SYNOPSIS OF CLINICAL STUDY REPORT **according to ANNEX I ICH E3**

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

Title of study:

ACEMg Mediated Hearing Preservation in Cochlear Implant Patients Receiving Different Electrode Lengths (EudraCT-No.: 2012-005002-22)

Protocol version 1.0, 02.07.2013

Protocol version 2.0, 16.04.2014

Protocol version 3.0, 19.08.2014

Final protocol version 4.0, 11.05.2015

Investigators:

Prof. Prof. h. c. Dr. med. Thomas Lenarz (Principal Investigator)

Dr. med. Nils Kristian Prenzler (Substitute)

Study coordination:

Dr. med. vet. Verena Scheper

Study centre(s):

Hannover Medical School, Department of Otorhinolaryngology, Carl-Neuberg-Str. 1, 30625 Hannover, Germany

Publication (reference):

1. Scheper V, Leifholz M, von der Leyen H, Keller M, Denkena U, Koch A, Karch A, Miller J, Lenarz T: ACEMg-mediated hearing preservation in cochlear implant patients receiving different electrode lengths (PROHEARING): study protocol for a randomized controlled trial, Trials, 2016 Aug 8; 17:394. doi: 10.1186/s13063-016-1526-7
2. Paper in preparation

Studied period (years): date of first enrolment: 11.03.2014 date of last completed: 21.07.2016 early termination: 14.09.2016	**Phase of development:** Phase II

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

Objectives:

Primary Objective:
The primary objective is to demonstrate that ACEMg is more efficacious than placebo in preserving residual hearing during cochlear implantation by comparing the hearing loss after 3 months at 500 Hz in air conducted pure tone audiometry.

Key Secondary Objectives:

- to investigate the drug effect over time (hearing loss in ACEMg compared to Placebo at 500 Hz 6, 9 and 12 months post First Fitting)
- to compare ACEMg and Placebo at different frequencies of pure tone audiometry (125, 250 and 750 Hz, 1, 1.5, 2, 3, 4, 6 and 8 kHz) over time (month 3, 6, 9 and 12 post First Fitting)
- to compare efficacy by means of speech perception, functional hearing and impedances
- to evaluate the effect of electrode length on hearing loss

Methodology:

Single center, randomized, placebo-controlled, double-blind phase II clinical trial

Number of patients (planned and analysed):

Planned:

To be allocated to trial: n=70 each treatment group

To be analysed: n=140 in total

Analysed:

Randomised: total n=51, Placebo group n=25 , ACEMg group n=26

The recruitment had to be stopped due to the fact that the study medication reached its end of stability. A new formulation of the study medication was approved by the BfArM, had been manufactured as batch, but was not released.

Patient 01-033 was randomized to ACEMg, but didn´t receive the allocated treatment due to post-randomization safety concerns. This patient is excluded from the ITT-population and the safety-population.

Patient 01-048 was randomized to placebo and received the allocated treatment, but surgery was not completed due to a cardiac arrest during surgery. This patient was excluded from the ITT-population, but included in the safety-population.

In primary analysis population (ITT-population): n=49 (Placebo group n=24 , ACEMg group n=25)

In safety population: n=50 (Placebo group n=25 , ACEMg group n=25)

SYNOPSIS OF CLINICAL STUDY REPORT **according to ANNEX I ICH E3**

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

Diagnosis and main criteria for inclusion:

Cochlear implant patients in whom a cochlear implant preserving residual hearing is medically indicated:

1. 18 years of age or older
2. No or little benefit of conventional hearing aid, defined as preoperative auditory speech understanding of less or equal 60% in Freiburger monosyllables at 65 dB SPL, best aided in the ear to be implanted
3. Residual hearing better or equal than 85 dB HL at 125, 90 dB HL at 250 Hz and better or equal than 95 dB HL at 500 Hz in the ear to be implanted
4. Ability to understand the study procedures, possible risks and benefits, and to give informed consent
5. Informed Consent is signed
6. Patients must agree not to use daily vitamin preparations containing vitamin A, C or E or magnesium during the course of the study, and beginning at least 48 hours prior to first intake of the study medication
7. Female patients ≥50 years of age at the day of inclusion who have been postmenopausal since at least 1 year
   OR
   female patients who have a negative hCG serum pregnancy test and meet one or more of the following criteria:
   - 6 weeks after surgical sterilization by bilateral tubal ligation or bilateral ovariectomy with or without hysterectomy
   - Using proven oral, injected or implanted hormonal contraceptive methods
   - Intrauterine Device (IUD) or intrauterine system (IUS)
   - Barrier methods: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide (foam / gel / film / cream / suppository)
   - Male sterilisation (if the absence of sperm in the ejaculate is documented. For female participants the vasectomized male partner should be the sole sexual partner for that subject)
   - True abstinence (Periodic abstinence and interruptus are not acceptable methods of contraception)
   - Only female sexual partners

Test product, dose and mode of administration, batch number:

ACEMg

2 times 3 pills per day

Dosage per pill:
Vitamin E acetate: 44.5 mg
Beta-carotene: 3 mg

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

Ascorbic acid: 83.33 mg
Magnesium: 52.5 mg

Oral administration

Batch number:
Manufacturing lot 3107655R was the source for packaging lots to be used in the clinical trial, manufactured on January 17th, 2013.

