# Clinical trial results:
# A randomised, controlled, open-label phase III clinical trial in patients with recurrent Clostridioides difficile (CD) infection, to evaluate the efficacy and safety of capsules of lyophilised faecal microbiota vs fidaxomicin

## Summary

| | |
|---|---|
| EudraCT number | 2020-004591-17 |
| Trial protocol | ES |
| Global end of trial date | 15 November 2023 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 12 February 2025 |
| First version publication date | 12 February 2025 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | ICD-01 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT05201079 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Mikrobiomik Healthcare Company S.L. |
| Sponsor organisation address | Astondo Bidea, building 612, Derio, Spain, 48160 |
| Public contact | Clinical trials, Mikrobiomik Healthcare Company S.L., ensayosclinicos@mikrobiomik.net |
| Scientific contact | Clinical trials, Mikrobiomik Healthcare Company S.L., ensayosclinicos@mikrobiomik.net |

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 | 09 January 2024 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 15 November 2023 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The main purpose of the study is to evaluate the efficacy of the investigational medicinal product (MBK-01) compared to the control medication (fidaxomicin), 8 weeks after the treatment completion.

Protection of trial subjects:

Regarding the lack of efficacy, patients with a new recurrence of Clostridioides difficile infection were withdrawn from the study and treated with rescue medication (vancomycin or fidaxomicin).

All patients who dropped out of the study and/or were discontinued before the end of the planned follow-up had an end-of-study visit ≥ 30 days after initiation of treatment, in which at least the relevant information for safety assessment (adverse events and concomitant treatments) was collected.

Background therapy:

Therapeutic support measures were allowed as deemed most appropriate (e.g., hydration-control of the patient's electrolytes and antipyretics in case of fever (>38°C) and as deemed appropriate by the treating medical team).

Evidence for comparator:

Fidaxomicin is the treatment of choice for primary episodes of Clostridiodes difficile infection (CDI), first recurrences, high risk of recurrence and multiple recurrences of CDI by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). The Infectious Diseases Society of America (IDSA) recommends both vancomycin and fidaxomicin as the initial treatment for CDI, and fidaxomicin as the treatment of choice for patients with CDI with a high risk of recurrences. European and Spanish expert groups recommend fidaxomicin for critically ill patients, for immunosuppressed patients, and for patients with chronic kidney failure, undergoing transplantation or cancer.

| | |
|---|---|
| Actual start date of recruitment | 29 October 2021 |
| 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 | Spain: 92 |
| Worldwide total number of subjects | 92 |
| EEA total number of subjects | 92 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| wk | |
|---|---|
| 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) | 42 |
| From 65 to 84 years | 39 |
| 85 years and over | 11 |

## Subject disposition

### Recruitment

Recruitment details:

The inclusion of the first patient was on 29 October 2021. The inclusion of the last patient was on 6 October 2023 (end of recruitment). All patients were recruited in sites in Spain.

### Pre-assignment

Screening details:

Screening period: within 24h after informed consent, patients were evaluated for study eligibility. Participants were tested to determine if they met all the inclusion criteria and none of the exclusion criteria.

93 patients were screened in the study. 1 of them was a screening failure and only 92 were finally included in the study.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 93[1] |
| Number of subjects completed | 92 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Screening failure: 1 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 93 patients were intially included in the study. 1 of these patients was a selection failure and there is no available data for this patient. Therefore, 92 patients completed the screening period and were randomised to any of the two treatment groups.

### Period 1

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

Blinding implementation details:

There are no bliding techniques in this study, as it is an open-label study.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | MBK-01 |

Arm description:

Patients randomized to MBK-01 received a single dose of 4 oral capsules of MBK-01.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | MBK-01 |
| Investigational medicinal product code | |
| Other name | Heterologous gut microbiota from healthy donors |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received  4 capsules of MBK-01 in a single dose (≥2.1-2.5 x 10^11 microorganisms) after being randomized. If patients had been treated with antibiotic they had to undergo a 24 hours washout period before randomization.

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

Arm description:

Patients randomized to fidaxomicin received treatment with oral fidaxomicin 200mg/12h for 10 days

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Fidaxomicin |
| Investigational medicinal product code | |
| Other name | Dificlir |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received an oral dose of 200 mg (one tablet) of fidaxomicin twice a day (every 12 hours) for 10 days since randomization. If patients had been treated with antibiotic they had to undergo a 24 hours washout period before randomization.

| **Number of subjects in period 1** | MBK-01 | Fidaxomicin |
|---|---|---|
| Started | 45 | 47 |
| Completed | 23 | 25 |
| Not completed | 22 | 22 |
| Physician decision | 1 | 1 |
| Consent withdrawn by subject | 1 | - |
| Transfer to other hospital | - | 1 |
| Death | 1 | 1 |
| Clinical conditions | 1 | - |
| Forbidden medication | 9 | 5 |
| Adverse event | 7 | 11 |
| Serious adverse event and sepsis | 1 | - |
| Lost to follow-up | - | 1 |
| Ineffective treatment | - | 2 |
| Protocol deviation | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | MBK-01 |
| Reporting group description: | |
| Patients randomized to MBK-01 received a single dose of 4 oral capsules of MBK-01. | |
| Reporting group title | Fidaxomicin |
| Reporting group description: | |
| Patients randomized to fidaxomicin received treatment with oral fidaxomicin 200mg/12h for 10 days | |

