



Clinical trial results:

A Multi-center, Open-label Study of the Human AntiTNF Monoclonal Antibody Adalimumab to Evaluate the Efficacy and the Long-term Safety and Tolerability of Repeated Administration of Adalimumab in Pediatric Subjects with Crohn's Disease Who Have Demonstrated a Clinical Response in the M06-806 Study

Summary

EudraCT number	2007-006494-90
Trial protocol	BE CZ GB Outside EU/EEA
Global end of trial date	04 April 2017

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	M06-807
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00686374
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 Services, AbbVie, 001 800-633-9110,
Scientific contact	Andreas Lazar, AbbVie, andreas.lazar@abbvie.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	04 April 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term maintenance of clinical response, safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohn's disease who participated in, and successfully completed, Protocol M06-806 through Week 52 and who met all the inclusion and none of the exclusion criteria of Protocol M06-807.

Protection of trial subjects:

Prior to any study-related screening procedures being performed, the investigator or his/her representative explained the nature of the study to the parent or guardian of the pediatric subject and answered all questions regarding the study. Subjects were included in all discussions. The informed consent form was reviewed, signed, and dated by the subject's parent or legal guardian, and by the person who administered the informed consent. If a subject became of legal age in the state of residence during the course of the study, another informed consent was to be obtained at that time. Additionally, in keeping with each institution's Institutional Review Board requirements, an informed assent was also to be obtained from the subject, as required. Subjects were to be included in all discussions in order to obtain their signature on an assent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 February 2008
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	Poland: 19
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	United States: 47
Country: Number of subjects enrolled	Canada: 14
Worldwide total number of subjects	100
EEA total number of subjects	39

Notes:

Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	20
Adolescents (12-17 years)	80
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects enrolled in and completed Study M06-806 through Week 52 who were responders at any time point during Study M06-806 (defined as having achieved at least a 15-point reduction in Pediatric Crohn's Disease Activity Index from Baseline).

Pre-assignment

Screening details:

36 subjects discontinued study drug when adalimumab became commercially available (received regulatory approval for pediatric Crohn's disease) in their country. These subjects were considered to have completed the study, and are included as study completers in the subject disposition.

Period 1

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

Arms

Arm title	Any adalimumab
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Arm description:

Adalimumab was administered via subcutaneous injection. Dosage was based on body weight and clinical status, and ranged from 10, 20, or 40 mg every other week to 20 or 40 mg every week.

Arm type	Experimental
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:

Subjects who enrolled into the study from blinded therapy in Protocol M06-806 received open-label (OL) therapy at a dose dependent on their body weight. Subjects who weighed ≥ 40 kg received 40 mg of adalimumab every other week (eow), while those who weighed < 40 kg received 20 mg of adalimumab eow. Beginning with Week 8, subjects who had a disease flare may have been switched to every week (ew) treatment at the same dose of adalimumab received while on eow treatment. Subjects who enrolled into the study from OL therapy in Protocol M06-806 continued to receive the same dose they were receiving (i.e., 40 mg ew or 20 mg ew) at the Week 52 visit of Protocol M06-806. Adalimumab dose could have been decreased to the next lower treatment level for those with body weight changes. Subjects who responded to treatment may have also had their dosage frequency decreased from ew to eow dosing, as well as a decrease in dosage.

Number of subjects in period 1	Any adalimumab
Started	100
Completed	39
Not completed	61
Consent withdrawn by subject	5
Adverse event, non-fatal	8
Other, not specified	4

Lost to follow-up	1
Missing reason	33
Lack of efficacy	10

Baseline characteristics

Reporting groups

Reporting group title	Any adalimumab
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Reporting group description:

Adalimumab was administered via subcutaneous injection. Dosage was based on body weight and clinical status, and ranged from 10, 20, or 40 mg every other week to 20 or 40 mg every week.

Reporting group values	Any adalimumab	Total	
Number of subjects	100	100	
Age categorical			
Age at Protocol M06-806 Baseline			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	20	20	
Adolescents (12-17 years)	80	80	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Age at Protocol M06-806 Baseline			
Units: years			
arithmetic mean	13.5		
standard deviation	± 2.5	-	
Gender categorical			
Units: Subjects			
Female	48	48	
Male	52	52	
Body weight			
Body weight at Protocol M06-806 Baseline			
Units: Subjects			
< 40 kg	38	38	
≥ 40 kg	62	62	

End points

End points reporting groups

Reporting group title	Any adalimumab
Reporting group description:	
Adalimumab was administered via subcutaneous injection. Dosage was based on body weight and clinical status, and ranged from 10, 20, or 40 mg every other week to 20 or 40 mg every week.	

Primary: Number of subjects who achieved Pediatric Crohn's Disease Activity Index (PCDAI) clinical remission over time

End point title	Number of subjects who achieved Pediatric Crohn's Disease Activity Index (PCDAI) clinical remission over time ^[1]
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. Clinical remission was defined as PCDAI ≤ 10.	
End point type	Primary
End point timeframe:	
Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408	

Notes:

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

Justification: Descriptive statistics are presented, per protocol.

