efdinir (5-day) vs Penicillin V (10-day) in the Treatment of Strep. occal Pharyngitis/Tonsillitis Infections in Pediat Patient

Summary of Adverse Events
All Patients

Protocol 983-056 (Subset=56_noinv.txt)

	Cefdinir 7 mg/kg BID (N=211)		Penicillin V (N=214)	
	N	%	N	%
Number of Patients Whose Treatment Was Discontinued Due to TESS AE	0	0.0	1	0.5
Number of Patients Whose Treatment Was Discontinued Due to Non-TESS AE	0	0.0	0	0.0
Number of Patients Withdrawn from Study Due to AE~	6	2.8	5	2.3

~Patients who did not discontinue treatment due to an AE

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efdinir (5-day) vs Penicillin V (10-day) in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patient

Summary of Associated Adverse Events
All Patients

Protocol 983-056 (Subset=56_noinv.txt)

	Cefdinir 7 mg/kg BID (N=211)		Penicillin V (N=214)	
	N	%	N	%
Number of Patients Reporting AE	13	6.2	11	5.1
Number of Patients Reporting Mild AE	9	4.3	8	3.7
Number of Patients Reporting Moderate AE	3	1.4	4	1.9
Number of Patients Reporting Severe AE	1	0.5	0	0.0
Number of Male Patients Reporting AE	6	5.4	5	4.6
Number of Female Patients Reporting AE	7	7.1	6	5.7
Number of Patients < 2 Years Old Reporting AE	0	0.0	0	0.0
Number of Patients 2 to < 6 Years Old Reporting AE	4	7.4	7	14.6
Number of Patients 6 to < 13 Years Old Reporting AE	9	5.8	4	2.5
Number of Patients 13 to < 18 Years Old Reporting AE	0	0.0	0	0.0
Number of White Patients Reporting AE	13	6.7	10	5.2
Number of Black Patients Reporting AE	0	0.0	1	12.5
Number of Asian Patients Reporting AE	0	0.0	0	0.0
Number of Hispanic Patients Reporting AE	0	0.0	0	0.0
Number of Other Patients Reporting AE	0	0.0	0	0.0

(CONTINUED)

-Patients who did not discontinue treatment due to an AE

TABLE 15. All and Associated Adverse Events: All Patients - Protocol 983-56
[Number (%) of Patients]
(Page 1 of 3)

BODY SYSTEM[a]/ Adverse Event	All Sites				Sites Excluding Iravani			
	Cefdinir N = 240		Penicillin N = 242		Cefdinir N = 211		Penicillin N = 214	
	All	Assoc	All	Assoc	All	Assoc	All	Assoc
BODY AS A WHOLE	45 (18.8)	1 (0.4)	33 (13.6)	1 (0.4)	43 (20.4)	1 (0.5)	32 (15.0)	1 (0.5)
Infection	24 (10.0)	0 (0.0)	12 (5.0)	0 (0.0)	23 (10.9)	0 (0.0)	12 (5.6)	0 (0.0)
Abdominal Pain	8 (3.3)	1 (0.4)	6 (2.5)	1 (0.4)	8 (3.8)	1 (0.5)	6 (2.8)	1 (0.5)
Headache	8 (3.3)	0 (0.0)	8 (3.3)	0 (0.0)	8 (3.8)	0 (0.0)	7 (3.3)	0 (0.0)
Accidental Injury	6 (2.5)	0 (0.0)	4 (1.7)	0 (0.0)	6 (2.8)	0 (0.0)	4 (1.9)	0 (0.0)
Allergic Reaction	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.9)	0 (0.0)	1 (0.5)	0 (0.0)
Flu Syndrome	2 (0.8)	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Chest Pain	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Fever	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.9)	0 (0.0)
Neck Pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Neck Rigidity	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
CARDIOVASCULAR SYSTEM	2 (0.8)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.9)	0 (0.0)
Hemorrhage	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Palpitation	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Supraventricular Tachycardia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
DIGESTIVE SYSTEM	26 (10.8)	9 (3.8)	23 (9.5)	7 (2.9)	22 (10.4)	9 (4.3)	23 (10.7)	7 (3.3)
Diarrhea	11 (4.6)	5 (2.1)	9 (3.7)	2 (0.8)	10 (4.7)	5 (2.4)	9 (4.2)	2 (0.9)
Vomiting	8 (3.3)	2 (0.8)	12 (5.0)	2 (0.8)	5 (2.4)	2 (0.9)	12 (5.6)	2 (0.9)
Gastroenteritis	4 (1.7)	0 (0.0)	1 (0.4)	1 (0.4)	4 (1.9)	0 (0.0)	1 (0.5)	1 (0.5)
Glossitis	2 (0.8)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.5)	0 (0.0)	0 (0.0)
Dyspepsia	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Gingivitis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (0.4)	0 (0.0)	4 (1.7)	2 (0.8)	1 (0.5)	0 (0.0)	4 (1.9)	2 (0.9)

Assoc = Associated (ie, considered by the investigator to be possibly, probably, or definitely related to treatment).

[a] The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have more than 1 adverse event per system.

TABLE 15. All and Associated Adverse Events: All Patients - Protocol 983-56

[Number (%) of Patients]

(Page 2 of 3)

BODY SYSTEM[a]/ Adverse Event	All Sites				Sites Excluding Iravani			
	Cefdinir N = 240		Penicillin N = 242		Cefdinir N = 211		Penicillin N = 214	
	All	Assoc	All	Assoc	All	Assoc	All	Assoc
DIGESTIVE SYSTEM (Continued)								
Flatulence	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Melena	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Mouth Ulceration	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Rectal Disorder	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
HEMIC AND LYMPHATIC SYSTEM	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Anemia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
METABOLIC AND NUTRITIONAL SYSTEM	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Peripheral Edema	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Dehydration	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lactic Dehydrogenase Increase	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
MUSCULOSKELETAL SYSTEM	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Leg Cramps	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
NERVOUS SYSTEM	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Convulsion	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
RESPIRATORY SYSTEM	35 (14.6)	0 (0.0)	23 (9.5)	1 (0.4)	35 (16.6)	0 (0.0)	22 (10.3)	1 (0.5)
Cough Increased	13 (5.4)	0 (0.0)	7 (2.9)	0 (0.0)	13 (6.2)	0 (0.0)	7 (3.3)	0 (0.0)
Rhinitis	13 (5.4)	0 (0.0)	10 (4.1)	0 (0.0)	13 (6.2)	0 (0.0)	9 (4.2)	0 (0.0)
Sinusitis	5 (2.1)	0 (0.0)	4 (1.7)	0 (0.0)	5 (2.4)	0 (0.0)	3 (1.4)	0 (0.0)
Pharyngitis	4 (1.7)	0 (0.0)	4 (1.7)	0 (0.0)	4 (1.9)	0 (0.0)	4 (1.9)	0 (0.0)
Epistaxis	2 (0.8)	0 (0.0)	2 (0.8)	1 (0.4)	2 (0.9)	0 (0.0)	2 (0.9)	1 (0.5)
Lung Disorder	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Voice Alteration	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Assoc = Associated (ie, considered by the investigator to be possibly, probably, or definitely related to treatment).

[a] The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have more than 1 adverse event per system.

TABLE 15. All and Associated Adverse Events: All Patients - Protocol 983-56
[Number (%) of Patients]
(Page 3 of 3)

BODY SYSTEM[a]/ Adverse Event	All Sites				Sites Excluding Iravani			
	Cefdinir N = 240		Penicillin N = 242		Cefdinir N = 211		Penicillin N = 214	
	All	Assoc	All	Assoc	All	Assoc	All	Assoc
SKIN AND APPENDAGES	10 (4.2)	5 (2.1)	15 (6.2)	4 (1.7)	8 (3.8)	5 (2.4)	15 (7.0)	4 (1.9)
Rash	5 (2.1)	4 (1.7)	7 (2.9)	3 (1.2)	5 (2.4)	4 (1.9)	7 (3.3)	3 (1.4)
Alopecia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dry Skin	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Fungal Dermatitis	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Maculopapular Rash	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)
Skin Disorder	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Acne	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Contact Dermatitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Erythema Multiforme	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Exfoliative Dermatitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Herpes Simplex	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Pustular Rash	0 (0.0)	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)	0 (0.0)
Vesiculobullous Rash	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
SPECIAL SENSES	13 (5.4)	0 (0.0)	18 (7.4)	0 (0.0)	12 (5.7)	0 (0.0)	15 (7.0)	0 (0.0)
Otitis Media	7 (2.9)	0 (0.0)	7 (2.9)	0 (0.0)	6 (2.8)	0 (0.0)	5 (2.3)	0 (0.0)
Ear Pain	4 (1.7)	0 (0.0)	7 (2.9)	0 (0.0)	4 (1.9)	0 (0.0)	6 (2.8)	0 (0.0)
Conjunctivitis	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.9)	0 (0.0)	1 (0.5)	0 (0.0)
Ear Disorder	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Eye Disorder	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Eye Pain	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Photophobia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
UROGENITAL SYSTEM	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Dysuria	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Hematuria	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Assoc = Associated (ie, considered by the investigator to be possibly, probably, or definitely related to treatment).
[a] The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have more than 1 adverse event per system.

TABLE 16. Withdrawals Due to Adverse Events - All Patients

Center	Patient Number	Age, Sex	Adverse Event	Relationship to Study Medication[a]	Study Day of Onset	Study Day Drug Discontinued	Outcome
Cefdinir							
3	48	7 yr, F	Possible Rheumatic Fever[b,c]	Unlikely	9	Completed	Recovered
2	29	19 mo, F	Otitis media	Definitely not	12	Completed medication	Unknown
7	14	5 yr, M	Otitis media	Definitely not	18	Completed medication	Recovered
8	7	11 yr, M	Otitis media, sinusitis	Definitely not	17	Completed medication	Recovered
9	36	6 yr, M	Otitis media	Definitely not	7	Completed medication	Recovered
14	3	10 yr, M	Sinusitis	Definitely not	16	Completed medication	Recovered
Penicillin							
5[c]	33	2 yr, F	Dehydration[b]	Definitely not	4	4	Recovered
3	58	8 yr, F	Stomach cramps, nausea	Possibly	2	2	Recovered
4	21	2 yr, M	Smashed thumb	Definitely not	2	Completed medication	Recovered
10	38	10 yr, F	Urinary tract infection	Definitely not	15	Completed medication	Recovered
10	47	9 yr, F	Otitis media	Definitely not	11	Completed medication	Recovered
11	9	2 yr, F	Sinusitis, conjunctivitis	Unlikely	18	Completed medication	Recovered
12	6	5 yr, M	Impetigo	Definitely not	18	Completed medication	Recovered

[a] As assessed by the investigator
[b] Serious adverse event
[c] Preferred term: infection

6.3.1.11. *Clostridium difficile*-Associated Diarrhea

No patients discontinued treatment for diarrhea, therefore, none were tested for *C. difficile.*

6.3.2. Physical Examinations[(ii)]

A review of the physical examinations performed at baseline, TOC, and LTFU showed no adverse findings associated with any treatment group.

[(ii)] Appendix C.55, Median Changes in Vital Signs

TABLE 19. Patients With Markedly Abnormal Laboratory Values at the First Posttherapy Visit
(Page 1 of 4)

Center	Patient No.	Race	Age (Yr), Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
Cefdinir									
2	3	White	9, F	39.5	Urine WBC	21-50 /HPF	21-50	1-5	No history noted
2	20	White	12, F	38.6	Alkaline phosphatase	516 U/L	486	25-480	No history noted
2	34	White	12, M	61.0	Urine protein	1+	Negative	Negative	ADD, methylphenidate, diptheria, hepatitis, MMR vaccines
3	12	White	11, F	48.1	WBC	26.1 × 10^9/L	18.8	4.5-13.5	Failure
					Lymphocytes	8 %	4	10-49	
3	19	White	6, M	24.0	PMNs	80 %	84	20-75	Failure AE: stuffy nose, otitis media, beclomethasone, acetaminophen
3	39	White	11, F	45.0	Urine protein	1+	Trace	Negative	No history noted
3	44	White	2, F	13.1	PMNs	76 %	NA	20-75	History otitis media, wheezy bronchitis AE: viral gastroenteritis
3	48	White	7, F	29.0	PMNs	80 %	57	20-75	History otitis media, pharyngitis AE: possible rheumatic fever, diarrhea, runny nose Acetaminophen, Ibuprofen
~~5~~	~~32~~	~~White~~	~~6, F~~	~~20.0~~	~~WBC~~	~~22.7 × 10^9/L~~	~~8.9~~	~~5-14.5~~	~~AE: viral syndrome, vomiting~~
					~~PMNs~~	~~87%~~	~~66~~	~~20-75~~	
					~~Lymphocytes~~	~~7 %~~	~~19~~	~~10-66~~	
~~5~~	~~41~~	~~White~~	~~7, M~~	~~21.0~~	~~PMNs~~	~~89 %~~	~~81~~	~~20-75~~	~~Failure~~
					Lymphocytes	6 %	11	10-66	
~~5~~	~~52~~	~~White~~	~~12, M~~	~~42.7~~	~~Eosinophils~~	~~12 %~~	~~10~~	~~0-7~~	~~ADD, Imipramine~~
7	25	Hispanic	5, M	18.4	PMNs	85 %	70	20-75	No history noted
					Lymphocytes	8 %	17	10-66	
8	10	White	7, F	20.9	PMNs	83 %	77	20-75	Failure
					Lymphocytes	9 %	12	10-66	
8	27	White	8, M	50.9	Alkaline phosphatase	408 U/L	367	25-350	ADD, methylphenidate AE: sprain, forearm
9	3	White	8, M	22.7	WBC	16.4 × 10^9/L	15.6	4.5-13.5	Failure
					Lymphocytes	9 %	6	10-49	
9	33	White	10, M	32.7	Bicarbonate	13 mmol/L	22	22-32	Seasonal allergies, recurrent strep throat Microbiological failure
					LDH	479 U/L	221	118-273	

WBC = White blood cells; PMN = polymorphonuclear leukocytes; LDH = Lactate dehydrogenase; ADD = Attention deficit disorder; MMR = Measles, mumps, rubella; NA = Not available; AE = Adverse event.

TABLE 19. Patients With Markedly Abnormal Laboratory Values at the First Posttherapy Visit (Page 2 of 4)

Center	Patient No.	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
9	36	White	6, F	19.5	WBC	3.3 × 10^9/L	8.8	5-14.5	AE: otitis media
10	3	White	6, F	19.3	Bicarbonate	11 mmol/L	15	22-32	Failure
					WBC	20.2 × 10^9/L	19.3	5-14.5	
					PMNs	81 %	87	20-75	
10	5	White	6, F	20.3	PMNs	78 %	79	20-75	Microbiological failure AE: cough, blood in urine
10	15	White	5, M	22.3	PMNs	88 %	71	20-75	Microbiological failure AE: intercurrent viral illness
					Lymphocytes	7 %	17	10-66	
10	17	White	7, F	30.9	Bilirubin	6.5 mg/dL	0.3	0.2-1.4	Specimen grossly hemolyzed
					AST	367 U/L	18	0-31	
					Potassium	15.9 mEq/L	3.9	3.5-5.1	
					LDH	4591 U/L	225	150-300	
					Sodium	124 mEq/L	136	136-146	
					Phosphorus	9.9 mg/dL	4.5	3.1-6.3	
					Total protein	10.2 g/dL	7.2	5.8-8	
10	20	White	5, F	17.7	LDH	450 U/L	226	150-300	No history noted
10	28	White	4, M	18.2	Platelets	683 × 10^9/L	228	140-450	Sodium fluoride
12	4	White	5, F	25.9	PMNs	77 %	78	20-75	Failure
12	18	White	4, F	15.9	Alkaline phosphatase	1173 U/L	2499	25-350	No history noted
13	6	White	7, M	30.2	LDH	451 U/L	208	150-300	Failure Specimen transit time=71 hours
13	15	White	10, F	35.7	Potassium	7.2 mEq/L	4.8	3.5-5.1	No history noted Specimen transit time=39 hours
14	16	White	8, M	34.5	Phosphorus	6.7 mg/dL	4.4	3-6	Allergic rhinitis, sinusitis Microbiological failure
PENICILLIN									
2	21	White	8, M	24.0	WBC	15.8 × 10^9/L	9.9	4.5-13.5	Microbiological failure
					Lymphocytes	8 %	14	10-49	
2	24	Caucasian/ Black	3, F	16.5	Urine protein	1+	Negative	Negative	No history noted
2	35	White	3, F	18.2	Alkaline phosphatase	451 U/L	331	25-350	No history noted
2	50	White	10, M	35.3	LDH	469 U/L	625	118-273	Elevated AST at baseline

WBC = White blood cells; PMN = polymorphonuclear leukocytes; LDH = Lactate dehydrogenase; AST = aspartate aminotransferase; AE = Adverse event.

TABLE 19. Patients With Markedly Abnormal Laboratory Values at the First Posttherapy Visit
(Page 3 of 4)

Center	Patient No.	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
3	18	White	7, M	22.0	AST	107 U/L	180	0-37	Iron deficiency anemia Elevation of liver enzymes due to viral etiology per site 65 U/L on Day 19
					ALT	134 U/L	225	0-40	75 U/L on Day 19
					LDH	414 U/L	594	150-300	339 U/L on Day 19
3	32	White	7, M	27.5	WBC	22.1 × 10^9/L	15.2	5-14.5	Earache Microbiological failure
					PMNs	80 %	70	20-75	
3	41	White	6, F	26.4	Alkaline phosphtase	407 U/L	350	25-350	Sinusitis, conjunctivitis
3	52	White	5, F	21.0	PMNs	82 %	77	20-75	AE: contact dermatitis, erythema multiform, prednisolone
4	31	White	7, F	23.9	Urine WBC	21-50 /HPF	1-5	1-5	No history noted
~~5~~	~~16~~	~~White~~	~~8, F~~	~~39.5~~	~~Urine WBC~~	~~21-50 /HPF~~	~~1-5~~	~~1-5~~	~~No history noted~~ 1-5 /HPF on Day 19
~~5~~	~~29~~	~~White~~	~~2, F~~	~~12.5~~	~~Alkaline phosphatase~~	~~438 U/L~~	~~217~~	~~25-350~~	~~No history noted~~
~~5~~	~~49~~	~~White~~	~~6, M~~	~~20.5~~	~~Urine RBC~~	~~21-50 /HPF~~	~~>50~~	~~0~~	~~ADD, hematuria, methylphenidate~~
~~5~~	~~54~~	~~Black~~	~~4, F~~	~~17.9~~	~~PMNs~~	~~11 %~~	~~48~~	~~20-75~~	~~No history noted~~
7	29	White	12, F	53.9	Urine specific gravity	1.042	1.025	1.005-1.03	Hay fever
8	1	White	7, F	25.0	LDH	533 U/L	264	150-300	Fifth disease, parvovirus
9	4	White	5, F	18.6	LDH	477 U/L	276	150-300	No history noted
9	8	White	6, M	33.6	Hematocrit	29.9 %	32.2	35-45	Impetigo Microbiological failure AE: URI, impetigo, pseudoephedrine
					LDH	410 U/L	259	150-300	
9	25	White	8, F	27.3	Urine protein	1+	Negative	Negative	URI, pseudoephedrine Microbiological failure
9	39	White	8, M	26.4	Urine protein	1+	Negative	Negative	ADD, methylphenidate
10	11	White	5, M	24.3	PMNs	80 %	78	20-75	Bronchospasm Microbiological failure
10	19	White	7, F	24.3	PMNs	85 %	87	20-75	Allergies Microbiological failure
					Lymphocytes	9 %	4	10-66	
13	3	White	10, F	37.7	Potassium	6.3 mEq/L	5.8	3.5-5.1	No history noted; specimen hemolyzed
					LDH	470 U/L	226	122-220	
13	10	White	7, F	28.2	Potassium	6.5 mEq/L	4.3	3.5-5.1	History of pharyngitis

WBC = White blood cells; PMN = polymorphonuclear leukocytes; LDH = Lactate dehydrogenase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; URI = Upper respiratory infection; ADD = Attention deficit disorder; AE = Adverse event.

TABLE 19. Patients With Markedly Abnormal Laboratory Values at the First Posttherapy Visit (Page 4 of 4)

Center	Patient No.	Race	Age, Sex	Weight (kg)	Parameter	Abnormal Value	Baseline Value	Normal Range	Comment
13	13	White	7, M	25.9	WBC	28.8 × 10^9/L	11.6	5-14.5	Failure Specimen transit time=46 hours; extensive leukocyte deterioration
13	16	White	9, F	33.4	Potassium	7.1 mEq/L	4.6	3.5-5.1	No history noted
13	22	White	11, F	47.3	Potassium	6.8 mEq/L	7.1	3.5-5.1	No history noted Specimen transit time=37 hours
13	23	White	9, F	29.1	Urine WBC	21-50 /HPF	1-5	1-5	Microbiological failure

WBC = White blood cells.

TABLE 20. Summary of Markedly Abnormal Laboratory Values More Abnormal at the First Posttherapy Visit Than at Baseline Excluding Site 5[a]

[Number (%) of Patients]

Parameter	Direction of Change	Cefdinir N = 211	Penicillin N = 214
Hematology			
Hematocrit	Decrease	0 (0.0)	1 (0.5)
Platelets	Increase	1 (0.5)	0 (0.0)
White Blood Cells	Decrease	1 (0.5)	0 (0.0)
	Increase	3 (1.4)	3 (1.4)
Polymorphonuclear Leukocytes	Decrease	0 (0.0)	0 (0.0)
	Increase	5 (2.4)[b]	3 (1.4)
Lymphocytes	Decrease	3 (1.4)	1 (0.5)
Eosinophils	Increase	0 (0.0)	0 (0.0)
Blood Chemistry			
Alkaline Phosphatase	Increase	2 (1.0)	2 (0.9)
Bilirubin	Increase	1 (0.5)	0 (0.0)
LDH	Increase	4 (1.9)	4 (1.9)
AST	Increase	1 (0.5)	0 (0.0)
Sodium	Decrease	1 (0.5)	0 (0.0)
Potassium	Increase	2 (1.0)	3 (1.4)
Total Protein	Increase	1 (0.5)	0 (0.0)
Phosphorus	Increase	2 (1.0)	0 (0.0)
Bicarbonate	Decrease	2 (1.0)	0 (0.0)
Urinalysis			
Urine Protein	Increase	2 (1.0)	3 (1.4)
WBCs	Increase	0 (0.0)	2 (0.9)
Specific Gravity	Increase	0 (0.0)	1 (0.5)
Any Parameter[c]		20 (9.5)	19 (8.9)

[a] This table does not include data from patients with markedly abnormal values at the STFU visit that were unchanged or improved relative to the baseline value. Does not include patients listed in Appendix E.22.

[b] One patient had no baseline value for comparison, but is included in this summary: in the cefdinir BID treatment group, Patient 44, Center 3, for PMNs

[c] Total number of patients in a treatment group experiencing a markedly abnormal laboratory parameter (more abnormal than at baseline) regardless of the laboratory parameter.

APPENDIX EP (EFFICACY PHARYNGITIS)

Protocol 51:

The table below presents the response rates and analysis results for the evaluable patient population, both including and excluding Site 14 (Iravani) based on the Sponsor's submission:

	Cefdinir QD	Cefdinir BID	Penicillin
Clinical Response Rates			
All Sites	97.6% (246/252)	96.4% (241/250)	86.8% (217/250)
Excluding Site 14	97.4% (222/228)	96.0% (218/227)	86.3% (196/227)
Microbiological Response by Patient			
All Sites	92.5% (233/252)	94.8% (237/250)	70.8% (177/250)
Excluding Site 14	94.3% (215/228)	94.3% (214/227)	70.0% (159/227)

	Cefdinir QD vs. Penicillin		Cefdinir BID vs. Penicillin	
	Unadjusted 95% CI	CMH p-value	Unadjusted 95% CI	CMH p-value
Clinical Response Rates				
All Sites	(6.2%, 15.4%)	<0.001	(4.8%, 14.4%)	<0.001
Excluding Site 14	(6.1%, 15.9%)	<0.001	(4.6%, 14.8%)	<0.001
Microbiological Response by Patient				
All Sites	(15.1%, 28.2%)	<0.001	(17.7%, 30.3%)	<0.001
Excluding Site 14	(17.6%, 30.9%)	<0.001	(17.5%, 30.9%)	<0.001

Excluding Site 14 had very little effect on response rates. Both cefdinir QD and cefdinir BID 1are still shown to be superior to penicillin for both clinical response rate and microbiological response by patient for the evaluable population.

Clinically Evaluable Patients

The table below presents the clinical response rates and analysis results for the clinically evaluable patient population, both including and excluding Site 14.

	Cefdinir QD	Cefdinir BID	Penicillin
Clinical Response Rates			
All Sites	97.3% (251/258)	96.5% (246/255)	86.2% (219/254)
Excluding Site 14	97.0% (226/233)	96.1% (222/231)	85.7% (198/231)

	Cefdinir QD vs. Penicillin		Cefdinir BID vs. Penicillin	
	Unadjusted 95% CI	CMH p-value	Unadjusted 95% CI	CMH p-value
All Sites	(6.4%, 15.7%)	<0.001	(5.4%, 15.1%)	<0.001
Excluding Site 14	(6.3%, 16.3%)	<0.001	(5.2%, 15.5%)	<0.001

Excluding Site 14 had very little effect on the clinical response rates. Both cefdinir QD and cefdinir BID are still shown to be superior to penicillin for the clinically evaluable population.

Protocol 56

Evaluable Patients

The table below presents the response rates and analysis results for the evaluable patient population, both including and excluding site 5 (Iravani).

	Cefdinir BID	Penicillin	Unadjusted 95% CI	CMH p-value
Clinical Response Rates				
All Sites	91.5% (205/224)	90.7% (196/216)	(-4.5%, 6.1%)	0.798
Excluding Site 5	91.3% (179/196)	89.6% (173/193)	(-4.1%, 7.5%)	0.567
Microbiological Response by Patient				
All Sites	89.7% (201/224)	71.8% (155/216)	(10.8%, 25.2%)	<0.001
Excluding Site 5	89.8% (176/196)	69.9% (135/193)	(12.1%, 27.6%)	<0.001

Excluding site 5 had very little effect on the response rates. Cefdinir is still shown to be equivalent to penicillin in clinical response rate, and superior to penicillin for microbiological response by patient, for the evaluable population.

Clinically Evaluable Patients

The table below presents the clinical response rates and analysis results for the clinically evaluable patient population, both including and excluding site 5.

	Cefdinir BID	Penicillin	Unadjusted 95% CI	CMH p-value
Clinical Response Rates				
All Sites	91.7% (209/228)	90.9% (200/220)	(-4.5%, 6.0%)	0.787
Excluding Site 5	91.5% (182/199)	89.7% (175/195)	(-4.1%, 7.5%)	0.552

Excluding site 5 had very little effect on the clinical response rates. Cefdinir and penicillin are still shown to be equivalent for the clinically evaluable population.

Statistical Reviewer's Comments: Based on the underlying sample sizes, recalculating confidence intervals, and incorporating Yates' Continuity Correction is not expected to result in considerably different inferences in either protocol 51 or 56.

APPEARS THIS WAY
ON ORIGINAL

PHARYNGITIS STUDIES FINAL CONCLUSIONS AND RECOMMENDATIONS:

The following tables summarize the efficacy findings of the studies evaluated for this pharyngitis NDA submission:

Indication	Study Number	Pathogen Eradication Rates (%)[a]			Clinical Cure Rates (%)[b]		
		Cefdinir QD	Cefdinir BID	Control Drug(s)	Cefdinir QD	Cefdinir BID	Control Drug(s)
Pharyngitis	983-7	91	92	83	95	96	89
	983-58	--	89	82	--	89	85
	983-51	93	95	71	98	96	87
	983-51 excludingIrivani	94	94	70	97	96	86
	983-56	--	90	72	--	92	91
	983-56 excluding Irivani		90	70		91	90

[a] Microbiologically evaluable patients.
[b] Microbiologically evaluable patients, except for otitis media and sinusitis studies, in which rates for clinically evaluable patients are used.

TABLE 52. Microbiologic and Clinical Outcomes - Microbiologically Evaluable Patients Pharyngitis Study 983-7

Parameter	Cefdinir QD		Cefdinir BID		Penicillin	
	n/N	%	n/N	%	n/N	%
S. pyogenes Eradication	192/210	91.4	199/217	91.7	181/217	83.4
Clinical Cure	199/210	94.8	209/217	96.3	193/217	88.9

TABLE 14. Summary of Efficacy Analyses at TOC-per applicant

Pairwise Comparison	Population	Rates (%)	95% CI	Interpretation
Microbiologic Eradication				
QD vs Penicillin	Evaluable*	91 vs 83	1.8, 14.3	QD Superior
	MITT	91 vs 84	1.5, 13.3	QD Superior
	ITT	70 vs 64	-2.1, 12.7	Equivalent
BID vs Penicillin	Evaluable*	92 vs 83	2.1, 14.5	BID Superior
	MITT	92 vs 84	2.1, 13.8	BID Superior
	ITT	71 vs 64	-0.9, 13.9	Equivalent
QD vs BID	Evaluable	91 vs 92	-5.5, 5.0	Equivalent
	MITT	91 vs 92	-5.5, 4.5	Equivalent
	ITT	70 vs 71	-8.5, 6.1	Equivalent
Clinical Response				
QD vs Penicillin	Evaluable	95 vs 89	0.7, 11.0	QD Superior
	Clinically Evaluable	91 vs 85	0.1, 11.3	QD Superior
	ITT	90 vs 85	-0.2, 10.2	QD at Least Equivalent
BID vs Penicillin	Evaluable	96 vs 89	2.5, 12.2	BID Superior
	Clinically Evaluable	93 vs 85	2.8, 13.5	BID Superior
	ITT	92 vs 85	1.6, 11.6	BID Superior
QD vs BID	Evaluable	95 vs 96	-5.5, 2.4	Equivalent
	Clinically Evaluable	91 vs 93	-7.1, 2.3	Equivalent
	ITT	90 vs 92	-6.2, 2.9	Equivalent

* Primary efficacy analysis

Table 53. Microbiologic and Clinical Outcomes-Microbiologically Evaluable Patients , Pharyngitis

Study 983-58

Parameter	Cefdinir			Penicillin	
	n/N	%	95%CI	n/N	%
S. pyogenes Eradication	193/218	88.5		176/214	82.2
Clinical Cure	194/218	89.0		181/214	84.6
MICRO			-.4,12.9		
CLIN			-2,10.8		

The table below presents the response rates and analysis results for the evaluable patient population, both including and excluding Site 14 (Iravani) . This is the FDA analysis with continuity correction.

Protocol 51:

Criteria	Cefdinir QD	Cefdinir BID	Penicillin	95% Confidence Interval (with continuity correction)
Clinical Efficacy				
All sites	246/252(97.6%)	241/250(96.4%)	217/250(86.8%)	Cefdinir QD vs Cefdinir BID $_{252,250}(-0.0216, 0.0459)_{97.6\%,96.4\%}$ Cefdinir QD vs Pen $_{252,250}(0.0582, 0.1582)_{97.6\%,86.8\%}$ Cefdinir BID vs Pen $_{250,250}(0.0441, 0.1479)_{96.4\%,86.8\%}$
Sites14 excluding Iravani	222/228(97.3%)	218/227(96%)	196/227(86.3%)	Cefdinir QID vs Cefdinir BID $_{228,227}(-0.0238, 0.0505)_{97.3\%,96\%}$ Cefdinir QID vs Penn $_{228,227}(0.0566, 0.1639)_{96\%,86.3\%}$ Cefdinir BID vs Penn $_{227,227}(0.0411, 0.1527)_{96\%,86.3\%}$
Microbiologic Eradication				
All sites	233/252(92.4%)	237/250(94.8%)	177/250(70.8%)	Cefdinir QD vs Cefdinir BID $_{252,250}(-0.0701, 0.0232)_{92.4\%,94.8\%}$ Cefdinir QD vs pen $_{252,250}(0.1475, 0.2857)_{92.4\%,70.8\%}$ Cefdinir BID vs Pen $_{250,2}50(0.1732, 0.3067)_{94.8\%,70.8\%}$

Criteria	Cefdinir QD	Cefdinir BID	Penicillin	95% Confidence Interval (with continuity correction)
Sites 14 excluding Iravani	215/228(94.3%)	214/227(94.3%)	159/227(70%)	Cefdinir QD vs Cefdinir BID $_{228,227}(-0.0468, 0.0473)_{94.3\%,\ 94.3\%}$ Cefdinir QD vs Pen $_{228,227}(0.1713, 0.3137)_{94.3\%,\ 70\%}$ Cefdinir BID vs Pen $_{227,227}(0.1711, 0.3135)_{94.3\%,70\%}$
Criteria	**Cefdinir QD**	**Cefdinir BID**	**Penicillin**	**95% Confidence Interval (with continuity correction)**
protocol 56 -Clinical Efficacy (all evaluable patients)				
All sites		205/224(91.5%)	196/216(90.7%)	$_{224,216}(-0.0499, 0.0655)_{91.5\%,90.7\%}$
Sites excluding Dr Iravani		179/196(91.3%)	173/193(89.6%)	$_{196,193}(-0.0465, 0.0804)_{91.3\%,89.6\%}$
Microbiologic Eradication				
All sites		201/224(89.7%)	155/216(71.7%)	$_{224,216}(0.1031, 0.2563)_{89.7\%,\ 71.7\%}$
Sites excluding Dr. Iravani		176/196(89.7%)	135/193(69.9%)	$_{196,193}(0.1160, 0.2809)_{89.7\%,\ 69.9\%}$
Clinical Efficacy (clinically evaluable patients)				
All sites		209/228(91.6%)	200/220(90.9%)	$_{228,220}(-0.0491, 0.0642)_{91.6\%,90.9\%}$
Sites excluding Dr Iravani		182/199(91.4%)	175/195(89.7%)	$_{199,195}(-0.0455, 0.0798)_{91.4\%,89.7\%}$

PROTOCOL 7

TABLE 17. Summary of Adverse Events - All Patients-Applicant
[Number (%) of Patients]
(Page 1 of 2)

	Cefdinir QD N = 305	Cefdinir BID N = 304	Penicillin N = 310
Adverse Events During Study			
All Adverse Events	169 (55.4)	157 (51.6)	140 (45.2)
Associated[a] Adverse Events	102 (33.4)	91 (29.9)	57 (18.4)

PROTOCOL 58

TABLE 13. Summary of Adverse Events - All Patients
[Number (%) of Patients]

	Cefdinir N = 278	Penicillin N = 280
Adverse Events During Study		
All Adverse Events	161 (57.9)	143 (51.1)
Associated[a] Adverse Events	61 (21.9)	47 (16.8)

PROTOCOL 51
adverse event rates and drug-associated adverse event rates, both including and excluding site 5

	Cefdinir QD	Cefdinir BID	Penicillin	Cef. QD vs Penicillin CMH p-value	Cef. BID vs Penicillin CMH p-value
All Adverse Events					
All Sites	41.2% (119/289)	44.6% (129/289)	37.9% (110/290)	0.393	0.087
Excluding Site 14	44.3% (117/264)	47.5% (125/263)	40.2% (106/264)	0.295	0.078
Drug-Associated Adverse Events					
All Sites	8.3% (24/289)	9.3% (27/289)	7.2% (21/290)	0.620	0.612
Excluding Site 14	8.7% (23/264)	10.3% (27/263)	8.0% (21/264)	0.727	0.364

PROTOCOL 56

The table below presents the adverse event rates and drug-associated adverse event rates, and the analysis results, for patients who took drug both including and excluding site 5.

	Cefdinir BID	Penicillin	CMH p-value
All Adverse Events			
All Sites	**38.3% (92/240)**	**33.1% (80/242)**	**0.212**
Excluding Site 5	**40.8% (86/211)**	**36.0% (77/214)**	**0.314**
Drug-Associated Adverse Events			
All Sites	**5.4% (13/240)**	**4.5% (11/242)**	**0.678**
Excluding Site 5	**6.2% (13/211)**	**5.4% (11/214)**	**0.678**

Medical Officer's Note: As reported adverse event rates were lower at Dr Iravani's site than the overall rate observed in the study, exclusion of data from his site resulted in increased adverse event rates in all treatment groups. Exclusion of data from Dr Iravani's site, however, did not alter analyses, showing that neither adverse event rates nor drug-associated adverse event rates were statistically significantly different between treatment groups at the p <0.05 level, for either study.

Medical Officer's FinalConclusions on Efficacy:

1. *Cefdinir, given as a 5-day (BID) capsule is eqivalent to penicillin in the eradication of GABHS from the throats of patients with streptococcal pharyngitis.*

- 5 day suspension or 10-day (QD or BID) regimen(capsule or suspension), more effective than penicillin in the eradication of GABHS from the throats of patients with streptococcal pharyngitis.

2. *Cefdinir, given as a 5-day (BID) regimen, is equivalent to penicillin in symptomatic relief in streptococcal pharyngitis*

-10-day (QD or BID) regimen is more effective than penicillin in symptomatic relief in streptococcal pharyngitis.

3. The 5-day regimen appears to give somewhat lower eradication rates than the 10-day regimen.

4.Cefdinir has not been studied for effectiveness in the prevention of rheumatic fever.

5. When Dr. Irivani's data was not included in the analysis for microbiologic and clinical efficacy, there was little effect on the outcome.

Medical Officer's Final Conclusions on Safety:

1.Cefdinir is well-tolerated.
2.Cefdinir appears to have a safety profile within the ranges reported for other recently approved

cephalosporins. Overall, the risk of adverse events during treatment with cefdinir is balanced by its clinical benefits.

3. When Dr. Irivani's data was not included in the analysis for safety (both the adverse event rates and drug-associated adverse event rates), there was very little effect on the adverse event rates).

Concur:

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cc:
Original NDA 50-739
Original NDA 50-749
HFD-520/Division Files
HFD-520/MO/R. Viraraghavan
HFD-40/DDMAC/J. Spearmon

NDA 50-739: Clinical and Statistical Review, Omnicef® (cefdinir axetil) for the treatment of acute otitis media

Reviewers' note: *The following review was performed, whenever possible, with the removal of data gathered by Dr. Robert Fiddes' and Dr. Abdollah Iravani's study sites. The data gathered by these study sites is believed to be unreliable.*

Indication: Acute Otitis Media (AOM)

Title and Study Number: Investigator-blinded, randomized, comparative, multicenter study of cefdinir versus amoxicillin/clavulanate in the treatment of AOM with effusion in pediatric patients (Protocol 983-10)

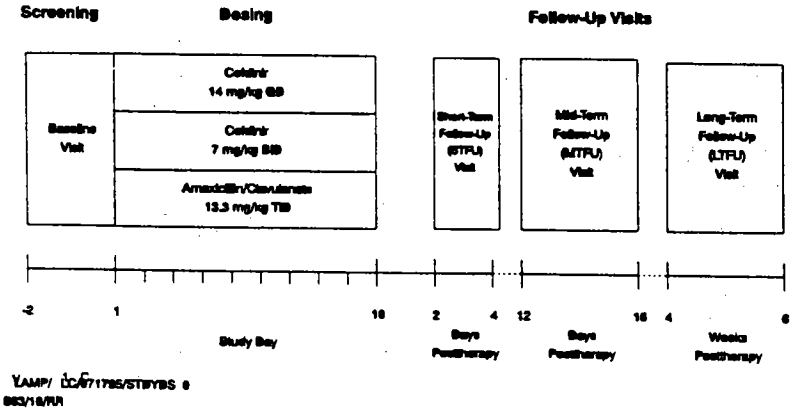
Objective: To compare the efficacy and safety of two 10-day dosage regimens of cefdinir suspension (14 mg/kg QD and 7 mg/kg BID) and one 10-day regimen of amoxicillin/clavulanate (Augmentin® at 13.3 mg/kg TID) in the treatment of pediatric patients with acute suppurative otitis media with effusion.

Reviewers' note: This selection of Augmentin as a comparator agent is an excellent choice -- this agent is widely used in the treatment of AOM because of successful use in this infection. It is well-recognized as having excellent activity agent the primary agents of AOM, Streptococcus pneumoniae, Haemophilus influenzae (including beta-lactamase producing strains) and Moraxella catarrhalis.

Study Design: This was an investigator-blinded, randomized, comparative, multicenter study with 3 parallel-treatment groups. An ear examination and clinical assessment were performed during the Days 3 to 5 interval of therapy. Patients who had not improved at this time discontinued treatment.

The protocol and case report forms specified that the mid-term follow-up (MTFU) visit be made 12 to 16 days posttherapy. However, many sites performed the MTFU visit beginning on Day 22. This was actually 11 days posttherapy for patients who started BID or TID treatment midday on Day 1 and therefore ended treatment on Day 11 instead of Day 10. For analysis purposes, the TOC window was widened to 11 to 16 days posttherapy and the long-term follow-up (LTFU) window to 27 to 42 days posttherapy to include these patient data.

Figure 1: Study Design



Procedure/Observation	Baseline[a]	Day 1	Days 3-5	Day 10 (End of Therapy)	Posttherapy		
					2-4 Days[b]	12-16 Days[c]	4-6 Weeks[d]
Medical History	X						
Physical Examination[e]	X				X	X	
Otoscopic Examination[e]	X		X		X	X	X
Tympanometry[e]	X		X		X	X	X
Tympanocentesis, Culture, and Susceptibility Testing[f]	X				X[g]	X[g]	X[g]
Clinical Assessment of Signs and Symptoms[e]	X		X		X	X	X
Adverse Event Monitoring[e]		X—					X
Clinical Laboratory Tests[e]	X				X	X[h]	X[i]
Study Drug Dosing		X—		X			

[a] Prior to treatment (within 48 hours)
[b] Short-term follow-up (STFU) visit
[c] Mid-term follow-up (MTFU) visit
[d] Long-term follow-up (LTFU) visit
[e] Also to be performed whenever therapy is discontinued early
[f] Performed only at selected study sites through January 14, 1993. Required for all study participants as of January 15, 1993 (see Amendment 2).
[g] For patients with baseline culture who do not show satisfactory clinical improvement
[h] Only if abnormalities were detected 2 to 4 days posttherapy
[i] Only if abnormalities were detected 12 to 16 days posttherapy

Table 1: Schedule of Clinical Observations and Laboratory Measurements

Methodology: After baseline screening, patients were randomized to receive cefdinir QD, cefdinir BID, or amoxicillin/clavulanate for 10 days. Patients returned for a short-term follow-up visit 2 to 4 days posttherapy, a mid-term follow-up visit 12 to 16 days posttherapy which served as the test-of-cure (TOC), and a long-term follow-up (LTFU) visit 4 to 6 weeks posttherapy. Results from ear examinations, tympanocentesis cultures, and clinical assessments were used to compare the efficacy of the treatments. Results from adverse event reporting, physical examinations, and clinical laboratory tests were used to compare the safety.

Reviewers' note: This study provided the microbiologic evidence required to support the indication of acute otitis media as required by DAIDP's Points-to-Consider Guidance document.

Patients and Inclusion/Exclusion Criteria: Patients were boys and girls aged from 6 months to 12 years, who had acute suppurative otitis media with effusion for less than one week. Patients needed to have erythema of the tympanic membrane and middle ear effusion, supported by tympanometry, in at least one ear. Postmenarch girls were required to have a negative pregnancy test prior to drug administration.

Medical officer's note: The inclusion criteria are not particularly stringent and are really minimal clinical findings for a diagnosis of AOM. For this study to provide sufficient evidence in support of the indication of AOM, it must demonstrate that subjects enrolled must, on average, possess signs and symptoms enough to support a diagnosis of AOM consistent with a bacterial etiology. Multiple other signs and symptoms were recorded and followed among those enrolled, but did not constitute entry criteria. Some of these were incorporated into assessment which determined outcome.

Patients were to be excluded from participating in the study for any of the following reasons:

- Subacute or chronic otitis media, acute exacerbations of chronic otitis media, or chronic middle ear effusion;
- A ventilation tube or perforated tympanic membrane in either ear at baseline;
- Diseases, complicating factors (eg, mastoiditis), or structural abnormalities that would confound evaluation of the therapeutic response;
- Hepatic disease, obstruction of the biliary tract, or baseline bilirubin or hepatic enzyme levels (AST, ALT) >2 times the upper limit of normal;
- Baseline serum creatinine >1.5 times the upper limit of normal;

- Hypersensitivity to ß-lactams (including penicillins and cephalosporins);
- Receipt of another systemic antibacterial agent within 7 days of study start;
- Use of a topical aural antibacterial within 2 days of study start;
- A baseline pathogen known to be resistant to cefdinir or amox/clav prior to randomization;
- Concomitant infections requiring systemic antibacterial therapy;
- Receipt of any other investigational compound within 4 weeks of study entry;
- Prior participation in this or any other cefdinir study;
- Iron supplements, including iron-containing multivitamins, required. Patients were allowed to participate in this study if they abstained from iron-containing products for the duration of therapy;
- Concomitant decongestant therapy required. Patients receiving decongestants at baseline were allowed to enter the study provided that they did not receive decongestants at any time during the study, including the follow-up period.

Reviewers' note: The first 3 exclusion criteria are unique to this indication. Current DAIDP's current Evaluability Criteria do not require that patients with "perforated eardrums..., recurrent episodes or chronic episodes" but that such patients should be enrolled with subset analysis planned. Almost no patients with such conditions were enrolled and little can be said about anything but those with fairly uncomplicated AOM. This will be considered later in this review. This application only seeks approval for AOM and does not seek approval for related conditions or highly resistant organisms such as penicillin resistant Streptococcus pneumoniae. Any labeling applied to this indication must reflect this.

The last 11 exclusion criteria are common to other indications in the application and some are generated by concerns relevant to cefdinir and some to cephalosporins as a class. Labeling will reflect any issues generated by these findings in its safety subsections.

Withdrawal from the study was allowed if: (1) a baseline pathogen resistant to both study drugs was isolated, (2) the patient had spontaneous perforation of the tympanic membrane, or (3) they required additional/other antibacterials for their otitis media. At the investigator's discretion, patients also could be withdrawn because of insufficient efficacy, an adverse event, a laboratory abnormality, or lack of cooperation.

Reviewers' note: If patients required additional antimicrobial therapy or condition worsened or did not cure on therapy causing the investigator to withdraw the patient, the patient was carried through as a failure. Patients who had assessments done early or had insufficient treatment duration became failures.

Evaluability Criteria: Four populations were analyzed: (1) clinically evaluable, (2) microbiologically-clinically (strictly evaluable), (3) an intent-to-treat (ITT) and (4) a modified intent-to-treat (MITT).

Evaluable populations for these analyses are had the following criteria:

Clinically evaluable
- clinical assessment of at least minimal required signs and symptoms complete and within predetermined range
- study medication taken as prescribed (80% of course completed)
- susceptible baseline pathogen
- no concurrent systemic antibacterial therapy and no systemic antibacterial within 7 days prior to the first dose of study medication
- did not have an intentional randomization violation

Strictly evaluable
- being clinically evaluable plus having a proven baseline pathogen
- off-schedule cultures

Reviewers' note: The criteria are acceptable provided (as stated elsewhere in the Sponsor's report and supported by review of data) that all early failures who required other antimicrobial therapy or had an off-schedule culture because of early failure are carried forward to TOC as failures.

MITT

- patients who had the correct indication
- received study medication
- had at least 1 baseline pathogen, and had a follow-up culture or a follow-up clinical assessment of signs and symptoms.

ITT

- all patients who were randomized to treatment

Included in the ITT population are patients who had no baseline tympanocentesis, no baseline pathogen, or no follow-up culture and no follow-up clinical assessment. These patients were considered to have microbiologic persistence in the ITT summaries and analyses. Patients who had no follow-up clinical assessment were categorized as clinical failures in the ITT summaries and analyses.

Reviewers' note: *Such a stringent analysis of the ITT population allows for a worst case scenario and is appropriate. Unfortunately, it is not particularly sensitive given that the outcome is demonstration of therapeutic equivalence.*

Endpoints: The measures of efficacy were clinical cure rate by patient and microbiologic eradication rate by patient and pathogen in the clinically evaluable, microbiologically-clinically (i.e., strictly) evaluable, modified intent-to-treat, and intent-to-treat populations.

The primary outcome measure was the clinical cure rate in clinically evaluable patients at the test-of-cure (TOC) visit which occurred 11 to 16 days posttherapy. See figure one above. Secondary outcome measures were the microbiologic eradication rate by pathogen and the microbiologic eradication rate by patient. The primary end point was the TOC visit; the LTFU visit was a secondary end point. Data from the LTFU visit were summarized and presented as supporting information. No statistical analyses of LTFU data were done.

Most microbiologic eradication rates were presumed from clinical responses. Superinfection and reinfection also were examined.

The measures of safety were adverse event data (occurrence, intensity, relationship to study drug, frequency, duration, management of study medication, and patient outcome), and the results from physical examinations and clinical laboratory tests (hematology, chemistry, urinalysis) in all patients randomized to treatment who received drug. Assessments of clinical and microbiologic responses at the TOC visit, 11 to 16 days posttherapy, were used to evaluate the efficacy of cefdinir QD, cefdinir BID, and amox/clav. The LTFU visit, 27 to 42 days posttherapy, provided information on recurrence of infection.

The patient clinical signs and symptoms used in determining clinical response in this study were: otalgia, irritability, anorexia, lethargy, decreased hearing, vertigo, and fever. In infants and young children, in whom some signs and symptoms were difficult to assess, otalgia could be expressed as ear pulling, decreased hearing could be based on the guardian's report, and vertigo could be expressed by stumbling, falling, or clumsiness. Based on the judgment of the investigator, the severity of all these signs and symptoms, except fever, were graded as Absent, Mild, Moderate, or Severe (0, 1, 2, or 3, respectively). Body temperature was recorded by the investigator and the presence of fever was determined by the Sponsor using an objective temperature guideline (see table below); the absence of fever was graded as 0 and the presence as 1.

Table 2. Determination of Presence of Fever

Method of Measurement	Fever	
	°F	°C
Oral	≥100.4	≥38.0
Axillary	≥99.1	≥37.3
Rectal	≥102.0	≥38.9
Aural	≥100.0	≥37.8

A total patient clinical signs and symptoms score for use by the Sponsor was obtained by the following method. Symptom severity scores for otalgia, irritability, anorexia, lethargy, decreased hearing, vertigo, and fever were each weighted (ie, multiplied) by a factor of 1. The resulting values were summed across all symptoms to provide a total patient clinical score which could range from 0 through 19 at baseline, TOC, or LTFU.

***Reviewers' note**: The scoring system appears to be a fair method by which to summarize outcomes, but the medical officer will review each category to assure that resolution occurred, patients were adequately symptomatic and that any single finding did not carry the entire weight of the score. It is unfortunate that temperature was treated as a binary finding with a low score: though not specific it is an excellent marker of illness in the subjects of interest. In addition, the sponsor makes no mention of reporting use of antipyretics prior to evaluation for entry. Valuable information which would be useful in validating the study has been lost.*

The otoscopic examination of each ear assessed the following: erythema of the tympanic membrane, evidence of middle ear effusion, loss of landmarks (opacity of tympanic membrane), loss of light reflex of tympanic membrane, bulging of tympanic membrane, drainage, perforation of tympanic membrane, and tympanic membrane movement. Tympanometry was done on each ear to confirm the presence or absence of middle ear effusion.

The ear signs and symptoms used in determining clinical response in this study were: erythema of the tympanic membrane, loss of landmarks, loss of light reflex of tympanic membrane, bulging of the tympanic membrane, and drainage. Based on the judgment of the investigator, erythema of the tympanic membrane was graded as Absent, Mild, Moderate, or Severe (0, 1, 2, or 3, respectively); loss of landmarks and loss of light reflex as No or Yes (0 or 1, respectively); and bulging of tympanic membrane and drainage as Absent or Present (0 or 1, respectively).

For each ear, a total ear clinical signs and symptoms score for use by the Sponsor was obtained by the following method. The symptom severity score for erythema of the tympanic membrane was weighted by a factor of 1; all of the other ear symptom severity scores were weighted by a factor of 2. The resulting values were summed across all ear symptoms to provide a total ear clinical score for each ear which could range from 0 through 11 at baseline and 0 through 11 at TOC and LTFU. The total ear clinical score was expected to equal at least 1 in either the left or right ear at baseline because erythema of the tympanic membrane in at least 1 ear was an inclusion criterion.

The calculated total patient and ear scores were used in determining the Sponsor assessment of clinical response.

***Reviewers' note**: The scoring system may be a fair method by which to summarize findings at enrollment and outcomes, but the medical officer will review each category to assure that resolution occurred and was satisfactory. A cure should be document resolution of signs, symptoms and findings. A residual finding of effusion is allowable. All outcomes but erythema are binary (ie, either present or absent). Erythema is graded as mild, moderate or severe -- it is not clear to this reviewer how investigators interpreted erythema for assignment.*

Sponsor's Assessment of Clinical Response at TOC:

- **Cure:** (≥50% decrease in patient clinical score at TOC relative to baseline) and (≥50% decrease in left ear clinical score at TOC relative to baseline [if baseline left ear score >0]) and (≥50% decrease in right ear clinical score at TOC relative to baseline [if baseline right ear score >0]);
- **Failure:** <50% decrease in the patient clinical score or either ear clinical score at TOC relative to baseline; or
- **Not Assessable:** No baseline signs and symptoms or no follow-up data.

Sponsor's Assessment of Clinical Response at LTFU:

- **Cure:** (Cure at TOC) and (≥50% decrease in patient clinical score at LTFU relative to baseline) and (≥50% decrease in left ear clinical score at LTFU relative to baseline [if baseline left ear score >0]) and (≥50% decrease in right ear clinical score at LTFU relative to baseline [if baseline right ear score >0]) and (no increase of more than 1 point in any clinical score at LTFU relative to TOC);
- **Recurrence:** (Cure at TOC) and ([≥2-point increase in patient clinical score or either ear clinical score at LTFU relative to TOC] or [<50% decrease in the patient clinical score or either ear clinical score at LTFU relative to baseline]);
- **Failure:** Clinical failure at TOC; or
- **Not Assessable:** No baseline signs and symptoms or no follow-up data.

Reviewers' note: There are limitations to this system as outlined. It will be reviewed and acceptable provided that the final score represents a cure: resolution of signs and symptoms with allowable residual effusion.

Investigator's Assessment of Clinical Response at TOC:

- **Cure:** Absence of all patient/ear clinical signs and symptoms (excluding presence of residual effusion);
- **Improvement:** Satisfactory remission but not complete absence of patient/ear clinical signs and symptoms;
- **Failure:** No significant remission of patient/ear clinical signs and symptoms; or
- **Not Assessable:** Unable to assess patient (no data).

Investigator's Assessment of Clinical Response at LTFU:

- **Cure:** Absence of all patient/ear clinical signs and symptoms (excluding presence of residual effusion);
- **Improvement:** Satisfactory remission but not complete absence of patient/ear clinical signs and symptoms;
- **Recurrence:** Worsening of patient/ear clinical signs and symptoms since previous visit; or
- **Not Assessable:** Unable to assess patient (no data).

Reviewers' note: The category of improvement is problematic. It is not clear whether this should be assigned cure or failure at TOC. Other aspects of the patient's course may be more valid is assigning such patients to an outcome category (for instance, did the patient require additional antimicrobial therapy at a later date, etc.)

Because the investigator assessment had been intended as the primary clinical response measure, it became necessary to devise a set of rules by which the investigator assessment of Improvement could be reclassified. This was accomplished by generating a Combined Investigator/Sponsor Clinical Assessment (Table 4). For the TOC visit, investigator assessments of Improvement were reclassified as either Cure, Failure, or Not Assessable in agreement with the Sponsor assessment. If the investigator clinical assessment at TOC was Not Assessable and quantitative clinical signs and symptoms data had been collected, the patient also was reclassified according to the Sponsor assessment. Investigator assessments of Cure and Failure were retained regardless of Sponsor assessment.

The combined assessment at the LTFU visit depended not only on the individual assessments at LTFU, but also on the combined assessment at the TOC visit. For patients with a combined assessment of Cure at TOC, the rules for the combined assessment at LTFU were analogous to those at the TOC visit: the investigator assessments of Cure and Recurrence took precedence over the Sponsor assessment, whereas investigator assessments of Improvement or Not Assessable were reclassified according to the Sponsor assessment (see table below). In contrast, patients with a combined assessment of Failure at the TOC visit were considered failures on the combined assessment scale at the LTFU visit, regardless of investigator determination. (Patients assessed as failures by the Sponsor at the TOC visit were automatically failures on the Sponsor assessment scale at the LTFU visit.).

Table 3. Rules for Determining the Combined Investigator/Sponsor Clinical Assessment at TOC and LTFU[a,b]

	Investigator Assessment at TOC			
Sponsor Assessment at TOC	Cure	Improvement	Failure	Not Assessable
Cure	**Cure**	**Cure**	**Failure**	**Cure**
Failure	**Cure**	**Failure**	**Failure**	**Failure**
Not Assessable	**Cure**	**Not Assessable**	**Failure**	**Not Assessable**

	Investigator Assessment at LTFU			
Sponsor Assessment at LTFU	Cure	Improvement	Recurrence	Not Assessable
Cure	**Cure**	**Cure**	**Recurrence**	**Cure**
Failure	**Cure**	**Failure**	**Recurrence**	**Failure**
Recurrence	**Cure**	**Recurrence**	**Recurrence**	**Recurrence**
Not Assessable	**Cure**	**Not Assessable**	**Recurrence**	**Not Assessable**

[a] The combined assessments are shown in bold typeface.

[b] Note: If a patient had a combined clinical assessment of Failure at the TOC visit, the patient was automatically a Failure on the combined assessment scale at the LTFU visit.

The resulting combined clinical assessment was selected as the primary measure of clinical response in this study. The clinical cure rate was the percentage of patients rated as cured on the combined assessment scale. Each patient provided one observation. Clinical cure rates were calculated separately for the TOC and LTFU visit data.

Reviewers' note: This begs an analysis of worse possible scenario: all improveds by investigator become failures, and all not assessable also become failures. If this analysis holds up and demonstrates equivalence, it suggests a certain robustness to the equivalence findings despite problems discussed above.

Microbiologic Response by Pathogen: If a middle ear effusion specimen was collected at baseline, the microbiologic response of each baseline pathogen was determined at the TOC and LTFU visits based on the results of follow-up culture(s) from the same ear or, if no follow-up cultures were done, from the results of patient and ear clinical assessments.

If a patient's ear showed erythema of the tympanic membrane, loss of landmarks, loss of light reflex, bulging of the tympanic membrane, effusion/fluid, drainage, perforation, or tympanic membrane movement at baseline, the Sponsor considered that ear to be affected. At the TOC and LTFU visits, the clinical response of each ear was classified as:

- **Ear Cure**: (Ear affected at baseline) and (Patient is a Cure at the follow-up visit) or (Patient is not cured but ear is not affected at the follow-up visit);
- **Ear Failure**: (Ear affected at baseline) and (Patient is not cured and ear is still affected at the follow-up visit); or
- **Ear Not Assessable**: (Ear not affected at baseline) or (Ear affected at baseline and no follow-up clinical assessment data).

The microbiologic response of each baseline pathogen was then classified at the TOC and LTFU visits as:

- **Eradication**: (Pathogen not present in follow-up culture from baseline ear) or (No follow-up culture performed from baseline ear and Ear Cure at the follow-up visit—presumed eradication);
- **Persistence**: (Pathogen present in follow-up culture from baseline ear) or (No follow-up culture performed from baseline ear and Ear Failure at the follow-up visit—presumed persistence); or
- **Not Assessable**: (No proven baseline pathogen) or (Ear not assessable).

The microbiologic eradication rate by pathogen was the percentage of eradicated baseline pathogens. Patients with multiple pathogens (including the isolation of the same species from both ears) provided multiple observations in the analyses of microbiologic efficacy on a per pathogen basis. The microbiologic eradication rate by pathogen was calculated separately for the TOC and LTFU visit data. Patients without baseline pathogens could become superinfected or reinfected.

Reviewers' note: This reviewer agrees with the above assignments provided that patients with multiple pathogens were graded as such: (1) Same organism in both ears counts as only one pathogen; and (2) Different pathogens, whether in the same ear or different ears, counted as distinct pathogens.

Microbiologic Response by Patient: If a patient had a positive baseline culture, the patient was classified by his/her overall microbiologic response at the TOC visit as:

- **Patient With Eradication**: (TOC culture shows absence of all baseline pathogens) or (No TOC culture performed and all baseline pathogens have presumed eradication at TOC);
- **Patient With Persistence**: (TOC culture shows presence of at least 1 baseline pathogen) or (No TOC culture performed and at least 1 baseline pathogen has presumed persistence at TOC); or
- **Not Assessable**: (No proven baseline pathogen) or (No baseline signs/symptoms) or (No follow-up clinical data).

If a patient had a positive baseline culture, the patient was classified by his/her overall microbiologic response at the LTFU visit as:

- **No Relapse**: (Patient With Eradication at TOC) and (Continued eradication or presumed eradication of all baseline pathogens at LTFU)
- **Relapse**: (Patient With Eradication at TOC) and (Persistence or presumed persistence of at least 1 baseline pathogen at LTFU)
- **Patient With Persistence**: Patient With Persistence at TOC; or
- **Not Assessable**: (No proven baseline pathogen) or (No baseline signs/symptoms) or (No follow-up clinical data).

The microbiologic eradication rate by patient was the percentage of patients with eradication of all baseline pathogens. Each patient provided only 1 observation. The microbiologic eradication rate by patient was calculated separately for the TOC and LTFU visit data.

Reviewers' note: This is acceptable and very similar to clinical cure outcome.

Appearance of New Pathogens: For patients with a baseline culture, the appearance of a new pathogen (causing infection) during and following therapy was classified as:

- **Superinfection:** (Appearance of a nonbaseline pathogen in any culture up to completion of study drug, defined for practical purposes as up to and including TOC) and (<50% decrease in the patient clinical score or either ear clinical score at the corresponding clinical assessment of signs and symptoms relative to baseline). In addition, all superinfections were reviewed by the Sponsor. Appearance of a new pathogen in any culture through TOC and a worsening of the clinical score relative to the previous visit also denoted superinfection; or
- **Reinfection:** (Appearance of a new pathogen—not appearing at any prior visit—in the LTFU culture) + (Classified clinically as Recurrence at LTFU).

If a patient had a new organism(s) isolated in any postbaseline culture, but had no corresponding clinical assessment of signs and symptoms, the determination of pathogenicity was made by the Sponsor.

Reviewers' note: Although not possible to statistically analyze these outcomes, the appearance of new pathogens is of critical importance and one would not expect to see differences in treatment arms.

Statistical Methods: Two methods were used to estimate clinical cure rates and their standard errors. The first method used pooled estimates, giving equal weight to each patient in the analysis. The second method used a categorical modeling procedure to obtain center-adjusted estimates, giving equal weight to each study center in the analysis. Two-tailed 95% confidence intervals were constructed from pairwise differences in these parameter estimates (cefdinir QD minus amox/clav, cefdinir BID minus amox/clav, and cefdinir QD minus cefdinir BID) using a standard normal approximation. The resulting confidence interval for each pairwise difference was compared to previously defined fixed criteria for evaluating treatment equivalence at TOC. A Cochran-Mantel-Haenszel (CMH) analysis compared clinical cure rates between treatments and the Breslow-Day method checked for treatment-by-center interaction. Descriptive statistics were calculated for microbiological data at TOC and for all efficacy data at LTFU; no statistical testing was performed on these data. Safety data were summarized for all patients who received study medications. A CMH analysis, adjusting for center, was used to compare treatment discontinuation rates due to adverse events, overall adverse event and associated adverse event rates, and incidence of diarrhea.

***Reviewers' note**: Pooled estimates, not center-adjusted estimates, are the method of analysis preferred by us. Two-tailed 95% confidence intervals about the difference in treatment arms are the main measure of interest. CMH analysis will carry no weight here; it may show equivalence among treatment arms when the two-tailed 95% CI does not. Descriptive statistics are of critical for outcomes that are not powered for statistical significance. Unfortunately, one can do little more for these than get a sense of the data.*

Table 4. List of Investigators

Center	Investigator(s)	Number of Patients			
		Randomized to Treatment	Completed Treatment	Clinically Evaluable	Strictly Evaluable
1	R. Paster	21	21	19	0
2	C. Khurana	60	59	57	0
3	**A. Iravani**	**131**	**117**	**120**	**42**
4	J. Hedrick	95	85	79	48
5	W. Gooch	25	21	20	0
6	S. Wiederhold	49	45	44	13
7	S. Chartrand	28	27	22	15
8	J. McCarty	170	143	140	57
9	E. Rothstein, H. Bernstein	34	33	32	0
10	J. Haddad	65	50	41	15
11	**R. Fiddes**	**60**	**55**	**50**	**8**
12	S. McLinn	81	78	63	35
13	G. Aronovitz	33	33	25	14
Total		852	767	712	247

***Reviewers' note**: The Table above demonstrates significant problems given the large numbers, particularly those microbiologically ("strictly") evaluable enrolled by a few investigators. It is also extremely unfortunate that data obtained from the two investigators above appearing in boldface had to be removed from analysis based on a recommendation from the FDA's Office of Compliance. After investigation, it was believed the data was not reliable. Thus, 50 strictly evaluable patients out of a total of 247 were lost for efficacy and safety analysis and 120 clinically evaluable patients out of 712 were lost to efficacy and safety analysis. This is an enormous loss. Quantitatively, the number of organisms available for evaluation is reduced by about 20%. The loss of 17% of the clinical sample is worrisome for the loss of power -- the confidence interval will no doubt be wider. However, because subsets as specific and small as particular microorganisms are not a feature of clinical outcome analysis, it may still be possible to demonstrate equivalence.*

Safety: The safety of cefdinir was assessed using adverse event data and the results from physical examinations and clinical laboratory tests. All patients randomized to treatment who received drug were evaluated for safety.

***Reviewers' note**: For a summary of how adverse events were recorded and analyzed, see Medical officer's review of CAP.*

Sample Size: This investigator-blinded, comparative study of cefdinir versus amox/clav was designed with a planned sample size of 190 clinically evaluable patients per randomized group. The sample size was designed to provide at least 80% probability (power) of having a "successful" study assuming an overall response rate of 90% and an equivalence threshold of ±10%.

***Reviewers' note**: Unfortunately, the observed response rate was less than anticipated by this optimistic estimate. However, review of other Medical officer reviews provides that the response rates found in this study is not unlike those found in previous studies. The IDSA Guidelines on Acute Otitis Media states only the following:*

"It is expected that an effective agent will sterilize middle-ear fluid of bacterial pathogens in >80% of infected ears within 72 hours" and that a Phase II study should demonstrate a favorable response with a "clinical and microbiologic response rate of ≥80%" to support launching a phase III study (pp. S70 and S71). In addition, the Division's Points to Consider (p. 39) does not provide any guidance on this issue; it merely states that the indication of AOM suggests one statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved agent.

Thus, no absolute level is predetermined. The IDSA Guidelines do state, however, "The control drug chosen for a clinical trial should be among the most effective and safe agents available for treatment" (p. S70). Amoxicillin-clavulanate is a widely endorsed and accepted as a highly effective treatment for AOM. Thus, this reviewer believes demonstration of equivalence or superiority to the comparator arm is the most important criteria in this clinical trial and not a predetermined cure rate.

The following table delineates the confidence intervals necessary to demonstrate equivalence given different maximum estimated response rates:

Table 5: Fixed Criteria for Evaluating Treatment Equivalence

Maximum Estimated Response Rate	Treatments are Equivalent if 95% Confidence Interval for Treatment Difference Is Within Bounds
90% or greater	-10%, +10%
80%-89%	-15%, +15%
70%-79%	-20%, +20%

Results

Demographic Information: Demographic information for all patients randomized to treatment (N = 852), the clinically evaluable patient population (N = 712), and the strictly evaluable patient population (N = 247) is presented, by treatment group in the following tables. Patients were similarly distributed across the 3 treatment groups by sex, race, and age in all populations studied with the following exceptions. In the all patient and clinically evaluable patient populations, greater percentages of patients <2 years received cefdinir QD or BID than received amox/clav and greater percentages of patients 2 to <6 years received amox/clav than received either cefdinir regimen. In the strictly evaluable population, greater percentages of patients <2 years received cefdinir QD than received either cefdinir BID or amox/clav and greater percentages of patients 2 to <6 years received amox/clav than received either cefdinir regimen.

The baseline characteristics of the clinically evaluable patients were similar to those of all patients randomized to treatment. The baseline characteristics of the strictly evaluable patients were similar to those of all patients randomized to treatment, except that in the strictly evaluable population a greater percentage of patients were white and the median age was lower for the total of all treatment groups combined.

Table 6. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir QD N = 218	Cefdinir BID N = 221	Amox/Clav N = 222	Total N = 661
Sex				
Male	119 (54.6)	123 (55.7)	118 (53.2)	360 (54.5)
Female	99 (45.4)	98 (44.3)	104 (46.8)	301 (45.5)
Race				
White	127 (58.3)	130 (58.8)	146 (65.8)	403 (61.0)
Black	27 (12.4)	20 (9.0)	16 (7.2)	63 (9.5)
Asian	1 (0.5)	5 (2.3)	5 (2.3)	11 (1.7)
Other	63 (28.9)	66 (29.9)	55 (24.8)	184 (27.8)
Age, yr				
Median	2.3	2.2	2.9	
Range	<1-13	1-13	1-13	<1-13
Distribution				
<2	101 (46.3)	104 (47.1)	86 (38.7)	291 (44.0)
2 to <6	77 (35.3)	71 (32.1)	83 (37.4)	231 (34.9)
6 to <13	40 (18.3)	46 (20.8)	53 (23.9)	208 (24.4)
Temperature, °C				
Median	37.3	37.3	37.3	37.3

Table 7. Patient Characteristics - Clinically Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir QD N = 181	Cefdinir BID N = 183	Amox/Clav N = 178	Total N = 542
Sex				
Male	99 54.7	106 57.9	99 55.6	304 56.1
Female	82 45.3	77 42.1	79 44.4	238 43.9
Race				
White	108 59.7	111 60.7	122 68.5	341 62.9
Black	19 10.5	17 9.3	14 7.9	50 9.2
Asian	1 0.6	5 2.7	5 2.8	11 2.0
Other	53 29.3	50 27.3	37 20.8	140 25.8
Age, yr				
Median	2.6	2.4	3.2	2.7
Range	<1 - 13	1 - 12	1 - 13	<1 - 13
Distribution				
<2	77 42.5	82 44.8	61 34.3	220 40.6
2 to <6	67 37.0	61 33.3	74 41.6	202 37.3
6 to <13	37 20.4	40 21.9	43 24.2	120 22.1
Temperature, °C				
Median	37.3	37.3	37.3	37.3

Table 8. Patient Characteristics - Strictly Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir QD N = 65	Cefdinir BID N = 66	Amox/Clav N = 66	Total N = 197
Sex				
Male	33 (50.8)	42 (63.6)	34 (51.5)	109 (55.3)
Female	32 (49.2)	24 (36.4)	32 (48.5)	88 (44.7)
Race				
White	44 (67.7)	45 (68.2)	50 (75.8)	139 (70.6)
Black	7 (10.8)	5 (7.6)	3 (4.5)	15 (7.6)
Other	14 (21.5)	16 (24.2)	13 (19.7)	43 (21.8)
Age, yr				
Median	1.4	1.9	2.3	1.9
Range	0.4-11.0	0.6-11.3	0.5-10.7	0.4-11.3
Distribution				
<2	40 (61.5)	33 (50.0)	30 (45.5)	103 (52.3)
2 to <6	17 (26.2)	24 (36.4)	24 (36.4)	65 (33.0)
6 to <13	8 (12.3)	9 (13.6)	12 (18.2)	29 (14.7)
Temperature, °C				
Median	37.3	37.4	37.2	37.4

Reviewers' note: *It is unfortunate that treatment arms are not balanced better respect to age. However, nothing can be done to correct this finding post hoc.*

Clinical Signs and Symptoms, Distribution at Enrollment: This data includes patients from Fiddes' and Iravani's sites.

Table 9. Mean Patient Clinical Scores at Baseline - All, Clinically Evaluable, and Strictly Evaluable Patients (includes Fiddes' and Iravani's sites)

Patient Population	Cefdinir		Amox/Clav
	QD	BID	
All Patients	5.4	5.3	5.1
Clinically Evaluable Patients	5.4	5.2	5.1
Strictly Evaluable Patients	6.3	5.7	5.5

Reviewers' note: The scores are close, but the reviewers have two comments (1) the enrolled subjects are not particulary symptomatic or ill; and (2) this distribution is slightly unfavorable for cefdinir, especially the QD regimen.

Ear: The ear clinical signs and symptoms used in the sponsor assessment of clinical cure were erythema of tympanic membrane, loss of light reflex, loss of landmarks, bulging of the tympanic membrane, and drainage. The other ear clinical signs and symptoms assessed (ie, effusion/fluid, perforation, tympanic membrane movement) contributed only to the assessment of microbiologic eradication for patients with baseline tympanocentesis who did not have follow-up cultures. In general, the presence and severity of ear clinical signs and symptoms at baseline were similar among the 3 treatment groups in all populations studied.

Table 10 . Mean Ear Clinical Scores at Baseline - All, Clinically Evaluable, and Strictly Evaluable Patients (includes Fiddes' and Iravani's site)

Ear/Patient Population	Cefdinir		Amox/Clav
	QD	BID	
Left Ear			
All Patients	5.5	5.1	5.2
Clinically Evaluable Patients	5.4	5.1	5.3
Strictly Evaluable Patients	5.9	5.6	5.3
Right Ear			
All Patients	5.3	5.4	5.2
Clinically Evaluable Patients	5.3	5.3	5.2
Strictly Evaluable Patients	5.5	5.9	6.0

Reviewers' note: This distribution is fairly evenly distributed by treatment arms. Once again, this population does not appear to be particularly ill.

Duration of therapy:

Table 11. Patient Exposure to Study Medication - All Patients, including those from Fiddes' and Iravani's sites

Days on Study Medication[a]	Cefdinir QD N = 280	Cefdinir BID N = 285	Amox/Clav N = 287
1	5	1	1
2	2	2	3
3	2	0	1
4	1	3	2
5	6	0	4
6	2	0	0
7	0	1	1
8	1	2	3
9	3	8	3
10	212	166	88
11	30	91	160
12	5	5	6
13	2	1	5
14	1	1	0
15	0	0	3
16	0	0	1
Median	10	10	11
Unknown	8	4	6

[a] In this table, days on study medication were determined from the dates of first and last dose recorded on the Medication Record (Case Report Form 13).

***Reviewers' note:** This distribution is as expected.*

Table 12. Patient Disposition - All Patients, includes patients from Fiddes' and Iravani's sites [Number (%) of Patients]

Patient Disposition	Cefdinir QD	Cefdinir BID	Amox/Clav	Total
Randomized to Treatment	280	285	287	852
Discontinued Treatment				
Lack of Compliance With the Protocol	8 (2.9)	7 (2.5)	11 (3.8)	26 (3.1)
Adverse Event	8 (2.9)	6 (2.1)	7 (2.4)	21 (2.5)
Other/Administrative	6 (2.1)	7 (2.5)	6 (2.1)	19 (2.2)
Failure at End of Therapy	8 (2.9)	5 (1.8)	6 (2.1)	19 (2.2)
Completed Treatment	250 (89.3)	260 (91.2)	257 (89.5)	767 (90.0)

***Reviewers' note:** Only a small number of patients discontinued treatment, even if one created a worst case scenario with those enrolled by Fiddes and Iravani. Thus, the therapies were well tolerated in all treatment arms.*

Results

Exclusions: See table below. Patients who were excluded from the clinically evaluable analyses were automatically also excluded from the strictly evaluable analyses.

Table 13 . Reasons Patients Were Excluded From Clinically Evaluable and Strictly Evaluable Analyses at TOC, including those enrolled by Fiddes and Iravani (Number of Patients)

	Cefdinir		Amox/Clav
	QD	BID	
Reasons Patients Were Excluded From Clinically Evaluable Analyses[a]			
Clinical Assessment of Signs and Symptoms Missed	10	4	7
Clinical Assessment of Signs and Symptoms Out of Time Range[b]	23	27	33
Concurrent Antibacterial[b]	2	1	1
Medication Not As Prescribed[b]	19	9	16
Prior Antibacterial	1	2	1
Resistant Baseline Pathogen(s)	8	6	9
Total Not Clinically Evaluable	44	42	54
Additional Reasons Patients Were Excluded From Strictly Evaluable Analyses[a]			
Culture Out of Time Range[b]	1	1	0
No Baseline Susceptibility Tests	0	1	4
No Proven Baseline Pathogen	74	65	64
Optional Microbiology Test Not Done	108	111	111
Total Not Strictly Evaluable	199	200	206

[a] Patients who had multiple reasons for being excluded from efficacy analyses were counted for each reason that applied.

[b] Patients who had assessments done early, took a concurrent antibacterial, or had insufficient treatment duration because they were early failures were not removed from the clinically evaluable or strictly evaluable analyses for these reasons but were carried forward as failures. Also, patients who had a culture done early because they were early failures were carried forward as failures in the strictly evaluable analyses.

Patients who were disqualified from the clinically qualified analyses at long term follow-up were automatically also disqualified from the strictly qualified analyses at long term follow-up.

Table 14. Reasons Patients Were Disqualified From the Clinically Qualified and Strictly Qualified Analyses at LTFU, includes patients enrolled by Fiddes and Iravani (Number of Patients)

	Cefdinir		Amox/Clav
	QD	BID	
Reasons Clinically Evaluable Patients Were Disqualified From Clinically Qualified Analyses[a]			
Clinical Assessment of Signs and Symptoms Missed	82	69	66
Clinical Assessment of Signs and Symptoms Out of Time Range[b]	6	5	6
Concurrent Antibacterial[b]	2	4	1
Total Not Clinically Qualified	89	77	73
Reasons Strictly Evaluable Patients Were Disqualified From Strictly Qualified Analyses[a]			
Clinical Assessment of Signs and Symptoms Missed	33	28	32
Clinical Assessment of Signs and Symptoms Out of Time Range[b]	2	3	1
Concurrent Antibacterial[b]	1	3	1
Culture Out of Time Range[b]	0	1	0
Total Not Strictly Qualified	36	34	34

[a] Patients who had multiple reasons for being disqualified were counted for each reason that applied.
[b] Patients who had assessments done early, took a concurrent antibacterial, or had insufficient treatment duration because they were early recurrences were not removed from the clinically qualified or strictly qualified analyses for these reasons. Also, patients who had a culture done early because they were early recurrences were not removed from the strictly qualified analyses for this reason.

Reviewers' note: *The reviewers agree that the exclusions tallied in the tables above are reasonable. In addition, carrying forward failures as described in footnotes a and b was appropriate. The reasons for nonevaluability are plausible and distribution fairly even. It is very unfortunate that the microbiology was not better -- many cases were lost.*

The table below shows the number of patients with data included in the clinically evaluable, clinically qualified, strictly evaluable, strictly qualified, MITT, and ITT populations.

Table 15. Patients With Data Included in Efficacy Summaries excluding those enrolled by Fiddes and Iravani
[Number (%) of Patients[a]]

Patient Population	Cefdinir				Amox/Clav	
	QD		BID			
Clinically Evaluable	181	(83.0)	183	(82.8)	178	(80.2)
Clinically Qualified	117	(53.7)	124	(56.1)	125	(56.3)
Strictly Evaluable	65	(29.8)	66	(29.9)	66	(29.7)
Strictly Qualified	37	(17.0)	37	(16.7)	38	(17.1)
Modified Intent-to-Treat (MITT)	77	(35.3)	87	(39.4)	83	(37.4)
Intent-to-Treat (ITT)	218	(100.0)	221	(100.0)	287	(100.0)

[a] Percentages are based on the number of patients randomized to treatment.

Reviewers' note: *Note that the clinically evaluable population falls short of the 190 clinically evaluable patients per treatment arm required by sample size calculation. Thus, the primary clinical outcome has a power less that 80%.*

Clinically Evaluable and Clinically Qualified Analyses

TOC Visit (11-16 Days Posttherapy)
Clinical Cure by Patient

Table 16. Clinical Cure Rate by Patient at TOC Clinically Evaluable Patients Investigator/Sponsor Determination

Clinically Evaluable Patients	Cefdinir				Amox/Clav	
	QD		BID		n/N	%
	n/N	%	n/N	%		
All	128/181	70.7	127/183	69.4	129/178	72.5
With Baseline Tympanocentesis	69/102	67.6	64/101	63.4	69/100	69.0
No Baseline Tympanocentesis	59/79	74.7	63/82	76.8	60/78	69.0

n/N = Number of patients with combined determination of cure/total number of patients.

95% confidence intervals about the difference in proportion

All

cefdinir QD versus amox/clav (-11.64, 8.13)
cefdinir BID versus amox/clav (-12.99, 6.84)
cefdinir QD versus cefdinir BID (-8.64, 11.28)

With baseline tympanocentesis

cefdinir QD versus amox/clav (-15.17, 12.47)
cefdinir BID versus amox/clav (-9.77, 18.33)
cefdinir QD versus cefdinir BID (-9.77, 18.33)

The clinical cure rates shown above are based on the combined investigator/sponsor assessments (see this review page 7 for discussion).

Reviewers' note: The cures rates are disappointing, but very close by treatment arm. Consequently, the 95% confidence intervals superficially meet the ±15% fixed criteria for a maximum cure rate of 70%. However, the sample size estimate was based on having 190 clinically evaluable patients per arm. The study appears to demonstrate equivalence, but is really underpowered. This is a great deficiency in a primary endpoint.

Tympanometry Results: The presence of middle ear effusion, determined by tympanometry, was used as an ancillary measure of clinical efficacy. The investigator's tympanometric assessment of the left or right ear was considered Satisfactory by the Sponsor if the specified ear was reported as Abnormal at baseline and Normal by TOC. The investigator's tympanometric assessment of the patient (ie, both ears) was considered Satisfactory by the Sponsor if both ears were reported as Normal at TOC.

Table. 17 Satisfactory Tympanometry Assessments at TOC Clinically Evaluable Patients excluding Fiddes and Iravani

	Left Ear		Right Ear		Patient	
	n/N[a]	%	n/N[a]	%	n/N[b]	%
Cefdinir QD	61/129	47.3	43/119	36.1	60/167	35.9
Cefdinir BID	51/128	39.8	50/131	38.2	57/167	34.1
Amox/Clav	47/135	34.8	41/129	31.8	58/167	34.7

[a] n/N = Number of patients with normal tympanometry assessment of specified ear at TOC/total number of patients with abnormal tympanometry assessment of specified ear at baseline.

[b] n/N = Number of patients with normal tympanometry assessment of both ears at TOC/total number of patients who had tympanometry at TOC.

Reviewers' note: *This is not a primary outcome measure. However, the tympanometry assessments by patient are very close.*

LTFU Visit (27-42 Days Posttherapy)

Clinical Cure by Patient: Clinically evaluable patients who continued to satisfy necessary protocol requirements between the TOC and LTFU visits were considered clinically qualified at LTFU.

Table 18. Clinical Cure Rate by Patient at LTFU - Clinically Qualified Patients Who Were Classified as Cures at TOC excluding Fiddes and Iravani

	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Cure Rate	103/117	88.0	104/124	83.9	101/125	80.8

n/N = Number of patients with combined determination of continued cure at LTFU (ie, no clinical recurrence)/total number of patients.

The clinical cure rates shown in above are based on the combined investigator/Sponsor assessments (see page 7).

95% confidence intervals about the difference in proportion

cefdinir QD versus amox/clav (-2.66, 17.13)

cefdinir BID versus amox/clav (-7.20, 13.34)

cefdinir QD versus cefdinir BID (-5.41, 13.74)

Reviewers' note: *This is not a primary outcome measure, and there are many patients lost to follow-up that could skew the endpoint. Nonetheless, the outcome measures are close and suggest that cefdinir is not worse than amoxicillin/clavulanate in the treatment of AOM.*

Tympanometry Results: In general, results from ear and patient tympanometry assessments in clinically evaluable patients were similar among the 3 treatment groups at the LTFU visit.

Table 19. Satisfactory Tympanometry Assessments at LTFU - Clinically Evaluable Patients excluding Fiddes and Iravani

	Left Ear		Right Ear		Patient	
	n/N[a]	%	n/N[a]	%	n/N[b]	%
Cefdinir QD	50/88	56.8	33/76	43.4	57/114	50.0
Cefdinir BID	49/87	56.3	54/91	59.3	65/118	55.1
Amox/Clav	53/99	53.5	46/90	51.1	68/124	54.8

[a] n/N = Number of patients with normal tympanometry assessment of specified ear at LTFU/total number of patients with abnormal tympanometry assessment of specified ear at baseline.

[b] n/N = Number of patients with normal tympanometry assessment of both ears at LTFU/total number of patients who had tympanometry at LTFU.

Reviewers' note: *This is not a primary outcome measure. Nonetheless, by patient the rates are again quite close.*

Strictly Evaluable and Strictly Qualified Analyses

TOC Visit (11-16 Days Posttherapy)

Clinical Cure by Patient

Table 20. Clinical Cure Rate by Patient (According to Baseline Pathogen) at TOC - Strictly Evaluable Patients excluding Fiddes and Iravani

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Staphylococcus aureus	1/1	100.0	0/0	0	0/0	0
Streptococcus pneumoniae	13/19	68.4	11/21	52.4	17/27	63.0
Streptococcus pyogenes	6/6	100.0	2/3	66.7	2/3	66.7
Haemophilus influenzae	11/16	68.8	17/22	77.3	14/18	77.8
Moraxella catarrhalis	3/5	60.0	6/7	85.7	3/6	50.0
Multiple						
Streptococcus pneumoniae	6/8	75.0	2/3	66.7	6/7	85.7
Haemophilus influenzae	7/10	70.0	5/10	50.0	5/6	83.3
Moraxella catarrhalis	2/6	33.3	0/0	0	1/3	33.3

n/N = Number of patients with combined determination of cure/total number of patients.
The clinical cure rates shown above are based on the combined investigator/Sponsor assessments (see page 7).

Reviewers' note: *The cure rates are disappointing overall, but the cure rates are comparable across treatment arms. Amoxicillin/clavulanate did not outperform the two cefdinir arms. Because the only organisms that can be evaluated for labeling based on these numbers are S. pneumoniae, H. influenzae and M. catarrhalis, these were the only organisms evaluated for cure with multiple pathogens. It appears that the cefdinir regimens are therapeutically comparable to amoxicillin/clavulanate against S. pneumoniae, H. influenzae and M. catarrhalis. Nonetheless, the reviewers are disappointed because the rates are low overall-- quite dismal, but similar rates have been seen in other submissions.*

Microbiologic Eradication by Pathogen:

Table 21. Microbiologic Eradication Rate by Baseline Pathogen at TOC - Pathogens From Strictly Evaluable Patients, excluding Fiddes and Iravani

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Staphylococcus aureus	2/3	66.7	1/1	100.0	0/3	--
Streptococcus pneumoniae	22/30	73.3	13/29	44.8	28/38	73.7
Streptococcus pyogenes	7/7	100.0	2/4	50.0	2/5	40.0
Haemophilus influenzae	22/32	68.8	25/39	64.1	20/25	80.0
Haemophilus parainfluenzae	0/0	--	1/1	100.0	0/0	--
Moraxella catarrhalis	6/12	50.0	6/7	85.7	5/10	50.0
Total	59/84	70.2	48/81	59.3	55/81	67.9

n/N = Number of pathogens eradicated or presumed eradicated/total number of pathogens.

Reviewers' note: *The numbers are too small to detect statistical significance, but eradications rates are similar overall. What the reviewers find peculiar and are entirely unable to explain is why cefdinir BID appears to lag here with respect to Streptococcus pneumoniae. This makes entirely no sense given other clinical, biopharmaceutical and microbiologic data submitted in this application.*

In general, the microbiologic eradication rates by pathogen achieved by cefdinir QD, cefdinir BID, and amox/clav were not decreased by the presence of β-lactamase for *Haemophilus influenzae* and *Moraxella catarrhalis*.

Table 22 . Microbiologic Eradication Rate by β-lactamase + *H. influenzae & M. catarrhalis* at TOC --Pathogens From Strictly Evaluable Patients, excluding Fiddes & Iravani

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
H. influenzae, βL+	8/15-10/14	53-71%	9/11-14/15	82-93%	18/23-20/22	78-91%
M. catarrhalis, βL+	4/8-5/9	50-55%	6/7	86%	4/9-5/9	44-56%

βL = β-Lactamase.
n/N = Number of pathogens eradicated or presumed eradicated/total number of pathogens.

Reviewers' note: *The Sponsor did not provide a breakup of the beta-lactamase status of the isolates once the Fiddes and Iravani sites were excluded. The above table presents the best and worst case scenario. Although numbers were lost, percentages were little changed. For Haemophilus influenzae, the original % eradication rate was 59%, 88%, and 85% for cefdinir QD, cefdinir BID and amoxicillin/clavulanate, respectively. For Moraxella catarrhalis, the original % eradication rate was 47%, 88%, and 60% for cefdinir QD, cefdinir BID and amoxicillin/clavulanate, respectively. Large numbers of organisms were not lost. Although not the most compelling data, when considered with the entire application, the evidence supports efficacy against beta-lactamase producing strains in this application.*

Microbiologic Eradication by Patient: This analysis will not be undertaken because the results are virtually the same as clinical cure rate at TOC by pathogen.

Intent-to-Treat Analyses

Test-of-Cure Visit (11-16 Days Posttherapy):

Table 23. Clinical and Microbiologic Efficacy Results at TOC - All Patients

	Clinical Cure Rate by Patient		Microbiologic Eradication Rate by Pathogen	
	n/N[a]	%	n/N[b]	%
Cefdinir QD	183/280	65.4	83/126	65.9
Cefdinir BID	199/285	69.8	83/129	64.3
Amox/Clav	205/287	71.4	92/138	66.7

[a] n/N = Number of patients with combined determination of cure/total number of patients.

[b] n/N = Number of pathogens eradicated or presumed eradicated/total number of pathogens.

95% confidence intervals about the difference in proportion

Clinical cure rate by patient

cefdinir QD versus amox/clav (-14.06, 1.92)

cefdinir BID versus amox/clav (-9.42, 6.21)

cefdinir QD versus cefdinir BID (-12.18, 3.24)

Reviewers note: Although underpowered, this analysis suggests therapeutic equivalence because the outcome measures are fairly close.

Long-Term Follow-Up Visit (27-42 Days Posttherapy):

Table 24. Clinical and Microbiologic Efficacy Results at LTFU - All Patients

	Clinical Cure Rate by Patient		Microbiologic Eradication Rate by Pathogen	
	n/N[a]	%	n/N[b]	%
Cefdinir QD	146/280	52.1	55/126	43.7
Cefdinir BID	167/285	58.6	73/129	56.6
Amox/Clav	161/287	56.1	63/138	45.7

[a] n/N = Number of patients with combined determination of cure at LTFU (ie, no clinical recurrence)/total number of patients.

[b] n/N = Number of pathogens eradicated or presumed eradicated/total number of pathogens.

***Reviewers' note**: Although the cure rates are fairly close, the efficacy is low. It is impossible to draw convincing conclusions from such analysis.*

Safety

All and Associated Adverse Events: Adverse events that occurred during this study primarily affected the digestive system and diarrhea was the most frequently reported adverse event and associated adverse event in all treatment groups.

Table 25. All and Associated Adverse Events by Body System and Treatment Group - All Patients excluding Fiddes and Iravani
[Number (%) of Patients]
(Page 1 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 218				Cefdinir BID N = 221				Amox/Clav N = 222			
	All		Assoc		All		Assoc		All		Assoc	
BODY AS A WHOLE	32[a]	(14.7)	2	(0.9)	40[a]	(18.1)	1	(0.5)	31[a]	(14.0)	4[a]	(1.8)
Infection	20	(9.2)	0	(0.0)	28	(12.7)	0	(0.0)	19	(8.6)	0	(0.0)
Accidental Injury	6	(2.8)	0	(0.0)	5	(2.3)	0	(0.0)	6	(2.7)	1	(0.3)
Fever	2	(0.9)	0	(0.0)	4	(1.8)	1	(0.5)	4	(1.8)	0	(0.0)
Headache	2	(0.9)	0	(0.0)	3	(1.4)	0	(0.0)	2	(0.9)	2	(0.9)
Abdominal Pain	2	(0.9)	2	(0.9)	2	(0.9)	0	(0.0)	4	(1.8)	3	(1.4)
Flu Syndrome	1	(05)	0	(0.0)	1	(0.5)	0	(0.0)	2	(0.9)	0	(0.0)
Sepsis	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)
DIGESTIVE SYSTEM	41[a]	(18.8)	32[a]	(14.7)	52[a]	(23.5)	39[a]	(17.6)	84[a]	(37.8)	70[a]	(31.5)
Diarrhea	33	(15.1)	29	(13.3)	36	(16.3)	28	(12.7)	71	(32.0)	66	(29.7)
Vomiting	9	(4.1)	5	(2.3)	10	(4.5)	4	(1.8)	20	(9.0)	12	(5.4)
Gastroenteritis	1	(0.5)	0	(0.0)	4	(1.8)	2	(0.9)	6	(2.7)	3	(1.4)
Abnormal Stools	0	(0.0)	0	(0.0)	2	(0.9)	2	(0.9)	0	(0.0)	0	(0.0)
Nausea	0	(0.0)	0	(0.0)	2	(0.9)	1	(0.5)	1	(0.5)	0	(0.0)
Constipation	1	(0.5)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Dyspepsia	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	2	(0.9)	1	(0.5)
Glossitis	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Mouth Ulceration	1	(0.5)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Flatulence	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)
Gastrointestinal Disorder	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal Hemorrhage	2	(0.9)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Table 25. All and Associated Adverse Events by Body System and Treatment Group - All Patients excluding Fiddes and Iravani
[Number (%) of Patients]
(Page 2 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 218				Cefdinir BID N = 2				Amox/Clav N = 287			
	All		'Assoc		All		Assoc		All		Assoc	
DIGESTIVE SYSTEM (cont'd)												
Liver Function Tests Abnormal	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oral Moniliasis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.7)	1	(0.3)
Rectal Hemorrhage	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
HEMIC AND LYMPHATIC SYSTEM	4	(1.8)	1	(0.5)	5	(2.3)	0	(0.0)	2	(0.9)	0	(0.0)
Lymphadenopathy	2	(0.9)	0	(0.0)	4	(1.8)	0	(0.0)	1	(0.5)	0	(0.0)
Anemia	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)
Leukopenia	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
METABOLIC AND NUTRITIONAL	2[a]	(0.9)	1	(0.5)	3[a]	(1.4)	2[a]	(0.9)	3[a]	(1.4)	2[a]	(0.9)
SGOT Increased	2	(0.9)	1	(0.5)	2	(0.9)	2	(0.9)	0	(0.0)	0	(0.0)
SGPT Increased	1	(0.5)	0	(0.0)	2	(0.9)	2	(0.7)	2	(0.7)	2	(0.7)
Dehydration	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Lactic Dehydrogenase Increased	1	(0.5)	0	(0.0)	1	(0.5)	1	(0.5)	2	(0.9)	1	(0.5)
NERVOUS SYSTEM	1	(0.5)	0	(0.0)	4	(1.8)	0	(0.0)	1	(0.5)	1	(0.5)
Convulsion	0	(0.0)	0	(0.0)	2	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
Dizziness	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Nervousness	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Insomnia	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vertigo	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)

Table 25. All and Associated Adverse Events by Body System and Treatment Group - All Patients excluding Fiddes and Iravani
[Number (%) of Patients]
(Page 3 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 280				Cefdinir BID N = 285				Amox/Clav N = 287			
	All		Assoc		All		Assoc		All		Assoc	
RESPIRATORY SYSTEM	30[a]	(13.8)	0	(0.0)	25[a]	(11.3)	0	(0.0)	21[a]	(9.5)	0	(0.0)
Cough Increased	7	(3.2)	0	(0.0)	7	(3.2)	0	(0.0)	3	(1.4)	0	(0.0)
Pharyngitis	7	(3.2)	0	(0.0)	6	(2.7)	0	(0.0)	8	(3.6)	0	(0.0)
Rhinitis	7	(3.2)	0	(0.0)	6	(2.7)	0	(0.0)	2	(0.9)	0	(0.0)
Sinusitis	5	(1.8)	0	(0.0)	4	(1.4)	0	(0.0)	3	(1.0)	0	(0.0)
Asthma	4	(1.8)	0	(0.0)	2	(0.9)	0	(0.0)	2	(0.9)	0	(0.0)
Laryngitis	0	(0.0)	0	(0.0)	2	(0.9)	0	(0.0)	1	(0.5)	0	(0.0)
Lung Disorder	2	(0.9)	0	(0.0)	2	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
Bronchiolitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)
Bronchitis	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
Pneumonia	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.9)	0	(0.0)
SKIN AND APPENDAGES	24[a]	(11.0)	19	(8.7)	32[a]	(14.5)	20	(9.0)	33[a]	(14.9)	26	(11.7)
Rash	14	(6.4)	13	(6.0)	20	(9.0)	13	(5.9)	23	(10.4)	19	(8.6)
Cutaneous Moniliasis	5	(2.3)	5	(2.3)	7	(3.2)	6	(2.7)	7	(3.2)	6	(2.7)
Alopecia	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Contact Dermatitis	2	(0.9)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)
Dry Skin	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Eczema	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	3	(1.4)	0	(0.0)
Maculopapular Rash	1	(0.5)	1	(0.5)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)
Pustular Rash	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Vesiculobullous Rash	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
Urticaria	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.9)	1	(0.5)

Table 25. All and Associated Adverse Events by Body System and Treatment Group - All Patients excluding Fiddes and Iravani
[Number (%) of Patients]
(Page 3 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 280				Cefdinir BID N = 285				Amox/Clav N = 287			
	All		Assoc		All		Assoc		All		Assoc	
SPECIAL SENSES	3	(1.4)	0	(0.0)	7	(3.2)	0	(0.0)	11	(4.1)	0	(0.0)
Conjunctivitis	2	(0.9)	0	(0.0)	4	(1.8)	0	(0.0)	3	(1.4)	0	(0.0)
Otitis Media	0	(0.0)	0	(0.0)	2	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
Otitis Externa	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	2	(0.9)	0	(0.0)
Corneal Lesion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)
Ear Disorder	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	3	(1.4)	0	(0.0)
Eye Disorder	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
UROGENITAL SYSTEM[b]	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	1	(0.0)	1	(0.0)
Vaginal Moniliasis[b]	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.5)	0	(0.0)	0	(0.0)

***Reviewers' note**: The adverse events recorded, both all and associated, are consistent with other cephalosporins and penicillins. The numbers above represent only one trial; the integrated review of the suspension evaluates the adverse event profile with the perspective of greater numbers exposed.*

Deaths: One patient who completed treatment with cefdinir QD died due to intussusception 51 days after completing study medication. This adverse event was considered definitely not related to study medication by the investigator.

Table 26. Deaths - All Patients

Treatment	Age, Sex	Study Day of Death	Study Day Drug Discontinued	Cause of Death	Relationship to Study Medication	Study Day of Onset of Adverse Event
Cefdinir QD	12 mo, M	61	Completed Medication	Intussusception (Gastrointestinal Disorder)	Definitely Not	58

***Reviewers' note**: After review of the narrative, the reviewers agree that the death was not related to study medication.*

Withdrawals Due to Adverse Events: Patients were considered withdrawn due to an adverse event if because of an adverse event they did not complete therapy or did not complete a follow-up visit. Twenty-one (2%) patients discontinued study medication because of adverse events: 8 (3%) treated with cefdinir QD, 6 (2%) with cefdinir BID, and 7 (2%) with amox/clav. In all groups, most treatment discontinuations were due to diarrhea and/or rash considered related to study medication by the investigators.

Twenty-one additional patients (10 treated with cefdinir QD, 3 with cefdinir BID, and 8 with amox/clav) were withdrawn due to adverse events after completing treatment but before the LTFU visit; none for adverse events considered related to study medication. Most (18) of these patients developed bacterial infections requiring systemic antibiotic therapy and therefore were not eligible to continue in the study; 3 of these patients had accidental injury.

Table 27. Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients
includes data from Fiddes and Iravani
(Page 1 of 4)

Treatment	Age, Sex	Adverse Event	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Cefdinir QD	9 yr, M	Sore Throat (Pharyngitis)	Unlikely	24	Completed Medication	Not Yet Recovered
	6 yr, F	Pharyngitis	Definitely Not	20	Completed Medication	Recovered
	14 mo, M	Scabies (Infection)	Unlikely	24	Completed Medication	Not Yet Recovered
	17 mo, M	Sinusitis	Definitely Not	13	Completed Medication	Unknown
	13 mo, F	Sinusitis	Unlikely	12	Completed Medication	Not Yet Recovered
	12 mo, M	Sinusitis	Definitely Not	8	9	Not Yet Recovered
	15 mo, M	Macular Rash (Maculopapular Rash)	Probably	3	3	Recovered
	10 mo, F	Diarrhea	Definitely	1	5	Recovered
	9 mo, F	Neck Laceration (Accidental Injury)	Definitely Not	9	Completed Medication	Recovered
	8 yr, M	Vomiting	Probably	1	1	Recovered
	7 mo, M	Diarrhea	Definitely	2	2	Recovered
	18 mo, M	Diaper Dermatitis (Rash)	Probably	2	3	Unknown
	10 mo, M	Diarrhea	Probably	2	2	Recovered
	9 mo, F	Generalized Rash (Rash)	Possibly	4	4	Recovered

Table 27. Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients includes data from Fiddes and Iravani
(Page 2 of 4)

Treatment	Age, Sex	Adverse Event	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Cefdinir QD (cont'd)	9 yr, F	Otitis Externa	Definitely Not	20	Completed Medication	Not Yet Recovered
	7 yr, M	Pharyngitis	Definitely Not	24	Completed Medication	Not Yet Recovered
	11 mo, M	Nasopharyngitis (Pharyngitis)	Definitely Not	25	Completed Medication	Recovered
	6 yr, F	Upper Respiratory Infection (Infection)	Definitely Not	24	Completed Medication	Not Yet Recovered
Cefdinir BID	12 yr, M	Acute Sinusitis (Sinusitis)	Definitely Not	19	Completed Medication	Not Yet Recovered
	16 mo, F	Sinusitis	Definitely Not	26	Completed Medication	Unknown
	5 yr, F	Sinusitis	Definitely Not	32	Completed Medication	Unknown
	14 mo, M	Vomiting	Probably	1	4	Recovered
		Loose Stools (Diarrhea)	Probably	3		Recovered
	6 mo, F	Diarrhea	Probably	1	1	Recovered
	6 yr, F	Diarrhea	Possibly	1	2	Unknown
		Nonpruritic Rash (Rash)	Probably	2		Not Yet Recovered
	13 mo, F	Febrile Seizure (Convulsion)	Unlikely	1	2	Recovered
		Dehydration	Unlikely	2		Recovered
	13 mo, F	Generalized Macular Rash - Face, Neck, Trunk (Maculopapular Rash)	Possibly	8	10	Not Yet Recovered
	9 mo, M	Diarrhea	Probably	6	9	Not Yet Recovered
Amox/Clav	3 yr, M	Diarrhea	Probably	3	4	Unknown
	2 yr, M	Anorexia	Possibly	1	5	Recovered
		Diarrhea	Definitely	2		Recovered
		Dehydration	Probably	4		Recovered

Table 27. Withdrawals Due to Adverse Events - All Patients
(Page 3 of 4)

Treatment	Age,[a] Sex	Adverse Event[b]	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Amox/Clav (cont'd)	7 mo, F	Diarrhea	Probably	1	5	Recovered
		Vomited (Vomiting)	Probably	2		Recovered
		Diaper Rash (Rash)	Probably	5		Recovered
	7 mo, F	Bronchiolitis	Definitely Not	21	Completed Medication	Not Yet Recovered
		Pneumonia	Definitely Not	21		Not Yet Recovered
	2 yr, M	Diarrhea	Definitely	2	7	Recovered
		Gastroenteritis	Definitely	2		Recovered
		Vomiting	Definitely	2		Recovered
	21 mo, M	URI (Infection)	Definitely Not	19	Completed Medication	Not Yet Recovered
	10 mo, F	Liquid Stools (Diarrhea)	Probably	2	2	Recovered
		Rash	Probably	2		Recovered
	6 yr, F	Exacerbation of Pre-existing Wound on Scalp (Accidental Injury)	Definitely Not	15	Completed Medication	Recovered
	15 mo, F	Loose Stools (Diarrhea)	Probably	2	8	Recovered
		Vomiting	Probably	8		Recovered
		Yeast Infection - Perineal Area (Cutaneous Moniliasis)	Probably	9		Unknown
	18 mo, M	URI (Infection)	Definitely Not	36	Completed Medication	Recovered
		Pneumonitis (Pneumonia)	Definitely Not	36		Recovered
	3 yr, M	Laceration Abdomen (Accidental Injury)	Definitely Not	19	Completed Medication	Recovered
	12 mo, F	Diarrhea	Possibly	1	2	Recovered

Table 27. Withdrawals Due to Adverse Events - All Patients
(Page 4 of 4)

Treatment	Age,[a] Sex	Adverse Event[b]	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Amox/Clav (cont'd)	11 yr, F	Otitis Externa	Definitely Not	20	Completed Medication	Not Yet Recovered
	14 mo, F	Nasopharyngitis (Pharyngitis)	Definitely Not	14	Completed Medication	Not Yet Recovered
	21 mo, M	Nasopharyngitis (Pharyngitis)	Definitely Not	13	Completed Medication	Recovered

***Reviewers' note**: Review of the narratives suggests that the investigators assigned relationshps are appropriate. The most common events that are related to discontinuation of therapy are skin rashes and events related to the gastrointestinal tract. This is consistent with other cephalosporins and penicillins.*

***Clostridium difficile*-Associated Diarrhea:** Fourteen patients (3 in the cefdinir QD group, 4 in the cefdinir BID group, and 7 in the amox/clav group) discontinued treatment due to diarrhea; 2 of these patients in the cefdinir BID group and 5 in the amox/clav group had other adverse events (eg, vomiting, rash) that also contributed to treatment being discontinued.

In November 1992, the Sponsor requested that all patients discontinuing treatment due to diarrhea be tested for *Clostridium difficile* toxin. Of the 9 patients who had diarrhea and discontinued treatment after that date none were tested. Seven of these patients (3 treated with cefdinir QD, 1 with cefdinir BID, and 3 with amox/clav) recovered from the diarrhea by study completion. For 1 patient treated with cefdinir BID (Patient 208, Center 983-10-10) and 1 treated with amox/clav (Patient 45, Center 983-10-3) the outcome was reported as unknown.

One patient who had diarrhea during treatment, but did not discontinue medication, was tested for *Clostridium difficile* toxin. Patient 225 (983-10-5), a 15-month-old girl who completed a 10-day course of cefdinir QD, had moderate diarrhea on Day 5, mild vomiting on Day 6, mild diaper rash on Day 8, and mild elevated liver function tests on Day 10. The vomiting and diarrhea were thought to be due to concomitant viral gastroenteritis. A fecal sample collected on Day 12 was negative for *Clostridium difficile* toxin. The diarrhea ended on Day 13, the vomiting on Day 10, and the elevated liver function values on Day 48. The diaper rash was continuing at the end of the study. The diarrhea was considered probably, the vomiting unlikely, and the diaper rash and elevated liver function tests possibly related to treatment.

***Reviewers' note:** It is unfortunate more patients were not tested for C. difficile-associated diarrhea. However, adverse event rates appear to be fairly evenly distributed by treatment arm and thus the diarrhea profile of cefdinir in pediatric patients is similar to that of amox/clav.*

Clinical Laboratory Measurements: In all 3 treatment groups, the most frequent markedly abnormal laboratory changes were increases in lymphocytes and lactate dehydrogenase (LDH) levels and decreases in bicarbonate levels. The increases in lymphocytes were most likely due to development of other infectious processes and the decreases in bicarbonate were most likely due to crying and expected to be transient. The increases in LDH are unexplained.

Table 28. Summary of Markedly Abnormal Laboratory Values More Abnormal at the First Posttherapy Visit Than at Baseline[a]
excluding Fiddes and Iravani
[Number (%) of Patients]

Parameter	Direction of Change	Cefdinir QD N = 218		Cefdinir BID N = 221		Amox/Clav N = 222	
Hematology							
Hemoglobin	Decrease	2	(0.9)	1	(0.4)		
Hematocrit	Decrease	2	(0.9)				
Erythrocytes	Decrease	1	(0.5)				
White Blood Cells	Increase					1	(0.4)
	Decrease	1	(0.5)	3	(1.4)	2	(0.9)
Lymphocytes	Increase	5	(2.3)	6	(2.7)	6	(2.7)
Eosinophils	Increase			2	(0.9)	2	(0.9)
Platelets	Increase	3	(1.4)	3	(1.4)	1	(0.5)
	Decrease	1	(0.5)				
Polymorphonuclear leukocytes	Increase					2	(0.9)
	Decrease	4	(1.8)	8	(3.6)	5	(2.3)
Blood Chemistry							
Alkaline Phosphatase	Increase	3	(1.4)	2	(0.9)	2	(0.9)
Aspartate Aminotransferase	Increase			2	(0.9)		
Alanine Aminotransferase	Increase			2	(0.9)		
Potassium	Increase	1	(0.5)	1	(0.4)		
Calcium	Decrease	2	(0.9)	4	(1.8)	1	(0.5)
Phosphorus	Increase	3	(1.4)	4	(1.8)	5	(2.3)
	Decrease	2	(0.9)			1	(0.5)
Bicarbonate	Decrease	4	(1.8)	6	(2.7)	3	(1.4)
Lactate Dehydrogenase	Increase	8	(2.9)	19	(6.6)	14	(4.9)
Urinalysis							
Protein	Increase	1	(0.5)				
Urine pH	Increase	4	(1.8)	3	(1.4)	1	(0.5)
Red Blood Cells	Increase			1	(0.4)		
Any Parameter[b]		36	(16.5)	40	(18.1)	27	(12.2)

[a] The first posttherapy visit was typically the STFU visit.

[b] Total number of patients in a treatment group experiencing a markedly abnormal laboratory value (more abnormal than at baseline) regardless of the laboratory parameter.

***Reviewers' note**: These laboratory abnormalities appear to be evenly distributed by treatment arm. The numbers are small, but the reviewers find nothing worrisome. Laboratory abnormalities will be reviewed in the integrated safety analysis of the suspension formation. This review will have the benefit of greater numbers.*

Conclusions: This application suffers (1) from losing a significant amount of data due to unreliable investigators and (2) low eradications rates. However, the data is not significantly worse than that found in other successful applications. It is impossible to explain the performance of cefdinir BID against *Streptococcus pneumoniae* given the performance of cefdinir QD and the similar clinical cures rates of the treatment arms. It follows that if cefdinir QD is approved, cefdinir BID must be approved. See the following chart:

Table 29. Microbiologic Eradication Rates by Pathogen Achieved by Cefdinir, Amox/Clav, Cefprozil, and Loracarbef Against the Most Common Pathogens in AOME--data from this NDA and other NDA reviewed by FDA.

Baseline Pathogen	Cefdinir[a]		Amox/Clav[a]	Cefprozil[b]	Loracarbef[b]
	QD	BID			
Streptococcus pneumoniae	73%	45%	74%	83%	68%
Haemophilus influenzae	69%	64%	80%	50%	65%
Moraxella catarrhalis	50%	86%	50%	60%	71%

[a] Data from this study, strictly evaluable patients at TOC
[b] Data from Medical Officers' Reviews

A strong comparator arm that is widely recommended for the treatment of AOM was utilized in this study. Equivalence was supported by multiple analyses, but cannot be irrefutably proved because of deficiencies in statistical power. It is very unfortunate that the second study submitted in support of this application has no microbiologic data. However, it is a strong clinical study with design nearly identical to this one and could pivotally swing evidence in favor of efficacy.

In AOM, DAIDP has not required trials to be powered at the level of statistical significance by pathogen. This would be a large burden that would clearly provide much more compelling data. There is enough microbiologic data in this application to support activity against the three major pathogens of AOM. Only one microbiologic study is required, and no absolute eradication rates are preset. The data submitted in this application meets that found in other successful submissions. In addition, the critical numbers of three pathogens recommended is also met. Thus, although the reviewer found much of the submission disappointing, it appears to meet at least minimal requirements to support the application.

Finally, this study provides no concerns with respect to safety that have not been seen before with other cephalosporins. ~~In fact, its safety profile is almost identical to other extended spectrum cephalosporins.~~

Indication: Acute Otitis Media (AOM)

Title and Study Number: Investigator-blinded, randomized, comparative, multicenter study of cefdinir versus amoxicillin/clavulanate in the treatment of AOM with effusion in pediatric patients (Protocol 983-11)

Reviewers' note: *~~This study is almost identical to protocol 983-10 but for two features:~~ (1) the study is designed to be clinical only, with microbiologic evaluation performed at the investigator's discretion; and (2) protocol 983-10 was a domestic study whereas protocol 983-11 only utilized study sites in Europe, South Africa and Australia.*

Objective, Study Design: Same as Study 983-10, but this is a study designed only for clinical evaluation. Therefore, no tympanocentesis was undertaken unless the investigator deemed it necessary. In addition, clinical laboratory tests were not performed on posttherapy visit 4 to 6 weeks after end of therapy.

Methodology: The design is identical to protocol 983-11.

Patients and Inclusion/Exclusion Criteria: The inclusion criteria are the same as protocol 983-10 with the following changes:

- Pneumotoscopy could be substituted for tympanometry to document middle ear effusion, but tympanometry was preferred.
- The is no requirement for a negative pregnancy test in postmenarchal girls.

Reviewers' note: *As mentioned in the medical officer's note in the review of 983-10. he inclusion criteria are not particularly stringent and are really minimal clinical findings for a diagnosis of AOM.*

The exclusion criteria were identical to those for protocol 983-10 with the following addition:

- Significant history or clinical evidence of significant cardiovascular, renal hepatic, hematological, gastrointestinal, neurological (including seizures), psychiatric, or other chronic disease;

Reviewers' note: *This is certainly a reasonable addition to the exclusion criteria..*

Permissible reasons for patient withdrawal were the same as allowed in protocol 983-10.

Evaluability Criteria: Three populations were analyzed: (1) clinically evaluable, (2) an intent-to-treat (ITT), and (3) all patients who received study medication.

Reviewers' note: *The difference between protocol 983-10 and this protocol is that this is not designed to be a microbiologically evaluable study. Therefore, there are no patient populations evaluable for microbiologic outcomes.*

The clinically evaluable patients differed from those in protocol 983-10 by the following reasons:

- Patients in 983-10 were required to have a susceptible baseline pathogen. Because this protocol had no microbiologic requirement, it could not be an issue.
- This protocol specified that the clinical evaluations had to be performed within the range of days specified in the protocol.

A population of clinically qualified patients was examined at LTFU. The were clinically evaluable patients who did not have any additional protocol violations between TOC and LTFU (same as protocol 983-10

The ITT population was all those randomized to treatment at both TOC and LTFU (same as protocol 983-10).

Endpoints: Assessment of clinical response at the TOC visit, 11 to 16 days posttherapy, was used to evaluate clinical efficacy. The primary measure of efficacy used in this study was clinical cure rate. The presence or absence of middle ear effusion determined by tympanometry (preferable) or pneumotoscopy at the TOC visit was an ancillary measure of clinical efficacy.

Patient clinical signs and symptoms and scoring system used in determining clinical response were the same as those used in protocol 983-10.

The otoscopic examination of each ear and the scoring system was assessed in the same manner as those in 983-10. However, this study allowed pneumotoscopy in addition to tympanometry (preferred) to confirm the presence or absence of middle ear effusion.

The calculated total patient and ear scores were used in determining the Sponsor assessment of clinical response. The investigator's global impression of clinical response was based on professional opinion after the evaluation done above.

Sponsor's Assessment of Clinical Response at TOC:
Same as that used in protocol 983-10.
Sponsor's Assessment of Clinical Response at LTFU:
Same as that used in protocol 983-10.

Investigator's Assessment of Clinical Response at TOC:
Same as that used in protocol 983-10.
Investigator's Assessment of Clinical Response at LTFU:
Same as that used in protocol 983-10.

As in protocol 983-10, a Combined Investigator/Sponsor Clinical Assessment was devised to reassign investigator assessments of Improvement to either Cure, Failure, or Not Assessable.

Statistical Methods and Sample Size Requirements: Statistical methods and sample size requirements are the same as those employed in protocol 983-10. Sample size estimates (190 patients randomized per treatment arm for a total of 570 clinically evaluable patients) are the same as protocol 983-10.

The following is the list of investigators.

Table 30. List of Investigators

Center	Investigator(s)	Number of Patients		
		Randomized to Treatment	Completed Treatment	Clinically Evaluable
1	S. Fradd/R. Martin	18	17	19
2	D. Miller	37	35	32
3	D. Moran	40	36	35
5	I. Patchett	51	51	46
7	M. Adler	96	76	78
9	P. David	40	37	37
10	L. Christiaen	56	54	53
12	S. Furman	80	78	68
13	F. Ascensi	8	4	2
14	C. Rodrigo	4	4	3
16	M. I. de José	3	2	2
18	A. Berger	50	31	39
19	C. von Sydow	21	17	1
20	A. Joensson	18	14	14
21	P. Rignér	12	10	9
22	P. MacDonald	32	28	28
23	A.M. Fasher/ S. Young	50	45	31
24	M. Fischer	13	13	1
25	R. Haas	19	18	15
26	E. Neumann	64	61	59
31	A. Ottaviani	1	1	0
32	D. Bassetti	4	4	2
37	D. Dutchman	34	28	27
38	H. Schumacher	1	1	1
Total		752	665	595

***Reviewers' note**: Protocol 983-10 is a domestic study that only included US study sites. Protocol 983-11, while almost identical to protocol 983-10, had two major differences: (1) a clinical only (microbiologic evaluation optional at investigator's discretion); and (2) study centers were located in Europe, South Africa, and Australia.*

Safety: The safety evaluation for this protocol is the same as in protocol 983-10.

Results

Demographic Information:

Table 33. Patient Characteristics - All Patients
[Number (%) of Patients]

Variable	Cefdinir QD N = 247	Cefdinir BID N = 254	Amox/Clav N = 251	Total N = 752
Sex				
Male	127 (51.4)	128 (50.4)	129 (51.4)	384 (51.1)
Female	120 (48.6)	126 (49.6)	122 (48.6)	368 (48.9)
Race				
White	224 (90.7)	233 (91.7)	222 (88.4)	679 (90.3)
Black	3 (1.2)	5 (2.0)	1 (0.4)	9 (1.2)
Asian	12 (4.9)	12 (4.7)	19 (7.6)	43 (5.7)
Other	8 (3.2)	4 (1.6)	9 (3.6)	21 (2.8)
Age, yr				
Median	4.5	4.5	4.7	4.5
Range	0.4-12.9	0.5-13.0	0.5-12.9	0.4-13.0
Distribution				
<2	47 (19.0)	41 (16.1)	42 (16.7)	130 (17.3)
2 to <6	108 (43.7)	126 (49.6)	119 (47.4)	353 (49.6)
6 to <13	92 (37.2)	86 (33.9)	90 (35.9)	268 (35.6)

Table 34. Patient Characteristics - Clinically Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir QD N = 195	Cefdinir BID N = 203	Amox/Clav N = 197	Total N = 595
Sex				
Male	99 (50.8)	101 (49.8)	103 (52.3)	303 (50.9)
Female	96 (49.2)	102 (50.2)	94 (47.7)	292 (49.1)
Race				
White	178 (91.3)	186 (91.6)	172 (87.3)	536 (90.1)
Black	3 (1.5)	3 (1.5)	1 (0.5)	7 (1.2)
Asian	11 (5.6)	10 (4.9)	16 (8.1)	37 (6.2)
Other	3 (1.5)	4 (2.0)	8 (4.1)	15 (2.5)
Age, yr				
Median	4.5	4.7	4.7	4.6
Range	0.4 - 12.9	0.5 - 12.7	0.5 - 12.9	0.4 - 12.9
Distribution				
<2	34 (17.4)	28 (13.8)	28 (14.2)	90 (15.1)
2 to <6	91 (46.7)	108 (53.2)	98 (49.7)	297 (49.9)
6 to <13	70 (35.9)	67 (33.0)	71 (36.0)	208 (35.0)

***Reviewers' note**: The differences between the population here and that in protocol 983-10 is that there are far fewer minorities enrolled here and that the patients tend to be older, with a median age two years older than that of 983-10. However, treatment arms are fairly well balanced with respect to demographic variables evaluated here.*

Clinical Signs and Symptoms, Distribution at Enrollment:

Table 35. Mean Patient Clinical Scores at Baseline - All and Clinically Evaluable Patients

Patient Population	Cefdinir		Amox/Clav
	QD	BID	
All Patients	8.4	8.5	8.7
Clinically Evaluable Patients	8.6	8.5	8.7

***Reviewers' note**: The scores in protocol 983-10 varied from 5.1 to 5.4. Here the scores are higher, supporting a more symptomatic population. With the same protocol, differences in populations emerge. Scores here are fairly well balanced by treatment arm.*

Ear:

Table 36. Mean Ear Clinical Scores at Baseline - All, Clinically Evaluable, and Strictly Evaluable Patients (includes Fiddes' and Iravani's site)

Ear/Patient Population	Cefdinir		Amox/Clav
	QD	BID	
Left Ear			
All Patients	5.2	5.0	5.5
Clinically Evaluable Patients	5.4	5.0	5.6
Right Ear			
All Patients	5.2	5.3	5.0
Clinically Evaluable Patients	5.1	5.4	5.0

***Reviewers' note**: This distribution is fairly evenly distributed by treatment arms. Once again, this population does not appear to be particularly ill. These scores are very similar to those derived in protocol 983-10.*

APPEARS THIS WAY
ON ORIGINAL

Duration of therapy:

Table 37. Patient Exposure to Study Medication - All Patients

Days on Study Medication	Cefdinir QD N = 247	Cefdinir BID N = 254	Amox/Clav N = 251
1	2	1	2
2	1	1	9
3	4	4	5
4	2	5	2
5	1	1	0
6	1	1	0
7	1	0	8
8	3	2	2
9	1	2	3
10	203	130	102
11	15	89	105
12	4	5	2
13	1	1	1
15	0	1	0
Median	10	10	10
Unknown	8	11	10

***Reviewers' note**: This distribution is as expected.*

Table 38. Patient Disposition - All Patients
[Number (%) of Patients]

Patient Disposition	Cefdinir QD		Cefdinir BID		Amox/Clav		Total	
Randomized to Treatment	247		254		251		752	
Discontinued Treatment								
Adverse Event	10	(4.0)	15	(5.9)	24	(9.6)	49	(6.5)
Lack of Compliance	3	(1.2)	4	(1.6)	13	(5.2)	20	(2.7)
Lack of Efficacy (Treatment Failure)	1	(0.4)	2	(0.8)	2	(0.8)	5	(0.7)
Spontaneous Perforation	1	(0.4)	0	(0.0)	0	(0.0)	1	(0.1)
Other/Administrative Reasons	6	(2.4)	4	(1.6)	2	(0.8)	12	(1.6)
Completed Treatment	226	(91.5)	229	(90.2)	210	(83.7)	665	(88.4)

***Reviewers' note**: Only a small number of patients discontinued treatment. Thus, the therapies were well tolerated in all treatment arms.*

Results

Exclusions: See table below. Patients who were excluded from the clinically evaluable analyses were automatically also excluded from the strictly evaluable analyses.

Table 39. Reasons Patients Were Not Clinically Evaluable at TOC or Disqualified at LTFU (Number of Patients)

	Cefdinir		Amox/Clav
	QD	BID	
Randomized to Treatment	247	254	251
Reasons Patients Were Not Clinically Evaluable at TOC Analyses			
Clinical Assessment Missed	10	11	12
Clinical Assessment Out of Time Range[b]	13	24	22
Concurrent Antibacterial[b]	3	5	2
Condition Prevented Assessment	1	2	2
Medication Not As Prescribed[b]	17	16	29
No Baseline Signs and Symptoms	20	17	17
Prior Antibacterial	2	0	1
Randomization Violation	1	0	0
Total Not Clinically Evaluable	52	51	54
Clinically Evaluable Patients at TOC	195	203	197
Reasons Patients Were Disqualified From LTFU Analyses			
Clinical Assessment Missed	22	27	22
Clinical Assessment Out of Time Range	5	9	9
Concurrent Antibacterial	15	16	12
Total Disqualified	31	42	33
Qualified Patients at LTFU	164	161	164

[a] Patients who had multiple reasons for being excluded from efficacy analyses were counted for each reason that applied.

[b] Patients who had assessments done early, took a concurrent antibacterial, or had insufficient treatment duration because they were early failures were not removed from the clinically evaluable or strictly evaluable analyses for these reasons but were carried forward as failures. Also, patients who had a culture done early because they were early failures were carried forward as failures in the strictly evaluable analyses.

***Reviewers' note**: The reviewers agree that the exclusions tallied in the tables above are reasonable. In addition, carrying forward failures as described in footnote b is appropriate. The reasons for nonevaluability are plausible and distribution fairly even.*

The table below shows the number of patients with data included in the clinically evaluable, clinically qualified, and ITT populations.

Table 40. Patients With Data Included in Efficacy Summaries
[Number (%) of Patients[a]]

Patient Population	Cefdinir				Amox/Clav	
	QD		BID			
Clinically Evaluable	195	(78.9)	203	(79.9)	197	(78.5)
Clinically Qualified	164	(84.1)	161	(79.3)	164	(83.2)
Intent-to-Treat (ITT)	247	(100.0)	254	(100.0)	251	(100.0)

[a] Percentages are based on the number of patients randomized to treatment.

