Sponsor

Alcon Research, Ltd.

Generic Drug Name

Dexa-Polyspectran® drops (PN+Dx)

Trial Indication(s)

Acute bacterial otitis externa

Protocol Number

C-04-72

Protocol Title

Efficacy and safety of Dexa-Polyspectran drops, preserved with benzalkonium chloride, vs Dexa-Polyspectran drops without dexamethasone phosphate, preserved with benzalkonium chloride, in patients with acute bacterial otitis externa – A double-blind, multicenter, prospective, randomized, controlled clinical phase III study

Clinical Trial Phase

Phase III

Study Start/End Dates

September 19, 2005 to July 17, 2006

Reason for Termination (if applicable)

Not applicable

Study Design/Methodology

This was a multicenter, double-blind, controlled, parallel group, randomized, adaptive group-sequential trial.

Centers

Subjects were recruited from 21 investigational sites located in Germany.

Objectives

The objective of this study was to compare the efficacy and safety of both preparations in the treatment of acute bacterial otitis externa and to show by a stronger reduction of inflammatory otic signs and symptoms a greater benefit of Dexa-Polyspectran preserved with benzalkonium chloride (PN+Dx) compared to Dexa-Polyspectran® without dexamethasone phosphate preserved with benzalkonium chloride (PN-Dx).

Test Product (s), Dose(s), and Mode(s) of Administration

Test Product: Dexa-Polyspectran drops (PN+Dx), an antibiotics combination of neomycin sulfate and polymyxin-B sulfate which contains additionally dexamethasone phosphate. At baseline visit (Day 1), the drops were applied by the investigator and instructions for application were given to the patient. In between the visits, the patient applied two drops three times a day. Test products were masked.

Reference Product: Dexa-Polyspectran drops without dexamethasone phosphate (PN-Dx) containing only the antibiotics combination of neomycin sulfate and polymyxin-B sulfate. At baseline visit (Day 1) the drops were applied by the investigator and instructions for application were given to the patient. In between the visits, the patient applied two drops three times a day. Reference products were masked.

Rescue Medication: The patients received paracetamol 500 mg tablets for oral use as rescue medication for pain. The use instruction was “on demand”.

Statistical Methods

The safety analysis set included all randomized patients who applied the study medication at least once.
The ITT analysis set included all patients who had a valid follow-up value of all primary efficacy variables.
The Treated-per-protocol (TPP) analysis set included all patients of the ITT analysis set, if the following criteria were additionally met:

- All of the major inclusion criteria, none of the major exclusion criteria fulfilled
- Absence of relevant protocol violations
- Correct allocation to treatment group
- Sufficient compliance concerning the application of the study medication
- A valid follow-up value of the primary efficacy parameter after having applied the study medication for at least two days

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Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Male or female patients from the age of 18 years up to the age of 75 years
- Diiagnosis of acute unilateral, bacterial otitis externa according to clinical criteria at Visit 1 (Day 1)
- Signed informed consent
- Patients with at least one prior episode of otitis externa within the last 12 months
- Other protocol-defined inclusion criteria may apply

Exclusion criteria:

- Use of medications outside protocol-specified parameters
- Signs, symptoms or history of any condition that, per protocol or in the opinion of the investigator, might compromise:
  1. the safety or well-being of the participant or study staff
  2. the safety or well-being of the participant's offspring (such as through or breast-feeding)
  3. the analysis of results
- Other protocol-defined exclusion criteria may apply

Participant Flow Table

Subject Disposition

Number of Patients	PN-Dx	PN+Dx	Total
Randomized	169	169	338
Analysed	169	168	337
Safety Analysis Set	169	168	337

Intent-to-Treat (ITT)	164	164	328
Completed	155	155	310
Discontinued	14	13	27
Reasons for discontinuation			
Lack of Efficacy	6	3	9
Patient does not appear to visit	5	6	11
Lost to Follow Up / Lack of Compliance	0	1	1
Inclusion (exclusion criterion not fulfilled)	0	2	2
Technical / Logistical Reason –Scheduling difficulty	1	1	2

Baseline Characteristics

Demographic Characteristics at Baseline by Treatment Group (ITT Analysis Set)			
Baseline Characteristic	**PN-Dx (N=164)**	**PN+Dx (N=164)**	**Total (N=328)**
Age (years)			
Mean (Standard Deviation)	48 (14)	48 (16)	48 (15)
Sex			

Male	92	99	191
Female	72	65	137

Summary of Efficacy

Primary Outcome Measure

Confirmatory Efficacy Analysis of Clinical Symptom Score* (CSS) by Treatment Group (ITT Analysis Set)			
	PN-Dx	**PN+Dx**	**p-value*** **
First Stage	N=60	N=63	
Day 1–Day 4** [Mean (Standard Deviation)]	3.6 (1.8)	3.9 (2.2)	0.3144
Second Stage	N=104	N=101	
Day 1–Day 4** [Mean (Standard Deviation)]	3.6 (2.1)	4.1 (2.1)	0.2184

*The CSS is the sum of the scores assessed at each visit for the individual symptoms redness, swelling, pain and secretion by a 4-item scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).
**Positive score indicates improvement
***P-value is calculated using the two-sided Wilcoxon-Mann-Whitney Test

Secondary Outcome Measures

This trial had no key secondary outcome measures.

Summary of Safety

Both study medications were safe and well tolerated. In total there were 14 adverse events (AEs) in 11 patients that were reported in this study. All AEs were non serious and mild to moderate in severity.

Serious Adverse Events

There were no serious adverse events or death in the study.

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Other Adverse Events by System Organ Class

Treatment System Organ Class / Preferred Term	PN-Dx	PN+Dx
Infections and infestations		
Nasopharyngitis	2	0
Influenza	0	1
Bronchitis	0	1
Ear and labyrinth disorders		
Ear pruritus	4	0
Ear pain	1	0
Nervous system disorders		
Headache	2	1
Eye disorders		
Conjunctivitis	1	0
Gastrointestinal disorders		

Nausea	1	0

Other Relevant Findings

No other relevant findings to disclose.

Date of Clinical Trial Report

June 8, 2007