



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
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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
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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
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Arm description:

10.0 mg/kg

Arm type	Experimental
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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 (\pm 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 (\pm 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 (\pm 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 (\pm 10 minutes) every 4 weeks from Week 12 to Week 48.

Arm title	Cohort 2 LTE
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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
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Arm description:

Placebo arm

Arm type	Placebo
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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
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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
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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
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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	-	-
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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
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Reporting group description: -

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

Subject analysis sets

Subject analysis set title	KHK4083 1.0 mg/kg SAS
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Subjects receiving KHK4083 in Cohort 1

Subject analysis set title	KHK4083 3.0 mg/kg SAS
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Subjects receiving KHK4083 in Cohort 2

Subject analysis set title	KHK4083 10.0 mg/kg SAS
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Subjects receiving KHK4083 in Cohorts 3 and 4

Subject analysis set title	Placebo SAS
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Subjects receiving placebo in all cohorts

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

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 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 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 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 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 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 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 Units: Subjects			
Adults (18-64 years)	21	15	
From 65-84 years	1	0	
85 years and over	0	0	

Age continuous			
Units: years			
arithmetic mean	43.1	34.2	
full range (min-max)	23 to 70	18 to 61	
Gender categorical			
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]
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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
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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
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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]
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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
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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]
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End point description:

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

End point type	Primary
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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
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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]
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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
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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
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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
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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 $\leq -30\%$ 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
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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
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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 $\leq -30\%$ 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
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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
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End point description:

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

End point type	Secondary
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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
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End point description:

Clinical Remission = A Total Mayo Clinic Score ≤ 2 and no subscores > 1 at Week 52.

End point type	Secondary
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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
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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 occurrences (all)	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1
Chest discomfort subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1
Chills subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 3	1 / 10 (10.00%) 1	1 / 9 (11.11%) 1
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0
Sneezing subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0	0 / 9 (0.00%) 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 occurrences (all)	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0	0 / 9 (0.00%) 0
Cardiac disorders Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0 0 / 9 (0.00%) 0	1 / 10 (10.00%) 1 1 / 10 (10.00%) 1	1 / 9 (11.11%) 1 0 / 9 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0	2 / 10 (20.00%) 2 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0	0 / 9 (0.00%) 0 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain lower subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Abdominal tenderness	0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 1 / 9 (11.11%) 1	1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0	0 / 9 (0.00%) 0 3 / 9 (33.33%) 3 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0

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

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

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 occurrences (all)	0 / 21 (0.00%) 0	0 / 49 (0.00%) 0	1 / 17 (5.88%) 1
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 49 (0.00%) 0	1 / 17 (5.88%) 1
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 49 (2.04%) 1	0 / 17 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	3 / 49 (6.12%) 3	1 / 17 (5.88%) 1
Joint swelling subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 49 (2.04%) 1	0 / 17 (0.00%) 0
Muscular weakness subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 49 (0.00%) 0	1 / 17 (5.88%) 1
Myalgia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 49 (2.04%) 1	1 / 17 (5.88%) 1
Infections and infestations Influenza subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 49 (0.00%) 0	1 / 17 (5.88%) 1
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 49 (0.00%) 0	1 / 17 (5.88%) 1
Oral herpes subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 49 (0.00%) 0	1 / 17 (5.88%) 1
Pharyngitis subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	1 / 49 (2.04%) 1	1 / 17 (5.88%) 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	<p>Updates:</p> <ul style="list-style-type: none">• 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).• 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.• 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.• 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.• 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.• Section 7.5.1, Subject Withdrawal – to further clarify when the Investigator(s) may withdraw a subject from the study.• 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.• Section 7.5.3, Criteria for Subject Removal from the Study – to identify additional reasons that a subject may be removed from the study.• Section 8.5, Prior and Concurrent Therapy – to clarify that daily, chronic antidiarrheal medications should not be taken.• 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