

# Double-Blind Placebo-Controlled Study of the Novel Peptide Drug OP-145 in Chronic Middle Ear Infection

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## BACKGROUND

OP-145 (Ac-I-G-K-E-F-K-R-I-V-E-R-I-K-R-F-L-R-E-L-V-R-P-L-R-NH<sub>2</sub>), a synthetic 24-amino acid derivative (MW 3094) of the human cathelicidin LL-37, binds lipopolysaccharide and lipoteichoic acid, degrades biofilms and has antimicrobial action. It has low chemotactic activity compared to its native predecessor LL-37. By virtue of this array of actions, OP-145 is expected to moderate inflammation in infection, and, importantly, to break the vicious cycle of chronic infection, enabling the body to eradicate the infectious agent. Hence, OP-145 is considered a novel approach to chronic infections, separate from conventional antibiotics and antimicrobial peptides. A preliminary open dose finding study in chronic suppurative otitis media (CSOM) patients had shown a favorable safety and tolerability profile of OP-145 (0.5 mg/ml) applied twice daily for 2 weeks, with improvement of CSOM symptom score. As a proof of concept, safety and efficacy of topical OP-145 were evaluated in the present placebo controlled blinded study in patients with chronic suppurative otitis media.

## STUDY OBJECTIVE

The primary objective of the study was to investigate whether OP-145 could be safely applied directly on the inflamed mucosa of the middle ear of adults with CSOM with perforation of the tympanic membrane, and without cholesteatoma.

The secondary objective of the study was to obtain proof of efficacy for OP-145 in inducing improvement in the mucosa of the middle ear of adults with CSOM, as compared to placebo.

## METHODS

This was a randomised, double blind, placebo-controlled, multicenter Phase II study to investigate the safety and efficacy of OP-145 in adults with CSOM, without cholesteatoma. Diagnosis and main criteria for inclusion were: male and female adult subjects, ≥18 years of age, who had a diagnosis of CSOM with chronic proliferative mucosal changes for > 6 months and had a clear perforation of the tympanic membrane. Eligible patients were proven antibiotic therapy resistant, defined as having received adequate treatment for CSOM for at least 2 periods of in total ≥ 6 weeks within the past year and the last treatment period having occurred within the last 6 months before screening.

A maximum of 52 subjects was planned to be included, 26 in each treatment group. A planned interim analysis was scheduled to be executed after 26 subjects had completed the week 12 visit. At the time of interim analysis, the week 12 data of 30 subjects were available. Because the formal stopping criteria for efficacy were met due to a large difference in efficacy between treatment groups, further accrual in the study was discontinued. These data present the safety and confirmatory efficacy results of all subjects treated in the study.

Subjects were randomised to be treated with eardrops containing OP-145 (0.5 mg/ml; active treatment) or consisting of vehicle only (placebo). The eardrops were to be applied twice a day for 2 weeks. Subjects were to attend the clinic at screening (week 0) and in weeks 1, 2, 4, 8 & 12.

The treatment was regarded a success if an improvement of ≥ 2 points was observed at one or more otoscopic inspections in the following score:

- 0: flat, dry mucosa of the middle ear
- 1: flat, discharging mucosa of the middle ear
- 2: thickened, polypoid, dry or discharging mucosa of the middle ear
- 3: thickened, polypoid middle ear mucosa with viscous mucosal discharge

In addition, the following quality of life (QoL) questionnaires were completed: the SF-36, the chronic ear survey (CES) and the Brief Illness Perception Questionnaire (IPQ-b). These assessments were included as pilot for further clinical development, since the present study was not powered to detect effects on QoL.

To assess safety, the following assessments were done: recording of AEs and concomitant medication, laboratory tests (specific peptide antibodies and general hematology), swabs from the middle ear and throat for bacterial culture, audiometry (including high frequency audiometry).

## SUBJECTS: BASELINE DEMOGRAPHICS

The majority of the subjects in the intention-to-treat (ITT) population were males, i.e. 71%. In the OP-145 group, the male to female ratio was 53:47, and in the placebo group this ratio was 88:12. Mean (range) age was 65 (44-82) years; mean time since initial diagnosis was 18 (1-60) years. Similar results were obtained for the per protocol (PP) population. There were no apparent differences between treatment groups with respect to age and duration of disease. All subjects completed treatment as planned.

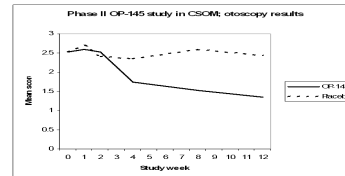
Variable	Statistic	OP-145 (n=17)	Placebo (n=17)	Overall (n=34)
Gender: Male	n (%)	9 (53)	15 (88)	24 (71)
	Female	8 (47)	2 (12)	10 (29)
Age (years)	Mean±SEM	65±2.9	65±2.9	65±1.8
	Median	68	63	68
Time since diagnosis (years)	Mean±SEM	21±4.9	16±4.0	18±3.2
	Median	10	7	10
	Range	1-60	1-50	1-60

## RESULTS: EFFICACY

Topical treatment with OP-145 resulted in a significant improvement in otoscopic inflammation and infection scoring, compared to placebo. The treatment was a success for 47% of the subjects in the OP-145 group, while this was the case for only 6% of the subjects in the placebo group (ITT analysis). The difference was statistically significant, p=0.017 for the ITT and p=0.012 for the PP analysis (Fisher exact test).

Treatment success	ITT Analysis				PP Analysis			
	OP-145 (n=17)		Placebo (n=17)		OP-145 (n=12)		Placebo (n=14)	
	n	(%)	n	(%)	n	(%)	n	(%)
Yes	8	47	1	6	7	58	0	0
No	9	53	16	94	5	42	14	100

The distribution of baseline otoscopic scores was the same in the two treatment groups, both resulting in 71% of the subjects having a score of 3 and none of the subjects having a score of 0 at baseline. From week 4 onwards, a difference in score distribution was apparent between treatment groups, with an outspoken decline of otoscopic scores in the active treatment group, whereas no essential change was noted in the placebo group.



As anticipated for the small sample size, the SF-36 and IPQ-b analyses did not show any relation between QoL scores and treatment, nor any correlation between QoL scores and the efficacy parameters themselves. The single question added to the CES "Do you think the treatment was effective" reached statistical significance in favor of the experimental arm.

## RESULTS: SAFETY

Topical OP-145 proved to be well tolerated. Ten subjects of the OP-145 group (59%) and 14 subjects of the placebo group (84%) experienced in total 37 adverse events (AEs) and in 2 (12%) and 4 (24%) subjects, respectively, one of these events were considered (possibly or probably) treatment-related. These 6 study treatment-related AEs, one occurring in one subject each, concerned middle ear disorders, infections and infestations affecting the middle ear, and headache.

Parameter	OP-145 (n=17)		Placebo (n=17)	
	n	%	n	%
Subjects with ≥1 AE	10	59	14	84
Subjects with ≥1 treatment-related AE	2	12	4	24
Subjects with ≥1 SAE	1	6	2	12
Subjects with ≥1 treatment-related SAE	0	0	0	0

1: arrhythmia of severe intensity in Week 8; recovered  
2: food poisoning of moderate intensity in Week 12; recovered  
3: treatment ischemic attack of mild intensity in Week 12; recovered

Similar AEs were reported for the two treatment groups in similar frequencies. Ear disorders and infections and infestations were the most frequently affected system organ classes, in 26% of the subjects each.

System Organ Class Preferred Term	OP-145 (n=17)		Placebo (n=17)		Total (n=34)	
	n	%	n	%	n	%
Any SDC	2	12	4	24	6	18
Any subject with AE	10	59	14	84	24	71
Ear and labyrinth disorders	0	0	1	5.9	1	2.9
Ear canal stenosis	0	0	1	5.9	1	2.9
Ear pain	1	5.9	0	0	1	2.9
Otitis externa	1	5.9	0	0	1	2.9
Otitis media	0	0	1	5.9	1	2.9
Infections and infestations	0	0	1	5.9	1	2.9
Nervous system disorders	0	0	1	5.9	1	2.9
Headache	0	0	1	5.9	1	2.9

All AEs were of mild to moderate intensity, except cardiac arrhythmia, which was severe and was reported as an SAE. In total 3 subjects experienced one SAE each, 1 subject in the OP-145 group (cardiac arrhythmia) and 2 subjects in the placebo group (food poisoning and transient ischemic attack). All SAEs had occurred > 28 days after last study drug administration and were considered to be unlikely related to study drug.

In general, small clinically insignificant changes from baseline were observed in hematology parameters. Variable decreases in mean neutrophil and lymphocyte counts were observed in the OP-145 treatment group. No statistically significant differences between groups were observed. No specific anti-OP-145 antibodies were detected at baseline and at 6 weeks after the last drug application. There were no other findings of clinical relevance with respect to laboratory assessments or other physical examinations, including audiometry.

## CONCLUSIONS

This double-blind placebo-controlled study evaluated topical ear drop treatment with the peptide OP-145 in patients with a mean duration of 18 years of CSOM since diagnosis. A statistically significant higher efficacy was achieved in the OP-145 group, with 47% of patients showing treatment success versus 6% on placebo (ITT analysis; p=0.017, Fisher exact test).

Topical OP-145 was safe and well tolerated. Similar AEs were reported for active treatment and placebo and in similar frequencies. Most AEs were disease-related and consisted of middle ear disorders or infections and infestations. Six AEs were considered study treatment-related, 2 AEs in the OP-145 group and 4 AEs in the placebo group. There were no SAEs within 28 days after the last drug application.

No specific antibodies to OP-145 were detected, and there were no other findings of clinical relevance with respect to safety assessments, including audiometry.

The affirmative outcome of this clinical proof-of-concept trial with OP-145 in CSOM supports further clinical development in this indication, as well as exploratory development in other chronic infectious disease indications.