



## 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
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##### 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
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Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	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
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## 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  $\leq 30\%$ , 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	Subject, Investigator, Data analyst

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	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

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

Reporting group values	Total		
Number of subjects	84		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)	0 0 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 + phenoxymethylpenicilli	Surgical treatment with placebo amoxicillin + metronidazole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26 <sup>[1]</sup>	26 <sup>[2]</sup>	24 <sup>[3]</sup>	
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 <sup>[4]</sup>	26 <sup>[5]</sup>	24 <sup>[6]</sup>	
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
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End point description:

End point type	Primary
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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 <sup>[7]</sup>	26 <sup>[8]</sup>	24 <sup>[9]</sup>	
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
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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
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End point description:

End point type	Primary
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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 <sup>[10]</sup>	26 <sup>[11]</sup>	24 <sup>[12]</sup>	
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:	
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:	
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 <sup>[13]</sup>	26 <sup>[14]</sup>	24 <sup>[15]</sup>	
Units: millimetre(s)				
arithmetic mean (standard deviation)	4.2 (± 2.2)	4.9 (± 1.8)	5.1 (± 2.0)	

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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:	
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
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### Dictionary used

Dictionary name	Free text
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Dictionary version	n/a
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### Reporting groups

Reporting group title	All study subjects
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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 %

<b>Non-serious adverse events</b>	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 occurrences (all)	3 / 84 (3.57%) 3		
Skin and subcutaneous tissue disorders			
Rash	Additional description: Skin rash		
subjects affected / exposed occurrences (all)	2 / 84 (2.38%) 2		
Itching			
subjects affected / exposed occurrences (all)	3 / 84 (3.57%) 3		
Allergy			
subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1		
Infections and infestations			
Cold like symptoms			
subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 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). Recruitment 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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported