Clinical trial results:
Adjunctive antimicrobial therapy of periodontitis: Long-term effects on disease progression and oral microbiological colonization

Summary

EudraCT number	2006-005854-61
Trial protocol	DE
Global end of trial date	31 December 2011

Results information

Result version number	v1 (current)
This version publication date	05 October 2019
First version publication date	05 October 2019

Trial information

Trial identification

Sponsor protocol code	KKS/MueParo/Antibiotics and Periodo

Additional study identifiers

ISRCTN number	ISRCTN64254080
ClinicalTrials.gov id (NCT number)	NCT00707369
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Muenster
Sponsor organisation address	Domagkstr. 5, Muenster, Germany, 48149
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 May 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2011
Global end of trial reached?	Yes
Global end of trial date	31 December 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The addressed research objectives are: (i) What is the size of the benefit of an adjunctive empiric antibiotic therapy compared to standard mechanical debridement and oral hygiene instructions in a representative sample of German periodontitis patients? (ii) Does the administration of the antibiotic therapy delay recurrence of periodontitis in the general population and in specific high risk groups (e.g. smokers) under standard supportive therapy? (iii) Is the presence of specific microbial complexes a useful predictor of outcome and recurrence of periodontitis? (iv) Does the administration of the antibiotic therapy affect the oral health related quality of life?

Protection of trial subjects:

In the proposed trial, control patients receive standard periodontal treatment and test patients standard therapy plus adjunctive antibiotics. In general, the side effects of these therapies are known and events causing early termination are extremely unlikely.
However, an early termination strategy is foreseen in the proposed trial. Early termination ("exit strategy") will depend on the incidence of "periodontal abscesses" as defined by Meng 1999, i.e., "localized purulent infection within the tissues adjacent to the periodontal pocket that may lead to destruction of periodontal ligament and alveolar bone". Periodontal abscesses represent a dental emergency situation in periodontal therapy. Such abscesses are most frequently seen in patients receiving inadequate periodontal therapy or in untreated patients. Teeth showing periodontal abscesses can be maintained over years if they are treated adequately (McLeod et al. 1997). Therefore, this parameter helps discover inadequate therapy throughout the study without causing irreversible harm (i.e., tooth loss) to the participants. During interim analysis the incidence of periodontal abscesses in both groups will be calculated. In case of a 50% difference (at least 20% of all patients in one group must suffer from this condition) between the groups, the trial will be terminated immediately.

Background therapy:

- Mechanical debridement
-Supportive periodontal therapy in 3-month intervals

Evidence for comparator:

Standard of care includes mechanical removal of the biofilm, i.e., initial subgingival debridement and lifelong supportive periodontal therapy. The outcome of mechanical therapy is variable and further disease progression may occur. Beyond this approach, patients might benefit from the adjunctive use of systemic antibiotics. Via saliva and serum, these agents may affect periodontal and intraoral sites inaccessible for mechanical therapy.
Although systemic antibiotics are frequently used therapeutic agents in dentistry, their prescription often is not evidence-based (Palmer et al. 2000). In two recent systematic reviews of the impact of various adjunctive antibiotic agents in periodontal therapy released by the European Federation of Periodontology (EFP, Herrera et al. 2002) and the American Academy of Periodontology (AAP, Haffajee et al. 2003), methodological weaknesses of existing studies were described. Due to various study designs, small sample sizes, mixed populations, use of weak parameters for disease progression determination, and short duration of the studies, definitive conclusions about the efficacy of adjunctive antimicrobial therapy have not yet been possible. Both reviews concluded that adjunctive antimicrobial therapy may offer a clinical benefit but further studies are needed.

Actual start date of recruitment	01 October 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 506
Worldwide total number of subjects	506
EEA total number of subjects	506

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	432
From 65 to 84 years	74
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

recruitment: October 2008-October 2009
Overall 3261 patients were screened, 1004 met the inclusion criteria, 461 declined to participate, and 506 were randomized.

Pre-assignment

Screening details:

All study centers (Departments of Periodontology of the Universities of Berlin (Humboldt), Dresden, Frankfurt, Gießen, Greifswald, Heidelberg, Münster (coordinating center), and Würzburg) have been selected with respect to their special expertise in the field of periodontology and their feasibility of adequate patient recruitment.
During one year

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	test group (antibiotics)

Arm description:

All patients receive routine supragingival and subgingival debridement with sonic/ultrasonic scalers using micro tips or hand instruments (curettes) under local anesthesia. Finally, polishing with an air powder device or pumice and rotating rubber cups is performed. Initial therapy is performed in two sessions on two consecutive days. After completion of mechanical debridement, patients receive an adjunctive antimicrobial therapy consisting of oral metronidazole 400mg and amoxicillin 500mg (three times daily, for seven days).

Arm type	Experimental
Investigational medicinal product name	Amoxicillin 3H2O 574 mg (Amoxicillin-ratiopharm 500mg®, Ratiopharm, Germany) and Metronidazole 400 mg (Flagyl® 400, Sanofi-Aventis, Germany)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients receive an adjunctive antimicrobial therapy consisting of oral metronidazole 400mg and amoxicillin 500mg (three times daily, for seven days)

Arm title	control group (placebo)

Arm description:

All patients receive routine supragingival and subgingival debridement with sonic/ultrasonic scalers using micro tips or hand instruments (curettes) under local anesthesia. Finally, polishing with an air powder device or pumice and rotating rubber cups is performed. Initial therapy is performed in two sessions on two consecutive days. After completion of mechanical debridement, patients receive two placebo drugs (three times daily, for seven days).

Arm type	Placebo

Investigational medicinal product name	Placebo P1 & P2 (Cellulosepowder, Lactose-Monohydrat, Magnesiumstearat (Ph. Eur.), mikrokristalline Cellulose)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two placebo drugs, to be taken three times a day for seven days.

Number of subjects in period 1	test group (antibiotics)	control group (placebo)
Started	251	255
Completed	206	200
Not completed	45	55
Adverse event, serious fatal	1	1
Adverse event, non-fatal	2	4
Protocol deviation	42	50

Baseline characteristics

Reporting groups	
Reporting group title	test group (antibiotics)
Reporting group description:	
All patients receive routine supragingival and subgingival debridement with sonic/ultrasonic scalers using micro tips or hand instruments (curettes) under local anesthesia. Finally, polishing with an air powder device or pumice and rotating rubber cups is performed. Initial therapy is performed in two sessions on two consecutive days. After completion of mechanical debridement, patients receive an adjunctive antimicrobial therapy consisting of oral metronidazole 400mg and amoxicillin 500mg (three times daily, for seven days).	
Reporting group title	control group (placebo)
Reporting group description:	
All patients receive routine supragingival and subgingival debridement with sonic/ultrasonic scalers using micro tips or hand instruments (curettes) under local anesthesia. Finally, polishing with an air powder device or pumice and rotating rubber cups is performed. Initial therapy is performed in two sessions on two consecutive days. After completion of mechanical debridement, patients receive two placebo drugs (three times daily, for seven days).	

Reporting group values	test group (antibiotics)	control group (placebo)	Total
Number of subjects	251	255	506
Age categorical			
Subjects included in the study aged from 18 to 75 years.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	212	220	432
From 65-84 years	39	35	74
85 years and over	0	0	0
Age continuous			
Age in years at screening visit 1			
Units: years			
median	51	49	
full range (min-max)	27 to 75	22 to 74	-
Gender categorical			
female and male			
Units: Subjects			
Female	122	124	246
Male	129	131	260
Stratum			
Randomization was performed stratified by "extent of periodontal disease", and "smoking habit". Stratum 1 (non-/light smokers, < 38% of teeth with pocket probing depth ≥ 6 mm) Stratum 2 (non-/light smokers, ≥ 38% of teeth with pocket probing depth ≥ 6 mm) Stratum 3 (smoker, < 38% of teeth with pocket probing depth ≥ 6 mm) Stratum 4 (smoker, ≥ 38% of teeth with pocket probing depth ≥ 6 mm)			
Units: Subjects			
Stratum 1	167	169	336

Stratum 2	21	18	39
Stratum 3	51	51	102
Stratum 4	12	17	29
Smoker Units: Subjects			
no	166	174	340
yes	85	81	166
Carbon monoxide status in the exhaled air Units: Subjects			
Missing	1	3	4
< 7 ppm	186	187	373
≥ 7 ppm	64	65	129
Self-reported diabetes mellitus Units: Subjects			
no diabetes	237	244	481
diabetes	14	11	25
Carbon monoxide in the exhaled air Units: part per million			
median	1	1	
inter-quartile range (Q1-Q3)	0 to 7	0 to 7	-
Number of teeth Units: Frequency			
median	25	26	
inter-quartile range (Q1-Q3)	22 to 27	23 to 28	-
Mean pocket probing depth Units: mm			
median	3.38	3.33	
inter-quartile range (Q1-Q3)	3.04 to 3.95	3.01 to 3.96	-
Proportion of sites per patient with bleeding on probing (BOP) Units: percent			
median	34.0	32.1	
inter-quartile range (Q1-Q3)	24.4 to 47.5	19.8 to 47.2	-
Mean attachment level per patient Units: mm			
median	3.98	3.92	
inter-quartile range (Q1-Q3)	3.39 to 4.63	3.42 to 4.73	-
Mean gingival recession Units: mm			
median	0.41	0.44	
inter-quartile range (Q1-Q3)	0.16 to 0.77	0.15 to 0.86	-
Proportion of sites per patient with plaque Units: percent			
median	36.1	31.3	
inter-quartile range (Q1-Q3)	20.0 to 53.1	16.1 to 53.5	-
OHIP summary score			
Summary score of the Oral Health Impact Profile – German Version (OHIP-G 49) questionnaire			
Units: Points			
median	38.7	31.6	
inter-quartile range (Q1-Q3)	19.5 to 65.2	17.4 to 58.0	-

Subject analysis sets

Subject analysis set title	Test group (antibiotics, ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat collective (test group) contains all patients who were randomized to receive antibiotics and had measurents at the baseline visit and final visit (27.5 months) after randomization. The patients will be analyzed using the intention-to-treat principle (ITT) according to the randomized treatment regardless of protocol violations. Within 1.5 months after baseline examination (visit 2), patients received supra- and subgingival debridement in up to two sessions on two consecutive days. All mechanical therapy was performed with different hand instruments and/or machine driven scalers. After completion of mechanical therapy, in the antibiotics group patients received two empiric antibiotics [amoxicillin 3H2O 574 mg (Amoxicillin-ratiopharm 500 mg®, Ratiopharm, Germany); metronidazole 400 mg (Flagyl® 400, Sanofi-Aventis, Germany)] each to be taken three times a day for seven days.

Subject analysis set title	Control group (placebo, ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat collective (test group) contains all patients who were randomized to receive placebo and had measurents at the baseline visit and final visit (27.5 months) after randomization. The patients will be analyzed using the intention-to-treat principle (ITT) according to the randomized treatment regardless of protocol violations. The patients will be analyzed using the intention-to-treat principle (ITT) according to the randomized treatment regardless of protocol violations.. Within 1.5 months after baseline examination (visit 2), patients received supra- and subgingival debridement in up to two sessions on two consecutive days. All mechanical therapy was performed with different hand instruments and/or machine driven scalers. After completion of mechanical therapy, in the placebo group patients received two placebo drugs each to be taken three times a day for seven days.

Subject analysis set title	Test group (antibiotics, PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol population (test groups) includes all patients who were randomized to receive antibiotics, had measurements of the relative attachment level at all visits (2, 4, 6, 8, 10, 12), and took the assigned drugs 18 to 23 times over 6-8 days.

Subject analysis set title	Control group (placebo, PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol population (control groups) includes all patients who were randomized to receive placebo, had measurements of the relative attachment level at all visits (2, 4, 6, 8, 10, 12), and took the assigned drugs 18 to 23 times over 6-8 days.

Reporting group values	Test group (antibiotics, ITT)	Control group (placebo, ITT)	Test group (antibiotics, PP)
Number of subjects	206	200	170
Age categorical			
Subjects included in the study aged from 18 to 75 years.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	174	169	143
From 65-84 years	32	31	27
85 years and over	0	0	0

Age continuous			
Age in years at screening visit 1			
Units: years			
median	52	51	52
full range (min-max)	27 to 75	22 to 74	27 to 75
Gender categorical			
female and male			
Units: Subjects			
Female	104	96	85
Male	102	104	85
Stratum			
Randomization was performed stratified by "extent of periodontal disease", and "smoking habit". Stratum 1 (non-/light smokers, < 38% of teeth with pocket probing depth ≥ 6 mm) Stratum 2 (non-/light smokers, ≥ 38% of teeth with pocket probing depth ≥ 6 mm) Stratum 3 (smoker, < 38% of teeth with pocket probing depth ≥ 6 mm) Stratum 4 (smoker, ≥ 38% of teeth with pocket probing depth ≥ 6 mm)			
Units: Subjects			
Stratum 1	142	141	123
Stratum 2	18	15	10
Stratum 3	39	33	35
Stratum 4	7	11	2
Smoker			
Units: Subjects			
no	145	147	121
yes	61	53	49
Carbon monoxide status in the exhaled air			
Units: Subjects			
Missing	1	3	1
< 7 ppm	159	156	132
≥ 7 ppm	46	41	37
Self-reported diabetes mellitus			
Units: Subjects			
no diabetes	197	190	163
diabetes	9	10	7
Carbon monoxide in the exhaled air			
Units: part per million			
median	1	1	1
inter-quartile range (Q1-Q3)	0 to 5	0 to 3	0 to 4
Number of teeth			
Units: Frequency			
median	25	26	25
inter-quartile range (Q1-Q3)	22 to 28	23 to 28	22 to 27
Mean pocket probing depth			
Units: mm			
median	3.35	3.33	3.34
inter-quartile range (Q1-Q3)	3.04 to 3.89	2.97 to 3.96	3.03 to 3.89
Proportion of sites per patient with bleeding on probing (BOP)			
Units: percent			
median	33.3	32.2	34.1
inter-quartile range (Q1-Q3)	24.2 to 46.7	20.6 to 47.2	24.4 to 48.5
Mean attachment level per patient			

Units: mm			
median	3.94	3.89	3.95
inter-quartile range (Q1-Q3)	3.41 to 4.55	3.43 to 4.72	3.37 to 4.56
Mean gingival recession			
Units: mm			
median	0.41	0.45	0.42
inter-quartile range (Q1-Q3)	0.16 to 0.79	0.16 to 0.87	0.16 to 0.79
Proportion of sites per patient with plaque			
Units: percent			
median	36.0	31.0	35.8
inter-quartile range (Q1-Q3)	20.4 to 54.2	16.0 to 53.2	18.6 to 53.1
OHIP summary score			
Summary score of the Oral Health Impact Profile – German Version (OHIP-G 49) questionnaire			
Units: Points			
median	36.0	30.0	36.0
inter-quartile range (Q1-Q3)	19.0 to 59.0	17.0 to 54.3	20.0 to 61.8

Reporting group values	Control group (placebo, PP)		
Number of subjects	175		
Age categorical			
Subjects included in the study aged from 18 to 75 years.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	145		
From 65-84 years	30		
85 years and over	0		
Age continuous			
Age in years at screening visit 1			
Units: years			
median	52		
full range (min-max)	22 to 74		
Gender categorical			
female and male			
Units: Subjects			
Female	87		
Male	88		
Stratum			
Randomization was performed stratified by "extent of periodontal disease", and "smoking habit". Stratum 1 (non-/light smokers, < 38% of teeth with pocket probing depth ≥ 6 mm) Stratum 2 (non-/light smokers, ≥ 38% of teeth with pocket probing depth ≥ 6 mm) Stratum 3 (smoker, < 38% of teeth with pocket probing depth ≥ 6 mm) Stratum 4 (smoker, ≥ 38% of teeth with pocket probing depth ≥ 6 mm)			
Units: Subjects			
Stratum 1	130		
Stratum 2	12		

Stratum 3	26		
Stratum 4	7		
Smoker Units: Subjects			
no	131		
yes	44		
Carbon monoxide status in the exhaled air Units: Subjects			
Missing	3		
< 7 ppm	138		
≥ 7 ppm	34		
Self-reported diabetes mellitus Units: Subjects			
no diabetes	165		
diabetes	10		
Carbon monoxide in the exhaled air Units: part per million			
median	1		
inter-quartile range (Q1-Q3)	0 to 3		
Number of teeth Units: Frequency			
median	26		
inter-quartile range (Q1-Q3)	23 to 28		
Mean pocket probing depth Units: mm			
median	3.34		
inter-quartile range (Q1-Q3)	2.97 to 3.96		
Proportion of sites per patient with bleeding on probing (BOP) Units: percent			
median	32.6		
inter-quartile range (Q1-Q3)	21.4 to 47.1		
Mean attachment level per patient Units: mm			
median	3.89		
inter-quartile range (Q1-Q3)	3.49 to 4.68		
Mean gingival recession Units: mm			
median	0.45		
inter-quartile range (Q1-Q3)	0.15 to 0.83		
Proportion of sites per patient with plaque Units: percent			
median	30.0		
inter-quartile range (Q1-Q3)	15.2 to 54.6		
OHIP summary score			
Summary score of the Oral Health Impact Profile – German Version (OHIP-G 49) questionnaire			
Units: Points			
median	29.3		
inter-quartile range (Q1-Q3)	16.0 to 51.0		

End points

End points reporting groups

Reporting group title	test group (antibiotics)

Reporting group description:

All patients receive routine supragingival and subgingival debridement with sonic/ultrasonic scalers using micro tips or hand instruments (curettes) under local anesthesia. Finally, polishing with an air powder device or pumice and rotating rubber cups is performed. Initial therapy is performed in two sessions on two consecutive days. After completion of mechanical debridement, patients receive an adjunctive antimicrobial therapy consisting of oral metronidazole 400mg and amoxicillin 500mg (three times daily, for seven days).

Reporting group title	control group (placebo)

Reporting group description:

All patients receive routine supragingival and subgingival debridement with sonic/ultrasonic scalers using micro tips or hand instruments (curettes) under local anesthesia. Finally, polishing with an air powder device or pumice and rotating rubber cups is performed. Initial therapy is performed in two sessions on two consecutive days. After completion of mechanical debridement, patients receive two placebo drugs (three times daily, for seven days).

Subject analysis set title	Test group (antibiotics, ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat collective (test group) contains all patients who were randomized to receive antibiotics and had measurents at the baseline visit and final visit (27.5 months) after randomization. The patients will be analyzed using the intention-to-treat principle (ITT) according to the randomized treatment regardless of protocol violations. Within 1.5 months after baseline examination (visit 2), patients received supra- and subgingival debridement in up to two sessions on two consecutive days. All mechanical therapy was performed with different hand instruments and/or machine driven scalers. After completion of mechanical therapy, in the antibiotics group patients received two empiric antibiotics [amoxicillin 3H2O 574 mg (Amoxicillin-ratiopharm 500 mg®, Ratiopharm, Germany); metronidazole 400 mg (Flagyl® 400, Sanofi-Aventis, Germany)] each to be taken three times a day for seven days.

Subject analysis set title	Control group (placebo, ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat collective (test group) contains all patients who were randomized to receive placebo and had measurents at the baseline visit and final visit (27.5 months) after randomization. The patients will be analyzed using the intention-to-treat principle (ITT) according to the randomized treatment regardless of protocol violations. The patients will be analyzed using the intention-to-treat principle (ITT) according to the randomized treatment regardless of protocol violations.. Within 1.5 months after baseline examination (visit 2), patients received supra- and subgingival debridement in up to two sessions on two consecutive days. All mechanical therapy was performed with different hand instruments and/or machine driven scalers. After completion of mechanical therapy, in the placebo group patients received two placebo drugs each to be taken three times a day for seven days.

Subject analysis set title	Test group (antibiotics, PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol population (test groups) includes all patients who were randomized to receive antibiotics, had measurements of the relative attachment level at all visits (2, 4, 6, 8, 10, 12), and took the assigned drugs 18 to 23 times over 6-8 days.

Subject analysis set title	Control group (placebo, PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol population (control groups) includes all patients who were randomized to receive placebo, had measurements of the relative attachment level at all visits (2, 4, 6, 8, 10, 12), and took the assigned drugs 18 to 23 times over 6-8 days.

Primary: Proportion of sites per patient with new clinical attachment loss (PSAL) ≥ 1.3 mm between baseline and the 27.5 months visit

End point title	Proportion of sites per patient with new clinical attachment loss (PSAL) ≥ 1.3 mm between baseline and the 27.5 months visit

End point description:

End point type	Primary

End point timeframe:

PSAL was determined for each patient by calculating the percentage of sites with a larger deterioration than 1.3 mm in the relative attachment level (mm) between baseline (visit 2) and 27.5 months (visit 12).

End point values	Test group (antibiotics, ITT)	Control group (placebo, ITT)	Test group (antibiotics, PP)	Control group (placebo, PP)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	206	200	170	175
Units: percent				
median (inter-quartile range (Q1-Q3))	5.3 (3.1 to 9.9)	7.8 (4.7 to 14.1)	5.3 (3.2 to 9.7)	7.5 (4.5 to 14.4)

Statistical analyses

Statistical analysis title	Primary efficacy analysis PSAL (ITT)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the intention-to-treat collective.
The confirmatory analysis of the primary endpoint was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, ITT) v Control group (placebo, ITT)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	Stratified Wilcoxon test (van Elteren)

Notes:

[1] - A two-sided p-value less than 0.05 will be considered as significant.

Statistical analysis title	Sensitivity analysis PSAL (PP)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the per-protocol collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, PP) v Control group (placebo, PP)

Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Stratified Wilcoxon test (van Elteren)

Secondary: Proportion of sites per patient with new clinical attachment gain (PSAG) ≥ 1.3 mm between baseline and the 27.5 months visit

End point title	Proportion of sites per patient with new clinical attachment gain (PSAG) ≥ 1.3 mm between baseline and the 27.5 months visit

End point description:

End point type	Secondary

End point timeframe:

PSAG was determined for each patient by calculating the percentage of sites with a larger improvement than 1.3 mm in the relative attachment level (mm) between baseline (visit 2) and 27.5 months (visit 12).

End point values	Test group (antibiotics, ITT)	Control group (placebo, ITT)	Test group (antibiotics, PP)	Control group (placebo, PP)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	206	200	170	175
Units: percent				
median (inter-quartile range (Q1-Q3))	19.4 (10.4 to 32.7)	12.2 (7.1 to 23.0)	19.6 (10.3 to 32.1)	12.8 (7.2 to 23.5)

Statistical analyses

Statistical analysis title	Secondary analysis (PSAG >= 1.3 mm) ITT

Statistical analysis description:

Comparison between the antibiotics and placebo group in the intention-to-treat collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, ITT) v Control group (placebo, ITT)
Number of subjects included in analysis	406
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0001
Method	Stratified Wilcoxon test (van Elteren)

Statistical analysis title	Secondary analysis (PSAG >= 1.3 mm) PP

Statistical analysis description:

Comparison between the antibiotics and placebo group in the per-protocol collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, PP) v Control group (placebo, PP)
Number of subjects included in analysis	345
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.0001
Method	Stratified Wilcoxon test (van Elteren)

Secondary: Proportion of sites per patient with new clinical attachment loss (PSAL) ≥ 1.3 mm between reevaluation (visit 4) and the 27.5 months visit

End point title	Proportion of sites per patient with new clinical attachment loss (PSAL) ≥ 1.3 mm between reevaluation (visit 4) and the 27.5 months visit

End point description:

End point type	Secondary

End point timeframe:

PSAL was determined for each patient by calculating the percentage of sites with a larger deterioration than 1.3 mm in the relative attachment level (mm) between reevalution (visit 4, after therapy) and 27.5 months (visit 12).

End point values	Test group (antibiotics, ITT)	Control group (placebo, ITT)	Test group (antibiotics, PP)	Control group (placebo, PP)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	206	200	170	175
Units: percent				
median (inter-quartile range (Q1-Q3))	8.3 (4.7 to 13.5)	10.6 (5.8 to 16.7)	8.2 (4.5 to 13.2)	10.7 (5.6 to 16.7)

Statistical analyses

Statistical analysis title	Secondary analysis PSAL from reevaluation (ITT)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the intention-to-treat collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, ITT) v Control group (placebo, ITT)

Number of subjects included in analysis	406
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0266
Method	Stratified Wilcoxon test (van Elteren)

Statistical analysis title	Secondary analysis PSAL from reevaluation (PP)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the intention-to-treat collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, PP) v Control group (placebo, PP)
Number of subjects included in analysis	345
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0124
Method	Stratified Wilcoxon test (van Elteren)

Secondary: Change in proportion of sites per patient with bleeding on probing (BOP) between baseline and 27.5 months

End point title	Change in proportion of sites per patient with bleeding on probing (BOP) between baseline and 27.5 months

End point description:

End point type	Secondary

End point timeframe:

The change in the proportion of sites per patient with bleeding on probing (BOP) was calculated between 27.5 months and baseline (visit 12 minus visit 2).

End point values	Test group (antibiotics, ITT)	Control group (placebo, ITT)	Test group (antibiotics, PP)	Control group (placebo, PP)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	204	200	170	175
Units: percent				
median (inter-quartile range (Q1-Q3))	-22.2 (-36.1 to -8.2)	-12.1 (-27.7 to -2.7)	-22.4 (-36.7 to -9.0)	-12.3 (-28.4 to -3.0)

Statistical analyses

Statistical analysis title	Change BOP (27.5 months - baseline) (ITT)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the intention-to-treat collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, ITT) v Control group (placebo, ITT)
Number of subjects included in analysis	404
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.0001
Method	Stratified Wilcoxon test (van Elteren)

Statistical analysis title	Change BOP (27.5 months - baseline) (PP)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the per-protocol collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, PP) v Control group (placebo, PP)
Number of subjects included in analysis	345
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0001
Method	Stratified Wilcoxon test (van Elteren)

Secondary: Change in mean pocket probing depth (27.5 months - baseline)

End point title	Change in mean pocket probing depth (27.5 months - baseline)

End point description:

End point type	Secondary

End point timeframe:

The absolute change in PPD was calculated between 27.5 months (visit 12) and baseline (visit 2).

End point values	Test group (antibiotics, ITT)	Control group (placebo, ITT)	Test group (antibiotics, PP)	Control group (placebo, PP)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	205	200	170	175
Units: mm				
median (inter-quartile range (Q1-Q3))	-1.05 (-1.59 to -0.58)	-0.80 (-1.28 to -0.42)	-1.04 (-1.58 to -0.66)	-0.82 (-1.29 to -0.43)

Statistical analyses

Statistical analysis title	Change PPD (27.5 months - baseline) (ITT)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the intention-to-treat collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Control group (placebo, ITT) v Test group (antibiotics, ITT)
Number of subjects included in analysis	405
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.0001
Method	Stratified Wilcoxon test (van Elteren)

Statistical analysis title	Change PPD (27.5 months - baseline) (PP)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the per-protocol collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, PP) v Control group (placebo, PP)
Number of subjects included in analysis	345
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.0001
Method	Stratified Wilcoxon test (van Elteren)

Secondary: Change in mean attachment level (27.5 months - baseline)

End point title	Change in mean attachment level (27.5 months - baseline)

End point description:

End point type	Secondary

End point timeframe:

Change in mean attachment level was calculated between 27.5 months (visit 12) and baseline (visit 2).

End point values	Test group (antibiotics, ITT)	Control group (placebo, ITT)	Test group (antibiotics, PP)	Control group (placebo, PP)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	205	200	170	175
Units: mm				
median (inter-quartile range (Q1-Q3))	-0.64 (-1.02 to -0.19)	-0.38 (-0.86 to 0.05)	-0.60 (-0.97 to -0.19)	-0.39 (-1.09 to -0.30)

Statistical analyses

Statistical analysis title	Change attachment (27.5 months - baseline) (ITT)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the intention-to-treat collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, ITT) v Control group (placebo, ITT)
Number of subjects included in analysis	405
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0004
Method	Stratified Wilcoxon test (van Elteren)

Statistical analysis title	Change attachment (27.5 months - baseline) (PP)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the per-protocol collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, ITT) v Control group (placebo, ITT)
Number of subjects included in analysis	405
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0017
Method	Stratified Wilcoxon test (van Elteren)

Secondary: Change in mean gingival recession (27.5 months - baseline)

End point title	Change in mean gingival recession (27.5 months - baseline)

End point description:

End point type	Secondary

End point timeframe:

Change in the mean gingival recession per patient was calculated between 27.5 months and baseline (visit 12 - visit 2)

End point values	Test group (antibiotics, ITT)	Control group (placebo, ITT)	Test group (antibiotics, PP)	Control group (placebo, PP)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	205	200	170	175
Units: mm				
median (inter-quartile range (Q1-Q3))	0.49 (0.22 to 0.90)	0.51 (0.19 to 0.85)	0.46 (0.19 to 0.80)	0.40 (0.16 to 0.71)

Statistical analyses

Statistical analysis title	Change Recession (27.5 months - baseline) (ITT)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the intention-to-treat collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, ITT) v Control group (placebo, ITT)
Number of subjects included in analysis	405
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2186
Method	Stratified Wilcoxon test (van Elteren)

Statistical analysis title	Change Recession (27.5 months - baseline) (PP)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the per-protocol collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, PP) v Control group (placebo, PP)
Number of subjects included in analysis	345
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.1011
Method	Stratified Wilcoxon test (van Elteren)

Secondary: Change in proportion of sites per patient with plaque between 27.5 months and baseline

End point title	Change in proportion of sites per patient with plaque between 27.5 months and baseline

End point description:

End point type	Secondary

End point timeframe:

Change of the proportion of sites per patient with detectable plaque was calculated between 27.5

End point values	Test group (antibiotics, ITT)	Control group (placebo, ITT)	Test group (antibiotics, PP)	Control group (placebo, PP)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	205	200	170	175
Units: percent				
median (inter-quartile range (Q1-Q3))	0.56 (-17.82 to 17.59)	0.90 (-17.1 to 20.15)	0.70 (-17.78 to 17.19)	0.33 (-17.59 to 22.39)

Statistical analyses

Statistical analysis title	Change Plaque (27.5 months - baseline) (ITT)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the intention-to-treat collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, ITT) v Control group (placebo, ITT)
Number of subjects included in analysis	405
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.9649
Method	Stratified Wilcoxon test (van Elteren)

Statistical analysis title	Change Plaque (27.5 months - baseline) (PP)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the intention-to-treat collective.
The analysis was performed using a stratified Wilcoxon-Test (van Elteren). The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

Comparison groups	Test group (antibiotics, PP) v Control group (placebo, PP)
Number of subjects included in analysis	345
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.8658
Method	Stratified Wilcoxon test (van Elteren)

Secondary: Change in OHIP summary score between 27.5 months and baseline

End point title	Change in OHIP summary score between 27.5 months and baseline

End point description:

End point type	Secondary

End point timeframe:

Change in the summary score of the Oral Health Impact Profile – German Version (OHIP-G 49) questionnaire between 27.5 months (visit 12) and baseline (visit 2)

End point values	Test group (antibiotics, ITT)	Control group (placebo, ITT)	Test group (antibiotics, PP)	Control group (placebo, PP)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	200	195	164	170
Units: Points				
median (inter-quartile range (Q1-Q3))	-7.8 (-26.2 to -3.4)	-4.3 (-17.0 to 5.4)	-7.0 (-25.7 to 4.0)	-3.6 (-16.0 to 6.0)

Statistical analyses

Statistical analysis title	Change OHIP score (27.5 months - baseline) (ITT)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the intention-to-treat collective.
The analysis was performed using a two-sided Mann-Whitney U test.

Comparison groups	Test group (antibiotics, ITT) v Control group (placebo, ITT)
Number of subjects included in analysis	395
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0432
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Change OHIP score (27.5 months - baseline) (PP)

Statistical analysis description:

Comparison between the antibiotics and placebo group in the per protocol collective.
The analysis was performed using a two-sided Mann-Whitney U test.

Comparison groups	Test group (antibiotics, PP) v Control group (placebo, PP)
Number of subjects included in analysis	334
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0731
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

01.10.2008 - 31.12.2011

Adverse event reporting additional description:

All adverse events occurring during the trial period including the 14 days after visit 12 (informed consent – visit 12) have to be documented in the AE-form of the CRF including assessment of severity.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Test group (antibiotics)
Reporting group description: -	
Reporting group title	control group (placebo)

Reporting group description: -

Serious adverse events	Test group (antibiotics)	control group (placebo)	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 251 (15.14%)	29 / 255 (11.37%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer metastatic			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Adenoidectomy			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Caecum operation			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia repair			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterectomy			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septal operation			
subjects affected / exposed	2 / 251 (0.80%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polypectomy			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus operation			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent placement			

subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic operation			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unevaluable event			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Laryngeal inflammation			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord cyst			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord inflammation			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord leukoplakia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Burnout syndrome			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Investigations			
Inflammatory marker increased			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 251 (0.00%)	2 / 255 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament injury			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	2 / 251 (0.80%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Angina pectoris			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 251 (0.40%)	2 / 255 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac discomfort			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 251 (0.40%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 251 (0.80%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
VIIIth nerve lesion			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macular fibrosis			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	0 / 251 (0.00%)	2 / 255 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ileus			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	2 / 251 (0.80%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Pelvi-ureteric obstruction			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	1 / 251 (0.40%)	2 / 255 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	2 / 251 (0.80%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal discomfort			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 251 (0.80%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	2 / 251 (0.80%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scleroderma			

subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 251 (0.40%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 251 (0.40%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	0 / 251 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Test group (antibiotics)	control group (placebo)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	178 / 251 (70.92%)	177 / 255 (69.41%)	
Injury, poisoning and procedural complications			
Tooth fracture			
subjects affected / exposed	9 / 251 (3.59%)	16 / 255 (6.27%)	
occurrences (all)	9	19	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 251 (1.99%)	8 / 255 (3.14%)	
occurrences (all)	5	8	
Surgical and medical procedures			
Artificial crown procedure			
subjects affected / exposed	6 / 251 (2.39%)	13 / 255 (5.10%)	
occurrences (all)	8	13	
Dental prosthesis placement			
subjects affected / exposed	7 / 251 (2.79%)	7 / 255 (2.75%)	
occurrences (all)	7	7	
Endodontic procedure			
subjects affected / exposed	4 / 251 (1.59%)	12 / 255 (4.71%)	
occurrences (all)	4	15	
Tooth extraction			
subjects affected / exposed	26 / 251 (10.36%)	20 / 255 (7.84%)	
occurrences (all)	28	21	
Tooth repair			
subjects affected / exposed	7 / 251 (2.79%)	10 / 255 (3.92%)	
occurrences (all)	9	14	
General disorders and administration site conditions			

Device failure			
subjects affected / exposed	28 / 251 (11.16%)	28 / 255 (10.98%)	
occurrences (all)	41	31	
Influenza like illness			
subjects affected / exposed	9 / 251 (3.59%)	14 / 255 (5.49%)	
occurrences (all)	9	15	
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	34 / 251 (13.55%)	33 / 255 (12.94%)	
occurrences (all)	40	36	
Dental pulp disorder			
subjects affected / exposed	22 / 251 (8.76%)	12 / 255 (4.71%)	
occurrences (all)	25	12	
Periodontitis			
subjects affected / exposed	7 / 251 (2.79%)	14 / 255 (5.49%)	
occurrences (all)	9	17	
Tooth disorder			
subjects affected / exposed	17 / 251 (6.77%)	17 / 255 (6.67%)	
occurrences (all)	21	23	
Toothache			
subjects affected / exposed	6 / 251 (2.39%)	13 / 255 (5.10%)	
occurrences (all)	7	16	
Diarrhoea			
subjects affected / exposed	11 / 251 (4.38%)	2 / 255 (0.78%)	
occurrences (all)	13	1	
Infections and infestations			
Influenza			
subjects affected / exposed	7 / 251 (2.79%)	6 / 255 (2.35%)	
occurrences (all)	9	7	
Nasopharyngitis			
subjects affected / exposed	18 / 251 (7.17%)	14 / 255 (5.49%)	
occurrences (all)	21	14	
Tooth abscess			
subjects affected / exposed	6 / 251 (2.39%)	23 / 255 (9.02%)	
occurrences (all)	6	31	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2007	-During visit eight a blood sample will be given on a DNA storage card (e.g. FTA Elute Microcard, Whatman). The cards can be stored at room temperature and will be shipped collectively to the coordinating center for further processing at the end of the study. -EDTA-blood (10ml, 1 sample) will be taken during visits 1, 8 and 12 to determine the course of inflammatory disease parameters (e.g. CRP, etc.) and HbA1c. The sample will be shipped immediately for further processing in special gusseted wallets (to ensure specimen containment) to the clinical chemistry laboratory of the University of Greifswald.
24 June 2008	- Changes made for: Subject Inclusion Criteria, Subject Exclusion Criteria and Subject Withdrawal Criteria -EDTA-blood (10ml, 1 sample) will be taken during visits 1, 8 and 12 to determine the course of inflammatory disease parameters (e.g. CRP, etc.) and HbA1c. -At every visit the examiner has to perform a routine inspection. First the medical health history (MHH) has to be checked. Changes have to be documented in the MHH and the CRF. Changes within the medication must be also documented in the MHH and additionally in the CRF if they belonging to the following six medication groups: 1. Antibiotics, 2. ASS for more than 4 weeks, 3. Medication for cardiovascular and/ or heart diseases, 4. Medication for thyroid diseases, 5. Medication for gastro-intestinal diseases, 6. Medication for asthma (allergic/ bronchial). The medication group should be marked with a cross in the CRF and the name and dosage should be documented. Following the clinical inspection will be done. The existence of periodontal abscesses has to be excluded. If there is a periodontal abscess, the tooth has to be documented in the CRF as well. Additionally, the examiner has to check the occlusal relief versus the intraoral photographs of visit 2 (occlusal inspection at visits 4, 6, 8, 10, 12). Changes have to be documented in the CRF. Finally, it has to be proved if there were any adverse or serious adverse events. If yes, it has to be specified on AE/ SAE form. - Change: OHIP-G was changed to OHIP-G49 -The HbA1c will be assessed centralized at the Institut für Klinische Chemie und Laboratoriumsmedizin (IKCL), University of Greifswald. HbA1c will be assessed in the blood samples which are taken at visit one, eight and twelve. - New definitions for: Adverse reaction (AR) and Serious adverse event or serious adverse reaction (SAE or SAR)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30326764

http://www.ncbi.nlm.nih.gov/pubmed/27393928

http://www.ncbi.nlm.nih.gov/pubmed/30825384

http://www.ncbi.nlm.nih.gov/pubmed/29668720

http://www.ncbi.nlm.nih.gov/pubmed/26250060