Clinical trial results:
Three versus five days of pivmecillinam 400 mg three times daily for community-acquired uncomplicated lower urinary tract infection: A randomised, double-blind, placebo-controlled superiority trial

Summary

EudraCT number	2014-001321-32
Trial protocol	DK
Global end of trial date	22 December 2017

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019
Summary attachment (see zip file)	Summary (Summary.docx)

Trial information

Trial identification

Sponsor protocol code	198809

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Department of Clinical Microbiology
Sponsor organisation address	Kettegård allé, Hvidovre, Denmark, 2650
Public contact	Department of Clinical Microbiology, Department of Clinical Microbiology, Hvidovre Hospital, 0045 36322428, Inge.Jenny.Dahl.Knudsen@regionh.dk
Scientific contact	Department of Clinical Microbiology, Department of Clinical Microbiology, Hvidovre Hospital, 0045 36322428, Inge.Jenny.Dahl.Knudsen@regionh.dk

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	12 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2017
Global end of trial reached?	Yes
Global end of trial date	22 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Identify and compare the efficacy of pivmecillinam 400 mg t.i.d in a 3-day respectively 5-day regimen, against community acquired lower urinary tract infections i.e. in women at the age of 18-70 years old.

Protection of trial subjects:

Diagnosis, treatment and management according to national guidelines for uncomplicated cystitis in primary care settings.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 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	Denmark: 368
Worldwide total number of subjects	368
EEA total number of subjects	368

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)	366
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

See open acces protocol and open acces manuscript publication:
MANUSCRIPT: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(19)30102-6/fulltext
Jansaker F, et al. 2019. eClinicalMedicine
PROTOCOL: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-016-2022-0
Jansaker F, et al. 2016. BMC inf dis.

Pre-assignment

Screening details:

PROTOCOL: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-016-2022-0
Jansaker F, et al. 2016. BMC inf dis.

Period 1

Period 1 title	12-05-2015 to 31-10-2017 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

See open acces protocol and open acces manuscript publication:
MANUSCRIPT: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(19)30102-6/fulltext
Jansaker F, et al. 2019. eClinicalMedicine
PROTOCOL: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-016-2022-0
Jansaker F, et al. 2016. BMC inf dis.

Arms

Are arms mutually exclusive?	Yes
Arm title	3-day

Arm description:

3 days of pivmecillinam 400 mg three times daily followed by two days of placebo (identical to pivmecillinam i coat, packing, color and look). Danish guidelines at the time.

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

Dosage and administration details:

400 mg tablet three times daily every 8th hour

Arm title	5-day

Arm description:

5 days of pivmecillinam 400 mg three times daily

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

Dosage and administration details:

400 mg tablet three times daily every 8th hour

Number of subjects in period 1	3-day	5-day
Started	188	180
Completed	163	161
Not completed	25	19
Lost to follow-up	25	19

Baseline characteristics

Reporting groups	
Reporting group title	3-day
Reporting group description:	
3 days of pivmecillinam 400 mg three times daily followed by two days of placebo (identical to pivmecillinam i coat, packing, color and look). Danish guidelines at the time.	
Reporting group title	5-day
Reporting group description:	
5 days of pivmecillinam 400 mg three times daily	

Reporting group values	3-day	5-day	Total
Number of subjects	188	180	368
Age categorical			
See table Table 1 and Appendix Table 2 in open acces manuscript publication: MANUSCRIPT: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(19)30102-6/fulltext Jansaker F, et al. 2019. eClinicalMedicine			
Units: Subjects			
women 18-70	188	180	368
Gender categorical			
Women 18-70 years			
Units: Subjects			
Female	188	180	368

Subject analysis sets	
Subject analysis set title	Analysed
Subject analysis set type	Per protocol
Subject analysis set description:	
368 women (18–70 years)	

Reporting group values	Analysed		
Number of subjects	368		
Age categorical			
See table Table 1 and Appendix Table 2 in open acces manuscript publication: MANUSCRIPT: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(19)30102-6/fulltext Jansaker F, et al. 2019. eClinicalMedicine			
Units: Subjects			
women 18-70	368		
Gender categorical			
Women 18-70 years			
Units: Subjects			
Female	368		

End points

End points reporting groups

Reporting group title	3-day
Reporting group description:	
3 days of pivmecillinam 400 mg three times daily followed by two days of placebo (identical to pivmecillinam i coat, packing, color and look). Danish guidelines at the time.	
Reporting group title	5-day
Reporting group description:	
5 days of pivmecillinam 400 mg three times daily	
Subject analysis set title	Analysed
Subject analysis set type	Per protocol
Subject analysis set description:	
368 women (18–70 years)	

Primary: Primary Clinical Outcome, Bacterial Outcome

End point title	Primary Clinical Outcome, Bacterial Outcome[1]

End point description:

Clinical success at the end of treatment occurred for 117 of 153 (76%) receiving the 5d-course and for 115 of 157 (73%) receiving the 3d course (difference 3.2% [95% CI -7.1% - 13.5%]; P = .601).

Mean time to symptom resolution was 2.91 (SD 1.46; [5d]) days and 2.94 (SD 1.42; [3d]) days (P = .894).

Bacteriological success was seen in 92 of 104 (88%) participants given the 5d course and in 86 of 99 (87%) given the 3d course (difference 1.6% [95% CI -8.4%-11.6%]; P = .895).

Please see final publication in open access journal for full details, supplementary data och RAW data fully available.

End point type	Primary

End point timeframe:

Clinical cure after end of intervention (i.e. five days therapy).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: For correct and to minimize risk of incorrect translation, please see statistical plan and statistical method under open access publication, which is done and written by professional statistican, which the uploader is not.
https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(19)30102-6/fulltext
(full article)
https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(19)30102-6/fulltext#secst0215
(here you find the statistical descriptions; supplementary data to article)

End point values	3-day	5-day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	153		
Units: 310	117	115		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

See open acces protocol and open acces manuscript publication:
MANUSCRIPT: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(19)30102-6/fulltext Jansaker F, et al. 2019. eClinicalMedicine
PROTOCOL: https://bmcinfectdis.biomedcentral.com/

Adverse event reporting additional description:

Appendix Table 8 in open acces manuscript publication:
MANUSCRIPT: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(19)30102-6/fulltext Jansaker F, et al. 2019. eClinicalMedicine

Assessment type	Systematic

Dictionary used

Dictionary name	Selexid label 2015
Dictionary version	1

Reporting groups

Reporting group title	Adverse events

Reporting group description:

Appendix Table 8 in open acces manuscript publication:
MANUSCRIPT: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(19)30102-6/fulltext Jansaker F, et al. 2019. eClinicalMedicine

"A total of 306 participants reported on adverse events in the diary (Appendix Table 8). There were no serious adverse events and no reported cases of Clostridium difficile associated diarrhoea"

Serious adverse events	Adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 368 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Adverse events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	117 / 368 (31.79%)		
Investigations			
Any known adverse reaction			
subjects affected / exposed	112 / 368 (30.43%)		
occurrences (all)	112		
Any unknown adverse reaction	Additional description: Depressive-like symptoms (n=1); palpitations (n=2); hot-flush/sweating (n=1); nosebleed (n=1); shaking hands (n=1); malaise (n=1).		

subjects affected / exposed	14 / 368 (3.80%)		
occurrences (all)	14		
Nervous system disorders			
Mild only	Additional description: Headach, tiredness, dizziness		
subjects affected / exposed	52 / 368 (14.13%)		
occurrences (all)	52		
Gastrointestinal disorders			
Gastrointestinal symptoms mild	Additional description: Diarrhoea; nausea; vomiting; stomach-ache; stomach-discomfort.		
subjects affected / exposed	72 / 368 (19.57%)		
occurrences (all)	72		
Skin and subcutaneous tissue disorders			
Skind mild	Additional description: Rashes; urticaria; pruritus; angioneurotic oedema		
subjects affected / exposed	7 / 368 (1.90%)		
occurrences (all)	7		
Infections and infestations			
Fungal infection	Additional description: Symptoms of vaginal candidiasis (n=17); symptoms of oral candidiasis (n=1).		
subjects affected / exposed	18 / 368 (4.89%)		
occurrences (all)	18		

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

See discuss section in open acces manuscript publication:
MANUSCRIPT: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(19)30102-6/fulltext
Jansaker F, et al. 2019. eClinicalMedicine

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31388664