# Clinical trial results:
# Surgical treatment of peri-implantitis with and without systemically adjunctive antibiotics
# A prospective, open, randomized, three armed, parallel, placebo controlled clinical trial

## Summary

| | |
|---|---|
| EudraCT number | 2013-004724-11 |
| Trial protocol | SE |
| Global end of trial date | 27 May 2022 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 13 July 2024 |
| First version publication date | 13 July 2024 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 294568 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Karolinska Institutet |
| Sponsor organisation address | Nobels väg 6, Solna, Sweden, |
| Public contact | Margareta Hultin, Karolinska Institute, +46 08524 882 48 , margareta.hultin@ki.se |
| Scientific contact | Margareta Hultin, Karolinska Institute, +46 08524 882 48 , margareta.hultin@ki.se |

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 | 27 May 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 May 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 May 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the present study is to evaluate the adjunctive effect of systemically administered antibiotics during surgical treatment of peri-implantitis.

Protection of trial subjects:

The study was approved by the Ethics Committee, Stockholm, Sweden (Dnr 2014-1331-31-1) and Swedish Medical Products Agency (EudraCT no 2013-004724-11) and conducted in accordance with the Helsinki Declaration as revised in 2013. CONSORT guidelines were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 14 April 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Scientific research |
| Long term follow-up duration | 12 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Sweden: 84 |
| Worldwide total number of subjects | 84 |
| EEA total number of subjects | 84 |

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) | 25 |
| From 65 to 84 years | 51 |

| | |
|---|---|
| 85 years and over | 8 |

## Subject disposition

### Recruitment

Recruitment details:

Patients were referred for peri-implantitis to the Department of Periodontology, Specialist Clinic Kaniken, Public Dental Health Service, Uppsala, Sweden and screened for eligibility prior to baseline examination. All patients were informed about the details of the study and asked to sign a consent before inclusion in the study.

### Pre-assignment

Screening details:

Included patients were > 18 years with peri-implantitis, full-mouth plaque score (FMPS) of <= 30%, partially or completely edentulous with healthy or treated periodontal conditions enrolled in a regular supportive program.

### 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 | Investigator, Data analyst, Subject |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Surgical treatment with amoxicillin + metronidazole |

Arm description:

Surgical treatment with amoxicillin 500mgx3x7 + metronidazole 400mgx3x7

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Amoxicillin |
| Investigational medicinal product code | |
| Other name | Amoxicillin Sandoz |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Amoxicillin Sandoz 500mgx3 for 7 days

| | |
|---|---|
| Investigational medicinal product name | Metronidazole |
| Investigational medicinal product code | |
| Other name | Flagyl Sanofi |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Metronidazole Sanofi 400mgx3 for 7 days

| | |
|---|---|
| **Arm title** | Surgical treatment with metronidazole + phenoxymethylpenicilli |

Arm description:

Surgical treatment with metronidazole 400mgx3x7 + phenoxymethylpenicillin (800mgx2), x3x7

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Metronidazole |
| Investigational medicinal product code | |
| Other name | Flagyl Sanofi |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Metronidazole Sanofi 400mgx3 for 7 days

| | |
|---|---|
| Investigational medicinal product name | PHENOXYMETHYLPENICILLIN |
| Investigational medicinal product code | |
| Other name | Kåvepenin |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

800mgx2x3 for 7 days

| | |
|---|---|
| **Arm title** | Surgical treatment with placebo amoxicillin + metronidazole |

Arm description:

Surgical treatment with placebo tablets amoxicillin 500mg and 400mg metronidazole, 2 capsules 3 times daily.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Amoxicillin placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Amoxicillin placebo 500mgx3 for 7 days

| | |
|---|---|
| Investigational medicinal product name | metronidazole placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Metronidazole placebo 400mgx3 for 7 days

| **Number of subjects in period 1** | Surgical treatment with amoxicillin + metronidazole | Surgical treatment with metronidazole + phenoxymethylpenicillin | Surgical treatment with placebo amoxicillin + metronidazole |
|---|---|---|---|
| Started | 28 | 28 | 28 |
| Completed | 26 | 26 | 24 |
| Not completed | 2 | 2 | 4 |
| Adverse event, serious fatal | - | 1 | - |
| Consent withdrawn by subject | 1 | - | 2 |
| started antibiotic treatment for other condition | - | - | 1 |
| patient needed other intervention | - | - | 1 |
| panic attack before surgery | 1 | - | - |
| Protocol deviation | - | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Surgical treatment with amoxicillin + metronidazole |
| Reporting group description: | |
| Surgical treatment with amoxicillin 500mgx3x7 + metronidazole 400mgx3x7 | |
| Reporting group title | Surgical treatment with metronidazole + phenoxymethylpenicilli |
| Reporting group description: | |
| Surgical treatment with metronidazole 400mgx3x7 + phenoxymethylpenicillin (800mgx2), x3x7 | |
| Reporting group title | Surgical treatment with placebo amoxicillin + metronidazole |
| Reporting group description: | |
| Surgical treatment with placebo tablets amoxicillin 500mg and 400mg metronidazole, 2 capsules 3 times daily. | |

| Reporting group values | Surgical treatment with amoxicillin + metronidazole | Surgical treatment with metronidazole + phenoxymethylpenicilli | Surgical treatment with placebo amoxicillin + metronidazole |
|---|---|---|---|
| Number of subjects | 28 | 28 | 28 |
| Age categorical<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 62.07 | 66.64 | 69.54 |
| standard deviation | ± 17.8 | ± 16.6 | ± 13.4 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 18 | 19 | 15 |
| Male | 10 | 9 | 13 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 84 | | |
| Age categorical<br>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) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 52 | | |
| Male | 32 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Surgical treatment with amoxicillin + metronidazole |
| Reporting group description: | |
| Surgical treatment with amoxicillin 500mgx3x7 + metronidazole 400mgx3x7 | |
| Reporting group title | Surgical treatment with metronidazole + phenoxymethylpenicilli |
| Reporting group description: | |
| Surgical treatment with metronidazole 400mgx3x7 + phenoxymethylpenicillin (800mgx2), x3x7 | |
| Reporting group title | Surgical treatment with placebo amoxicillin + metronidazole |
| Reporting group description: | |
| Surgical treatment with placebo tablets amoxicillin 500mg and 400mg metronidazole, 2 capsules 3 times daily. | |

### Primary: Peri-implant pocket reduction at 6 months

| | |
|---|---|
| End point title | Peri-implant pocket reduction at 6 months |
| End point description: | |

| | |
|---|---|
| End point type | Primary |
| End point timeframe: | |
| From baseline to 6 months | |

| End point values | Surgical treatment with amoxicillin + metronidazole | Surgical treatment with metronidazole + phenoxymethyl penicilli | Surgical treatment with placebo amoxicillin + metronidazole | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 26[1] | 26[2] | 24[3] | |
| Units: millimetre(s) | | | | |
| arithmetic mean (standard deviation) | -3.23 (± 1.78) | -3.26 (± 1.54) | -2.81 (± 2.00) | |

Notes:

[1] - Number of implants = 40

[2] - Number of implants = 35

[3] - Number of implants = 29

### Statistical analyses

| Statistical analysis title | Mean probing depth changes (mm) between groups |
|---|---|
| Statistical analysis description: | |
| Mean probing depth changes (mm) between baseline and 6 months and between groups | |
| Comparison groups | Surgical treatment with amoxicillin + metronidazole v Surgical treatment with metronidazole + phenoxymethylpenicilli v Surgical treatment with placebo amoxicillin + metronidazole |

| | |
|---|---|
| Number of subjects included in analysis | 76 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.458 |
| Method | Kruskal-wallis |

## Primary: Peri-implant pocket reduction at 12 months

| | |
|---|---|
| End point title | Peri-implant pocket reduction at 12 months |

End point description:

| | |
|---|---|
| End point type | Primary |

End point timeframe:

From baseline to 12 months

| End point values | Surgical treatment with amoxicillin + metronidazole | Surgical treatment with metronidazole + phenoxymethyl penicilli | Surgical treatment with placebo amoxicillin + metronidazole | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 26[4] | 26[5] | 24[6] | |
| Units: millimetre(s) | | | | |
| arithmetic mean (standard deviation) | -3.38 (± 1.72) | -3.29 (± 1.47) | -3.07 (± 2.23) | |

Notes:

[4] - Number of implants = 40

[5] - Number of implants = 35

[6] - Number of implants = 29

### Statistical analyses

| Statistical analysis title | Mean probing depth changes (mm) between groups |
|---|---|

Statistical analysis description:

Mean probing depth changes (mm) between baseline and 12 months and between groups

| | |
|---|---|
| Comparison groups | Surgical treatment with amoxicillin + metronidazole v Surgical treatment with metronidazole + phenoxymethylpenicilli v Surgical treatment with placebo amoxicillin + metronidazole |
| Number of subjects included in analysis | 76 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.565 |
| Method | Kruskal-wallis |

## Primary: Marginal bone level stability at baseline

| | |
|---|---|
| End point title | Marginal bone level stability at baseline |

End point description:

| End point type | Primary |
|---|---|

End point timeframe:

Baseline

| **End point values** | Surgical treatment with amoxicillin + metronidazole | Surgical treatment with metronidazole + phenoxymethyl penicilli | Surgical treatment with placebo amoxicillin + metronidazole | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 26[7] | 26[8] | 24[9] | |
| Units: millimetre(s) | | | | |
| arithmetic mean (standard deviation) | 5.1 (± 2.3) | 5.1 (± 1.8) | 5.1 (± 2.0) | |

Notes:

[7] - Number of implants = 40

[8] - Number of implants = 35

[9] - Number of implants = 29

### Statistical analyses

| **Statistical analysis title** | Mean marginal bone level (mm) between groups |
|---|---|

Statistical analysis description:

Mean marginal bone level (mm) between groups at baseline

| Comparison groups | Surgical treatment with amoxicillin + metronidazole v Surgical treatment with metronidazole + phenoxymethylpenicilli v Surgical treatment with placebo amoxicillin + metronidazole |
|---|---|
| Number of subjects included in analysis | 76 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.926 |
| Method | Wilcoxon signed rank test |

## Primary: Marginal bone level stability Postoperatively

| End point title | Marginal bone level stability Postoperatively |
|---|---|

End point description:

| End point type | Primary |
|---|---|

End point timeframe:

Postoperatively

| End point values | Surgical treatment with amoxicillin + metronidazole | Surgical treatment with metronidazole + phenoxymethyl penicilli | Surgical treatment with placebo amoxicillin + metronidazole | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 26[10] | 26[11] | 24[12] | |
| Units: millimetre(s) | | | | |
| arithmetic mean (standard deviation) | 5.2 (± 2.3) | 5.2 (± 1.8) | 5.4 (± 2.0) | |

Notes:

[10] - Number of implants = 40

[11] - Number of implants = 35

[12] - Number of implants = 29

## Statistical analyses

| Statistical analysis title | Mean marginal bone level (mm) between groups |
|---|---|
| Statistical analysis description:<br>Mean marginal bone level (mm) between groups - Postoperatively | |
| Comparison groups | Surgical treatment with amoxicillin + metronidazole v Surgical treatment with metronidazole + phenoxymethylpenicilli v Surgical treatment with placebo amoxicillin + metronidazole |
| Number of subjects included in analysis | 76 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.76 |
| Method | Wilcoxon signed rank test |

## Primary: Marginal bone level stability at 12 months

| End point title | Marginal bone level stability at 12 months |
|---|---|
| End point description: | |
| End point type | Primary |
| End point timeframe:<br>at 12 months | |

| End point values | Surgical treatment with amoxicillin + metronidazole | Surgical treatment with metronidazole + phenoxymethyl penicilli | Surgical treatment with placebo amoxicillin + metronidazole | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 26[13] | 26[14] | 24[15] | |
| Units: millimetre(s) | | | | |
| arithmetic mean (standard deviation) | 4.2 (± 2.2) | 4.9 (± 1.8) | 5.1 (± 2.0) | |

Notes:
[13] - Number of implants = 40
[14] - Number of implants = 35
[15] - Number of implants = 29

## Statistical analyses

| **Statistical analysis title** | Mean marginal bone level (mm) between groups |
|---|---|
| Statistical analysis description:<br>Mean marginal bone level (mm) between groups at 12 months | |
| Comparison groups | Surgical treatment with amoxicillin + metronidazole v Surgical treatment with metronidazole + phenoxymethylpenicilli v Surgical treatment with placebo amoxicillin + metronidazole |
| Number of subjects included in analysis | 76 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.118 |
| Method | Wilcoxon signed rank test |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From 2015-04-14 to 2022-05-27

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | Free text |
| Dictionary version | n/a |

### Reporting groups

| | |
|---|---|
| Reporting group title | All study subjects |

Reporting group description: -

| Serious adverse events | All study subjects | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 84 (8.33%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma | Additional description: Malignant tumor | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Stroke | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Reproductive system and breast disorders | | | |
| Testicular cancer | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Primary biliary cholangitis | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Bladder cancer | Additional description: Urine bladder cancer | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | All study subjects | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 36 / 84 (42.86%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | | |
| occurrences (all) | 2 | | |
| Panic attack | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Waldenstrom's macroglobulinaemia | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | | |
| occurrences (all) | 2 | | |

| | | | |
|---|---|---|---|
| Pain | | | |
| subjects affected / exposed | 3 / 84 (3.57%) | | |
| occurrences (all) | 3 | | |
| Swelling | | | |
| subjects affected / exposed | 7 / 84 (8.33%) | | |
| occurrences (all) | 7 | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences (all) | 1 | | |
| Sinus disorder | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | | |
| occurrences (all) | 2 | | |
| Obstruction | Additional description: Obstruction sublingual caruncle | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Taste disorder | Additional description: Bad taste | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences (all) | 1 | | |
| Flatulence | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | | |
| occurrences (all) | 2 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 84 (3.57%) | | |
| occurrences (all) | 3 | | |
| Nausea | | | |
| subjects affected / exposed | 5 / 84 (5.95%) | | |
| occurrences (all) | 5 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 11 / 84 (13.10%) | | |
| occurrences (all) | 11 | | |
| Heartburn | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences (all) | 1 | | |
| Appetite disorder | Additional description: No appetite | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 84 (3.57%) | | |
| occurrences (all) | 3 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | Additional description: Skin rash | | |
| subjects affected / exposed | 2 / 84 (2.38%) | | |
| occurrences (all) | 2 | | |
| Itching | | | |
| subjects affected / exposed | 3 / 84 (3.57%) | | |
| occurrences (all) | 3 | | |
| Allergy | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Cold like symptoms | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | | |
| occurrences (all) | 1 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 12 December 2016 | Closing of one study center (Folktandvården Skanstull). Recruitement of patients only made to study center in Uppsala. |
| 11 April 2018 | Changes in inclusioncriteria 1 and 6. Change in exclusioncriteria 2. Changes made in follow-up visits (Visit 1 and Visit 2 became Visit 1. Visit 5 was removed.) |
| 18 August 2020 | Extension made on shelf-life for placebo capsules from 24 months to 36 months. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported