Clinical trial results:
The safety and pharmacokinetics of intraperitoneal administration of granulocyte-macrophage colony-stimulating factor, fosfomycin, and metronidazole in patients undergoing appendectomy for uncomplicated appendicitis

Summary

EudraCT number	2015-005772-16
Trial protocol	DK
Global end of trial date	07 December 2017

Results information

Result version number	v1 (current)
This version publication date	27 June 2019
First version publication date	27 June 2019

Trial information

Trial identification

Sponsor protocol code	HEH-SF-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03046758
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of Surgery, Herlev Hospital
Sponsor organisation address	Herlev Ringvej 75, Herlev, Denmark, 2730
Public contact	CPO office, Department of Surgery, 0045 38683414, siv.fonnes@regionh.dk
Scientific contact	CPO office, Department of Surgery, 0045 38683414, siv.fonnes@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	14 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The safety of intraperitoneal administration is evaluated through the white blood cell counts 4 hours postoperatively. A toxic effect is defined by a drop below the lower reference range.

Protection of trial subjects:

The trial would be stopped if severe adverse effects or severe complications, which were not expected, arose from the trial treatment. This was to be decided by the sponsor.

Assessment of harms
The participants were asked if they had experienced any changes both 12 hours and 10 days after the surgery in combination with an objective examination. This was documented in the CRF. Further, the patient was asked if they have experienced any adverse events defined as any unfavourable and unintended sign, symptom, or disease associated with the intraperitoneal treatment, whether or not related to that treatment. A follow-up was conducted 30 days after surgery. This was also be documented in the CRF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 February 2017
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: 14
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	13
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients planed for an acute surgery were approached by the trial personnel and informed about the trial. Patients, who fulfilled the inclusion criteria and presented none of the exclusion criteria, apart from those criteria that can only be clarified at surgery, were enrolled in the trial after informed consent.

Pre-assignment

Screening details:

A total of 121 patients were screened. 26 participants were enrolled and 12 of these were excluded prior to or during surgery. The most common reasons for exclusion were a normal or perforated appendix found during surgery.

Period 1

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

Arms

Arm title	Experimental

Arm description:

A combination of fosfomycin, metronidazole and GM-CSF i.p.
All drugs will be administered together intraperitoneally at the end of the surgery after the appendix has been removed.

Arm type	Experimental
Investigational medicinal product name	Repomol
Investigational medicinal product code	PR1
Other name	molgramostim, rhGM-CSF
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intraperitoneal use

Dosage and administration details:

A dose of 50 microgram Repomol (molgramostim/rhGM-CSF) in 0.2 ml of solution (water for injection) in combination with 4 g of fosfomycin and 1 g metronidazole, which were administered intraperitoneally and will remain as local installation.

Investigational medicinal product name	Fosfomycin disodium salt
Investigational medicinal product code	PR2
Other name	fosfomycin
Pharmaceutical forms	Powder for injection
Routes of administration	Intraperitoneal use

Dosage and administration details:

A dose of 4 g of fosfomycin diluted in 300 ml of sterile water for injections in combination with 50 microgram Repomol (molgramostim/rhGM-CSF) and 1 g metronidazole, which wereadministered intraperitoneally and remained as local installation.

Investigational medicinal product name	Metronidazole
Investigational medicinal product code	PR2
Other name	Metronidazole
Pharmaceutical forms	Infusion
Routes of administration	Intraperitoneal use

Dosage and administration details:

A dose of 1 g metronidazole corresponing to 200 ml in combination with 50 microgram Repomol (molgramostim/rhGM-CSF) and 4 g of fosfomycin and 1 g metronidazole, which were administered intraperitoneally and remained as local installation.1 g metronidazole

Number of subjects in period 1	Experimental
Started	14
Completed	14

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	14	14	
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 Units: years			
median	24		
full range (min-max)	18 to 67	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	14	14	
Height Units: cm			
median	183		
full range (min-max)	172 to 198	-	
Weight Units: kg			
median	88		
full range (min-max)	65 to 110	-	
BMI Units: kg/m^2			
median	26		
full range (min-max)	20 to 32	-	

End points

End points reporting groups

Reporting group title	Experimental

Reporting group description:

A combination of fosfomycin, metronidazole and GM-CSF i.p.
All drugs will be administered together intraperitoneally at the end of the surgery after the appendix has been removed.

Primary: Primary, postoperative WBC

End point title	Primary, postoperative WBC[1]

End point description:

The safety of intraperitoneal administration was evaluated through the white blood cell counts (WBC) 4 hours postoperatively. A toxic effect was defined by a drop below the lower reference range. Furthermore, postoperative and baseline WBC was compared with Wilcoxon signed-rank test, which found no difference (p=0.65).

End point type	Primary

End point timeframe:

Preoperatively (baseline) and 4 hours ± 30 minutes postoperatively

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: The statistical analysis is described. The statistical analyses could not be filled correctly as only one group but two time points are compared and not two groups.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ×10^9/l				
median (full range (min-max))	10.6 (7.10 to 20.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the administration until 30 days postoperatively.

Adverse event reporting additional description:

Adverse events were collected through interview with participants the first postoperative day, at visit 10 days postoperatively and through medical records and contact with the participant by telephone.

Assessment type	Systematic

Dictionary used

Dictionary name	ICD
Dictionary version	10

Reporting groups

Reporting group title	Overall

Reporting group description: -

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 14 (28.57%)		
Cardiac disorders			
Hypotension			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		

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.

No control group was included and low number of participants was included in this pilot trial. The recorded harms could be directly related to the trial treatment, the anaesthesia, or the surgery itself.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31040341