***Reviewers' note**: Fortunately, this study is not underpowered. There are at least 190 clinically evaluable patients in each treatment arm yielding a power of 80%*

Clinically Evaluable and Clinically Qualified Analyses

TOC Visit (11-16 Days Posttherapy)
Clinical Cure by Patient

Table 41. Clinical Cure Rate by Patient at TOC, Clinically Evaluable Patients

Clinically Evaluable Patients	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Investigator determination	171/195	87.7	173/203	85.2	171/197	86.8
Combined Sponsor/Investigator determination	166/195	85.1	169/203	83.2	155/197	78.7

n/N = Number of patients with combined determination of cure/total number of patients.
95% confidence intervals about the difference in proportion
Investigator determination
cefdinir QD versus amox/clav (-6.22, 8.00)
cefdinir BID versus amox/clav (-8.88, 5.71)
cefdinir QD versus cefdinir BID (-4.75, 9.69)
Combined Sponsor/Investigator determination
cefdinir QD versus amox/clav (-1.66, 14.55)
cefdinir BID versus amox/clav (-3.62, 12.76)
cefdinir QD versus cefdinir BID (-5.79, 9.04)

***Reviewers' note**: Both analyses demonstrate therapeutic equivalence with acceptable cure rates..*

LTFU Visit (27-42 Days Posttherapy)

Clinical Cure by Patient

Table 42. Clinical Cure Rate by Patient at LTFU, Clinically Evaluable Patients

Clinically Evaluable Patients	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Investigator determination	149/164	90.8	148/161	91.9	140/164	85.4
Combined Sponsor/Investigator determination	153/164	93.3	145/161	90.0	143/164	87.2

n/N = Number of patients with combined determination of cure/total number of patients.

95% confidence intervals about the difference in proportion

Investigator determination

cefdinir QD versus amox/clav (-2.10, 13.08)

cefdinir BID versus amox/clav (-0.91, 14.03)

cefdinir QD versus cefdinir BID (-7.78, 5.64)

Combined Sponsor/Investigator determination

cefdinir QD versus amox/clav (-0.90, 13.10)

cefdinir BID versus amox/clav (-4.64, 10.38)

cefdinir QD versus cefdinir BID (-7.78, 5.64)

Reviewers' note: *This is not a primary outcome measure, but once again both analyses demonstrate at least therapeutic equivalence of cefdinir to itself and amoxicillin/clavulanate.*

ITT Analysis

Table 43. Clinical Cure Rate by Patient at TOC

	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
All patients enrolled, TOC	211/247	85.4	212/254	83.5	204/251	81.3
All patients enrolled, LTFU	183/247	74.1	190/254	74.8	171/251	68.1

n/N = Number of patients with combined determination of cure/total number of patients.

95% confidence intervals about the difference in proportion, ITT analysis at TOC

cefdinir QD versus amox/clav (-2.78, 11.08)

cefdinir BID versus amox/clav (-4.85, 9.23)

cefdinir QD versus cefdinir BID (-4.78, 8.70)

95% confidence intervals about the difference in proportion, ITT analysis at LTFU

cefdinir QD versus amox/clav (-2.38, 14.31)

cefdinir BID versus amox/clav (-1.58, 14.93)

cefdinir QD versus cefdinir BID (-8.75, 7.32)

Reviewers' note: *This analysis supports the therapeutic equivalence of cefdinir to itself and to amoxicillin/clavulanate.*

Safety:

Table 44. All and Associated[a] Adverse Events by Body System and Treatment Group - All Patients Receiving Study Medication

[Number (%) of Patients]
(Page 1 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 246				Cefdinir BID N = 251				Amox/Clav N = 248			
	All		Associated		All[b]		Associated		All		Associated	
DIGESTIVE SYSTEM	42[c]	(17.1)	34[c]	(13.8)	50[c]	(19.9)	41[c]	(16.3)	55[c]	(22.2)	45[c]	(18.1)
Diarrhea	34	(13.8)	30	(12.2)	43	(17.1)	40	(15.9)	36	(14.5)	28	(11.3)
Vomiting	6	(2.4)	1	(0.4)	8	(3.2)	5	(2.0)	19	(7.7)	16	(6.5)
Nausea	1	(0.4)	1	(0.4)	3	(1.2)	0	(0.0)	6	(2.4)	5	(2.0)
Constipation	2	(0.8)	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Gastritis	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Glossitis	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Colitis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)
Flatulence	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal Disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Hepatitis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Melena	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oral Moniliasis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
RESPIRATORY SYSTEM	22	(8.9)	0	(0.0)	24[c]	(9.6)	0	(0.0)	25[c]	(10.1)	0	(0.0)
Pharyngitis	10	(4.1)	0	(0.0)	9	(3.6)	0	(0.0)	11	(4.4)	0	(0.0)
Cough Increased	5	(2.0)	0	(0.0)	7	(2.8)	0	(0.0)	3	(1.2)	0	(0.0)
Rhinitis	0	(0.0)	0	(0.0)	5	(2.0)	0	(0.0)	6	(2.4)	0	(0.0)
Asthma	4	(1.6)	0	(0.0)	2	(0.8)	0	(0.0)	3	(1.2)	0	(0.0)
Bronchitis	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Sinusitis	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Laryngitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Pneumonia	2	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)

Table 44. All and Associated[a] Adverse Events by Body System and Treatment Group - All Patients Receiving Study Medication

[Number (%) of Patients]
(Page 2 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 246				Cefdinir BID N = 251				Amox/Clav N = 248			
	All		Associated		All[b]		Associated		All		Associated	
BODY AS A WHOLE	9[c]	(3.7)	2[c]	(0.8)	18[c]	(7.2)	4	(1.6)	22[c]	(8.9)	4	(1.6)
Abdominal Pain	2	(0.8)	2	(0.8)	4	(1.6)	1	(0.4)	3	(1.2)	1	(0.4)
Infection	5	(2.0)	0	(0.0)	4	(1.6)	0	(0.0)	5	(2.0)	0	(0.0)
Flu Syndrome	0	(0.0)	0	(0.0)	2	(0.8)	1	(0.4)	2	(0.8)	0	(0.0)
Headache	1	(0.4)	1	(0.4)	2	(0.8)	0	(0.0)	2	(0.8)	0	(0.0)
Mucous Membrane Disorder	1	(0.4)	0	(0.0)	2	(0.8)	0	(0.0)	3	(1.2)	0	(0.0)
Overdose	0	(0.0)	0	(0.0)	2	(0.8)	1	(0.4)	3	(1.2)	3	(1.2)
Accidental Injury	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Face Edema	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)	1	(0.4)	0	(0.0)
Fever	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)	2	(0.8)	0	(0.0)
Lab Test Abnormal	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Neck Pain	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.8)	0	(0.0)
SKIN AND APPENDAGES	5	(2.0)	2	(0.8)	8	(3.2)	7	(2.8)	11	(4.4)	7	(2.8)
Rash	3	(1.2)	2	(0.8)	6	(2.4)	6	(2.4)	9	(3.6)	6	(2.4)
Eczema	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Fungal Dermatitis	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)	1	(0.4)	1	(0.4)
Angioedema	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Maculopapular Rash	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pustular Rash	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
SPECIAL SENSES	10	(4.1)	1	(0.4)	8	(3.2)	0	(0.0)	6	(2.4)	0	(0.0)
Ear Disorder	5	(2.0)	0	(0.0)	6	(2.4)	0	(0.0)	3	(1.2)	0	(0.0)
Conjunctivitis	2	(0.8)	0	(0.0)	1	(0.4)	0	(0.0)	2	(0.8)	0	(0.0)
Otitis Externa	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Otitis Media	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Taste Perversion	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Table 44. All and Associated[a] Adverse Events by Body System and Treatment Group - All Patients Receiving Study Medication

[Number (%) of Patients]
(Page 3 of 3)

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 246				Cefdinir BID N = 251				Amox/Clav N = 248			
	All		Associated		All[b]		Associated		All		Associated	
NERVOUS SYSTEM	1	(0.4)	0	(0.0)	3	(1.2)	1	(0.4)	2	(0.8)	0	(0.0)
CNS Stimulation	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)
Nervousness	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Vertigo	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Insomnia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Somnolence	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)
Torticollis	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
UROGENITAL SYSTEM	0	(0.0)	0	(0.0)	3	(1.2)	0	(0.0)	1	(0.4)	0	(0.0)
Urinary Tract Infection	0	(0.0)	0	(0.0)	2	(0.8)	0	(0.0)	1	(0.4)	0	(0.0)
Balanitis	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
CARDIOVASCULAR SYSTEM	2	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Palpitation	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Syncope	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
HEMIC & LYMPHATIC SYSTEM	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.8)	0	(0.0)
Anemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.8)	0	(0.0)
Thrombocytopenic Purpura	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
METABOLIC & NUTRITIONAL DISORDERS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)
Bilirubinemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)

[a] Considered by the investigator to be possibly, probably, or definitely related to treatment.
[b] All and drug-associated adverse events for each body system are arranged in decreasing frequency based on all adverse events from cefdinir BID treatment.
[c] The totals for each body system may be less than the number of patients with adverse events in that body system because a patient can have ≥ 1 adverse event per system.

***Medical officer's note**: The adverse event profile is typical of cephalosporins. Gastrointestinal events, particularly diarrhea are prominent.*

Table 45. Serious Nonfatal Adverse Events - All Patients Receiving Study Medication

Treatment	Age[a], Sex	Serious Adverse Event[b]	Intensity	Relationship to Study Medication[c]	Study Day of Onset of Adverse Event	Management of Study Drug	Outcome
Cefdinir QD	15 mo, F	Salmonella infection colon (Colitis)	Severe	Definitely Not	4	Interrupted	Recovered
	15 mo, F	Amigdalitis viral (Pharyngitis)	Moderate	Definitely Not	34	None	Recovered
	3 yr, M	Recurrence of otitis media (Otitis media)	Severe	Definitely Not	59[d]	None	Unknown
Cefdinir BID	4 yr, M	Abdominal pain	Moderate	Definitely Not	4	None	Recovered
		Constipation	Moderate	Definitely Not	4	None	Recovered
	19 mo, F	Streptococcus angina (Pharyngitis)	Severe	Definitely Not	43	None	Recovered
	4 yr, M	Sinusitis	Severe	Definitely Not	15	None	Recovered
	9 yr, F	Diarrhoea (Diarrhea)	Severe	Probably	2	Discontinued	Recovered/Sequelae
Amox/Clav	7 yr, F	Acute appendicitis (Gastrointestinal disorder)	Severe	Definitely Not	1	Discontinued	Recovered
	4 yr, M	Diarrhea	Severe	Definitely	3	Discontinued	Recovered
		Vomiting	Severe	Definitely	3	Discontinued	Recovered
		Intense persistent cough (Cough increased)	Severe	Definitely Not	3	None	Recovered
		Cough (Cough increased)	Mild	Definitely Not	6	None	Recovered
	7 mo, M	Asthma,	Moderate	Definitely Not	21	None	Recovered
		Croup (Laryngitis)	Moderate	Definitely Not	21	None	Recovered

[a] Age at baseline
[b] When the investigator term and COSTART IV term differ, the COSTART IV adverse event term appears in parentheses.
[c] As determined by the investigator
[d] Day 49 was the last follow-up visit.

Medical officer's note: *Review of narratives supports investigator assignment of relationship to study drug. Once again gastrointestinal events are prominent. However, cefdinir does not appear to be worse than amoxicillin/clavulanate on this count. This issue will be addressed in the integrated summary of safety for the suspension formulation.*

Table 46. Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients Receiving Study Medication (Page 1 of 4)

Treatment	Age, Sex	Adverse Event	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Cefdinir QD	10 yr, F	Diarrhea	Probably	2	6	Not Yet Recovered
	4 yr, M	Diarrhea	Definitely	2	3	Recovered
	2 yr, M	Diarrhea	Probably	2	2	Recovered
	6 yr, M	Upper Respiratory Tract Infection (Pharyngitis)	Definitely Not	22	10	Recovered
	7 mo, M	Diarrhea	Probably	1	Unknown	Recovered
	16 mo, F	Tonsillitis (Pharyngitis)	Definitely Not	19	10	Recovered
	11 yr, F	Vaso-Vagal Attack (Syncope)	Unlikely	1	1	Recovered
	14 mo, M	Diarrhea	Probably	4	3	Recovered
	5 yr, F	Left Bronchopneumonia (Pneumonia)	Definitely Not	20	10	Not Yet Recovered
	21 mo, F	Diarrhea	Probably	2	3	Recovered
	4 yr, M	Diarrhea	Probably	4	7	Recovered
	2 yr, F	Pneumonia	Unlikely	5	5	Recovered
	15 mo, F	Diarrhea	Definitely	4	4	Recovered
Cefdinir BID	9 yr, F	Abdominal Pain	Probably	9	9	Recovered
	11 yr, M	Diarrhea	Definitely	3	3	Recovered
	15 mo, F	Diarrhea	Probably	2	2	Recovered
	8 yr, M	Vomiting	Probably	1	1	Recovered
	8 mo, M	Tonsillitis (Pharyngitis)	Definitely Not	15	11	Not Yet Recovered
	2 yr, F	Diarrhea	Probably	2	Not Available	Recovered
	7 mo, F	Diarrhea	Definitely	1	Not Available	Recovered
		Vomiting	Definitely	1	1	Recovered

Table 46. Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients Receiving Study Medication

(Page 2 of 4)

Treatment	Age, Sex	Adverse Event	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Cefdinir BID	9 mo, F	Diarrhea	Possibly	3	4	Not Yet Recovered
	11 yr, F	Diarrhea	Probably	3	3	Not Yet Recovered
	19 mo, M	Diarrhea	Probably	2	6	Not Yet Recovered
	4 yr, F	Hyperexcitability (CNS Stimulation)	Possibly	3	4	Recovered
	7 yr, M	Diarrhea	Probably	4	4	Recovered
		Vomiting	Probably	4		Recovered
	14 mo, F	Rash	Probably	3	4	Recovered
	9 yr, F	Diarrhea	Probably	2	3	Recovered/ Sequelae[c]
	11 yr, F	Gastric Flu (Flu Syndrome)	Possibly	7	8	Recovered
	20 mo, M	Diarrhea	Definitely	2	3	Recovered
Amox/Clav	5 yr, M	Overdose	Definitely	1	4	Recovered
		Nausea	Definitely	2		Recovered/ Sequelae[c]
	8 yr, F	Vomiting	Possibly	7	7	Recovered
	6 yr, F	Urinary Tract Infection	Definitely Not	14	10	Unknown
	5 yr, M	Tonsillitis (Pharyngitis)	Definitely Not	19	11	Recovered
	12 yr, F	Allergic Rash (Rash)	Probably	2	2	Recovered
	2 yr, F	Vomiting	Definitely	1	1	Recovered
	7 yr, F	Diarrhea	Probably	2	2	Recovered
	2 yr, F	Pharyngitis	Definitely Not	34	11	Recovered
	7 yr, F	Vomiting	Possibly	1	2	Recovered
	6 yr, F	Vomiting	Probably	1	2	Recovered

Table 46. Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients Receiving Study Medication

(Page 3 of 4)

Treatment	Age, Sex	Adverse Event	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Amox/clav	18 mo, M	Diarrhea	Definitely	7	7	Recovered
	2 yr, M	Vomiting	Definitely	1	2	Recovered
	7 yr, F	Vomiting	Probably	1	2	Recovered
	3 yr, M	Vomiting	Possibly	6	7	Recovered
	22 mo, F	Diarrhea	Definitely	2	2	Recovered
	6 yr, M	Vomiting	Definitely	1	2	Recovered
	2 yr, F	Colitis	Possibly	7	7	Recovered
		Itching Erythema (Rash)	Unlikely	7		Recovered
	7 yr, F	Acute Appendicitis (Gastrointestinal Disorder)	Definitely Not	1	1	Recovered
	4 yr, M	Diarrhea	Definitely	3	3	Recovered
		Vomiting	Definitely	3		Recovered
	21 mo, F	Diarrhea	Definitely	2	3	Recovered
	10 mo, M	Diarrhea	Definitely	3	Not Available	Not Yet Recovered
	8 mo, M	Rash	Possibly	9	9	Recovered
	9 mo, M	Diarrhea	Probably	2	3	Recovered
	2 yr, F	Diarrhea	Possibly	5	9	Recovered
	19 mo, F	Allergic Erythema (Rash)	Probably	2	2	Recovered
	7 mo, F	Allergic Skin Rash (Rash)	Probably	3	3	Recovered

Table 46. Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients Receiving Study Medication

(Page 4 of 4)

Treatment	Age, Sex	Adverse Event	Relationship to Study Medication	Study Day of Onset of Adverse Event	Study Day Drug Discontinued	Outcome
Amox/clav	19 mo, M	Acute Right Otitis Externa (Otitis Externa)	Unlikely	9	10	Not Yet Recovered
	19 mo, F	Diarrhea	Probably	1	4	Recovered
	10 yr, F	Tonsillitis (Pharyngitis)	Definitely Not	22	10	Not Yet Recovered
		Congested Nose (Rhinitis)	Definitely Not	22		Not Yet Recovered

***Reviewers' note**: The reviewers agree with the relationship of event to study medication assigned by the investigator. There are no surprising findings with respect to this chart.*

Table 47 . Summary of Treatment Discontinuations and Study Withdrawals Due to Adverse Events - All Patients

BODY SYSTEM/ Adverse Event	Cefdinir QD N = 246	Cefdinir BID N = 251	Amox/Clav N = 248
BODY AS A WHOLE	0	2	1
Abdominal Pain	0	1	0
Flu Syndrome	0	1	0
Overdose	0	0	1
CARDIOVASCULAR SYSTEM	1	0	0
Syncope	1	0	0
DIGESTIVE SYSTEM	8	11[a]	20[a]
Diarrhea	8	10	9
Vomiting	0	3	9
Colitis	0	0	1
Gastrointestinal Disorder	0	0	1
Nausea	0	0	1
NERVOUS SYSTEM	0	1	0
CNS Stimulation	0	1	0
RESPIRATORY SYSTEM	4	1	3[a]
Pharyngitis	2	1	3
Pneumonia	2	0	0
Rhinitis	0	0	1
SKIN AND APPENDAGES	0	1	5
Rash	0	1	5
SPECIAL SENSES	0	0	1
Otitis Externa	0	0	1
UROGENITAL SYSTEM	0	0	1
Urinary Tract Infection	0	0	1

[a] The total number for each body system may be less than the number of patients in that body system total because a patient can have ≥ 1 adverse event per system.

Reviewers' note: *There are no surprises in this list. It appears that cefdinir has adverse events similar in profile to other cephalosporins. Diarrhea is prominent; this is not unexpected.*

Deaths: There were no deaths in this study.

***Clostridium difficile*-Associated Diarrhea:** Twenty-seven patients (8 in the cefdinir QD group, 10 in the cefdinir BID group, and 9 in the amox/clav group) discontinued treatment due to diarrhea. None of the investigators considered an episode of diarrhea to be indicative of pseudomembranous colitis. Therefore, only 2 of these patients were tested for *C. difficile* and neither was positive. All 27 patients recovered from their diarrhea by study completion.

Reviewers' note: *It is unfortunate that more patients were not tested. However, cefdinir appears to have a diarrhea profile comparable, and not worse, than the amoxicillin clavulanate arm.*

Table 48. Summary of Markedly Abnormal Laboratory Values More Abnormal at the First Posttherapy Visit Than at Baseline[a]

[Number (%) of Patients]

Parameter	Direction of Change	Cefdinir QD N = 246		Cefdinir BID N = 251		Amox/Clav N = 248	
Hematology							
Hemoglobin	Decrease	3	(1.2)	0	(0.0)	0	(0.0)
Hematocrit	Decrease	4	(1.6)	2	(0.8)	0	(0.0)
Erythrocytes	Decrease	0	(0.0)	1	(0.4)	0	(0.0)
White Blood Cells	Increase	2	(0.8)	2	(0.8)	2	(0.8)
	Decrease	2	(0.8)	0	(0.0)	4	(1.6)
Polymorphonuclear Neutrophils	Increase	2	(0.8)	2	(0.8)	1	(0.4)
	Decrease	2	(0.8)	2	(0.8)	1	(0.4)
Lymphocytes	Increase	4	(1.6)	2	(0.8)	4	(1.6)
	Decrease	2	(0.8)	1	(0.4)	1	(0.4)
Eosinophils	Increase	5	(2.0)	7	(2.8)	4	(1.6)
Basophils	Increase	1	(0.4)	0	(0.0)	0	(0.0)
Platelets	Increase	3	(1.2)	6	(2.4)	3	(1.2)
Blood Chemistry							
Glucose, Random	Decrease	9	(3.7)	4	(1.6)	9	(3.6)
Blood Urea	Increase	1	(0.4)	0	(0.0)	0	(0.0)
Alkaline Phosphatase	Increase	9	(3.7)	12	(4.8)	10	(4.0)
Bilirubin	Increase	0	(0.0)	0	(0.0)	1	(0.4)
Lactate Dehydrogenase	Increase	40	(16.3)	33	(13.1)	36	(14.5)
Aspartate Aminotransferase	Increase	1	(0.4)	0	(0.0)	0	(0.0)
Alanine Aminotransferase	Increase	2	(0.8)	0	(0.0)	0	(0.0)
Gamma Glutamyl Transferase	Increase	0	(0.0)	2	(0.8)	1	(0.4)
Sodium	Increase	1	(0.4)	0	(0.0)	1	(0.4)
	Decrease	0	(0.0)	1	(0.4)	0	(0.0)
Potassium	Increase	7	(2.9)	9	(3.6)	10	(4.0)
	Decrease	0	(0.0)	0	(0.0)	1	(0.4)
Phosphorus	Increase	14	(5.7)	12	(4.8)	14	(5.7)
	Decrease	3	(1.2)	4	(1.6)	4	(1.6)
Chloride	Increase	0	(0.0)	0	(0.0)	1	(0.4)
Bicarbonate	Increase	0	(0.0)	0	(0.0)	1	(0.4)
	Decrease	2	(0.8)	0	(0.0)	3	(1.2)
Urinalysis							
Protein	Increase	1	(0.4)	1	(0.4)	1	(0.4)
Glucose	Increase	0	(0.0)	0	(0.0)	2	(0.8)
White Blood Cells	Increase	2	(0.8)	2	(0.8)	2	(0.8)
Red Blood Cells	Increase	1	(0.4)	2	(0.8)	0	(0.0)
Urine pH	Increase	2	(0.8)	1	(0.4)	0	(0.0)
Urine Specific Gravity	Increase	5	(2.0)	5	(2.0)	7	(2.8)
	Decrease	0	(0.0)	2	(0.8)	0	(0.0)
Any Parameter[b]		81	(32.9)	81	(32.3)	91	(36.7)

[a] The first posttherapy visit was typically the STFU visit.
[b] Total number of patients in a treatment group experiencing a markedly abnormal laboratory value (more abnormal than at baseline) regardless of the laboratory parameter.

Reviewers' note: *The changes in laboratory parameters are comparable by treatment arm. The lactate dehydrogenase increase appears unusual, but nothing else is remarkable. This can be more fully evaluated in the integrated safety summary.*

Conclusions for studies 983-10 and 983-11:
The data from study 983-10 is problematic: the sample size is smaller than calculated for and the study does not meet 80% power. The cure rates overall are disappointingly low, but other applications have demonstrated similar dismal cure rates. However, the data, when analyzed several ways, suggests that response rates, both microbiologic and clinical, are therapeutically equivalent among the cefdinir QD, cefdinir BID and amoxicillin/clavulanate arms. There is are enough isolates to demonstrate efficacy against *Streptococcus pneumoniae*, *Haemophilus influenzae* (including beta-lactamase producing strains) and *Moraxella catarrhalis*.

The data from study 983-11 involves clinical cure only. This adequately powered study supports the therapeutic equivalence of the three treatment arms with good cure rates.

Studies 983-10 and 983-11 revealed no surprises with respect to adverse events. The profile of cefdinir is similar to other cephalosporins with diarrhea being prominent. The integrated safety review for the suspension formulation will determine the adequacy of the Sponsor's label with respect to adverse events.

Recommendations: That cefdinir suspension be labeled for efficacy against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the treatment of AOM at the dose of 14 mg/kg QD for 10 days and 7 mg/kg BID for 10 days.

That the Sponsor's labeling with respect to safety be accepted; this will be determined by the integrated safety review of the suspension formulation.

/S/

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Concurrences:
HFD-520/TL/Jan Soreth, MD 3/18/99
HFD-520/DivDir/Gary Chikami, MD 3/19/99

Concurrence:
HFD-725/TL/DLin, PhD

cc: Orig NDAs 50-739 & 50-749
HFD-520/Division File
HFD-520/CSO BDuvall-Miller
HFD-520/Microbiology/ASheldon
HFD-520/Chemistry/DKatague
HFD-520/Pharm/FPelsor
HFD-520/MO/HHamilton
HFD-520/TL/JSoreth
HFD-725/Stat/AChakravarty
HFD-725/Stat/TL/DLin

Medical Officer's Review of New Drug Application for Acute Maxillary Sinusitis

NDAs: 50-739, 50-749

SPONSOR: Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company

Date of Submission: 3 September 1997
CDER Stamp Date: 4 September 1997
Date of Assignment: 1 November 1996
Date of First Draft: 1 June 1997
Date of Final Draft: 1 July 1997; 30 June 1999

Materials submitted with application:

1. Parke-Davis CANDA for Cefdinir
2. NDA 50-739, Vols. No. 197-232
3. Diskette with file sinusitis2.doc, study 983-006, acute maxillary sinusitis
4. Diskette with file sinusitis reanalysis summary

Proposed INDICATION AND USAGE section (pertinent to sinusitis):

Acute Maxillary Sinusitis caused by susceptible strains of *Haemophilus influenzae* (including β-lactamase producing strains), *Haemophilus parainfluenzae* (including β-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains), *Staphylococcus aureus* (methicillin-susceptible strains), *Moraxella catarrhalis* (including β-lactamase producing strains), *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcus pyogenes*.

Proposed DOSAGE AND ADMINISTRATION section (pertinent to sinusitis):

Capsules
The recommended dosage and duration of treatment for various infections in adults and adolescents are described in the following chart; the total daily dose for all infections is 600 mg. OMNICEF may be taken without regard to meals.

Adults and Adolescents (Age 13 Years and Older)

Type of Infection	Dosage	Duration
Acute Maxillary Sinusitis	300 mg q12h	10 days
	or 600 mg q24h	10 days

INTRODUCTION

The following is excerpted from the sponsor's introductory comments:

Sinusitis is a common disorder of both adults and children and can lead to potentially life-threatening complications such as epidural or subdural empyema, brain abscess, or cavernous sinus thrombosis. Therefore, early diagnosis and effective antimicrobial therapy are crucial. The bacterial etiology of sinusitis can only be determined by sinus aspiration, a procedure considered invasive and not routinely performed. Therapy is usually empirically selected based on the most likely pathogen(s) involved. Because the incidence of β-lactamase-producing strains among respiratory pathogens is rising, commonly used agents such as ampicillin and amoxicillin are becoming increasingly ineffective. Unfortunately, agents that are resistant to β-lactamase activity are often associated with unpleasant side effects. Thus, the development of drugs that are stable in the presence of β-lactamase and are well-tolerated is of considerable importance.

Cefdinir (CI-983, PD 134393, FK 482) is a semisynthetic, extended-spectrum cephalosporin antibiotic intended for use in the treatment of mild to moderate bacterial infections. Cefdinir acts by inhibiting cell-wall synthesis and is highly stable in the presence of β-lactamase enzymes. As a result, many β-lactamase-producing organisms that confer resistance to penicillins and to some cephalosporins are susceptible to cefdinir.

Cefdinir is active in vitro against organisms commonly associated with sinus infections, including *Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Haemophilus parainfluenzae*, *Streptococcus pyogenes*, anaerobic gram-positive cocci, and many other gram-negative bacteria. Phase 2/3 studies have shown clinical efficacy of cefdinir and other cephalosporins in the treatment of patients with acute and chronic sinusitis.

The sponsor has conducted two active-controlled trials (#983-36 and 983-37) comparing cefdinir (600mg daily) to amoxicillin/clavulanate (Augmentin®) (500/125 mg TID) in the treatment of adults with acute maxillary sinusitis. The trials were identical in rationale, design, and objectives with one important difference: in #983-36, some patients consented to sinus puncture, while others did not; in #983-37, it was required of <u>all</u> patients to undergo sinus puncture at study entry.

TRIAL # 983-6

OBJECTIVE/RATIONALE

The objective of this study was to evaluate the efficacy and safety of two 10-day dosage regimens of cefdinir (600 mg QD or 300 mg BID) versus a 10-day regimen of amoxicillin/clavulanate (amox/clav; Augmentin®) (500/125 mg TID) in the treatment of adult patients with acute maxillary sinusitis.

STUDY DESIGN

This was an investigator-blinded, randomized, comparative, multi center study with 3 parallel-treatment groups. Patients with acute maxillary sinusitis were randomly assigned to receive either cefdinir QD, cefdinir BID, or amox/clav TID for 10 days. The protocol specified a treatment group ratio of 1:1:1. The protocol and Case Report Forms (CRFs) specified that the test-of-cure (TOC) visit was to occur during the 7- to 14-day post-therapy interval and the long-term follow-up (LTFU) visit during the 21- to 35-day post-therapy interval. However, patients who began BID or TID treatment in the afternoon or evening of Day 1 did not complete therapy until Day 11. Therefore, a TOC visit scheduled for Study Day 17 corresponded to Day 6 post-therapy. For purposes of analysis, the TOC window was widened to 6 to 15 days post-therapy to include these patients.

The study was designed to enroll both patients who did, and patients who did not, consent to undergo a sinus puncture at baseline (for the purpose of pathogen isolation). Patients who did not have a sinus puncture were potentially clinically evaluable only, whereas, patients who *did* have a baseline sinus puncture were potentially microbiologically and clinically evaluable. When adequate enrollment of clinically evaluable patients was achieved (i.e., met and surpassed the required number designated in the protocol), study centers were provided written notification that, beginning January 15, 1993, only patients who consented to a baseline sinus puncture were to be enrolled.

STUDY MANAGEMENT

Forty-two centers in the United States participated in this study, which was monitored by Parke-Davis Pharmaceutical Research. Investigators met to review the protocol on April 5, 1992. Identical protocols and case report forms were used by all centers. The study was conducted under the Good Clinical Practice Guidelines. Institutional review board approvals and written informed patient consents were obtained from each center prior to patient enrollment.

Amendment 1 required that magnesium- or aluminum-containing antacids should be withheld for 2 hours before and after study drug dosing. This amendment applied to all active centers. Addendum A was implemented to further characterize the pharmacokinetics of cefdinir in

patients with acute maxillary sinusitis. This addendum applied only to Centers 5, 20, 26, and 33. The pharmacokinetic results are reported separately in RR-MEMO 764-02163.

There were no intentional code breaks in this study. Center 30 inadvertently used the investigator's copy of the randomization code card for dispensing drug. However, this did not constitute a true code break, and the investigator blinding was not compromised. The blind was broken on March 16, 1995.

A total of 1229 patients entered the study and 1109 patients (90%) completed treatment (Table 1). The first patient began treatment on May 21, 1992, and the last patient completed the last follow-up visit on August 4, 1994. Clinical laboratory and microbiologic data were measured by a central laboratory.

Medical Officer's Comments:

The medical officer agreed with the design and management of the study as appropriate for testing cefdinir against standard comparator therapy for acute maxillary sinusitis.

TABLE 1. List of Investigators

Center	Investigator	Number of Patients		
		Randomized to Treatment	Completed Treatment	Clinically Evaluable[a]
1	J. Applegate	13	9	8
2	C. Banov	27	25	26
3	S. Barton	4	4	3
4	S. Chartrand	4	4	4
5	R. Chiulli	35	28	28
6	M. Dennington	79	73	62
7	R. Slavin	9	9	7
8	D. Dvorin	11	10	6
9	S. Goldstein	6	5	4
10	W. Gooch III	59	58	51
11	G. Handley	18	11	11
12	H. Harris	18	14	16
13	J. Hedrick	36	35	33
14	S. Hirsch	61	57	50
15	J. Johnson	1	1	1
16	J. Klimas	4	2	1
17	M. Lawrence	12	11	9
18	T. Littlejohn III	42	39	37
19	H. Loveless	21	18	13

Table 1 (continued)

20	J. McCarty	63	59	54
21	D. McCluskey	22	18	18
23	R. Nielsen	68	64	60
24	D. Pearlman	1	0	0
25	A. Puopolo	33	27	23
26	J. Scott	39	36	35
27	J. Salisbury	48	45	39
28	W. Schoenwetter	12	12	10
29	G. Shapiro	35	35	31
30	S. Wiederhold	43	34	32
33	S. Weakley	17	17	16

[a] Included in clinically evaluable patient analyses at TOC

TABLE 1. List of Investigators (Continued)

Center	Investigator	Number of Patients		
		Randomized to Treatment	Completed Treatment	Clinically Evaluable[a]
34	S. Weisberg	2	2	2
35	A. Shah	12	11	9
36	J. Gwaltney	75	72	63
38	R. Fiddes	116	94	81
39	R. Gore	2	2	1
41	N. Garrison	48	43	37
42	R. Ziering	23	20	19
43	A. Goforth	36	35	35
46	P. Obert	6	5	4
48	K. Gien-Gia Hoang	18	18	13
50	R. Schwartz	29	28	16
Total		1229	1109	982

[a] Included in clinically evaluable patient analyses at TOC

Materials

Cefdinir capsules and amox/clav tablets were packaged and provided by Parke-Davis Pharmaceutical Research (Table 2).

TABLE 2. Study Medication

	Lot	Formulation
Cefdinir 300-mg Capsules	CM 080051 9	134393-25
	CM 086051 9	134393-25
	CM 106061 9	134393-25
	CM 1781292 9	134393-25
Amox/Clav '500' mg Tablets	TB2616 9	Marketed
	TM2947 9	Marketed
	TS0111 9	Marketed
	WR0924 9	Marketed

Drug Administration

Study medications were administered orally on a QD, BID, or TID schedule and were taken without regard to meals (Table 3). To maintain investigator blinding, medications were dispensed by a third party and all records concerning medication information were kept in a separate location. Additionally, patients were instructed not to reveal the dose regimen or formulation of study medication to the investigator.

TABLE 3. Dosing Schedule

Treatment Group	Dose (Number of Capsules or Tablets)		
	Morning	Afternoon	Evening
Cefdinir QD	2 × 300 mg	None	None
Cefdinir BID	1 × 300 mg	None	1 × 300 mg
Amox/Clav TID	1 × 500 mg	1 × 500 mg	1 × 500 mg

Methods of Assigning Patients to Treatment

An independent randomization schedule was prepared for each center. A block size of 6 patients was used, with 2 treatment replicates per block, consistent with the protocol-specified 1:1:1 treatment group ratio.

At each center, patients who met the entry criteria at screening were assigned the next consecutive patient number according to the randomization schedule and were dispensed the corresponding study medication. The patient number and dose regimen were preprinted on each package of study medication; the treatment group and total daily dose were recorded on the appropriate case report form by the third party who dispensed the medication (not the investigator).

Inclusion Criteria

Eligible patients were:

- at least 13 years of age,
- either males or nonpregnant, nonlactating females who were unable or unlikely to become pregnant during treatment (postmenopausal, surgically sterilized, sexually inactive, or using barrier or hormonal method of birth control),
- were to be diagnosed with acute maxillary sinusitis (current episode ≤4 weeks duration) confirmed by x-ray, and present with purulent nasal discharge and localized facial pain.

Exclusion Criteria

Patients were excluded from the study if they had:

- Chronic maxillary sinusitis or a primary diagnosis of acute or chronic frontal or ethmoid sinusitis;
- Complicating factors or diseases that precluded evaluation of response to study medication;
- Indwelling nasogastric tubes or drains;
- Hepatic disease, obstruction of the biliary tract, or hepatic enzyme levels >2 times the upper limit of normal;
- Serum creatinine >1.5 times the upper limit of normal or creatinine clearance <30 mL/min;
- Hypersensitivity to β-lactam drugs;
- A concomitant infection requiring systemic antimicrobial therapy or local intranasal antibiotics;
- Received any other investigational drug within the 4 weeks prior to this study;
- Received cefdinir at any previous time; or
- Received another systemic or intranasal antibiotic within 48 hours or <5 of the prior antibiotic's half-lives before the first dose of study medication.

Medical Officer's Comments

The medical officer agreed with the inclusion and exclusion criteria established for the study.

Prohibited Medications or Precautions

Concurrent treatment with other systemic antibiotics, local intranasal antibiotics, or probenecid was not allowed during the study. Probenecid has been reported to inhibit renal tubular secretion of concomitantly administered cefdinir, resulting in a 50% increase in the elimination half-life.[15]

Concurrent dietary iron supplements, including iron-containing multivitamins, were also not allowed. This was because of concerns that the bioavailability of cefdinir may be decreased following formation of a nonabsorbable cefdinir-iron complex in the gastrointestinal tract.[16]

Magnesium- or aluminum-containing antacids were to be withheld 2 hours before and after study-drug dosing.

Antihistamines, oral and topical steroids, and nasal decongestants were discouraged but not prohibited.

Guidelines for Patient Withdrawal

Treatment could be discontinued early because of lack of efficacy, an adverse event, a laboratory abnormality, lack of compliance, or patient request. Patients could also be withdrawn from the study after completing treatment but before the LTFU visit. All patients who received at least 3 days of therapy were to have a complete physical examination, clinical assessment, clinical laboratory tests, and x-ray assessment at the time of withdrawal. These patients were also evaluated at the TOC and LTFU visits, provided they had received no additional antibacterial therapy in the interim.

Criteria for Evaluation

Efficacy

Efficacy assessments were based on clinical and microbiologic responses at the TOC visit: clinical cure rate summarized by patient, microbiologic eradication rate summarized by pathogen, and microbiologic eradication rate summarized by patient. The LTFU visit provided information on recurrence of infection.

TABLE 4. Clinical Observations and Laboratory Measurements

	Baseline[a]	Day 1	Days 3 to 5	Day 10	Posttherapy Visits	
					Days 6-15[b]	Days 21-35[c]
Medical History	X					
Physical Examination[d]	X				X	X
Clinical Assessment of Disease[d]	X		X		X	X
Clinical Laboratory Tests[d,e]	X				X	X[f]
Efficacy Assessment[d]					X	X
Sinus X-Ray[d]	X				X	X
Sinus Aspiration	X[g]				X[h]	X[h]
Adverse Events		X----------				----------X
Dosing		X----------		---------- X		

[a] Forty-eight hours prior to start of therapy
[b] Test-of-cure (TOC) visit
[c] Long-term follow-up (LTFU) visit
[d] Perform also after early withdrawal
[e] Hematology, blood chemistry, urinalysis, and a baseline pregnancy test for women of childbearing potential
[f] If abnormalities detected at the TOC or early termination visits
[g] Optional prior to January 15, 1993.
[h] Only 1 posttherapy aspiration was requested for those patients who had a culture-positive baseline aspirate and who were not showing satisfactory (or continuing satisfactory for LTFU) clinical improvement.

Clinical Response

The clinical signs and symptoms in this study were purulent nasal discharge, localized facial pain, localized tenderness, nasal obstruction, headache, alteration of smell, and fever (>100.4°F or >38°C). The clinical response for each patient was assessed separately by the investigator and the sponsor. The investigator assessment of clinical response rate was defined as the percentage of patients cured or improved based on the investigator's opinion as to clinical outcome. The sponsor assessment of clinical response rate was defined as the percentage of patients cured and was based on a quantitative analysis of signs and symptoms, or clinical score (see Appendix A.4). In the original protocol, the sponsor assessment also included an Improved category, but in subsequent discussions with FDA Parke-Davis agreed to delete this category and response criteria were redefined to accommodate this change (Table 5).

TABLE 5. Rules for Determining the Combined Investigator/Sponsor Clinical Assessment at TOC and LTFU[a,b]

	Investigator Assessment at TOC			
Sponsor Assessment at TOC	Cure	Improvement	Failure	Not Assessable
Cure	**Cure**	**Cure**	**Failure**	**Cure**
Failure	**Cure**	**Failure**	**Failure**	**Failure**
Not Assessable	**Cure**	**Not Assessable**	**Failure**	**Not Assessable**

	Investigator Assessment at LTFU			
Sponsor Assessment at LTFU	Cure	Improvement	Recurrence	Not Assessable
Cure	**Cure**	**Cure**	**Recurrence**	**Cure**
Failure	**Cure**	**Failure**	**Recurrence**	**Failure**
Recurrence	**Cure**	**Recurrence**	**Recurrence**	**Recurrence**
Not Assessable	**Cure**	**Not Assessable**	**Recurrence**	**Not Assessable**

[a] The combined assessments are shown in bold typeface.
[b] If a patient had a combined clinical assessment of failure at TOC, the patient was automatically a failure on both the sponsor and combined assessment scales at LTFU, regardless of any subsequent assessments.

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Microbiological Response

The microbiologic eradication rate by pathogen was defined as the percentage of eradicated baseline pathogens. Patients with multiple pathogens provided multiple observations in the analyses of microbiologic efficacy on a per pathogen basis. The microbiologic eradication rate by pathogen was calculated separately for the TOC and LTFU visit data. Pathogens could be cultured from 1 or both sinuses. The sinus side (right or left) from which each pathogen was obtained was recorded. If the same pathogen was isolated from both sinuses, they were counted as multiple pathogens.

For patients who underwent antral puncture for the culture of a baseline pathogen, the microbiologic response of each baseline pathogen was defined as:

- **Eradication**: Pathogen not present in follow-up culture from baseline side *or* no follow-up culture performed from baseline side but patient assessed as a clinical cure on baseline side (presumed eradication);
- **Persistence**: Pathogen present in follow-up culture from baseline side *or* no follow-up culture performed from baseline side but patient assessed as a clinical failure/recurrence on baseline side (presumed persistence); or
- **Not Assessable**: No proven baseline pathogen or no follow-up data on baseline side.

Microbiologic Response by Patient

The microbiologic eradication rate by patient was defined as the percentage of patients with eradication of all baseline pathogens. Each patient provided only 1 observation. The microbiologic eradication rate was calculated separately for the TOC and LTFU visits.

At the TOC visit, patients with a positive baseline culture were classified according to their overall microbiologic response based on baseline and 6- to 15-days posttherapy results:

- **Eradication**: All baseline pathogens eradicated at TOC *or* no TOC culture performed and presumed eradication;
- **Persistence**: Persistence of at least 1 baseline pathogen at TOC *or* no TOC culture performed and presumed persistence; or
- **Not Assessable**: No proven baseline pathogen *or* no baseline signs/symptoms *or* no follow-up clinical data.

At the LTFU visit, patients with a positive baseline culture were classified according to their overall microbiologic results based on baseline, 6- to 15-days posttherapy, and 21- to 35-days posttherapy results.

- **No Relapse**: Patients with eradication or presumed eradication of all baseline pathogens at TOC *and* continued eradication or presumed eradication of all baseline pathogens at LTFU;
- **Relapse**: Patients with eradication or presumed eradication at TOC *and* persistence or

presumed persistence of at least 1 baseline pathogen at LTFU;

- **Persistence**: All patients with persistence at TOC *or* no TOC culture and presumed persistence; or
- **Not Assessable**: No proven baseline pathogen *or* no baseline signs/symptoms/ *or* no follow-up clinical data.

Summaries and analysis populations examined in this report are: a clinically evaluable population, a population of patients who were both microbiologically and clinically evaluable, a modified intent-to-treat (MITT) population, and an intent-to-treat (ITT) population.

Clinically Evaluable Population

Patients in the clinically evaluable population had the correct indication as documented by sinus imaging results and the minimum required clinical signs and symptoms at baseline; took study medication as prescribed; did not take nonstudy systemic antibacterial therapy for other concurrent infections; did not take a prior systemic antibacterial within 48 hours prior to the first dose of study medication; had their clinical assessments of signs and symptoms performed within the TOC window; and did not have a randomization violation, resistant baseline pathogen, or a condition preventing clinical evaluation. Patients were not excluded from this data set due to having no baseline pathogen, missing microbiologic data at baseline or follow-up, or microbiologic data collected outside the TOC window specified in the protocol.

Microbiologically-Clinically Evaluable Population

The microbiologically-clinically evaluable patients had no known protocol violations that might have affected the efficacy assessments. Any of the protocol violations that resulted in exclusion from the clinically evaluable analyses plus missing microbiologic data at baseline, no proven baseline pathogen, or off-schedule cultures resulted in exclusion of patient data from the microbiologically-clinically evaluable patient analyses.

MITT Population

Patients in the MITT population had the correct indication as documented by sinus imaging results, received study medication, had at least 1 baseline pathogen, and had a follow-up culture or clinical assessment of signs and symptoms.

The ITT population

The ITT population were those patients randomized to treatment. Patients who had no baseline pathogen or no follow-up culture plus no follow-up clinical assessment were considered to have microbiologic persistence in the ITT analyses. Patients who had no follow-up clinical assessment were categorized as clinical failures in the ITT analyses.

Clinically qualified patients were clinically evaluable patients who did not have any additional protocol violations between the TOC and LTFU visits, had a clinical assessment performed within the LTFU window, and did not develop any confounding infection between the TOC and LTFU visits. Microbiologically-clinically qualified patients also had to meet these criteria but

could be disqualified if they had the LTFU culture outside of the LTFU window.

Sample Size

An estimated sample size of 190 clinically evaluable patients per randomized group was required to provide at least 80% probability (power) of demonstrating the equivalence of clinical cure rates of cefdinir and amox/clav. An overall response rate of 90% and an equivalence threshold of ±10% were assumed to assess the equivalence of the cefdinir and amox/clav clinical cure rates at the TOC visit, using the two-tailed, 95% confidence interval method.

The efficacy objectives of this study were to estimate the clinical and microbiologic response rates of cefdinir QD, cefdinir BID, and amox/clav; and to evaluate the equivalence of the clinical response rates of cefdinir QD versus amox/clav, cefdinir BID versus amox/clav, and cefdinir QD versus cefdinir BID at the TOC visit, based on predefined fixed criteria.

The primary outcome measure was the clinical cure rate in the clinically evaluable patients at the TOC visit. Secondary outcome measures were the microbiologic eradication rate by pathogen and the microbiologic eradication rate by patient. No inferential analyses were performed on microbiologic eradication data. The primary analysis time point was the TOC visit; the LTFU visit was a secondary analysis time point. Data from the LTFU visit were summarized and presented as supporting information. No inferential analyses were performed on LTFU data.

Descriptive statistics used in this study consisted primarily of frequency counts and response rates. Means, standard errors, minima, maxima, and medians were used where appropriate.

At baseline, the demographic data, microbiologic results, clinical signs and symptoms, and some history data were summarized to facilitate baseline treatment group comparisons.

At TOC, the clinical cure rates and mean patient and sinus clinical signs/symptoms scores were calculated for each treatment group in the clinically evaluable, microbiologically-clinically evaluable, and ITT patient populations. The microbiologic eradication rates by pathogen and by patient were calculated for each treatment group in the microbiologically-clinically evaluable, MITT, and ITT patient populations.

At LTFU, the clinical cure rates (i.e., the "no recurrence" rates) and mean patient and sinus clinical signs/symptoms scores were calculated for each treatment group in the clinically qualified, microbiologically-clinically qualified, and ITT patient populations. The microbiologic eradication rates by pathogen and by patient (i.e., the "no relapse" rates) were calculated for each treatment group in the microbiologically-clinically qualified patient population.

Statistical Methods

Two methods of investigating treatment equivalence at TOC were used. One method was based

on pooled estimates of the treatment group response rates. The pooled estimates gave equal weight to each patient in the analysis, and were calculated as the total number of cures in the study population, divided by the total number of cases.

The second method used a categorical modeling procedure to obtain center-adjusted estimates of the response rates and their standard errors. The model contained terms for study center, treatment group, and treatment-by-center interaction. The resulting parameter estimates were used to construct estimates of the treatment group response rates and standard errors in which each center was given equal weight.

Pairwise treatment differences were defined as cefdinir QD or BID minus amox/clav, and cefdinir QD minus cefdinir BID. The estimated response rate differences and their standard errors were used to construct a two-tailed, 95% confidence interval for each treatment difference, using a standard normal approximation[18]. Each 95% confidence interval was evaluated by comparing it to the fixed criterion for equivalence, which was selected on the basis of the 2 rates (pooled or center-adjusted) under comparison (Table 7). To demonstrate equivalence, each 95% confidence interval must contain zero and its limits must fall within the indicated bounds.

TABLE 6. Fixed Criteria for Evaluating Treatment Equivalence

Maximum Estimated Response Rate of the 2 Treatment Groups	Treatments Are Equivalent If 95% Confidence Interval for Treatment Difference Is Within Bounds
90% or greater	-10%, +10%
80% - 89%	-15%, +15%
70% - 79%	-20%, +20%

Results of the 2 methods were compared for consistency. When the 2 methods agreed, the pooled analysis was presented as the final analysis. If results from the 2 methods disagreed, the differences were addressed and results from both methods were presented. A side-by-side comparison of all results from the 2 analysis methods is shown in Appendix D.1.

An exploratory Cochran-Mantel-Haenzel (CMH) analysis adjusting for center was performed to look for possible treatment group differences in the clinical cure rates. Results of the Breslow-Day test were reviewed in evaluating the consistency of the relationship between treatment and response among centers.

For each statistical procedure adjusting for center, study centers contributing 12 or fewer patients, or 2 or fewer patients in any treatment group were pooled prior to analysis. Pooling was performed independently for each analysis population after any required data exclusions were made.

TABLE 7. Patient Characteristics - ITT Patients
[Number (%) of Patients]

Variable	Cefdinir QD N = 403		Cefdinir BID N = 412		Amox/Clav N = 414		Total N = 1229	
Sex								
Male	150	(37.2)	148	(35.9)	155	(37.4)	453	(36.9)
Female	253	(62.8)	264	(64.1)	259	(62.6)	776	(63.1)
Race								
White	358	(88.8)	366	(88.8)	356	(86.0)	1080	(87.9)
Hispanic	23	(5.7)	21	(5.1)	23	(5.6)	67	(5.5)
Black	19	(4.7)	18	(4.4)	32	(7.7)	69	(5.6)
Other[a]	3	(0.7)	6	(1.5)	3	(0.7)	12	(1.0)
Age, yr								
Median	36		36		36		36	
Range	12-83		13-88		13-79		12-88	
Distribution								
6 to <13[b]	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.1)
13 to <18	32	(7.9)	31	(7.5)	33	(8.0)	96	(7.8)
18 to <65	351	(87.1)	354	(85.9)	363	(87.7)	1068	(86.9)
≥65	19	(4.7)	27	(6.6)	18	(4.3)	64	(5.2)

[a] Black/White mix, Caucasian/Tongan, Filipino, Hispanic, Jordanian, Native American, Oriental, Pakistan, Romanian, Spanish, Tongan

[b] One patient was 12 years old at the start of the study.

TABLE 8. Patient Exposure to Study Medication - All Patients
[Number of Patients]

Days of Study Medication	Cefdinir		Amox/Clav N = 414
	QD N = 403	BID N = 412	
1	2	1	5
2	3	4	3
3	4	4	5
4	4	5	8
5	3	6	5
6	1	1	3
7	2	5	3
8	3	4	4
9	2	3	0
10	339	242	122
11	27	128	234
12	3	2	8
13	0	1	2
14	1	0	1
15	0	0	1
16	0	0	1
Median	10	10	11
Unknown[a]	8	6	8

[a] Includes 4 patients who received no study medication

Table 9. Selected Demographics, All Enrolled Patients (Intent-to-Treat Population)

Baseline Parameters		Cefdinir 600mg QD	Cefdinir 300 mg BID	Augmentin 500 mg TID
Age (years)	med.	36.0	36.0	36.0
	min.	12.0	13.0	13.0
	max.	83.0	88.0	79.0
Weight (kg)	med.	73.2	71.2	73.6
	min.	40.0	43.2	36.4
	max.	151.8	140.9	141.8
Height (cm)	med.	167.6	167.6	167.6
	min.	146.8	134.6	133.4
	max.	203.2	198.1	198.1

Table 10. Selected Demographics, Clinically Evaluable Patients

Baseline Parameters		Cefdinir 600mg QD	Cefdinir 300 mg BID	Augmentin 500 mg TID
Age (years)	med.	36.0	35.0	36.0
	min.	12.0	13.0	13.0
	max.	83.0	88.0	79.0
Weight (kg)	med.	72.7	72.7	72.7
	min.	40.0	43.2	36.4
	max.	151.8	140.9	141.8
Height (cm)	med.	167.6	167.6	167.6
	min.	148.1	134.6	133.4
	max.	203.2	198.1	198.1

Table 11. Selected Demographics, Microbiologically-Clinically Evaluable Patients

Baseline Parameters		Cefdinir 600mg QD	Cefdinir 300 mg BID	Amox./clav. 500 mg TID
Age (years)	med.	36.0	36.0	36.0
	min.	13.0	13.0	14.0
	max.	83.0	88.0	72.0
Weight (kg)	med.	76.6	72.3	76.4
	min.	40.5	43.2	51.4
	max.	143.2	113.6	141.8
Height (cm)	med.	170.2	170.2	168.9
	min.	152.4	146.3	152.4
	max.	203.2	193.0	188.0

Medical Officer's Comment

The comparison of demographic characteristics between ITT patients, clinically-evaluable patients, and microbiologically-clinically evaluable patients show no significant differences in the median age, weight, or stature between treatment groups or between populations for analysis. The median stature of the patients in the Cefdinir treatment groups of the microbiologically-clinically evaluable population was about 2.4 cm taller than the median stature of those treatment groups in the ITT and the clinically evaluable population. The median stature of the patients in the Augmentin treatment group of the microbiologically-clinically evaluable population was about 1.3 cm taller than the median stature of that treatment groups in the ITT and the clinically evaluable population.

Clinical Signs and Symptoms

Sixteen patients (1%) had no baseline nasal discharge and 33 patients (3%) had no baseline facial pain. Only 2 patients (Patient 13, Center 21 and Patient 264, Center 36) were missing both of these signs/symptoms at baseline. Most patients entered the study with facial tenderness and nasal obstruction on at least one side, and also had headache and alteration of smell. Only 2% of patients had a fever at baseline. There were no apparent differences in baseline signs and symptoms between treatment groups, or between the ITT, clinically evaluable, and microbiologically-clinically evaluable patient populations (Table 13).

TABLE 12. Signs and Symptoms at Baseline
(Percent of Patients)

	ITT Patients N = 1229	Clinically Evaluable Patients N = 977	Microbiologically-Clinically Evaluable Patients N = 242
Patient Signs and Symptoms			
Headache	87	87	82
Alteration of Smell	60	61	60
Fever	2	2	3
Sinus Signs and Symptoms			
Left Purulent Nasal Discharge	90	90	89
Right Purulent Nasal Discharge	88	89	86
Left Facial Pain	86	86	82
Right Facial Pain	85	86	81
Left Facial Tenderness	76	76	73
Right Facial Tenderness	75	75	71
Left Nasal Obstruction	85	85	85
Right Nasal Obstruction	83	84	82

TABLE 13. Distribution of Patients by Baseline Pathogen - All Patients With Baseline Pathogens
(Number of Patients)

Baseline Pathogen	Cefdinir QD N = 403[a]	Cefdinir BID N = 412[a]	Amox/Clav N = 414[a]
Gram-Positive			
Staphylococcus aureus	12	19	8
Staphylococcus epidermidis	0	0	1
Staphylococcus salivarius	0	1	0
Streptococcus agalactiae	1	0	2
Streptococcus anginosus	2	2	0
Streptococcus equi	1	0	0
Streptococcus equisimilis	0	2	1
Streptococcus pneumoniae	19	21	17
Streptococcus pyogenes	4	1	5
Streptococcus Group G	0	1	0
Gram-Negative			
Citrobacter diversus	0	0	1
Enterobacter aerogenes	1	1	1
Escherichia coli	1	1	2
Eikenella corrodens	1	0	0
Haemophilus influenzae	16	15	21
Haemophilus parahaemolyticus	0	1	1
Haemophilus parainfluenzae	2	5	6
Klebsiella pneumoniae	1	0	2
Moraxella catarrhalis	10	9	9
Morganella morganii	1	0	0
Neisseria meningitidis	1	0	0
Proteus mirabilis	0	0	1
Multiple[b]	25	22	33
Total[c]	98	101	111

[a] Number of patients randomized to treatment.

[b] See Appendix C.4, Vol. 198, NDA 50-739, for a complete summary.

[c] Patients with baseline pathogens.

Clinical Outcome Evaluation by Medical Officer

A random sampling of ten percent of the patients from each treatment arm of the study was made. Among the random sample of forty (40) patients of the treatment group receiving Cefdinir 600 mg q.d., there were two patients whose sponsor-designated outcome the medical officer disputed. One was deemed a failure by sponsor, but a cure by medical officer (site 13, patient 11). The other was deemed a cure by the sponsor and a failure by the medical officer (site 18, patient 223). The medical officer questioned but did not absolutely disagree with the outcomes for five of the patients deemed cures by the sponsor. Among the random sample of forty-one (41) patients of the treatment group receiving Cefdinir 300 mg b.i.d., there were five patients whose sponsor-designated outcome the medical officer questioned. Three of these were deemed failures by the sponsor. The medical officer deemed site 10, patient 211 and site 21, patient 8 each to have a good clinical response. The medical officer would have excluded site 30, patient 6 at the outset for lack of findings on sinus radiographs. The sponsor deemed site 43, patient 225 a cure, and although this patient was not deemed "cured" by the investigator, the combined investigator/sponsor clinical assessment of "cured" was within the protocol's rules for clinical assessment.

Among the random sample of forty-one (41) patients of the treatment group receiving Amoxicillin/clavulanate 500 mg t.i.d., there were twelve patients whose sponsor-designated outcome the medical officer questioned. Six of the twelve were deemed failures and six were deemed cures by the sponsor. Any effect of disputed interpretation should have been canceled by the equal numbers of questioned outcomes.

Assuming that the random ten percent samplings accurately reflect the validity of the sponsor's assessments overall, the sponsor's evaluation of clinical efficacy can be reviewed.

Table 14. Patients by Treatment Arm and by Analysis Population.

	Cefdinir QD	Cefdinir BID	Amox/Clav	Total (%)
Enrolled (ITT)	403	412	414	1229 (100%)
Clinically Evaluable	323	326	333	982 (79.9%)
Micro-Clinically Evaluable	74	79	89	242 (19.7%)

Table 15. Clinical and Microbiologic/Clinical Outcomes.

Clinically Cured: at TOC at LTFU	233/323 (72%) 182/209 (87%)	240/326 (74%) 184/212 (87%)	248/333 (74%) 189/216 (88%)	721/982 (73%) 555/637 (87%)
Micro/Clin Cured at LTFU	43/49 (88%)	48/56 (86%)	57/66 (86%)	148/171 (87%)

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TABLE 16. Patient Characteristics - Clinically Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir QD N = 323		Cefdinir BID N = 326		Amox/Clav N = 333		Total N = 982	
Sex								
Male	124	(38.6)	119	(36.5)	127	(38.4)	370	(38.1)
Female	199	(61.6)	207	(63.5)	206	(61.9)	612	(62.3)
Race								
White	292	(90.4)	291	(89.3)	285	(85.6)	868	(88.4)
Hispanic	18	(5.6)	18	(5.5)	20	(6.0)	56	(5.7)
Black	13	(4.0)	10	(3.1)	26	(7.9)	49	(5.0)
Other[a]	0	(0.0)	6	(1.8)	2	(0.6)	8	(0.8)
Age, yr								
Median	36		35		36		36	
Range	12-83		13-88		13-79		12-88	
Distribution								
6 to <13[b]	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)
13 to <18	28	(8.7)	26	(8.0)	26	(7.8)	80	(8.1)
18 to <65	278	(86.1)	278	(85.3)	292	(87.7)	848	(86.4)
≥65	16	(5.0)	22	(6.7)	15	(4.5)	53	(5.4)

[a] Caucasian/Tongan, Hispanic, Jordanian, Native American, Oriental, Pakistan, Romanian, Spanish
[b] One patient was 12 years old at the start of the study.

Medical Officer's Comments

Clinical cure rates were similar between both Cefdinir treatment arms, and both were comparable to the Augmentin treatment arm. Clinical cure rates were comparable both with and without the patients from site 38 included in the analysis. There was a slightly higher rate of clinical cure with the regimen of Cefdinir 600 mg qd versus Cedinir 300 mg bid in the analysis excluding site 38 (67.5% versus 63.7%), but the difference was not statistically significant.

Table 17. Statistical Comparisons of Clinically Evaluable Patients by Treatment Arms.

	Cefdinir QD	Cefdinir BID	Amox/Clav
Clinical Response Rates			
All Sites	72.1% (233/323)	73.6% (240/326)	74.5% (248/333)
Excluding Site 38	72.0% (216/300)	70.8% (209/295)	72.5% (222/306)

	Cefdinir QD vs. Amox/Clav		Cefdinir BID vs. Amox/Clav	
	Unadjusted 95% CI	CMH p-value	Unadjusted 95% CI	CMH p-value
All Sites	(-9.1%, 4.4%)	0.677	(-7.6%, 5.8%)	0.817
Excluding Site 38	(-7.7%, 6.7%)	0.925	(-8.9%, 5.5%)	0.739

	Cefdinir QD vs. Cefdinir BID	
	Unadjusted 95% CI	CMH p-value
All Sites	(-8.3%, 5.4%)	0.792
Excluding Site 38	(-6.1%, 8.4%)	0.706

Table 18. Statistical Comparisons of ITT Patients by Treatment Arms.

	Cefdinir QD	Cefdinir BID	Amox/Clav
Clinical Response Rates			
All Sites	67.0% (270/403)	66.0% (272/412)	68.8% (285/414)
Excluding Site 38	67.5% (247/366)	63.7% (237/372)	68.5% (257/375)

	Cefdinir QD vs. Amox/Clav		Cefdinir BID vs. Amox/Clav	
	Unadjusted 95% CI	CMH p-value	Unadjusted 95% CI	CMH p-value
All Sites	(-8.2%, 4.6%)	0.597	(-9.2%, 3.6%)	0.375
Excluding Site 38	(-7.8%, 5.7%)	0.793	(-11.6%, 2.0%)	0.156

	Cefdinir QD vs. Cefdinir BID	
	Unadjusted 95% CI	CMH p-value
All Sites	(-5.5%, 7.5%)	0.737
Excluding Site 38	(-3.1%, 10.6%)	0.261

Confirmed Microbiologic Diagnosis and Baseline Susceptibility

At the baseline visit, 45% (547/1229) of patients randomized to treatment underwent a sinus aspiration. Of these, 57% (310/547) had a confirmed baseline pathogen(s). The most common single pathogens were *Streptococcus pneumoniae* (57 patients), *Haemophilus influenzae* (52 patients), *Staphylococcus aureus* (39 patients), and *Moraxella catarrhalis* (28 patients). Multiple pathogens were cultured from 80 patients (Table 11).

A total of 405 pathogens were isolated at baseline (Table 12). Of these, 16 isolates were resistant to cefdinir and 17 were resistant to amox/clav. Of *H. influenzae* isolates with documented β-lactamase results 34/80 (43%) were β-lactamase positive; none were resistant to cefdinir and 1 was resistant to amox/clav. Except for 1 isolate that had intermediate susceptibility to cefdinir, all β-lactamase-negative *H. influenza* isolates were susceptible to both study drugs (1 isolate had unknown susceptibility to both drugs). A total of 40/44 (91%) of *M. catarrhalis* isolates with β-lactamase results were β-lactamase positive; none were resistant to either cefdinir or amox/clav. All β-lactamase-negative *M. catarrhalis* isolates were also sensitive to both study drugs.

TABLE 19. Distribution of Patients by Baseline Pathogen - All Patients With Baseline Pathogens
(Number of Patients)

Baseline Pathogen	Cefdinir QD N = 403[a]	Cefdinir BID N = 412[a]	Amox/Clav N = 414[a]
Gram-Positive			
Staphylococcus aureus	12	19	8
Staphylococcus epidermidis	0	0	1
Staphylococcus salivarius	0	1	0
Streptococcus agalactiae	1	0	2
Streptococcus anginosus	2	2	0
Streptococcus equi	1	0	0
Streptococcus equisimilis	0	2	1
Streptococcus pneumoniae	19	21	17
Streptococcus pyogenes	4	1	5
Streptococcus Group G	0	1	0
Gram-Negative			
Citrobacter diversus	0	0	1
Enterobacter aerogenes	1	1	1
Escherichia coli	1	1	2
Eikenella corrodens	1	0	0
Haemophilus influenzae	16	15	21
Haemophilus parahaemolyticus	0	1	1
Haemophilus parainfluenzae	2	5	6
Klebsiella pneumoniae	1	0	2
Moraxella catarrhalis	10	9	9
Morganella morganii	1	0	0
Neisseria meningitidis	1	0	0
Proteus mirabilis	0	0	1
Multiple[b]	25	22	33
Total[c]	98	101	111

[a] Number of patients randomized to treatment.
[b] See Appendix C.4 for a complete summary.
[c] Patients with baseline pathogens.

TABLE 20. Patient Characteristics - Microbiologically-Clinically Evaluable Patients
[Number (%) of Patients]

Variable	Cefdinir QD N = 74	Cefdinir BID N = 79	Amox/Clav N = 89	Total N = 242
Sex				
Male	33 (44.6)	37 (46.8)	35 (39.3)	105 (43.4)
Female	41 (55.4)	42 (53.2)	54 (60.7)	137 (56.6)
Race				
White	68 (91.9)	71 (89.9)	71 (79.8)	210 (86.8)
Hispanic	4 (5.4)	4 (5.1)	11 (12.4)	19 (7.9)
Black	2 (2.7)	2 (2.5)	7 (7.9)	11 (4.5)
Other[a]	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.4)
Age, yr				
Median	36	36	36	36
Range	13-83	13-88	14-72	13-88
Distribution				
13 to <18	4 (5.4)	5 (6.3)	3 (3.4)	12 (5.0)
18 to <65	66 (89.2)	69 (87.3)	79 (88.8)	214 (88.4)
≥65	4 (5.4)	5 (6.3)	7 (7.9)	16 (6.6)

[a] Hispanic, Jordanian

Clinical Cure

For microbiologically-clinically evaluable patients, the clinical cure rate was 55/74 (74%) for the cefdinir QD group, 63/79 (80%) for the cefdinir BID group, and 76/89 (85%) for the amox/clav group. These rates were similar to those of clinically evaluable patients with a baseline sinus aspiration (see Section 6.2.1.1, Table 20).

Microbiologic Eradication by Pathogen

The microbiologic eradication rate by pathogen was 69/92 (75%) for the cefdinir QD group, 76/94 (81%) for the cefdinir BID group, and 100/118 (85%) for the amox/clav group. Because of the small number of microbiologically-clinically evaluable patients, no pairwise analyses are presented for the microbiologic eradication rates. These eradication rates were based primarily

on presumed eradication (i.e., if no follow-up sinus puncture was performed, microbiologic eradication was presumed based on clearing of clinical signs and symptoms). Of the pathogens considered eradicated, 58/69 (84%) in the cefdinir QD group, 70/76 (92%) in the cefdinir BID group, and 90/100 (90%) in the amox/clav group were presumed eradicated. There were no major differences between treatment groups in eradication rates according to pathogen (Table 21). Cefdinir QD treatment showed the highest eradication rate for *H. influenzae* (84% versus 71% to 73%), whereas cefdinir BID showed the highest eradication rate for *S. aureus* (85% versus 71% to 76%), and amox/clav showed the highest eradication rate for *S. pneumoniae* (96% versus 82% to 88%). Cefdinir BID had a lower eradication rate for *M. catarrhalis* (69%) than either cefdinir QD (92%) or amox/clav (91%).

The microbiologic eradication rates were 56/74 (76%) for the cefdinir QD group, 64/79 (81%) for the cefdinir BID group, and 74/89 (83%) for the amox/clav group. There were no apparent differences in microbiologic eradication rate by patient according to baseline pathogen(s) for the different treatment groups (Table 23). Of the patients who were assessed as having their pathogen(s) eradicated, 48/56 (86%) in the cefdinir QD group, 59/64 (92%) in the cefdinir BID group, and 69/74 (93%) in the amox/clav group had presumed eradication.

Clinical Cure

The microbiologically-clinically evaluable patients who achieved a cure at TOC and continued to satisfy protocol requirements until the LTFU visit were assessed for continued response. The clinical cure rate at LTFU was 43/49 (88%) for the cefdinir QD group, 48/56 (86%) for the cefdinir BID group, and 57/66 (86%) for the amox/clav group. Therefore, for microbiologically-clinically evaluable patients, the percentage of patients who were cured at TOC and remained cured at LTFU was high and similar for all 3 treatment groups.

Microbiologic Eradication by Pathogen

Microbiologically-clinically evaluable patients who had persistence at TOC were automatically considered to have persistence at LTFU. Of the qualified patients who had presumed eradication at the TOC visit, 53/60 (88%) in the cefdinir QD group, 55/64 (86%) in the cefdinir BID group, and 76/87 (87%) in the amox/clav group also had microbiologic eradication at the LTFU visit. Thus, the observed relapse rates were similar for all treatment groups.

Microbiologic Eradication by Patient

In microbiologically-clinically evaluable patients with eradication at TOC, the continued presumed eradication rate by patient was similar for all treatment groups: 42/49 (86%) for the cefdinir QD group, 47/55 (86%) for the cefdinir BID group, and 56/64 (88%) for the amox/clav group.

Modified Intent-to-Treat Analyses

Test-of-Cure Visit (6-15 Days Post-therapy)

In the MITT population, the amox/clav treatment group achieved a higher eradication rate by pathogen and by patient than either cefdinir group (Table 24).

TABLE 21. Microbiologic Efficacy Results at TOC - MITT Patients

Treatment Group	Eradication Rate by Pathogen		Eradication Rate by Patient	
	n/N[a]	%	n/N[b]	%
Cefdinir QD	93/124	75.0	68/93	73.1
Cefdinir BID	91/120	75.8	74/97	76.3
Amox/Clav	118/143	82.5	85/104	81.7

[a] Number of pathogens eradicated or presumed eradicated/total number of pathogens
[b] Number of patients with eradication or presumed eradication/total number of patients

Intent-to-Treat Analyses

Test-of-Cure Visit (6-15 Days Post-therapy)

The clinical cure rates for the ITT population at TOC were 270/403 (67%) for the cefdinir QD group, 272/412 (66%) for the cefdinir BID group, and 285/414 (69%) for the amox/clav group. The 95% CIs about each pairwise comparison showed that the ITT cure rates for the cefdinir treatment groups were statistically equivalent to amox/clav and to each other based on predefined criteria for equivalence. The 95% CIs were (-8.25%, 4.56%) about the difference between the cefdinir QD group and the amox/clav group, (-9.21%, 3.57%) about the difference between the cefdinir BID group and the amox/clav group, and (-5.50%, 7.46%) about the difference between the 2 cefdinir groups. The exploratory CMH test showed no significant difference between cefdinir QD and amox/clav treatment ($p = 0.597$) or between cefdinir BID and amox/clav treatment ($p = 0.375$).

Long-Term Follow-Up Visit (21-35 Days Post-therapy)

The clinical cure rates for all patients at the LTFU visit were 206/403 (51%) for the cefdinir QD group, 206/412 (50%) for the cefdinir BID group, and 218/414 (53%) for the amox/clav group. These rates were calculated from all patients randomized to treatment regardless of clinical assessment at TOC.

Table 22. Microbiological Eradication, by Pathogen

	Cefdinir QD	Cefdinir BID	Amox/Clav
Eradication	69/92 (75%)	76/94 (81%)	100/118(85%)
Proportion presumed eradicated	58/69 (84%)	70/76 (92%)	90/100 (100%)
Eradication proved by repeat culture (clinical failure)	11/69 (16%)	6/76 (8%)	- 0 -

TABLE 23. Microbiologic Eradication Rate by Pathogen at TOC - Pathogens From Microbiologically-Clinically Evaluable Patients

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Gram-Positive						
Staphylococcus aureus	10/14	71.4	23/27	85.2	16/21	76.2
Staphylococcus salivarius	0/0	–	1/1	100.0	0/0	–
Streptococcus agalactiae	2/2	100.0	0/0	–	3/3	100.0
Streptococcus anginosus	2/2	100.0	1/1	100.0	0/0	–
Streptococcus equi	1/1	100.0	0/0	–	0/0	–
Streptococcus equisimilis	1/1	100.0	2/2	100.0	1/1	100.0
Streptococcus pneumoniae	14/17	82.4	14/16	87.5	21/22	95.5
Streptococcus pyogenes	2/5	40.0	1/1	100.0	7/7	100.0
Streptococcus simulans	0/0	–	1/1	100.0	0/0	–
Streptococcus Group G	0/0	–	0/1	0.0	0/0	–
Gram-Negative						
Acinetobacter calcoaceticus var *anitratus*	0/0	–	0/1	0.0	0/0	–
Acinetobacter calcoaceticus var *lwoffi*	0/1	0.0	0/0	–	3/3	100.0
Citrobacter diversus	0/0	–	1/1	100.0	2/2	100.0
Enterobacter aerogenes	0/0	–	0/0	–	1/1	100.0
Enterobacter cloacae	0/0	–	0/0	–	1/1	100.0
Escherichia coli	3/5	60.0	0/1	0.0	4/5	80.0
Eikenella corrodens	0/1	0.0	0/0	–	0/0	–
Haemophilus influenzae	16/19	84.2	12/17	70.6	19/26	73.1
Haemophilus parahaemolyticus	0/0	–	1/1	100.0	0/1	0.0
Haemophilus parainfluenzae	3/5	60.0	5/5	100.0	9/10	90.0
Klebsiella oxytoca	1/1	100.0	0/0	–	0/0	–
Klebsiella pneumoniae	2/4	50.0	3/3	100.0	½	50.0
Moraxella catarrhalis	11/12	91.7	9/13	69.2	10/11	90.9
Neisseria meningitidis	0/1	0.0	0/0	–	0/0	–
Proteus mirabilis	1/1	100.0	2/2	100.0	2/2	100.0
Total	69/92	75.0	76/94	80.9	100/118	84.7

n/N = Number of pathogens eradicated/total number of pathogens

Among the microbiologically-clinically evaluable patients there were 24/62 β-lactamase-positive *H. influenzae* isolates and 33/36 β-lactamase-positive *M. catarrhalis* isolates. It did not appear that the presence of β-lactamase decreased the microbiologic eradication rates for either cefdinir or amox/clav (Table 24).

TABLE 24. Microbiologic Eradication Rate by β-Lactamase Status of *Haemophilus influenzae* and *Moraxella catarrhalis* at TOC - Pathogens From Microbiologically-Clinically Evaluable Patients

Baseline Pathogen	Cefdinir				Amox/Clav	
	QD		BID			
	n/N	%	n/N	%	n/N	%
Haemophilus influenzae						
βL+	6/6	100.0	5/6	83.3	8/12	66.7
βL-	10/13	76.9	7/11	63.6	11/14	78.6
Moraxella catarrhalis						
βL+	11/12	91.7	7/11	63.6	9/10	90.0
βL-	0/0	--	2/2	100.0	1/1	100.0

βL = β-Lactamase
n/N = Number of pathogens eradicated or presumed eradicated/total number of pathogens

Microbiologic Eradication by Patient

The microbiologic eradication rates were 56/74 (76%) for the cefdinir QD group, 64/79 (81%) for the cefdinir BID group, and 74/89 (83%) for the amox/clav group. There were no apparent differences in microbiologic eradication rate by patient according to baseline pathogen(s) for the different treatment groups (Table 23). Of the patients who were assessed as having their pathogen(s) eradicated, 48/56 (86%) in the cefdinir QD group, 59/64 (92%) in the cefdinir BID group, and 69/74 (93%) in the amox/clav group had presumed eradication.

Table 25. Microbiological Eradication by Patient.

	Cefdinir QD	Cefdinir BID	Amox/Clav
Eradication	56/74 (76%)	64/79 (81%)	74/89 (83%)
Proportion presumed eradicated	48/56 (86%)	59/64 (92%)	69/74 (93%)
Eradication proved by repeat culture (clinical failure)	8/56 (14%)	5/64 (8%)	5/74 (7%)