



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 |
|-----------------------|----------------|

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 |
| Scientific contact | Christian Lodberg Hvas, Aarhus University Hospital, 0045 78463895, christian.hvas@auh.rm.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 | 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 fidamoxacin 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 |
| Arm title | 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.

| | |
|------------------|-------------|
| Arm title | Fidaxomicin |
|------------------|-------------|

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

| | |
|------------------|------------|
| Arm title | Vancomycin |
|------------------|------------|

Arm description:

Capsule vancomycin 125 mg QDS for 10 days

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|------------|
| 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

| Number of subjects in period 1 | 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 | FMTv 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

| | |
|--|---------------------|
| Statistical analysis title | 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 |

| | |
|-----------------------------------|--------------------|
| 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 | < 0.0001 |
| 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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 23 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|------|
| Reporting group title | FMTv |
|-----------------------|------|

Reporting group description:

Randomisation group 1, faecal microbiota transplantation preceded by vancomycin

| | |
|-----------------------|-------------|
| Reporting group title | Fidaxomicin |
|-----------------------|-------------|

Reporting group description:

Randomisation group 2, fidaxomicin mono therapy

| | |
|-----------------------|------------|
| Reporting group title | Vancomycin |
|-----------------------|------------|

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

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:

Online references

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