Non-surgical treatment of peri-implantitis

RESEARCH PROTOCOL

PROTOCOL TITLE 'Non-surgical treatment of peri-implantitis with/without systemic antibiotics'

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Peri-implantitis is an inflammation of the tissues around dental implants. Interventions to treat this disease include removal of the dental biofilm around the titanium implants. In this study two recognized treatment options of peri-implantitis are compared. Mechanical cleaning of the implant surface combined with systemic antibiotics is compared to mechanical cleaning alone.

Objective: The objective is to compare two existing peri-implantitis treatment protocols, by evaluating the adjunctive effect of systemic antibiotics for the treatment of peri-implantitis in comparison to treatment without systemic antibiotics on the difference in clinical attachment level (CAL) three and twelve months after treatment.

Study design: Randomized controlled trial, single blind.

Study population: Adult patients (> 18 years) with peri-implantitis with at least one oral implant in function.

Intervention: One group receives a non-surgical treatment of peri-implantitis (mechanical debridement of the surface of dental implants) in combination with systemic antibiotics (amoxicillin 375 mg and metronidazole 250 mg three times a day for 7 days). The other group receives the same non-surgical treatment of peri-implantitis without the adjunctive use of systemic antibiotics. This is a recognized treatment for periodontitis, an inflammation of the tissues around natural teeth.

Main study parameters/endpoints: The main outcome is the difference in clinical attachment level (CAL) of the deepest site of the target implant (baseline versus three months after treatment)

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden and risks in this study are not different when compared to regular clinical treatment. The antibiotics (amoxicillin 375 mg and metronidazole 250 mg three times a day for 7 days) used in this study are regularly used in dental practices and may cause side effects. The appointments will be performed according to regular treatment appointments; the extra time in this study for each subject is about 40 minutes.

1. INTRODUCTION AND RATIONALE

Peri-implantitis is an inflammation of the peri-implant tissues around dental implants with bleeding and/or suppuration on probing and crestal bone loss (Lang & Berglundh, 2011, Linde & Meyle, 2008). Swelling and redness of the marginal tissues may or may not be present, and there is usually no pain (Mombelli & Décaillet, 2011). In the worst case peri-implantitis may lead to loss of the dental implant.

The prevalence of peri-implantitis in subjects with dental implants is 28-56% (Zitzmann & Berglundh, 2008). With the increasing use of dental implants, the amount of subjects with peri-implantitis is rising. Evaluation of excisting non-surgical treatment for peri-implantitis is therefore necessary (Renvert et al., 2008).

The oral microbiome plays an important role in peri-implantitis. As soon as a dental implant is exposed to the oral cavity, a bacterial biofilm covers the surface of the implant. (Mombelli, 2002; Fürst et al., 2007; Kotsovilis et al., 2008; Salvi et al., 2008; Heuer et al., 2011; Mombelli & Décaillet, 2011). Mainly commensal Gram-negative anaerobe microbiota similar to that found in periodontal disease is found in implant biofilm. (Persson et al., 2006; Renvert et al., 2007). Bacterial component alone is not able to cause peri-implant disease and therefore peri-implantitis is considered as a multi factorial disease.

Several life style factors can increase the risk of peri-implantitis. Smoking is a well studied risk for peri-implantitis (Bahrami et al., 2006; van der Weijden et al., 2001; Stoker et al., 2011). Peri-implant alveolar bone showed twice as much loss in subjects who smoked in comparison with non-smokers after eight years (Stoker et al., 2011).

Peri-implantitis and periodontitis show similarities in clinical processes; deepened sites (pockets) next to a tooth or implant, bleeding on probing, plaque accumulation, pus, mobility and in worst case loss of a tooth or implant (Heitz-Mayfield & Lang, 2010). Similar to non-surgical treatment of periodontitis, the non-surgical treatment of peri-implantitis consists of mechanical cleaning of the tooth/implant surfaces and oral hygiene instruction, which may be supported with systemic antibiotics or not. Despite the confirmed success of mechanical cleaning of the tooth (Haffajee et al 1997, Colombo et al. 2005) this is less effective in deeper pockets (more than 3 mm) (Rabbani, 1981, Waerhaug, 1978a, 1987b, Stambaugh et al, 1981). A further reduction of the pathogens can be established by additional use of local or systemic antibiotics (van Winkelhoff, 1996). The use of metronidazole in combination with amoxicillin is proven to be effective in the treatment of periodontitis (Lindhe et al, 1982, 1983, Loesche et al, 1992, Elter et al, 1997, Winkel et al, 1997, Berglundh et al, 1998, Winkel et al, 1998, 2001). Additional effect of systemic antibiotics in the non-surgical treatment of periodontitis has been – in contrast with peri-implantitis - widely investigated (Berglundh et

al., 1998; Sgolastra et al., 2012). These studies support the effectiveness of mechanical cleaning - which is similar to the mechanical non-surgical treatment of implant surface– with the possible adjunctive use of antibiotics, such as amoxicillin and metronidazole. Berglundh et al. (1998) found that mechanical cleaning in combination with systemic antimicrobial therapy was more effective than mechanical therapy alone in terms of eliminating deep pockets (≥6mm) and promoting probing attachment gain at such sites. This was also found in previous studies of Kornman et al. (1989), van Winkelhoff et al. (1989, 1992) and Pavicic et al.(1994).

Amoxicillin is a broad-spectrum, bacteriocidal ß-lactam antibiotic, whereas metronidazole is a nitroimidazole that is particularly active against anaerobic bacteria. The combination of metronidazole and amoxicillin targets a broad spectrum of bacteria involved in peri-implant and periodontal infection (Mombelli & Decaillet 2011). The combination of metronidazole and amoxicillin has been also shown to have synergistic effects (Pavicic et al., 1991).

Peri-implant health is difficult to achieve. Nowadays, treatment of peri-implantitis is directed towards divergent orientations without an optimal treatment regimen (Charalampakis et al., 2011). In clinical settings different treatment protocols for peri-implantitis are used with little scientific evidence. In 1996 Buchmann et al. described case series on treating peri-implantitis with mechanical cleaning and adjunctive systemic antibiotics (metronidazole and amoxicillin). They found a reduction in pocket depth and bone defect when compared to baseline.

In 1996 Ericsson et al. evaluated the effect of systemic antibiotics and local debridement in the treatment of experimentally induced peri-implantitis lesions in dogs. In this animal study they found that systemic antimicrobial therapy, combined with implant cleaning and plaque control resulted in stability of the peri-implantitis lesion and a significant recession of the marginal peri-implant mucosa.

In 1992 Mombelli & Lang described case series of 9 human subjects with peri-implantitis; they treated the peri-implant lesions with systemic antibiotics and local cleaning including mechanical debridement and irrigation of pockets >3 mm with 0,5% chlorhexidine. The authors reported that the combined interventions reduced symptoms associated with peri-implantitis.

Mattheos et al. (2012) described that interventions clinical practitioners in Australia and in the United Kingdom use to treat peri-implant diseases. Systemic antibiotics were always used by 37% of Australian and 15% of UK practitioners. A total of 11% of the UK and 1,5% of the Australian practitioners never used systemic antibiotics to treat peri-implant diseases. Both countries are consistent in the use of amoxicillin and metronidazole as their ‘first-choice’ systemic antibiotic (Mattheos et al., 2012).

The current clinical protocols are based on case reports and the evidence is low (Klinge et al., 2002; Renvert et al.,2008; Mattheos et al., 2012). Worldwide there is insufficient evidence to support a specific treatment protocol. Dependant on the physician different treatments are applied, one physician treats peri-implantitis always without antibiotics and another one treats the peri-implantitis always with the adjunctive use of antibiotics. Therefore there is a need for randomized controlled trials investigating the additional effect of antibiotics (amoxicillin 375 mg and metronidazole 250 mg three times a day for 7 days) for non-surgical treatment of peri-implantitis.

2. OBJECTIVES

Primary Objective:

To investigate the additional effect of systemic antibiotics (amoxicillin 375 mg and metronidazole 250 mg three times a day for 7 days) for non-surgical treatment of peri-implantitis in comparison to non-surgical treatment of peri-implantitis without the adjunctive use of systemic antibiotics on the difference in clinical attachment level (CAL) between baseline and three and twelve months.

Secondary Objective(s):

The secondary objectives are to investigate the additional effect of systemic antibiotics (amoxicillin 375 mg and metronidazole 250 mg three times a day for 7 days) for non-surgical treatment of peri-implantitis in comparison to non-surgical treatment of peri-implantitis without the adjunctive use of systemic antibiotics on the differences in clinical pocket probing depth (PPD), bleeding on probing (BoP), plaque-accumulation and bone loss and microbiological parameters between baseline and three and twelve months.

In addition, the third objective is to compare the effect of systemic antibiotics (amoxicillin 375 mg and metronidazole 250 mg three times a day for 7 days) on the differences in clinical and microbiological parameters between smokers and non-smokers and with the data of the periodontitis study with the same non-surgical treatment protocol.

The protocol of periodontitis study 'Het effect van de behandeling van parodontitis op markers van hart-en vaatziekten' has been approved by METC of AMC. Please see ABR domein NL19679.018.07, MEC 07/264#08.17.0079. The research protocol of the current proposal follows the protocol of the periodontitis study NL19679.018.07.

3. STUDY DESIGN

Single-blind randomized controlled trial.

The clinical study will take place from 2012 in the Academic Centre of Dentistry Amsterdam until we included the acquired amount of patients needed in the study. We expect about twelve months for recruiting and treating patients (Figure 1). For each subject the study has a time span of 18 weeks and an appointment after one year for a second evaluation (Figure 2). This time span is based on the regular peri-implantitis treatment protocol, please see Amendement1.

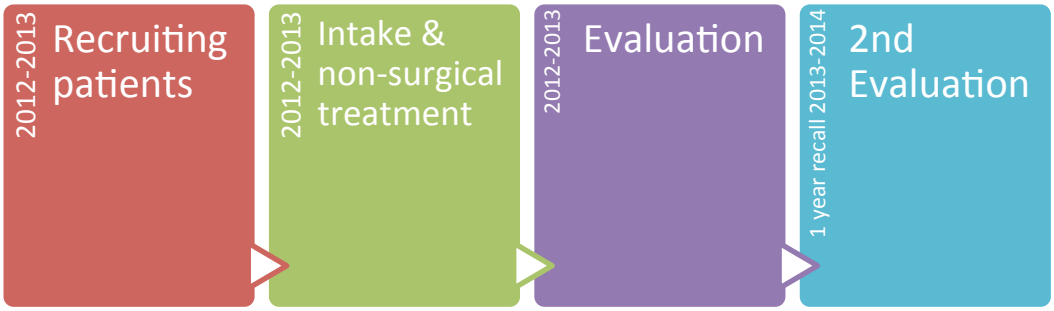

Figure 1. Duration of the study.

Figure 2. Time span for an individual subject.

4. STUDY POPULATION

4.1 Population (base)

The subjects will be selected from the patient population visiting the Section Oral Implantology, ACTA for regular dental implant maintenance. The section Oral Implantology is part of the department of Functional and Restorative Dentistry in the ACTA. When subjects meet the inclusion criteria they will be asked to participate in this study.

The likelihood that the acquired amount of patients needed in the study subjects can be recruited is based on the fact that the dental hygienist working at the section Oral Implantology is performing regular dental implant maintenance for roughly 24 patients per week. With a prevalence of 28-56% for peri-implantitis, the prediction of the number of peri-implantitis subjects the dental hygienist will see is approximately 6 – 13 subjects per week.

In three months of treating patients we estimate to see 72 – 156. Assuming that 20% of the patients are not willing or able to participate, that gives an estimate of 58 – 125 possible subjects. Please see paragraph 4.4 for the sample size calculation.

4.2 Inclusion criteria

- Dentate or edentate patients with at least one screw-type titanium implant
- The implant should be in function for at least a period of 12 months
- Peri-implant intraosseous defect with at least 3 mm depth measured from the neck. The extent of bone loss will be measured on the basis of peri-apical radiographs
- Probing depth at the deepest site at least 5mm combined with bleeding and/or suppuration
- Patient above 18 years of age
- Psychological appropriateness
- Signed Informed Consent

4.3 Exclusion criteria

- Patient with a history of taking systemic antibiotics in the preceding 3 months
- Patient allergic to penicillin (amoxicillin) or metronidazole
- Systemic diseases like diabetes, HIV, Sjögren, SLE, Renal insufficiency, patients with disturbed blood behavior, patients with neurologic disorders etc.
- Use of NSAID's in the last 4 weeks
- Current pregnancy or lactating
- Mobile implants

The worst implant site of each patient will be selected as a target site.

List of medications that cannot be used in combination with antibiotics

Amoxicillin

- Probenecide
- Fenylbutazon
- Oxyfenbutazon
- Acetylsalicylzuur (to a lesser extent)
- Indometacine (to a lesser extent)
- Sulfinpyrazon (to a lesser extent)
- Tetracyclinen (nullifying)
- Macroliden (nullifying)
- Chlooramfenicol (nullifying)
- Aminoglycosiden (synergistic)
- Oral contraceptives (reduced efficacy of the oral contraceptive)

Metronidazole

- Fenobarbital o fenytoïne
- Cimetidine
- Disulfiram
- Ciclospoine
- 5-fluorouracil
- Busulfan
- Anticoagulantia of the coumarine type
- Lithium

Alcohol can not be used during and at least 48 hours after finishing the antibiotic treatment because of a disulfiram-like reaction.

4.4 Sample size calculation

In periodontal literature a general consensus is used for pocket probing depth (PPD) or clinical attachment level (CAL). A difference of 1 mm between treatments for PPD or CAL changes at initially deep pockets would be clinically relevant (Silva et al., 2011). Because there is no general consensus in peri-implantitis literature available - the sample size was calculated on basis of periodontitis considering differences of 1 mm between the intervention group and control group for the mean CAL change in pockets ≥ 7 mm. The standard deviation of 1 mm for CAL change in initially deep pockets was set based on a study of subjects receiving non-surgical treatment alone or combined with metronidazole and amoxicillin (Silva et al.,2011). Based on these calculations, it was determined that 16 subjects per group would be sufficient to provide a power of 80% with an α of 0.05. We need two groups:

a. Non-surgical treatment of peri-implantitis with the adjunctive use of systemic antibiotics (amoxicillin 375 mg and metronidazole 250 mg three times a day for 7 days).
b. Non-surgical treatment of peri-implantitis without the adjunctive use of systemic antibiotics.

Taking a drop out of 20% and a loss to follow up of 30% after one year into account, we need **48 subjects**, 24 in each group (Overall et al., 1998).

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

Peri-implantitis treatment:

Group a: Non-surgical treatment[1] (mechanical cleaning of the implant surface) of peri-implantitis with adjunctive use of systemic antibiotics (amoxicillin 375mg and metronidazole 250mg three times a day for 7 days).

Group b: Non-surgical treatment of peri-implantitis without the adjunctive use of systemic antibiotics.

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable

[1] Please see amendment 1 for the description of the standard treatment protocol of peri-implantitis.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Name and description of investigational medicinal product(s)

Amoxicillin 375 mg and metronidazole 250 mg.

6.2 Summary of findings from non-clinical studies

Antibiotics amoxicillin 375 mg and metronidazole 250 mg are used in this study. For further information please see section D2 of the study dossier for the Summary of Product Characteristics (SPC) for amoxicillin 375mg and for the Summary of Product Characteristics (SPC) for metronidazole please see section D2 of the study dossier. SPC's were downloaded via: http://www.cbg-meb.nl/CBG/nl/humane-geneesmiddelen/geneesmiddeleninformatiebank/ on the 31st of January 2012.

6.3 Summary of findings from clinical studies

Mombelli & Lang (1992) described a case report of 9 human subjects and the treatment of peri-implant lesions with systemic antibiotics and mechanical debridement, which resulted in reduction of the pocket probing depth and bleeding on probing around the implant when compared with baseline measurements. Buchmann et al. (1996) also made a case report, about 14 human subjects and peri-implantitis treatment with mechanical scaling and additional systemic antibiotics (metronidazole and amoxicillin). They found a larger reduction in pocket probing depth and bone defect when compared with baseline data.

An animal study showed that systemic antimicrobial therapy, combined with mechanical debridement and plaque control in experimental peri-implantitis in animals resulted in resolution of the peri-implantitis lesion and a significant recession of the marginal peri-implant mucosa when compared with baseline (Ericsson, 1996).

The effect of metronidazole in combination with amoxicillin in addition to the treatment of inflammated deep pockets around natural teeth has been widely investigated (Lindhe et al., 1982, 1983, Kornman et al., 1989, van Winkelhoff et al., 1989, Loesche et al., 1992, Pavicic et al., 1994, Elter et al., 1997, van Winkelhoff et al., 1996, Winkel et al., 1997, Berglundh et al., 1998, Winkel et al., 1998, 2001)

6.4 Summary of known and potential risks and benefits

Subjects in both groups can expect benefit from the treatment by reducing the peri-implant infection.

Subjects in group a can experience side effects with the use of systemic antibiotics. Please see section D2 of the study dossier for the Summary of Product Characteristics (SPC) for Amoxicillin 375mg for the possible side effects of amoxicillin. Please see section D2 of the study dossier for the Summary of Product Characteristics (SPC) for Metronidazole 250 mg for the possible side effects of metronidazole.

6.5 Description and justification of route of administration and dosage

The route of administration of both systemic antibiotics is oral. The single dose of metronidazole is 250 mg and the dose of amoxicillin is 375 mg. Subjects in group a will take 750 mg of metronidazol per day for seven days and 1125 mg of amoxicillin per day for seven days.

Tabel 1. Antibiotics dosage

Antibiotic	Dosage	Dosage per day (3 x a day)	Total dosage (7 days)
Metronidazole	250 mg	250 x 3 = 750 mg	750 x 7 = 5250 mg
Amoxicillin	375 mg	375 x 3 = 1125 mg	1125 x 7 = 7875 mg

6.6 Dosages, dosage modifications and method of administration

Dosage: metronidazol 250 mg, three capsules per day for seven days. Amoxicillin 375 mg, three capsules per day for seven days. There are no dosage modifications and the method of administration is oral.

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Subjects are asked to go to their own pharmacist with the receipt to get the antibiotics. The antibiotics receipt is signed by D. Anssari, dentist and randomly assigned by H. Thijm – independent co-worker - to the subjects. We use the same protocol and the same drug accountability as described in the previously by METC of AMC approved protocol *'Het effect van behandeling van parodontitis op markers van hart-en vaatzieken'*, section Periodontology, ACTA (ABR domain NL19679.018.07, MEC 07/264#08.17.0079)

Treatment protocol *'Het effect van behandeling van parodontitis op markers van hart-en vaatziekten'*

Parodontale behandeling

De patiënten worden random verdeeld in 2 groepen, welke volgens verschillende modaliteiten parodontale behandeling ondergaan:

Groep A: SRP alléén (de normale standaard behandeling)

Groep B: SRPC met ondersteuning van antibiotica

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The main focus of the evaluation is the clinical attachment level (CAL) change.

7.1.2 Secondary study parameters/endpoints

Secondary study endpoints are:

- plaque-accumulation (measured with the Plaque Control Record and bleeding index originally developed by O'Leary, Drake and Naylor in 1972)
- Bleeding on probing
- Recession (measured with the probe PC-15)
- Furcation (measured with the Birfurcation Probe Nabers#2N)
- Bone loss
- Mobility
- Loss of implant
- Composition of submucosal/subgingival plaque

7.1.3 Randomisation, blinding and treatment allocation

This is a randomized single blind controlled trial. The study is randomized using block design which will insure that the number of subjects receiving the different treatments is randomly and evenly allocated. The randomization is performed by H. Thijm. Leaflets with allocations to both groups will be placed in sealed envelopes (24 for each group). The code will be broken after the evaluation. Subjects are enrolled consecutively and each subject is given a unique research number. The allocation is saved in an excel file protected by a password and only known by Dr. M. Laine, dentist. Written instructions as well as verbal instructions will be given by H. Thijm on the use of the systemic antibiotics. Prior to the first treatment H. Thijm checks in which group the subject is assigned and the subjects in the test group will take the first dose of antibiotics. Other clinicians are blinded in this study.

7.2 Study procedures

Before the baseline appointment a short summary of the research is given during regular maintenance if the patient meets the inclusion criteria. When a patient wants to participate an appointment for an intake is made. During the intake appointment an oral explanation of the study is given and the patient takes home the written information letter.

The study procedures for this randomised controlled trial are explicated in table 1. Subsequent to the research protocol regular treatment procedures are performed. Please see amendment 1 for the description of the regular treatment protocol of peri-implantitis. Any diagnostic procedures or treatments are not postponed. Clinical measurements and anamneses are standard procedures during treatment appointments and will be adopted from the electronic health record of the subject.

Table 1. Procedures during research

Appointment	**Study procedure**
Baseline (BL) Performed by D. Anssari-Moin, dentist, section Periodontology	Signed informed consent Standard clinical measurements and anamneses 10 min. Plaque samples from the deepest pocket of the target implant and from the deepest pockets of a natural teeth (if present)
Randomisation (R) Performed by H. Thijm, independent co-worker, Section Oral Implantology	10 min. See paragraph 7.1.4
1st non-surgical treatment (T1) Performed by J. van der Horst, dental hygienist, Section Oral Implantology	(Dental hygiene instruction)
H. Thijm	2 min. First intake of antibiotics for the test group
2nd non-surgical treatment (T2) Performed by J. van der Horst	(Non-surgical treatment quadrant I and VI)
3rd non-surgical treatment (T3) Performed by J. van der Horst	(Non-surgical treatment quadrant II and III)
4th non-surgical treatment (T4 Performed by J. van der Horst	(Dental prophylaxis, removing all the staining, calculus and plaque)
Evaluation (E) Performed by D. Anssari-Moin	10 min. Plaque samples from the deepest pocket of the target implant(s) and from the deepest pockets of a natural teeth (if present)
Evaluation (E2) 1 year Performed by D. Anssari-Moin	10 min. Plaque samples from the deepest pocket of the target implant(s) and from the deepest pockets of a natural teeth (if present)
	Time for research: 42 minutes

Subjects will spend an average of 40 minutes more for the research when compared to the regular non-surgical peri-implantitis treatment with or without antibiotics.

Timeline research:

--------//--------(BL)---(R),(T1)---(T2)---(T3)--------(T4)----------(E)--------//-------(E2).

When there is a need for the microbiological findings due to the clinical situation after the first non-surgical treatment - before the evaluation - the code can be broken by M. Laine and the microbiological findings will be reported to the clinician.

After finishing the research protocol subjects will enroll to the regular maintenance program at the section of Oral Implantology (ACTA).

7.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The treatment of the subject if he/she wishes may be continued at ACTA outside the study without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.3.1 Specific criteria for withdrawal

A subject will quit the study protocol before the end of the study under the following circumstances:

1. Subjects not returning for controls (no-shows).

7.4 Replacement of individual subjects after withdrawal

After withdrawal an additional subject can be included. Twelve extra envelopes (six for each group) are available for the randomisation in a safe.

7.5 Follow-up of subjects withdrawn from treatment

Follows normal treatment procedures of ACTA.

7.6 Premature termination of the study

Subject: Reasons for premature termination of the study subject not returning for controls (no-shows) and loss of implant(s). If the subject will no longer participate in the study and if he/she wishes, treatment can be continued at ACTA (outside the study) without any consequences.

SAFETY REPORTING

7.7 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

7.8 Adverse and serious adverse events

If an adverse event occurs the patient should come to the clinic of the section Oral Implantology or Periodontology (ACTA). One of the clinical investigators has to see the patient and fill in the form '*adverse events form: safety reporting'* (see section C2 amendments). If certain serious adverse events do not require immediate reporting, these events are as well reported.

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the treatment and/or systemic antibiotics (amoxicillin and/or metronidazole). An adverse event can also be related to a diagnostic procedure or to an already existing condition. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

7.8.1 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 7.8);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;

The investigator will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same investigator and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The investigator will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

The key to the code is safeguarded by dr. M. Laine. If the code needs to be broken the clinician contacts dr. M. Laine.

7.8.2 Annual safety report

In addition to the expedited reporting of SUSARs, the investigator will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

7.9 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

7.10 Data Safety Monitoring Board (DSMB)

Not applicable

8. STATISTICAL ANALYSIS

8.1 Descriptive statistics

The categorical data will be displayed in frequency tables, one for the group a and one for group b. The quantitative continuous variables will be presented as means and standard deviations (normal distribution) or median and inter quartile range (no normal distribution). All statistical analyses will be performed using statistics software (SPSS PASW Statistics version 18.0 for Windows, Chicago, IL, USA).

8.2 Univariate analysis

Confidence intervals will be employed to estimate the difference in CAL (clinical attachment level) between all treatment groups.

Group a: Non-surgical treatment (mechanical cleaning of the implant surface) of peri-implantitis with the adjunctive use of systemic antibiotics (amoxicillin 375mg and metronidazole 250mg three times a day for 7 days).

Group b: Non-surgical treatment of peri-implantitis without the adjunctive use of systemic antibiotics.

If possible, statistical comparison between the groups will be performed by applying the ANCOVA test, with appropriate covariates (such as gender, age, smoking habits). Otherwise the distribution will be compared using the Mann-Whitney U-test. Two tailed p values < 0.05 will be considered significant. Differences in categorical variables will be tested by the Chi-squared test or Fisher's exact test, as appropriate.

8.3 Multivariate analysis

The contribution of risk factors for the effect of the peri-implantitis treatment – other than pathogenic bacteria, – will be assessed by multiple linear regression analysis.

8.4 Interim analysis (if applicable)

Not applicable

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (sixth revision (2008)) developed by the Working Group for consideration by the Ethics Committee and finally the General Assembly and in accordance with the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and consent

Subjects will be recruited when they visit the section of Oral Implantology and Periodontology for regular dental implant maintenance. Subjects need to be 18 years of age or older and mentally competent (psychological appropriateness). When a patient meets the inclusion criteria the dental hygienist will inform and ask the subject to participate. During intake, information about the study will be given orally and in writing. The patient information letter and informed consent are provided in section E of the study dossier. The patient takes the information letter and informed consent at home and is asked to bring it to the baseline appointment. If the patient is willing to participate he can sign the informed consent.

The minimum time given to a patient to consider his/her decision is one week.

Table 3. Recruitment and consent

Action	**By who?**
Recruitment and global explanation of the study	J. van der Horst, dental hygienist
Oral explanation of the study	D. Anssari, dentist
Hand out information letter and informed consent	D. Anssari, dentist
Consider decision (at least 1week)	Patient
Signed informed consent when patient agrees	D. Anssari, dentist

9.3 Objection by minors or incapacitated subjects

Not applicable.

9.4 Benefits and risks assessment, group relatedness

Non-surgical treatment of peri-implantitis by mechanical debridement of the biofilm with/without the adjunctive use of systemic antibiotics is implemented in the daily dental practice according to several standard protocols in the Netherlands and throughout the world. It had been reported that both treatment protocols may be successful treatment regimes for peri-implantitis (Mombelli & Lang, 1992; Buchmann et al., 1996; Khoury & Buchmann, 2001;Renvert et al., 2008; Mattheos et al.,2012).

The relevance of this study is to determine whether the non-surgical treatment with or without antibiotics is more beneficial in treating peri-implantitis.
We expect that subjects in both groups will benefit from the treatment by reducing the peri-implant infection which can lead to better maintenance of the peri-implant tissue. This may result in less need for surgical treatments of peri-implant lesions and less implant failure in the future.

Subjects can experience side effects with the use of systemic antibiotics.
Please see section D2 of the study dossier for the Summary of Product Characteristics (SPC) for amoxicillin 375mg for the possible side effects of amoxicillin.
Please see section D2 of the study dossier for the Summary of Product Characteristics (SPC) for metronidazole 250 mg for the possible side effects of metronidazole.

9.5 Compensation for injury

The investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

9.6 Incentives (if applicable)

Subjects receive the peri-implantitis treatment (non-surgical mechanical debridement of the biofilm).

10. ADMINISTRATIVE ASPECTS AND PUBLICATION

10.1 Handling and storage of data and documents

All data will be handled confidentially and anonymously under a unique study number. Where it is necessary the data is traceable to an individual subject identification code list, every subject gets a unique study number. The subject is not traceable. No initials or birth-dates are used. The key to the code is safeguarded by M. Laine. If material is left after the study, it can be used anonymously for other experiments at the section of Oral Implantology or Periodontology (ACTA), for education purposes, and the material cannot be led to the subject.

10.2 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

10.3 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.4 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last subject's last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination.

Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

10.5 Public disclosure and publication policy

The study will be registered in a public trial registry. The results of the study will be published in peer-reviewed international medical journals.

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AMENDEMENT 1

Regular peri-implantitis treatment protocol in sections Oral Implantology and Periodontology, ACTA.

Regular peri-implantitis treatment protocol in sections Oral Implantology and Periodontology	
1st appointment	Medical, oral hygiene and dental anamneses Intra and extra oral examination Complete periodontal chart natural elements and dental implants - Clinical attachment level (CAL) - Plaque index and bleeding index - Pocket probing depth (PDD< measured with the probe PC-15) - Recession (measured with the probe PC-15) - Furcation (measured with the Bifurcation Probe Nabers32N) - Mobility Radiographs Light photographs Take microbiological samples
2nd appointment	Dental hygiene instruction - Toothbrush - Interdental brushes, wood sticks - Superfloss - Chlorhexidine 0,12% 4 weeks, 2times a day Non-surgical treatment under local anaesthetics. - Ultrasonic instrument with implant tip - Hand instruments for dental implants - Polish Give antibiotics (amoxicillin 375 mg and metronidazole 250 mg three times a day for 7 days) recipe, when necessary
3rd and 4th appointment (if applicable)	Scaling and root planing natural elements
Dental hygiene check, six weeks after non-surgical treatment	Anamneses update Oral examination update Visual inspection (plaque) Repeat dental hygiene instruction Full dental hygiene prophylaxis
Evaluation, six weeks after dental hygiene check	Anamneses update Complete periodontal chart (plaque index, bleeding index, pocket probing depth, recession) Full dental hygiene prophylaxis (when necessary) Take microbiological samples, when necessary
Recall, every three months	Anamneses update Oral examination update Visual inspection (plaque) Repeat dental hygiene instruction Full dental hygiene prophylaxis
Evaluation, once a year	Anamneses update

	Complete periodontal chart (plaque index, bleeding index, pocket probing depth, recession) Full dental hygiene prophylaxis (when necessary)