## Secondary Efficacy Results (Historical Studies)

'e E-38 presents the results reported for the secondary efficacy measures in Protocls 0013, 0014, and .).

**Table E-38. Summary: Results of Secondary Efficacy Measures in Protocols 0013, 0014, & 0060**

| Protocol<br>No. Pts | Long-Term Follow-up | Super-infections | Clinical Observations | Temperature | WBC Count | Follow-Up Pneumatic Otoscopy/ Tympanometry |
|---|---|---|---|---|---|---|
| : 0013<br>CFD = 95<br>A/C = 48 | Bacteriologic cure: 71% in both groups<br><br>Clinical cure or improvement:<br>CFD (65%),<br>A/C (63%)<br><br>Recurrence (%; # pts):<br>CFD (25%; 24/95),<br>A/C (25%; 12/48) | 2% of both the CFD and A/C groups had superinfec-tions | Earache, irritability, and otorrhea disappeared with therapy in both groups. | Both treatment groups had significant within-group decreases from baseline at the interim, EOT, and LTF visits. No significant between-group differences | At the EOT, both treatment groups had statistically significant mean decreases from pretreatment counts. | External auditory canals:most were normal in both groups.<br><br>Tympanic membranes: some patients in both groups exhibited a variety of abnormalities. |
| 0014<br><br>CFD = 56<br>A/C = 37 | Bacteriologic cure:<br>CFD (67%),<br>A/C (78%)<br><br>Clinical cure or improve-ment of clinical symp-toms: CFD (63%),<br>A/C (81%)<br><br>Recurrence (%; # pts):<br>CFD (18%; 10/56),<br>A/C (11%; 4/37) | CFD: 11%,<br>A/C: 14% | Earache, irritability, and otorrhea disappeared with therapy in both groups. | Both treatment groups had significant within-group decreases from baseline at the interim, EOT, and LTF visits. No significant between-group differences | At the EOT, both treatment groups had statistically significant mean decreases from pretreatment counts. | External auditory canals:most were normal in both groups.<br><br>Tympanic membranes: some patients in both groups exhibited a variety of abnormalities. |
| 0060<br><br>CFD = 54<br>A/C = 56 | Bacteriologic Cure: Not Investigated<br><br>EOT of Therapy Progress of Infection:<br>CFD (81%)<br>A/C (86%)<br><br>Final Visit Progress of Infection (CI + PI)*<br>CFD ([18+16]/44 = 77%)<br>A/C ([24+18]/47 = 89%)<br><br>Recurrence (CI + PI)*:<br>CFD ([6+4]/44=23%),<br>A/C ([2+3]/47=11%) | Not Investi-gated | Earache, irritability, coryza, and otorrhea generally dissipated by EOT | Both treatment groups had significant within-group decreases from baseline at the EOT, and LTF visits. No clinically important between-group differences. | At the EOT, both treatment groups had statistically significant mean decreases from pretreatment counts. No clinically important between group differences. | External auditory canals: most were normal in both groups.<br><br>Tympanic membranes: generally normal. Pneumatic otoscopy findings were generally normal, tympanometry generally not done. |

A/C = amoxicillin/clavulanate, CFD = Cefpodoxime, EOT = End of Therapy Visit,
LTF = Long-Term Follow-up Visit

* This evaluation included both the clinical investigator's evaluation of cure/improvement (or recurrence) and the patient or guardian's opinion of cure/improvement as reported during a telephone interview

*Reference: [3, 4, 5]*

## 3. Efficacy Summary and Conclusions (10 day Studies)

The efficacy and safety profile of the 5-day cefpodoxime regimen, as determined from integrated data from Protocols 0098-A and 0098-B, was retrospectively compared with that of a )-day cefpodoxime regimen. The 10-day data for this comparison were obtained from three studies (Protocols M/1140/0013, M/1140/0014, and M/1140/0060 ) in which pediatric patients with otitis media were treated with either cefpodoxime at a dose of 5 mg/kg every 12 hours for 10 days or amoxicillin/clavulanate potassium at a dose of 13.3 mg/kg every 8 hours for 10 days. This was

ve to provide a framework in which to place the five day data. Also given the choice of parator in the five day data, endpoints side-by-side could be reviewed with the 10 day study which had Augmentin as the comparator.

The results from three studies (Protocols 0013, 0014, and 0060) showed that cefpodoxime proxetil oral suspension (administered every 12 hours for 10 days at a total daily dosage of 10 mg/kg) was equally as effective as amoxicillin/clavulanate (given every 8 hours at a total daily dosage of 40 mg/kg) for the treatment of acute suppurative otitis media in pediatric patients. The results of two of these studies (Protocols 0013 and 0014) showed that the two regimens were equally effective in eradicating *H influenzae* (beta-lactamase-positive and -negative), *M catarrhalis* (beta-lactamase-positive), *S pneumoniae*, and *S pyogenes* from the ears of infected children.

Summary Table of Results of Protocol 13,14 and 60

| | | End of Therapy | | | Long Term Follow Up | | |
|---|---|---|---|---|---|---|---|
| Protocol | Treatment Group [No. Pts] | Clinical Cure | By infection | By Pathogen | Clinical Cure | By infection | By Pathogen |
| 13 | CFD [N=95] | 91 *84/98 (85)* | 93 | 93 | 65 | 71 | |
| | AMC/CA [N=48] | 88 *40/47 (86)* | 88 | 89 | 63 | 71 | |
| 14 | CFD [N=56] | 64 *31/52 (60)* | 79 | 82 | 63 | 67 | |
| | AMC/CA [N=37] | 62 | 84 | 86 | 81 | 78 | |
| 60 | CFD N=54 | 78 | | | 77 | | |
| | AMC/CA [N=56] | 84 | | | 89 | | |
| 60 | CFD(N=54) | 78 | | | 77 | | |
| | AMC/CA [N=56] | 84 | | | 89 | | |

## IV. Safety Results

### 1) Current Studies
### Patient Disposition

A total of 969 patients were enrolled in Protocols 0098-A and 0098-B (ISS Appendix A, Table 1.1): 481 patients were randomized to receive cefpodoxime, and 488 patients were randomized to receive cefixime.

Of the 969 randomized patients, 968 (481 in the cefpodoxime group and 487 in the cefixime group) received at least one dose of study medication. The remaining patient, who was randomized to cefixime, never received any study medication. However, this patient was included in the denominator for the cefixime group. Thus, all 969 patients (481 in the cefpodoxime group and 488 in the cefixime group) were included in the safety analyses.

Two percent (12/481) of the patients in the cefpodoxime group and 3% (14/488) of the patients in the cefixime group discontinued from the studies due to medical events (ISS Appendix A: Table 1.1; see Section 8. Deaths, Dropouts Due to Medical Events, and Other Serious or Potentially Serious Medical Events for further discussion).

**Medical Events**

*Medical Officer's Note: Evaluation of safety data was based on review of adverse events within treatment groups for all subjects who received at least one dose of study drug. The statistical review was conducted of the safety analyses with the following variables: the rate of at least one adverse event, the rate of at least one treatment related adverse event, the rate of severe adverse events, and the rate of discontinuation due to adverse events. The statistical comparisons between the two treatment groups were performed using Fisher's exact test.*

#### Overall Summary

No clinically relevant differences were noted between the cefpodoxime and cefixime groups in the percentage of patients who experienced at least one medical event or in the percentage of patients who experienced at least one drug-related medical event. Likewise, no clinically relevant differences were noted between treatment groups in the percentage of patients who experienced serious medical events or in the percentage of patients who discontinued from the studies due to medical events. Table E-41 provides an overall summary of medical-event data.

**Table E-41. Medical Event (ME) Summary (Protocols 0098-A and 0098-B)**

| No. (%) | Cefpodoxime N=481 | Cefixime N=488 |
|---|---|---|
| Patients With No Mes | 304 (63%) | 303 (62%) |
| Patients With at Least One ME | 177 (37%) | 185 (38%) |
| Patients With at Least One Drug-related ME | 58 (12%) | 59 (12%) |
| Patients With Serious MEs* | 0 | 3 (<1%) |
| Patients Who Discontinued Because of Mes | 12 (2%)† | 14 (3%) |
| Deaths | 0 | 0 |

* An event that was fatal, life-threatening or permanently disabling, that required or prolonged hospitalization, or that was a congenital anomaly, cancer, or a medication overdose.

† Eleven patients in the cefpodoxime group were reported by the investigators to have discontinued from the studies due to medical events (ISS Appendix A: Table 1.1). An additional patient (Protocol 0098-A, Patient No. 307), who was discontinued from the study because she failed to meet the protocol entry criteria (ie, she had no isolated pathogen at pretreatment), was subsequently determined to have discontinued from the study due to medical events. As such, this patient has been included in the calculations and discussions of the number of patients who discontinued treatment due to medical events, even though she was not included in this category in ISS Appendix A: Table 1.1.

*Reference: ISS Appendix A: Tables 1.1, 4.2, 4.6, and 4.11*

*Medical Officer's Note: For all subjects who were randomized to treatment and received at least one dose of study medication, the rates of at least one adverse event, the rates of at least one treatment related adverse event, the rates of serious adverse events, and the rate of discontinued due to adverse events are presented in Table 2.34 for Study A. No significant differences were detected regarding all these safety parameters between the two treatment groups.*

*No deaths were reported during the study.*

**TABLE 2.34: STUDY 0098A: MEDICAL EVENT RATES**

| Safety Outcome | Cefpodoxime (N=225) | Cefixime (N=230) | Fisher's P-value |
|---|---|---|---|
| Subject with at Least one AE | 74 (32.9%) | 66 (28.7%) | 0.361 |
| Body as a Whole | 28 (12.4%) | 17 (7.4%) | 0.084 |
| Digestive | 26 (11.6%) | 31 (13.5%) | 0.573 |
| Hemic and Lymphatic | 2 (0.9%) | 2 (0.9%) | 1.000 |
| Nervous | 2 (0.9%) | 2 (0.9%) | 1.000 |
| Respiratory | 17 (7.6%) | 16 (7.0%) | 0.858 |
| Skin | 12 (5.3%) | 15 (6.5%) | 0.693 |
| Special Senses | 7 (3.1%) | 4 (1.7%) | 0.377 |
| Urogenital | 0 (0) | 3 (1.3%) | 0.248 |
| Subject with Treatment Related AEs | 23 (18.6%) | 24 (13.4%) | 0.307 |
| Body as a Whole | 1 (0.4%) | 1 (0.4%) | 1.000 |
| Digestive | 18 (8.0%) | 19 (8.3%) | 1.000 |
| Nervous | 1 (0.4%) | 1 (0.4%) | 1.000 |
| Skin | 5 (2.2%) | 9 (3.9%) | 0.417 |
| Urogenital | 0 (0) | 1 (0.4%) | 1.000 |
| Subject with Serious AEs | 0 (0) | 2 (0.9%) | 0.499 |
| Subject Discontinued due to AEs | 7 (3.1%) | 9 (1.6%) | 0.684 |

*Medical Officer's Note: For all subjects who were randomized to treatment and received at least one dose of study medication, the rates of at least one adverse event, the rates of at least one treatment related adverse event, the rates of serious adverse events, and the rate of discontinued due to adverse events are presented in Table 3.33. No significant differences were detected*

*regarding all these safety parameters between the two treatment groups.*

*No deaths were reported during the study.*

| TABLE 3.33: STUDY 0098B: MEDICAL EVENT RATES | | | |
|---|---|---|---|
| Safety Outcome | Cefpodoxime (N=256) | Cefixime (N=258) | Fisher's P-value |
| Subject with at Least one AE | 103 (40.2%) | 119 (46.1%) | 0.183 |
| Body as a Whole | 44 (17.2%) | 44 (17.1%) | 1.000 |
| Cardiovascular | 0 (0) | 1 (0.4%) | 1.000 |
| Digestive | [illegible] | 50 (19.4%) | 0.650 |
| Hemic and Lymphatic | [illegible] | 2 (0.8%) | 0.499 |
| Metabolic and Nutritional | 0 (0%) | 2 (0.8%) | 0.499 |
| Nervous | 5 (2.0%) | 1 (0.4%) | 0.122 |
| Respiratory | 36 (14.1%) | 41 (15.9%) | 0.621 |
| Skin | 11 (4.3%) | 17 (6.6%) | 0.331 |
| Special Senses | 9 (3.5%) | 13 (5.0%) | 0.514 |
| Urogenital | 1 (0.4%) | 1 (0.4%) | 1.000 |
| Subject with Treatment Related AEs | 35 (13.7%) | 35 (13.6%) | 1.000 |
| Body as a Whole | 1 (0.4%) | 1 (0.4%) | 1.000 |
| Digestive | 18 (7.0%) | 19 (7.4%) | 1.000 |
| Nervous | 1 (0.4%) | 1 (0.4%) | 1.000 |
| Skin | 5 (2.0%) | 9 (3.5%) | 0.417 |
| Urogenital | 0 (0) | 1 (0.4%) | 1.000 |
| Subject with Serious AEs | 0 (0) | 1 (0.4%) | 1.000 |
| Subject Discontinued due to AEs | 4 (1.6%) | 5 (1.9%) | 1.000 |

All Medical Events

A total of 287 medical events were reported for 177 (37%) of the 481 cefpodoxime-treated patients, and a total of 300 medical events were reported for 185 (38%) of the 488 cefixime-treated patients (ISS Appendix A: Tables 4.2 and 4.4). Medical events were most frequently related to the digestive (eg, diarrhea), body as a whole (eg, upper respiratory infection or fever), and respiratory (eg, cough, rhinitis, pharyngitis) systems, with more than 10% of patients in each group reporting medical events in these body systems. The number and percentage of patients who reported medical events are shown by treatment group, body system, and event in the tables above.

The majority of events in each treatment group were rated mild to moderate in intensity: 70% (200/287) of the events in the cefpodoxime group and 68% (203/300) of the events in the cefixime group were rated mild in intensity, and 27% (77/287) and 30% (91/300) of the events in each group, respectively, were rated moderate in intensity. Only 3% (9/287) of the events in the cefpodoxime group and 2% (6/300) of the events in the cefixime group were rated severe in intensity.

In the medical events that were reported in 1% or more of the patients in either treatment group, the medical-event profile of cefpodoxime was similar to that of cefixime; no clinically relevant differences were observed between treatments in the frequency of individual medical events.

Drug-Related Medical Events

Sixty-nine drug-related events were reported for 58 (12%) of the 481 cefpodoxime-treated patients, and 76 drug-related events were reported for 59 (12%) of the 488 cefixime-treated patients. Diarrhea, vomiting, and rash were the primary drug-related medical events in each treatment group; all other drug-related events were reported in fewer than 1% of the patients in either group.

The majority of drug-related medical events (>97%) in each group were rated mild to moderate in intensity (ISS Appendix A: Table 4.7): 77% (53/69) of the drug-related events in the cefpodoxime group and 74% (56/76) of the drug-related events in the cefixime group were rated mild in intensity, and 20% (14/69) and 26% (20/76) of the drug-related events in each group, respectively, were rated moderate in intensity. Two (3%) drug-related events (diarrhea and rash) in the cefpodoxime group and no events in the cefixime group were rated severe in intensity.

Deaths, Dropouts due to Medical Events, and Other Serious Medical Events

Deaths

There were no deaths during the studies.

Dropouts Due to Medical Events

Twelve (2%) of the 481 patients in the cefpodoxime group and 14 (3%) of the 488 patients in the cefixime group discontinued from the studies due to medical events.

Of the 12 cefpodoxime-treated patients who discontinued due to medical events, 8 discontinued during the 5-day, cefpodoxime-treatment period, and 4 discontinued during the posttreatment, follow-up period. Similarly, of the 14 patients in the cefixime group who discontinued from the studies due to medical events, 10 discontinued during the 10-day, cefixime-treatment period, and 4 discontinued during the posttreatment, follow-up period. Thus, the on-treatment rate of discontinuation due to medical events was 2% (8/481) in the cefpodoxime group and 2% (10/488) in the cefixime group.

Serious Medical Events

No serious medical events were reported among the 481 cefpodoxime-treated patients. Three (<1%) of the 488 cefixime-treated patients were reported to have experienced serious medical events, which included dysphagia, cachexia, and pulmonary obstruction in one patient during the 10-day, cefixime-treatment period and bronchitis in one patient and vomiting in another during the posttreatment, follow-up period subsequent to the 10-day, cefixime-treatment period. None of these events were judged by the investigators to be related to administration of the study medication. The patients who experienced serious medical events are listed, along with their serious event(s), in Table E-46. A narrative summary for each patient is included in ISS Appendix B.

**Retrospective Comparison Of Medical Events For The 5-Day, Twice-Daily Cefpodoxime Regimen Versus The 10-Day, Twice-Daily Cefpodoxime Regimen In Pediatric Patients With Otitis Media**

The medical-event profile of cefpodoxime when administered at a dose of 5 mg/kg twice daily for 5 days to pediatric patients with otitis media, as investigated in Protocols 0098-A and 0098-B, was retrospectively compared with that of cefpodoxime when administered at a dose of 5 mg/kg twice daily for 10 days to pediatric patients with otitis media, as investigated in Protocols 0013, 0014, and 0060. The comparative agents in these studies were cefixime, administered at a dose of 8 mg/kg once daily for 10 days, in Protocols 0098-A and 0098-B and amoxicillin/clavulanate potassium, administered at a dose of 13.3 mg/kg thrice daily for 10 days, in Protocols 0013, 0014, and 0060. The medical events that were reported in 1% or more of the patients in any treatment group are summarized in Table E-47.

The medical events reported for the 5- and 10-day cefpodoxime regimens were similar. However, the frequency of individual events, particularly the frequency of the events that are commonly associated with administration of cefpodoxime, eg, diarrhea, vomiting, and rash, was generally lower for the 5-day cefpodoxime regimen than for the 10-day cefpodoxime regimen. As previously noted, no clinically relevant differences were noted between the 5-day cefpodoxime regimen and the 10-day cefixime regimen with which it was compared in Protocols 0098-A and 0098-B.

The medical events reported for the 10-day cefpodoxime regimen were similar to those reported for the 10-day amoxicillin/clavulanate potassium regimen with which it was compared in Protocols 0013, 0014, and 0060. However, clinically relevant differences were noted between regimens in the frequency of diarrhea and rash, each of which was reported at least 1.5 times more frequently for the 10-day amoxicillin/clavulanate potassium regimen than for the 10-day cefpodoxime regimen. When compared with the 5-day cefpodoxime regimen (as investigated in Protocols 0098-A and 0098-B), these events were reported at least twice as frequently for the 10-day amoxicillin/clavulanate potassium regimen as for the 5-day cefpodoxime regimen. Additionally, urticaria, auditory disorders, skin moniliasis, otitis externa, otitis media, otorrhea, increased SGPT, and thrombocytopenia were reported at least twice as frequently for the 10-day amoxicillin/clavulanate potassium regimen as for the 5-day cefpodoxime regimen.

Table E-47. Medical Events Reported by ≥1% of Patients in Any Treatment Group: Cefpodoxime 5-Day Regimen Versus Cefpodoxime 10-Day Regimen Versus Cefixime and Amoxicillin/Clavulanate Potassium

| Event (COSTART) | Cefpodoxime 5-Day Regimen*† N=481 | Cefpodoxime 10-Day Regimen†‡ N=332 | Cefixime*§ N=488 | Amoxicillin/ Clavulanate Potassium‡¶ N=195 |
|---|---|---|---|---|
| Diarrhea | 10% | 15% | 12% | 24% |
| Vomiting | 6% | 8% | 6% | 7% |
| Upper Respiratory Infection | 5% | 2% | 5% | <1% |
| Cough | 4% | 3% | 5% | 3% |
| Fever | 4% | 4% | 3% | 6% |
| Rash | 4% | 5% | 4% | 9% |
| Rhinitis | 3% | 4% | 4% | 3% |
| Pharyngitis | 2% | 1% | 1% | 2% |
| Trauma | 2% | 1% | 1% | 3% |
| Abdominal Pain Localized | 2% | 1% | <1% | <1% |
| Conjunctivitis | 2% | <1% | 1% | 0% |
| Infection Viral NOS** | 1% | 2% | 1% | 2% |
| Wheezing | 1% | 1% | 1% | 1% |
| Sinusitis | 1% | <1% | 1% | 0% |
| Ear Pain | 1% | 1% | 1% | 1% |
| Nervousness | 1% | 1% | <1% | 2% |
| Urticaria | <1% | 3% | 0% | 4% |
| Disorder Auditory | <1% | <1% | 0% | 2% |
| Moniliasis Skin | <1% | 4% | <1% | 6% |
| Otitis Externa | <1% | 0% | <1% | 2% |
| Otitis Media | 0% | 4% | <1% | 3% |
| Otorrhea | 0% | 6% | 1% | 8% |
| Reaction Unevaluable | 0% | 1% | 0% | 2% |
| Increased SGPT | 0% | 0% | 0% | 2% |
| Thrombocythemia | 0% | 3% | 0% | 2% |

* Data from Protocols 0098-A and 0098-B
† 5 mg/kg/d q 12 h (total dose, 10 mg/kg/d)
‡ Data from Protocols 0013, 0014, and 0060
§ 8 mg/kg/d q 24 h x 10 d (total dose, 8 mg/kg/d)
¶ 13.3 mg/kg/d q 8 h x 10 d (total dose, 40 mg/kg/d)
** Not otherwise specified

## 3) Summary And Conclusions

- The data from the two -controlled studies in pediatric patients with acute suppurative otitis media showed that cefpodoxime proxetil oral suspension administered every 12 hours at a total daily dosage of 10 mg/kg for 5 days is as effective as cefixime, considered first-line therapy at the time the studies were initiated, administered every 24 hours at a dosage of 8 mg/kg for 10 days. The pathogens eradicated from the ears of infected children included *S pneumoniae, S pyogenes,* and beta-lactamase positive and negative strains of both *H influenzae* and *M catarrhalis.* The low incidence of superinfections (1%-2%) was comparable in both treatment groups, as was the incidence of side effect failures (2%-3%). A lower percentage of patients in the cefpodoxime group (~1%) than in the cefixime group (4%-5%) was treated with

antibiotics other than the assigned study medication.

- The efficacy demonstrated by cefpodoxime (5 mg/kg administered every 12 hours for 5 days) in the pivotal studies is comparable to that of cefpodoxime administered every 12 hours at a total dosage of 10 mg/kg for 10 days and to that of amoxicillin/clavulanate administered every 8 hours at a total dosage of 40 mg/kg for 10 days, as shown in the data from three studies that compared the latter three regimens. The difference between the pivotal studies and the historical studies is that a sufficient number of patients with otitis media due to *S pyogenes* were enrolled in the pivotal studies to show that eradication of this pathogen occurs with the 5-day cefpodoxime regimen.

- The medical-event profile of cefpodoxime when administered at a dose of 5 mg/kg every 12 hours for 5 days, as determined from integrated data from 481 patients who received the drug according to this regimen in two Phase III studies (Protocols 0098-A and 0098-B), was consistent with the known medical-event profile for cefpodoxime. Gastrointestinal events, primarily diarrhea and vomiting, and rash were the most frequently reported medical events and were the primary events that led to discontinuation of cefpodoxime therapy. No clinically relevant differences in medical-event profiles, discontinuations due to medical events, or serious medical events were noted between this cefpodoxime regimen and the 10-day cefixime regimen with which it was compared in these studies.

The medical-event profile of the 5-day cefpodoxime regimen (ie, 5 mg/kg every 12 hours for 5 days) in pediatric patients with acute otitis media (as determined from integrated data from Protocols 0098-A and 0098-B) was consistent with that which has previously been reported for the 10-day cefpodoxime regimen (ie, 5 mg/kg every 12 hours for 10 days) in a similar patient population (as determined from integrated data from the historical studies, Protocols 0013, 0014, and 0060). Although these retrospective comparisons do not allow for definitive conclusions to be reached, the data suggest that the frequency of individual events is lower for the 5-day cefpodoxime regimen than for the 10-day cefpodoxime. This finding may imply that patients who receive a 5-day cefpodoxime regimen are at a lower risk for side effects, particularly diarrhea, than those who receive a 10-day regimen.

- The medical-event profile of the 5-day cefpodoxime regimen, as investigated in Protocols 0098-A and 0098-B, was similar to that of the 10-day amoxicillin/clavulanate potassium regimen, as investigated in Protocols 0013, 0014, and 0060. However, clinically relevant differences were noted between regimens in the frequency of diarrhea, rash, urticaria, auditory disorders, skin moniliasis, otitis externa, otitis media, otorrhea, increased SGPT, and thrombocytopenia, each of which was reported at least twice as frequently for the 10-day amoxicillin/clavulanate potassium regimen as for the 5-day cefpodoxime regimen. Although this comparison is based on a retrospective comparison of data from different studies, it again suggests a lower risk of adverse events with a shorter duration of exposure to cefpodoxime.

- In conclusion, the pivotal studies showed that the cefpodoxime 5-day regimen (5 mg/kg every 12 hours) is as effective in clinical studies as a 10-day regimen of cefixime (8 mg/kg every 24 hours) for the treatment of acute otitis media due to pathogens susceptible to both cefpodoxime and cefixime. The retrospective comparison of efficacy data from historical studies showed that the 5-day regimen of cefpodoxime is as effective as the 10-day twice-daily regimen of

cefpodoxime and the 10-day amoxicillin/clavulanate regimen (13.3 mg/kg three times daily). The medical-event profile of cefpodoxime administered at a dose of 5 mg/kg twice daily for 5 days is consistent with that which has been reported previously for cefpodoxime. No new safety concerns have been identified.

## '. INTEGRATED SUMMARY OF EFFICACY AND SAFETY

**Introduction**

This supplemental New Drug Application (sNDA) seeks to gain approval for cefpodoxime for the treatment of pediatric patients with otitis media at a dose of 5 mg/kg every 12 hours for 5 days (total daily dose, 10 mg/kg). Evidence of the efficacy and safety of this cefpodoxime dosage regimen is provided by two phase III, prospective, randomized, evaluator-blind studies in which cefpodoxime was administered at a dose of 5 mg/kg every 12 hours for 5 days to 481 pediatric patients with otitis media and cefixime was administered at a dose of 8 mg/kg every 24 hours for 10 days to 488 pediatric patients with otitis media (protocols M/1140/0098-A & M/1140/0098-B).

## Results

**Primary Efficacy Results (Current Studies)**

*Comparisons (95% confidence intervals) of the difference between the two treatment groups show that cefpodoxime was therapeutically equivalent to cefixime with respect to overall bacteriologic outcomes.*

**Table E-19. Summary of "Test of Cure" Overall Bacteriologic Evaluation* at 4-21 Days Posttherapy (Protocols 0098-A & 0098-B)**

| Evaluation | Results | Cefpodoxime N=254† | Cefixime N=257† |
|---|---|---|---|
| Cure | Bacteriologic Cure | – | – |
| | Presumptive Cure | 171 (67%) | 165 (64%) |
| | Total Cures | 171 (67%) | 165 (64%) |
| Failure | Bacteriologic Failure | 3 (1%) | 11 (4%) |
| | Presumptive Failure | 67 (26%) | 59 (23%) |
| | Superinfection | 6 (2%) | 5 (2%) |
| | Side Effect Failure | 5 (2%) | 6 (2%) |
| | Antibiotic Noninvestigational Medication | 2 (1%) | 11 (4%) |
| | Total Failures | 83 (33%) | 92 (36%) |

* Because of rounding, percentages may not total 100

† N= 254 and 257 in the cefpodoxime and cefixime treatment groups, respectively, because 21 patients considered evaluable for efficacy (6 in the cefpodoxime group and 15 in the cefixime group) had no data available in the 4-21 day window.

*Reference: ISE Appendix Tables 4.9-4.10*

"Test of Cure" By-Pathogen Bacteriologic Evaluation

ISE Appendix Table 4.11 lists the "Test of Cure" by-pathogen eradication rates of all the pathogens isolated at Pretreatment. Table E-20 summarizes the eradication rates for *H influenzae, M catarrhalis, S pneumoniae,* and *S pyogenes* isolates. Cefpodoxime had higher eradication rates than did cefixime for *S pneumoniae* (72% versus 58%) and *S pyogenes* (80% versus 57%), comparable rates for *H influenzae* (66% and 75%, respectively) and *M catarrhalis* (56% in both treatment groups).

**Table E-20. Summary of "Test of Cure" Eradication Rates (by Pathogen) at 4-21 Days Posttherapy (Protocols 0098-A & 0098-B)**

| Pathogen | Cefpodoxime | | Cefixime | |
|---|---|---|---|---|
| | n/N | % | n/N | % |
| Haemophilus influenzae | 1/1 | 100 | 6/9 | 67 |
| Haemophilus influenzae (β-lactamase negative) | 27/41 | 66 | 30/37 | 81 |
| Haemophilus influenzae (β-lactamase positive) | 22/34 | 65 | 25/35 | 71 |
| Moraxella catarrhalis | 2/4 | 50 | 4/7 | 57 |
| Moraxella catarrhalis (β-lactamase negative) | ¾ | 75 | 2/3 | 67 |
| Moraxella catarrhalis (β-lactamase positive) | 17/31 | 55 | 17/31 | 55 |
| Streptococcus pneumoniae | 88/122 | 72 | 72/124 | 58 |
| Streptococcus pyogenes | 20/25 | 80 | 13/23 | 57 |

"Test of Cure" Overall Clinical Evaluation

"Test of Cure"

Table E-18 shows the results of the overall clinical evaluation at the "Test of Cure" Visit. The overall clinical success rates (cured plus improved) for the two treatment groups (67% for cefpodoxime versus 64% for cefixime) were statistically equivalent (95% CI: -5.24% to 11.98%).

**Table E-18. Summary of "Test of Cure" Overall Clinical Evaluation* at 4-21 Days Posttherapy (Protocols 0098-A & 0098-B)**

| Evaluation | Results | Cefpodoxime N=254† | Cefixime N=258† |
|---|---|---|---|
| Success | Cured | 111 (44%) | 125 (48%) |
| | Improved | 60 (24%) | 40 (16%) |
| | Total Clinical Successes | 171 (67%) | 165 (64%) |
| Failure | Failure | 76 (30%) | 76 (29%) |
| | Side Effect Failure | 5 (2%) | 6 (2%) |
| | Antibiotic Noninvestigational Medication | 2 (1%) | 11 (4%) |
| | Total Clinical Failures | 83 (33%) | 93 (36%) |

* Because of rounding, percentages may not total 100

† N= 254 and 258 in the cefpodoxime and cefixime treatment groups, respectively, because 20 patients considered evaluable for efficacy (6 in the cefpodoxime group and 14 in the cefixime group) had no data available in the 4-21 day window.

*Reference: ISE Appendix Tables 4.7-4.8*

## Ancillary Efficacy Outcomes:

**Table E-30. Summary of Clinical Success and Bacteriologic Cure Rates (%) of Cefpodoxime Proxetil 5-Day Twice Daily Regimen in Pediatric Patients with Acute Suppurative Otitis Media (Protocols 0098-A & 0098-B)**

| Treatment Group | End of Therapy | | "Test of Cure" | | Visit 2 | | Visit 3 | | Final Visit | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Clin. | Bacter. | Clin. | Bacter. | Clin. | Bacter. | Clin. | Bacter. | Clin. | Bacter. |
| CFD | 87 | 87 | 67 | 67 | 87 | 87 | 74 | 74 | 65 | 65 |
| CFX | 79 | 79 | 64 | 64 | 87 | 87 | 79 | 79 | 65 | 65 |

CFD = Cefpodoxime; CFX = Cefixime

"Test of Cure" = 4-21 days posttherapy; End of Therapy = Days 7-10 for CFD and Days 12-15 for CFX

Visit 2 = Days 7-10; Visit 3 = Days 12-15, and Final Visit = Days 25-38

Table E-31. Comparison of By-Pathogen Eradication Rates (%) of Cefpodoxime Proxetil 5-Day Twice Daily Regimen in Pediatric Patients with Acute Suppurative Otitis Media (Protocols 0098-A & 0098-B)

| Evaluation | M catarrhalis | | H Influenzae | | S pneumoniae | | S pyogenes | |
|---|---|---|---|---|---|---|---|---|
| | CFD | CFX | CFD | CFX | CFD | CFX | CFD | CFX |
| End of Therapy | 70 | 75 | 91 | 85 | 88 | 71 | 88 | 79 |
| "Test of Cure" | 56 | 56 | 66 | 75 | 72 | 58 | 80 | 57 |
| Visit 2 | 70 | 75 | 91 | 92 | 94 | 89 | 88 | 83 |
| Visit 3 | 59 | 75 | 72 | 85 | 79 | 77 | 84 | 71 |
| Final Visit | 68 | 63 | 57 | 74 | 69 | 58 | 70 | 61 |

CFD = cefpodoxime
CFX = cefixime

## Historical Bacteriologic Studies

Studies classified as Other Studies in this ISE are Protocols 0013, 0014, and 0060. These studies compare 10-day regimens of cefpodoxime proxetil 5 mg/kg administered every 12 hours and amoxicillin/clavulanate 13.3 mg/kg administered every 8 hours.

Primary Efficacy Results (Other Studies)

Table F-31 summarizes the primary efficacy results for the evaluable patients in Protocols 0013, 0014, and 0060. Clinical success in each of the three studies included both clinical cure (complete disappearance of signs and symptoms of acute otitis media) and clinical improvement (significant abatement of clinical signs and symptoms, but without complete resolution), while bacteriologic cure/eradication (evaluated only in Protocols 0013 and 014) was defined as either eradication of pretreatment pathogen from middle ear fluid at the Interim (or End of Therapy Visit) or the lack of middle ear fluid for culture.

The individual statistical analyses of these three studies showed no significant differences between treatment groups in either study for any of the primary efficacy variables. Note that statistical significance was not reported for *S pyogenes* in Protocols 0013 and 0014; the numbers of patients with this pathogen were so small that it is unlikely that the differences seen are clinically important.

**Table F-31. Primary Efficacy Results (Percent Clinical Success and Bacteriologic Cure at End of Therapy*) in the Evaluable Patient Populations of the Other Studies**

| Protocol No. | Treatment Group [No. Pts] | Clinical Success† | Bacteriologic Cure | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | By Patient† | By Ear† [‡] | By Pathogen †,§ | | | |
| | | | | | *S pneu* | *S pyog* | *H infl*†† | *M cat*†† |
| 0013 | CFD¶ [N=95] | 91 | 93 | 56 [93] | 94 | 100§§ | 92 | 94 |
| | A/C** [N=48] | 88 | 89 | 51 [89] | 91 | 75§§ | 90 | 67 |
| 0014 | CFD¶ [N=56] | 64 | 79 | 57 [82] | 87 | – | 96 | 65 |
| | A/C** [N=37] | 62 | 84 | 65 [86] | 100 | 100§§ | 71 | 93 |
| 0060 | CFD¶ [N=54] | 78 | Not done | | | | | |
| | A/C** [N=56] | 84 | | | | | | |

* End of Therapy = Days 10-14 in Protocols 0013 & 0014 and Days 8-22 in Protocol 0060

† There were no statistically significant differences between treatment groups for percent clinical success or percent bacteriologic eradication by patient, by ear, or by pathogen (with the exception of *S pyogenes* for which statistical significance was not reported)

‡ Percent shown in brackets excludes nonassessable patients

§ *S pneu = Streptococcus pneumoniae, S pyog = Streptococcus pyogenes, H infl = Haemophilus influenzae, M cat = Moraxella catarrhalis*

¶ CFD = cefpodoxime twice daily x 10 d

** A/C = amoxicillin/clavulanate thrice daily x 10 d

†† Includes beta lactamase-negative and -positive strains

§§ Protocol 0013: 100% = 7/7patients and 75% = 3/4 patients; Protocol 0014: 100% = 1/1 patient

Summary Table of Results of Protocol 13,14 and 60

| Protocol | Treatment Group [No. Pts] | End of Therapy Clinical Cure | By infection | By Pathogen | Long Term Follow Up Clinical Cure | By infection | By Pathogen |
|---|---|---|---|---|---|---|---|
| 13 | CFD [N=95] | 91 *84/98 (85)* | 93 | 93 | 65 | 71 | |
| | AMC/CA [N=48] | 88 *40/47 (86)* | 88 | 89 | 63 | 71 | |
| 14 | CFD [N=56] | 64 *31/52 (60)* | 79 | 82 | 63 | 67 | |
| | AMC/CA [N=37] | 62 | 84 | 86 | 81 | 78 | |
| 60 | CFD N=54 | 78 | | | 77 | | |
| | AMC/CA [N=56] | 84 | | | 89 | | |
| 60 | CFD(N=54) | 78 | | | 77 | | |
| | AMC/CA [N=56] | 84 | | | 89 | | |

## pK trial

Protocol M/1140/0116 was a randomized, open-label study in which the penetration of cefpodoxime into the middle ear of 50 pediatric patients (age: 6 months to 10 years) with acute otitis media was evaluated after administration of cefpodoxime proxetil oral suspension 5 mg/kg twice a day (BID) or 10 mg/kg once daily (QD). After at least one complete day of treatment, tympanocentesis was performed at either 2, 4, 6, or 8 hours after the morning dose; a blood sample was collected at the same time as the MEE. Drug concentrations in MEE and plasma were determined using an HPLC method with tandem mass spectrometric detection. Median (range) cefpodoxime concentrations in MEE are shown in Table D-2 for the 34 evaluable patients:

**Table D-2. Median (Range) Cefpodoxime Concentrations in Middle Ear Effusion of Pediatric Patients with Otitis Media**

| Target Collection Time (h) | 5 mg/kg BID (n=17) | | 10 mg/kg QD (n=17) | |
|---|---|---|---|---|
| | No. of Samples | Concentration (µg/mL) | No. of Samples | Concentration (µg/mL) |
| 2 | 5 | 2.28 (0.90–3.27) | 5 | 1.72 (0.65–1.92) |
| 4 | 6 | 0.98 (0.36–1.55) | 6 | 3.24 (2.11–12.2) |
| 6 | 6 | 0.88 (0.33–1.41) | 3 | 0.55 (0.20–3.12) |
| 8 | 5 | 0.97 (0.53–1.28) | 5 | 1.55 (0.92–4.03) |

Cefpodoxime levels ≥0.50 µg/mL were attained in the MEE of approximately 91% of the patients in the study. These levels exceed the minimum inhibitory concentration for the majority of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* isolates, the most common etiologic agents of acute otitis media. Approximately 73% of the MEE samples collected in this study had concentrations in excess of the $MIC_{90}$ for penicillin-susceptible *Streptococcus pneumoniae* (0.05 µg/mL), *Haemophilus influenzae* (0.24 µg/mL), and *Moraxella catarrhalis* (0.63 µg/mL). The MEE/plasma cefpodoxime concentration ratio ranged from 0.14 to 12 and from 0.13 to 3.2 in the 5 mg/kg BID and 10 mg/kg QD groups, respectively. There were no differences in the MEE/plasma cefpodoxime concentration ratios between dose groups (p>.14), suggesting a similar extent of penetration for the two regimens.

## SAFETY DATA

### a. Overall Summary

No clinically relevant differences were noted between the cefpodoxime and cefixime groups in the proportion of patients who experienced at least one medical event or in the proportion of patients who experienced at least one drug-related medical event. Likewise, no clinically relevant differences were noted between treatment groups in the proportion of patients who experienced serious medical events or in the proportion of patients who discontinued from the studies due to medical events. Table G.5 provides an overall summary of medical-event data.

### a. All Medical Events

Forty-two percent (896/2128) of the patients experienced at least one medical event during

treatment with cefpodoxime oral suspension (Appendix A, Table 6.1). The most frequently reported medical events were diarrhea and vomiting, which were reported by 8.7% (186/2128) and 7.0% (149/2128) of the patients, respectively. The medical events that were reported by 1% or more of the 2128 patients who received treatment with cefpodoxime oral suspension are summarized by regimen and across regimens in the following table.

**Medical Events Reported in ≥1% of Patients Who Were Treated With Cefpodoxime Proxetil Oral Suspension in Clinical Studies**

| Body System/Event | Cefpodoxime Proxetil Regimen | | | All Regimens N=2128 |
|---|---|---|---|---|
| | 10 mg/kg q 24 h x 10 d* N=454 | 5 mg/kg q 12 h x 10 d† N=817 | 5 mg/kg q 12 h x 5 d‡ N=857 | |
| **Body** | | | | |
| Fever | 19 (4.2) | 49 (6.0) | 29 (3.4) | 97 (4.6) |
| Upper Respiratory Infection | 21 (4.6) | 34 (4.2) | 36 (4.2) | 91 (4.3) |
| Headache | 15 (3.3) | 20 (2.4) | 16 (1.9) | 51 (2.4) |
| Infection Viral NOS§ | 23 (5.1) | 11 (1.4) | 16 (1.9) | 50 (2.4) |
| Abdominal Pain Localized | 3 (0.7) | 13 (1.6) | 13 (1.5) | 29 (1.4) |
| Trauma | 7 (1.5) | 10 (1.2) | 11 (1.3) | 28 (1.3) |
| **Digestive** | | | | |
| Diarrhea | 36 (7.9) | 87 (10.7) | 63 (7.4) | 186 (8.7) |
| Vomiting | 41 (9.0) | 60 (7.3) | 48 (5.6) | 149 (7.0) |
| Nausea | 7 (1.5) | 19 (2.3) | 3 (0.4) | 29 (1.4) |
| **Hemic and Lymphatic** | | | | |
| Thrombocythemia | 9 (2.0) | 12 (1.5) | 0 (0.0) | 21 (1.0) |
| **Respiratory** | | | | |
| Cough | 34 (7.5) | 34 (4.2) | 36 (4.2) | 104 (4.9) |
| Rhinitis | 24 (5.3) | 40 (4.9) | 22 (2.6) | 86 (4.0) |
| Pharyngitis | 10 (2.2) | 27 (3.3) | 21 (2.4) | 58 (2.7) |
| **Skin** | | | | |
| Rash | 10 (2.2) | 30 (3.7) | 18 (2.1) | 58 (2.7) |
| Urticaria | 19 (4.2) | 17 (2.1) | 4 (0.5) | 40 (1.9) |
| Moniliasis skin | 8 (1.8) | 15 (1.8) | 1 (0.1) | 24 (1.1) |
| **Special Senses** | | | | |
| Otorrhea | 41 (9.0) | 20 (2.4) | 0 (0.0) | 61 (2.9) |
| Otitis Media | 16 (3.5) | 25 (3.1) | 3 (0.4) | 44 (2.1) |
| Ear Pain | 17 (3.7) | 9 (1.1) | 7 (0.8) | 33 (1.6) |

* Includes data from Pharmacia & Upjohn protocols M/1140/0043, 0054, and 0059
† Includes data from Pharmacia & Upjohn protocols M/1140/0013, 0014, 0020, 0027, 0028, and 0060
‡ Includes data from Pharmacia & Upjohn protocols M/1140/0054, 0059, and 0098 and from Roussel protocol FF/89/807/37

§ Not otherwise specified
*Reference: Appendix A, Table 6.1*

**b. Drug-Related Medical Events**

t least one medical event considered drug-related or of unkown relationship was reported for % (270/2128) of the patients. Diarrhea, vomiting, and rash were the only drug-related events that were reported at a frequency of at least 1%. The frequency of these events is summarized by regimen and across regimens in the following table.

**Drug-Related Medical Events Reported in ≥1% of Patients Who Were Treated With Cefpodoxime Proxetil Oral Suspension in Clinical Studies**

| Event | Cefpodoxime Proxetil Regimen | | | All Regimens N=2128 |
|---|---|---|---|---|
| | 10 mg/kg q 24 h x 10 d* N=454 | 5 mg/kg q 12 h x 10 d† N=817 | 5 mg/kg q 12 h x 5 d‡ N=857 | |
| Diarrhea | 28 (6.2) | 55 (6.7) | 44 (5.1) | 127 (6.0) |
| Vomiting | 17 (3.7) | 14 (1.7) | 19 (2.2) | 50 (2.3) |
| Rash | 8 (1.8) | 19 (2.3) | 12 (1.4) | 39 (1.8) |

* Includes data from Pharmacia & Upjohn protocols M/1140/0043, 0054, and 0059
† Includes data from Pharmacia & Upjohn protocols M/1140/0013, 0014, 0020, 0027, 0028, and 0060
‡ Includes data from Pharmacia & Upjohn protocols M/1140/0054, 0059, and 0098 and from Roussel protocol FF/89/807/37

*Reference: Appendix A, Table 9.1*

The overall frequency of diarrhea was 6.0% (127/2128) (Appendix A, Table 9.1); the frequency of diarrhea in infants and toddlers (ages 1 month to 2 years) was 12.8% (62/2128)

he frequency of drug-related diaper rash/fungal skin infection was determined by listing the rbatim events for patients for whom rash was reported and then counting the number of patients who had a verbatim term that was consistent with diaper rash or fungal skin infection. The frequency of diaper rash/fungal skin rash in all patients was 2.0% (43/2128) (Appendix A, Table 12); the frequency of diaper rash/fungal skin rash in infants and toddlers (ages 1 month to 2 years) was 8.5% (41/483) (Appendix A, Table 12). The frequency of other skin rashes was 1.8% (39/2128)

The drug-related events that were reported in fewer than 1% of patients are summarized in the table that follows.

**Drug-Related Medical Events Reported in <1 % of Patients Treated With Cefpodoxime Proxetil Oral Suspension in Clinical Studies**

| Body System/Event | Cefpodoxime Proxetil Regimen | | | All Regimens N=2128 |
|---|---|---|---|---|
| | 10 mg/kg q 24 h x 10 d* N=454 | 5 mg/kg q 12 h x 10 d† N=817 | 5 mg/kg q 12 h x 5 d‡ N=857 | |
| **Body** | | | | |
| Abdominal Pain Localized | 1 (0.2) | 2 (0.2) | 4 (0.5) | 7 (0.3) |
| Abdominal Cramp | 0 (0.0) | 2 (0.2) | 3 (0.4) | 5 (0.2) |
| Headache | 0 (0.0) | 4 (0.5) | 0 (0.0) | 4 (0.2) |
| Moniliasis | 1 (0.2) | 1 (0.1) | 2 (0.2) | 4 (0.2) |
| Abdominal Pain Generalized | 1 (0.2) | 1 (0.1) | 0 (0.0) | 2 (0.1) |
| Asthenia | 0 (0.0) | 0 (0.0) | 2 (0.2) | 2 (0.1) |
| Overdose | 0 (0.0) | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Fever | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (<0.1) |
| Infection Fungal NOS§ | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (<0.1) |
| Reaction Unevaluable | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (<0.1) |
| **Digestive** | | | | |
| Nausea | 4 (0.9) | 6 (0.7) | 2 (0.2) | 12 (0.6) |
| Monilia Oral | 2 (0.4) | 1 (0.1) | 0 (0.0) | 3 (0.1) |
| Anorexia | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (<0.1) |
| Dry Mouth | 1 (0.2) | 0 (0.0) | 0 (0.0) | 1 (<0.1) |
| Stomatitis | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (<0.1) |
| **Hemic and Lymphatic** | | | | |
| Thrombocythemia | 9 (2.0) | 9 (1.1) | 0 (0.0) | 18 (0.8) |
| Coomb's Test Direct Positive | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (<0.1) |
| Eosinophilia | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (<0.1) |
| Leukocytosis | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (<0.1) |
| Leukopenia | 1 (0.2) | 0 (0.0) | 0 (0.0) | 1 (<0.1) |
| Prolonged PTT | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (<0.1) |
| Purpura Thrombocytopenic | 0 (0.0) | 0 (0.0) | 1 (0.2) | 1 (<0.1) |
| **Metabolic and Nutritional** | | | | |
| SGPT Increased | 3 (0.7) | 0 (0.0) | 0 (0.0) | 3 (0.1) |
| **Musculo-Skeletal** | | | | |
| Myalgia | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (<0.1) |

continued

| | | | | |
|---|---|---|---|---|
| **Nervous** | | | | |
| Hallucination | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (<0.1) |
| Hyperkinesia | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (<0.1) |

**Drug-Related Medical Events Reported in <1% of Patients Treated With Cefpodoxime Proxetil Oral Suspension in Clinical Studies**

| Body System/Event | Cefpodoxime Proxetil Regimen | | | All Regimens N=2128 |
|---|---|---|---|---|
| | 10 mg/kg q 24 h x 10 d* N=454 | 5 mg/kg q 12 h x 10 d† N=817 | 5 mg/kg q 12 h x 5 d‡ N=857 | |
| Nervousness | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (<0.1) |
| Somnolence | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (<0.1) |
| Respiratory | | | | |
| Epistaxis | 0 (0.0) | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Skin | | | | |
| Moniliasis Skin | 6 (1.3) | 12 (1.5) | 0 (0.0) | 18 (0.8) |
| Uricaria | 9 (2.0) | 8 (1.0) | 1 (0.1) | 18 (0.8) |
| Dermatitis Fungal | 1 (0.2) | 1 (0.1) | 1 (0.1) | 3 (0.1) |
| Acne | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (<0.1) |
| Dermatitis Exfoliative | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (<0.1) |
| Rash Maculo-papular | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (<0.1) |
| Special Senses | | | | |
| Taste Perversion | 0 (0.0) | 2 (0.2) | 0 (0.0) | 2 (0.1) |

*Includes data from Pharmacia & Upjohn protocols M/1140/0043, 0054, and 0059
†Includes data from Pharmacia & Upjohn protocols M/1140/0013, 0014, 0020, 0027, 0028, and 0060
‡Includes data from Pharmacia & Upjohn protocols M/1140/0054, 0059, and 0098 and from Roussel protocol FF/89/807/37
§Not otherwise specified
*Reference: Appendix A, Table 9.1*

**Discontinuations Due to Medical Events**

A total of 31 (1.5%) of the 2128 patients dropped out of the studies due to medical events (Appendix A, Table 8.1), primarily vomiting (0.6%; 12/2128), rash (0.2%; 5/2128), and diarrhea (0.2%; 4/2128). Twenty (0.9%) of the 2128 patients who were reported to have dropped out of the studies due to medical events had drug-related events, primarily drug-related vomiting (0.4%; 8/2128), diarrhea (0.2%; 4/2128), or rash (0.2%; 4/2128).

Twenty-four (1.1%) of the 2128 patients discontinued medication due to medical events that were judged by the investigators to be possibly or probably related to treatment with cefpodoxime Primarily, these discontinuations were for gastrointestinal disturbances, usually diarrhea or vomiting, and for rash.

**d. Deaths**

There were no deaths among the 2128 patients who have been treated with cefpodoxime oral suspension in clinical studies.

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# VII. Overall Conclusions

## 1. Overall efficacy conclusions:

## TOC:

**Table E-18. Summary of "Test of Cure" Overall Clinical Evaluation* at 4-21 Days Posttherapy (Protocols 0098-A & 0098-B)**

| Evaluation | Results | Cefpodoxime N=254† | Cefixime N=258† |
|---|---|---|---|
| Success | Cured | 111 (44%) | 125 (48%) |
| | Improved | 60 (24%) | 40 (16%) |
| | Total Clinical Successes | 171 (67%) | 165 (64%) |
| Failure | Failure | 76 (30%) | 76 (29%) |
| | Side Effect Failure | 5 (2%) | 6 (2%) |
| | Antibiotic Noninvestigational Medication | 2 (1%) | 11 (4%) |
| | Total Clinical Failures | 83 (33%) | 93 (36%) |

**Table E-20. Summary of "Test of Cure" Eradication Rates (by Pathogen) at 4-21 Days Posttherapy (Protocols 0098-A & 0098-B)**

| Pathogen | Cefpodoxime | | Cefixime | |
|---|---|---|---|---|
| | n/N | % | n/N | % |
| Haemophilus influenzae | 1/1 | 100 | 6/9 | 67 |
| Haemophilus influenzae (β-lactamase negative) | 27/41 | 66 | 30/37 | 81 |
| Haemophilus influenzae (β-lactamase positive) | 22/34 | 65 | 25/35 | 71 |
| Moraxella catarrhalis | 2/4 | 50 | 4/7 | 57 |
| Moraxella catarrhalis (β-lactamase negative) | ¾ | 75 | 2/3 | 67 |
| Moraxella catarrhalis (β-lactamase positive) | 17/31 | 55 | 17/31 | 55 |
| Streptococcus pneumoniae | 88/122 | 72 | 72/124 | 58 |
| Streptococcus pyogenes | 20/25 | 80 | 13/23 | 57 |

* Because of rounding, percentages may not total 100

† N= 254 and 258 in the cefpodoxime and cefixime treatment groups, respectively, because 20 patients considered evaluable for efficacy (6 in the cefpodoxime group and 14 in the cefixime group) had no data available in the 4-21 day window.

*Reference: ISE Appendix Tables 4.7-4.8*

**Final Conclusions:**

- The data from two adequate and well-controlled studies in pediatric patients with acute suppurative otitis media showed that cefpodoxime proxetil oral suspension administered every 12 hours at a total daily dosage of 10 mg/kg for 5 days is as effective as cefixime, considered first-line therapy at the time the studies were initiated, administered every 24 hours at a dosage of 8 mg/kg for 10 days. The pathogens eradicated from the ears of infected children included *S pneumoniae, S pyogenes,* and beta-lactamase positive and negative strains of both *H influenzae* and *M catarrhalis.*

  - The low incidence of superinfections (1%-2%) was comparable in both treatment groups, as was the incidence of side effect failures (2%-3%).
  - A lower percentage of patients in the cefpodoxime group (~1%) than in the cefixime group (4%-5%) was treated with antibiotics other than the assigned study medication.
  - The efficacy demonstrated by cefpodoxime (5 mg/kg administered every 12 hours for 5 days) in the pivotal studies is comparable to that of cefpodoxime administered every 12 hours at a total dosage of 10 mg/kg for 10 days and to that of amoxicillin/ clavulanate administered every 8 hours at a total dosage of 40 mg/kg for 10 days, as shown in the data from three historical studies comparing the latter three regimens.
  - The difference between the pivotal studies and the historical studies is that a sufficient number of patients with otitis media due to *S pyogenes* were enrolled that eradication of this pathogen could be demonstrated with the 5-day cefpodoxime regimen.

- This shorter duration of treatment with cefpodoxime offers the potential advantage of better compliance with the dosage schedule.

- A problem in the evaluating the bacteriologic outcome in this study is the fact that the control drug, Suprax® does not have approval for *S. pneumoniae* in the indication of otitis media. As noted in the clinical studies section of the Suprax® label, Suprax had a cure rate for *S. pneumoniae* which was 10% lower than for the drugs it was tested against during its approval process. This Medical Officer also reviewed the original MOR (Dr. Renata Albrecht) of the approval for Suprax® in the indication of AOM.

⇒ The potential problem with using Suprax® as a control for this current study is that even if Vantin ® shows an equivalence to Suprax ®, this equivalence will not be sufficient to establish the appropriate level of efficacy against *S. pneumoniae* for Vantin ®.

⇒ In order to assess the bacteriological outcome against the pathogen *S. pneumoniae,* we must take into consideration that Vantin currently has approval in the indication of AOM at a dose of 5 mg/kg/dose bid for 10 days. After review of the original MOR (Dr. Susan Alpert). The clinical cure rates of protocol 13 were roughly comparable: 65% for protocol 13(LTFU) and 60% &70% respectively in studies A &B. In addition, the bacteriological eradication rate for *S. pneumoniae* was 58% in protocol 13 and was 65% and 76% respectively in studies A &B of 5 mg/kg/dose bidx5days. Thus despite the fact that the current studies used a control drug which does not currently have approval for *S. pneumoniae,* we can consider approval of *S. pneumoniae* based on a comparison with the historical Vantin study and the overall result of the current studies.

- When comparing the clinical and microbiologic outcome to the only approved oral short course agent Azithromycin the following is noted:

⇒ TOC was noted at day thirty because of the long half-life of this agent

⇒ The overall efficacy for Azithromycin was 68% at this clinical time point day 30.

⇒ The clinical cure rates at "TOC" of 60% &70% respectively in studies A &B for Vantin®.

**Final Conclusion pK**

- Cefpodoxime reaches clinically relevant levels in MEE following dosing with either 5 or 10 mg/kg in pediatric

patients with acute otitis media

## Final Conclusions Safety

Table G.S. Medical Event (ME) Summary
Protocols 0098-A and 0098-B

| | Cefpodoxime N=481 | Cefixime N=488 |
|---|---|---|
| No. (%) of Patients With No Mes | 304 (63%) | 303 (62%) |
| No. (%) of Patients With at Least One ME | 177 (37%) | 185 (38%) |
| No. (%) of Patients With at Least One Drug-related ME | 58 (12%) | 59 (12%) |
| No. (%) of Patients With Serious MEs* | 0 | 3 (<1%) |
| No. (%) of Patients Who Discontinued Because of MEs | 12 (2%) | 14 (3%) |
| No. (%) of Deaths | 0 | 0 |

- The medical-event profile of cefpodoxime when administered at a dose of 5 mg/kg every 12 hours for 5 days, as determined from integrated data from 481 patients who received the drug according to this regimen in two phase III studies (protocols 0098-A ad 0098-B), was consistent with the known medical-event profile for cefpodoxime.
- Gastrointestinal events, primarily diarrhea and vomiting, and rash were the most frequently reported medical events and were the primary events that led to discontinuation of cefpodoxime therapy.
- No clinically relevant differences in medical-event profiles, discontinuations due to medical events, or serious medical events were noted between this cefpodoxime regimen and the 10-day cefixime regimen with which it was compared in these studies.

**Concur:**

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End of Therapy

*Medical Officer's Note:: The overall bacteriologic responses at End of Therapy are shown for the intent-to-treat, the evaluable, and the Medical Officer sub-population in Tables 2.16, 2.17, and 2.18, respectively. All comparisons (95% confidence intervals) of the difference between the two treatment groups illustrate the superiority of cefpodoxime to cefixime at this time point in Study A.*

| TABLE 2.16: STUDY 0098A: OVERALL BACTERIOLOGIC RESPONSE OF THE ITT SUBJECTS AT END OF THERAPY | | |
|---|---|---|
| Bacteriological Response | Cefpodoxime (N=225) | Cefixime (N=230) |
| Cure | 127 (56.4%) | 101 (43.9%) |
| Failure | 98 (43.6%) | 129 (56.1%) |
| Cefpodoxime vs Cefiximef by Cure | 12.5%, 95% C.I.: 3.0%, 22.1% | |

| TABLE 2.17: STUDY 0098A: OVERALL BACTERIOLOGIC RESPONSE OF THE EVALUABLE SUBJECTS AT END OF THERAPY | | |
|---|---|---|
| Bacteriological Response | Cefpodoxime (N=124) | Cefixime (N=132) |
| Cure | 108 (87.1%) | 95 (72.0%) |
| Failure | 16 (12.9%) | 37 (28.0%) |
| Cefpodoxime vs Cefixime by Cure | 15.1%, 95% C.I.: 4.7%, 25.6% | |

| TABLE 2.18: STUDY 0098A: OVERALL BACTERIOLOGIC RESPONSE OF THE MO SUB-POPULATION AT END OF THERAPY | | |
|---|---|---|
| Bacteriological Response | Cefpodoxime (N=125) | Cefixime (N=128) |
| Cure | 107 (85.6%) | 90 (70.3%) |
| Failure | 18 (14.4%) | 38 (29.7%) |
| Cefpodoxime vs Cefixime by Cure | 15.3%, 95% C.I.: 4.5%, 26.1% | |

*Medical Officer's Note: The overall bacteriologic responses at End of Therapy are shown for the intent-to-treat, the evaluable, and the Medical Officer sub-population in Tables 3.15, 3.16, and 3.17, respectively. All comparisons (95% confidence intervals) of the difference between the two treatment groups illustrate the equivalence between cefpodoxime and cefixime in Study B.*

| TABLE 3.15: STUDY 0098B: OVERALL BACTERIOLOGIC RESPONSE OF THE ITT SUBJECTS AT END OF THERAPY | | |
|---|---|---|
| Bacteriological Response | Cefpodoxime (N=256) | Cefixime (N=258) |
| Cure<br>Failure | 136 (53.1%)<br>120 (46.9%) | 134 (51.9%)<br>124 (48.1%) |
| Cefpodoxime vs Cefixime by Cure | 1.2%, 95% C.I.: -7.8%, 10.2% | |

| TABLE 3.16: STUDY 0098B: OVERALL BACTERIOLOGIC RESPONSE OF THE EVALUABLE SUBJECTS AT END OF THERAPY | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=136) | Cefiximef (N=140) |
| Cure<br>Failure | 118 (86.8%)<br>18 (13.2%) | 120 (85.7%)<br>20 (14.3%) |
| Cefpodoxime vs Cefixime by Cure | 1.1%, 95% C.I.: -7.8%, 9.9% | |

| TABLE 3.17: STUDY 0098B: OVERALL BACTERIOLOGIC RESPONSE OF THE MO SUB-POPULATION AT END OF THERAPY | | |
|---|---|---|
| Bacteriological Response | Cefpodoxime (N=126) | Cefixime (N=130) |
| Cure<br>Failure | 89 (70.6%)<br>37 (29.4%) | 85 (65.4%)<br>45 (34.6%) |
| Cefpodoxime vs Cefixime by Cure | 5.3%, 95% C.I.: -6.9%, 17.4% | |

End of Therapy By Pathogen Bacteriologic Evaluation

ISE Appendix Table 4.5 lists the End of Therapy by-pathogen eradication rates of all the pathogens isolated at Pretreatment. Table E-31 summarizes the eradication rates for *H influenzae, M catarrhalis, S pneumoniae,* and *S pyogenes* isolates. Cefpodoxime and cefixime had comparable eradication rates for *H influenzae* (91% and 85%, respectively) and *M catarrhalis* (70% and 75%, respectively), while cefpodoxime had higher eradication rates than did cefixime for *S pneumoniae* (94% versus 77%) and *S pyogenes* (88% versus 71%).

***Medical Officer's Note:*** *The pathogen eradication rates for the most common isolated baseline pathogens at End of Therapy are summarized for the intent-to-treat, the evaluable, and the Medical Officer sub-population in Table 2.19, 2.20, and 2.21, respectively for Study A.*

| TABLE 2.19: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE ITT SUBJECTS AT END OF THERAPY (FOR MOST COMMON ISOLATED BASELINE PATHOGENS) | | | |
|---|---|---|---|
| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
| *H. influenzae* | 46/53 (86.8%) | 38/48 (79.2%) | 7.6%, 95% C.I.: -9.0%, 24.3% |

| | | | |
|---|---|---|---|
| *M. catarrhalis* | 15/21 (71.4%) | 19/29 (65.5%) | 5.9%, 95% C.I.: -24.1%, 36.0% |
| *S. pneumoniae* | 64/69 (92.8%) | 44/66 (66.7%) | 26.1%, 95% C.I.: 11.7%, 40.5% |
| *S. pyogenes* | 11/12 (91.7%) | 9/13 (69.2%) | 22.4%, 95% C.I.: -15.1%, 60.0% |

**TABLE 2.20**: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE EVALUABLE SUBJECTS AT END OF THERAPY (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)

| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
|---|---|---|---|
| *H. influenzae* | 40/44 (90.9%) | 37/47 (78.7%) | 12.2%, 95% C.I.: -4.5%, 28.8% |
| *M. catarrhalis* | 13/19 (68.4%) | 18/27 (66.7%) | 1.8%, 95% C.I.: -30.2%, 33.7% |
| *S. pneumoniae* | 54/57 (94.7%) | 40/61 (65.6%) | 29.2%, 95% C.I.: 14.2%, 44.1% |
| *S. pyogenes* | 10/11 (90.9%) | 8/12 (66.7%) | 24.2%, 95% C.I.: -16.1%, 64.6% |

**TABLE 2.21**: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE MO SUB-POPULATION AT END OF THERAPY (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)

| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
|---|---|---|---|
| *H. influenzae* | 39/43 (90.7%) | 35/45 (77.8%) | 12.9%, 95% C.I.: -4.3%, 30.1% |
| *M. catarrhalis* | 12/18 (66.7%) | 16/25 (64.0%) | 2.7%, 95% C.I.: -30.9%, 36.2% |
| *S. pneumoniae* | 55/58 (94.8%) | 40/59 (67.8%) | 27.0%, 95% C.I.: 12.1%, 42.0% |
| *S. pyogenes* | 11/12 (91.7%) | 7/11 (63.6%) | 28.0%, 95% C.I.: -13.1%, 69.2% |

*Medical Officer's Note:The pathogen eradication rates for the most common isolated baseline pathogens at End of Therapy are summarized for the intent-to-treat, the evaluable, and the Medical Officer sub-population in Tables 3.18, 3.19, and 3.20, respectively for Study B.*

| TABLE 3.18: STUDY 0098B: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE ITT SUBJECTS AT END OF THERAPY (FOR MOST COMMON ISOLATED BASELINE PATHOGENS) | | | |
|---|---|---|---|
| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
| *H. influenzae* | 37/41 (90.2%) | 43/51 (84.3%) | 5.9%, 95% C.I.: -9.8%, 21.6% |
| *M. catarrhalis* | 18/25 (72.0%) | 16/18 (88.9%) | -16.9%, 95% C.I.: -44.5%, 10.7% |
| *S. pneumoniae* | 72/79 (91.1%) | 64/77 (83.1%) | 8.0%, 95% C.I.: -3.7%, 19.8% |
| *S. pyogenes* | 14/16 (87.5%) | 12/16 (75.0%) | 12.5%, 95% C.I.: -20.4%, 45.4% |

| TABLE 3.19: STUDY 0098B: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE EVALUABLE SUBJECTS AT END OF THERAPY (FOR MOST COMMON ISOLATED BASELINE PATHOGENS) | | | |
|---|---|---|---|
| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
| *H. influenzae* | 34/38 (89.5%) | 36/42 (85.7%) | 3.8%, 95% C.I.: -13.1%, 20.7% |
| *M. catarrhalis* | 16/23 (69.6%) | 15/17 (88.2%) | -18.7%, 95% C.I.: -48.0%, 10.7% |
| *S. pneumoniae* | 66/72 (91.7%) | 61/74 (82.4%) | 9.2%, 95% C.I.: -2.9%, 21.4% |
| *S. pyogenes* | 12/14 (85.7%) | 12/16 (75.0%) | 10.7%, 95% C.I.: -24.0%, 45.4% |

| TABLE 3.20: STUDY 0098B: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE MO SUB-POPULATION AT END OF THERAPY (FOR MOST COMMON ISOLATED BASELINE PATHOGENS) | | | |
|---|---|---|---|
| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
| *H. influenzae* | 30/34 (88.2%) | 34/39 (87.2%) | 1.1%, 95% C.I.: -16.8%, 18.9% |
| *M. catarrhalis* | 15/21 (71.4%) | 15/16 (93.8%) | -22.3%, 95% C.I.: -50.5%, 5.9% |
| *S. pneumoniae* | 58/64 (90.6%) | 53/65 (81.5%) | 9.1%, 95% C.I.: -4.3%, 22.5% |
| *S. pyogenes* | 13/15 (86.7%) | 12/16 (75.0%) | 11.7%, 95% C.I.: -22.1%, 45.4% |

End of Therapy Overall Clinical Evaluation

Table E-30 summarizes the results of the overall clinical evaluation. The overall clinical success rate (cured plus improved) was significantly higher in the cefpodoxime group than in the cefixime group (87% versus 79%). The 95% confidence interval (CI) was 1.51% to 14.99% for difference in success rates (ISE Appendix Table 4.2). The lower percentage of cures in the cefpodoxime group (32%: 83/260) compared to that in the cefixime group (53%: 145/272) is probably due to the fact that only 7-10 days had elapsed since cefpodoxime therapy was initiated compared to 12-15 days for cefixime; thus, the patients in the cefpodoxime group had had a shorter interval for the natural course of healing that begins following eradication of otitis media pathogens.

*edical Officer's Note: Tables 2.22, 2.23, and 2.24 show clinical responses of the intent-to-treat, the evaluable, and the Medical Officer evaluable subjects at End of Therapy, respectively. Confidence interval results from these populations show that the two treatment groups were therapeutically equivalent with respect to the success rates at this time point for Study A.*

| TABLE 2.22: STUDY 0098A: OVERALL CLINICAL RESPONSE OF THE ITT SUBJECTS AT END OF THERAPY | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=225) | Cefiximef (N=230) |
| Success<br>Failure | 129 (57.3%)<br>96 (42.7%) | 101 (43.9%)<br>129 (56.1%) |
| Cefpodoxime vs Cefiximef by Success | 13.4%, 95% C.I.: 3.9%, 23.0% | |

| TABLE 2.23: STUDY 0098A: OVERALL CLINICAL RESPONSE OF THE EVALUABLE SUBJECTS AT END OF THERAPY | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=124) | Cefiximef (N=132) |
| Success<br>Failure | 108 (87.1%)<br>16 (12.9%) | 94 (71.2%)<br>38 (28.8%) |
| Cefpodoxime vs Cefiximef by Success | 15.9%, 95% C.I.: 5.4%, 26.4% | |

| TABLE 2.24: STUDY 0098A: OVERALL CLINICAL RESPONSE OF THE MO SUB-POPULATION AT END OF THERAPY | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=125) | Cefiximef (N=128) |
| Success<br>Failure | 107 (85.6%)<br>18 (14.4%) | 90 (70.3%)<br>38 (29.7%) |
| Cefpodoxime vs Cefiximef by Success | 15.3%, 95% C.I.: 4.5%, 26.1% | |

*Medical Officer's Note: Tables 3.21, 3.22, and 3.23 show clinical responses of the intent-to-treat, the evaluable, and the Medical Officer Sub-Population at End of Therapy, respectively. Confidence interval results from these populations show that the two treatment groups were therapeutically equivalent with respect to the success rates at this time point for Study B.*

| TABLE 3.21: STUDY 0098B: OVERALL CLINICAL RESPONSE OF THE ITT SUBJECTS AT END OF THERAPY | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=256) | Cefiximef (N=258) |
| Success<br>Failure | 139 (54.3%)<br>117 (45.7%) | 136 (52.7%)<br>122 (47.3%) |
| Cefpodoxime vs Cefiximef by Success | 1.6%, 95% C.I.: -7.4%, 10.6% | |

| TABLE 3.22: STUDY 0098B: OVERALL CLINICAL RESPONSE OF THE EVALUABLE SUBJECTS AT END OF THERAPY | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=136) | Cefiximef (N=140) |
| Success | 118 (86.8%) | 120 (85.7%) |

| | | |
|---|---|---|
| Failure | 18 (13.2%) | 20 (14.3%) |
| Cefpodoxime vs Cefixime by Success | 1.1%, 95% C.I.: -7.8%, 9.9% | |

| TABLE 3.23: STUDY 0098B: OVERALL CLINICAL RESPONSE OF THE MO SUB-POPULATION AT END OF THERAPY | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=126) | Cefiximef (N=130) |
| Success | 109 (86.5%) | 110 (84.6%) |
| Failure | 17 (13.5%) | 20 (15.4%) |
| Cefpodoxime vs Cefixime by Success | 1.9%, 95% C.I.: -7.5%, 11.3% | |

*The following nine tables (Tables 2.25 to Table 2.33) present other ancillary efficacy data of the Medical Officer sub-population including bacteriologic and clinical responses at Visit 2, Visit 3, and Final Visit. Confidence interval results show that the two treatment groups were therapeutically equivalent with respect to the overall bacteriological responses and the overall clinical responses at these time points.*

Visit 2 Overall Bacteriologic Evaluation

Table E-30 summarizes the results of the overall bacteriologic response at Visit 2. The overall bacteriologic cure rates (87%) for the cefpodoxime group (226/260) and the cefixime group (236/271) were not significantly different (95% CI: -6.26% to 5.94%).

| TABLE 2.25: STUDY 0098A: OVERALL BACTERIOLOGIC RESPONSE OF THE MO SUB-POPULATION AT VISIT 2 | | |
|---|---|---|
| Bacteriological Response | Cefpodoxime (N=125) | Cefixime (N=128) |
| Cure<br>Failure | 107 (85.6%)<br>18 (14.4%) | 102 (79.7%)<br>26 (20.3%) |
| Cefpodoxime vs Cefixime by Cure | 5.9%, 95% C.I.: -4.2%, 16.0% | |

| TABLE 3.24: STUDY 0098B: OVERALL BACTERIOLOGIC RESPONSE OF THE MO SUB-POPULATION AT VISIT 2 | | |
|---|---|---|
| Bacteriological Response | Cefpodoxime (N=126) | Cefixime (N=130) |
| Cure<br>Failure | 109 (86.5%)<br>17 (13.5%) | 119 (91.5%)<br>11 (8.5%) |
| Cefpodoxime vs Cefixime by Cure | -5.0%, 95% C.I.: -13.5%, 3.4% | |

Visit 3 Overall Bacteriologic Evaluation

Table E-30 summarizes the results of the overall bacteriologic response at Visit 3 (Days 12-15). The overall bacteriologic cure rates for the cefpodoxime group (74%: 191/257) and the cefixime group (79%: 215/272) were not significantly different (95% CI: -12.31% to 2.86%).

| TABLE 2.26: STUDY 0098A: OVERALL BACTERIOLOGIC RESPONSE OF THE MO SUB-POPULATION AT VISIT 3 | | |
|---|---|---|
| Bacteriological Response | Cefpodoxime (N=125) | Cefixime (N=128) |
| Cure<br>Failure | 86 (68.8%)<br>39 (31.2%) | 90 (70.3%)<br>38 (29.7%) |
| Cefpodoxime vs Cefixime by Cure | -1.5%, 95% C.I.: -13.6%, 10.6% | |

| TABLE 3.25: STUDY 0098B: OVERALL BACTERIOLOGIC RESPONSE OF THE MO SUB-POPULATION AT VISIT 3 | | |
|---|---|---|
| Bacteriological Response | Cefpodoxime (N=126) | Cefixime (N=130) |
| Cure<br>Failure | 97 (77.0%)<br>29 (23.0%) | 110 (84.6%)<br>20 (15.4%) |
| Cefpodoxime vs Cefixime by Cure | -7.6%, 95% C.I.: -18.0%, 2.8% | |

Final Visit Overall Bacteriologic Evaluation

Table E-30 summarizes the results of the overall bacteriologic response at Final Visit (Days 25-38). The overall bacteriologic cure rates for the cefpodoxime group (65%: 161/249) and the cefixime group (65%: 170/262) were not significantly different (95% CI: -8.9% to 8.45%).

TABLE 15: STUDY 0098A: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF THE OVERALL BACTERIOLOGICAL CURE RATES OF THE EVALUABLE SUBJECTS AT FINAL

| VISIT | | | | |
|---|---|---|---|---|
| Subset | Cefpodoxime (N=124) | Cefixime (N=132) | 95% C.I. | P-value Breslow-Day's |
| Male | 37/64 (57.8%) | 47/72 (65.3%) | (-25.3%, 10.4%) | 0.309 |
| Female | 35/60 (58.3%) | 32/60 (53.3%) | (-14.4%, 24.4%) | |
| < 2 yrs. | 23/52 (44.2%) | 37/66 (56.1%) | (-31.6%, 7.9%) | 0.194 |
| ≥ 2 yrs. | 49/72 (68.1%) | 42/66 (63.6%) | (-12.9%, 21.7%) | |
| White | 39/66 (59.1%) | 43/72 (59.7%) | (-18.5%, 17.2%) | 0.748 |
| Black | 6/10 (60.0%) | 5/9 (55.6%) | NA | |
| Hispanic | 25/43 (58.1%) | 30/50 (60.0%) | (-24.1%, 20.3%) | |
| Other | 2/5 (40.0%) | 1/1 (100%) | NA | |

**TABLE 16**: STUDY 0098A: OVERALL BACTERIOLOGIC RESPONSE OF THE ITT SUBJECTS AT FINAL VISIT

| Bacteriological Response | Cefpodoxime (N=225) | Cefixime (N=230) |
|---|---|---|
| Cure | 82 (36.4%) | 84 (36.5%) |
| Failure | 143 (63.6%) | 146 (63.5%) |
| Cefpodoxime vs Cefixime by Cure | -0.1%, 95% C.I.: -9.4%, 9.2% | |

**TABLE 17**: STUDY 0098A: OVERALL BACTERIOLOGIC RESPONSE OF THE EVALUABLE SUBJECTS AT FINAL VISIT

| Bacteriological Response | Cefpodoxime (N=124) | Cefixime (N=132) |
|---|---|---|
| Cure | 72 (58.1%) | 79 (59.9%) |
| Failure | 52 (41.9%) | 53 (40.1%) |
| Cefpodoxime vs Cefixime by Cure | -1.8%, 95% C.I.: -14.6%, 11.1% | |

**TABLE 3.26**: STUDY 0098A: OVERALL BACTERIOLOGIC RESPONSE OF THE MO SUB-POPULATION AT FINAL VISIT

| Bacteriological Response | Cefpodoxime (N=126) | Cefixime (N=130) |
|---|---|---|
| Cure | 84 (66.7%) | 85 (65.4%) |
| Failure | 42 (33.3%) | 45 (34.6%) |
| Cefpodoxime vs Cefixime by Cure | 1.3%, 95% C.I.: -11.1%, 13.7% | |

**TABLE 18**: STUDY 0098B: OVERALL BACTERIOLOGIC RESPONSE OF THE ITT SUBJECTS AT FINAL VISIT

| Bacteriological Response | Cefpodoxime (N=256) | Cefixime (N=258) |
|---|---|---|
| Cure | 103 (40.2%) | 108 (41.9%) |
| Failure | 153 (59.8%) | 150 (58.1%) |
| Cefpodoxime vs Cefixime by Cure | -1.6%, 95% C.I.: -10.5%, 7.3% | |

| TABLE 19: STUDY 0098B: OVERALL BACTERIOLOGIC RESPONSE OF THE EVALUABLE SUBJECTS AT FINAL VISIT | | |
|---|---|---|
| Bacteriological Response | Cefpodoxime (N=136) | Cefixime (N=140) |
| Cure | 89 (65.4%) | 91 (65.0%) |
| Failure | 47 (34.6%) | 49 (35.0%) |
| Cefpodoxime vs Cefiximef by Cure | 0.4%, 95% C.I.: -11.5%, 12.4% | |

| TABLE 20: STUDY 0098B: SUBSET ANALYSES BY DEMOGRAPHIC ASPECTS OF THE OVERALL BACTERIOLOGICAL CURE RATES OF THE EVALUABLE SUBJECTS AT FINAL VISIT | | | | |
|---|---|---|---|---|
| Subset | Cefpodoxime (N=136) | Cefiximef (N=140) | 95% C.I. | P-value Breslow-Day's |
| Male | 56/80 (70.0%) | 56/84 (66.7%) | (-12.1%, 18.8%) | 0.580 |
| Female | 33/56 (58.9%) | 35/56 (62.5%) | (-23.4%, 16.3%) | |
| < 2 yrs. | 30/57 (52.6%) | 33/58 (56.9%) | (-24.2%, 15.7%) | 0.782 |
| ≥ 2 yrs. | 59/79 (74.7%) | 58/82 (70.7%) | (-11.0%, 18.9%) | |
| White | 72/110 (65.5%) | 78/114 (68.4%) | (-16.2%, 10.2%) | 0.088 |
| Black | 10/16 (62.5%) | 8/14 (57.1%) | (-36.5%, 47.2%) | |
| Hispanic | 7/10 (70.0%) | 3/8 (37.5%) | NA | |
| Other | 0/0 (NA) | 2/4 (50.0%) | NA | |

| TABLE 2.27: STUDY 0098B: OVERALL BACTERIOLOGIC RESPONSE OF THE MO SUB-POPULATION AT FINAL VISIT | | |
|---|---|---|
| Bacteriological Response | Cefpodoxime (N=125) | Cefixime (N=128) |
| Cure | 70 (56.0%) | 72 (56.3%) |
| Failure | 55 (44.0%) | 56 (43.8%) |
| Cefpodoxime vs Cefixime by Cure | -0.2%, 95% C.I.: -13.3%, 12.8% | |

Visit 2 By-Pathogen Bacteriologic Evaluation

ISE Appendix Table 5.5 lists the Visit 2 by-pathogen eradication rates of all the pathogens isolated at Pretreatment. Table E-31 summarizes the eradication rates for *H influenzae, M catarrhalis, S pneumoniae,* and *S pyogenes* isolates. Cefpodoxime and cefixime had comparable eradication rates for all four organisms at the Visit 2 analysis: *H influenzae* (91% and 92%, respectively) and *M catarrhalis* (70% and 75%, respectively), *S pneumoniae* (94% and 89%, respectively), and *S pyogenes* (88% and 83%, respectively).

| TABLE 2.28: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE MO SUB-POPULATION AT VISIT 2 (FOR MOST COMMON ISOLATED BASELINE PATHOGENS) | | | |
|---|---|---|---|
| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
| *H. influenzae* | 39/43 (90.7%) | 40/45 (88.9%) | 1.8%, 95% C.I.: -13.1%, 16.7% |
| *M. catarrhalis* | 12/18 (66.7%) | 18/25 (72.0%) | -5.3%, 95% C.I.: -38.1%, 27.4% |
| *S. pneumoniae* | 55/58 (94.8%) | 48/59 (81.4%) | 13.5%, 95% C.I.: 0.3%, 26.6% |

| | | | |
|---|---|---|---|
| *S. pyogenes* | 11/12 (91.7%) | 9/11 (81.8%) | 9.8%, 95% C.I.: -26.5%, 46.2% |

**TABLE 3.27: STUDY 0098B: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE MO SUB-POPULATION AT VISIT 2 (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)**

| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
|---|---|---|---|
| *H. influenzae* | 30/34 (88.2%) | 38/39 (97.4%) | -9.2%, 95% C.I.: -23.9%, 5.5% |
| *M. catarrhalis* | 15/21 (71.4%) | 13/16 (81.3%) | -9.8%, 95% C.I.: -42.5%, 22.9% |
| *S. pneumoniae* | 58/64 (90.6%) | 60/65 (92.3%) | -1.7%, 95% C.I.: -12.9%, 9.5% |
| *S. pyogenes* | 13/15 (86.7%) | 14/16 (87.5%) | -0.8%, .95% C.I.: -30.9%, 29.3% |

Visit 3 By-Pathogen Bacteriologic Evaluation

ISE Appendix Table 5.11 lists the Visit 3 by-pathogen eradication rates of all the pathogens isolated at Pretreatment. Table E-31 summarizes the eradication rates for *H influenzae, M catarrhalis, S pneumoniae,* and *S pyogenes* isolates. Cefpodoxime had eradication rates higher than those of cefixime for *S pyogenes* (84% versus 71%), comparable to those of cefixime for *S pneumoniae* (79% versus 77%), and lower than those of cefixime for *H influenzae* (72% versus 85%) and *M catarrhalis* (59% versus 75%).

| TABLE 2.29: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE MO SUB-POPULATION AT VISIT 3 (FOR MOST COMMON ISOLATED BASELINE PATHOGENS) | | | |
|---|---|---|---|
| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
| *H. influenzae* | 39/43 (90.7%) | 40/45 (88.9%) | 1.8%, 95% C.I.: -13.1%, 16.7% |
| *M. catarrhalis* | 12/18 (66.7%) | 18/25 (72.0%) | -5.3%, 95% C.I.: -38.1%, 27.4% |
| *S. pneumoniae* | 55/58 (94.8%) | 40/59 (67.8%) | 27.0%, 95% C.I.: 12.1%, 42.0% |
| *S. pyogenes* | 11/12 (91.7%) | 9/11 (81.8%) | 9.8%, 95% C.I.: -26.5%, 46.2% |

| TABLE 3.28: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE MO SUB-POPULATION AT VISIT 3 (FOR MOST COMMON ISOLATED BASELINE PATHOGENS) | | | |
|---|---|---|---|
| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
| *H. influenzae* | 25/34 (73.5%) | 34/39 (87.2%) | -13.7%, 95% C.I.: -34.6%, 7.3% |
| *M. catarrhalis* | 11/20 (55.0%) | 15/16 (93.8%) | -38.8%, 95% C.I.: -69.2%, -8.3% |
| *S. pneumoniae* | 53/64 (82.8%) | 53/65 (81.5%) | 1.3%, 95% C.I.: -13.5%, 16.0% |
| *S. pyogenes* | 12/14 (85.7%) | 12/16 (75.0%) | 10.7%, 95% C.I.: -24.0%, 45.4% |

Final Visit By-Pathogen Bacteriologic Evaluation

NE Appendix Table 5.11 lists the Final Visit by-pathogen eradication rates of all the pathogens isolated at Pretreatment. Table E-31 summarizes the eradication rates for *H influenzae, M catarrhalis, S pneumoniae,* and *S pyogenes* isolates. Cefpodoxime had eradication rates higher than those of cefixime for *S pneumoniae* (69% versus 58%) and *S pyogenes* (70% versus 61%), comparable to those of cefixime for *M catarrhalis* (68% versus 63%) and lower than those of cefixime for *H influenzae* (57% versus 74%).

| TABLE 21: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE ITT SUBJECTS AT FINAL VISIT (FOR MOST COMMON ISOLATED BASELINE PATHOGENS) | | | |
|---|---|---|---|
| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
| *H. influenzae* | 0/0 (NA) | 2/3 (66.7%) | NA |
| *H. influenzae (ß-l. -)* | 18/25 (72.0%) | 17/23 (73.9%) | -1.9%, 95% C.I.: -31.2%, 27.4% |
| *H. influenzae (ß-l. +)* | 13/19 (68.4%) | 13/19 (68.4%) | 0%, 95% C.I.: -34.8%, 34.8% |
| *M. catarrhalis* | 0/1 (0%) | 4/6 (66.7%) | NA |
| *M. catarrhalis (ß-l. -)* | 2/4 (50.0%) | 3/3 (100%) | NA |
| *M. catarrhalis (ß-l. +)* | 9/13 (69.2%) | 11/18 (61.1%) | 8.1%, 95% C.I.: -32.2%, 48.5% |
| *S. pneumoniae* | 41/63 (65.1%) | 33/63 (52.4%) | 12.7%, 95% C.I.: -5.9%, 31.3% |
| *S. pyogenes* | 7/10 (70.0%) | 6/12 (50.0%) | 20.0%, 95% C.I.: -29.3%, 69.3% |

| TABLE 22: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE EVALUABLE SUBJECTS AT FINAL VISIT (FOR MOST COMMON ISOLATED BASELINE PATHOGENS) | | | |
|---|---|---|---|
| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
| *H. influenzae* | 0/0 (NA) | 2/3 (66.7%) | NA |
| *H. influenzae (ß-l. -)* | 16/23 (69.6%) | 16/22 (72.7%) | -3.2%, 95% C.I.: -34.1%, 27.7% |
| *H. influenzae (ß-l. +)* | 13/19 (68.4%) | 13/19 (68.4%) | 0%, 95% C.I.: -34.8%, 34.8% |

| | | | |
|---|---|---|---|
| *M. catarrhalis* | 0/1 (0%) | 4/6 (66.7%) | NA |
| *M. catarrhalis (ß-l. -)* | 2/3 (66.7%) | 3/3 (100%) | NA |
| *M. catarrhalis (ß-l. +)* | 9/13 (69.2%) | 11/18 (61.1%) | 8.1%, 95% C.I.: -32.2%, 48.5% |
| *S. pneumoniae* | 35/56 (62.5%) | 31/60 (51.7%) | 10.8%, 95% C.I.: -8.8%, 30.5% |
| *S. pyogenes* | 6/9 (66.7%) | 5/11 (45.5%) | 21.2%, 95% C.I.: -31.5%, 73.9% |

**TABLE 2.30**: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE MO SUB-POPULATION AT FINAL VISIT (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)

| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
|---|---|---|---|
| *H. influenzae* | 30/42 (71.4%) | 35/45 (77.8%) | -6.3%, 95% C.I.: -26.9%, 14.2% |
| *M. catarrhalis* | 10/17 (58.8%) | 16/25 (64.0%) | -5.2%, 95% C.I.: -40.1%, 29.8% |
| *S. pneumoniae* | 44/56 (78.6%) | 40/59 (67.8%) | 10.8%, 95% C.I.: -7.0%, 28.6% |
| *S. pyogenes* | 10/12 (83.3%) | 7/11 (63.6%) | 19.7%, 95% C.I.: -24.4%, 63.8% |

**TABLE 23**: STUDY 0098A: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE SUBJECTS OF THE MO SUB-POPULATION AT FINAL VISIT (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)

| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
|---|---|---|---|
| *H. influenzae* | 0/0 (NA) | 2/3 (66.7%) | NA |
| *H. influenzae (ß-l. -)* | 16/23 (69.6%) | 15/21 (71.4%) | -1.9%, 95% C.I.: -33.4%, 29.7% |
| *H. influenzae (ß-l. +)* | 11/17 (64.7%) | 11/17 (64.7%) | 0%, 95% C.I.: -38.0%, 38.0% |
| *M. catarrhalis* | 0/1 (0%) | 3/5 (60.0%) | NA |
| *M. catarrhalis (ß-l. -)* | 1/2 (50.0%) | 3/3 (100%) | NA |
| *M. catarrhalis (ß-l. +)* | 8/12 (66.7%) | 10/17 (58.8%) | 7.8%, 95% C.I.: -34.7%, 50.4% |
| *S. pneumoniae* | 36/57 (63.2%) | 29/57 (50.9%) | 12.3%, 95% C.I.: -7.5%, 32.1% |
| *S. pyogenes* | 7/10 (70.0%) | 4/10 (40.0%) | 30.0%, 95% C.I.: -21.6%, 81.6% |

**TABLE 24**: STUDY 0098B: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE ITT SUBJECTS AT FINAL VISIT (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)

| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
|---|---|---|---|
| *H. influenzae* | 2/2 (100%) | 5/7 (71.4%) | NA |
| *H. influenzae (β-l. -)* | 8/16 (50.0%) | 12/16 (75.0%) | -25.0%, 95% C.I.: -63.7%, 13.7% |
| *H. influenzae (β-l. +)* | 8/21 (38.1%) | 18/24 (75.0%) | -36.9%, 95% C.I.: -68.4%, -5.4% |
| *M. catarrhalis* | 2/4 (50.0%) | 1/2 (50.0%) | NA |
| *M. catarrhalis (β-l. -)* | 1/1 (100%) | 0/0 (NA) | NA |
| *M. catarrhalis (β-l. +)* | 11/17 (64.7%) | 9/15 (60.0%) | 4.7%, 95% C.I.: -35.2%, 44.6% |
| *S. pneumoniae* | 56/78 (71.8%) | 49/77 (63.6%) | 8.2%, 95% C.I.: -7.8%, 24.1% |
| *S. pyogenes* | 12/16 (75.0%) | 11/16 (68.8%) | 6.3%, 95% C.I.: -31.1%, 43.6% |

**TABLE 25**: STUDY 0098B: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE EVALUABLE SUBJECTS AT FINAL VISIT (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)

| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
|---|---|---|---|
| *H. influenzae* | 1/1 (100%) | 4/6 (66.7%) | NA |
| *H. influenzae (β-l. -)* | 8/16 (50.0%) | 9/12 (75.0%) | -25.0%, 95% C.I.: -66.9%, 16.9% |
| *H. influenzae (β-l. +)* | 6/19 (31.6%) | 14/20 (70.0%) | -38.4%, 95% C.I.: -72.5%, -4.3% |
| *M. catarrhalis* | 2/4 (50.0%) | 1/2 (50.0%) | NA |
| *M. catarrhalis (β-l. -)* | 1/1 (100%) | 0/0 (NA) | NA |
| *M. catarrhalis (β-l. +)* | 11/17 (64.7%) | 8/14 (57.1%) | 7.6%, 95% C.I.: -33.4%, 48.5% |
| *S. pneumoniae* | 51/71 (71.8%) | 45/73 (61.6%) | 10.2%, 95% C.I.: -6.5%, 26.9% |
| *S. pyogenes* | 10/14 (71.4%) | 11/16 (68.8%) | 2.7%, 95% C.I.: -36.8%, 42.2% |

**TABLE 26**: STUDY 0098B: BY PATHOGEN BACTERIAL ERADICATION RATES OF THE MO SUB-POPULATION AT FINAL VISIT (FOR MOST COMMON ISOLATED BASELINE PATHOGENS)

| Pathogen | Cefpodoxime | Cefixime | Cefpodoxime vs Cefixime by Eradication |
|---|---|---|---|
| *H. influenzae* | 1/1 (100%) | 4/6 (66.7%) | NA |
| *H. influenzae (β-l. -)* | 8/16 (50.0%) | 9/11 (81.8%) | -31.8%, 95% C.I.: -73.0%, 9.3% |
| *H. influenzae (β-l. +)* | 5/15 (33.3%) | 12/18 (66.7%) | -33.3%, 95% C.I.: -71.7%, 5.1% |
| *M. catarrhalis* | 2/4 (50.0%) | ½ (50.0%) | NA |
| *M. catarrhalis (β-l. -)* | 1/1 (100%) | 0/0 (NA) | NA |
| *M. catarrhalis (β-l. +)* | 10/15 (66.7%) | 8/13 (61.5%) | 5.1%, 95% C.I.: -37.7%, 47.9% |
| *S. pneumoniae* | 47/63 (74.6%) | 41/65 (63.1%) | 11.5%, 95% C.I.: -5.9%, 29.0% |
| *S. pyogenes* | 11/15 (73.3%) | 11/16 (68.8%) | 4.6%, 95% C.I.: -33.8%, 42.9% |

Visit 2

Visit 2 Overall Clinical Evaluation

Table E-30 summarizes the results of the overall clinical response at Visit 2. The overall clinical success rates (87%) for the cefpodoxime group (226/260) and the cefixime group (236/271) were not significantly different (95% CI: -6.26% to 5.94%).

| TABLE 2.31: STUDY 0098A: OVERALL CLINICAL RESPONSE OF THE MO SUB-POPULATION AT VISIT 2 | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=125) | Cefixime (N=128) |
| Success | 107 (85.6%) | 103 (80.5%) |
| Failure | 18 (14.4%) | 25 (19.5%) |
| Cefpodoxime vs Cefixime by Success | 5.1%, 95% C.I.: -4.9%, 15.1% | |

| TABLE 3.30: STUDY 0098B: OVERALL CLINICAL RESPONSE OF THE MO SUB-POPULATION AT VISIT 2 | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=126) | Cefixime (N=130) |
| Success | 109 (86.5%) | 119 (91.5%) |
| Failure | 17 (13.5%) | 11 (8.5%) |
| Cefpodoxime vs Cefixime by Success | -5.0%, 95% C.I.: -13.5%, 3.4% | |

Visit 3 Overall Clinical Evaluation

Table E-30 summarizes the results of the overall clinical response at Visit 3. The overall clinical success rates for the cefpodoxime group (74%: 191/257) and the cefixime group (79%: 214/272) were not significantly different (95% CI: -11.96% to 3.25%).

| TABLE 2.32: STUDY 0098A: OVERALL CLINICAL RESPONSE OF THE MO SUB-POPULATION AT VISIT 3 | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=125) | Cefixime (N=128) |
| Success | 86 (68.8%) | 90 (70.3%) |
| Failure | 39 (31.2%) | 38 (29.7%) |
| Cefpodoxime vs Cefixime by Success | -1.5%, 95% C.I.: -13.6%, 10.6% | |

| TABLE 3.31: STUDY 0098B: OVERALL CLINICAL RESPONSE OF THE MO SUB-POPULATION AT VISIT 3 | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=126) | Cefiximef (N=130) |
| Success<br>Failure | 97 (77.0%)<br>29 (23.0%) | 110 (84.6%)<br>20 (15.4%) |
| Cefpodoxime vs Cefiximef by Success | -7.6%, 95% C.I.: -18.0%, 2.8% | |

Final Visit Overall Clinical Evaluation

Table E-30 summarizes the results of the overall clinical response at Final Visit (Days 25-38). The overall clinical success rates for the cefpodoxime group (65%: 161/249) and the cefixime group (65%: 170/262) were not significantly different (95% CI: -8.9% to 8.45%)

| TABLE 27: STUDY 0098A: OVERALL CLINICAL RESPONSE OF THE ITT SUBJECTS AT FINAL VISIT | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=225) | Cefiximef (N=230) |
| Success<br>Failure | 83 (36.9%)<br>142 (63.1%) | 85 (37.0%)<br>175 (63.0%) |
| Cefpodoxime vs Cefiximef by Success | -0.1%, 95% C.I.: -9.4%, 9.2% | |

| TABLE 28: STUDY 0098A: OVERALL CLINICAL RESPONSE OF THE EVALUABLE SUBJECTS AT FINAL VISIT | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=124) | Cefiximef (N=132) |
| Success<br>Failure | 72 (58.1%)<br>52 (41.9%) | 79 (59.8%)<br>53 (40.2%) |
| Cefpodoxime vs Cefiximef by Success | -1.8%, 95% C.I.: -14.6%, 11.1% | |

| TABLE 2.33: STUDY 0098A: OVERALL CLINICAL RESPONSE OF THE MO SUB-POPULATION AT FINAL VISIT | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=125) | Cefiximef (N=128) |
| Success<br>Failure | 70 (56.0%)<br>55 (44.0%) | 73 (57.0%)<br>55 (43.0%) |
| Cefpodoxime vs Cefixime by Success | -1.0%, 95% C.I.: -14.0%, 12.0% | |

| TABLE 29: STUDY 0098B: OVERALL CLINICAL RESPONSE OF THE ITT SUBJECTS AT FINAL VISIT | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=256) | Cefiximef (N=258) |
| Success<br>Failure | 104 (40.6%)<br>152 (59.4%) | 110 (42.6%)<br>148 (57.4%) |
| Cefpodoxime vs Cefixime by Success | -2.0%, 95% C.I.: -10.9%, 16.7% | |

| TABLE 30: STUDY 0098B: OVERALL CLINICAL RESPONSE OF THE EVALUABLE SUBJECTS AT FINAL VISIT | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=136) | Cefiximef (N=140) |
| Success<br>Failure | 89 (65.4%)<br>47 (34.6%) | 91 (65.0%)<br>49 (35.0%) |
| Cefpodoxime vs Cefixime by Success | 0.4%, 95% C.I.: -11.5%, 12.4% | |

| TABLE 3.32: STUDY 0098B: OVERALL CLINICAL RESPONSE OF THE MO SUB-POPULATION AT FINAL VISIT | | |
|---|---|---|
| Clinical Response | Cefpodoxime (N=126) | Cefiximef (N=130) |
| Success<br>Failure | 84 (66.7%)<br>42 (33.3%) | 85 (65.4%)<br>45 (34.6%) |
| Cefpodoxime vs Cefixime by Success | 1.3%, 95% C.I.: -11.1%, 13.7% | |

cc:
NDA 50-675/S-014
HFD-520/Division Files
HFD-520/MO/R. Viraraghavan
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