Clinical trial results:
A Multicenter, Double-Blind Study to Evaluate the Safety, Efficacy and Pharmacokinetics of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Crohn's Disease

Summary

EudraCT number	2006-004814-41
Trial protocol	FR CZ BE NL GB IT Outside EU/EEA
Global end of trial date	29 July 2010

Results information

Result version number	v1 (current)
This version publication date	20 April 2016
First version publication date	07 June 2015

Trial information

Trial identification

Sponsor protocol code	M06-806

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00409682
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	1 North Waukegan Road, North Chicago, IL, United States, 60064
Public contact	Global Medical Information, AbbVie, 001 800-633-9110,
Scientific contact	Roopal Thakkar, MD, AbbVie, roopal.thakkar@abbvie.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000036-PIP01-08
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	29 July 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine Efficacy, Pharmacokinetics, and Safety of Adalimumab in Pediatric Subjects with Moderate to Severe Crohn's Disease.

Protection of trial subjects:

The subject and/or parent or legal guardian read and understood information provided about the study and signed an informed consent form. Additionally, a written informed assent was obtained from all children in accordance with individual IRB recommendations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 May 2007
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	Netherlands: 7
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	United States: 103
Worldwide total number of subjects	192
EEA total number of subjects	55

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)	37
Adolescents (12-17 years)	155
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 45 investigative sites in Belgium, Canada, Czech Republic, France, Italy, Netherlands, Poland, the United Kingdom, and the United States.

Pre-assignment

Screening details:

Paediatric subjects (6-17 years of age) with moderate to severe Crohn's disease (CD) (defined by Pediatric Crohn's Disease Activity Index [PCDAI > 30]) who had either failed conventional therapy for CD or previously received infliximab and lost response/had intolerance to infliximab. Screening occurred 1-3 weeks prior to open-label induction phase.

Period 1

Period 1 title	Open-label Induction Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open-label Adalimumab (Week 0 to Week 4)

Arm description:

All subjects received an open-label adalimumab induction regimen. Subjects weighing greater than or equal to 40 kg at Baseline received 160 mg at Week 0 and 80 mg at Week 2. Subjects weighing less than 40 kg at Baseline received 80 mg at Week 0 and 40mg at Week 2.

Arm type	Active comparator
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

All subjects received an open-label adalimumab induction regimen. Subjects weighing greater than or equal to 40 kg at Baseline received 160 mg at Week 0 and 80 mg at Week 2. Subjects weighing less than 40 kg at Baseline received 80 mg at Week 0 and 40mg at Week 2.

Number of subjects in period 1[1]	Open-label Adalimumab (Week 0 to Week 4)
Started	188
Completed	188

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 192 subjects received at least one dose of adalimumab and participated in the the 4- week Open-label induction period of the study. Of these, 4 discontinued and 188 subjects participated in the DB Maintenance period and are included in the analysis (intent-to-treat population was defined as all randomized subjects who received at least one dose of double-blind study medication).

Period 2

Period 2 title	EOW Double-blind Maintenance Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52)

Arm description:

Subjects randomized to the Low-Dose treatment group received either 20 mg adalimumab every other week (eow) (if Week 4 body weight [BW] was greater than or equal to 40 kg) or 10 mg adalimumab eow (if Week 4 BW less than 40 kg). Starting at the Week 12 study visit, subjects who experienced a disease flare or were non-responders could be switched from blinded eow dosing to blinded every week (ew) dosing, continuing with the same blinded dose. If a subject continued to experience a flare or met the definition of non-response following an 8-week course of double-blind (DB) ew therapy they could be switched to open-label ew therapy.

Arm type	Active comparator
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects randomized to the Low-Dose treatment group received either 20 mg adalimumab every other week (eow) (if Week 4 body weight [BW] was greater than or equal to 40 kg) or 10 mg adalimumab eow (if Week 4 BW less than 40 kg). Starting at the Week 12 study visit, subjects who experienced a disease flare or were non-responders could be switched from blinded eow dosing to blinded every week (ew) dosing, continuing with the same blinded dose. If a subject continued to experience a flare or met the definition of non-response following an 8-week course of double-blind (DB) ew therapy they could be switched to open-label ew therapy.

Arm title	High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52)

Arm description:

Subjects randomized to the High-Dose treatment group received either 40 mg adalimumab every other week (eow) (if Week 4 body weight [BW] was greater than or equal to 40 kg) or 20 mg adalimumab eow (if Week 4 BW less than 40 kg). Starting at the Week 12 study visit, subjects who experienced a disease flare or were non-responders could be switched from blinded eow dosing to blinded every week (ew) dosing, continuing with the same blinded dose. If a subject continued to experience a flare or met the definition of non-response following an 8-week course of double-blinded (DB) ew therapy they could be switched to open-label ew therapy.

Arm type	Experimental
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects randomized to the High-Dose treatment group received either 40 mg adalimumab every other week (eow) (if Week 4 body weight [BW] was greater than or equal to 40 kg) or 20 mg adalimumab eow (if Week 4 BW less than 40 kg). Starting at the Week 12 study visit, subjects who experienced a disease flare or were non-responders could be switched from blinded eow dosing to blinded every week (ew) dosing, continuing with the same blinded dose. If a subject continued to experience a flare or met the definition of non-response following an 8-week course of double-blinded (DB) ew therapy they could be switched to open-label ew therapy.

Number of subjects in period 2	Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52)	High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52)
Started	95	93
Completed	58	66
Not completed	37	27
Consent withdrawn by subject	4	2
Adverse event, non-fatal	10	12
Non-compliance	-	1
Lost to follow-up	1	-
Protocol deviation	4	1
Lack of efficacy	18	11

Baseline characteristics

Reporting groups

Reporting group title	Open-label Adalimumab (Week 0 to Week 4)

Reporting group description:

All subjects received an open-label adalimumab induction regimen. Subjects weighing greater than or equal to 40 kg at Baseline received 160 mg at Week 0 and 80 mg at Week 2. Subjects weighing less than 40 kg at Baseline received 80 mg at Week 0 and 40mg at Week 2.

Reporting group values	Open-label Adalimumab (Week 0 to Week 4)	Total	
Number of subjects	188	188	
Age categorical Units: Subjects			
< 13	66	66	
>= 13	122	122	
Age continuous Units: years			
arithmetic mean	13.6		
standard deviation	± 2.49	-	
Gender categorical Units: Subjects			
Female	83	83	
Male	105	105	
Race/Ethnicity, Customized Units: Subjects			
White	166	166	
Black	11	11	
Asian	3	3	
American Indian/Alaska Native	0	0	
Native Hawaiian or other Pacific Islander	0	0	
Multi-race	3	3	
Other	5	5	
Weight (kg) Units: Subjects			
< 40	67	67	
>= 40	121	121	

Subject analysis sets

Subject analysis set title	Low-Dose Adalimumab: 20 mg or 10 mg (Week 4 to Week 52)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects randomized to the Low-Dose treatment group received either 20 mg adalimumab every other week (eow) (if Week 4 body weight [BW] was greater than or equal to 40 kg) or 10 mg adalimumab eow (if Week 4 BW less than 40 kg). Starting at the Week 12 study visit, subjects who experienced a disease flare or were non-responders could be switched from blinded eow dosing to blinded every week (ew) dosing, continuing with the same blinded dose. If a subject continued to experience a flare or met the definition of non-response following an 8-week course of double-blind (DB) ew therapy they could be switched to open-label ew therapy. The intent-to-treat (ITT) population included all randomized subjects

who received at least one dose of double-blind study medication.

Subject analysis set title	High-Dose Adalimumab: 40 mg or 20 mg Eow (Week 4 to Week 52)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects randomized to the High-Dose treatment group received either 40 mg adalimumab every other week (eow) (if Week 4 body weight [BW] was greater than or equal to 40 kg) or 20 mg adalimumab eow (if Week 4 BW less than 40 kg). Starting at the Week 12study visit, subjects who experienced a disease flare or were non-responders could be switched from blinded eow dosing to blinded every week (ew) dosing, continuing with the same blinded dose. If a subject continued to experience a flare or met the definition of non-response following an 8-week course of double-blinded (DB) ew therapy they could be switched to open-label ew therapy. The intent-to-treat (ITT) population included all randomized subjects who received at least one dose of double-blind study medication.

Reporting group values	Low-Dose Adalimumab: 20 mg or 10 mg (Week 4 to Week 52)	High-Dose Adalimumab: 40 mg or 20 mg Eow (Week 4 to Week 52)	
Number of subjects	95	93	
Age categorical Units: Subjects			
< 13	35	31	
>= 13	60	62	
Age continuous Units: years			
arithmetic mean	13.5	13.7	
standard deviation	± 2.47	± 2.52	
Gender categorical Units: Subjects			
Female	41	42	
Male	54	51	
Race/Ethnicity, Customized Units: Subjects			
White	85	81	
Black	6	5	
Asian	0	3	
American Indian/Alaska Native	0	0	
Native Hawaiian or other Pacific Islander	0	0	
Multi-race	2	1	
Other	2	3	
Weight (kg) Units: Subjects			
< 40	35	32	
>= 40	60	61	

End points

End points reporting groups

Reporting group title	Open-label Adalimumab (Week 0 to Week 4)

Reporting group description:

All subjects received an open-label adalimumab induction regimen. Subjects weighing greater than or equal to 40 kg at Baseline received 160 mg at Week 0 and 80 mg at Week 2. Subjects weighing less than 40 kg at Baseline received 80 mg at Week 0 and 40mg at Week 2.

Reporting group title	Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52)

Reporting group description:

Subjects randomized to the Low-Dose treatment group received either 20 mg adalimumab every other week (eow) (if Week 4 body weight [BW] was greater than or equal to 40 kg) or 10 mg adalimumab eow (if Week 4 BW less than 40 kg). Starting at the Week 12 study visit, subjects who experienced a disease flare or were non-responders could be switched from blinded eow dosing to blinded every week (ew) dosing, continuing with the same blinded dose. If a subject continued to experience a flare or met the definition of non-response following an 8-week course of double-blind (DB) ew therapy they could be switched to open-label ew therapy.

Reporting group title	High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52)

Reporting group description:

Subjects randomized to the High-Dose treatment group received either 40 mg adalimumab every other week (eow) (if Week 4 body weight [BW] was greater than or equal to 40 kg) or 20 mg adalimumab eow (if Week 4 BW less than 40 kg). Starting at the Week 12 study visit, subjects who experienced a disease flare or were non-responders could be switched from blinded eow dosing to blinded every week (ew) dosing, continuing with the same blinded dose. If a subject continued to experience a flare or met the definition of non-response following an 8-week course of double-blinded (DB) ew therapy they could be switched to open-label ew therapy.

Subject analysis set title	Low-Dose Adalimumab: 20 mg or 10 mg (Week 4 to Week 52)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects randomized to the Low-Dose treatment group received either 20 mg adalimumab every other week (eow) (if Week 4 body weight [BW] was greater than or equal to 40 kg) or 10 mg adalimumab eow (if Week 4 BW less than 40 kg). Starting at the Week 12 study visit, subjects who experienced a disease flare or were non-responders could be switched from blinded eow dosing to blinded every week (ew) dosing, continuing with the same blinded dose. If a subject continued to experience a flare or met the definition of non-response following an 8-week course of double-blind (DB) ew therapy they could be switched to open-label ew therapy. The intent-to-treat (ITT) population included all randomized subjects who received at least one dose of double-blind study medication.

Subject analysis set title	High-Dose Adalimumab: 40 mg or 20 mg Eow (Week 4 to Week 52)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects randomized to the High-Dose treatment group received either 40 mg adalimumab every other week (eow) (if Week 4 body weight [BW] was greater than or equal to 40 kg) or 20 mg adalimumab eow (if Week 4 BW less than 40 kg). Starting at the Week 12study visit, subjects who experienced a disease flare or were non-responders could be switched from blinded eow dosing to blinded every week (ew) dosing, continuing with the same blinded dose. If a subject continued to experience a flare or met the definition of non-response following an 8-week course of double-blinded (DB) ew therapy they could be switched to open-label ew therapy. The intent-to-treat (ITT) population included all randomized subjects who received at least one dose of double-blind study medication.

Primary: Percent of Participants With Clinical Remission as Defined by Pediatric Crohn's Disease Activity Index (PCDAI) Score ≤ 10 at Week 26

End point title	Percent of Participants With Clinical Remission as Defined by Pediatric Crohn's Disease Activity Index (PCDAI) Score ≤ 10 at Week 26

End point description:

Pediatric Crohn's Disease Activity Index (PCDAI) is an index used to measure disease activity of pediatric patients with Crohn's Disease assessing abdominal pain, stool frequency, patient functioning,

hematocrit, erythrocyte sedimentation rate, albumin, weight, height, abdomen, perirectal disease, and extraintestinal manifestations. It ranges from 0 to 100; higher scores indicate more active disease. The primary endpoint was clinical remission as defined by PCDAI score ≤ 10. The comparison was between High-Dose adalimumab versus Low-Dose adalimumab in the intent-to-treat population.

End point type	Primary

End point timeframe:

Week 26

End point values	Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52)	High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	93		
Units: percent of participants				
number (not applicable)	28.4	38.7		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The point estimates for the number of subjects who achieved PCDAI clinical remission in each treatment group and the difference in number between the groups were provided. The P value and 95% confidence intervals (CIs) for the difference were provided. The P value is from the CMH test adjusted for infliximab use and response status at Week 4. The primary analysis was performed for the intent-to-treat (ITT) population using the non-responder (NRI) imputation method.

Comparison groups	High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52) v Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52)
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.075 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	10.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.14
upper limit	23.71

Notes:

[1] - There is no adjustment for multiple comparison on the primary outcome measure.

Secondary: Percent of Participants With Clinical Remission as Defined by Pediatric Crohn's Disease Activity Index (PCDAI) Score ≤ 10 at Week 52

End point title	Percent of Participants With Clinical Remission as Defined by Pediatric Crohn's Disease Activity Index (PCDAI) Score ≤ 10 at Week 52

End point description:

Pediatric Crohn's Disease Activity Index (PCDAI) is an index used to measure disease activity of pediatric patients with Crohn's Disease assessing abdominal pain, stool frequency, patient functioning, hematocrit erythrocyte sedimentation rate, albumin, weight, height, examination of abdomen, perirectal disease, and extraintestinal manifestations. It ranges from 0 to 100 with higher scores indicating more active disease. Clinical remission was defined as PCDAI score of ≤ 10. The comparison was between High-Dose adalimumab versus Low-Dose adalimumab in the intent-to treat population. Non-responder imputation (NRI)was used.

End point type	Secondary

End point timeframe:

Week 52

End point values	Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52)	High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	93		
Units: percent of participants				
number (not applicable)	23.2	33.3		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The point estimates for the number of subjects who achieved PCDAI clinical remission in each arm, the difference in number between the arms, and the P value and 95% CI for the difference were provided. The analysis was performed for the ITT population using the NRI method. A significance test for any individual major secondary efficacy endpoint in the hierarchy was to be inferential only if the hypothesis tests of all preceding major secondary endpoints were statistically significant at 0.050.

Comparison groups	Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52) v High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52)
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	10.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.62
upper limit	22.97

Notes:

[2] - The hierarchical stepwise closed testing procedure was implemented to control the overall significance level at 0.05 in the ITT population.

Secondary: Percent of Participants With Clinical Response as Defined by Pediatric

Crohn's Disease Activity Index (PCDAI) Score at Week 26

End point title	Percent of Participants With Clinical Response as Defined by Pediatric Crohn's Disease Activity Index (PCDAI) Score at Week 26

End point description:

Pediatric Crohn's Disease Activity Index (PCDAI) is an index used to measure disease activity of pediatric patients with Crohn's Disease assessing abdominal pain, stool frequency, patient functioning, hematocrit, erythrocyte sedimentation rate, albumin, weight, height, examination of abdomen, perirectal disease, and extraintestinal manifestations. It ranges from 0 to 100; higher scores indicate more active disease. Clinical response was defined as a decrease from Baseline in the PCDAI score of at least 15 points. The comparison was High-Dose adalimumab versus Low-Dose in the ITT population. Non-responder imputation (NRI) was used.

End point type	Secondary

End point timeframe:

Week 26

End point values	Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52)	High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	93		
Units: percent of participants				
number (not applicable)	48.4	59.1		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The point estimates for the number of subjects who achieved PCDAI clinical remission in each arm, the difference in number between the arms, and the P value and 95% CI for the difference were provided. The analysis was performed for the ITT population using the NRI method. A significance test for any individual major secondary efficacy endpoint in the hierarchy was to be inferential only if the hypothesis tests of all preceding major secondary endpoints were statistically significant at 0.050

Comparison groups	Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52) v High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52)
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.073 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	10.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.45
upper limit	24.89

Notes:

[3] - The hierarchical stepwise closed testing procedure was implemented to control the overall significance level at 0.05 in the ITT population

Secondary: Percent of Participants With Clinical Response as Defined by Pediatric Crohn's Disease Activity Index (PCDAI) Score at Week 52

End point title	Percent of Participants With Clinical Response as Defined by Pediatric Crohn's Disease Activity Index (PCDAI) Score at Week 52

End point description:

Pediatric Crohn's Disease Activity Index (PCDAI) is an index used to measure disease activity of pediatric patients with Crohn's Disease assessing abdominal pain, stool frequency, patient functioning, hematocrit, erythrocyte sedimentation rate, albumin, weight, height, examination of abdomen, perirectal disease, and extraintestinal manifestations. It ranges from 0 to 100; higher scores indicate more active disease. Clinical response was defined as a decrease from Baseline in the PCDAI score of at least 15 points. The comparison was High-Dose adalimumab versus Low-Dose in the ITT population. Non-responder imputation (NRI) was used.

End point type	Secondary

End point timeframe:

Week 52

End point values	Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52)	High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	93		
Units: percent of participants				
number (not applicable)	28.4	41.9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The point estimates for the number of subjects who achieved PCDAI clinical remission in each arm, the difference in number between the arms, and the P value and 95% CI for the difference were provided. The analysis was performed for the ITT population using the NRI method. A significance test for any individual major secondary efficacy endpoint in the hierarchy was to be inferential only if the hypothesis tests of all preceding major secondary endpoints were statistically significant at 0.050

Comparison groups	Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52) v High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52)
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.038 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	13.51

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	27.04

Notes:

[4] - The hierarchical stepwise closed testing procedure was implemented to control the overall significance level at 0.05 in the ITT population

Secondary: Change From Baseline IMPACT III Scores at Week 26 (Observed Case)

End point title	Change From Baseline IMPACT III Scores at Week 26 (Observed Case)

End point description:

The IMPACT III questionnaire is a 35-item assessment of health-related quality of life in patients with inflammatory bowel disease (Crohn's disease [CD] or ulcerative colitis). In this study, subjects greater than or equal 10 years old who had CD at baseline completed an IMPACT III questionnaire at Baseline, Week 26, and Week 52. Subjects marked an option from 1 to 5 for each item left to right with numbers 5 (good 'quality of life' condition) through 1 (bad 'quality of life' condition). The total scores, range from 35 to 175 with higher scores representing a better quality of life.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52)	High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	56		
Units: scores on a scale				
arithmetic mean (standard deviation)	26.4 (± 15.589)	23.7 (± 18.99)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analyzed as change from Baseline to Week 26, and compared between the 2 treatment arms. The estimated treatment mean difference, P values, and 95% CI for the treatment difference were provided. Analysis was conducted in the ITT population for OC. P value is from the ANCOVA model with treatment as a factor, adjusted for the baseline value, and the strata (response status at Week 4 and prior infliximab experience). Baseline means include subjects with both Baseline and post-Baseline measurements.

Comparison groups	Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52) v High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52)

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.161 [5]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.86
upper limit	1.66
Variability estimate	Standard error of the mean
Dispersion value	2.903

Notes:

[5] - The hierarchical stepwise closed testing procedure was implemented to control the overall significance level at 0.05 in the ITT population

Secondary: Change From Baseline IMPACT III Scores at Week 52 (Observed Case)

End point title	Change From Baseline IMPACT III Scores at Week 52 (Observed Case)

End point description:

The IMPACT III questionnaire is a 35-item assessment of health-related quality of life in patients with inflammatory bowel disease (Crohn's disease [CD] or ulcerative colitis). In this study, subjects greater than or equal 10 years old who had CD at baseline completed an IMPACT III questionnaire at Baseline, Week 26, and Week 52. Subjects marked an option from 1 to 5 for each item left to right with numbers 5 (good 'quality of life' condition) through 1 (bad 'quality of life' condition). The total scores, range from 35 to 175 with higher scores representing a better quality of life.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52)	High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	38		
Units: scores on a scale				
arithmetic mean (standard deviation)	26.49 (± 16.182)	24.25 (± 14.678)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analyzed as change from Baseline to Week 52, and compared between the two treatment arms. The estimated treatment mean difference, P values, and 95% CI for the treatment difference were provided. Analysis was conducted in the ITT population for OC. Difference is between adalimumab High-dose and adalimumab Low-dose groups. Baseline means include subjects who had both Baseline and post-

Baseline means. Baseline means include subjects who had both Baseline and post-Baseline measurements.

Comparison groups	Low-Dose Adalimumab: 20 mg or 10 mg eow (Week 4 to Week 52) v High-Dose Adalimumab: 40 mg or 20 mg eow (Week 4 to Week 52)
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.735
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.88
upper limit	4.88
Variability estimate	Standard error of the mean
Dispersion value	2.941

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) reported from the time of study drug administration until 70 days after discontinuation of study drug were collected. Serious AEs were collected from the time the subject or parent/legal guardian signed the informed consent.

Adverse event reporting additional description:

Open-label (OL) Adalimumab (Wk 0 - Wk 4): AEs from first OL dose to 70 days after last OL induction adalimumab dose or until first double-blind (DB) dose Low-Dose/High-Dose Adalimumab (Wk 4 - Wk 52): AEs from first DB dose to 70 days after last DB every other week (eow) or until switch to every week (ew) dosing or OL extension.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Open-label Adalimumab (Week 0 to Week 4)
Reporting group description: -	
Reporting group title	Low-Dose Adalimumab: 20 mg or 10 mg Eow (Week 4 to Week 52)
Reporting group description: -	
Reporting group title	High-Dose Adalimumab: 40 mg or 20 mg Eow (Week 4 to Week 52)

Reporting group description: -

Serious adverse events	Open-label Adalimumab (Week 0 to Week 4)	Low-Dose Adalimumab: 20 mg or 10 mg Eow (Week 4 to Week 52)	High-Dose Adalimumab: 40 mg or 20 mg Eow (Week 4 to Week 52)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 192 (3.13%)	19 / 95 (20.00%)	22 / 93 (23.66%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Heart rate irregular			
subjects affected / exposed	1 / 192 (0.52%)	0 / 95 (0.00%)	0 / 93 (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
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 192 (0.00%)	1 / 95 (1.05%)	0 / 93 (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

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 192 (0.00%)	0 / 95 (0.00%)	4 / 93 (4.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	2 / 192 (1.04%)	15 / 95 (15.79%)	12 / 93 (12.90%)
occurrences causally related to treatment / all	0 / 3	0 / 15	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammatory bowel disease			
subjects affected / exposed	1 / 192 (0.52%)	0 / 95 (0.00%)	0 / 93 (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
Pancreatitis acute			
subjects affected / exposed	0 / 192 (0.00%)	1 / 95 (1.05%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 192 (0.00%)	0 / 95 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychosomatic disease			
subjects affected / exposed	0 / 192 (0.00%)	0 / 95 (0.00%)	1 / 93 (1.08%)
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			
Abdominal abscess			
subjects affected / exposed	0 / 192 (0.00%)	0 / 95 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			

subjects affected / exposed	0 / 192 (0.00%)	0 / 95 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bartholin's abscess			
subjects affected / exposed	0 / 192 (0.00%)	1 / 95 (1.05%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 192 (0.00%)	0 / 95 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	0 / 192 (0.00%)	0 / 95 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Histoplasmosis disseminated			
subjects affected / exposed	0 / 192 (0.00%)	0 / 95 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scarlet fever			
subjects affected / exposed	0 / 192 (0.00%)	1 / 95 (1.05%)	0 / 93 (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
Tooth abscess			
subjects affected / exposed	0 / 192 (0.00%)	1 / 95 (1.05%)	0 / 93 (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
Viral infection			
subjects affected / exposed	1 / 192 (0.52%)	0 / 95 (0.00%)	0 / 93 (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
Yersinia infection			

subjects affected / exposed	1 / 192 (0.52%)	0 / 95 (0.00%)	0 / 93 (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

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

Non-serious adverse events	Open-label Adalimumab (Week 0 to Week 4)	Low-Dose Adalimumab: 20 mg or 10 mg Eow (Week 4 to Week 52)	High-Dose Adalimumab: 40 mg or 20 mg Eow (Week 4 to Week 52)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 192 (33.33%)	62 / 95 (65.26%)	69 / 93 (74.19%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 192 (0.00%)	5 / 95 (5.26%)	2 / 93 (2.15%)
occurrences (all)	0	6	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 192 (0.52%)	3 / 95 (3.16%)	5 / 93 (5.38%)
occurrences (all)	1	4	5
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 192 (1.04%)	5 / 95 (5.26%)	1 / 93 (1.08%)
occurrences (all)	2	5	2
Headache			
subjects affected / exposed	9 / 192 (4.69%)	20 / 95 (21.05%)	16 / 93 (17.20%)
occurrences (all)	15	26	27
Blood and lymphatic system disorders			
Lymphadenectomy			
subjects affected / exposed	0 / 192 (0.00%)	6 / 95 (6.32%)	3 / 93 (3.23%)
occurrences (all)	0	6	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 192 (1.56%)	4 / 95 (4.21%)	5 / 93 (5.38%)
occurrences (all)	3	4	6
Injection site pain			

subjects affected / exposed	12 / 192 (6.25%)	4 / 95 (4.21%)	2 / 93 (2.15%)
occurrences (all)	15	5	13
Injection site reaction			
subjects affected / exposed	10 / 192 (5.21%)	4 / 95 (4.21%)	5 / 93 (5.38%)
occurrences (all)	11	4	9
Pain			
subjects affected / exposed	2 / 192 (1.04%)	2 / 95 (2.11%)	5 / 93 (5.38%)
occurrences (all)	2	2	5
Pyrexia			
subjects affected / exposed	1 / 192 (0.52%)	8 / 95 (8.42%)	10 / 93 (10.75%)
occurrences (all)	1	13	14
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 192 (2.60%)	6 / 95 (6.32%)	9 / 93 (9.68%)
occurrences (all)	5	9	13
Abdominal pain upper			
subjects affected / exposed	2 / 192 (1.04%)	3 / 95 (3.16%)	7 / 93 (7.53%)
occurrences (all)	3	4	8
Crohn's disease			
subjects affected / exposed	5 / 192 (2.60%)	15 / 95 (15.79%)	11 / 93 (11.83%)
occurrences (all)	6	18	16
Diarrhoea			
subjects affected / exposed	3 / 192 (1.56%)	9 / 95 (9.47%)	8 / 93 (8.60%)
occurrences (all)	3	14	9
Nausea			
subjects affected / exposed	9 / 192 (4.69%)	6 / 95 (6.32%)	10 / 93 (10.75%)
occurrences (all)	10	9	14
Vomiting			
subjects affected / exposed	3 / 192 (1.56%)	10 / 95 (10.53%)	6 / 93 (6.45%)
occurrences (all)	3	17	6
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 192 (0.00%)	7 / 95 (7.37%)	9 / 93 (9.68%)
occurrences (all)	0	7	13
Oropharyngeal pain			

subjects affected / exposed	3 / 192 (1.56%)	8 / 95 (8.42%)	9 / 93 (9.68%)
occurrences (all)	3	10	11
Rhinorrhoea			
subjects affected / exposed	1 / 192 (0.52%)	8 / 95 (8.42%)	3 / 93 (3.23%)
occurrences (all)	1	11	3
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 192 (0.00%)	5 / 95 (5.26%)	5 / 93 (5.38%)
occurrences (all)	0	6	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 192 (2.08%)	4 / 95 (4.21%)	8 / 93 (8.60%)
occurrences (all)	4	4	11
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 192 (1.56%)	11 / 95 (11.58%)	9 / 93 (9.68%)
occurrences (all)	3	14	11
Pharyngitis			
subjects affected / exposed	2 / 192 (1.04%)	2 / 95 (2.11%)	7 / 93 (7.53%)
occurrences (all)	2	6	10
Pharyngitis streptococcal			
subjects affected / exposed	0 / 192 (0.00%)	5 / 95 (5.26%)	2 / 93 (2.15%)
occurrences (all)	0	5	2
Upper respiratory tract infection			
subjects affected / exposed	5 / 192 (2.60%)	10 / 95 (10.53%)	10 / 93 (10.75%)
occurrences (all)	5	11	11
Viral infection			
subjects affected / exposed	0 / 192 (0.00%)	6 / 95 (6.32%)	4 / 93 (4.30%)
occurrences (all)	0	6	4
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 192 (3.13%)	3 / 95 (3.16%)	5 / 93 (5.38%)
occurrences (all)	6	3	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2007	To provide procedural and safety clarification; update exclusion criteria based on postmarketing report (subjects with chronic or active hepatitis B will be excluded); update primary efficacy variable (clinical remission at Week 26 irrespective of responder status at Week 4).
08 August 2007	To include approval of adalimumab for Crohn's Disease in the US; clarify withdrawal criteria for subjects that continue to flare, develop another flare, or continue to have a non-response while receiving open-label weekly therapy; to clarify rescreening of subjects; clarify subject eligibility bases on age (between 6 and 17 years of age, inclusive prior to baseline dosing); clarify eligibility criteria (simplify stable dose of corticosteroids; expand choice of birth control methods; exclude subjects with a history of histoplasmosis, active tuberculosis, moderate to severe heart failure; daily dose of prednisone < 10 mg; certain concomitant medications); clarify that subjects with a positive C.difficile stool assay at Screening were not permitted to re-screen. and to prohibit abatacept and therapeutic enemas and suppositories during the study.
04 February 2008	To allow subjects with a positive C. difficile stool assay at Screening to re-screen.
02 October 2008	To revise the stopping rules based on new data available and agreed upon by the Data Monitoring Committee; clarify that assent from the subject may be verbal and/or written; provide clarification regarding permitted medications; allow baseline visits as soon as all screening assessments are complete for subjects < 13 years of age; clarify statistical analyses of primary and secondary endpoints.
30 March 2010	To analyze the primary endpoint for concomitant immunomodulator use (at baseline) as well as serious infection incidence and rates (patient years); clarify endpoint analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Absence of placebo group comparative data.

Notes: