



## Clinical trial results:

### A Phase 4, Multicenter, Open-label Study of Serum Infliximab Concentrations and Efficacy and Safety of Dose Escalation in Pediatric Patients With Inflammatory Bowel Disease

#### Summary

EudraCT number	2015-001653-32
Trial protocol	Outside EU/EEA
Global end of trial date	20 August 2019

#### Results information

Result version number	v2 (current)
This version publication date	08 May 2020
First version publication date	26 January 2020
Version creation reason	

#### Trial information

##### Trial identification

Sponsor protocol code	C0168IBD4020
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02566889
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Janssen Scientific Affairs
Sponsor organisation address	1000 U.S. Route 202 South, Raritan, United States, NJ 08869
Public contact	Clinical Registry Group, Janssen Scientific Affairs, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Scientific Affairs, ClinicalTrialsEU@its.jnj.com

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?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 August 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 August 2019
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The purpose of study was to evaluate whether trough serum infliximab concentrations at the time of loss of clinical response will identify pediatric subjects with IBD who would benefit (regain clinical response) from dose escalation above the currently approved dose (5 mg/kg every 8 weeks [q8wk])

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety evaluations were based upon the type, incidence, and severity of treatment-emergent adverse events (TEAEs) and adverse events (AEs) of special interest reported throughout the study, and on changes in vital sign measurements, clinical laboratory test results, physical examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	United States: 49
Worldwide total number of subjects	53
EEA total number of subjects	0

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)	7
Adolescents (12-17 years)	46
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 75 subjects were screened out of which 53 subjects were enrolled in the study and a total of 35 subjects completed the study. Reference arm was planned only for safety analysis in subjects being treated with labeled dosing of infliximab.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Reference Group

Arm description:

Subjects received infliximab 5 mg/kg intravenous (IV) infusion every 8 weeks (q8wk) up to 56 weeks with a final safety visit at Week 64. Those who lost clinical response during participation in the study were eligible to cross over to the Dose Escalation Group and receive a total of 56 weeks of therapy with infliximab, which included duration of therapy while in the Reference Group prior to dose escalation.

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

Dosage and administration details:

Subjects received infliximab 5 mg/kg infusion q8wk.

<b>Arm title</b>	Dose Escalation Group
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Arm description:

Subjects received infliximab 10 mg/kg IV infusion q8wk from Week 0 to 56 with a final safety visit at Week 64.

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

Dosage and administration details:

Subjects received infliximab 10 mg/kg infusion q8wk.

Number of subjects in period 1	Reference Group	Dose Escalation Group
Started	45	8
Cross-over to Dose escalation Group	1 <sup>[1]</sup>	0 <sup>[2]</sup>
Completed	32	3
Not completed	13	5
Consent withdrawn by subject	3	1
Adverse event, non-fatal	4	2
Other	6	2

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects reported in the baseline period are 53 and the worldwide number of enrolled subjects in the trial is also 53.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only 1 subject was crossed over from Reference group to Dose escalation group instead of all subjects.

## Baseline characteristics

### Reporting groups<sup>[1]</sup>

Reporting group title	Reference Group
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Reporting group description:

Subjects received infliximab 5 mg/kg intravenous (IV) infusion every 8 weeks (q8wk) up to 56 weeks with a final safety visit at Week 64. Those who lost clinical response during participation in the study were eligible to cross over to the Dose Escalation Group and receive a total of 56 weeks of therapy with infliximab, which included duration of therapy while in the Reference Group prior to dose escalation.

Reporting group title	Dose Escalation Group
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Reporting group description:

Subjects received infliximab 10 mg/kg IV infusion q8wk from Week 0 to 56 with a final safety visit at Week 64.

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects reported in the baseline period are 53 and the worldwide number of enrolled subjects in the trial is also 53.

Reporting group values	Reference Group	Dose Escalation Group	Total
Number of subjects	45	8	53
Title for AgeCategorical Units: subjects			
Children (2-11 years)	5	2	7
Adolescents (12-17 years)	40	6	46
Adults (18-64 years)	0	0	0
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	14.1	12.9	
standard deviation	± 1.9	± 2.7	-
Title for Gender Units: subjects			
Female	16	4	20
Male	29	4	33

## End points

### End points reporting groups

Reporting group title	Reference Group
Reporting group description: Subjects received infliximab 5 mg/kg intravenous (IV) infusion every 8 weeks (q8wk) up to 56 weeks with a final safety visit at Week 64. Those who lost clinical response during participation in the study were eligible to cross over to the Dose Escalation Group and receive a total of 56 weeks of therapy with infliximab, which included duration of therapy while in the Reference Group prior to dose escalation.	
Reporting group title	Dose Escalation Group
Reporting group description: Subjects received infliximab 10 mg/kg IV infusion q8wk from Week 0 to 56 with a final safety visit at Week 64.	