Duration of treatment:

Per patient: 105 days + 13 months follow-up

Reference therapy, dose and mode of administration, batch number:

Placebo

2 times 3 pills per day

Oral administration

Batch number:
Manufacturing batch 3107656R/packaging batch 3108915

Endpoints/Outcomes

Primary Endpoint:

1) Hearing loss at the implanted ear at 500 Hz 3 months post First Fitting (hearing loss = 3 months post First Fitting threshold minus 1-2 days pre-operatively threshold) measured by air conducted pure tone audiometry measured in ear with cochlear implant.

   Residual hearing is improved if and only if change from baseline value (post-pre) is negative.

Key Secondary Endpoint(s):

1) Hearing loss measured by pure tone audiometry at 500 Hz 6, 9 and 12 months post First Fitting
2) Hearing loss measured by pure tone audiometry for other frequencies (125, 250 and 750 Hz, 1, 1.5, 2, 3, 4, 6 and 8 kHz) over time (month 3, 6, 9 and 12 post First Fitting)
3) Speech perception by OLSA, month 12
4) Functional Hearing questionnaire NCIQ, month 3 and 12
5) Impedances [Ω] at all time points (post-operative)
6) Occurrence of Tinnitus: questionnaire at all time points

Safety Endpoints:

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

1) All SAEs

All AEs leading to discontinuation of IMP intake

Statistical methods:

Efficacy: The type I error is set to 5% (two-sided).

Primary Endpoint:

The primary analysis is conducted on the intention-to-treat (ITT) population.
The primary endpoint reduction in air conducted residual hearing at 500 Hz (change from baseline: 3 months post First Fitting minus baseline) is analysed with an ANCOVA including the treatment (ACEMg or placebo), the baseline residual hearing, the surgeon (with each surgeon as distinct levels) and the anticipated electrode length (with levels 'Flex 20', 'Flex 24' and 'Flex 28') as covariates. Additionally a covariate about the administered formulation of the medication was planned to be included (pills or softgel capsules).

Based on the blinded review the following post-hoc changes have been conducted:

1. Since no patient has been treated with ACEMg administered in softgel formular, the formulation was not included as a covariate in the analysis model.
2. Due to the high number of surgeries conducted by surgeon 2 and the small number of surgeries conducted by all other surgeons, surgeon was not included as a covariate with all surgeons as categories but was included as a covariate with categories 'surgeon 2' and 'other surgeon'.

A smaller reduction in hearing loss due to ACEMg is proven, if the *p*-value for the treatment effect of the ANCOVA-model is less than the two-sided type I error of 5% and the effect estimate for difference in change from baseline (ACEMg minus Placebo) is negative, or, equivalent, if the upper bound of the ANCOVA-derived two-sided 95% confidence interval of the difference in change from baseline means (ACEMg minus placebo) is less than 0.
If the patient reaches the upper air conducted detection limit of the audiometer (110 dB) without hearing, the measurement is set to 120 dB. Missing values was replaced by worst possible value (that means upper detection limit +10 dB).

Key Secondary Endpoints:

In secondary analyses, differences between ACEMg and placebo in speech perception, NCIQ, impedances and tinnitus are tested with appropriate statistical tests adjusted for the same covariates as the primary analysis (but no adjustment for baseline values in impedances). Differences of the treatment effects among the electrode length are evaluated descriptively.

Safety:
Frequencies of (serious) adverse events are listed for each treatment group separately. Differences between treatment groups are analysed in a descriptive manner.

Primary analysis population characteristics

In the ITT-population a total of 49 patients (ACEMg group: n=25; Placebo group: n=24) are analyzed.

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

In the ITT-population 19/49=38.8% are male (ACEMg group: 10/25=40%; Placebo group: 9/24=37.5%). Mean age is 55.47 (±13.70) years (ACEMg group: 53.64 (±16.85); Placebo group: 57.38 (±9.37)).The difference in mean age of 3.74 years with two-sided 95% confidence interval of [-4.11; 11.58] and t-test derived p-value of 0.3413 is not significantly different from 0.
Surgery was planned in 17/49=34.7% of the patients in the left ear (ACEMg group: 11/25=44%; Placebo group: 6/24=25%) and surgery was conducted in 18/49=36.7% of the patients in the left ear (ACEMg group: 11/25=44%; Placebo group: 7/24=29.2%). In 4/49=8.2% of the patients a Flex 20 electrode was planned, in 13/49=26.5% a Flex 24 electrode was planned and in 32/49=65.3% a Flex 28 electrode was planned. (ACEMg group: 2/25=8%, 7/25=28% and 16/25=64%; Placebo group: 2/24=8.3%, 6/24=25%, 16/24=66.7%).
In contrast to the study protocol, for patient 01-018 (Placebo) and 01-049 (ACEMg) a Flex 16 was used; in the study data, these patients are included in the Flex 20 group for used electrode length, now comprising all patients with electrode Flex 16 or Flex 20. This categorization is used in all analyses. Given this categorization the used electrode is distributed as follows: In 7/49=14.3% of the patients a Flex 20 electrode was used, in 10/49=20.4% a Flex 24 electrode was used and in 32/49=65.3% a Flex 28 electrode was used. (ACEMg group: 3/25=12%, 6/25=24% and 16/25=64%; Placebo group: 4/24=16.7%, 4/24=16.7%, 16/24=66.7%). Surgery was conducted by surgeon 2 in 29/49 = 59.2% of the patients and another surgeon in 20/49=40.8% of the patients (ACEMg group: 16/25=64% and 9/25=36%; Placebo group: 13/24=54.2% and 11/24=45.8%).
For more detailed descriptive analyses of the population characteristics see Table 5 in the appendix.

Efficacy results:

Hearing loss in air conducted audiometry measured at 500 Hz 3 months post first fitting compared to baseline in the Placebo group (Hearing threshold 3 months post first fitting – baseline) is 30.21 (±15.84) dB and 26.00 (±17.56) dB in the ACEMg group. The primary analysis model effect estimate for the difference in hearing loss (ACEMg – Placebo) is -4.15 with 95% confidence interval [-12.95, 4.65] and p-value 0.3468. Thus, superiority of ACEMg over Placebo could not be demonstrated.
Detailed results of the primary analysis are given in Table 6, Table 7 and Table 8 in the appendix of the synopsis: Table 6 states descriptive statistics, Table 7 gives the effect estimates derived from the primary analysis model and the results of the test of an overall effect of the factor electrode length are given in Table 8.

Safety results:

There is no increased risk of AEs or SAEs in the ACEMg group compared to the Placebo group. No AE resulting in death and consequently no AE with CTC grade 5 occurred in this study.

A summary of the AE categorized by CTC grade is given in the following tables by treatment group analyzing number of patients with AEs and number of events:

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

Table 1: CTC grades of AEs by patients

Adverse events by CTC grade - safety population - Number of patients

	Treatment	
	Placebo N=25	**ACEMg N=25**
Number of patients with at least one AE	11 (44.0%)	8 (32.0%)
1	7 (28.0%)	6 (24.0%)
2	1 (4.0%)	1 (4.0%)
3	3 (12.0%)	1 (4.0%)
4	1 (4.0%)	-

Table includes each adverse event term only once per patient. Percentages are calculated using the total number of patients per treatment group as the denominator.

Table 2: CTC grades of AEs by events

Adverse events by CTC grade - safety population - Number of events

	Treatment	
	Placebo N=25	**ACEMg N=25**
Total number of AE	18	11
1	12 (66.7%)	8 (72.7%)
2	1 (5.6%)	2 (18.2%)
3	4 (22.2%)	1 (9.1%)
4	1 (5.6%)	-

Table includes all adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

A summary of the SAEs categorized by CTC grade is given in the following tables by treatment group analysing number of patients with AEs and number of events:

Table 3: CTC grades of SAEs by patients

Serious adverse events by CTC grade - safety population - Number of patients

	Treatment	
	Placebo N=25	**ACEMg N=25**
Number of patients with at least one SAE	7 (28.0%)	3 (12.0%)
1	3 (12.0%)	1 (4.0%)
2	1 (4.0%)	1 (4.0%)
3	3 (12.0%)	1 (4.0%)
4	1 (4.0%)	-

Table includes each SAE term only once per patient. Percentages are calculated using the total number of patients per treatment group as the denominator.

Table 4: CTC grades of SAEs by events

Serious adverse events by CTC grade - safety population - Number of events

	Treatment	
	Placebo N=25	**ACEMg N=25**
Total number of SAE	11	3
1	5 (45.5%)	1 (33.3%)
2	1 (9.1%)	1 (33.3%)
3	4 (36.4%)	1 (33.3%)
4	1 (9.1%)	-

Table includes all SAEs. Percentages are calculated using the total number of events per treatment group as the denominator.

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

Detailed information on the AEs is given in the appendix in Table 9 to Table 18 showing AEs of each CTC grade by treatment group and Table 19 giving the listing of all AEs with detailed information.

Conclusion

No increased risk compared to placebo could be observed in ACEMg treated patients.
The mean hearing loss in air conducted audiometry measured at 500 Hz 3 months post first fitting compared to baseline in the Placebo group is 30.21 (±15.84) dB whereas in the ACEMg group the hearing loss is 26.00 (±17.56) dB. The study did not reach the recruitment goal, the number of included patients was 51/140=36% of the planned sample size. In this trial superiority of ACEMg compared to Placebo in reducing hearing loss could not be demonstrated (primary analysis model estimate for mean difference ACEMg – Placebo: -4.15; 95% confidence interval [-12.95, 4.65]; p=0.3468).

Date of report

25.08.2017

Prof. Prof. Dr. Th. Lenarz	Prof. Dr. Baum
Dept. of Otorhinolaryngology, MHH	Hannover Medical School, Sponsor
Prof. Dr. D. Stichtenoth	Prof. Dr. A. Koch
Dept. of Clinical Pharmacology	Dept. of Biostatistics

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

1 Appendix of Synopsis

Table 5: Baseline-characteristic - ITT-set

	Treatment		
	Placebo N=24	**ACEMg N=25**	**Total N=49**
Sex			
male	9 (37.5%)	10 (40.0%)	19 (38.8%)
female	15 (62.5%)	15 (60.0%)	30 (61.2%)
p-VALUE (CHI²)			0.8575
Age			
N	24	25	49
MISSING	0	0	0
MEAN	57.38	53.64	55.47
STD	9.37	16.85	13.70
MIN	40	26	26
MEDIAN	56	50	55
MAX	81	80	81
95% CI MEAN	[53.42 ; 61.33]	[46.68 ; 60.60]	[51.53 ; 59.40]
MEAN DIFFERENCE			3.74
95% CI MEAN DIFFERENCE			[-4.11 ; 11.58]
p-VALUE (T-TEST)			0.3413
Planned ear			
Left	6 (25.0%)	11 (44.0%)	17 (34.7%)
Right	18 (75.0%)	14 (56.0%)	32 (65.3%)
p-VALUE (CHI²)			0.1625
Planned length of electrode			
Flex 20	2 (8.3%)	2 (8.0%)	4 (8.2%)
Flex 24	6 (25.0%)	7 (28.0%)	13 (26.5%)
Flex 28	16 (66.7%)	16 (64.0%)	32 (65.3%)
p-VALUE (CHI²)			0.9721
Treated ear			
Left	7 (29.2%)	11 (44.0%)	18 (36.7%)
Right	17 (70.8%)	14 (56.0%)	31 (63.3%)

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

	Treatment		
	Placebo N=24	**ACEMg N=25**	**Total N=49**
p-VALUE (CHI²)			0.2816
Used electrode length			
Flex 20	4 (16.7%)	3 (12.0%)	7 (14.3%)
Flex 24	4 (16.7%)	6 (24.0%)	10 (20.4%)
Flex 28	16 (66.7%)	16 (64.0%)	32 (65.3%)
p-VALUE (CHI²)			0.7700
Surgeon			
Surgeon 1	2 (8.3%)	1 (4.0%)	3 (6.1%)
Surgeon 2	13 (54.2%)	16 (64.0%)	29 (59.2%)
Surgeon 3	2 (8.3%)	0 (0.0%)	2 (4.1%)
Surgeon 4	2 (8.3%)	3 (12.0%)	5 (10.2%)
Surgeon 7	1 (4.2%)	2 (8.0%)	3 (6.1%)
Surgeon 9	1 (4.2%)	0 (0.0%)	1 (2.0%)
Surgeon 10	1 (4.2%)	3 (12.0%)	4 (8.2%)
Surgeon 11	1 (4.2%)	0 (0.0%)	1 (2.0%)
Surgeon 12	1 (4.2%)	0 (0.0%)	1 (2.0%)
p-VALUE (CHI²)			0.5195
surgeon (categorized)			
Surgeon 2	13 (54.2%)	16 (64.0%)	29 (59.2%)
Other surgeon	11 (45.8%)	9 (36.0%)	20 (40.8%)
p-VALUE (CHI²)			0.4839

Table 6: Descriptive analysis of the primary endpoint with imputation of not measurable values – ITT-set

