



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 |
| Public contact | Prof. Dr. med. dent. Benjamin Ehmke University of Muenster Department of Periodontology, Prof. Dr. med. dent. Benjamin Ehmke University of Muenster Department of Periodontology, +49 251 8347059, ehmke@uni-muenster.de |
| Scientific contact | Prof. Dr. med. dent. Benjamin Ehmke University of Muenster Department of Periodontology, Prof. Dr. med. dent. Benjamin Ehmke University of Muenster Department of Periodontology , +49 251 8347059, ehmke@uni-muenster.de |

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 06 December 2007 | <ul style="list-style-type: none">-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 | <ul style="list-style-type: none">- 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>

