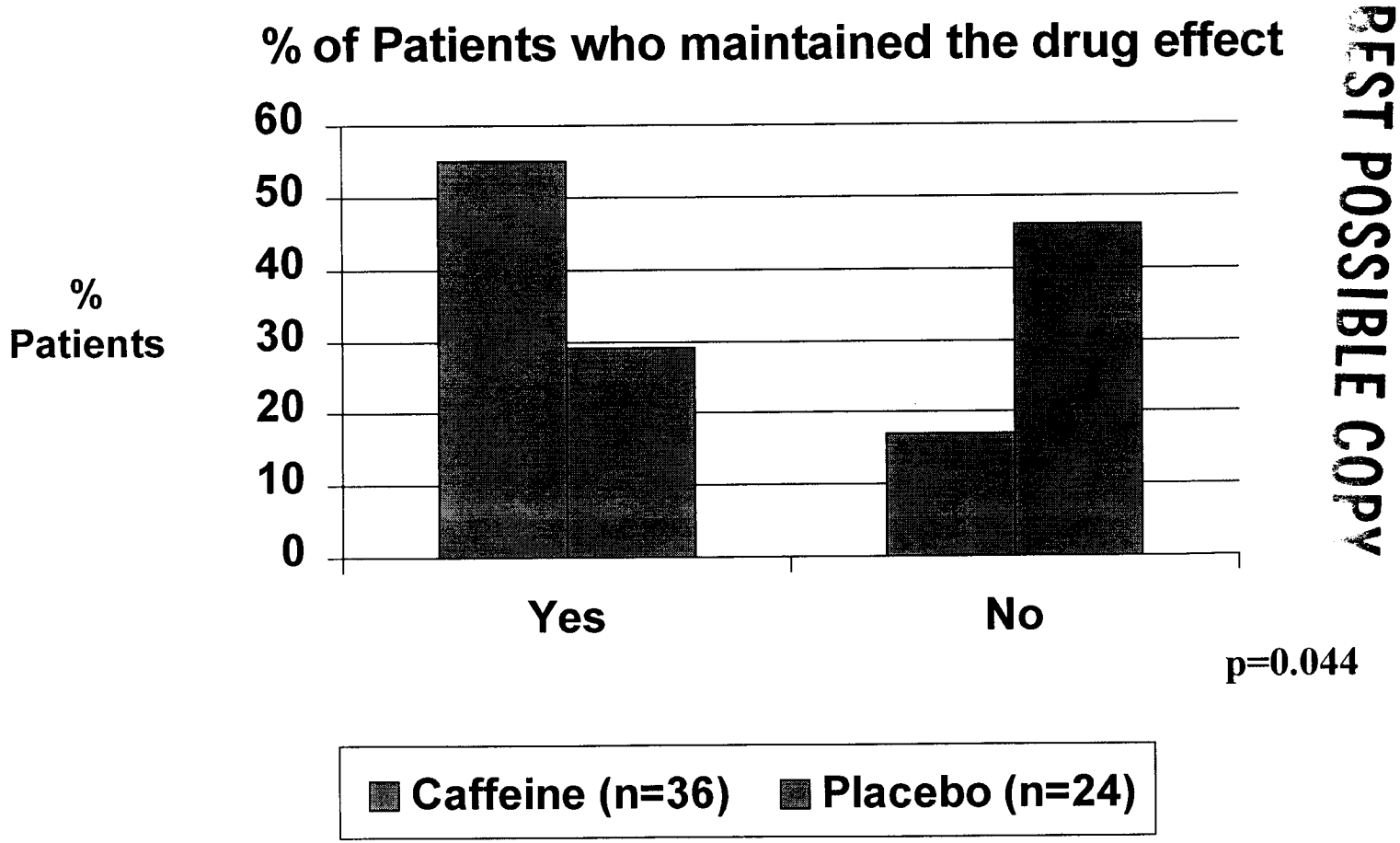


p=0.0715

Cafcit
50% Reduction of Apnea Events, by Treatment Day



Cafcit
50% Reduction of Apnea Events



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Secondary Endpoints

- Post hoc analysis
  - Zero Apnea Events

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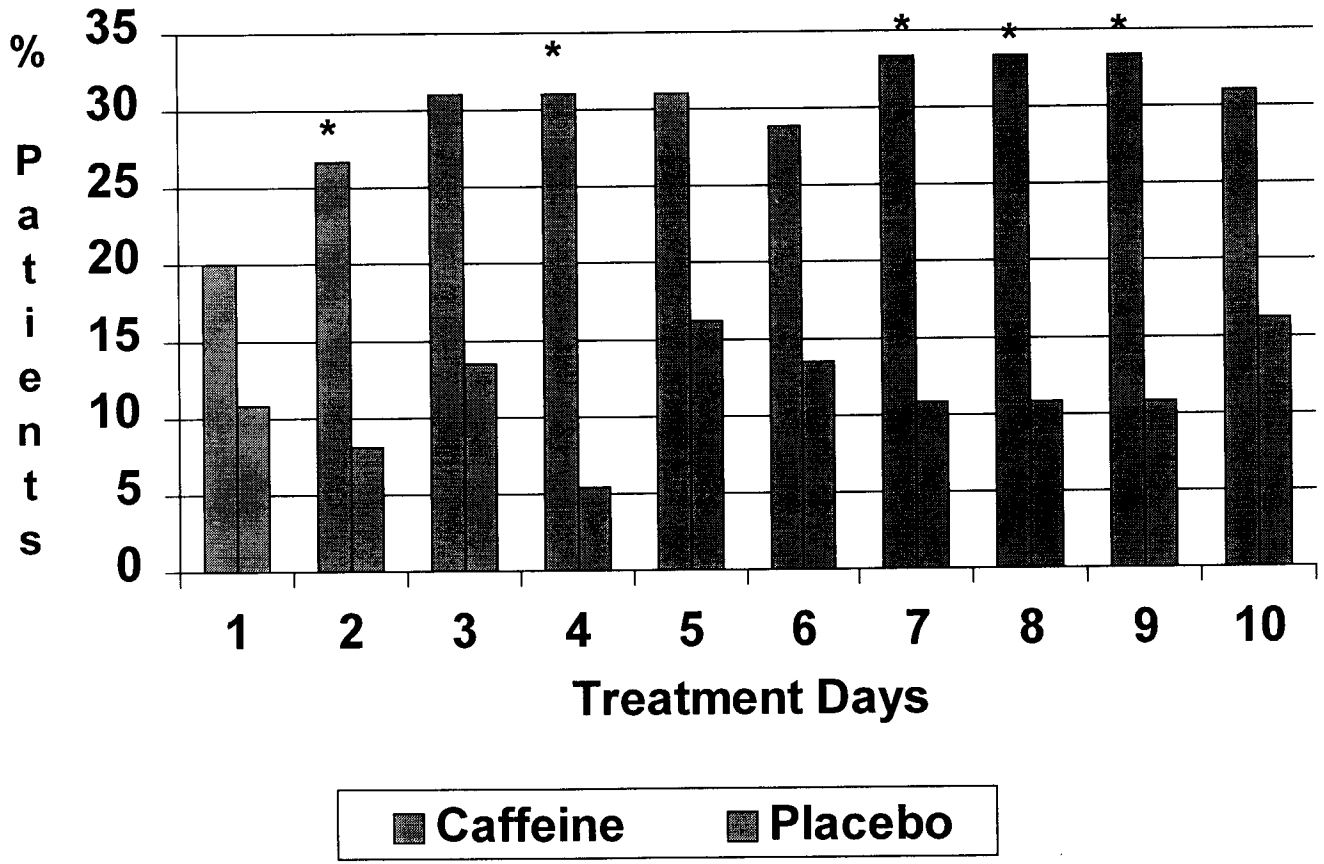
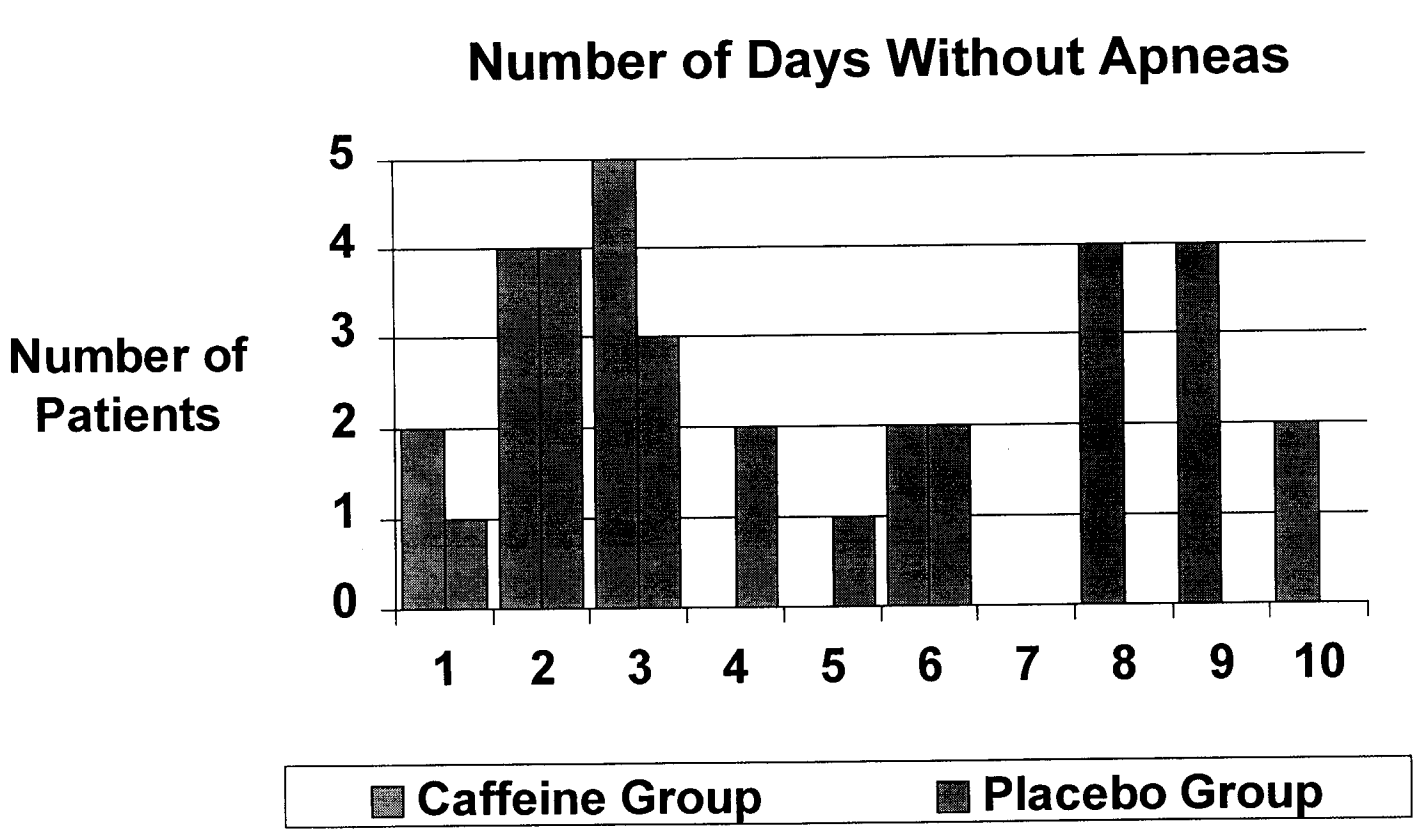
Patients With Zero Apneas by Treatment Day

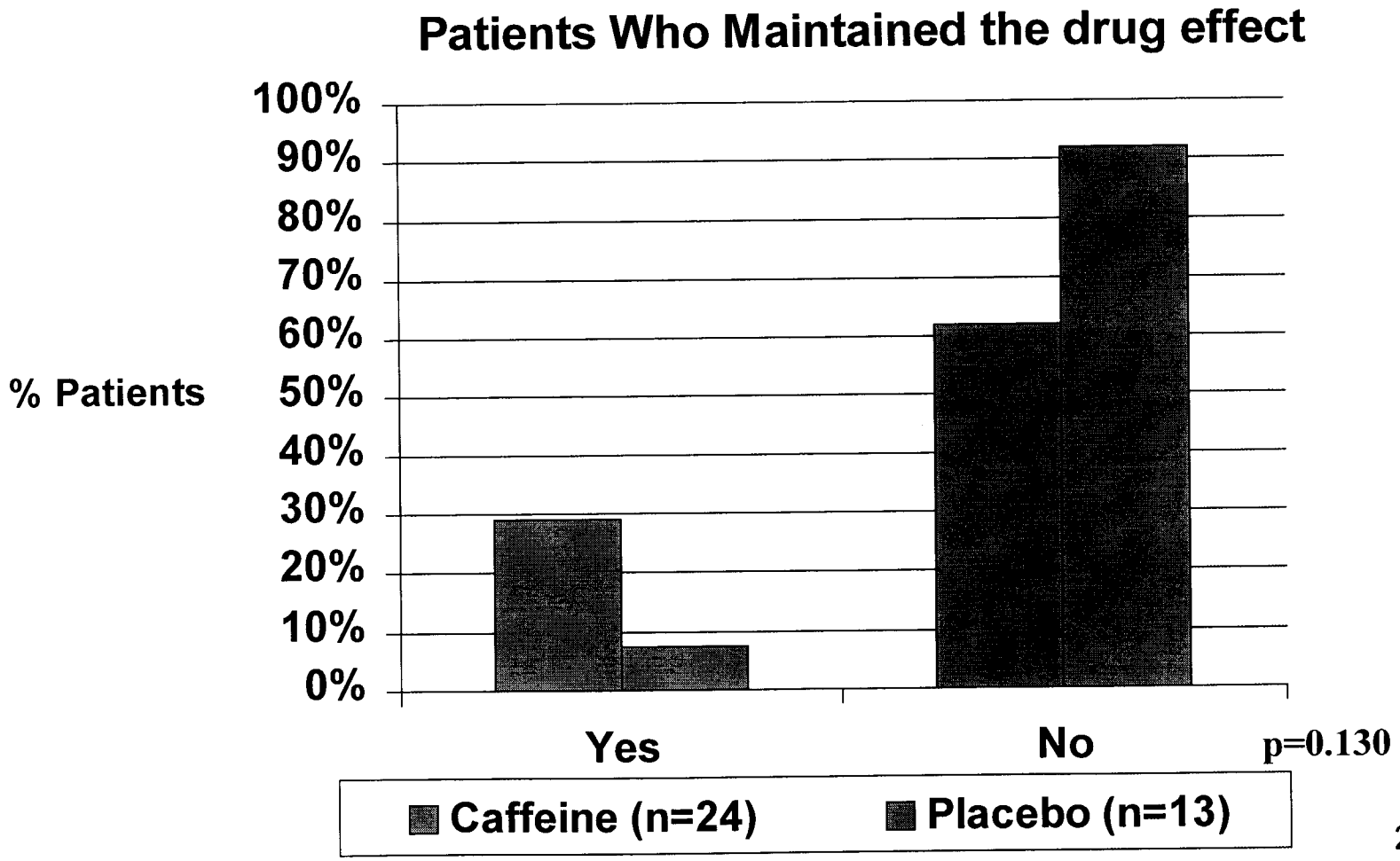


* p<0.05

Cafcit
Patients With Zero Apneas



Cafcit
Patients with Zero Apneas



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Subset Comparisons

Parameter	50% reduction for >7 days (n=12)	Zero apneas for >7 days (n=8)	Never had a >50% reduction (n=9)
Gestational Age (weeks)*	29.7 ± 2.0	30.8 ± 1.0	30.6 ± 1.6
Baseline Apnea Rate (# /24 hrs.)*	10.2 ± 5.1	8.6 ± 1.8	9.3 ±5.8
Weight at entry (Kg)*	1.28 ± 0.25	1.51± 0.30	1.22 ± 0.14
Caffeine plasma level (mg/L)*	13.1 ± 2.5	13.7 ± 4.3	17.1 ± 8.7

* Mean + SD

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Other Secondary Efficacy Endpoints

- **Lowest Heart rate associated with Apneas**

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Other Secondary Efficacy Endpoints

- **Lowest Oxygen Saturation (%) associated with Apneas**

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Other Secondary Efficacy Endpoints

- **Duration of Apnea Events**
  - Unreliable
  - No significant effect

Cafcit
Safety Overview

- Adverse Events
- Deaths

Cafcit
Safety Overview

- **Adverse Events**
  - By exposure
  - By randomization

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Main Adverse events by exposure to caffeine

Adverse Event	Exposed (N = 63)	Not Exposed (N = 22)
Any event	43 (68%)	18 (81%)
Necrotizing enterocolitis	5 (7.9%)	1 (4.5%)
Sepsis	8 (13%)	0 (0%)
Anemia	11 (17.5%)	6 (27%)
Vomiting	2 (3 %)	0 (0%)
Death	3 (4.7%)	0 (0%)

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Main Adverse Events by Randomization

Adverse Event	Caffeine group (N = 46)	Placebo group (N = 39)
Any event	36 (78%)	35 (90%)
Necrotizing enterocolitis	4 (8.6%)	2 (5%)
Sepsis	6 (13%)	2 (5%)
Anemia	6 (13%)	11 (28%)
Vomiting	0 (0%)	2 (5%)
Death	2 (4.3%)	1 (2.5%)

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Safety Overview

- Deaths
  - Caffeine group: 2 deaths
  - Placebo group: 1 death (transferred to open-label caffeine on day 2)

Summary of the Literature

Summary of the Literature

- Efficacy : 27 articles
  - Controlled (10 articles)
    - Untreated or Historical controls
    - Caffeine versus Theophylline
  - Uncontrolled (17 articles)
- Safety : 59 articles

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Summary of the Literature Efficacy

- 10 controlled and 17 uncontrolled trials were submitted and reviewed
  - No study was placebo-controlled
  - All were open-label
  - Several different clinical endpoints were studied
  - Except for one study, there were no follow-up data

Summary of the Literature Efficacy

- Results

  Caffeine was consistently shown to improve the patients apnea endpoint when compared to the patient's own baseline.

Summary of the Literature Efficacy

- Study by Murat et al, 1981
  - Prospective, randomized, parallel controlled
  - Dosage regimen similar to that used in trial OPR-001
  - 24-hour recordings monitored apnea events on day 1, 5 , 15 and on day 8 after therapy was discontinued
  - Primary endpoint: apnea index on days 1, 5, and 15

Summary of the Literature Efficacy

- Study by Murat et al. Results.

  - Showed a statistically significant improvement of the apnea index in the treated group on days 1 and 5;
  - No apnea recurrence after discontinuation of caffeine was noted.

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Summary of the Literature Safety

- The database from published clinical trials, included over 830 premature infants exposed to caffeine.
  - Necrotizing enterocolitis
  - Drug-drug interactions

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Summary of the Literature Safety

- In general, the adverse events reported in the literature for caffeine are similar to those reported for trial OPR-001
- Compared to theophylline, caffeine had similar safety profile, but milder and less frequent.

Summary of the Literature Safety

- Necrotizing Enterocolitis.

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  - Background.
    - Major cause of morbidity and mortality in premature infants.
    - The reported incidence ranges from 2 to 13.5%
    - The reported mortality varies from 20 to 50%
    - Cause (s) not well established

Summary of the Literature Safety

- Necrotizing Enterocolitis.
  - Issues
    - 1980, Robinson et al., suggested the association of xanthine treatment with the development of NEC.
    - 1983, Grosfeld et al., suggested that aminophylline had an adverse effect in animals with ischemic bowel insults.

Summary of the Literature Safety

- Necrotizing enterocolitis (cont..)
  - In most cases theophylline was the xanthine studied.
    - 1986, Davis J. et al., studied 124 infants treated with theophylline who had a similar incidence of NEC as did 151 infants who were not treated with theophylline.

Summary of the Literature Safety

- Necrotizing enterocolitis (cont..)
  - Some compared theophylline to caffeine
    - Bairam et al (1986)
    - Larsen et al (1995)

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Summary of the Literature Safety

- Necrotizing enterocolitis (cont..)

  The findings in the Literature are not conclusive whether the exposure to methylxanthines is associated with an increased incidence of NEC.

Summary of the Literature Safety

- Drug-Drug Interactions

  - 71 articles submitted
    - 70 of the studies were performed in adults
    - 1 study in premature infants
  - Limited information on dose adjustment

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Efficacy Issues

- Study OPR-001
  - Is the only placebo-controlled study
  - Failed to show a statistically significant difference in the primary endpoint in favor of caffeine citrate
  - Showed a statistically significant effect in reducing/eliminating apnea events

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Efficacy Issues (cont...)

- Published Literature
  - Most trials were small and not adequate and well controlled
  - The results consistently showed that caffeine improved the apnea endpoint studied.

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Question on Efficacy

- Is there enough evidence to support the efficacy of caffeine citrate for the treatment of Apnea of Prematurity?

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Safety Issues

- Study OPR-001
  - Had a complex trial design with a high rate of drop outs early in the study
  - Showed no statistically significant differences in adverse events by body system between caffeine and placebo treated patients

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Safety Issues (cont...)

- The association of caffeine with the increased incidence of NEC in the target population discussed in the literature could not be substantiated, but the numerical increase of NEC cases in the caffeine group raises concern.

Cafcit
Safety Issues (cont…)

- Published Literature
  - The findings in the literature were consistent with those in the clinical trial.
  - The reports regarding the association of NEC with the use of xanthines are not conclusive in either direction.
  - No data are available to adjust caffeine dose with coadministration of other drugs.

Cafcit
Question on Safety

- Is there enough evidence to support the safety of caffeine citrate for the treatment of Apnea of Prematurity?