### Primary: Clinical Response at Week 16 After Dose Escalation (DE) as Evaluated by Pediatric Crohn's Disease Activity Index (PCDAI) in Crohn's disease (CD) Subjects

End point title	Clinical Response at Week 16 After Dose Escalation (DE) as Evaluated by Pediatric Crohn's Disease Activity Index (PCDAI) in Crohn's disease (CD) Subjects <sup>[1][2]</sup>
End point description: Clinical response: Crohn's disease (CD) subjects with decrease from baseline in PCDAI of greater than or equal to ( $\geq$ ) 15 points with total score of less than or equal to ( $\leq$ ) 30 points. PCDAI included 3 history items (abdominal pain, number of liquid stools, general wellbeing), 5 physical examination items (abdominal examination, perirectal disease, extraintestinal manifestations, weight, height), and 3 laboratory tests (hematocrit, albumin, erythrocyte sedimentation rate). Items are scored on a 3-point scale (0, 5, or 10) except for hematocrit and erythrocyte sedimentation rate which are scored as 0, 2.5 or 5. PCDAI scores can range from 0 to 125 with higher scores indicating more active disease. Data for this endpoint was planned to be analyzed for DE group only.	
End point type	Primary
End point timeframe: Week 16	

#### 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: Since the study was terminated early, no statistical analysis were performed for any primary or secondary endpoints.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All endpoints were planned to analyze the Dose Escalation arm only and the Reference arm was planned for safety analysis in subjects being treated with labeled dosing of infliximab. Hence, endpoint is not reporting statistical analysis for all the arms.

End point values	Dose Escalation Group			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[3]</sup>			
Units: Subjects				

#### Notes:

[3] - As study terminated early with fewer subjects than planned, hence data is not summarized.

### Statistical analyses

No statistical analyses for this end point

## Primary: Clinical Response at Week 16 After Dose Escalation as Evaluated by Mayo Score in Ulcerative Colitis (UC) Subjects

End point title	Clinical Response at Week 16 After Dose Escalation as Evaluated by Mayo Score in Ulcerative Colitis (UC) Subjects <sup>[4]</sup> <sup>[5]</sup>
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### End point description:

Clinical Response as per Mayo score was defined as decrease from baseline in partial Mayo score of  $\geq 2$  points and  $\geq 30$  percent (%) and decrease in rectal bleeding sub-score by  $\geq 1$  point or achievement of an absolute sub-score of less than or equal to ( $\leq$ ) 1 point (for UC subjects). A Partial Mayo Score which is Mayo score without endoscopy ranges from 0 (normal or inactive disease) to 9 (severe disease) and calculated as the sum of 3 subscores (stool frequency, rectal bleeding and physician's global assessment [PGA]) with each ranging from 0 to 3 (0=normal, 1=mild, 2=moderate, 3=severe). Data for this endpoint was planned to be analyzed for DE group only.

End point type	Primary
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### End point timeframe:

Week 16

### 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: Since the study was terminated early, no statistical analysis were performed for any primary or secondary endpoints.

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All endpoints were planned to analyze the Dose Escalation arm only and the Reference arm was planned for safety analysis in subjects being treated with labeled dosing of infliximab. Hence, endpoint is not reporting statistical analysis for all the arms.

End point values	Dose Escalation Group			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[6]</sup>			
Units: Subjects				

### Notes:

[6] - As study terminated early with fewer subjects than planned, hence data is not summarized.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Sustained Clinical Response Through 56 Weeks After Dose Escalation

End point title	Sustained Clinical Response Through 56 Weeks After Dose Escalation <sup>[7]</sup>
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### End point description:

Sustained clinical response at Week 56 was defined as achieving clinical response per the primary endpoint definitions at Week 16 and maintaining clinical response at 1 year after dose escalation (Week 56). Clinical response was defined as a decrease from baseline in PCDAI of  $\geq 15$  points with total score of  $\leq 30$  points (for CD subjects) and a decrease from baseline in partial Mayo score of  $\geq 2$  points and  $\geq 30\%$  and a decrease in rectal bleeding sub-score by  $\geq 1$  point or achievement of an absolute sub-score of  $\leq 1$  point (for UC subjects). Data for this endpoint was planned to be analyzed for Dose escalation (DE) group only.

End point type	Secondary
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### End point timeframe:

Up to Week 56

### Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All endpoints were planned to analyze the Dose Escalation arm only and the Reference arm was planned for safety analysis in subjects being treated with labeled dosing of infliximab. Hence, endpoint is not reporting statistical analysis for all the arms.



End point values	Dose Escalation Group			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[8]</sup>			
Units: Subjects				
number (not applicable)				

Notes:

[8] - As study terminated early with fewer subjects than planned, hence data is not summarized.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Abdominal Pain and Loose/Watery Stool Frequency Sub-scores of the PCDAI at Week 16 and Week 56 in CD Subjects

End point title	Change From Baseline in Abdominal Pain and Loose/Watery Stool Frequency Sub-scores of the PCDAI at Week 16 and Week 56 in CD Subjects <sup>[9]</sup>
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End point description:

Abdominal and loose/watery stool frequency was evaluated by using the relevant sub-scores of the PCDAI. PCDAI includes three history items (abdominal pain, number of liquid stools, general wellbeing), five physical examination items (abdominal examination, perirectal disease, extraintestinal manifestations, weight, height), and three laboratory tests (hematocrit, albumin, erythrocyte sedimentation rate). Items are scored on a three-point scale (zero, 5, or 10 points) except for hematocrit and erythrocyte sedimentation rate which are scored as zero, 2.5 or 5 points. PCDAI scores can range from zero to 125 with higher scores indicating more active disease. Data for this endpoint was planned to be analyzed for DE group only.

End point type	Secondary
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End point timeframe:

Baseline, Week 16 and Week 56

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All endpoints were planned to analyze the Dose Escalation arm only and the Reference arm was planned for safety analysis in subjects being treated with labeled dosing of infliximab. Hence, endpoint is not reporting statistical analysis for all the arms.

End point values	Dose Escalation Group			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[10]</sup>			
Units: Score on a scale				
number (not applicable)				

Notes:

[10] - As study terminated early with fewer subjects than planned, hence data is not summarized.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Abdominal Pain Using the Wong-Baker FACES scale at Week 16 and Week 56 in CD Subjects

End point title	Change from Baseline in Abdominal Pain Using the Wong-Baker FACES scale at Week 16 and Week 56 in CD Subjects <sup>[11]</sup>
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**End point description:**

Change from baseline in abdominal pain using the Wong-Baker FACES scale at Week 16 and Week 56 in CD subjects was reported. The Wong-Baker FACES Pain Scale is a pain scale that combines pictures and numbers to allow pain to be rated by children over the age of 3. The scale shows a series of faces ranging from a happy face at 0, "No hurt" to a crying face at 10 "Hurts worst". The subject must choose the face that best describes how they are feeling. Data for this endpoint was planned to be analyzed for DE group only.

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End point type	Secondary
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**End point timeframe:**

Baseline, Week 16 and Week 56

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**Notes:**

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All endpoints were planned to analyze the Dose Escalation arm only and the Reference arm was planned for safety analysis in subjects being treated with labeled dosing of infliximab. Hence, endpoint is not reporting statistical analysis for all the arms.

End point values	Dose Escalation Group			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[12]</sup>			
Units: Score on a scale				
number (not applicable)				

**Notes:**

[12] - As study terminated early with fewer subjects than planned, hence data is not summarized.

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Change From Baseline in Absolute Stool Frequency at Week 16 and Week 56 in CD Subjects**

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End point title	Change From Baseline in Absolute Stool Frequency at Week 16 and Week 56 in CD Subjects <sup>[13]</sup>
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**End point description:**

Change from baseline in Absolute stool frequency at Week 16 and Week 56 in CD subjects were reported. Mayo score consists of 4 subscores (stool frequency, rectal bleeding, endoscopy findings, and PGA), rated as 0 (normal) to 3 (severe). Total score was calculated as sum of 4 subscores and values range from 0 to 12 scores, where 3-5=mild; 6-10=moderate; and 11-12=severe; higher scores indicate worsening of the disease. An absolute stool frequency subscore of  $\leq 1$  point was indicative of mild disease. Data for this endpoint was planned to be analyzed for DE group only.

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End point type	Secondary
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**End point timeframe:**

Baseline, Week 16 and Week 56

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**Notes:**

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All endpoints were planned to analyze the Dose Escalation arm only and the Reference arm was planned for safety analysis in subjects being treated with labeled dosing of infliximab. Hence, endpoint is not reporting statistical analysis for all the arms.

End point values	Dose Escalation Group			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[14]</sup>			
Units: Score on a scale				
number (not applicable)				

Notes:

[14] - As study terminated early with fewer subjects than planned, hence data is not summarized.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Stool Frequency Sub-Score of the Partial Mayo Score at Week 16 and Week 56 in UC Subjects

End point title	Change From Baseline in Stool Frequency Sub-Score of the Partial Mayo Score at Week 16 and Week 56 in UC Subjects <sup>[15]</sup>
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End point description:

Change from baseline in Stool frequency sub-score of the partial Mayo score at Week 16 and Week 56 in UC subjects were reported. A Partial Mayo Score which is Mayo score without endoscopy ranges from 0 (normal or inactive disease) to 9 (severe disease) and calculated as the sum of 3 subscores (stool frequency, rectal bleeding and PGA) with each ranging from 0 to 3 (0=normal, 1=mild, 2=moderate, 3=severe). An absolute stool frequency subscore of  $\leq 1$  point was indicative of mild disease. Higher scores indicate more severe disease. Data for this endpoint was planned to be analyzed for DE group only.

End point type	Secondary
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End point timeframe:

Baseline, Week 16 and Week 56

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All endpoints were planned to analyze the Dose Escalation arm only and the Reference arm was planned for safety analysis in subjects being treated with labeled dosing of infliximab. Hence, endpoint is not reporting statistical analysis for all the arms.

End point values	Dose Escalation Group			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[16]</sup>			
Units: Score on a scale				
number (not applicable)				

Notes:

[16] - As study terminated early with fewer subjects than planned, hence data is not summarized.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Rectal Bleeding Sub-Scores of the Partial Mayo Score at Week 16 And Week 56 in UC Subjects

End point title	Change From Baseline in Rectal Bleeding Sub-Scores of the Partial Mayo Score at Week 16 And Week 56 in UC Subjects <sup>[17]</sup>
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**End point description:**

Change from baseline in rectal bleeding sub-scores of the partial Mayo score at Week 16 and Week 56 in UC subjects were reported. A Partial Mayo Score which is Mayo score without endoscopy ranges from 0 (normal or inactive disease) to 9 (severe disease) and calculated as the sum of 3 subscores (stool frequency, rectal bleeding and PGA) with each ranging from 0 to 3 (0=normal, 1=mild, 2=moderate, 3=severe). An absolute rectal bleeding subscore of  $\leq 1$  point was indicative of mild disease. Higher scores indicate more severe disease. Data for this endpoint was planned to be analyzed for DE group only.

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End point type	Secondary
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**End point timeframe:**

Baseline, Week 16 And Week 56

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**Notes:**

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All endpoints were planned to analyze the Dose Escalation arm only and the Reference arm was planned for safety analysis in subjects being treated with labeled dosing of infliximab. Hence, endpoint is not reporting statistical analysis for all the arms.

End point values	Dose Escalation Group			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[18]</sup>			
Units: Score on a scale				
number (not applicable)				

**Notes:**

[18] - As study terminated early with fewer subjects than planned, hence data is not summarized.

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Change From Baseline in Abdominal Pain Using the Wong-Baker FACES Scale at Week 16 and Week 56 in UC Subjects**

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End point title	Change From Baseline in Abdominal Pain Using the Wong-Baker FACES Scale at Week 16 and Week 56 in UC Subjects <sup>[19]</sup>
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**End point description:**

Change from baseline in Abdominal pain using the Wong-Baker FACES scale at Week 16 and Week 56 in UC subjects were reported. The Wong-Baker FACES Pain Scale is a pain scale that combines pictures and numbers to allow pain to be rated by children over the age of 3. The scale shows a series of faces ranging from a happy face at 0, "No hurt" to a crying face at 10 "Hurts worst". The subject must choose the face that best describes how they are feeling. Data for this endpoint was planned to be analyzed for DE group only.

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End point type	Secondary
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**End point timeframe:**

Baseline, Week 16 And Week 56

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**Notes:**

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All endpoints were planned to analyze the Dose Escalation arm only and the Reference arm was planned for safety analysis in subjects being treated with labeled dosing of infliximab. Hence, endpoint is not reporting statistical analysis for all the arms.

End point values	Dose Escalation Group			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[20]</sup>			
Units: Score on a scale				
number (not applicable)				

Notes:

[20] - As study terminated early with fewer subjects than planned, hence data is not summarized.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Absolute Stool Frequency at Week 16 and Week 56 in UC Subjects

End point title	Change From Baseline in Absolute Stool Frequency at Week 16 and Week 56 in UC Subjects <sup>[21]</sup>
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End point description:

Change from baseline in Absolute stool frequency at Week 16 and Week 56 in UC subjects were reported. The Mayo score consists of 4 subscores (stool frequency, rectal bleeding [RB], endoscopy findings, and physician's global assessment [PGA]), rated as 0 (normal) to 3 (severe). Total score was calculated as the sum of 4 subscores and values range from 0 to 12 scores, where 3 to 5 = mild; 6 to 10 = moderate; and 11 to 12 = severe; higher scores indicate worsening of the disease. An absolute rectal bleeding subscore of ≤1 point was indicative of mild disease. Data for this endpoint was planned to be analyzed for DE group only.

End point type	Secondary
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End point timeframe:

Baseline, Week 16 And Week 56

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All endpoints were planned to analyze the Dose Escalation arm only and the Reference arm was planned for safety analysis in subjects being treated with labeled dosing of infliximab. Hence, endpoint is not reporting statistical analysis for all the arms.

End point values	Dose Escalation Group			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[22]</sup>			
Units: Score on a scale				
number (not applicable)				

Notes:

[22] - As study terminated early with fewer subjects than planned, hence data is not summarized.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Correlates of Wong-Baker FACES Scale with Clinical Remission and Response at Week 16

End point title	Correlates of Wong-Baker FACES Scale with Clinical Remission and Response at Week 16 <sup>[23]</sup>
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End point description:

Correlates of Wong-Baker FACES Scale with Clinical Remission and Response at Week 16 was assessed. The Wong-Baker FACES Pain Scale is a pain scale that combines pictures and numbers to allow pain to be rated by children over the age of 3. The scale shows a series of faces ranging from a happy face at 0, "No hurt" to a crying face at 10 "Hurts worst". Data for this endpoint was planned to be analyzed for DE group only.

End point type	Secondary
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End point timeframe:

Week 16

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All endpoints were planned to analyze the Dose Escalation arm only and the Reference arm was planned for safety analysis in subjects being treated with labeled dosing of infliximab. Hence, endpoint is not reporting statistical analysis for all the arms.

End point values	Dose Escalation Group			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[24]</sup>			
Units: Percentage of subjects				
number (not applicable)				

Notes:

[24] - As study terminated early with fewer subjects than planned, hence data is not summarized.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Association Between Abdominal Pain PCDAI Sub-Score And the Wong-Baker Faces Scale For CD Subjects

End point title	Association Between Abdominal Pain PCDAI Sub-Score And the Wong-Baker Faces Scale For CD Subjects <sup>[25]</sup>
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End point description:

Association between abdominal pain PCDAI subscore and Wong-Baker FACES scale for CD subjects was reported. PCDAI is a validated clinical tool used to assess disease severity in pediatric CD subjects. PCDAI collects data on following disease-related variables: Total number of liquid stools, abdominal pain, general well-being (scored by subject or subject's legal representative); Extra-intestinal manifestations; Physical examinations of abdominal mass and, perirectal disease; Weight change and height change or, height velocity; and Hematocrit, erythrocyte sedimentation rate, and albumin. PCDAI score is calculated as sum of individual component scores and ranges from 0-100 points. Wong-Baker FACES Pain Scale is a pain scale that combines pictures and numbers to allow pain to be rated by children over age of 3. Scale shows a series of faces ranging from a happy face at 0 "No hurt" to a crying face at 10 "Hurts worst". Data for this endpoint was planned to be analyzed for DE group only.

End point type	Secondary
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End point timeframe:

Week 16 and 56

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All endpoints were planned to analyze the Dose Escalation arm only and the Reference arm was planned for safety analysis in subjects being treated with labeled dosing of infliximab. Hence, endpoint is not reporting statistical analysis for all the arms.

<b>End point values</b>	Dose Escalation Group			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[26]</sup>			
Units: Score on scale				
number (not applicable)				

Notes:

[26] - As study terminated early with fewer subjects than planned, hence data is not summarized.

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Week 64

Adverse event reporting additional description:

Safety analysis population included all subjects who received at least 1 infusion of infliximab after enrollment. Reference arm was planned only for safety analysis in subjects being treated with infliximab. 1 subject who had crossed-over from reference group to DE group was counted in both arms and safety is presented accordingly.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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### Reporting groups

Reporting group title	Reference Group
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Reporting group description:

Subjects received infliximab 5 mg/kg intravenous (IV) infusion every 8 weeks (q8wk) up to 56 weeks with a final safety visit at Week 64. Those who lost clinical response during participation in the study were eligible to cross over to the Dose Escalation Group and receive a total of 56 weeks of therapy with infliximab, which included duration of therapy while in the Reference Group prior to dose escalation.

Reporting group title	Dose Escalation Group
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Reporting group description:

Subjects received infliximab 10 mg/kg IV infusion q8wk from Week 0 to 56 with a final safety visit at Week 64.

Serious adverse events	Reference Group	Dose Escalation Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 45 (4.44%)	1 / 9 (11.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Colitis Ulcerative			
subjects affected / exposed	0 / 45 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis Viral			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis Streptococcal			



subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Reference Group	Dose Escalation Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 45 (80.00%)	8 / 9 (88.89%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Papilloma			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Orthostatic Hypertension			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest Discomfort			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Chest Pain			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	2 / 45 (4.44%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Pain			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pyrexia			

subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Immune system disorders Allergy to Arthropod Bite subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Food Allergy subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Reproductive system and breast disorders Ovarian Cyst subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Asthma Exercise Induced subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Cough subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	1 / 9 (11.11%) 1	
Dyspnoea subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 4	0 / 9 (0.00%) 0	
Dyspnoea Exertional subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Epistaxis subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	1 / 9 (11.11%) 1	
Nasal Congestion subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	0 / 9 (0.00%) 0	
Oropharyngeal Pain subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	1 / 9 (11.11%) 1	
Respiratory Tract Congestion			

subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Tonsillolith			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 45 (4.44%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Depression			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 45 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Investigations			
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
C-Reactive Protein Increased			
subjects affected / exposed	2 / 45 (4.44%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Faecal Calprotectin Increased			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Heart Rate Irregular			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hepatic Enzyme Increased			
subjects affected / exposed	1 / 45 (2.22%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Transaminases Increased			

subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Vitamin D Decreased			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
White Blood Cell Count Increased			
subjects affected / exposed	0 / 45 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Animal Bite			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Burns Second Degree			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Joint Dislocation			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Joint Injury			
subjects affected / exposed	2 / 45 (4.44%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Ligament Sprain			
subjects affected / exposed	2 / 45 (4.44%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Limb Injury			
subjects affected / exposed	2 / 45 (4.44%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Lip Injury			
subjects affected / exposed	0 / 45 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Soft Tissue Injury			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			

Palpitations subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Nervous system disorders			
Dizziness Postural subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	6 / 45 (13.33%) 9	1 / 9 (11.11%) 1	
Hemianopia subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Lethargy subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Migraine subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Paraesthesia subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Syncope subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	0 / 9 (0.00%) 0	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 9 (11.11%) 1	
Eye disorders			
Dry Eye subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 9 (11.11%) 1	
Gastrointestinal disorders			
Abdominal Pain subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 5	2 / 9 (22.22%) 4	

Abdominal Pain Upper		
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)
occurrences (all)	2	0
Anorectal Disorder		
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)
occurrences (all)	1	0
Colitis Ulcerative		
subjects affected / exposed	1 / 45 (2.22%)	2 / 9 (22.22%)
occurrences (all)	1	2
Constipation		
subjects affected / exposed	2 / 45 (4.44%)	0 / 9 (0.00%)
occurrences (all)	2	0
Diarrhoea		
subjects affected / exposed	5 / 45 (11.11%)	0 / 9 (0.00%)
occurrences (all)	9	0
Epigastric Discomfort		
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)
occurrences (all)	1	0
Faeces Soft		
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)
occurrences (all)	1	0
Gastritis		
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)
occurrences (all)	1	0
Haematochezia		
subjects affected / exposed	1 / 45 (2.22%)	1 / 9 (11.11%)
occurrences (all)	1	1
Lip Swelling		
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)
occurrences (all)	1	0
Mouth Haemorrhage		
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)
occurrences (all)	1	0
Nausea		
subjects affected / exposed	2 / 45 (4.44%)	0 / 9 (0.00%)
occurrences (all)	2	0

Stomatitis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Tongue Erythema			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Tooth Disorder			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Tooth Impacted			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Acne Cystic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Blister			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dry Skin			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Psoriasis			
subjects affected / exposed	2 / 45 (4.44%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Rash			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Skin Warm			

subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 9 (11.11%) 1	
Renal and urinary disorders Hydronephrosis subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4	0 / 9 (0.00%) 0	
Back Pain subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Costochondritis subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Neck Pain subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Pain in Extremity subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	1 / 9 (11.11%) 1	
Synovial Cyst subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Torticollis subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Infections and infestations Adenovirus Infection subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Cellulitis subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 9 (0.00%) 0	
Clostridium Difficile Infection			



subjects affected / exposed	0 / 45 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	1
Conjunctivitis		
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)
occurrences (all)	1	0
Ear Infection		
subjects affected / exposed	3 / 45 (6.67%)	0 / 9 (0.00%)
occurrences (all)	3	0
Eczema Infected		
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)
occurrences (all)	1	0
Epstein-Barr Virus Infection		
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)
occurrences (all)	1	0
Eye Infection		
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)
occurrences (all)	1	0
Folliculitis		
subjects affected / exposed	2 / 45 (4.44%)	0 / 9 (0.00%)
occurrences (all)	2	0
Gastroenteritis		
subjects affected / exposed	1 / 45 (2.22%)	1 / 9 (11.11%)
occurrences (all)	1	2
Gingivitis		
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)
occurrences (all)	1	0
Herpes Zoster		
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)
occurrences (all)	1	0
Impetigo		
subjects affected / exposed	2 / 45 (4.44%)	0 / 9 (0.00%)
occurrences (all)	2	0
Influenza		
subjects affected / exposed	0 / 45 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	2
Nasopharyngitis		

subjects affected / exposed	5 / 45 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Otitis Media			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Paronychia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pharyngitis Streptococcal			
subjects affected / exposed	2 / 45 (4.44%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Pneumonia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	3 / 45 (6.67%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Staphylococcal Impetigo			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 45 (6.67%)	0 / 9 (0.00%)	
occurrences (all)	5	0	
Urinary Tract Infection			
subjects affected / exposed	2 / 45 (4.44%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Viral Infection			
subjects affected / exposed	2 / 45 (4.44%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	4 / 45 (8.89%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Metabolism and nutrition disorders			
Decreased Appetite			

subjects affected / exposed	0 / 45 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Vitamin D Deficiency			
subjects affected / exposed	1 / 45 (2.22%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2016	The overall reasons for the amendment are to revise entry criteria regarding prior maintenance doses of infliximab and time of loss of response, and to correct or clarify inadvertent errors.
07 December 2016	The overall reasons for the amendment are to: Modify the inclusion criteria (for PCDAI and partial Mayo score) to ensure adequate disease severity; Define loss of response; Obtain history of infliximab treatment at initiation, time of response and loss of response, including number of infliximab doses, for the Dose Escalation group; Define "initial response"; Add 2 secondary endpoints (and the corresponding analyses), to evaluate any association between clinical remission/response; Revise wording for several entry criteria, for clarity; Correct or clarify inadvertent errors
20 February 2018	The overall reasons for the amendment are to: Clarify several entry criteria; Extend the screening period; Add details for corticosteroid tapering; Include complete instructions to ensure safety procedures related to any potential cases of hepatotoxicity; and Update text describing informed consent procedures.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The reference arm was planned to monitor the safety characteristics for subjects being treated with labeled dosing of infliximab, hence the endpoint results were not reported for the reference group.
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Notes: