Clinical trial results:
Ibuprofen versus mecillinam for uncomplicated cystitis in adult, non-pregnant women

Summary

EudraCT number	2012-002776-14
Trial protocol	NO DK SE
Global end of trial date	07 June 2016

Results information

Result version number	v1 (current)
This version publication date	10 June 2021
First version publication date	10 June 2021

Trial information

Trial identification

Sponsor protocol code	97

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01849926
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oslo
Sponsor organisation address	Postboks 1130, Blindern, Oslo, Norway, 0318
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Scientific contact	Ingvild Vik, University of Oslo, 0047 23487000, ingvild.vik@medisin.uio.no

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	08 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 June 2016
Global end of trial reached?	Yes
Global end of trial date	07 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Although uncomplicated cystitis is considered to be a mild condition and mostly self limiting, most patients who see a doctor will be treated with antibiotics. Antibiotics are known to give a quick relief of symptoms and shorten the course of the condition by a few days.
The aim of this study is to evaluate ibuprofen versus mecillinam in the treatment of uncomplicated cystitis in otherwise healthy, non-pregnant women.
Our main objective is to see whether symptomatic treatment with ibuprofen is equally efficiant as treatment with mecillinam in this group.

Protection of trial subjects:

The patients received information about the trial, intervention and follow-up at inclusion by a doctor or a study nurse. All study personnel were trained in GCP. The patients received contact information to the study site and to the study doctor and were welcome to contact the study site or the study doctor at any time throughout the trial if they had any questions or concerns.

Background therapy: -

Evidence for comparator:

We chose to use an NSAID instead of paracetamol because of its greater anti-inflammatory effect, presumably providing better pain relief. We chose to use ibuprofen over other NSAIDs because of its relatively beneficial adverse effect profile. We decided to use a relatively high dosage, 600 mg three times a day, in order to achieve the best possible pain relief. The dosage is well within the maximum recommended daily intake (2400 mg). We chose pivmecillinam because it is a narrow spectrum antibiotic and a first line treatment option for uUTIs in Scandinavia. It has selective activity against Gram-negative bacteria, especially E. coli, a relatively low resistance-driving effect and beneficial adverse effect profile.
In Norway and Sweden, the guidelines recommend 200 mg of pivmecillinam three times a day for three days as standard empirical treatment for uUTIs. In Denmark, however, they recommend 400 mg three times a day for three days. Both regimens have proven effectiveness, and since two out of three countries recommend the lower dosage we agreed upon using that regimen in the trial.
The study was designed to establish the non-inferiority of ibuprofen compared to pivmecillinam treatment regarding symptomatic relief four days after treatment initiation by a 10% inferiority margin. There is ample evidence that immediate antibiotics are superior to placebo in the treatment of uUTIs. The non-inferiority design was chosen because we wanted to test whether ibuprofen was a good enough treatment for uUTIs with regards to symptomatic relief, compared to the established treatment regimen. The trial was designed and conducted according to the CONSORT criteria with relevant extensions for non-inferiority trials.

Actual start date of recruitment	11 April 2013
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	Norway: 300
Country: Number of subjects enrolled	Sweden: 37

Country: Number of subjects enrolled	Denmark: 46
Worldwide total number of subjects	383
EEA total number of subjects	383

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)	383
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were assessed for eligibility from 11 April 2013 to 22 April 2016, and the last follow-up was made on 7 June 2016. The largest recruitment site was the AEOC in Oslo (260 patients), followed by the AEOC in Bergen (40 patients). In Denmark study personnel recruited 47 patients, and in Sweden they recruited 37 patients.

Pre-assignment

Screening details:

We recruited non-pregnant women aged 18–60 years with symptoms of an uncomplicated UTI. Inclusion criteria were dysuria combined with either increased urinary frequency or urinary urgency or both. 2,942 women were screened: 1,290 patients met 1 or more exclusion criteria, 1,269 patients were eligible, and 383 patients were enrolled in the trial.

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, Monitor, Data analyst, Carer

Blinding implementation details:

The study medicine was over-encapsulated. They used gelatin capsules where red iron oxide was used for color and titanium oxide as an opacifier. The study medicine was packed in 2 different kits, one with 9 capsules containing 200 mg pivmecillinam each, the other with 9 capsules containing 600 mg ibuprofen each .Each kit was labeled with a study number following a computer-generated randomization list created by an independent statistician using randomized block sizes of 2, 4, 6, or 8.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pivmecillinam

Arm description:

Pivmecillinam, 200 mg x3 for three days.

Arm type	Active comparator
Investigational medicinal product name	Pivmecillinam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

200mg x3 for three days.

Arm title	Ibuprofen

Arm description:

Ibuprofen 600mg x3 for three days

Arm type	Active comparator
Investigational medicinal product name	Ibuprofen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ibuprofen 600 mg x3 for three days

Number of subjects in period 1	Pivmecillinam	Ibuprofen
Started	189	194
Completed	154	150
Not completed	35	44
Adverse event, non-fatal	2	-
Drop outs (no post baseline information	-	13
Drop outs	11	-
Lost to follow-up	17	19
Felt well	5	4
Lack of efficacy	-	8

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	383	383	
Age categorical 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			
Women, 18-60 years.			
Units: years			
median	25		
standard deviation	± 8	-	
Gender categorical			
Women only			
Units: Subjects			
Female	383	383	
Male	0	0	

End points

End points reporting groups

Reporting group title	Pivmecillinam
Reporting group description:	
Pivmecillinam, 200 mg x3 for three days.	
Reporting group title	Ibuprofen
Reporting group description:	
Ibuprofen 600mg x3 for three days	
Subject analysis set title	Full analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The primary efficacy analyses were performed in the FAS, consisting of all randomized patients with at least 1 efficacy assessment after randomization. There were no missing data for the primary endpoint in the FAS.	

Primary: The proportion of patients who felt cured by day 4

End point title	The proportion of patients who felt cured by day 4
End point description:	
The main outcome measure of this trial was the proportion of patients who felt cured by day 4 as recorded in the patient diary. If we did not have information from the diary, we used the number of days until cure reported by the patient during the telephone follow-up.	
End point type	Primary
End point timeframe:	
4 days	

End point values	Pivmecillinam	Ibuprofen	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	178	181	359	
Units: 73.6%				
number (not applicable)	131	70	201	

Statistical analyses

Statistical analysis title	Non-inferiority, logistic regression
Statistical analysis description:	
Assuming no difference between the treatment groups in the proportion of patients feeling cured after 4 days, we calculated that 316 patients were required in the primary full analysis set (FAS) analyses to be 80% confident that the 1-sided 95% confidence limit would exclude a difference in favor of pivmecillinam of more than 10%. The primary and secondary dichotomous endpoints were analyzed using logistic regression or mixed effects logistic regression with treatment as a fixed effect.	
Comparison groups	Pivmecillinam v Ibuprofen

Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	> 0.99 [2]
Method	Regression, Linear
Parameter estimate	Risk difference (RD)
Point estimate	35
Confidence interval	
level	90 %
sides	2-sided
lower limit	27
upper limit	43

Notes:

[1] - The null hypothesis of this study was that treatment with ibuprofen would be inferior to pivmecillinam regarding the proportion of patients feeling cured after 4 days by a 10% margin. The alternative hypothesis was that ibuprofen would be non-inferior regarding the proportion of patients feeling cured after 4 days by at most 10%.

[2] - In the ibuprofen group, 70 patients (38.7%) felt cured by day 4 versus 131 patients (73.6%) in the pivmecillinam group (Table 2). Adjusted risk difference with 90% CI was 35% (27% to 43%), which is outside the predefined non-inferiority margin.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
4 weeks/28 days	
Adverse event reporting additional description:	
All adverse events were registered in the patient diary and reported. Serious adverse events were recorded and reported to the authorities according to GCP.	
Assessment type	Systematic

Dictionary used	
Dictionary name	ICD-10
Dictionary version	2017

Reporting groups	
Reporting group title	Pivmecillinam
Reporting group description:	
Patients who received treatment with pivmecillinam	
Reporting group title	Ibuprofen
Reporting group description:	
Patients who received treatment with ibuprofen	

Serious adverse events	Pivmecillinam	Ibuprofen	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 189 (0.53%)	6 / 181 (3.31%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Pyelonephritis	Additional description: Serious adverse events were defined as any event leading to hospitalization. In the pivmecillinam group there was one hospitalization not related to the study, in the ibuprofen group 5 hospitalizations were related to the study, 1 unclear.		
subjects affected / exposed	1 / 189 (0.53%)	6 / 181 (3.31%)	
occurrences causally related to treatment / all	0 / 1	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Pivmecillinam	Ibuprofen	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 189 (20.11%)	32 / 181 (17.68%)	
General disorders and administration site conditions			

Various symptoms and signs	Additional description: I have reported the total number of non serious adverse events, they are listed in detail in table 4 in the result article in PLOS Medicine.		
subjects affected / exposed	38 / 189 (20.11%)	32 / 181 (17.68%)	
occurrences (all)	49	40	

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.

A weakness was the extensive list of exclusion criteria, eliminating almost half of the patients presenting with symptoms of an uncomplicated UTI.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29763434