# Clinical trial results:
# A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Multiple Ascending Dose Study (Induction Therapy) and Long-term Extension Therapy of an Anti-OX40 Monoclonal Antibody (KHK4083) in Subjects with Moderately Active Ulcerative Colitis

## Summary

| | |
|---|---|
| EudraCT number | 2015-001555-69 |
| Trial protocol | HU CZ PL |
| Global end of trial date | 04 October 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 29 December 2019 |
| First version publication date | 29 December 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 4083-002 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02647866 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Kyowa Kirin Pharmaceutical Development, Inc. |
| Sponsor organisation address | 212 Carnegie Center, Suite 400, Princeton, United States, 08540 |
| Public contact | Kaoru Okada, Kyowa Hakko Kirin Co., Ltd., +81 3 5205-7219, kaoru.okada@kyowa-kirin.co.jp |
| Scientific contact | Kaoru Okada, Kyowa Hakko Kirin Co., Ltd., +81 3 5205-7219, kaoru.okada@kyowa-kirin.co.jp |

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 | 06 June 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 21 September 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 October 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

• Induction Therapy - Part A:  To determine the safety and tolerability of administration of multiple ascending doses of KHK4083 and to select the highest dose tolerated by subjects with moderately active ulcerative colitis (UC) to recommend for use in Part B;
• Induction Therapy - Part B:  To determine if the recommended dose of KHK4083 identified in Part A improves the mucosa in subjects with moderately active UC at Week 12 as measured by the modified Mayo endoscopy subscore (mMES).

Protection of trial subjects:

This study was conducted in full accordance with the Declaration of Helsinki, the ICH consolidated guideline E6 - GCP, and any applicable national and local laws and regulations. The Investigators were responsible for performing the study in accordance with the protocol and ICH E6 GCP, for collecting, recording, and reporting the data accurately and properly. Agreement of the Investigator to conduct and administer this study in accordance with the protocol was documented in separate study agreements with the Sponsor and other forms as required by national authorities in the country where the study center was located.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 10 December 2015 |
| 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 | Poland: 25 |
| Country: Number of subjects enrolled | Romania: 2 |
| Country: Number of subjects enrolled | Czech Republic: 3 |
| Country: Number of subjects enrolled | Hungary: 6 |
| Country: Number of subjects enrolled | Russian Federation: 20 |
| Country: Number of subjects enrolled | Serbia: 9 |
| Country: Number of subjects enrolled | United States: 1 |
| Worldwide total number of subjects | 66 |
| EEA total number of subjects | 36 |

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) | 60 |
| From 65 to 84 years | 6 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Investigative sites in the US, Poland, Czech Republic, Russia, Romania, Serbia, and Hungary recruited patients from January 2016 until June 2017.

### Pre-assignment

Screening details:

A total of 109 patients were screened during the recruiting period. Male and female subjects ≥18 years of age with moderately active UC, defined as a total Mayo Clinic score of 4 to 9 & an mMES of at least 2 as determined by a central reader, and disease that extends ≥ 15 cm from the anal verge were eligible to participate in this study.

### Period 1

| | |
|---|---|
| Period 1 title | Double-Blind Induction Therapy |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Cohort 1 |

Arm description:

1.0 mg/kg

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | KHK4083 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received 1.0 mg/kg of investigational product by IV infusion over 60 minutes (± 10 minutes) every 2 weeks from Week 0 (Day 1) to Week 10.

| | |
|---|---|
| **Arm title** | Cohort 2 |

Arm description:

3.0 mg/kg

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | KHK4083 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received 3.0 mg/kg of investigational product by IV infusion over 60 minutes (± 10 minutes) every 2 weeks from Week 0 (Day 1) to Week 10.

| | |
|---|---|
| **Arm title** | Cohort 3 |

Arm description:

10.0 mg/kg

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | KHK4083 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received 10.0 mg/kg of investigational product by IV infusion over 60 minutes (± 10 minutes) every 2 weeks from Week 0 (Day 1) to Week 10.

| **Arm title** | Cohort 4 |
|---|---|

Arm description:

maximum tolerated dose (10.0 mg/kg)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | KHK4083 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received the maximum tolerated dose (10.0 mg/kg) of investigational product by IV infusion over 60 minutes (± 10 minutes) every 2 weeks from Week 0 (Day 1) to Week 10.

| **Arm title** | Placebo |
|---|---|

Arm description:

Placebo arm

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects in this cohort received placebo by IV infusion over 60 minutes (± 10 minutes) every 2 weeks from Week 0 (Day 1) to Week 10.

| **Number of subjects in period 1** | Cohort 1 | Cohort 2 | Cohort 3 |
|---|---|---|---|
| Started | 9 | 10 | 9 |
| Completed | 7 | 8 | 4 |
| Not completed | 2 | 2 | 5 |
| Consent withdrawn by subject | - | 1 | 2 |
| Physician decision | - | - | 1 |
| Adverse event, non-fatal | - | - | 2 |
| Patient moved to another country | 1 | - | - |
| Lack of efficacy | 1 | 1 | - |

| **Number of subjects in period 1** | Cohort 4 | Placebo |
|---|---|---|
| Started | 21 | 17 |

| | | |
|---|---|---|
| Completed | 17 | 15 |
| Not completed | 4 | 2 |
| Consent withdrawn by subject | 3 | - |
| Physician decision | - | 1 |
| Adverse event, non-fatal | 1 | - |
| Patient moved to another country | - | - |
| Lack of efficacy | - | 1 |

## Period 2

| | |
|---|---|
| Period 2 title | Long Term Extension (LTE) Therapy |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Cohort 1 LTE |

Arm description:

1.0 mg/kg

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | KHK4083 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received 1.0 mg/kg of investigational product by IV infusion over 60 minutes (± 10 minutes) every 4 weeks from Week 12 to Week 48.

| | |
|---|---|
| **Arm title** | Cohort 2 LTE |

Arm description:

3.0 mg/kg

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | KHK4083 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects in this cohort were to receive one 3.0 mg/kg IV infusion every 4 weeks from Week 12 to Week 48 followed by an End-of-LTE Therapy visit at Week 52, and then proceed to the LTE Therapy Follow-up Period (Week 56 through Week 64).

| | |
|---|---|
| **Arm title** | Placebo LTE |

Arm description:

Placebo arm

| | |
|---|---|
| Arm type | Placebo |

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The LTE was only active for subjects who entered it prior to approval of Protocol Amendment 2. Subjects in this cohort were to receive one IV infusion of placebo every 4 weeks from Week 12 to Week 48 followed by an End-of-LTE Therapy visit at Week 52, and then proceed to the LTE Therapy Follow-up Period.

| **Number of subjects in period 2** | Cohort 1 LTE | Cohort 2 LTE | Placebo LTE |
|---|---|---|---|
| Started | 3 | 5 | 1 |
| Completed | 1 | 0 | 0 |
| Not completed | 2 | 5 | 1 |
| Consent withdrawn by subject | 1 | - | - |
| Transferred from LTE to OLE | - | 5 | 1 |
| Lack of efficacy | 1 | - | - |

## Period 3

| | |
|---|---|
| Period 3 title | Open Label Extension (OLE) Therapy |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Cohort 2 OLE |

Arm description:

3.0 mg/kg

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | KHK4083 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Each subject eligible to enroll in OLE was to receive 10 treatments of open-label KHK4083 as maintenance therapy, one IV infusion of 3.0 mg/kg every 4 weeks from Week 12 to Week 48 followed by an End-of-OLE Therapy visit at Week 52, and then proceed to the OLE Therapy Follow-up Period (Week 56 through Week 64).

| | |
|---|---|
| **Arm title** | Cohort 3 OLE |

Arm description:

10.0 mg/kg

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | KHK4083 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Each subject eligible to enroll in OLE was to receive 10 treatments of open-label KHK4083 as maintenance therapy, one IV infusion of 10.0 mg/kg every 4 weeks from Week 12 to Week 48 followed by an End-of-OLE Therapy visit at Week 52, and then proceed to the OLE Therapy Follow-up Period (Week 56 through Week 64).

| **Arm title** | Cohort 4 OLE |
|---|---|

Arm description:

maximum tolerated dose (10.0 mg/kg)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | KHK4083 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Each subject eligible to enroll in OLE was to receive 10 treatments of open-label KHK4083 as maintenance therapy, one IV infusion of 10.0 mg/kg every 4 weeks from Week 12 to Week 48 followed by an End-of-OLE Therapy visit at Week 52, and then proceed to the OLE Therapy Follow-up Period (Week 56 through Week 64).

| **Arm title** | Placebo OLE |
|---|---|

Arm description:

Placebo subjects now receiving study drug as maintenance therapy

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | KHK4083 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received either 1.0 mg/kg, 3.0 mg/kg, or 10.0 mg/kg of investigational product by IV infusion every 4 weeks from Week 12 to Week 48 as maintenance therapy, depending on which cohort they were enrolled in during Double-Blind Induction Therapy.

| **Number of subjects in period 3** | Cohort 2 OLE | Cohort 3 OLE | Cohort 4 OLE |
|---|---|---|---|
| Started | 3 | 8 | 24 |
| Completed | 6 | 5 | 21 |
| Not completed | 2 | 3 | 3 |
| Adverse event, serious fatal | 1 | - | - |
| Physician decision | 1 | - | - |
| Consent withdrawn by subject | - | 3 | 1 |
| Adverse event, non-fatal | - | - | 2 |
| Joined | 5 | 0 | 0 |

| | | | |
|---|---|---|---|
| Transferred from LTE to OLE | 5 | - | - |

| **Number of subjects in period 3** | Placebo OLE |
|---|---|
| Started | 12 |
| Completed | 9 |
| Not completed | 5 |
| Adverse event, serious fatal | - |
| Physician decision | 1 |
| Consent withdrawn by subject | 3 |
| Adverse event, non-fatal | 1 |
| Joined | 2 |
| Transferred from LTE to OLE | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Double-Blind Induction Therapy |
| Reporting group description: - | |

| Reporting group values | Double-Blind Induction Therapy | Total | |
|---|---|---|---|
| Number of subjects | 66 | 66 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 60 | 60 | |
| From 65-84 years | 6 | 6 | |
| 85 years and over | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 40.8 | | |
| full range (min-max) | 18 to 78 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 25 | 25 | |
| Male | 41 | 41 | |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | KHK4083 1.0 mg/kg SAS |
| Subject analysis set type | Safety analysis |
| Subject analysis set description:<br>Subjects receiving KHK4083 in Cohort 1 | |
| Subject analysis set title | KHK4083 3.0 mg/kg SAS |
| Subject analysis set type | Safety analysis |
| Subject analysis set description:<br>Subjects receiving KHK4083 in Cohort 2 | |
| Subject analysis set title | KHK4083 10.0 mg/kg SAS |
| Subject analysis set type | Safety analysis |
| Subject analysis set description:<br>Subjects receiving KHK4083 in Cohorts 3 and 4 | |
| Subject analysis set title | Placebo SAS |
| Subject analysis set type | Safety analysis |
| Subject analysis set description:<br>Subjects receiving placebo in all cohorts | |
| Subject analysis set title | KHK4083 1.0 mg/kg FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>All subjects who received at least one full dose of investigational product and who had Baseline data and at least one post-treatment assessment of the primary efficacy variable. | |
| Subject analysis set title | KHK4083 3.0 mg/kg FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>all subjects who received at least one full dose of investigational product and who had Baseline data and | |

at least one post-treatment assessment of the primary efficacy variable.

| | |
|---|---|
| Subject analysis set title | KHK4083 10.0 mg/kg FAS |
| Subject analysis set type | Full analysis |

Subject analysis set description:

all subjects who received at least one full dose of investigational product and who had Baseline data and at least one post-treatment assessment of the primary efficacy variable.

| | |
|---|---|
| Subject analysis set title | Placebo FAS |
| Subject analysis set type | Full analysis |

Subject analysis set description:

all subjects who received at least one full dose of investigational product and who had Baseline data and at least one post-treatment assessment of the primary efficacy variable.

| **Reporting group values** | KHK4083 1.0 mg/kg SAS | KHK4083 3.0 mg/kg SAS | KHK4083 10.0 mg/kg SAS |
|---|---|---|---|
| Number of subjects | 9 | 10 | 30 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 7 | 8 | 28 |
| From 65-84 years | 2 | 2 | 2 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 42.9 | 46.1 | 41.1 |
| full range (min-max) | 18 to 67 | 21 to 75 | 18 to 78 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 4 | 2 | 11 |
| Male | 5 | 8 | 19 |

| **Reporting group values** | Placebo SAS | KHK4083 1.0 mg/kg FAS | KHK4083 3.0 mg/kg FAS |
|---|---|---|---|
| Number of subjects | 17 | 7 | 8 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 17 | 4 | 7 |
| From 65-84 years | 0 | 1 | 1 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 33.8 | 47.9 | 44.8 |
| full range (min-max) | 18 to 61 | 18 to 67 | 21 to 75 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 8 | 3 | 2 |
| Male | 9 | 4 | 6 |

| **Reporting group values** | KHK4083 10.0 mg/kg FAS | Placebo FAS | |
|---|---|---|---|
| Number of subjects | 22 | 15 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 21 | 15 | |
| From 65-84 years | 1 | 0 | |
| 85 years and over | 0 | 0 | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years | | | |
| arithmetic mean | 43.1 | 34.2 | |
| full range (min-max) | 23 to 70 | 18 to 61 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 7 | 6 | |
| Male | 15 | 9 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Cohort 1 |
| Reporting group description: 1.0 mg/kg | |
| Reporting group title | Cohort 2 |
| Reporting group description: 3.0 mg/kg | |
| Reporting group title | Cohort 3 |
| Reporting group description: 10.0 mg/kg | |
| Reporting group title | Cohort 4 |
| Reporting group description: maximum tolerated dose (10.0 mg/kg) | |
| Reporting group title | Placebo |
| Reporting group description: Placebo arm | |
| Reporting group title | Cohort 1 LTE |
| Reporting group description: 1.0 mg/kg | |
| Reporting group title | Cohort 2 LTE |
| Reporting group description: 3.0 mg/kg | |
| Reporting group title | Placebo LTE |
| Reporting group description: Placebo arm | |
| Reporting group title | Cohort 2 OLE |
| Reporting group description: 3.0 mg/kg | |
| Reporting group title | Cohort 3 OLE |
| Reporting group description: 10.0 mg/kg | |
| Reporting group title | Cohort 4 OLE |
| Reporting group description: maximum tolerated dose (10.0 mg/kg) | |
| Reporting group title | Placebo OLE |
| Reporting group description: Placebo subjects now receiving study drug as maintenance therapy | |
| Subject analysis set title | KHK4083 1.0 mg/kg SAS |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects receiving KHK4083 in Cohort 1 | |
| Subject analysis set title | KHK4083 3.0 mg/kg SAS |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects receiving KHK4083 in Cohort 2 | |
| Subject analysis set title | KHK4083 10.0 mg/kg SAS |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Subjects receiving KHK4083 in Cohorts 3 and 4

| | |
|---|---|
| Subject analysis set title | Placebo SAS |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Subjects receiving placebo in all cohorts

| | |
|---|---|
| Subject analysis set title | KHK4083 1.0 mg/kg FAS |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All subjects who received at least one full dose of investigational product and who had Baseline data and at least one post-treatment assessment of the primary efficacy variable.

| | |
|---|---|
| Subject analysis set title | KHK4083 3.0 mg/kg FAS |
| Subject analysis set type | Full analysis |

Subject analysis set description:

all subjects who received at least one full dose of investigational product and who had Baseline data and at least one post-treatment assessment of the primary efficacy variable.

| | |
|---|---|
| Subject analysis set title | KHK4083 10.0 mg/kg FAS |
| Subject analysis set type | Full analysis |

Subject analysis set description:

all subjects who received at least one full dose of investigational product and who had Baseline data and at least one post-treatment assessment of the primary efficacy variable.

| | |
|---|---|
| Subject analysis set title | Placebo FAS |
| Subject analysis set type | Full analysis |

Subject analysis set description:

all subjects who received at least one full dose of investigational product and who had Baseline data and at least one post-treatment assessment of the primary efficacy variable.

## Primary: Proportion of subjects with treatment-related adverse events

| | |
|---|---|
| End point title | Proportion of subjects with treatment-related adverse events[1] |

End point description:

A TEAE was an AE which started after the first dose of Investigational Product (KHK4083 or Placebo) but was within 16 weeks after the last dose.

Overall, KHK4083 had a safety profile that was in line with expectations, the TEAEs were mostly mild or moderate by intensity and were manageable by the current standard of care therapies.
The single case of death due to myocardial infarction in a subject with pre-existing coronary heart disease was considered as not study drug related by the Investigator.

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

End point timeframe:

up to 52 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was used for this primary end point.

| End point values | KHK4083 1.0 mg/kg SAS | KHK4083 3.0 mg/kg SAS | KHK4083 10.0 mg/kg SAS | Placebo SAS |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 10 | 30 | 17 |
| Units: Subjects | | | | |
| With Any TEAE | 5 | 7 | 21 | 13 |
| With Any Drug-related TEAE | 3 | 2 | 6 | 2 |
| With Any TEAE with an Outcome of Death | 0 | 1 | 0 | 0 |
| With Any TEAE Leading to Discontinuation (DC) | 0 | 1 | 3 | 1 |

| | | | | |
|---|---|---|---|---|
| With Any Drug-related TEAE Leading to DC | 0 | 0 | 1 | 0 |

## Statistical analyses

No statistical analyses for this end point

## Primary: Proportion of subjects with treatment-related serious adverse events

| End point title | Proportion of subjects with treatment-related serious adverse events[2] |
|---|---|

End point description:

A TEAE was an AE which started after the first dose of Investigational Product (KHK4083 or Placebo) but was within 16 weeks after the last dose.

Overall, KHK4083 had a safety profile that was in line with expectations, the TEAEs were mostly mild or moderate by intensity and were manageable by the current standard of care therapies.
The single case of death due to myocardial infarction in a subject with pre-existing coronary heart disease was considered as not study drug related by the Investigator.

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

End point timeframe:

up to 52 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was used for this primary end point.

| End point values | KHK4083 1.0 mg/kg SAS | KHK4083 3.0 mg/kg SAS | KHK4083 10.0 mg/kg SAS | Placebo SAS |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 10 | 30 | 17 |
| Units: Subjects | | | | |
| With Any Serious TEAE | 1 | 1 | 4 | 3 |
| With Any Drug-related Serious TEAE | 0 | 0 | 0 | 0 |
| Who Died | 0 | 1 | 0 | 0 |

## Statistical analyses

No statistical analyses for this end point

## Primary: Proportion of subjects who show improvement in the mucosa at Week 12

| End point title | Proportion of subjects who show improvement in the mucosa at Week 12[3] |
|---|---|

End point description:

Measured by the modified Mayo endoscopy sub-score (mMES)

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

End point timeframe:

12 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis is provided in attached summary table.

| **End point values** | KHK4083 1.0 mg/kg FAS | KHK4083 3.0 mg/kg FAS | KHK4083 10.0 mg/kg FAS | Placebo FAS |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 22 | 15 |
| Units: Subjects | | | | |
| mMES Improvement | 2 | 4 | 9 | 5 |
| Modified Baron Endoscopic Score Improvement | 3 | 5 | 8 | 6 |

| **Attachments (see zip file)** | Summary of Change from Baseline of UCEIS/4083-002 Mucosa |
|---|---|

### Statistical analyses

No statistical analyses for this end point

### Primary: Proportion of subjects who show improvement in the mucosa at Week 52

| End point title | Proportion of subjects who show improvement in the mucosa at Week 52[4] |
|---|---|

End point description:

Improvement in the Mucosa at Week 52 was observed in 14.3% (1 of 7 subjects) of the subjects receiving 1.0 mg/kg KHK4083; there were no subjects in the 3.0 mg/kg or 10.0 mg/kg KHK4083 or Placebo groups in the Double-Blind Therapy Period. During OLE Therapy Period, Improvement in the Mucosa at Week 52 was observed in 37.5% (3 of 8 subjects) and 42.9% (9 of 21 subjects) of the subjects receiving 3.0 mg/kg and 10.0 mg/kg KHK4083, respectively. There were no subjects in the 1.0 mg/kg KHK4083 group in the OLE Therapy Period.

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

End point timeframe:

52 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was used for this primary endpoint.

| **End point values** | KHK4083 1.0 mg/kg FAS | KHK4083 3.0 mg/kg FAS | KHK4083 10.0 mg/kg FAS | Placebo FAS |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 21 | 14 |
| Units: Subjects | 1 | 3 | 9 | 4 |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Subjects Who Achieve Mucosal Healing at Week 12

| End point title | Proportion of Subjects Who Achieve Mucosal Healing at Week |
|---|---|

| | |
|---|---|
| | 12 |

End point description:

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

End point timeframe:

12 Weeks

| End point values | KHK4083 1.0 mg/kg FAS | KHK4083 3.0 mg/kg FAS | KHK4083 10.0 mg/kg FAS | Placebo FAS |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 22 | 15 |
| Units: Subjects | 1 | 3 | 8 | 4 |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Proportion of Subjects Who Achieve Mucosal Healing at Week 52**

| | |
|---|---|
| End point title | Proportion of Subjects Who Achieve Mucosal Healing at Week 52 |

End point description:

Mucosal healing is defined as modified Mayo endoscopy sub-score (mMES) of 0 or 1

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

End point timeframe:

52 Weeks

| End point values | KHK4083 1.0 mg/kg FAS | KHK4083 3.0 mg/kg FAS | KHK4083 10.0 mg/kg FAS | Placebo FAS |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 21 | 14 |
| Units: Subjects | 1 | 3 | 7 | 3 |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Proportion of Subjects Who Achieve Clinical Improvement at Week 12**

| | |
|---|---|
| End point title | Proportion of Subjects Who Achieve Clinical Improvement at Week 12 |

End point description:

Improvement will be based on a reduction in the total Mayo Clinic score (0 to 12).

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

End point timeframe:

12 Weeks

| End point values | KHK4083 1.0 mg/kg FAS | KHK4083 3.0 mg/kg FAS | KHK4083 10.0 mg/kg FAS | Placebo FAS |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 22 | 15 |
| Units: Subjects | 2 | 4 | 9 | 5 |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Subjects Who Achieve a Clinical Response at Week 12

| End point title | Proportion of Subjects Who Achieve a Clinical Response at Week 12 |
|---|---|

End point description:

Clinical Response indicates the change from Baseline in the Total Mayo Clinic score <= -3 and the percentage change from Baseline in the Total Mayo Clinic score <= -30% to Week 12, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of <= 1.

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

End point timeframe:

12 Weeks

| End point values | KHK4083 1.0 mg/kg FAS | KHK4083 3.0 mg/kg FAS | KHK4083 10.0 mg/kg FAS | Placebo FAS |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 22 | 15 |
| Units: Subjects | 3 | 8 | 11 | 9 |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Subjects Who Achieve a Clinical Response at Week 52

| End point title | Proportion of Subjects Who Achieve a Clinical Response at Week 52 |
|---|---|

End point description:

Clinical Response indicates the change from Baseline in the Total Mayo Clinic score <= -3 and the percentage change from Baseline in the Total Mayo Clinic score <= -30% to Week 12, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of <= 1.

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

End point timeframe:
52 Weeks

| End point values | KHK4083 1.0 mg/kg FAS | KHK4083 3.0 mg/kg FAS | KHK4083 10.0 mg/kg FAS | Placebo FAS |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 21 | 14 |
| Units: Subjects | 2 | 4 | 14 | 5 |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Subjects Who Achieve Clinical Remission at Week 12

| End point title | Proportion of Subjects Who Achieve Clinical Remission at Week 12 |
|---|---|

End point description:
Clinical remission is defined as a total Mayo Clinic score of ≤ 2 and no subscores > 1

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

End point timeframe:
12 Weeks

| End point values | KHK4083 1.0 mg/kg FAS | KHK4083 3.0 mg/kg FAS | KHK4083 10.0 mg/kg FAS | Placebo FAS |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 22 | 15 |
| Units: Subjects | 1 | 3 | 10 | 3 |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Subjects Who Achieve Clinical Remission at Week 52

| End point title | Proportion of Subjects Who Achieve Clinical Remission at Week 52 |
|---|---|

End point description:
Clinical Remission = A Total Mayo Clinic Score <= 2 and no subscores > 1 at Week 52.

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

End point timeframe:
52 Weeks

| End point values | KHK4083 1.0 mg/kg FAS | KHK4083 3.0 mg/kg FAS | KHK4083 10.0 mg/kg FAS | Placebo FAS |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 21 | 14 |
| Units: Subjects | 1 | 3 | 6 | 5 |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Subjects were monitored for any untoward medical occurrences from the time of signed Informed Consent through 16 weeks post dose.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Cohort 1 1.0 mg/kg |
| Reporting group description: - | |
| Reporting group title | Cohort 2 3.0 mg/kg |
| Reporting group description: - | |
| Reporting group title | Cohort 3 10.0 mg/kg |
| Reporting group description: - | |
| Reporting group title | Cohort 4 10.0 mg/kg |
| Reporting group description: - | |
| Reporting group title | COMBINED |
| Reporting group description: - | |
| Reporting group title | PLACEBO |

Reporting group description: -

| Serious adverse events | Cohort 1 1.0 mg/kg | Cohort 2 3.0 mg/kg | Cohort 3 10.0 mg/kg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 10 (10.00%) | 1 / 9 (11.11%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | | 0 | |
| Investigations | | | |
| Blood albumin decreased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Surgical and medical procedures | | | |
| Abscess drainage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Cohort 4 10.0 mg/kg | COMBINED | PLACEBO |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 6 / 49 (12.24%) | 3 / 17 (17.65%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | | 0 | |
| Investigations | | | |
| Blood albumin decreased | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Surgical and medical procedures | | | |
| Abscess drainage | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Colitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 3 / 49 (6.12%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Cohort 1 1.0 mg/kg | Cohort 2 3.0 mg/kg | Cohort 3 10.0 mg/kg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 9 (55.56%) | 7 / 10 (70.00%) | 7 / 9 (77.78%) |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Chills | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 9 (33.33%) | 1 / 10 (10.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 3 | 1 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sneezing | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Amylase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aspartate aminotransferase abnormal | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatine phosphokinase abnormal | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood folate decreased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Scar | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Congenital, familial and genetic disorders | | | |
| Renal aplasia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 10 (10.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 | 1 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 2 / 10 (20.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 3 / 9 (33.33%) |
| occurrences (all) | 0 | 0 | 3 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Abdominal tenderness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 10 (10.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 1 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mouth ulceration | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 0 | 1 |
| Mucous stools | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Hepatic steatosis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 10 (10.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 10 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | Cohort 4 10.0 mg/kg | COMBINED | PLACEBO |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 21 (61.90%) | 32 / 49 (65.31%) | 13 / 17 (76.47%) |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chills | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 3 / 49 (6.12%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 6 / 49 (12.24%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 6 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sneezing | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Aspartate aminotransferase abnormal | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 2 / 17 (11.76%) |
| occurrences (all) | 0 | 0 | 2 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 2 / 17 (11.76%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood creatine phosphokinase abnormal | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 2 / 49 (4.08%) | 1 / 17 (5.88%) |
| occurrences (all) | 2 | 3 | 1 |
| Blood folate decreased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Scar | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Congenital, familial and genetic disorders | | | |
| Renal aplasia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 49 (4.08%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 2 | 1 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 7 / 49 (14.29%) | 3 / 17 (17.65%) |
| occurrences (all) | 3 | 7 | 4 |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 2 / 49 (4.08%) | 1 / 17 (5.88%) |
| occurrences (all) | 1 | 2 | 1 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 3 / 49 (6.12%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 3 | 1 |
| Abdominal pain lower | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal tenderness | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 5 / 49 (10.20%) | 5 / 17 (29.41%) |
| occurrences (all) | 2 | 5 | 5 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 49 (4.08%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Mucous stools | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 | 1 |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Hepatobiliary disorders | | | |
| Hepatic steatosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 3 / 49 (6.12%) | 1 / 17 (5.88%) |
| occurrences (all) | 1 | 3 | 1 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 49 (2.04%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 | 1 |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 49 (2.04%) | 1 / 17 (5.88%) |
| occurrences (all) | 1 | 1 | 1 |

| | | | |
|---|---|---|---|
| Sinusitis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 2 / 49 (4.08%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 49 (2.04%) | 1 / 17 (5.88%) |
| occurrences (all) | 1 | 1 | 1 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 49 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 15 October 2015 | Updates:<br>• Section 5, OBJECTIVES; Section 10.1.1, Primary Endpoints, Efficacy; and Section 12.3.1, Primary Efficacy Analysis – to change the primary objective/variable from the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score to the FDA suggested modified Mayo endoscopy subscore (mMES) with an amended endoscopy finding scoring (i.e., mild friability excluded from a subscore of 1).<br>• Section 5, OBJECTIVES; Section 10.2, Secondary Efficacy Endpoints; and Section 12.3.2, Secondary Efficacy Analyses – to change the secondary objective/variable from Mayo Clinic Endoscopy subscore to UCEIS.<br>• Section 5, OBJECTIVES; Section 10.3, Exploratory Endpoints; and Section 12.3.3, Exploratory Efficacy Analysis – to add the exploratory objective/variable of a more stringent definition of remission; defined as an mMES of 0 or 1, a stool frequency subscore of 0 or 1, and a rectal bleeding subscore of 0.<br>• Section 7.2, Inclusion Criteria 6)a) – to increase the minimal dose of budesonide from 6 mg/day to 9 mg/day in the definition of an unsuccessful prior treatment.<br>• Section 7.2, Inclusion Criteria 6)c) – to specify the minimal doses and duration of anti-TNFα antagonists in the definition of an unsuccessful prior treatment.<br>• Section 7.5.1, Subject Withdrawal – to further clarify when the Investigator(s) may withdraw a subject from the study.<br>• Section 7.5.2, Study or Investigative Site Termination – to define unacceptable overall safety risks that may result in recommendation for termination of the study.<br>• Section 7.5.3, Criteria for Subject Removal from the Study – to identify additional reasons that a subject may be removed from the study.<br>• Section 8.5, Prior and Concurrent Therapy – to clarify that daily, chronic antidiarrheal medications should not be taken.<br>• Section 8.6.1, Study Visit Outside of Planned Scheduled - Delay in Dosing - to describe the handling of IP administration when visits are not within the study visit window. |
| 04 October 2016 | The changes that were made to the protocol are listed in the following table, along with the rationale for each change: |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported