Reviewers' note: *The above investigators are acceptable with the exception of Ziering. This data was excluded from the Sponsor's and reviewers' analysis because of concerns regarding the reliability of Dr. Ziering's data.*

Study Results

Demographics, Evaluability:

Chart 18: Demograhic Distribution of Patient Populations

	ITT	Sponsor evaluable	FDA evaluable
Mean age (years)	41.8±12.5	41.3±11.5	41.8±11.6
Race (N(%))			
White	393(80.5%)	99 (78.6%)	69(84.1%)
Hispanic	31(6.4%)	11(8.7%)	5(6.1%)
Black	60(12.3%)	15(11.9%)	7(8.5%)
Other	4(0.8%)	1(0.8%)	1(1.2%)
Women (N(%))	283(58%)	71(56.3%)	44(53.7%)
Men (N(%))	205(42%)	55 (43.7%)	38(46.3%)
Smoking status			
None	306(62.7%)	85(67.5%)	53(64.6%)
Past	85(17.4%)	21(16.7%)	13(15.9%)
Current	97(19.9%)	20(15.9%)	16(19.5%)
Weight (kg)	79.4±19.4	83.6±19.1	81.3±19.7

Reviewers' note: *The population demographics are roughly comparable suggesting no bias present in group selection.*

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Chart 19: Reasons for Nonevaluability or Discontinuance

	FDA	Sponsor
Evaluable*	83(17.0%)	126 (25.8%)
Nonevaluable**	406(83.2%)	362(74.1%)
Negative pretreatment culture	265(65.3%)	265(73.2%)
Organism resistant *in vitro* to drug	7(1.7%)	7(1.9%)
Failed to meet entry criteria	6(1.5%)	5(1.4%)
Failed to follow protocol	5(1.2%)	5(1.4%)
Concomitant antibiotic therapy	7(1.7%)	5(1.4%)
Missed ≥ 2 consecutive doses of drug	2(0.5%)	2(0.6%)
Received <16 doses of drug	4(1.0%)	4(1.1%)
Other	110(27.1%)	69(19.0%)
Total evaluable and nonevaluable **	488 (100.0%)	488 (100.0%)
Discontinued	406(83.2%)	362(74.2%)
Lack of efficacy	10(12.2%)	20(15.9%)
Medical event		
Serious medical event	0	0
Nonserious medical event	0	0
Protocol violation	2(2.4%)	2(1.6%)
Other		
Ineligible after medication started	0	0
Subject request	0	0
Lost to follow-up	0	0
Completed study	64(78.0%)	97(77.0%)
Total discontinued & completed study	488 (100.0%)	488 (100.0%)

* The entire intent-to-treat population is 488 subjects.

** Some patients had more than one reason for being nonevaluable.

***Reviewers' note**: Differences between evaluable populations are largely due to removal of those patients in Sponsor's population with S. aureus isolates from the reviewers' population.*

Chart 20: Medical History

	ITT population	FDA evaluable	Sponsor evaluable
Allergic rhinitis	213(43.7%)	36(43.9%)	61(48.4%)
Nasal polyps	42(8.6%)	9(11.0%)	14(11.1%)
Septal deviation	79(16.2%)	20(24.4%)	24(19.0%)
Previous ENT surgery	115(23.6%)	18(22.0%)	30(23.8%)
Previous dental infection	14(2.9%)	1(1.2%)	3(2.4%)

***Reviewers' note**: The medical history of the patient population is reasonable for a sinusitis population. There are some small differences among the different populations: this is mostly due to the elimination of patients removed by the reviewers who did not meet criteria for S. aureus sinusitis.*

Chart 21: Physical findings

	At enrollment			At posttreatment		
	ITT	FDA evaluable	Sponsor evaluable	ITT	FDA evaluable	Sponsor evaluable
Body temperature ^	98.2±1.0	98.3± 1.0	98.3±1.0	97.9±0.8	97.9±0.9	97.9±0.9
White blood cell count ^	8.3±3.1	9.2±2.6	8.8±2.6	7.2±2.1	7.5±1.9	7.3±2.0
Purulent nasal discharge*	433(88.7%)	76(92.7%)	117(92.9%)	147(30.1%)	22(26.8%)	37(29.4%)
Facial pain*	413(84.6%)	75(91.5%)	111(88.1%)	76(15.6%)	8(9.8%)	16(12.7%)
Tenderness over sinus*	420(86.1%)	71(86.6%)	111(88.1%)	88(18.0%)	9(11.0%)	18(14.3%)
Malaise*	379(77.7%)	65(79.3%)	99(78.6%)	88(18.0%)	12(14.6%)	22(17.5%)
Aching of teeth*	228(46.7%)	39(47.6%)	56(44.4%)	42(8.6%)	4(4.9%)	10(7.9%)
Headache*	396(81.1%)	61(74.4%)	97(77.0%)	100(20.5%)	13(15.9%)	23(18.3%)
Fever	105(21.5%)	24(29.3%)	31(24.6%)	5(1.0%)	1(1.2%)	2(1.6%)

^ mean value and standard deviation

* Treated as dichotomous values. Among those with findings at posttreatment, almost all were assessed as "mild" by the investigator.

***Reviewers' note**: Physical findings are distributed fairly evenly across the populations and posttreatment evaluation demonstrates acceptable resolution of these findings. See clinical outcomes below: there is a fairly large "improved" category. This has been seen in other applications and provides many of the residual findings seen in the chart above.*

Chart 22: Radiologic findings

	ITT	FDA evaluable	Sponsor evaluable
Opacification	227(46.5%)	46(56.1%)	65(51.6%)
Fluid level	128(26.2%)	33(40.2%)	45(35.7%)
Mucosal swelling ≥ 4mm	337(69.1%)	46(56.1%)	77(61.1%)

***Reviewers' note**: The reviewers accept this as an entry criteria, but radiologic findings may lag behind a clinical cure. Thus, the reviewers do not consider this an appropriate outcome measure.*

Chart 23: Clinical outcomes

	ITT	FDA evaluable	Sponsor evaluable
Cured	242(49.6%)	51(62.2%)	73 (57.9%)
Improved	179 (36.7%)	26(31.7%)	43(34.1%)
Failure	67 (13.7%)	5(6.1%)	10(7.9%)
Success(cured + improved)	421(86.3%)	87(93.9%)	116(92.1%)
Failure	67(13.7%)	5(6.1%)	10(7.9%)
Cured	242(49.6%)	51(62.2%)	73(57.9%)
Failure(failure + improved)	246(50.4%)	31(37.8%)	53(42.1%)

Subset analyses of demographic aspects (sex, age and race) by clinical outcomes did not reveal any differences in cure rates.

***Reviewers' note**: The cure and success rates are acceptable. The trial is uncontrolled, but comparing these rates to other applications in support of efficacy against sinusitis, the rates are acceptable. The recent application for levofloxacin which was approved for the treatment of acute sinusitis had an overall clinical cure rate of 75% for levofloxacin and 74% for amoxicillin/clavulanate. No intermediate category of "improved" was permitted in this review. Recent review's evaluating the efficacy of ciprofloxacin in acute sinusitis found "resolution" in 81.0-87.3% on ciprofloxacin, 83.1% on cefuroxime, and 85.9% on clarithromycin. The rates above are comparable, and to be expected in a clinical trial of acute sinusitis.*

Rates reported in the literature are similar.[2,3] The reviewers do not believe that the above trial demonstrates superiority when compared to the other trials mentioned. The test-of-cure visit occurred very shortly after completion of therapy. The time frame would not meet ODE IV's current Evaluability Criteria for acute sinusitis. A test-of-cure visit intermediate between the current posttreatment and final follow-up would more accurately yield an appropriate cure rate.

In addition, much uncertainly is added by the "improved" category; DAIDP's Points-to-Consider has eliminated this as a clinical outcome. Even though this trial is uncontrolled, it appears to offer few surprises. When compared to study M/1140/109, the controlled clinical only trial, the cure rates here appear to be a bit higher. Failure rate in study 109 was 10.4% for cefpodoxime and 16.5% for loracarbef, the comparator. In addition, the cure + improvement rates were 89% and 83% for cefpodoxime and loracarbef, respectively. These numbers from study 109 resemble the ITT population in this study rather than the evaluable population: this may be a consequence of the lack of microbiologic certainty and more subjects enrolled who would not be expected to respond to therapy because they do not have bacteriologically documented community acquired acute sinusitis.

Chart 24: Bacteriologic Responses at Posttreatment

Bacteriologic response	ITT	FDA evaluable	Sponsor evaluable
Cured	125(25.6%)	76(92.7%)	115(91.3%)
Failure	13(2.7%)	5(6.1%)	10(7.9%)
Superinfection	3(0.6%)	1(1.2%)	1(0.8%)

Subset analyses of demographic aspects (sex, age and race) by bacteriologic response did not reveal any differences in cure rates.

Chart 25: Clinical responses at final follow-up

Clinical response	ITT	FDA evaluable	Sponsor evaluable
Cured	312 (63.9%)	56(75.7%)	85(75.2%)
Failure	107(21.9%)	18(24.3%)	28(24.8%)
Missing	69(14.1%)	0(0%)	0(0%)

Chart 26: Bacteriological responses at final follow-up

Bacteriological response	ITT	FDA evaluable	Sponsor evaluable
Cured	96(19.7%)	56(75.7%)	85(75.2%)
Failure	29(5.9%)	18(23.0%)	27(23.9%)
Superinfection	1(0.2%)	1(1.4%)	1(0.9%)
Missing	362(74.2%)	0(0%)	0(0%)

Reviewers' note: *No surprises in the above three charts. The reviewers find the rates acceptable.*

Chart 27: Pathogen eradication rates at posttreatment

Pathogen	ITT	FDA evaluable	Sponsor evaluable
S. pneumoniae	41/44(92.3%)	36/38(94.7%)	36/38(94.7%)
H. influenzae	38/41(92.7%)	34/37(91.9%)	34/37(91.9%)
M. catarrhalis	14/14(100%)	13/13(100%)	13/13(100%)
S. pyogenes	7/8(87.5%)	6/7(85.7%)	6/7(85.7%)
S. aureus	42/49(85.7%)	0(0%)	40/45(88.9%)

[2] Gwaltney, Jr., JM. Acute Community-Acquired Sinusitis. CID 1996;23:1209-1225.

[3] Gwaltney Jr., JM, Schooled WMS, Sande, MA, Sydnor A. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: A fifteen-year experience at the University of Virginia and review of other selected studies. J Allergy Clin Immunol 1992;90:457-462.

Chart 28: Pathogen eradication rates at final follow-up

Pathogen	ITT	FDA evaluable	Sponsor evaluable
S. pneumoniae	31/43(72.1%)	28/37(75.7%)	28/37(75.7%)
H. influenzae	30/42(71.4%)	26/35(74.3%)	23/31(74.2%)
M. catarrhalis	11/14(78.6%)	10/13(76.9%)	10/13(76.9%)
S. pyogenes	6/8(75.0%)	5/6(83.3%)	5/6(83.3%)
S. aureus	31/46(67.4%)	0(0%)	0(0%)

Reviewers' note: *The above reflects presumed eradication, as almost no patients underwent repeat sinus aspiration. This study is uncontrolled and no approved comparator arm is available. However, the above rates are acceptable and in keeping with previously reported rates. For instance, in the recent ciprofloxacin application, the pivotal microbiologic study reported the following microbiologic eradication rates: Haemophilus influenzae 25/27 (92.5%), Streptococcus pneumoniae 17/20 (85%), Moraxella catarrhalis 10/14 (71.4%) for ciprofloxacin and Haemophilus influenzae 14/19 (73.6%), Streptococcus pneumoniae 12/18 (66.6%), Moraxella catarrhalis 12/15 (80.0%) for cefuroxime. Levofloxacin demonstrated the following microbiologic eradication rates: Haemophilus influenzae 25/34 (73%), Streptococcus pneumoniae 27/29(93%), and Moraxella catarrhalis 8/13(62%). Thus, the rates above are similar to those DAIDP has reviewed before and found acceptable for efficacy claim.*

The sponsor meets DAIDP's Points-to-Consider requisite numbers for approval of Streptococcus pneumoniae (N=25) and Haemophilus influenzae (N=25). The same document requires 15 isolates of Moraxella catarrhalis for approval. The sponsor submitted another study, Study 0045, which yielded an additional patient with Moraxella catarrhalis so that the total number of patients in this application receiving cefpodoxime with this isolate is 14. However, the eradication rate appears acceptable and the Division has acceptable fewer than 15 isolates on occasion where it is believed efficacy is well-demonstrated.

The patient population enrolled was not especially stringent. In order to evaluate response in a population more selected for acute maxillary bacterial sinusitis, patients with the finding of air-fluid level on radiologic study were stratified and evaluated and evaluated separately. The following is revealed:

Chart 29: Clinical Cure Rates among Patients with Air Fluid Levels at Enrollment

	With opacification			With air-fluid levels		
Clinical Outcome	ITT population	FDA evaluable	Sponsor evaluable	ITT population	FDA evaluable	Sponsor evaluable
Cure	102/227(44.9)	26/46(56.5)	34/65(52.3)	66/128(51.6)	20/33(60.6)	26/45(57.8)
Improved	91/227(40.1)	18/46(39.1)	27/65(41.5)	47/128(36.7)	12/33(36.4)	18/45(40.0)
Failure	34/227(15.0)	2/46(4.4)	4/65(6.2)	15/128(11.7)	1/33(3.0)	1/45(2.2)

	With opacification and air-fluid levels		
Clinical Outcome	ITT population	FDA evaluable	Sponsor evaluable
Cure	168/355(47.3)	46/79(58.2)	60/110(54.5)
Improved	138/355(38.9)	30/79(40.0)	45/110(41.0)
Failure	49/355(13.8)	3/79(3.8)	5/110(4.5)

Chart 30: Presumed Bacteriologic Cure Rates among Patients with Air Fluid Levels/Opacification at Enrollment

	With opacification			With air-fluid levels		
Clinical Outcome	ITT population	FDA evaluable	Sponsor evaluable	ITT population	FDA evaluable	Sponsor evaluable
Cure	155/227(68.3)	43/46(93.5)	60/65(92.3)	75/128(58.6)	31/33(93.9)	43/45(95.6)
Improved	64/227(28.2)	0/46(0.0)	0/65(0.0)	49/128(38.3)	0/33(0.0)	0/45(0.0)
Failure	8/227(3.5)	3/46(4.5)	5/65(7.7)	4/128(3.1)	2/33(6.6)	2/45(4.42)

	With opacification and air-fluid levels		
Clinical Outcome	ITT population	FDA evaluable	Sponsor evaluable
Cure	230/355(64.8)	74/79(93.7)	103/110(93.6)
Improved	113/355(31.8)	0/79(0.0)	0/110(0.0)
Failure	12/355(3.4)	5/79(6.3)	7/110(6.4)

Reviewers' note: *Although this should be an enriched population with a greater percentage truly having acute bacterial maxillary sinusitis than those demonstrating other radiologic findings, the ratio of cure:improved:failure is among the clinical outcomes is little different from the population overall. For the entire ITT population, this ratio is 49.6%:36.7%:13.7%. For the entire FDA evaluable population, this ratio is 62.2%:31.7%:6.1%, and for the entire Sponsor evaluable population, this ratio is 57.9%:34.1%:7.9%. However, the presumed bacteriologic cure rates, which reflect cured or improved in the absence of need for any further bacteriologic evaluation demonstrate that this population might be more apt to have acute bacterial maxillary sinusitis. It is unfortunate that this study is uncontrolled because a comparator would have allowed for more analysis here.*

Safety

Chart 30: Medical Event Rates

Safety outcome	Cefpodoxime (N=488)
Subjects with AEs	292(59.8%)
Body	185(37.9%)
Cardiovascular	6(1.2%)
Digestive	101(20.7%)
Endocrine	1(0.2%)
Hematologic & Lymphatic	5(1.0%)
Metabolic & Nutritional	1(0.2%)
Musculo-skeletal	6(1.2%)
Nervous	14(2.9%)
Respiratory	130(26.6%)
Skin	14(2.9%)
Special senses	30(6.1%)
Urogenital	13(2.7%)
Subjects with AEs believed related to medication	75(15.4%)
Body	22(4.5%)
Cardiovascular	0(0%)
Digestive	48(9.8%)
Endocrine	0(0%)
Hematologic & Lymphatic	2(0.4%)
Metabolic & Nutritional	0(0%)
Musculo-skeletal	1(0.2%)
Nervous	5(1.0%)
Respiratory	0(0%)
Skin	2(0.4%)
Special Senses	0(0%)
Urogenital	8(1.6%)
Subject with serious AEs	4(0.8%)
Subject discontinued due to AEs	11(2.3%)

The most frequent treatment related adverse events were diarrhea (5.1%), nausea (2.5%), fungal infections (1.8%), and headache (1.0%). The first three of these are common side effects of antibiotics. One case of severe colitis and one of severe *Clostridium difficile* infection occurred in the study.

Eleven (2.3%) of patients discontinued the study drug because of side effects. Two of these events, erythematous rash and colitis, were serious.

No patient died during the study. Four patients were considered to have serious medical events during the study. Those described above are deemed related to study drug. Two other serious events were believed unrelated to treatment: a patient lost a finger in an industrial accident and a patient had a spontaneous abortion 31 days after completing therapy.

Reviewers' note: *The above information does not provide any information not reflected in the current labeling. The labeling currently reports an overall diarrhea rate of 7.2%; it is dose related with patients receiving an 800 milligram dose having a 10.6% rate and those receiving 200 milligrams having a 5.9% rate. Vaginal fungal infections are reported to occur at a rate of 3.1%, nausea at 3.8%, rash at 1.4% and headache at 1.1%. Pseudomembranous colitis is reported at a rate of <1%. The safety information provided by study 108 does not provide any refinement to the current label. It should be remembered that*

the sample size is not large (N=488 with some exposure range) and the current label reflects information obtained from exposure of 3338 patients to the formulation used in this study.

Conclusions

(1) At posttreatment TOC, 61.4% (51/83) of the reviewers' evaluable population had a clinical response of cure, and 31.3% (26/83) had a clinical response of improved. Only 5/83 (6.0%) were failures. These are acceptable cure and improved rates despite the uncontrolled nature of the study.
(2) Bacteriologic eradication rate in the reviewers' evaluable population was 91.6% (76/83). This is an acceptable bacteriologic response rate.
(3) Numbers were adequate and eradication rates acceptable so that cefpodoxime has demonstrated efficacy in the treatment of acute sinusitis due to *Streptococcus pneumoniae* (36/38, 94.7%) and *Haemophilus influenzae* (34/37, 91.9%). *Moraxella catarrhalis* (13/13, 100%) has almost the appropriate number of isolates required and a very acceptable eradication rate. Numbers were inadequate to demonstrate efficacy against *Streptococcus pyogenes* and *Staphylococcus aureus*. In addition, there were significant shortcomings in the data submitted in support of a claim of efficacy against *Staphylococcus aureus*.
(4) There were 59.8% (292/488) subjects with adverse events, 15.4% (75/488) subjects who recorded cefpodoxime related adverse events, 0.8% (4/488) subjects who experienced serious adverse events, and 2.3% (11/488) subjects who discontinued study drug due to adverse events.

Recommendations

(1) The sponsor add the indication of acute sinusitis to its Vantin® labeling with efficacy claims *against Haemophilus influenzae* and *Streptococcus pneumoniae*. Efficacy claims against *Moraxella catarrhalis* will also be permitted as the cure rate was acceptable and the application was only one organism short of the requisite 14.
(2) The safety labeling for Vantin® will remain unchanged as the information provided in this application does not provide additional information on adverse drug reaction rates

Study Title: Comparison of Oral Cefpodoxime Proxetil (VANTIN® Tablets) with Oral Amoxicillin/Clavulanate (Augmentin ®) in the Treatment of Acute Maxillary Sinusitis in Adults (Protocol M/1140/0045)

Study dates: The study was active from November, 1990 until September, 1992.

Study objectives: To compare clinical and bacteriologic efficacy, tolerance and safety of cefpodoxime proxetil 200 mg q 12 hours for 10 days and amoxicillin/clavulanate 500 mg q 8 hours for 10 days.

Study design: This is an prospective, randomized, observer-blind, multicenter, controlled study. See Chart 27 (following) for specifics of study design, observations and measurements.

Chart 31: Observations and Measurements, Study M/1140/0045

Initial Visit: Day 0 Day 0	Interim Visit Days 3-6, inclusive	Posttreatment Visit Days 12-18, inclusive	Final Follow-up Visit (Phone): Days 25-32, inclusive
• History & Physical Exam			
• Maxillary Sinus Imaging		• Repeat maxillary sinus imaging	
• Sinus aspiration for culture	• Repeat Sinus aspiration, if failure	• Sinus aspiration, if failure	• Sinus aspiration, if failure
• Hematology parameters		• Hematology parameters	• Follow-up hematology if abnormal
• Chemistry parameters		• Chemistry parameters	• Follow-up chemistry if abnormal
	• Clinical examination	• Clinical examination	• Clinical examination
		• Bacteriologic evaluation	
			• Inquire about patient's condition
			• Patient evaluation of efficacy

Reviewers' note: *The above design will be accepted. However, these reviewers can find no record of discussions with the Sponsor regarding an appropriate time frame for a test of cure visit and ODE IV's current Evaluability Criteria for acute sinusitis recommends that a post-therapy test of cure visit, which will be the primary outcome measure occur approximately 1 to 2 weeks after the completion of therapy. In this protocol that would be days 17 to 24. Days 17 to 24 falls between posttreatment visit and final follow-up visit as designed by the sponsor. Equivalence to the comparator arm will be accepted as an acceptable outcome measure, but the time frame for determining "cure" is too short and the cure rates will be probably be inflated due to early follow-up. Thus, these reviewers are resistant to allow promulgation of the post-therapy test-of-cure rates. Should they be disclosed, fairness would require that presentation of final follow-up cure rates in addition: this will provide a more reliable reflection of the actual cure rate in comparison to other studies.*

Inclusion criteria:

- symptoms and signs compatible with acute maxillary sinusitis including at least two of the following: facial pain, purulent nasal discharge, tenderness over sinus.
- age 18 to 70 years
- abnormal transillumination of the sinus (opaque or dull)
- abnormal radiographic study compatible with acute maxillary sinusitis
- signed informed consent
- positive bacteriologic culture from sinus aspirate.

Exclusion criteria:
- allergy to penicillin or cephalosporin
- postoperative sinusitis
- antibiotic treatment within previous 4 days
- pregnant or nursing women
- chronic sinusitis (symptoms longer than 4 weeks)
- severe sinusitis requiring intravenous antibiotics
- the presence of significant neoplastic disease, immunosuppressive therapy or seropositive HIV status
- significant hematologic disorder
- significant cardiac, renal or hepatic disease
- females of childbearing potential not on acceptable birth control method (e.g., oral contraceptive pills, diaphragm, etc.)
- current enrollment in another investigational protocol or previous enrollment in this study

Evaluability criteria: Patients in the following categories were removed from the study and listed as nonevaluable for efficacy, but were included in the safety analysis:

- patients with a pathogen resistant to cefpodoxime or amoxicillin/clavulanate
- patients with concomitant antibiotic therapy (unless prescribed as a treatment failure)
- patients who received less than 80% of the therapy or missed two or more consecutive doses of cefpodoxime or three or more doses of augmentin/clavulanate

Patients in whom no pathogenic organism is isolated will be analyzed separately for an analysis of clinical only. Patients who fail to have adequate clinical and/or bacteriologic response by the interim visit (3-6 days) or who deteriorate after two full days of therapy will be taken off protocol therapy and treated as the investigator deems appropriate. These patients will be listed as evaluable failures.

***Reviewers' note**: The above Inclusion, Exclusion and Evaluability criteria are acceptable. Pathogens considered in this application include Streptococcus pneumoniae, Haemophilus influenzae , Moraxella catarrhalis and Staphylococcus aureus. DAIDP requires that patients microbiologically evaluable for sinusitis have their cultures obtained by sinus aspirate. This criteria was met in this study. Because S. aureus can colonized the area in question and contiguous areas, it can be a contaminant on sinus aspirate cultures. Thus, the following criteria must be met for patients to be evaluable for acute sinusitis due to S. aureus.*

- *Staphylococcus aureus isolated in pure, not mixed, culture*
- *adequate organism burden as demonstrated by a quantitation of 10^4 cfu/ml or semiquantitation of 3+ or 4+ of S. aureus*
- *PMNs present on gram stain.*

Endpoints defined: The Sponsor defined the primary measures of efficacy as clinical and bacteriologic efficacy at the posttreatment visit (visit at Days 12-18, inclusive. See Chart 27 above.).

***Reviewers' note**: The reviewers find the primary measures of efficacy acceptable.*

Outcome measures
Clinical efficacy at the posttreatment visit was recorded as follows
- Cured -- Disappearance of all clinical signs and symptoms
- Improved -- Disappearance of most, but not all, clinical signs and symptoms
- Failure – Little or no improvement in clinical findings

Clinical efficacy at the final follow-up was recorded as follows
- Cure -- Disappearance of all clinical signs and symptoms
- Improved -- Significant improvement in signs and symptoms
- Failure -- Little or no improvement in clinical symptoms

- Recurrence/Relapse -- Return of signs and symptoms at late follow-up after cure at posttreatment evaluation
- Side Effect Failure -- Unable to complete protocol therapy due to an adverse reaction caused by study medication. This will be carried forward as a failure in efficacy evaluation.

***Reviewers' note**: The Reviewers consider the above outcome assignments acceptable.*

Bacteriologic efficacy at the posttreatment visit was recorded as

- Cure -- Eradication of or a greater than or equal 10^4-fold reduction in the titer of pathogen(s) at post therapy visit, or when no culture is obtained and patient is cured clinically
- Failure -- Initial pathogen(s) not eradicated or less than a 10^4-fold reduction in the titer of pathogen(s) at post therapy visit
- Superinfection -- Isolation of one or more new pathogens from the sinus culture during therapy or at posttreatment visit

***Reviewers' note**: The requirement for eradication of greater than or equal to 10^4-fold reduction in the titer of pathogen(s) was dropped and clinical cure alone became the requirement for Cure. The above outcome assignments, with the noted modification, are acceptable.*

Patient populations analyzed:

Intent to Treat Population (ITT) -- All patients who took at least one dose of study medication were include in the ITT population. This was the Sponsor's population for safety analysis.

Evaluable Patient Population -- As described above in "Evaluability criteria".

***Reviewers' note**: All patients enrolled were kept in the ITT analysis which reflects safety and clinical outcome. The Reviewers elected to use the sponsor's evaluable population for two reasons: (1) the study is too small to be anything but supporting data for studies 108 and 109 -- it will merely serve a corroborative function; and (2) after review of the line listings and CRFs submitted by the sponsor, very few patients would have been reassigned to another outcome.*

Statistical methods: Sample sizes were established by the availability of appropriate patients and not using statistical power considerations. Power curves based on the null hypothesis that the success rate for amoxicillin/clavulanate is at least a given "percentage" better than cefpodoxime were used by the sponsor. The power curve assumes that the true probability of success with amoxicillin/clavulanate is 0.80 and the number of patients given cefpodoxime will be twice as many as the number receiving amoxicillin/clavulanate.

Assuming that 10% is the "percentage" advantage of amoxicillin/clavulanate over cefpodoxime, the probability of correctly concluding equivalence between the two treatment arms is 0.42.

***Reviewers' note**: The study is very small and will lack power to demonstrate equivalence either clinically or bacteriologically. Thus, this trial can be used as supporting data for trials 108 and 109. It is unfortunate because this is the only available controlled microbiologic data.*

Since the sample sizes of the cefpodoxime and amoxicillin/clavulanate treatment groups are too small, no meaningful statistical conclusions can be drawn with regard to efficacy. Statistical evaluation of efficacy is described by summarizing data collected on the efficacy variables. The primary efficacy variables are clinical cures rates or clinical success (cure + improvement) rates, and bacteriological eradication rates at posttreatment in the evaluable subjects. Statistical evaluation of safety is based upon the comparison of adverse event rates between the treatment groups in all subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

Investigators: The following investigators participated in study M/1140/0045:

Ralph Ascher, MD Vista CA	Thomas A. Hansbrough, MD Baton Rouge, LA	James A Mechenbier, MD Columbus, OH
James J. Bushnell, MD Birmingham,, AL	Charles Harper, MD Cape Coral, FL	David A. Milko, DO Kalamazoo, MI
Michael L. Dennington, MD Aurora, CO	Anthony S. Krausen, MD Milwaukee, WI	David J. Miller, MD Morrisville, PA
John T. Klimas, MD Charlotte, NC	Terrance C. Kurtz, DO Des Moines, IA	Kathleen Murphy, MD Houston, TX
Robert A. Fiddes, MD Morgantown, WV	Lyndon E. Mansfield, MD El Paso, TX	Donald R. Prough, MD Wenatchee, WA
R. Brooks Gainer, II, MD Morgantown, WV	John S. Matlock, MD San Antonio, TX	Nathan Segall, MD Atlanta,.GA

Reviewers' note: *At our request, the sponsor removed the data obtained by Dr. Fiddes. In addition, Drs. Gainer and Harper contributed no patients. Otherwise, the list of investigators is acceptable.*

Study Results

Demographics, Evaluability:

Chart 31: Demograhic Distribution of Patient Populations

	ITT			Evaluable		
	cefpodoxime	amox/clav	p-value	cefpodoxime	amox/clav	p-value
Mean age (years)	41.7±13.2	41.3±12.9	0.875*	41.4±15.4	36.6±10.1	0.492*
Race (N(%))			1.000			0.806
White	67(85.9%)	66(88.0%)		23(88.5%)	15(83.3%)	
Hispanic	6(7.7%)	5(6.7%)		2(7.7%)	1(5.6%)	
Black	4(5.1%)	4(5.3%)		1(3.9%)	2(11.1%)	
Other	1(1.3%)	0(0%)		0(0%)	0(0%)	
Women (N(%))	44(56.4%)	39(52.9%)	0.628	9(34.6%)	11(61.1%)	0.125
Men (N(%))	34(43.6%)	36(48.0%)		17(65.4%)	7(38.9%)	
Smoking status						0.268
None	56(71.8%)	53(70.7%)	0.525	20(76.9%)	10(55.6%)	
Past	12(15.4%)	8(10.7%)		2(7.7%)	1(5.6%)	
Current	10(12.8%)	14(18.7%)		4(15.4%)	4(22.2%)	
Weight (kg)	169.6±38.0	166.4±36.6	0.595*	172.9±44.3	169.1±30.0	0.757*

* p-value is obtained by t-test, otherwise, by Fisher's exact test.

Reviewers' note: *The demographic features appear to be adequately distributed given the limitations of the sample size.*

Chart 32: Reasons for Nonevaluability

	cefpodoxime	amox/clav
Evaluable*	26	18
Nonevaluable**	52	57
Negative pretreatment culture	43(55.1%)	45(60.0%)
Organism resistant *in vitro* to drug	1(1.3%)	7(9.3%)
Failed to meet entry criteria	1(1.3%)	3(4.0%)
Failed to follow protocol	4(5.1%)	2(2.7%)
Concomitant antibiotic therapy	1(1.3%)	0(0%)
Missed ≥ 2 consecutive doses of drug	1(1.3%)	0(0%)
Received <16 doses of drug	0(0%)	0(0%)
Other	2(2.6%)	0(0%)
Total evaluable and nonevaluable	78	75

***Reviewers' note**: There is a great loss of patients due to negative pretreatment cultures. Other reasons for nonevaluability are reasonable – it is unfortunate that so many were lost. The numbers are small but there does not appear to be bias by treatment arm with respect to evaluability.*

Chart 33: Reasons for Discontinuance

	ITT		Evaluable	
	cefpodoxime (n=78)	amox/clav (n=75)	cefpodoxime (n=26)	amox/clav (n=18)
Reasons for discontinuation				
End of planned study course	41(52.6%)	32(42.7%)	25(96.2%)	18(100%)
Lack of efficacy	0(0%)	0(0%	0(0%)	0(0%)
Medical event				
Serious medical event	2(2.6%)	0(0%)	1(3.9%)	0(0%)
Nonserious medical event	3(3.9%)	1(1.3%)	0(0%)	0(0%)
Protocol violation	3(3.9%)	1(1.3%)	0(0%)	0(0%)
Other	0(0%)	2(2.7%)	0(0%)	0(0%)
Ineligible after medication started	29(37.2%)	39(52.0%)	0(0%)	0(0%)
Subject request	0(0%)	0(0%)	0(0%)	0(0%)
Lost to follow-up	0(0%)	0(0%)	0(0%)	0(0%)

***Reviewers' note**: It is fortunate that few evaluable patients were lost due to discontination There does not appear to be bias by treatment arm with respect to discontinuation.*

Chart 34: Medical History

	ITT		Evaluable	
	cefpodoxime	amox/clav	cefpodoxime	amox/clav
Allergic rhinitis	12(15.4%)	14(18.7%)	4(15.4%)	4(22.2%)
Nasal polyps	5(6.4%)	7(9.3%)	3(11.5%)	2(11.1%)
Septal deviation	15(19.2%)	14(18.7%)	8(30.8%)	2(11.1%)
Previous ENT surgery	25(32.1%)	20(26.7%)	10(38.5%)	6(33.3%)
Previous dental infection	3(3.9%)	9(12.0%)	0(0%)	1(5.6%)

***Reviewers' note**: Despite the small sample size, the above medical histories are pretty evenly distributed by treatment arm.*

Chart 35: Physical findings

	At enrollment				At posttreatment			
	ITT		Evaluable		ITT		Evaluable	
	cefpodox	amox/clav	cefpodox	amox/clav	cefpodox	amox/clav	cefpodox	amox/clav
Body temperature ^	98.2±0.7	98.2±0.8	98.3±0.6	98.2±0.7	98.1±0.7	98.2±0.6	97.9±0.8	98.4±0.8
White blood cell count ^	8.1±3.1	7.7±1.8	8.8±2.5	7.3±1.6	7.5±4.1	6.9±1.8	7.1±1.6	6.7±2.2
Purulent nasal discharge*	75(97.4)	71(94.7)	26(#)	18(#)	28(38.4)	21(31.8)	7(28)	5(27.8)
Facial pain*	73(94.8)	74(98.7)	26(#)	18(#)	18(24.6)	19(25.3)	4(16.0)	3(16.7)
Tenderness over sinus*	75(97.4)	74(98.7)	26(#)	18(#)	19(26.0)	12(17.9)	3(12.0)	2(11.1)
Malaise*	50(64.1)	55(73.3)	18(69.2)	15(83.3)	16(20.5)	20(26.7)	4(15.4)	4(22.2)
Aching of teeth*	32(41.6)	34(45.9)	15(57.7)	11(64.7)	8(11.0)	4(59.7)	0(0)	1(5.9)
Headache*	59(76.6)	58(77.3)	20(76.9)	13(72.2)	16(21.9)	13(19.4)	2(8.0)	5(27.8)
Fever	12(15.6)	14(18.7)	5(19.2)	3(16.7)	1(13.9)	1(14.9)	1(4.2)	0(0)

^ mean value and standard deviation

* Treated as dichotomous values. Among those with findings at posttreatment, almost all were assessed as "mild" by the investigator.

The sponsor has no data which would provide a denominator for this variable.

Reviewers' note: *The data is confusing and numbers small, but there does not appear to be differences in distribution or resolution of physical findings by treatment arm. Amoxicllin/clavulanate has an acceptable cure rate in acute maxillary sinusitis, and cefpodoxime appear to be comparable in efficacy from this crude table.*

Chart 36: Radiologic findings

	ITT		Evaluable	
	cefpodoxime	amox/clav	cefpodoxime	amox/clav
Opacification	46(59.7)	51(68)	18(69.2)	13(72.2)
Fluid level	30(39)	25(33.3)	12(46.1)	4(22.2)
Mucosal swelling ≥ 4mm	46(59.7)	41(54.7)	13(50)	11(61.1)

Reviewers' note: *The reviewers accept this as an entry criteria, but radiologic findings may lag behind a clinical cure. Thus, the reviewers do not consider this an appropriate outcome measure. There does not appear to be a difference between cefpodoxime and amoxicillin/clavulanate radiologic findings at enrollment.*

Chart 37: Clinical Response at Posttreatment Visit

	ITT		Evaluable	
	cefpodoxime	amox/clav	cefpodoxime	amox/clav
Cured	26(33.3%)	28(37.3%)	14(53.8%)	9(50.0%)
Improved	36(46.2%)	34(45.3%)	10(38.5%)	8(44.4%)
Failure	16(20.5%)	13(17.3%)	2(7.7%)	1(5.6%)
Success(cured + improved)	62(79.5%)	62(82.7%)	24(92.3%)	17(94.4%)
Failure	16(20.5%)	13(17.3%)	2(7.7%)	1(5.6%)
Cured	26(33.3%)	28(37.3%)	14(53.8%)	9(50.0%)
Failure(failure + improved)	52(66.7%)	47(62.7%)	12(46.2%)	9(50.0%)
cefpod vs am/cl by Cure	-4.0%, 95% CI:	-20.4%, 12.4%	3.8%, 95% CI:	-30.9%, 38.6%
cefpod vs am/cl by Success	-3.2%, 95% CI:	-16.9%, 10.5%	-2.1%, 95% CI:	21.6%, 17.3%

Reviewers' note: *The clinical response rates at posttreatment visit are close. However, the sample size is inadequate and the confidence intervals for the evaluable population fails on this basis. The clinical success rates in the evaluable population is similar to that seen in study 108 and other recent applications reviewed by DAIDP in addition to be similar to that seen in the literature (see note on pages 22-23 in this review).*

Chart 38: Bacteriologic Responses at Posttreatment

Bacteriologic response	ITT		Evaluable	
	cefpodoxime n=78	amox/clav n=75	cefpodoxime n=26	amox/clav n=18
Cured	26(33.3%)	28(37.3%)	14(53.8%)	9(50.0%)
Failure	48(61.5%)	40(53.3%)	12(46.2%)	9(50.0%)
Missing/Not reported	4(5.1%)	7(9.3%)	0(0%)	0(0%)
Cefpodoxime vs am/cl by cure	-4.0%, 95 % CI:	-20.4%, 12.4%	3.8%, 95% CI:	-30.9%, 38.6%

Reviewers' note: *The bacteriological response rates at posttreatment appear are close. However, the sample size is inadequate and the confidence intervals for both the evaluable and ITT populations fail on this basis.*

Chart 39: Clinical responses at final follow-up

Clinical response	ITT		Evaluable	
	cefpodoxime	amox/clav	cefpodoxime	amox/clav
Cured	31(40%)	28(39%)	14(54%)	10(56%)
Improved	31(40%)	31(43%)	9(35%)	6(33%)
Failure	15(20%)	13(18%)	3(12%)	2(11%)

Reviewers' note: *There does not appear to be any differences in clinical cure by treatment arm between cefpodoxime and amoxicllin/clavulanate in the ITT and evaluable populations.*

Bacteriological responses at final follow-up

None of the subjects required subsequent sinus taps. Therefore, successful bacteriologic outcomes were considered to be those patients who had a successful clinical outcome.

Reviewers' note: *Presumed eradication will be considered in the subjects with successful clinical outcome.*

Chart 40: Pathogen eradication rates* at posttreatment in evaluable subjects

Pathogen	Evaluable	
	cefpodoxime	amox/clav
S. pneumoniae	8/8(100%)	5/5(100%)
H. influenzae	7/7(100%)	5/5(100%)
M. catarrhalis	1/1(100%)	3/3(100%)
S. pyogenes	0(na)	0(na)
S. aureus	4/5(80%)	2/2(100%)

* Eradication includes clinical cure and improved – no further procedures or antibiotics required.

Reviewers' note: *The reviewers found the data submitted by sponsor in support of S. pneumoniae, H. influenzae and M. catarrhalis acceptable and will accept these numbers. This is in addition to those cases in study 108, which actually has the requisite number of these organisms to support an efficacy claim without this data. Inadequate data was submitted to support a claim of S. aureus. Study 108 did not provide enough numbers of S. aureus to support a claim for efficacy against this organism. The numbers here, even as the sponsor has presented, are too small to support and require no further scrutiny. Even if all the S. aureus cultures met DAIDP's criteria (pure culture, quantitation in excess of 10^4 cfus/ml, gram stain with PMNs, and culture obtained by sinus aspirate), the number of cultures available is short of the 20-25 required by DAIDP in the past.*

The largely presumed eradication rates reported here are acceptable although the sample size is small. See Reviewers' note on page 7 (Study 108) for a more complete discussion and comparison of eradication rates.

Chart 41: Pathogen eradication rates* at final follow-up in evaluable subjects

Pathogen	Evaluable	
	cefpodoxime	amox/clav
S. pneumoniae	8/8(100%)	5/5(100%)
H. influenzae	7/7(100%)	5/5100%)
M. catarrhalis	1/1(100%)	2/3(67.7%)
S. pyogenes	3/5(60%)	2/2(100%)
S. aureus	0(0)	0(0)

* Eradication includes clinical cure and improved – no further procedures or antibiotics required.

Reviewers' note: *The pathogen eradication rates at final follow-up are acceptable. The numbers are extremely small, but it appears that the two therapies are equivalent.*

Safety

Chart 42: Medical Event Rates

Safety outcome	Cefpodoxime (n=78)	Amox/clav(n=75)	Fisher's P-value
Subjects with at least one AE	34(43.6%)	33(44.0%)	1.000
Allergy	1 (1.3%)	2 (2.7%)	0.615
Dermatologic	1 (1.3%)	1 (1.3%)	1.000
Gastrointestinal	14 (17.9%)	14 (18.7%)	1.000
Genital Tract	4 (5.1%)	3 (4.0%)	1.000
Hematologic	0 (0%)	1 (1.3%)	0.490
Metabolic & Nutritional	1 (1.3%)	0 (0%)	1.000
Miscellaneous	9(11.5%)	9 (12.0%)	1.000
Musculo-Skeletal	0 (0%)	1 (1.3%)	0.490
Neurologic	2 (2.6%)	4 (5.3%)	0.439
Respiratory	13(16.7%)	11(14.7%)	0.825
Special Senses	1 (1.3%)	2 (2.7%)	0.615
Surgical Procedures	3 (3.8%)	0 (0%)	0.245
Subjects with at least one AE thought treatment related	12(15.4%)	13(17.3%)	0.828
Allergy	0 (0%)	1 (1.3%)	0.490
Dermatologic	1(1.3%)	1 (1.3%)	1.000
Gastrointestinal	9(11.5%)	9(12.0%)	1.000
Genital Tract	2 (2.6%)	3 (4.0%)	0.677
Miscellaneous	1 (1.3%)	0 (0%)	1.000
Neurologic	0 (0%)	1 (1.3%)	0.490
Respiratory	1 (1.3%)	0 (0%)	1.000
Subjects with serious AEs	3(3.9%)	0(0%)	0.245
Subjects discontinued due to AEs	5(6.4%)	1(1.3%)	0.210

Reviewers' note: *There are no new findings here: rates of all events are greater than in trials 108 and 109, larger, pivotal trials submitted in support of this application. However, the sample size of this study is so small that it is not possible to draw any conclusions regarding the occurrence of adverse events.*

Conclusions:

(1) For evaluable subjects at posttreatment, the clinical cure rates (i.e., cure vs. improved + failure) were as follows: 53.8% (14/26) in cefpodoxime and 50.0% (9/18) in the amoxicillin/clavulanate group. For evaluable subjects at posttreatment, the clinical success rates (i.e., cure + improved vs. failure) were as follows: 92.3% (24/26) in the cefpodoxime and 94.4% (17/18) in the amoxicillin clavulanate arm. These numbers are too small to be robust, and for that reason alone not meet the standard of equivalence by confidence interval. However, the rates are similar and close to those observed in studies 108 and 109 submitted in support of this application.
(2) No significant differences between the cefpodoxime and amoxicillin/clavulanate treatment groups were detected with respect to the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of discontinuation due to adverse events, and the rates of serious adverse events. However, the sample size is too small to allow this to be a firm conclusion.

Recommendation:

Study 0045 corroborates pivotal Studies 108 and 109 in support of an indication of acute sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*.

Integrated Efficacy Summary

Chart 43: Study Results – Clinical Evaluation at Posttreatment TOC (95 % Confidence Intervals)

Protocol		ITT Population			Evaluable Population			
		cefpodoxime	loracarbef	95% CI		cefpodoxime	loracarbef	95% CI
	cure	99(52.7%)	80(42.3%)		cure	87(53.4%)	75(44.1%)	
	improved	62(33.0%)	71(37.6%)		improved	59(36.2%)	67(39.4%)	
	failure	27(14.4%)	38(20.1%)		failure	17(10.4%)	28(16.5%)	
M/1140/0109								
	cure + improved	161(85.6%)	151(79.9%)	(-0.2%, 20.9%)	cure + improved	146(89.6%)	142(83.5%)	(-2.0%, 20.6%)
	failure	27(14.4%)	38(20.1%)		failure	17(10.4%)	28(16.5%)	
	cure	99(52.7%)	80(42.3%)	(-2.4%, 13.9%)	cure	87(53.4%)	75(44.1%)	(-1.8%, 13.9%)
	failure + improved	89(47.3%)	109(57.7%)		failure + improved	76(46.6%)	95(55.9%)	
		cefpodoxime	uncontrolled	95% CI		cefpodoxime	uncontrolled	95% CI
	cure	242(49.6%)			cure	51(62.2%)		
M/1140/0108[1]	improved	179(36.7%)			improved	26(31.7%)		
(FDA evaluable	failure	67(13.7%)			failure	5 (6.1%)		
population)								
	cure + improved	421(86.3%)		NA	cure + improved	87(93.9%)		NA
	failure	67(13.7%)			failure	5 (6.1%)		
	cure	242(49.6%)		NA	cure	51(62.2%)		NA
	failure + improved	246(50.4%)			failure + improved	31(37.8%)		
		cefpodoxime	amox/clav	95% CI		cefpodoxime	amox/clav	95% CI
	cure	26(33.3%)	28(37.3%)		cure	14(53.8%)	9(50.0%)	
M/1140/0045[2]	improved	36(46.2%)	34(45.3%)		improved	10(38.5%)	8 (44.4%)	
	failure	16(20.5%)	13(17.3%)		failure	2 (7.7%)	1 (5.6%)	
	cure + improved	62(79.5%)	62(82.7%)	(-20.4%, 12.4%)	cure + improved	24(92.3%)	17(94.4%)	(-30.9%, 38.6%)
	failure	16(20.5%)	13(17.3%)		failure	2 (7.7%)	1 (5.6%)	
	cure	26(33.3%)	28(37.3%)	(-16.9%, 10.5%)	cure	14(53.8%)	9(50.0%)	(-21.6%, 17.3%)
	failure + improved	52(66.7%)	47(62.7%)		failure + improved	12(46.2%)	9(50.0%)	

[1] This study is uncontrolled and statistical analysis is not applicable. See review for discussion of acceptable cure rate.
[2] This study is extremely small and statistical power is inadequate.

Chart 44: Study Results – Microbiological Evaluation

Protocol	ITT Population				Evaluable Population			
M/1140/0109	Not applicable: no microbiologic evaluation				Not applicable: no microbiologic evaluation			
M/1140/0108[1] (FDA evaluable population)		cefpodoxime	uncontrolled	95% CI		cefpodoxime	uncontrolled	95% CI
	cure	125(25.6%)			cure	76(92.7%)		
	failure	13 (2.7%)		NA	failure	5 (6.1%)		NA
	superinfection	3(0.6%)			superinfection	1 (1.2%)		
		cefpodoxime	amox/clav	95% CI		cefpodoxime	amox/clav	95% CI
M/1140/0045[2]	cure	26(33.3%)	28(37.3%)		cure	14(53.8%)	9(50.0%)	
	failure	48(61.5%)	40(53.3%)	(-20.4%, 12.4%)	failure	12(46.2%)	9(50.0%)	(-30.9%, 38.6%)
	missing/ not reported	4(5.1%)	7(9.3%)		missing/ not reported	0 (0%)	0 (0%)	

[1] This study is uncontrolled and statistical analysis is not applicable. See review for discussion of acceptable cure rate.

[2] This study is extremely small and statistical power is inadequate.

Chart 45: Pathogen Eradication Rates at Posttreatment

Protocol	ITT Population			Evaluable Population		
M/1140/0109	Not applicable: no microbiologic evaluation			Not applicable: no microbiologic evaluation		
		cefpodoxime	**uncontrolled**		**cefpodoxime**	**uncontrolled**
M/1140/0108[1]	*S. pneumoniae*	41/44(92.3%)		*S. pneumoniae*[3]	36/38(94.7%)	
	H. influenzae	38/41(92.7%)		*H. influenzae*[4]	34/37(91.9%)	
	M. catarrhalis	14/14(100%)		*M. catarrhalis*[5]	13/13(100%)	
	S. pyogenes	7/8 (87.5%)		*S. pyogenes*	6/7 (85.7%)	
	S. aureus	42/49 (85.7%)		*S. aureus*	0 (NA)	
		cefpodoxime	**amox/clav**		**cefpodoxime**	**amox/clav**
M/1140/0045[2]	*S. pneumoniae*			*S. pneumoniae*[3]	8/8(100%)	5/5(100%)
	H. influenzae			*H. influenzae*[4]	7/7(100%)	5/5(100%)
	M. catarrhalis			*M. catarrhalis*[5]	1/1 (100%)	1/1(100%)
	S. pyogenes			*S. pyogenes*	0 (NA)	0 (NA)
	S. aureus			*S. aureus*	4/5 (80.0%)	2/2(100%)

[1] This study is uncontrolled and statistical analysis is not applicable. See review for discussion of acceptable cure rate.
[2] This study is extremely small and statistical power is inadequate.
[3] Number of penicillin intermediate and resistant isolates not noted by sponsor.
[4] Sixteen of the 44 (36.4%) *Haemophilus influenzae* isolates were beta-lactamase producers, and 16/16(100 %) were eradicated at TOC.
[5] Twelve of the 14 (85.7%) *Moraxella catarrhalis* isolates were beta-lactamase producers, and all were eradicated.

Reviewers' note: *The cure rates are fairly consistent. A discrepancy is seen between the microbiological cure rates among the evaluable populations between studies M/1140/0108 and M/1140/0045 (92.7% versus 53.8%). Questions are raised because M/1140/0045 is too small to be statistically sound and M/1140/0108 is uncontrolled. Although the studies support effectiveness of cefpodoxime proxetil in the treatment of acute maxillary sinusitis, the actual cure rate is an issue. The pathogen eradication rates are more consistent across studies. As discussed earlier, M/1140/0045 will serve merely as supportive data and M/1140/0108 is a pivotal trial.*

Integrated Safety Summary

Chart 46: Medical Event Rates (Studies M/1140/0108, M/1140/0109 and M/1140/0045)[1]

Adverse Event	cefpodoxime (N=754)	comparator (N=264)	Fisher's P-value
Subject with at least one adverse event not necessarily attributed to study drug	437(58.0%)	139(52.7%)	0.149
Allergy [2]	1(1.3%)	2 (2.7%)	0.615
Body [3]	252(37.3%)	70(37.0%)	1.000
Cardiovascular [3]	9(1.3%)	5(2.6%)	0.202
Digestive	140(20.7%)	38(20.1%)	1.000
Endocrine [3]	1(0.1%)		NA
Hematologic & Lymphatic [3]	5(0.7%)		0.591
Metabolic & Nutritional	1 (0.1%)	1(0.4%)	0.452
Miscellaneous [2]	9(11.5 %)	9 (12.0%)	1.000
Musculo-Skeletal [3]	7(1.0%)	2(1.0%)	1.000
Nervous	16 (2.1%)	4(1.5%)	0.797
Respiratory	189 (25.1%)	53(20.5%)	0.111
Skin	18 (2.4%)	2(0.8%)	0.124
Special Senses	40 (5.3%)	11(4.2%)	0.516
Surgical Procedures [2]	3 (3.8%)	0(0%)	0.245
Urogenital	22 (3.9%)	8(3.0%)	1.000
Subject with at least one adverse event attributed to study drug	121 (16.0%)	35(13.3%)	0.321
Allergy [2]	0(0%)	1(1.3%)	0.490
Body [3]	31(4.6%)	11(5.8%)	0.450
Cardiovascular [3]	1(0.1%)	0(0%)	1.000
Digestive	70 (10.3%)	9(4.8%)	0.021
Hematologic & Lymphatic [3]	2(0.3%)		NA
Miscellaneous [2]	1 (1.3%)	0(0%)	1.000
Musculo-Skeletal [3]	1(0.1%)		NA
Nervous [3]	6(1.0%)	1(0.5%)	1.000
Respiratory	2 (0.3%)	1(0.4%)	1.000
Skin	5 (0.7%)	3(1.1%)	0.434
Urogenital	12 (1.6%)	3(1.1%)	0.772
Subject with Serious AEs	9 (1.2%)	0(0%)	0.122
Subject discontinued due to AEs	22 (2.9%)	7(2.7%)	1.000

[1] Study M/1140/0045 used different AE terminology from studies M/1140/0108 and M/1140/0109. Thus, not all terminology is comparable. The reviewers compiled the information where organ systems had correlates. Where no correlate exists, percentages were corrected for denominator. Studies M/1140/0108 and M/1140/0109 had a denominator of 754 in the cefpodoxime arms. Study M/1140/0045 had a denominator of 78 in the cefpodoxime arm. Study M/1140/0108 was uncontrolled and had no comparator arm. Study M/1140/0109 had 189 subjects enrolled in the loracarbef arm. Study M/1140/0045 had 75 subjects enrolled in the amoxicillin/clavulanate arm.

[2] These terms were used in study M/1140/0045 and have no comparable terms in M/1140/0108 and M/1140/0109.

[3] These terms were used in studies M/1140/0108 and M/1140/0109 and have no comparable terms in M/1140/0045

Reviewers' note: *The medical event rates are consistent with the current safety labeling which requires no changes based on this data.*

Pharmacokinetic Considerations for Pediatric Labeling:

The Sponsor studied the pharmacokinetic profile of Vantin® (cefpodoxime proxetil) 29 patients aged 1 to 17.2 years, and demonstrated the equivalence of the tablet formulation to oral suspension. In addition, the mean time the plasma levels are above the MIC_{90} was determined for the major pathogens of sinusitis. This is summarized in the following Chart:

Chart 47: Time above the MIC_{90} for the Common Pathogens of Sinusitis

		Percent (%) of Time Plasma Levels are above the MIC90 with 12 hour dosing				
	MIC_{90}(µg/mL)	0.5-2 years	3-6 years	7-12 years	13-18 years	Adults
S. pneumoniae	0.05	>90	>90	>90	>90	>90
H. influenzae	0.24	>75	>75	>80	>80	>80
M. catarrhalis	0.67	~50	~50	~60	~60	~60

The above data demonstrates that the pharmacokinetics of cefpodoxime proxitel is similar between adults and children older than 6 years of age. The pharmacokinetic profile is slightly less favorable for the pediatric population aged 6 and younger. With respect to *Streptococcus pneumoniae*, the time above the MIC_{90} with a dosing interval is >90% for all patients. For *Haemophilus influenzae*, the time above the MIC_{90} with a dosing interval is only slightly less favorable for those less than 7 years of age, dropping from >80% to >75%. *Moraxella catarrhalis* is less favorable, the time above the MIC_{90} within the dosing interval dropping from ~60% to ~50% in the younger age group.

Medical Officer's note: *Further information regarding the pharmacokinetic profile in the pediatric population can be obtained from the Clinical Pharmacology and Biopharmaceutics Review completed by DAIDP. Vantin® has demonstrated pharmacokinetic equivalence between the pediatric and adult population, and success in the adult population in treating acute bacterial maxillary sinusitis. Children under one year of age were not studied. From the above data, we can see that time above the MIC90 within the 12 hour dosing interval is very acceptable for Streptococcus pneumoniae and Haemophilus influenzae in all populations. The Moraxella catarrhalis is somewhat less favorable but still acceptable – the clinical cure rate for adults with sinusitis due to Moraxella catarrhalis in the trials submitted was 100% (14/14). Thus, this reviewer believes that the clinical claims made for the adult population can be extrapolated to the pediatric population under the pediatric rule.*

Conclusions:

The pivotal studies, M/1140/109 and M/1140/108, and supporting study, M/1140/0045, document the efficacy of Vantin® in the treatment of acute maxillary sinusitis due to *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* in the adult population.

No information was provided on intermediate- or fully- resistant strains of *S. pneumoniae*. Thus, efficacy against fully susceptible, but not other, strains is assumed.

Enough evidence was submitted to support labeling against beta-lactamase producing strains of *Haemophilus influenzae*. Of the 44 cases of sinusitis due to *Haemophilus influenzae*, 16 (36.3%) were beta-lactamase producing, and Vantin® was effective in treating these isolates. Twelve of 14 (85.7%) strains of *Moraxella catarrhalis* were beta-lactamase producing and Vantin® was effective in treating these isolates.[4]

[4] The addition of "beta-lactamase producing strains" to *Moraxella catarrhalis* is ridiculously redundant as currently the rates of beta-lactamase production among clinical isolates of *Moraxella catarrhalis* are over 95% and many, many clinical microbiology laboratories tentatively identify *Moraxella catarrhalis* isolates by colony morphology ("hockey puck test"), oxidase test, gram stain, and cefinase disc test. These reviewers believe firmly that this language should be eliminated. DAIDP has allowed this language before in the interests of fairness and consistency; however, the science does not support it.

The data, in the instances of certain microbiologic outcomes, does not provide a reliable measure of cure, but as a whole suggests efficacy equivalent, and not superior, to already marketed agents. Data submitted is insufficient to support efficacy against *Streptococcus pyogenes* and *Staphylococcus aureus*.

Pharmacokinetic data submitted on pediatric subjects supports a profile equivalent to that in adults. Thus, the clinical efficacy demonstrated in adults can be extrapolated to the pediatric population under the pediatric rule.

The safety data associated with the above trials provides no information over that which is contained in the existing label.

Recommendations:

That the following be added to the current Vantin® label:

That no clinical studies information be added to the existing label based on this application.

/S/

Holli Hamilton, MD, MPH
Medical Officer
HFD-520 FDA

/S/

Joel Jiang, PhD
Statistician
HFD-725 FDA

Concurrences:
HFD-520/TL/Jan Soreth, MD Jan Soreth 11/18/98
HFD-520/DivDir/Gary Chikami, MD
11/20/98

Concurrences:
HFD-725/TL/Daphne Lin, PhD,draft 10/30/98
DL 11/19/98

cc: Orig NDAs 50-674 & 50-675

[5] Children under 12 months of age were not studied.

HFD-520/Division File
HFD-520/CSO/CDeBellas
HFD-520/Microbiology/ASheldon
HFD-520/Chemistry/DKatague
HFD-520/Pharm/FPelsor
HFD-520/MO/HHamilton
HFD-520/MTL/JSoreth
HFD-725/Stat/JJiang
HFD-725/Stat/TL/DLin
HFD-725/ActDivDir/MHuque

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