| Reporting group values | MBK-01 | Fidaxomicin | Total |
|---|---|---|---|
| Number of subjects | 45 | 47 | 92 |
| Age categorical | | | |
| Age was calculated as the difference in years between the date of signing the informed consent form and the date of birth. | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 18 | 24 | 42 |
| From 65-84 years | 21 | 18 | 39 |
| 85 years and over | 6 | 5 | 11 |
| Age continuous | | | |
| Age was calculated as the difference in years between the date of signing the informed consent form and the date of birth. | | | |
| Units: years | | | |
| arithmetic mean | 65.22 | 65.26 | |
| standard deviation | ± 17.24 | ± 14.65 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 30 | 30 | 60 |
| Male | 15 | 17 | 32 |
| Type of Clostridioides difficile infection episode | | | |
| A primary episode would be the first episode of Clostridiodes difficile (CD) infection confirmed by laboratory tests. A patient with a recurrent episode would be one with previous episodes. | | | |
| Units: Subjects | | | |
| Primary | 25 | 28 | 53 |
| Recurrent | 20 | 19 | 39 |
| Previous antibiotic | | | |
| The number of patients that received antibiotic treatment previous to receiving MBK-01/fidaxomicin. | | | |
| Units: Subjects | | | |
| Yes | 23 | 29 | 52 |
| No | 22 | 18 | 40 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | MBK-01 |
| Reporting group description: Patients randomized to MBK-01 received a single dose of 4 oral capsules of MBK-01. | |
| Reporting group title | Fidaxomicin |
| Reporting group description: Patients randomized to fidaxomicin received treatment with oral fidaxomicin 200mg/12h for 10 days | |
| Subject analysis set title | Patients with a primary episode of CDI assigned to MBK-01 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Patients in MBK-01 group that presented a primary episode of CDI | |
| Subject analysis set title | Patients with a primary episode of CDI assigned to fidaxomicin |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Patients in fidaxomicin group that presented a primary episode of CDI | |
| Subject analysis set title | Patients with a recurrence of CDI assigned to MBK-01 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Patients in MBK-01 group that presented a recurrent episode of CDI | |
| Subject analysis set title | Patients with a recurrence of CDI assigned to fidaxomicin |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Patients in fidaxomicin group that presented a recurrent episode of CDI | |
| Subject analysis set title | Patients with no previous antibiotic assigned to MBK-01 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Patients in MBK-01 group that did not receive antibiotic pre-treatment before the treatment with MBK-01 | |
| Subject analysis set title | Patients with no previous antibiotic assigned to fidaxomicin |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Patients in MBK-01 group that did not receive antibiotic pre-treatment before the treatment with fidaxomicin | |
| Subject analysis set title | Baseline visit, MBK-01 group |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Patients from the MBK-01 group in whom the quality of life measured by the SF-36 questionnaire was reported and analysed at the baseline visit (V1). | |
| Subject analysis set title | Baseline visit, fidaxomicin group |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Patients from the fidaxomicin group in whom the quality of life measured by the SF-36 questionnaire was reported and analysed at the baseline visit (V1). | |
| Subject analysis set title | Visit 4, MBK-01 group |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Patients from the MBK-01 group in whom the quality of life measured by the SF-36 questionnaire was reported and analysed at visit 4 (V4, 8 weeks). | |
| Subject analysis set title | Visit 4, fidaxomicin group |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Patients from the fidaxomicin group in whom the quality of life measured by the SF-36 questionnaire was reported and analysed at visit 4 (V4, 8 weeks).

| Subject analysis set title | Visit 6, MBK-01 group |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Patients from the MBK-01 group in whom the quality of life measured by the SF-36 questionnaire was reported and analysed at visit 6 (V6, 6 months).

| Subject analysis set title | Visit 6, fidaxomicin group |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Patients from the fidaxomicin group in whom the quality of life measured by the SF-36 questionnaire was reported and analysed at visit 6 (V6, 6 months).

## Primary: Absence of diarrhoea from Clostridioides difficile

| End point title | Absence of diarrhoea from Clostridioides difficile |
|---|---|

End point description:

Absence of recurrence (a new episode of Clostridioides difficile infection within 8 weeks after the onset of the previous episode).

| End point type | Primary |
|---|---|

End point timeframe:

8 weeks after the onset of the previous episode of Clostridiodes difficile infection (8 weeks after the start of the treatment with MBK-01/fidaxomicin).

| **End point values** | MBK-01 | Fidaxomicin | Patients with a primary episode of CDI assigned to MBK-01 | Patients with a primary episode of CDI assigned to fidaxomicin |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 | 40 | 21 | 27 |
| Units: patients | | | | |
| Recurrence | 4 | 9 | 1 | 1 |
| No recurrence | 33 | 31 | 20 | 26 |

| **End point values** | Patients with a recurrence of CDI assigned to MBK-01 | Patients with a recurrence of CDI assigned to fidaxomicin | Patients with no previous antibiotic assigned to MBK-01 | Patients with no previous antibiotic assigned to fidaxomicin |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 16 | 13 | 17 | 15 |
| Units: patients | | | | |
| Recurrence | 3 | 8 | 0 | 3 |
| No recurrence | 13 | 5 | 17 | 12 |

## Statistical analyses

| **Statistical analysis title** | Non-inferiority analysis of recurrence probability |
|---|---|

Statistical analysis description:

The compared efficacy of the two treatments was assessed as a difference of proportions between MBK-01 (P1) and fidaxomicin group (P2). The proportions indicate the probability of no recurrence among the total patients in each group.

There are 77 evaluable for recurrence (37 in MBK-01 group and 40 in Fidaxomicin group). Reasons for non-evaluable are: death, forbidden medication, investigator decision, adverse event, informed consent withdrawal and transfer to another hospital.

| Comparison groups | Fidaxomicin v MBK-01 |
|---|---|
| Number of subjects included in analysis | 77 |
| Analysis specification | Post-hoc |
| Analysis type | non-inferiority[1] |
| P-value | = 0.013 [2] |
| Method | Miettinen-Nurminen |
| Parameter estimate | Difference of proportions |
| Point estimate | 2.228 |
| Confidence interval | |
| level | Other: 97.06 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 100 |

Notes:

[1] - Non inferiority margin: -0.10.
Null hypothesis: P1-P2 ≤-0.10
Alternative hypothesis: P1-P2 > -0.10
α=0.0221

[2] - Confidence interval for the point estimate was not calculated. It is inputed as 0 and 100.

| **Statistical analysis title** | Superiority analysis of recurrence probability |
|---|---|

Statistical analysis description:

The compared efficacy of the two treatments was assessed as an Odds Ratio of the probability of no recurrence in each group, using the MBK-01 group as a reference.

There are 77 evaluable for recurrence (37 in MBK-01 group and 40 in Fidaxomicin group). Reasons for non-evlauable are: death, forbidden medication, investigator decision, adverse event, informed consent withdrawal and transfer to another hospital.

| Comparison groups | MBK-01 v Fidaxomicin |
|---|---|
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.228 |
| Method | Wald method |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.395 |
| Confidence interval | |
| level | Other: 97.79 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 10.624 |

Notes:

[3] - α=0.0221

| **Statistical analysis title** | Non-inferiority analysis of primary CDI subgroup |
|---|---|

Statistical analysis description:

The compared efficacy of the two treatments was assessed as a difference of proportions between MBK-01 (P1) and fidaxomicin group (P2). The proportions indicate the probability of no recurrence among the total patients in each group.

There are 48 evaluable for recurrence (21 in MBK-01 group and 27 in Fidaxomicin group). Reasons for non-evaluable are: adverse event, forbidden medication and death.

| | |
|---|---|
| Comparison groups | Patients with a primary episode of CDI assigned to MBK-01 v Patients with a primary episode of CDI assigned to fidaxomicin |
| Number of subjects included in analysis | 48 |
| Analysis specification | Post-hoc |
| Analysis type | non-inferiority[4] |
| P-value | = 0.013 [5] |
| Method | Miettinen-Nurminen |
| Parameter estimate | Difference of proportions |
| Point estimate | 2.228 |
| Confidence interval | |
| level | Other: 97.06 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 100 |

Notes:

[4] - Non inferiority margin: -0.10.
Null hypothesis: P1-P2 ≤-0.10
Alternative hypothesis: P1-P2 > -0.10
α=0.0294

[5] - Confidence interval for the point estimate was not calculated. It is inputed as 0 and 100.

| **Statistical analysis title** | Superiority analysis of primary CDI subgroup |
|---|---|

Statistical analysis description:

The compared efficacy of the two treatments was assessed as an Odds Ratio of the probability of no recurrence in each group, using the MBK-01 group as a reference.

There are 48 evaluable for recurrence (21 in MBK-01 group and 27 in Fidaxomicin group). Reasons for non-evaluable are: adverse event, forbidden medication and death.

| | |
|---|---|
| Comparison groups | Patients with a primary episode of CDI assigned to MBK-01 v Patients with a primary episode of CDI assigned to fidaxomicin |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[6] |
| P-value | = 1 |
| Method | Wald method |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.769 |
| Confidence interval | |
| level | Other: 97.79 % |
| sides | 2-sided |
| lower limit | 0.019 |
| upper limit | 31.82 |

Notes:

[6] - α=0.0294

| **Statistical analysis title** | Non-inferiority analysis of recurrent CDI subgroup |
|---|---|

Statistical analysis description:

The compared efficacy of the two treatments was assessed as a difference of proportions between MBK01 (P1) and fidaxomicin group (P2). The proportions indicate the probability of no recurrence among the total patients in each group.

There are 29 evaluable for recurrence (16 in MBK-01 group and 13 in Fidaxomicin group). Reasons for non-evaluable are: investigator decision, forbidden medication, transfer to another hospital, death and adverse event.

| | |
|---|---|
| Comparison groups | Patients with a recurrence of CDI assigned to MBK-01 v Patients with a recurrence of CDI assigned to fidaxomicin |
| Number of subjects included in analysis | 29 |
| Analysis specification | Post-hoc |
| Analysis type | non-inferiority[7] |
| P-value | = 0.003 [8] |
| Method | Miettinen-Nurminen |
| Parameter estimate | Difference of proportions |
| Point estimate | 2.744 |
| Confidence interval | |
| level | Other: 97.06 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 100 |

Notes:

[7] - Non inferiority margin: -0.10.
Null hypothesis: P1-P2 ≤-0.10
Alternative hypothesis: P1-P2 > -0.10
α=0.0294
[8] - Confidence interval for the point estimate was not calculated. It is inputed as 0 and 100.

| **Statistical analysis title** | Superiority analysis of recurrent CDI subgroup |
|---|---|

Statistical analysis description:

The compared efficacy of the two treatments was assessed as an Odds Ratio of the probability of no recurrence in each group, using the MBK-01 group as a reference.

There are 29 evaluable for recurrence (16 in MBK-01 group and 13 in Fidaxomicin group). Reasons for non-evaluable are: investigator decision, forbidden medication, transfer to another hospital, death and adverse event.

| | |
|---|---|
| Comparison groups | Patients with a recurrence of CDI assigned to fidaxomicin v Patients with a recurrence of CDI assigned to MBK-01 |
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[9] |
| P-value | = 0.027 |
| Method | Wald method |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 6.933 |
| Confidence interval | |
| level | Other: 97.79 % |
| sides | 2-sided |
| lower limit | 0.762 |
| upper limit | 63.12 |

Notes:

[9] - α=0.0294

| **Statistical analysis title** | Non-inferiority analysis of no pretreated subgroup |
|---|---|

Statistical analysis description:

The compared efficacy of the two treatments was assessed as a difference of proportions between MBK-01 (P1) and fidaxomicin group (P2). The proportions indicate the probability of no recurrence among the total patients in each group.

There are 32 evaluable for recurrence (17 in MBK-01 group and 15 in Fidaxomicin group). Reasons for non-evaluable are: forbidden medication, adverse event, transfer to another hospital and investigator decision.

| | |
|---|---|
| Comparison groups | Patients with no previous antibiotic assigned to MBK-01 v Patients with no previous antibiotic assigned to fidaxomicin |
| Number of subjects included in analysis | 32 |
| Analysis specification | Post-hoc |
| Analysis type | non-inferiority[10] |
| P-value | = 0.008 [11] |
| Method | Miettinen-Nurminen |
| Parameter estimate | Difference of proportion |
| Point estimate | 2.396 |
| Confidence interval | |
| level | Other: 97.06 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 100 |

Notes:

[10] - Non inferiority margin: -0.10.
Null hypothesis: P1-P2 ≤-0.10
Alternative hypothesis: P1-P2 > -0.10
α=0.0294
[11] - Confidence interval for the point estimate was not calculated. It is inputed as 0 and 100.

## Secondary: Favourable/unfavourable outcome

| | |
|---|---|
| End point title | Favourable/unfavourable outcome |

End point description:

An unfavourable outcome is defined as the detection within 48-72 hours from the start of treatment of a worsening of the episode of diarrhoea (defined as at least one stool more than at baseline, with baseline being considered as the time of initiation of study treatment) and, additionally, at least one of the following criteria:
1. Increase of the C-reactive protein (CRP) value (>5% of the value at baseline).
2. Increase of the absolute value of leukocytes (>5% of the value at baseline).
3. Progression to sepsis: hypotension or organ failure with no other apparent cause.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

48-72 hours from the start of study treatment.

| **End point values** | MBK-01 | Fidaxomicin | Patients with a primary episode of CDI assigned to MBK-01 | Patients with a primary episode of CDI assigned to fidaxomicin |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 43 | 45 | 25 | 27 |
| Units: patients | | | | |
| Favourable | 43 | 44 | 25 | 26 |
| Unfavourable | 0 | 1 | 0 | 1 |

| End point values | Patients with a recurrence of CDI assigned to MBK-01 | Patients with a recurrence of CDI assigned to fidaxomicin | Patients with no previous antibiotic assigned to MBK-01 | Patients with no previous antibiotic assigned to fidaxomicin |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 18 | 20 | 17 |
| Units: patients | | | | |
| Favourable | 19 | 18 | 20 | 16 |
| Unfavourable | 0 | 0 | 0 | 1 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to recurrence

| End point title | Time to recurrence |
|---|---|

End point description:

The baseline visit is taken as the start date. The end date will depend on whether the patient has had a recurrence at visit 4 (8 weeks after the start of study treatment):
- If the patient has had a recurrence, the end date is the date on which the recurrence occurred.
- If the patient has not had a recurrence, the end date is either the end of study date or the last available date.
- If the patient has not had a recurrence and is ongoing, the last available date is imputed as the end date.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 6 months after the start of study treatment.

| End point values | MBK-01 | Fidaxomicin | Patients with a primary episode of CDI assigned to MBK-01 | Patients with a primary episode of CDI assigned to fidaxomicin |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 | 40 | 21 | 27 |
| Units: weeks | | | | |
| arithmetic mean (standard deviation) | 24.70 (± 1.34) | 22.40 (± 1.53) | 26.30 (± 1.268) | 26.70 (± 0.872) |

| End point values | Patients with a recurrence of CDI assigned to MBK-01 | Patients with a recurrence of CDI assigned to fidaxomicin | Patients with no previous antibiotic assigned to MBK-01 | Patients with no previous antibiotic assigned to fidaxomicin |
|---|---|---|---|---|

| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
|---|---|---|---|---|
| Number of subjects analysed | 16 | 13 | 17 | 15 |
| Units: weeks | | | | |
| arithmetic mean (standard deviation) | 22.40 (± 2.240) | 13.10 (± 3.01) | 0 (± 0) | 22.40 (± 2.31) |

**Statistical analyses**

| **Statistical analysis title** | Time to recurrence analysis |
|---|---|
| Comparison groups | Fidaxomicin v MBK-01 |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3 [12] |
| Method | Regression, Cox |
| Parameter estimate | Likelihood Ratio Test |
| Point estimate | 1.29 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 100 |

Notes:

[12] - The Likelihood Ratio Test does not provide a confidence interval. It is inputed as 0 and 100.

| **Statistical analysis title** | Time to recurrence of primary CDI subgroup |
|---|---|
| Comparison groups | Patients with a primary episode of CDI assigned to MBK-01 v Patients with a primary episode of CDI assigned to fidaxomicin |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8 [13] |
| Method | Regression, Cox |
| Parameter estimate | Likelihood Ratio Test |
| Point estimate | 0.07 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 100 |

Notes:

[13] - The Likelihood Ratio Test does not provide a confidence interval. It is inputed as 0 and 100.

| **Statistical analysis title** | Time to recurrence of recurrent CDI subgroup |
|---|---|
| Comparison groups | Patients with a recurrence of CDI assigned to MBK-01 v Patients with a recurrence of CDI assigned to fidaxomicin |

| | |
|---|---|
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 [14] |
| Method | Regression, Cox |
| Parameter estimate | Likelihood Ratio Test |
| Point estimate | 5.35 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 100 |

Notes:

[14] - The Likelihood Ratio Test does not provide a confidence interval. It is inputed as 0 and 100.

| **Statistical analysis title** | Time to recurrence of no pretreated subgroup |
|---|---|

Statistical analysis description:

Arithmetic mean and standard deviation of time to recurrence in MBK-01 group are inputed as 0 because there were no recurrences in this group.

| | |
|---|---|
| Comparison groups | Patients with no previous antibiotic assigned to MBK-01 v Patients with no previous antibiotic assigned to fidaxomicin |
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.04 [15] |
| Method | Regression, Cox |
| Parameter estimate | Likelihood Ratio Test |
| Point estimate | 4.09 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 100 |

Notes:

[15] - The Likelihood Ratio Test does not provide a confidence interval. It is inputed as 0 and 100.

| **Secondary: Overall survival: patients** | |
|---|---|
| End point title | Overall survival: patients |

End point description:

Deaths indicated as number of events.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Up to 6 months after the start of the treatment.

| End point values | MBK-01 | Fidaxomicin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 47 | | |
| Units: patients | | | | |
| Events | 1 | 1 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall survival: time

| End point title | Overall survival: time |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 6 months after the start of the treatment

| End point values | MBK-01 | Fidaxomicin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 47 | | |
| Units: weeks | | | | |
| arithmetic mean (standard error) | 26.80 (± 0.712) | 27 (± 0.581) | | |

## Statistical analyses

| Statistical analysis title | Overall survival analysis |
|---|---|
| Comparison groups | MBK-01 v Fidaxomicin |
| Number of subjects included in analysis | 92 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9 [16] |
| Method | Regression, Cox |
| Parameter estimate | Likelihood Ratio Test |
| Point estimate | 0.02 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 100 |

Notes:

[16] - The Likelihood Ratio Test does not provide a confidence interval. It is inputed as 0 and 100.

## Secondary: Quality of life

| End point title | Quality of life |
|---|---|

End point description:

Quality of life is measured by the Short Form-36 Health Survey (SF-36), which consists of 36 questions (items) that assess both positive and negative states of quality of life. These 36 items cover the following areas: physical function, physical role, bodily pain, general health, vitality, social role, emotional role and mental health. For each area, the scale ranges from 0 (the worst health status for that dimension) to 100 (the best health status).

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 6 months after the start of study treatment. It was assesed at baseline visit (V1), visit 4 (V4, 8 weeks) and visit 6 (V6, 6 months).

| **End point values** | Baseline visit, MBK-01 group | Baseline visit, fidaxomicin group | Visit 4, MBK-01 group | Visit 4, fidaxomicin group |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 42 | 46 | 30 | 31 |
| Units: punctuation | | | | |
| arithmetic mean (standard deviation) | | | | |
| Physical function | 56.9 (± 35.9) | 57.07 (± 33.71) | 68.5 (± 30.6) | 62.58 (± 30.44) |
| Bodily pain | 52.91 (± 29.84) | 57.25 (± 29.07) | 35.19 (± 29.19) | 40.5 (± 28.33) |
| General health | 55.13 (± 17.07) | 54.85 (± 20.62) | 47.18 (± 18.04) | 49.13 (± 17.5) |
| Vitality | 38.1 (± 11.52) | 35.69 (± 18.56) | 36.39 (± 17.02) | 40.86 (± 11.85) |
| Social role | 65.08 (± 15.53) | 63.77 (± 19.02) | 63.33 (± 14.78) | 63.44 (± 11.72) |
| Emotional role | 59.13 (± 39.04) | 68.3 (± 32.18) | 82.78 (± 25.7) | 70.43 (± 28.04) |
| Mental health | 55.27 (± 16.92) | 56.06 (± 17.17) | 60 (± 16.42) | 57.83 (± 13.84) |
| Physical role | 33.48 (± 33.44) | 36.55 (± 32.81) | 69.17 (± 35.84) | 57.46 (± 30.64) |

| **End point values** | Visit 6, MBK-01 group | Visit 6, fidaxomicin group | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 11 | | |
| Units: punctuation | | | | |
| arithmetic mean (standard deviation) | | | | |
| Physical function | 77.5 (± 27.01) | 77.73 (± 27.14) | | |
| Bodily pain | 35.19 (± 33.78) | 27.27 (± 28.27) | | |

| | | | | |
|---|---|---|---|---|
| General health | 41.03 (± 15.5) | 38.46 (± 16.14) | | |
| Vitality | 35.42 (± 7.22) | 36.36 (± 8.56) | | |
| Social role | 59.72 (± 11.14) | 69.7 (± 10.05) | | |
| Emotional role | 86.11 (± 22.29) | 84.09 (± 20.57) | | |
| Mental health | 63.69 (± 11.97) | 62.34 (± 12.81) | | |
| Physical role | 72.92 (± 29.95) | 74.43 (± 34.51) | | |

## Statistical analyses

| **Statistical analysis title** | Analysis of the group and physical function |
|---|---|

Statistical analysis description:

The relationship between the treatment group and the changes in physical function was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[17] |
| P-value | = 0.749 |
| Method | ANOVA |

Notes:

[17] - α=0.0221. F (contrast statistic) = 0.104. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the time and physical function |
|---|---|

Statistical analysis description:

The relationship between the passing of time and the changes in physical function was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[18] |
| P-value | = 0.62 |
| Method | ANOVA |

Notes:

[18] - α=0.0221. F (contrast statistic) = 0.249. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of group-time and physical function |
|---|---|

Statistical analysis description:

The relationship between the interaction treatment group-passing of time and the changes in physical function was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[19] |
| P-value | = 0.16 |
| Method | ANOVA |

Notes:

[19] - α=0.0221. F (contrast statistic) = 2.024. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the group and bodily pain |
|---|---|

Statistical analysis description:

Therelationship between the treatment group and the changes in bodily pain was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[20] |
| P-value | = 0.614 |
| Method | ANOVA |

Notes:

[20] - α=0.0221. F (contrast statistic) = 0.257. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the time and bodily pain |
|---|---|

Statistical analysis description:

The relationship between the passing of time and the changes in bodily pain was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[21] |
| P-value | = 0.007 [22] |
| Method | ANOVA |

Notes:

[21] - α=0.0221. F (contrast statistic) = 7.705. Degrees of freedom: 1, 56

[22] - Effect size = 0.046

| **Statistical analysis title** | Analysis of group-time and bodily pain |
|---|---|

Statistical analysis description:

The relationship between the interaction treatment group-passing of time and the changes in bodily pain was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group |

| | |
|---|---|
| | v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[23] |
| P-value | = 0.718 |
| Method | ANOVA |

Notes:

[23] - α=0.0221. F (contrast statistic) = 0.132. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the group and general health |
|---|---|

Statistical analysis description:

The relationship between the treatment group and the changes in general health was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[24] |
| P-value | = 0.494 |
| Method | ANOVA |

Notes:

[24] - α=0.0221. F (contrast statistic) = 0.474. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the time and general health |
|---|---|

Statistical analysis description:

The relationship between the passing of time and the changes in general health was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[25] |
| P-value | = 0.339 |
| Method | ANOVA |

Notes:

[25] - α=0.0221. F (contrast statistic) = 0.932. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of group-time and general health |
|---|---|

Statistical analysis description:

The relationship between the interaction treatment group-passing of time and the changes in general health was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |

| | |
|---|---|
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[26] |
| P-value | = 0.38 |
| Method | ANOVA |

Notes:

[26] - α=0.0221. F (contrast statistic) = 0.783. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the group and vitality |
|---|---|

Statistical analysis description:

The relationship between the treatment group and the changes in vitality was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[27] |
| P-value | = 0.79 |
| Method | ANOVA |

Notes:

[27] - α=0.0221. F (contrast statistic) = 0.072. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the time and vitality |
|---|---|

Statistical analysis description:

The relationship between the passing of time and the changes in vitality was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[28] |
| P-value | = 0.498 |
| Method | ANOVA |

Notes:

[28] - α=0.0221. F (contrast statistic) = 0.465. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of group-time and vitality |
|---|---|

Statistical analysis description:

The effect of the interaction between the treatment group and the passing of time in the changes in vitality was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |

| | |
|---|---|
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[29] |
| P-value | = 0.023 |
| Method | ANOVA |

Notes:

[29] - α=0.0221. F (contrast statistic) = 5.490. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the group and social role |
|---|---|

Statistical analysis description:

The relationship between the treatment group and the changes in social role was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[30] |
| P-value | = 0.553 |
| Method | ANOVA |

Notes:

[30] - α=0.0221. F (contrast statistic) = 0.356. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the time and social role |
|---|---|

Statistical analysis description:

The relationship between the passing of time and the changes in social role was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[31] |
| P-value | = 0.718 |
| Method | ANOVA |

Notes:

[31] - α=0.0221. F (contrast statistic) = 0.132. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of group-time and social role |
|---|---|

Statistical analysis description:

The relationship between the interaction treatment group-passing of time and the changes in social role was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |

| | |
|---|---|
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[32] |
| P-value | = 0.574 |
| Method | ANOVA |

Notes:

[32] - α=0.0221. F (contrast statistic) = 0.319. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the group and emotional role |
|---|---|

Statistical analysis description:

The relationship between the treatment group and the changes in emotional role was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[33] |
| P-value | = 0.49 |
| Method | ANOVA |

Notes:

[33] - α=0.0221. F (contrast statistic) = 0.482. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the time in emotional role |
|---|---|

Statistical analysis description:

The relationship between the passing of time and the changes in emotional role was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[34] |
| P-value | = 0.032 |
| Method | ANOVA |

Notes:

[34] - α=0.0221. F (contrast statistic) = 4.850. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of group-time and emotional role |
|---|---|

Statistical analysis description:

The relationship between the interaction treatment group-passing of time and the changes in emotional role was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |

| | |
|---|---|
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[35] |
| P-value | = 0.145 |
| Method | ANOVA |

Notes:

[35] - α=0.0221. F (contrast statistic) = 2.181. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the group and mental health |
|---|---|

Statistical analysis description:

The relationship between the treatment group and the changes in mental health was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[36] |
| P-value | = 0.467 |
| Method | ANOVA |

Notes:

[36] - α=0.0221. F (contrast statistic) = 0.535. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the time and mental health |
|---|---|

Statistical analysis description:

The relationship between the passing of time and the changes in mental health was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[37] |
| P-value | = 0.1 |
| Method | ANOVA |

Notes:

[37] - α=0.0221. F (contrast statistic) = 2.795. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of group-time and mental health |
|---|---|

Statistical analysis description:

The relationship between the interaction treatment group-passing of time and the changes in mental health was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |

| | |
|---|---|
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[38] |
| P-value | = 0.89 |
| Method | ANOVA |

Notes:

[38] - α=0.0221. F (contrast statistic) = 0.019. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the group and physical role |
|---|---|

Statistical analysis description:

The relationship between the treatment group and the changes in physical role was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[39] |
| P-value | = 0.742 |
| Method | ANOVA |

Notes:

[39] - α=0.0221. F (contrast statistic) = 0.109. Degrees of freedom: 1, 56

| **Statistical analysis title** | Analysis of the time and physical role |
|---|---|

Statistical analysis description:

The relationship between the passing of time and the changes in physical role was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[40] |
| P-value | < 0.001 [41] |
| Method | ANOVA |

Notes:

[40] - α=0.0221. F (contrast statistic) = 21.912. Degrees of freedom: 1, 56

[41] - Effect size = 0.109

| **Statistical analysis title** | Analysis of group-time and physical role |
|---|---|

Statistical analysis description:

The relationship between the interaction treatment group-passing of time and the changes in physical role was analysed with ANOVA. The total number of subjects in this analysis (172) is calculated as the addition of the number of patients in all the visits, and does not reflect the actual number of patients analysed.

| | |
|---|---|
| Comparison groups | Baseline visit, MBK-01 group v Baseline visit, fidaxomicin group v Visit 4, MBK-01 group v Visit 4, fidaxomicin group v Visit 6, MBK-01 group v Visit 6, fidaxomicin group |

| | |
|---|---|
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[42] |
| P-value | = 0.089 |
| Method | ANOVA |

Notes:

[42] - α=0.0221. F (contrast statistic) = 2.986. Degrees of freedom: 1, 56

## Secondary: Number of Adverse Events

| | |
|---|---|
| End point title | Number of Adverse Events |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Adverse events were assessed continuously during the study for up to 6 months after treatment, until the end-of-study visit.

| End point values | MBK-01 | Fidaxomicin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 47 | | |
| Units: Adverse events | 89 | 103 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of patients who have had Adverse Events

| | |
|---|---|
| End point title | Number of patients who have had Adverse Events |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Adverse events were assessed continuously during the study for up to 6 months after treatment, until the end-of-study visit.

| End point values | MBK-01 | Fidaxomicin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 47 | | |
| Units: Adverse events | 36 | 38 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Serious Adverse Events

| End point title | Number of Serious Adverse Events |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Serious adverse events were assessed continuously during the study for up to 6 months after treatment, until the end-of-study visit.

| End point values | MBK-01 | Fidaxomicin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 47 | | |
| Units: Serious Adverse Events | 11 | 5 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of patients who have had Serious Adverse Events

| End point title | Number of patients who have had Serious Adverse Events |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Serious adverse events were assessed continuously during the study for up to 6 months after treatment, until the end-of-study visit.

| End point values | MBK-01 | Fidaxomicin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 47 | | |
| Units: Serious Adverse Events | 9 | 4 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of treatment-related Adverse Events

| End point title | Number of treatment-related Adverse Events |
|---|---|

End point description:

Adverse events classified under the categories "Likely" and "Definitely related" are considered treatment-related Adverse Events.

| End point type | Secondary |
|---|---|

End point timeframe:

Adverse events were assessed continuously during the study for up to 6 months after treatment, until the end-of-study visit.

| **End point values** | MBK-01 | Fidaxomicin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 47 | | |
| Units: Adverse Events | | | | |
| Unrelated | 93 | 79 | | |
| Unlikely | 2 | 2 | | |
| Possible | 5 | 7 | | |
| Likely | 3 | 1 | | |
| Definitely related | 0 | 0 | | |

### Statistical analyses

| **Statistical analysis title** | Analysis of relation to treatment |
|---|---|

Statistical analysis description:

Relationship between the treatment groups and the Adverse Events related to treatment is analysed. Adverse events classified under the categories "Likely" and "Definitely related" are considered treatment-related Adverse Events.

| Comparison groups | Fidaxomicin v MBK-01 |
|---|---|
| Number of subjects included in analysis | 92 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.692 [43] |
| Method | Chi-squared corrected |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.459 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 100 |

Notes:

[43] - The assumption according to which no more than 25% of the cells in the table should have an expected frequency is violated. Yates' continuity correction is reported.

Confidence interval was not calculated. It is inputed as 0 and 100.

### Secondary: Severity of Adverse Events

| End point title | Severity of Adverse Events |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Adverse events were assessed continuously during the study for up to 6 monthsafter treatment, until the end-of-study visit.

| **End point values** | MBK-01 | Fidaxomicin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 47 | | |
| Units: Adverse Events | | | | |
| Mild | 77 | 70 | | |
| Moderate | 22 | 17 | | |
| Severe | 4 | 1 | | |
| Life threatening | 0 | 0 | | |
| Death | 0 | 1 | | |

## Statistical analyses

| **Statistical analysis title** | Analysis of severity |
|---|---|

Statistical analysis description:

Relationship between the treatment groups and the severity of the Adverse Events is analysed.

| Comparison groups | MBK-01 v Fidaxomicin |
|---|---|
| Number of subjects included in analysis | 92 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.429 [44] |
| Method | Chi-squared corrected |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.768 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 100 |

Notes:

[44] - The assumption according to which no more than 25% of the cells in the table should have an expected frequency is violated. Yates' continuity correction is reported.

Confidence interval was not calculated. It is inpupted as 0 and 100.

## Secondary: Adverse Events in relation to Clostridium difficile infection

| End point title | Adverse Events in relation to Clostridium difficile infection |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Adverse events were assessed continuously during the study por up to 6 months after treatment, until the end-of-study visit.

| End point values | MBK-01 | Fidaxomicin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 47 | | |
| Units: Adverse Events | | | | |
| Diarrhoea | 17 | 28 | | |
| Clostridium diffcile colitis | 0 | 1 | | |
| Clostridium difficile infection | 3 | 4 | | |
| Positive Clostridium test | 1 | 0 | | |
| Total | 21 | 33 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mortality associated with CDI

| End point title | Mortality associated with CDI |
|---|---|

End point description:

The number of deaths related to Clostridium difficile infection is assessed.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 6 months after the start of the treatment.

| End point values | MBK-01 | Fidaxomicin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 47 | | |
| Units: patients | 0 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: ICU admissions

| End point title | ICU admissions |
|---|---|

End point description:

The number of Intensive Care Unit Admissions related to Clostridium difficile infection or to the treatment was assessed.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 6 months after the start of the treatment.

| End point values | MBK-01 | Fidaxomicin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 47 | | |
| Units: patients | | | | |
| Related to CDI | 0 | 0 | | |
| Related to the treatment | 0 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Adverse Events of Special Interest

| End point title | Number of Adverse Events of Special Interest |
|---|---|

End point description:

AESI (Adverse Events of Special Interest) have also been considered either AEs or SAEs.

AESI defined by protocol and Statistical Analysis Plan (SAP) are as follows: abdominal cramping, bloating and pain; flatulence, nausea, vomiting, transient fever (>38ºC), increased C-reactive protein (>20 mg/L), fatigue, weight gain, headache, anorexia, constipation, diarrhea, ulcerative colitis, bacteremia, inflammatory bowel disease and enteropathogenic infections.

Some events that, in the clinician’s opinion should be considered AESI despite not being isted as such in the list provided in the protocol and the SAP, are included in this analysis. In addition, some events were not considered AESI by the clinician despite being listed as such in the protocol and the SAP, hence they were not included in this analysis.

| End point type | Secondary |
|---|---|

End point timeframe:

Adverse events were assessed continuously during the study for up to 6 months afer treatment, until the end-of-study visit.

| End point values | MBK-01 | Fidaxomicin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 47 | | |
| Units: Adverse events | 64 | 63 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Regarding safety assessments, adverse events were assessed continuously during the study for up for 6 months after treatment until the end-of-study visit (End of Study date: 15 Nov 2023).

Adverse event reporting additional description:

For the adverse events, System Organ Class (SOC) and Preferred Term (PT) were reported.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 26.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | MBK-01 |

Reporting group description:

Patients randomized to MBK-01 received a single dose of 4 oral capsules of MBK-01.

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

Reporting group description:

Patients randomized to fidaxomicin received treatment with oral fidaxomicin 200mg/12h for 10 days.

| Serious adverse events | MBK-01 | Fidaxomicin | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 45 (20.00%) | 4 / 47 (8.51%) | |
| number of deaths (all causes) | 1 | 1 | |
| number of deaths resulting from adverse events | 1 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Renal cancer | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Colitis ulcerative | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inflammatory bowel disease | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intra-abdominal fluid collection | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (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 | | | |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 1 / 47 (2.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Necrotising fasciitis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 2.13 %

| **Non-serious adverse events** | MBK-01 | Fidaxomicin | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 36 / 45 (80.00%) | 38 / 47 (80.85%) | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Surgical and medical procedures | | | |

| | | | |
|---|---|---|---|
| Prophylaxis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth extraction | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Medical device site reaction | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Pain | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 1 / 47 (2.13%) | |
| occurrences (all) | 3 | 1 | |
| Polyp | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 2 / 47 (4.26%) | |
| occurrences (all) | 3 | 2 | |
| Reproductive system and breast disorders | | | |
| Prostatitis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Catarrh | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Insomnia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Mixed anxiety and depressive disorder | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 11 / 45 (24.44%) | 6 / 47 (12.77%) | |
| occurrences (all) | 13 | 7 | |
| Cardiac murmur | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Clostridium test positive | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 2 / 47 (4.26%) | |
| occurrences (all) | 0 | 2 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Synovial rupture | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiac disorders | | | |

| | | | |
|---|---|---|---|
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Headache | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | 4 / 47 (8.51%) | |
| occurrences (all) | 3 | 4 | |
| Migraine | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 2 / 47 (4.26%) | |
| occurrences (all) | 1 | 2 | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 45 (8.89%) | 3 / 47 (6.38%) | |
| occurrences (all) | 4 | 3 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|---|---|---|
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 1 / 47 (2.13%) | |
| occurrences (all) | 1 | 1 | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 2 / 47 (4.26%) | |
| occurrences (all) | 1 | 2 | |
| Dental discomfort | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 16 / 45 (35.56%) | 22 / 47 (46.81%) | |
| occurrences (all) | 17 | 27 | |
| Erosive duodenitis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Flatulence | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 4 / 47 (8.51%) | |
| occurrences (all) | 2 | 4 | |
| Gastrointestinal sounds abnormal | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Haemorroids | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 1 / 47 (2.13%) | |
| occurrences (all) | 2 | 1 | |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 2 / 47 (4.26%) | |
| occurrences (all) | 3 | 3 | |

| | | | |
|---|---|---|---|
| Odynophagia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Reflux gastritis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | 1 / 47 (2.13%) | |
| occurrences (all) | 4 | 2 | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Hidradenitis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Toxic skin eruption | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Vascular purpura | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Renal and urinary disorders | | | |
| Microalbuminuria | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Oliguria | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 1 / 47 (2.13%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|---|---|---|---|
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 1 / 47 (2.13%) | |
| occurrences (all) | 1 | 1 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 3 / 47 (6.38%) | |
| occurrences (all) | 2 | 3 | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 1 / 47 (2.13%) | |
| occurrences (all) | 1 | 1 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 0 / 47 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Perineal abscess | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 47 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | 2 / 47 (4.26%) | |
| occurrences (all) | 3 | 2 | |
| Metabolism and nutrition disorders | | | |
| Folate deficiency | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Vitamin B12 deficiency | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 47 (2.13%) | |
| occurrences (all) | 0 | 1 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 23 August 2021 | Changes in the exclusion criteria were made, which directly impact on the recruitment capacity of the study. The modification of the exclusion criteria was motivated by the following causes:<br><br>1. The modification or elimination of some of the initially proposed exclusion criteria significantly favours the recruitment capacity of the centres involved in the study.<br><br>2. The proposed modifications of the exclusion criteria do not affect the fulfilment of the objectives (primary and secondary) of the study. The increase in the study's recruitment capacity favours the fulfilment of the study's objectives within the established timeframe.<br><br>3. The population of patients treated in the clinical trial is more heterogeneous than the previous one, and therefore more representative of the population intended to be treated with MBK-01. |
| 15 December 2021 | Four new sites were added to the clinical trial. |
| 07 February 2022 | Changes in the inclusion and exclusion criteria were made, by allowing the use of antibiotic pre-treatment for patients included in the study, making necessary to consider a washout period prior to the administration of the study treatment.<br><br>The modification of the inclusion and exclusion criteria was motivated by the following reasons:<br>1. Due to the low recruitment rate and the fact that the modification of inclusion and exclusion criteria directly impacts on recruitment capacity, the aim is to improve the recruitment capacity of the sites involved.<br>2. The proposed modifications do not affect the fulfilment of the objetives of the study. Increased recruitment capactiy woul help meet the objectives within the stablished timeframe.<br>3. The population to be treated in the study is more representative of the population intended to be treated with MBK-01.<br><br>In addition, the time for carrying out the intermediate analysis of the study was modified, so that it would be performed when half of the patients had completed treatment. In this way, the partial efficacy results of the study would be known earlier. |
| 12 May 2022 | Two new sites were added to the clinical trial. |

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|---|---|
| 16 September 2022 | The clinical trial population was broadened and the study inclusion criteria were modified, motivated by the following reasons:<br>1. Due to the low recruitment rate and the fact that the modification of inclusion criteria directly impacts on recruitment capacity, the aim is to improve the recruitment capacity of the sites involved.<br>2. The proposed modifications do not affect the fulfilment of the objetives of the study. An increased recruitment capacitiy woul help meet the objectives within the stablished timeframe.<br>3. The adjustments that were made allow an additional group of patients with Clostridioides difficile infection to have access to a potentially effective treatment, while still using the same patient population as before and without compromising the data already collected in the study.<br>4. The extension of the deadline for detection of Clostridioides difficile toxin within the 7 days prior to enrolment of the patient in the trial was made to take into account the duration of vancomycin treatment and the washout period that may be required by some participants.<br><br>The statistical analysis was adapted to include the assessment of an additional secondary safety variable, which would provide more information on the safety of the investigational medicinal product. The sample size was adapted without affecting the achievement of the study objectives.<br><br>Some aspects of the study design were modified, allowing the inclusion in the trial of patients previously treated with fidaxomicin if the duration of treatment was not therapeutic. In addition, it was included that the interim analysis of the study could lead to early discontinuation of the study, with the aim of early termination of the study, in order to maintain the safety of the participants. |
| 21 July 2023 | The measures taken in October 2022 were included in the protocol, following the recommendations of the guidance document 'Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Additional Safety Protections Pertaining to Monkeypox Virus', issued by the FDA in 2022, and which were notified to the AEMPS by Urgent Safety Notification on 21/10/2022. The donor inclusion criteria were modified in line with these measures.<br><br>The sample size was adapted from 66 to 82 patients, in order to adjust the expected number of patients recruited to the actual observed drop-out rate of the study, without affecting the achievement of the study objectives.<br><br>A new planned study schedule was established, taking into account the changes in the number of patients to be recruited. |

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| 09 October 2023 | The definition of the study variables were revised to add the odds ratio and logistic regression in the analysis of the main efficacy variable, thus allowing the study of the probability of recurrence in addition to the number of episodes of diarrhea. The variable "Duration of hospitalisation" was deleted as many patients were treated as outpatients or the reason of admission was not CDI. The variable "Duration of the treatment" was also deleted.<br><br>Complementary ITT subpopulations were added for the analysis of probability of recurrence and time to recurrence. The analysis of covariates was eliminated.<br><br>In addition, a revision of the definition of recurrence of CDI was added.<br><br>The reformulation of the primary variable resulted in the revision of the statiscal calculation of the sample size, which would be based on a confidence level of 97.06%, Odds Ratio of 2.5, stastical power of 80% and loss rate of 50%, generating a sample size of 104 subjects. The dropout rate was maintained at 50%.<br><br>Criteria were defined to allow the early termination of the clinical trial. The possibility of early termination could provide advantages such as minimisation of risks to subjects, greater efficiency in the management of research resources, and/or, where appropriate, acceleration of product development and market access.<br><br>The possibility of early termination of the trial makes it necessary to plan for a second, intermediate statistical analysis to assess trends in efficacy and safety outcomes.<br><br>The high rate of loss to follow-up, as well as the possibility of premature trial termination, made it necessary to define a strategy for the follow-up of patients withdrawn before completing the scheduled follow-up. Thus, it was defined that all patients withdrawn before the end of the planned follow-up should have an end-of-study visit ≥ 30 days after initiation of treatment, in which, as a minimum, relevant safety information should be collected. |

Notes:

## 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.

The statistical power of the study was limited due to the small sample size, which may have prevented finding statistically significant differences between MBK-01 and fidaxomicin in some analyses.

Notes: