Clinical trial results:
A randomised study of 5 and 10 days treatment with phenoxymethyl penicillin against streptococcal pharyngotonsillitis.

Summary

EudraCT number	2015-001752-30
Trial protocol	SE
Global end of trial date	15 June 2018

Results information

Result version number	v1 (current)
This version publication date	31 August 2019
First version publication date	31 August 2019
Summary attachment (see zip file)	clinical study report (2019-06-25_Clinical study report_2015-001752-30.docx) code book (Code book pdf.pdf) full data set (dataCRF_2019-02-19.xlsx)

Trial information

Trial identification

Sponsor protocol code	FoHM/Tonsillit2015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02712307
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Public health Agency of Sweden
Sponsor organisation address	Nobels väg 18, Solna, Sweden, 171 82
Public contact	Antibiotics and Infection Control, Public Health Agency of Sweden, 46 102052000, charlotta.edlund@folkhalsomyndigheten.se
Scientific contact	Antibiotics and Infection Control, Public Health Agency of Sweden, 46 102052000, charlotta.edlund@folkhalsomyndigheten.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	25 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 June 2018
Global end of trial reached?	Yes
Global end of trial date	15 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the clinical efficacy of 5 days (800 mg x 4) versus 10 days (1000 mg x 3) treatment with phenoxymethylpenicillin in adults, adolecsents and children with streoptococcal tonsillitis.

Protection of trial subjects:

None specific.

Background therapy:

No medication with immunomodulating treatment corresponding to ≥15 mg prednisolone at inclussion. No treatment with antibiotics for pharyngotonsillitis in the last month (relapse), or any antibiotic treatment during the last 72 h before inclusion.

Evidence for comparator:

It is the recommended dose regimen to patients with pharyngotonsillitis caused by GAS in Sweden.

Actual start date of recruitment	11 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 422
Worldwide total number of subjects	422
EEA total number of subjects	422

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)	72
Adolescents (12-17 years)	33
Adults (18-64 years)	314
From 65 to 84 years	3

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Open randomised study. Patients were recruited from 17 PHCC in Sweden, from September 2015 to February 2018.

Pre-assignment

Screening details:

Patient aged 6 years or older with confirmed pharyngotonsillitis caused by Streptococcus Group A. Signed informed consent form.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	5 days treatment

Arm description:

Penicillin V 800 mg x 4 for 5 days

Arm type	Experimental
Investigational medicinal product name	Phenoxymethylpenicillin
Investigational medicinal product code	
Other name	Penicillin V
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

800 mg x 4 for 5 days

Arm title	10 days treatment

Arm description:

Penicillin V 1000 mg x 3 for 10 days

Arm type	Active comparator
Investigational medicinal product name	Phenoxymethylpenicillin
Investigational medicinal product code	
Other name	Penicillin V
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg x 3 for 10 days

Number of subjects in period 1	5 days treatment	10 days treatment
Started	212	210
Completed	212	210

Baseline characteristics

Reporting groups	
Reporting group title	5 days treatment
Reporting group description:	
Penicillin V 800 mg x 4 for 5 days	
Reporting group title	10 days treatment
Reporting group description:	
Penicillin V 1000 mg x 3 for 10 days	

Reporting group values	5 days treatment	10 days treatment	Total
Number of subjects	212	210	422
Age categorical			
age			
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)	41	31	72
Adolescents (12-17 years)	14	19	33
Adults (18-64 years)	155	159	314
From 65-84 years	2	1	3
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	138	132	270
Male	74	78	152

Subject analysis sets	
Subject analysis set title	Per protocol population
Subject analysis set type	Per protocol
Subject analysis set description:	
No violations to the study protocol	
Subject analysis set title	MITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Had at least one dose of study drug	

Reporting group values	Per protocol population	MITT	
Number of subjects	397	422	
Age categorical			
age			
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)		72	
Adolescents (12-17 years)		33	
Adults (18-64 years)		314	
From 65-84 years		3	
85 years and over		0	
Gender categorical			
Units: Subjects			
Female		138	
Male		74	

End points

End points reporting groups

Reporting group title	5 days treatment
Reporting group description: Penicillin V 800 mg x 4 for 5 days	
Reporting group title	10 days treatment
Reporting group description: Penicillin V 1000 mg x 3 for 10 days	
Subject analysis set title	Per protocol population
Subject analysis set type	Per protocol
Subject analysis set description: No violations to the study protocol	
Subject analysis set title	MITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Had at least one dose of study drug	

Primary: Clinical cure at TOC

End point title	Clinical cure at TOC
End point description:	
End point type	Primary
End point timeframe: 5-7 Days after last dose of study drug	

End point values	5 days treatment	10 days treatment	Per protocol population	MITT
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	212	210	397	422
Units: no of paients with clinical cure at TOC	190	197	363	387

Statistical analyses

Statistical analysis title	primary endpoint
Statistical analysis description: Categorical variables were presented as numbers (n) and percentages (%) and tested with Fisher´s exact test.	
Comparison groups	5 days treatment v 10 days treatment

Number of subjects included in analysis	422
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.05
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.7
upper limit	2.2

Notes:

[1] - The primary efficacy variable, clinical cure, was presented with n (%), and the risk difference between the two treatment arms was presented with an approximate two-sided 95% confidence interval (CI). The analysis for the primary endpoint was performed on the PP population, supplemented by the MITT population. The non-inferiority margin of 10%.

Secondary: bacteriological eradication at TOC

End point title	bacteriological eradication at TOC

End point description:

End point type	Secondary

End point timeframe:

5 - 7 Days after last dose of study drug

End point values	5 days treatment	10 days treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	182		
Units: no of paients with bacteriologica at TOC				
bacteriological eradication	156	165		

Statistical analyses

Statistical analysis title	secondary endpoint, bacteriological eradication
Comparison groups	5 days treatment v 10 days treatment
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	-10.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.8
upper limit	-2.7

Secondary: relapse within one month

End point title	relapse within one month

End point description:

End point type	Secondary

End point timeframe:

1 month after inclusion

End point values	5 days treatment	10 days treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	180		
Units: no of pations with relapse				
relapse	8	7		

Statistical analyses

No statistical analyses for this end point

Secondary: complications within 3 months

End point title	complications within 3 months

End point description:

End point type	Secondary

End point timeframe:

within 3 months after inclusion

End point values	5 days treatment	10 days treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	189		
Units: no of pations with complications within				
complication	0	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to three months after inclusion	
Adverse event reporting additional description:	
Reported to doctor	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups	
Reporting group title	MITT
Reporting group description:	
All patients who received at least one dose of study drug	

Serious adverse events	MITT		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 422 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	MITT		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	219 / 422 (51.90%)		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	78 / 422 (18.48%)		
occurrences (all)	78		
Nausea			
subjects affected / exposed	68 / 422 (16.11%)		
occurrences (all)	68		
Vomiting			
subjects affected / exposed	8 / 422 (1.90%)		
occurrences (all)	8		
Abdominal pain			

subjects affected / exposed occurrences (all)	15 / 422 (3.55%) 15		
Reproductive system and breast disorders Vaginal disorder subjects affected / exposed occurrences (all)	 36 / 422 (8.53%) 36		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 14 / 422 (3.32%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported