



## Clinical trial results:

### Perioperative metformin treatment for colon cancer - a randomized trial Summary

EudraCT number	2017-000722-35
Trial protocol	DK
Global end of trial date	08 October 2021

#### Results information

Result version number	v1 (current)
This version publication date	13 June 2024
First version publication date	13 June 2024

#### Trial information

##### Trial identification

Sponsor protocol code	ECO-01
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03359681
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Ismail Gögenur
Sponsor organisation address	Fælledvej 11, Slagelse, Denmark,
Public contact	Department of surgery, Department of surgery Slagelse Hospital, 45 61335122, eco@regionsjaelland.dk
Scientific contact	Department of surgery, Department of surgery Slagelse Hospital, 45 61335122, eco@regionsjaelland.dk
Sponsor organisation name	Ismail Gögenur
Sponsor organisation address	Lykkebækvej 1, Køge, Denmark, 4600
Public contact	Ismail Gögenur, Ismail Gögenur, +45 26336426, igo@regionsjaelland.dk
Scientific contact	Ismail Gögenur, Ismail Gögenur, +45 26336426, igo@regionsjaelland.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	01 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 October 2021
Global end of trial reached?	Yes
Global end of trial date	08 October 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The aim of the study is to investigate the effect of treatment with metformin on cell proliferation and on metabolic and immunological changes in non-diabetic patients with colon cancer.

The primary outcome is determination of the difference of the level of proliferation after the intervention (time of surgery) adjusted for the level seen at baseline (time of colonoscopy). Another primary outcome is the difference in tumorinfiltrating CD3 and CD8 positive lymphocytes after the intervention adjusted for the level seen at baseline.

Protection of trial subjects:

Study medication was added as an extra treatment to existing standard of care

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2018
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: 59
Worldwide total number of subjects	59
EEA total number of subjects	59

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)	15
From 65 to 84 years	43
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details:

59 patients were included and randomized. Of these 11 left the trial before surgery and were thus not included in the analyses (no data available). Out of the 11, four never received study medication. The seven patients that did receive study medication were included in the report of adverse events.

### Pre-assignment

Screening details:

The lists for all multidisciplinary team conferences were screened for eligible patients

### Period 1

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

### Arms

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

Arm description:

metformin treatment 500mg three times a day

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

Dosage and administration details:

First two days with 500mg once a day, then two days with 500mg twice a day and finally 500mg three times a day. Patients were treated for 20 days before surgery and 10 days after.

<b>Arm title</b>	Placebo
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Arm description:

placebo capsules looking identical to the ones in the metformin arm

Arm type	Placebo
Investigational medicinal product name	metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

500mg three times a day

Investigational medicinal product name	metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

500mg three times a day

<b>Number of subjects in period 1<sup>[1]</sup></b>	metformin	Placebo
Started	28	27
surgery	23	25
Completed	22	25
Not completed	6	2
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	5	-
Surgery cancelled	-	1

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: four patients were randomized but never received the intervention - one because of reduced kidney function and three because they withdrew consent to participate before starting the medication

## Baseline characteristics

### Reporting groups

Reporting group title	metformin
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Reporting group description:

metformin treatment 500mg three times a day

Reporting group title	Placebo
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Reporting group description:

placebo capsules looking identical to the ones in the metformin arm

Reporting group values	metformin	Placebo	Total
Number of subjects	28	27	55
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			
Age is reported for the 48 patients that completed the trial at least until surgery and so were included in the analyses of outcomes			
Units: years			
arithmetic mean	66.5	69.7	
standard deviation	± 7.9	± 10.2	-
Gender categorical			
Units: Subjects			
Female	16	15	31
Male	12	12	24

## End points

### End points reporting groups

Reporting group title	metformin
Reporting group description:	metformin treatment 500mg three times a day
Reporting group title	Placebo
Reporting group description:	placebo capsules looking identical to the ones in the metformin arm

### Primary: CD3 lymphocytes in tumor

End point title	CD3 lymphocytes in tumor
End point description:	Tumor cells were classified as positive or negative for CD3 within an area of interest and the density of positive nuclei was calculated. The difference from before treatment to after treatment was compared between the two groups
End point type	Primary
End point timeframe:	before and after treatment with metformin or placebo

End point values	metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	23		
Units: cells per area of interest				
median (inter-quartile range (Q1-Q3))	-153.1 (-355.7 to 133.2)	-58.96 (-342.05 to 85.61)		

### Statistical analyses

Statistical analysis title	CD3 lymphocytes in tumor
Comparison groups	metformin v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.98
Method	Willcoxon rank sum

### Primary: CD8 lymphocytes in tumor

End point title	CD8 lymphocytes in tumor
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End point description:

Tumor cells were classified as positive or negative for C83 within an area of interest and the density of positive nuclei was calculated. The difference from before treatment to after treatment was compared between the two groups

End point type	Primary
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End point timeframe:

Before and after treatment with metformin or placebo

End point values	metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	23		
Units: cells				
median (inter-quartile range (Q1-Q3))	-108.1 (-189.89 to -8.15)	-16.34 (-142.61 to 46.68)		

## Statistical analyses

Statistical analysis title	CD8 lymphocytes in tumor
Comparison groups	metformin v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.36
Method	Willcoxon rank sum

## Secondary: Blood glucose above 10mmol/l

End point title	Blood glucose above 10mmol/l
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End point description:

End point type	Secondary
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End point timeframe:

The number of patients with at least one glucose measurement above 10.0mmol/l within the first two days after surgery

End point values	metformin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23 <sup>[1]</sup>	25 <sup>[2]</sup>		
Units: people	5	13		

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Notes:

[1] - 5 patients left the study before surgery

[2] - 2 patients left the study before surgery

### Statistical analyses

<b>Statistical analysis title</b>	Blood glucose above 10.0mmol/l
Comparison groups	metformin v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.04
Method	Fisher exact



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

from the day the patients started taking the study medication until 24 hours after last ingestion of study medication

Assessment type	Systematic
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### Dictionary used

Dictionary name	none
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Dictionary version	0
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### Reporting groups

Reporting group title	metformin
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Reporting group description:

metformin treatment 500mg three times a day

Reporting group title	Placebo
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Reporting group description:

placebo capsules looking identical to the ones in the metformin arm

Serious adverse events	metformin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 28 (21.43%)	4 / 27 (14.81%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events		0	
Cardiac disorders			
Cardiac arrest	Additional description: at home before surgery, experienced chest discomfort in the evening and was found dead in her bed the next morning		
subjects affected / exposed	0 / 28 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Perforated ulcer	Additional description: perforated ulcer after colon resection leading to surgery and prolonged length of stay		
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic leak			
subjects affected / exposed	0 / 28 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection	Additional description: wound opened bedside and later resutured under general anaesthesia. Prolonged length of stay		

subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
colon perforation	Additional description: readmitted after colonoscopy med removal og polyp with perforation. Treated with antibiotics.		
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal bleeding	Additional description: readmitted after surgery with rectal bleeding. Bleeding stopped spontaneously with no need of interventions or blood transfusions		
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain	Additional description: abdominal pain and elevated inflammatory markers after surgery. Diagnostic laparoscopy with ileus but no other signs of complications. Prolonged length of stay due to this.		
subjects affected / exposed	0 / 28 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence	Additional description: reoperated		
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: readmitted due to vominting after surgery		
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia	Additional description: leading to readmission		
subjects affected / exposed	0 / 28 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	metformin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 28 (85.71%)	22 / 27 (81.48%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 28 (0.00%)	3 / 27 (11.11%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 28 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
edema			
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Vomiting or nausea			
subjects affected / exposed	9 / 28 (32.14%)	3 / 27 (11.11%)	
occurrences (all)	13	3	
Abdominal pain			
subjects affected / exposed	6 / 28 (21.43%)	8 / 27 (29.63%)	
occurrences (all)	10	11	
change in bowel movements			
subjects affected / exposed	10 / 28 (35.71%)	6 / 27 (22.22%)	
occurrences (all)	13	8	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 28 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 28 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Pneumonia	Additional description: not leading to readmission or prolonged length of stay		
subjects affected / exposed	3 / 28 (10.71%)	3 / 27 (11.11%)	
occurrences (all)	3	3	
Candida infection	Additional description: oral		

subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

**More information**

**Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2021	CD3 and CD8 were added as primary outcomes instead of secondary outcomes

Notes:

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**Interruptions (globally)**

Were there any global interruptions to the trial? No

**Limitations and caveats**

None reported