



## Clinical trial results: Faecal microbiota transplantation for relapsing Clostridium difficile infection

### Summary

EudraCT number	2015-003004-24
Trial protocol	DK
Global end of trial date	15 February 2019

### Results information

Result version number	v1 (current)
This version publication date	17 December 2020
First version publication date	17 December 2020
Summary attachment (see zip file)	Publication primary (Hvas 2019 FMT RCT published.pdf)

### Trial information

#### Trial identification

Sponsor protocol code	2015-003004-24
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02743234
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, Aarhus N, Denmark, 8200
Public contact	Christian Lodberg Hvas, Aarhus University Hospital, 0045 78463895, christian.hvas@auh.rm.dk
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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	18 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 August 2018
Global end of trial reached?	Yes
Global end of trial date	15 February 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Compare 8-week cure rates from relapsing *Clostridium difficile* colitis following one of three treatments:

- 1) capsule vancomycin 125 mg 4 times daily 10 days + faecal microbiota transplantation
- 2) tablet fidaxomicin 200 mg twice daily 10 days
- 3) capsule vancomycin 125 mg 4 times daily 10 days

Protection of trial subjects:

Individually tailored treatment and application method. Follow-up with protocolled opportunity for rescue treatment in case of treatment failure.

Background therapy:

FMT was superior to vancomycin in small randomised studies. No study compared FMT with fidaxomicin, a new antibiotics for *C difficile*.

Evidence for comparator:

Both vancomycin and fidaxomicin are established treatments for *C difficile* infection. We wishes to compare efficacies of the three in a head-to-head investigator-initiated clinical trial.

Actual start date of recruitment	04 April 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 64
Worldwide total number of subjects	64
EEA total number of subjects	64

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)	32
From 65 to 84 years	27
85 years and over	5

## Subject disposition

### Recruitment

Recruitment details:

Adult patients with mental capacity were recruited from an outpatient clinic in a referral centre for gastroenterology at a public teaching hospital in Denmark. Patients could be referred for treatment from neighbouring hospitals.

### Pre-assignment

Screening details:

Recurrent (< 8 weeks) of C difficile infection, negative tests for other pathogens, no concomitant antibiotics treatment, no pregnancy, ability to speak and understand Danish, no fulminant colitis in which case open label FMT was offered for ethical reasons.

### Period 1

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

Blinding implementation details:

FMT was administered by colonoscopy, and we deemed it unethical to perform placebo colonoscopy. Medical treatment (in experimental and comparator arms) were administered open label using marketed products.

### Arms

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

Arm description:

4-10 days of vancomycin followed by a single FMT, delivered by colonoscopy or nasojejunal tube

Arm type	Experimental
Investigational medicinal product name	FMT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intestinal use

Dosage and administration details:

Minimally processed donor faeces, unstandardised, derived from 50 grams of donor faeces. Delivered by colonoscopy or nasojejunal tube.

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

Tablet fidaxomixin (Dificlir(R)) 200 mg BID for 10 days

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

Dosage and administration details:

Tablet 200 mg BID, oral intake

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

Capsule vancomycin 125 mg QDS for 10 days

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

Dosage and administration details:

Tablet, 125 mg four times daily, oral intake for 10 days

<b>Number of subjects in period 1</b>	FMTv	Fidaxomicin	Vancomycin
Started	24	24	16
8 weeks global resolution (clinical+PCR)	24	24	16
Completed	24	24	16

## Baseline characteristics

### Reporting groups

Reporting group title	FMTv
Reporting group description: 4-10 days of vancomycin followed by a single FMT, delivered by colonoscopy or nasojejunal tube	
Reporting group title	Fidaxomicin
Reporting group description: Tablet fidaxomixin (Dificlir(R)) 200 mg BID for 10 days	
Reporting group title	Vancomycin
Reporting group description: Capsule vancomycin 125 mg QDS for 10 days	

Reporting group values	FMTv	Fidaxomicin	Vancomycin
Number of subjects	24	24	16
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age			
Units: years			
median	68	64	72
full range (min-max)	22 to 90	24 to 87	21 to 92
Gender categorical Units: Subjects			
Female	20	13	11
Male	4	11	5

Reporting group values	Total		
Number of subjects	64		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years)	0 0 0 0 0 0		

Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Age			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	44		
Male	20		

## End points

### End points reporting groups

Reporting group title	FMTv
Reporting group description: 4-10 days of vancomycin followed by a single FMT, delivered by colonoscopy or nasojejunal tube	
Reporting group title	Fidaxomicin
Reporting group description: Tablet fidaxomixin (Dificlir(R)) 200 mg BID for 10 days	
Reporting group title	Vancomycin
Reporting group description: Capsule vancomycin 125 mg QDS for 10 days	

### Primary: Global resolution (clinical + PCR)

End point title	Global resolution (clinical + PCR)
End point description: Clinical resolution (normalisation of bowel habits) AND negative C difficile toxin test by PCR	
End point type	Primary
End point timeframe: 8 weeks	

End point values	FMTv	Fidaxomicin	Vancomycin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	24	16	
Units: yes/no				
No	7	16	13	
Yes	17	8	3	

### Statistical analyses

Statistical analysis title	FMVv vs fidaxomicin
Comparison groups	FMTv v Fidaxomicin
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	Chi-squared

Statistical analysis title	FMTv vs vancomycin
Comparison groups	FMTv v Vancomycin



Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Chi-squared

## Secondary: Clinical resolution

End point title	Clinical resolution
End point description:	
Clinical resolution	
End point type	Secondary
End point timeframe:	
8 weeks	

End point values	FMTv	Fidaxomicin	Vancomycin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	24	16	
Units: Yes or no				
No	2	14	13	
Yes	22	10	3	

## Statistical analyses

<b>Statistical analysis title</b>	FMTv vs fidaxomicin
Statistical analysis description:	
Chi-square analysis of primary endpoint, bivariate comparisons	
Comparison groups	FMTv v Fidaxomicin
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Chi-squared

<b>Statistical analysis title</b>	FMTV vs vancomycin
Comparison groups	FMTv v Vancomycin

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

8 weeks

Adverse event reporting additional description:

Adverse events that occurred more than 2 days and up to 8 weeks after finalising primary treatment were reported.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23
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### Reporting groups

Reporting group title	FMTv
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Reporting group description:

Randomisation group 1, faecal microbiota transplantation preceded by vancomycin

Reporting group title	Fidaxomicin
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Reporting group description:

Randomisation group 2, fidaxomicin mono therapy

Reporting group title	Vancomycin
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Reporting group description:

Randomisation group 3, vancomycin monotherapy

Serious adverse events	FMTv	Fidaxomicin	Vancomycin
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 12 (41.67%)	6 / 9 (66.67%)	4 / 8 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Hospitalisation	Additional description: Hospitalisation (any cause) within 8 weeks after finalising primary treatment		
subjects affected / exposed	5 / 12 (41.67%)	6 / 9 (66.67%)	4 / 8 (50.00%)
occurrences causally related to treatment / all	0 / 5	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	FMTv	Fidaxomicin	Vancomycin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)	3 / 9 (33.33%)	4 / 8 (50.00%)
General disorders and administration site conditions			

Other AE, possibly related  subjects affected / exposed occurrences (all)	Additional description: Headache, dizziness, shivering, blurred vision, weight loss, weight gain		
	3 / 12 (25.00%) 3	2 / 9 (22.22%) 2	1 / 8 (12.50%) 1
Other AE unrelated  subjects affected / exposed occurrences (all)	Additional description: Alcohol intoxication, hoarseness, cerebral commotion,		
	4 / 12 (33.33%) 4	3 / 9 (33.33%) 3	3 / 8 (37.50%) 3
Gastrointestinal disorders  GI symptoms, no treatment, probably related subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 4	3 / 9 (33.33%) 3	2 / 8 (25.00%) 2
	GI symptoms, treatment, probably related subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	3 / 9 (33.33%) 3
Infections and infestations  Non-GI infections subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 4	2 / 9 (22.22%) 2	2 / 8 (25.00%) 2

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

Longterm follow-up was not included in the primary analysis.

Very few patients with subtype CD027 C difficile were included, and our results may not be generalisable to these patients.

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30610862>