Hearing loss 3 months post fitting compared to baseline - ITT set

Subgroup	N	Mean	Std. Dev.	Minimum	Median	Maximum
Placebo	24	30.21	15.84	5.00	25.00	75.00
ACEMg	25	26.00	17.56	-10.00	25.00	55.00
Flex 20	4	11.25	12.50	5.00	5.00	30.00

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

Hearing loss 3 months post fitting compared to baseline - ITT set

Subgroup	N	Mean	Std. Dev.	Minimum	Median	Maximum
Flex 24	13	32.69	17.87	10.00	35.00	75.00
Flex 28	32	28.28	15.74	-10.00	25.00	55.00
Surgeon 2	29	26.90	14.04	-10.00	25.00	50.00
other Surgeon	20	29.75	20.23	5.00	22.50	75.00

Table 7: Results of primary analysis model

Hearing loss 3 months post fitting compared to baseline - ITT set

	Estimate	Standard Error	p-Value	Lower CL	Upper CL
ACEMG - Placebo	-4.15	4.3641140	0.3468	-12.95	4.65
Surgeon 2 - other surgeon	-2.03	4.7141858	0.6688	-11.54	7.48
Flex 24 - Flex 20	35.32	9.9561928	0.0010	15.24	55.40
Flex 28 - Flex 20	42.14	12.2218146	0.0013	17.49	66.79
Flex 28 - Flex 24	6.82	6.8177036	0.3231	-6.93	20.56
Baseline	-0.48	0.1849977	0.0136	-0.85	-0.10

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

Table 8: Results of primary analysis model for overall electrode effect

Hearing loss 3 months post fitting compared to baseline - ITT set

	Degrees of freedom	Contrast sum of squares	Mean sum of squares	F-value	p-value
Electrode effect	2	3089.803194	1544.901597	6.70	0.0029

Table 9: AEs with CTC grade 1 by patients

All adverse events with CTC grade 1 - safety population - Number of patients

	Treatment	
Type of AE Specification	**Placebo N=25**	**ACEMg N=25**
Number of patients with at least one AE	7 (28.0%)	6 (24.0%)
Ear and labyrinth disorders	-	1 (4.0%)
Vertigo	-	1 (4.0%)
Gastrointestinal disorders	6 (24.0%)	5 (20.0%)
Constipation	1 (4.0%)	-
Diarrhoea	3 (12.0%)	-
Flatulence	1 (4.0%)	-
Gastric disorder	-	1 (4.0%)
Gastrointestinal disorder	1 (4.0%)	-
Gingival bleeding	-	1 (4.0%)
Nausea	3 (12.0%)	3 (12.0%)
Vomiting	1 (4.0%)	1 (4.0%)
General disorders and administration site conditio	-	1 (4.0%)
Chest pain	-	1 (4.0%)
Investigations	1 (4.0%)	-
Blood thyroid stimulating hormone increased	1 (4.0%)	-
Skin and subcutaneous tissue disorders	1 (4.0%)	-
Alopecia	1 (4.0%)	-

Table includes each adverse event term only once per patient. Percentages are calculated using the total number of patients per treatment group as the denominator.

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

Table 10: AEs with CTC grade 1 by events

All adverse events with CTC grade 1 - safety population - Number of events

	Treatment	
Type of AE Specification	**Placebo N=25**	**ACEMg N=25**
Total number of AE	12	8
Ear and labyrinth disorders	-	1 (12.5%)
Vertigo	-	1 (12.5%)
Gastrointestinal disorders	10 (83.3%)	6 (75.0%)
Constipation	1 (8.3%)	-
Diarrhoea	3 (25.0%)	-
Flatulence	1 (8.3%)	-
Gastric disorder	-	1 (12.5%)
Gastrointestinal disorder	1 (8.3%)	-
Gingival bleeding	-	1 (12.5%)
Nausea	3 (25.0%)	3 (37.5%)
Vomiting	1 (8.3%)	1 (12.5%)
General disorders and administration site conditio	-	1 (12.5%)
Chest pain	-	1 (12.5%)
Investigations	1 (8.3%)	-
Blood thyroid stimulating hormone increased	1 (8.3%)	-
Skin and subcutaneous tissue disorders	1 (8.3%)	-
Alopecia	1 (8.3%)	-

Table includes all adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

Table 11: AEs with CTC grade 2 by patients

All adverse events with CTC grade 2 - safety population - Number of patients

	Treatment	
Type of AE Specification	**Placebo N=25**	**ACEMg N=25**
Number of patients with at least one AE	1 (4.0%)	1 (4.0%)
Ear and labyrinth disorders	-	1 (4.0%)
Ear pain	-	1 (4.0%)
Vascular disorders	1 (4.0%)	-
Hypertension	1 (4.0%)	-

Table includes each adverse event term only once per patient. Percentages are calculated using the total number of patients per treatment group as the denominator.

Table 12: AEs with CTC grade 2 by events

All adverse events with CTC grade 2 - safety population - Number of events

	Treatment	
Type of AE Specification	**Placebo N=25**	**ACEMg N=25**
Total number of AE	1	2
Ear and labyrinth disorders	-	2 (100.0%)
Ear pain	-	2 (100.0%)
Vascular disorders	1 (100.0%)	-
Hypertension	1 (100.0%)	-

Table includes all adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

Table 13: AEs with CTC grade 3 by patients

All adverse events with CTC grade 3 - safety population - Number of patients

	Treatment	
Type of AE Specification	**Placebo N=25**	**ACEMg N=25**
Number of patients with at least one AE	3 (12.0%)	1 (4.0%)
Ear and labyrinth disorders	1 (4.0%)	-
Tympanic membrane perforation	1 (4.0%)	-
Injury, poisoning and procedural complications	1 (4.0%)	-
Upper limb fracture	1 (4.0%)	-
Neoplasms benign, malignant and unspecified (incl	-	1 (4.0%)
Breast cancer	-	1 (4.0%)
Nervous system disorders	2 (8.0%)	-
Cerebrospinal fluid leakage	1 (4.0%)	-
Cerebrovascular accident	1 (4.0%)	-

Table includes each adverse event term only once per patient. Percentages are calculated using the total number of patients per treatment group as the denominator.

Table 14: AEs with CTC grade 3 by events

All adverse events with CTC grade 3 - safety population - Number of events

	Treatment	
Type of AE Specification	**Placebo N=25**	**ACEMg N=25**
Total number of AE	4	1
Ear and labyrinth disorders	1 (25.0%)	-
Tympanic membrane perforation	1 (25.0%)	-
Injury, poisoning and procedural complications	1 (25.0%)	-
Upper limb fracture	1 (25.0%)	-

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

All adverse events with CTC grade 3 - safety population - Number of events

	Treatment	
Type of AE Specification	**Placebo N=25**	**ACEMg N=25**
Neoplasms benign, malignant and unspecified (incl	-	1 (100.0%)
Breast cancer	-	1 (100.0%)
Nervous system disorders	2 (50.0%)	-
Cerebrospinal fluid leakage	1 (25.0%)	-
Cerebrovascular accident	1 (25.0%)	-

Table includes all adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

Table 15: AEs with CTC grade 4 by patients

All adverse events with CTC grade 4 - safety population - Number of patients

	Treatment	
Type of AE Specification	**Placebo N=25**	**ACEMg N=25**
Number of patients with at least one AE	1 (4.0%)	0
Cardiac disorders	1 (4.0%)	-
Cardiac arrest	1 (4.0%)	-

Table includes each adverse event term only once per patient. Percentages are calculated using the total number of patients per treatment group as the denominator.

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

Table 16: AEs with CTC grade 4 by events

All adverse events with CTC grade 4 - safety population - Number of events

	Treatment	
Type of AE Specification	**Placebo N=25**	**ACEMg N=25**
Total number of AE	1	0
Cardiac disorders	1 (100.0%)	-
Cardiac arrest	1 (100.0%)	-

Table includes all adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

Table 17: All AEs by patients

All adverse events - safety population - Number of patients

	Treatment	
Type of AE Specification	**Placebo N=25**	**ACEMg N=25**
Number of patients with at least one AE	11 (44.0%)	8 (32.0%)
Cardiac disorders	1 (4.0%)	-
Cardiac arrest	1 (4.0%)	-
Ear and labyrinth disorders	1 (4.0%)	2 (8.0%)
Ear pain	-	1 (4.0%)
Tympanic membrane perforation	1 (4.0%)	-
Vertigo	-	1 (4.0%)
Gastrointestinal disorders	6 (24.0%)	5 (20.0%)
Constipation	1 (4.0%)	-
Diarrhoea	3 (12.0%)	-
Flatulence	1 (4.0%)	-
Gastric disorder	-	1 (4.0%)

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

All adverse events - safety population - Number of patients

	Treatment	
Type of AE Specification	**Placebo N=25**	**ACEMg N=25**
Gastrointestinal disorder	1 (4.0%)	-
Gingival bleeding	-	1 (4.0%)
Nausea	3 (12.0%)	3 (12.0%)
Vomiting	1 (4.0%)	1 (4.0%)
General disorders and administration site conditio	-	1 (4.0%)
Chest pain	-	1 (4.0%)
Injury, poisoning and procedural complications	1 (4.0%)	-
Upper limb fracture	1 (4.0%)	-
Investigations	1 (4.0%)	-
Blood thyroid stimulating hormone increased	1 (4.0%)	-
Neoplasms benign, malignant and unspecified (incl	-	1 (4.0%)
Breast cancer	-	1 (4.0%)
Nervous system disorders	2 (8.0%)	-
Cerebrospinal fluid leakage	1 (4.0%)	-
Cerebrovascular accident	1 (4.0%)	-
Skin and subcutaneous tissue disorders	1 (4.0%)	-
Alopecia	1 (4.0%)	-
Vascular disorders	1 (4.0%)	-
Hypertension	1 (4.0%)	-

Table includes each adverse event term only once per patient. Percentages are calculated using the total number of patients per treatment group as the denominator.

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

Table 18: All AEs by events

All adverse events - safety population - Number of events

Type of AE Specification	Treatment Placebo N=25	 ACEMg N=25
Total number of AE	18	11
Cardiac disorders	1 (5.6%)	-
Cardiac arrest	1 (5.6%)	-
Ear and labyrinth disorders	1 (5.6%)	3 (27.3%)
Ear pain	-	2 (18.2%)
Tympanic membrane perforation	1 (5.6%)	-
Vertigo	-	1 (9.1%)
Gastrointestinal disorders	10 (55.6%)	6 (54.5%)
Constipation	1 (5.6%)	-
Diarrhoea	3 (16.7%)	-
Flatulence	1 (5.6%)	-
Gastric disorder	-	1 (9.1%)
Gastrointestinal disorder	1 (5.6%)	-
Gingival bleeding	-	1 (9.1%)
Nausea	3 (16.7%)	3 (27.3%)
Vomiting	1 (5.6%)	1 (9.1%)
General disorders and administration site conditio	-	1 (9.1%)
Chest pain	-	1 (9.1%)
Injury, poisoning and procedural complications	1 (5.6%)	-
Upper limb fracture	1 (5.6%)	-
Investigations	1 (5.6%)	-
Blood thyroid stimulating hormone increased	1 (5.6%)	-
Neoplasms benign, malignant and unspecified (incl	-	1 (9.1%)
Breast cancer	-	1 (9.1%)
Nervous system disorders	2 (11.1%)	-
Cerebrospinal fluid leakage	1 (5.6%)	-
Cerebrovascular accident	1 (5.6%)	-

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

All adverse events - safety population - Number of events

	Treatment	
Type of AE Specification	**Placebo N=25**	**ACEMg N=25**
Skin and subcutaneous tissue disorders	1 (5.6%)	-
Alopecia	1 (5.6%)	-
Vascular disorders	1 (5.6%)	-
Hypertension	1 (5.6%)	-

Table includes all adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

Table 19: Listing of all AEs

CTC grade	Treatment	Patient	Highest population	Serious	SOC	PT	Outcome	Reporter causality to study drug	Action taken regarding study medication	Start date of AE	End date of AE	Duration of AE (in days)
1	ACEMg	01-011	PP	yes	General disorders and administration site conditions	Chest pain	completely recovered/back to baseline conditions	no	no action	19/08/2014	26/08/2014	7
		01-025	ITT	no	Gastrointestinal disorders	Nausea	completely recovered/back to baseline conditions	yes	withdrawn/stopped	21/08/2014	22/08/2014	1
		01-036	ITT	no	Gastrointestinal disorders	Nausea	completely recovered/back to baseline conditions	no	withdrawn/stopped	02/12/2014	08/12/2014	6
					Gastrointestinal disorders	Vomiting	completely recovered/back to baseline conditions	no	withdrawn/stopped	03/12/2014	08/12/2014	5
					Ear and labyrinth disorders	Vertigo	completely recovered/back to baseline conditions	no	withdrawn/stopped	02/12/2014	08/12/2014	6
		01-038	PP	no	Gastrointestinal disorders	Gastric disorder	completely recovered/back to baseline conditions	yes	withdrawn/stopped	16/01/2015	16/01/2015	0

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

CTC grade	Treatment	Patient	Highest population	Serious	SOC	PT	Outcome	Reporter causality to study drug	Action taken regarding study medication	Start date of AE	End date of AE	Duration of AE (in days)
		01-052	ITT	no	Gastrointestinal disorders	Gingival bleeding	completely recovered/back to baseline conditions	yes	withdrawn/stopped	07/03/2015	18/03/2015	11
		01-053	PP	no	Gastrointestinal disorders	Nausea	completely recovered/back to baseline conditions	yes	withdrawn/stopped	24/03/2015	24/03/2015	0
	Placebo	01-016	ITT	yes	Gastrointestinal disorders	Flatulence	completely recovered/back to baseline conditions	yes	withdrawn/stopped	26/06/2014	03/09/2014	69
					Gastrointestinal disorders	Nausea	completely recovered/back to baseline conditions	yes	withdrawn/stopped	26/08/2014	03/09/2014	8
		01-024	ITT	yes	Investigations	Blood thyroid stimulating hormone increased	completely recovered/back to baseline conditions	yes	withdrawn/stopped	16/10/2014	27/10/2014	11
		01-026	ITT	yes	Gastrointestinal disorders	Diarrhoea	completely recovered/back to baseline conditions	yes	withdrawn/stopped	25/09/2014	29/10/2014	34
					Skin and subcutaneous tissue disorders	Alopecia	completely recovered/back to baseline conditions	yes	withdrawn/stopped	25/09/2014	18/11/2014	54

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

CTC grade	Treatment	Patient	Highest population	Serious	SOC	PT	Outcome	Reporter causality to study drug	Action taken regarding study medication	Start date of AE	End date of AE	Duration of AE (in days)
		01-034	ITT	no	Gastrointestinal disorders	Diarrhoea	completely recovered/back to baseline conditions	yes	withdrawn/stopped	20/10/2014	23/10/2014	3
					Gastrointestinal disorders	Nausea	completely recovered/back to baseline conditions	yes	withdrawn/stopped	08/11/2014	10/11/2014	2
					Gastrointestinal disorders	Constipation	completely recovered/back to baseline conditions	no	withdrawn/stopped	08/11/2014	10/11/2014	2
		01-037	ITT	no	Gastrointestinal disorders	Gastrointestinal disorder	completely recovered/back to baseline conditions	no	withdrawn/stopped	11/12/2014	14/12/2014	3
		01-039	ITT	no	Gastrointestinal disorders	Diarrhoea	completely recovered/back to baseline conditions	yes	withdrawn/stopped	27/11/2014	03/12/2014	6
					Gastrointestinal disorders	Nausea	completely recovered/back to baseline conditions	yes	withdrawn/stopped	29/11/2014	03/12/2014	4
		01-055	PP	no	Gastrointestinal disorders	Vomiting	completely recovered/back to baseline conditions	yes	unknown	10/04/2015	10/04/2015	0

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

CTC grade	Treatment	Patient	Highest population	Serious	SOC	PT	Outcome	Reporter causality to study drug	Action taken regarding study medication	Start date of AE	End date of AE	Duration of AE (in days)
2	ACEMg	01-017	PP	no	Ear and labyrinth disorders	Ear pain	completely recovered/back to baseline conditions	no	withdrawn/stopped	10/07/2014	20/07/2014	10
				yes	Ear and labyrinth disorders	Ear pain	completely recovered/back to baseline conditions	no	no action	31/07/2014	05/08/2014	5
	Placebo	01-026	ITT	yes	Vascular disorders	Hypertension	recovered with sequel	no	withdrawn/stopped	25/09/2014	28/11/2014	64
3	ACEMg	01-060	ITT	yes	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer	not recovered (persistently not changing)	no	not applicable	22/06/2016	.	.
	Placebo	01-009	PP	yes	Injury, poisoning and procedural complications	Upper limb fracture	recovered with sequel	no	withdrawn/stopped	30/06/2014	30/06/2014	0
		01-010	ITT	yes	Nervous system disorders	Cerebrospinal fluid leakage	completely recovered/back to baseline conditions	no	withdrawn/stopped	11/05/2014	16/05/2014	5
					Ear and labyrinth disorders	Tympanic membrane perforation	completely recovered/back to baseline conditions	no	no action	06/05/2014	05/11/2014	183
		01-018	PP	yes	Nervous system disorders	Cerebrovascular accident	unknown	no	not applicable	.	.	.

SYNOPSIS OF CLINICAL STUDY REPORT **according to ANNEX I ICH E3**

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: ACEMg	Volume:	
Name of Active Ingredient: Micronutrient combination of (pro-)vitamins A (beta-carotene), C (magnesium ascorbate) and E (DL-α-tocopheryl acetate) together with magnesium (magnesium citrate, magnesium ascorbate, magnesium stearate)	Page:	

CTC grade	Treatment	Patient	Highest population	Serious	SOC	PT	Outcome	Reporter causality to study drug	Action taken regarding study medication	Start date of AE	End date of AE	Duration of AE (in days)
4	Placebo	01-048	Safety Population	yes	Cardiac disorders	Cardiac arrest	completely recovered/back to baseline conditions	no	withdrawn/stopped	29/01/2015	29/01/2015	0