Short Title

Topical CIPRODEX versus Oral AUGMENTIN in AOMT

Long Title

Safety and Efficacy of Topical CIPRODEX Otic (Ciprofloxacin 0.3%, Dexamethasone 0.1%) Suspension Compared to AUGMENTIN ES-600™ Oral Suspension in the Treatment of Acute Otitis Media with Otorrhea through Tympanostomy Tubes (AOMT)

1. TITLE PAGE

Operations Unit Number / Name:	65/ENT Otic/Nasal			
Project Name/Number:	CIPRODEX Otic/625211			
Name of Test Article/ Investigational Product:	CIPRODEX Otic Suspension			
Indication Studied/Supported:	Acute Otitis Media with otorrhea through tympanostomy tubes (AOMT) in pediatric patients			
Study Design:	Randomized, parallel group, multicenter, observer-masked, active-controlled, two-armed			
Name of Sponsor:	Alcon Research, Ltd.			
Protocol Number:	C-02-57			
Development Phase of Study:	Phase IV			
Study Initiation Date:	May 6, 2003			
Date of Early Termination:	Not Applicable			
Study Completion Date:	May 10, 2004			
Name and Affiliation of Principal or Coordinating Investigator(s) or Sponsor's Responsible Medical Officer:	Medical Monitor: Peter S. Roland, M.D. Professor and Chairman, Department of Otolaryngology University of Texas Southwestern Medical School Dallas, TX Coordinating Investigator: Roderick D. Moe, M.D. Pediatric ENT Institute of South Texas San Antonio, TX			
Name of Company/Sponsor Signatory:	G. Michael Wall, Ph.D. Sr. Director, Otic/Nasal Products Development			
Authors:	Sheryl Dupre, M.S., Susan Potts, M.S., Ralph Good, M.B.A.			
Report Status:		Interim		Abbreviated
	X	Final	X	Full
Is This the Core Clinical Study Report?		No		
	X	Yes – TDOC 0001815		
Other Associated Clinical Study Report Nos.	TDOC 0001817 (CRFs); TDOC 0001816 (Pt Listings)			

This study was performed in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice (GCP), including the archiving of essential documents. This clinical study report was prepared according to the ICH E3 "Guideline for Industry: Structure and Content of Clinical Study Reports", effective for studies commencing after July 1996.

1.1 Comprehensive Cumulative History

Not applicable

2. SYNOPSIS

Name of Sponsor/Company: Alcon Research, Ltd. Name of Finished Product: CIPRODEX Otic Suspension Name of Active Ingredient: Ciprofloxacin 0.3%/ dexamethasone 0.1%	Individual Study Table Referring to Part IV of the Dossier Volume: Page:	*(For National Authority Use Only)*
Title of Study: Safety and Efficacy of Topical CIPRODEX Otic (Ciprofloxacin 0.3%, Dexamethasone 0.1%) Suspension Compared to AUGMENTIN ES-600™ Oral Suspension in the Treatment of Acute Otitis Media with Otorrhea through Tympanostomy Tubes (AOMT)		
Investigator(s): Eight (8) investigators participated in this U.S. study.		
Study Center: This multicenter study was conducted at 8 U.S. medical facilities.		
Publication(s): One (1) publication has resulted from the study		
Study Period: May 6, 2003 through May 10, 2004		Phase of Development: IV
Objectives: To describe the safety and efficacy of CIPRODEX Otic Suspension relative to AUGMENTIN ES-600 Oral Suspension for the treatment of acute otitis media with otorrhea through tympanostomy tubes (AOMT) in pediatric patients based on time to cessation of otorrhea and the proportion of patients rated as cured at test-of-cure (TOC).		
Methodology: Randomized, parallel group, multicenter, observer-masked, active-controlled, two-armed.		
Number of Patients Planned/Analyzed: 60 planned/80 enrolled		
Diagnosis and Main Criteria for Inclusion: Pediatric patients, 6 months to 12 years of age, with post-tympanostomy tube otorrhea visible by the parent/guardian of 3 weeks or less duration meeting inclusion/exclusion criteria.		
Test Product, Dose and Mode of Administration, Batch Number(s): CIPRODEX Otic (ciprofloxacin 0.3%/dexamethasone 0.1%) Suspension; topical otic administration of 4 drops into the infected ear(s) twice daily (BID) for 7 days. Batch number: 02-500406-1		
Duration of Treatment: Patients were required to undergo treatment for either seven (7) days if randomized to receive CIPRODEX or ten (10) days if randomized to receive AUGMENTIN.		
Reference Therapy, Dose and Mode of Administration, Batch Number(s): AUGMENTIN ES-600 Oral Suspension (600 mg Amoxicillin, 42.9 mg Clavulanic acid) - 90 mg/kg/day divided into two doses (every 12 hours) for 10 days. Batch numbers: 03-500486-1, 03-500506-1, 03-500541-1, 04-500585-1		

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Criteria for Evaluation: All patients who received drug were evaluable for safety analyses. All patients who receive drug and had at least one on-therapy visit were evaluable for intent-to-treat (ITT) analyses. All patients who received drug, had at least one on-therapy visit, met pre-therapy inclusion/exclusion criteria, and were pathogen positive for bacteria on Day 1 (detected and recovered bacteria) were evaluable for detected and recovered modified intent-to-treat (DRMITT) analyses. All patients who received drug, had at least one on-therapy visit, met pre-therapy inclusion/exclusion criteria, and were pathogen positive for bacteria on Day 1 (recovered bacteria) were evaluable for modified intent-to-treat (MITT) analyses. For the ITT, DRMITT and MITT data sets, patients who had no measurements after baseline were included as treatment failures. All patients who received drug, met pre-therapy inclusion/exclusion criteria and had baseline and test-of-cure (or exit if patient exited from the study early) visits were evaluable for per protocol (PP) analyses. All per protocol patients who were culture positive for bacteria on day 1 (detected and recovered bacteria) were evaluable for the detected and recovered modified per protocol (DRMPP) analyses. All per protocol patients who were culture positive for bacteria on day 1 (recovered bacteria) were evaluable for the modified per protocol (MPP) analyses. Additionally, all patients with positive baseline cultures for *Pseudomonas aeruginosa* were excluded from the PP, DRMPP and MPP analyses.

Statistical Methods:
There were two primary statistical objectives in this study. They were to describe 1) the time to cessation of otorrhea for CIPRODEX Suspension relative to AUGMENTIN and 2) the proportion of patients whose clinical response was rated as "cured" by the investigator at the test-of-cure (TOC) visit for CIPRODEX Suspension relative to AUGMENTIN.

Efficacy: The primary efficacy variables were 1) time to cessation of otorrhea as recorded in the patient diary and 2) the proportion of patients with a clinical response of "cured" as rated by the investigator at TOC. Time to cessation of otorrhea was defined as the first day on which the otorrhea was noted as absent and subsequently remained absent in the ear declared as the worse ear. The secondary efficacy variables were 1) the proportion of patients at TOC with successful eradication of disease-specific organisms that were present at enrollment, 2) the proportion of patients at each follow-up visit with a clinical response of "cured" as rated by the investigator and 3) the proportion of patients with an investigator assessment of no otorrhea at each follow-up visit.

Safety: The safety evaluation was conducted on all patients who were randomized into the study and received at least one dose of study drug. The safety analysis was based on extent of exposure to study drug, adverse events, and audiometry examination.

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Summary – Conclusions:

EVALUABILITY AND DEMOGRAPHICS:
Of the 80 patients enrolled in this study, all were evaluable for the safety and intent-to-treat (ITT) analyses. Of these, 60 were evaluable for the detected and recovered modified intent-to-treat (DRMITT) analyses, 55 were evaluable for the modified intent-to-treat (MITT) analyses, 66 were evaluable for the per protocol (PP) analyses, 51 were evaluable for the detected and recovered modified per protocol (DRMPP) analyses and 47 were evaluable for the modified per protocol (MPP) analyses. In the ITT data set, the average age was 1.9 years (range 205 days to 8 years). Males comprised 52.5% and 78.8% were Caucasian, 10.0% were Black, 1 patient (1.3%) was Asian, 7.5% were Hispanic, and 2.5% were of other races.

EFFICACY RESULTS:
The results of this study showed that CIPRODEX is effective in treating acute otitis media with tympanostomy tubes (AOMT). This conclusion is based on an assessment of the totality of the evidence, including both primary and secondary endpoints.

At the Day 18 (TOC) visit, the percent of clinical cures was 81% in the CIPRODEX treatment group and 55% in the AUGMENTIN treatment group in the MPP data set. A similar result (i.e. 81% for CIPRODEX and 55% for AUGMENTIN) was observed for the microbiological eradication rate at the Day 18 (TOC) visit. Additionally, the median time to cessation of otorrhea was 4 days in the CIPRODEX treatment group and 10 days in the AUGMENTIN treatment group. These data demonstrate the effectiveness of CIPRODEX in treating AOMT and additionally demonstrate that CIPRODEX is more effective than AUGMENTIN for clinical cures, microbiological eradication and time to cessation of otorhea.

SAFETY RESULTS:

The safety of CIPRODEX and AUGMENTIN was evaluated in 80 pediatric patients. No deaths or other serious adverse events were reported during the study. Twelve patients (CIPRODEX: 10; AUGMENTIN:2) were discontinued from the study due to adverse events, of which 2 patients (1 from each treatment group) were due to treatment-related events (device block in the CIPRODEX group, dermatitis and diarrhea in the AUGMENTIN group).

A total of 43 of the 80 patients (53.8%) participating in the study reported adverse events, which included 22 of the 39 patients (56.4%) with exposure to CIPRODEX and 21 of the 41 patients (51.2%) with exposure to AUGMENTIN. Ear pain (5.1%) and diarrhea (19.5%) were the most frequently reported treatment-related adverse events in the CIPRODEX group and AUGMENTIN group, respectively. Similar types of otic and nonotic adverse events were noted in the infant/toddler (28 days to 23 months) population and the children

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(2 to 11 years) population for CIPRODEX and AUGMENTIN. No overall safety concerns were noted, based upon a review of the adverse events in all pediatric patients in both treatment groups.

No clinically relevant difference in mean change of speech reception threshold (SRT) from baseline was observed between CIPRODEX and AUGMENTIN. No clinically relevant decrease in hearing from baseline was observed for the CIPRODEX or AUGMENTIN groups, based upon an assessment of bone and air conduction audiometry parameters.

EFFICACY CONCLUSIONS:

Overall Efficacy

- **CIPRODEX dosed 2 times a day for 7 days is effective in treating acute otitis media with tympanostomy tubes (AOMT) and results in 81% patients with clinical cure, 81% patients with microbiological success, and a 4-day median time to cessation of otorrhea.**

Primary Analyses

- **CIPRODEX is superior to AUGMENTIN for time to cessation of otorrhea p=0.0030**
- **CIPRODEX is more effective than AUGMENTIN for clinical cure at the TOC visit, however this difference is marginally non-significant in the planned analysis data set p=0.0969**

Secondary Analyses

- **CIPRODEX is more effective than AUGMENTIN for microbiological eradication of the baseline bacterial pathogens at the TOC visit, however this difference is marginally non-significant p=0.0969**

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- **CIPRODEX is more effective than AUGMENTIN for clinical cure at the EOT and TOC visits, however these differences are marginally non-significant p=0.0500 and p=0.0969, respectively**

- **CIPRODEX is superior to AUGMENTIN at the EOT visit for the absence of otorrhea (p=0.0176). This difference was marginally non-significant, in favor of CIPRODEX, at the TOC visit p=0.0969**

SAFETY CONCLUSIONS:

- **CIPRODEX administered twice-daily for 7 days is safe and well tolerated in pediatric patients with acute otitis media with otorrhea through tympanostomy tubes, based upon a review of adverse events and an assessment of audiometry parameters.**

C-02-57
Anlage zur Synopse

1. Teilnehmende Prüfzentren in Deutschland

Keine

Sonstige Prüfzentren

1	Ogden Research 4650 Harrison Blvd. Ogden, UT 84403 USA
2	Square-One Clinical Research 3256 West 26th Street Erie, PA 16506 USA
3	Arkansas Otolaryngology 10201 Kanis Road Little Rock, AR 72205 USA
4	Children's Hospital of Pittsburgh Dept. of Ped Otolaryngology 3705 Fifth Ave. At Desoto Street Pittsburgh, PA 15213 USA
5	CENTA Medical Group, P.A. Nine Richland Medical Park Columbia, SC 29203 USA
6	Pediatric ENT Institute of South TX 16723 Huebner San Antonio, TX 78248 USA
7	Florida Otolaryngology Group, PA 5979 Vineland Road Orlando, FL 32819 USA
8	Bascom Palmer Eye Institute 900 NW 17th Street Miami, FL 33136 USA

2. Wesentliche Änderungen des Prüfprotokolls:

Amendment 1:

- Number of participating centers increased
- Sample size is clarified consistently as 60 enrolled patients (30 per arm) rather than 60 patients per treatment arm.
- Patients with baseline cultures of *Pseudomonas aeruginosa* will be discontinued from the study.
- Patients presenting at any follow-up visit with a contralateral ear infection will be discontinued.
- The Test of Cure visit will occur on the same post randomization day for each arm of the study.
- Clarification is made regarding the timing of the patient's first dose
- Dosing instructions are modified
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Amendment 2:

The comparator drug is not effective against *Pseudomonas aeruginosa*. The design of the study requires discontinuation of patients with baseline cultures of *Pseudomonas aeruginosa*. To avoid discontinuation for patients due to *Pseudomonas aeruginosa* the purpose of this amendment was to modify the follow up procedures for patients with baseline cultures of *Pseudomonas aeruginosa* to allow the patients to begin treatment with Cilodex instead of being discontinued from the study

Amendment 3:

additional bottle sizes

3. Datum des Berichts:

22. August 2017