Sponsor

Alcon Research, Ltd.

Generic Drug Name

Polyspectran® drops (PS)

Trial Indication(s)

Acute bacterial otitis externa

Protocol Number

C-04-73

Protocol Title

Efficacy and safety of Polyspectran® drops, preserved with benzalkonium chloride vs. Glycerol ear drops in patients with acute bacterial otitis externa – A double-blind, multicenter, prospective, randomized, and controlled clinical phase III study

Clinical Trial Phase

Phase III

Study Start/End Dates

September 15, 2005 to April 10, 2006

Reason for Termination

Not applicable

Study Design/Methodology

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

Centers

Subjects were enrolled at 19 investigational sites, all located in Germany.

Objectives

The objective of this study is to compare the efficacy and safety of Polyspectran®, preserved with benzalkonium chloride, to Glycerol, a well-established standard treatment of exterior ear infections, and to show a greater benefit of Polyspectran® compared to Glycerol in terms of inflammatory signs and symptoms in acute bacterial otitis externa.

Test Products, Doses, and Modes of Administration

Test Product: Polyspectran drops (PS). At the 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. All samples were masked.

Reference Product: Glycerol drops. At the 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. All samples 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

Summary statistics and Wilcoxon-Mann-Whitney Test

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
- Diagnosis of acute unilateral, bacterial otitis externa according to clinical criteria at Visit 1 (baseline, Day 1)
- Signed informed consent

Exclusion criteria:

- Known viral, fungal or tubercular ear infection, otitis media, mastoiditis, mastoid cavities, stenosing exostosis, cholesteatoma, perforated tympanic membrane
- Invasive malignant chronic otitis externa
- Pre-treatment of the current otitis externa with local/systemic antibiotics or corticoids
- Possible use of other analgesics than paracetamol as pain medication during the study
- Diabetic patients
- Use of immunosupressants
- Need of antibiotic or corticoid local otic / systemic treatment during the study (other than study drug)
- Nonsteroidal anti-inflammatory drugs (NSAID)
- Vaccination reactions
- Severe hepatic or renal insufficiencies
- Alcohol abuse
- Known intolerance/hypersensitivity to ingredients of the study drugs or paracetamol
- Pregnancy, lactation; no adequate contraceptive protection
- Well-founded doubt about the patient‘s cooperation
- Participation in another clinical trial within the last 30 days, simultaneous participation in another clinical trial, or previous participation in this trial

Participant Flow Table

Subject Disposition

Number of Patients	Polyspectran	Glycerol	Total
Randomized	122	122	244
Analysed	121	122	243
Safety Analysis	121	122	243
Intent-to-Treat (ITT)	118	118	236
Treated per Protocol (TPP)	110	108	218
Completed	114	109	223

Discontinued	7	13	20
Reasons for discontinuation			
Lack of Efficacy	4	4	8
Intolerable Adverse Event	0	1	1
Lost to Follow Up / Lack of Compliance	1	4	5
Patient's Request	0	1	1
Technical / Logistical Reason	1	2	3
Other – Reason not specified	1	1	2

Baseline Characteristics

Demographic Characteristics at Baseline by Treatment Group (ITT Analysis Set)			
Demographic Characteristic	**Glycerol (N=118)**	**PS (N=118)**	**Total (N=236)**
Age (years)			
Mean (Standard deviation)	50 (16)	46 (16)	48 (16)
Sex			
Male	65	61	126
Female	53	57	110

Summary of Efficacy

There was a statistically significant difference between Polyspectran and Glycerol using the adaptive design with two stages and the primary efficacy variable Clinical Symptom Score (CSS), favoring Polyspectran. This result as well as the secondary efficacy variables confirms the superiority of PS over Glycerol for efficacy.

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Primary Outcome Results

Confirmatory Efficacy Analysis of Clinical Symptom Score* (CSS) by Treatment Group (ITT Analysis Set)			
	Glycerol (N=118)	**PS (N=118)**	**p-value**
First Stage	N=62	N=59	
Day 1	7.3 (2.2)	7.3 (2.1)	0.8279
Day 4	4.7 (2.8)	3.9 (2.0)	0.1467
Day 1–Day 4	2.6 (2.4)	3.4 (2.1)	0.0464
Second Stage	N=56	N=59	
Day 1	7.0 (2.3)	7.2 (2.3)	0.6254
Day 4	3.9 (2.6)	3.7 (2.3)	0.8193
Day 1–Day 4	3.1 (1.9)	3.5 (1.9)	0.2986

Data are presented as mean (standard deviation).
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).
P-value is calculated using the two-sided Wilcoxon-Mann-Whitney Test.

Secondary Outcome Results

Efficacy Analysis of CSS in Pooled Data (Stage 1 + Stage 2) Day 1 to Day 10 (Visit 3) by Treatment Group (ITT Analysis Set)			
	Glycerol (N=118)	**PS (N=118)**	**p-value**

Day 1–Day 10	5.0 (2.8)	5.9 (2.8)	0.0047
Day 4 – Day 10	2.1 (2.2)	2.4 (1.9)	0.4379

Data are presented as mean (standard deviation).
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).

P-value is calculated using the two-sided Wilcoxon-Mann-Whitney Test.Individual Scores for CSS Symptoms in Pooled Data (Stage 1 + Stage 2) Day 1 to Day 10 (Visit 3) (ITT Analysis Set)

	Glycerol	PS	p-value
Change of the CSS item **redness**			
Day 1 – Day 4 (n=118,118)	0.7 (0.7)	0.8 (0.7)	0.2881
Day 1 – Day 10 (n=117,115)	1.3 (0.9)	1.5 (0.9)	0.0856
Day 4 – Day 10 (n=117,115)	0.6 (0.7)	0.7 (0.6)	0.1555
Change of the CSS item **swelling**			
Day 1 – Day 4 (n=118,118)	0.6 (0.8)	0.9 (0.8)	0.0109
Day 1 – Day 10 (n=117,115)	1.2 (0.9)	1.5 (1.0)	0.0032
Day 4 – Day 10 (n=117,115)	0.6 (0.8)	0.7 (0.8)	0.6081
Change of the CSS item **secretion**			
Day 1 – Day 4 (n=118,118)	0.9 (0.8)	1.0 (0.8)	0.3455
Day 1 – Day 10 (n=117,115)	1.3 (1.0)	1.6 (1.0)	0.0609
Day 4 – Day 10 (n=117,115)	0.5 (0.8)	0.6 (0.7)	0.2197
Change of the CSS item **pain**			
Day 1 – Day 4 (n=118,118)	0.7 (0.8)	0.9 (0.8)	0.2128
Day 1 – Day 10 (n=117,115)	1.2 (1.0)	1.3 (1.0)	0.5717
Day 4 – Day 10 (n=117,115)	0.5 (0.7)	0.4 (0.6)	0.5541

Data are presented as mean (standard deviation).
Positive mean for differences indicates improvement.
P-value is calculated using the two-sided Wilcoxon-Mann-Whitney Test.

Disease severity (pain perception) as measured on a visual analogue scale (VAS) (ITT Analysis Set)			
	Glycerol	**PS**	**p-value**
Day 1 – Day 4 (n=109,112)	1.8 (2.7)	2.0 (2.8)	0.4572
Day 1 – Day 10 (n=71,69)	3.1 (3.6)	3.8 (3.3)	0.2790
Day 4 – Day 10 (n=72,70)	1.3 (2.2)	1.1 (2.3)	0.7489

Disease severity using VAS Score changes (cm), VAS Score varied between 0 and 10 cm; 0: no pain; 10: maximum pain.
Positive mean for differences indicates improvement.
P-value is calculated using the two-sided Wilcoxon-Mann-Whitney Test.

Patients' Global Assessment of Efficacy at Day 10 (ITT Analysis Set)			
	Glycerol (n=118)	**PS (n=116)**	**p-value**
Poor	19	9	0.0779
Satisfactory	16	9	
Good	38	42	
Very good	45	56	

Unit: patients
P-value is calculated using two-sided Fisher´s Exact Test comparing the independency of treatment and outcome for each variable.

Number of Paracetamol 500 mg Tablets Taken between Day 1 and Day 10 (ITT Analysis Set)			
	Glycerol	**PS**	**p-value**
Day 1 – Day 4 (n=117,117)	1.6 (3.0)	1.9 (3.6)	0.8498
Day 4 – Day 10 (n=117,116)	1.1 (3.7)	1.0 (3.0)	0.9004

Data are presented as mean (standard deviation).
Positive mean for differences indicates improvement.
P-value is calculated using the two-sided Wilcoxon-Mann-Whitney Test.

Summary of Safety

Both study medications were safe and well tolerated. In total, eleven (11) adverse events (Glycerol: 2 AEs; PS: 9 AEs) in eight (8) patients (Glycerol: 2 patients; PS: 6 patients) were reported during the whole treatment period of the study. All AEs were non serious and mild to moderate in severity.

Safety Results

In total, eleven (11) adverse events (Glycerol: 2 AEs; PS: 9 AEs) in eight (8) patients (Glycerol: 2 patients; PS: 6 patients) were reported during the whole treatment period of the study. All AEs were non serious and mild to moderate in severity.

Serious Adverse Events by System Organ Class

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

Other Adverse Events by System Organ Class

Treatment **System Organ Class / Preferred Term [n(events)]**	**Glycerol (N=118)**	**PS (N=118)**
Infections and infestations		
Nasopharyngitis	0(0)	1(1)
Laryngopharyngitis	0(0)	1(1)

Infection	0(0)	1(1)
Ear and labyrinth disorders		
Ear pain	1(1)	0(0)
Nervous system disorders		
Headache	1(1)	2(5)
Respiratory, thoracic and mediastinal disorders		
Rhinitis allergic	0(0)	1(1)

Other Relevant Findings

There are no other relevant findings to disclose.

Date of Clinical Trial Report

July 6, 2007