End point values	Any adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	100 ^[2]			
Units: Subjects				
Week 0 (n=100)	67			
Week 4 (n=98)	65			
Week 8 (n=97)	67			
Week 12 (n=96)	60			
Week 24 (n=94)	59			
Week 36 (n=87)	60			
Week 48 (n=82)	54			
Week 60 (n=79)	60			
Week 72 (n=76)	49			
Week 84 (n=74)	54			
Week 96 (n=77)	54			
Week 108 (n=72)	54			
Week 120 (n=67)	52			
Week 144 (n=64)	51			
Week 168 (n=58)	44			
Week 192 (n=55)	44			
Week 216 (n=50)	36			
Week 240 (n=46)	37			
Week 264 (n=37)	31			

Week 288 (n=29)	24			
Week 312 (n=18)	14			
Week 336 (n=11)	8			
Week 360 (n=8)	7			
Week 384 (n=2)	2			
Week 408 (n=0)	0			

Notes:

[2] - ITT population: subjects who rcvd ≥ 1 dose of adalimumab and had ≥ 1 non-missing efficacy measurement

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with clinical response as defined by Pediatric Crohn's Disease Activity Index (PCDAI) score over time

End point title	Number of subjects with clinical response as defined by Pediatric Crohn's Disease Activity Index (PCDAI) score over time ^[3]
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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 baseline PCDAI value was defined as the last non-missing value on or before the date of the first dose of study drug during Protocol M06-806. Clinical response was defined as a PCDAI ≥ 15 points lower than the Protocol M06-806 baseline PCDAI value.

End point type	Primary
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End point timeframe:

Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics are presented, per protocol.

End point values	Any adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	100 ^[4]			
Units: subjects				
Week 0 (n=100)	95			
Week 4 (n=98)	90			
Week 8 (n=97)	92			
Week 12 (n=96)	87			
Week 24 (n=94)	88			
Week 36 (n=87)	82			
Week 48 (n=82)	74			
Week 60 (n=79)	76			
Week 72 (n=76)	72			
Week 84 (n=74)	69			
Week 96 (n=77)	72			
Week 108 (n=72)	70			
Week 120 (n=67)	65			
Week 144 (n=64)	64			

Week 168 (n=58)	53			
Week 192 (n=55)	52			
Week 216 (n=50)	46			
Week 240 (n=46)	43			
Week 264 (n=37)	35			
Week 288 (n=29)	28			
Week 312 (n=18)	15			
Week 336 (n=11)	10			
Week 360 (n=8)	8			
Week 384 (n=2)	2			
Week 408 (n=0)	0			

Notes:

[4] - ITT population: subjects who received ≥ 1 dose of adalimumab and had ≥ 1 non-missing efficacy measurement

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who were in Crohn's Disease Activity Index (CDAI) clinical remission over time

End point title	Number of subjects who were in Crohn's Disease Activity Index (CDAI) clinical remission over time
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End point description:

The CDAI includes 8 variables encompassing both subject-reported (symptoms, general well-being) and objective (medication usage, laboratory variables, presence of abdominal mass or complications, and weight) variables. For symptoms scores, subjects kept track of daily symptoms on a diary card, and the daily symptom scores were summed for the week. Each item in the CDAI is assigned a specific weight, and the weighted values of the items are totaled to produce the CDAI score. Higher CDAI scores indicate greater disease activity; 0 is the lower limit with no set upper limit. The scale for the score is as follows: < 150 to indicate remission, 150 - 219 to define mildly active disease, 220 - 450 to define moderately active disease, and > 450 to define severely active disease. A CDAI was calculated at each visit for subjects who were age 13 or older at Protocol M06-806 entry. The Protocol M06-806 Week 52 visit served as the baseline visit for this study.

End point type	Secondary
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End point timeframe:

Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408

End point values	Any adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	65 ^[5]			
Units: subjects				
Week 0 (n=65)	58			
Week 4 (n=63)	55			
Week 8 (n=62)	58			
Week 12 (n=61)	53			
Week 24 (n=59)	54			
Week 36 (n=55)	52			
Week 48 (n=53)	48			
Week 60 (n=52)	49			
Week 72 (n=50)	47			

Week 84 (n=50)	46			
Week 96 (n=50)	45			
Week 108 (n=49)	45			
Week 120 (n=43)	42			
Week 144 (n=41)	40			
Week 168 (n=35)	35			
Week 192 (n=33)	31			
Week 216 (n=30)	27			
Week 240 (n=29)	26			
Week 264 (n=24)	23			
Week 288 (n=18)	17			
Week 312 (n=15)	15			
Week 336 (n=9)	8			
Week 360 (n=7)	7			
Week 384 (n=1)	1			
Week 408 (n=0)	0			

Notes:

[5] - Subjects ≥ 13 years old at M06-806 entry;rcvd ≥ 1 dose adalimumab;had ≥ 1 non-missing efficacy meas

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who were in Crohn's Disease Activity Index (CDAI) clinical response over time

End point title	Number of subjects who were in Crohn's Disease Activity Index (CDAI) clinical response over time
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End point description:

The CDAI includes 8 variables: subject-reported (symptoms, general well-being) and objective (medication usage, laboratory variables, presence of abdominal mass or complications, and weight). Subjects kept track of symptoms on a diary card, and scores were summed for the week. Each item is assigned a specific weight, and the weighted values of the items are totaled to produce the CDAI score. Higher CDAI scores indicate greater disease activity; 0 is the lower limit with no set upper limit. Scale: < 150 (remission), 150 - 219 (mildly active disease), 220 - 450 (moderately active disease), and > 450 (severely active disease). A CDAI was calculated at each visit for subjects ≥ 13 yrs old at M06-806 entry. Clinical response was defined as a decrease from M06-806 Baseline CDAI value of ≥ 70 pts. The M06-806 Baseline value was defined as the last non-missing value on or before the date of the 1st dose of study drug in M06-806.

End point type	Secondary
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End point timeframe:

Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408

End point values	Any adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	64 ^[6]			
Units: subjects				
Week 0 (n=64)	55			
Week 4 (n=63)	56			
Week 8 (n=62)	56			
Week 12 (n=61)	51			

Week 24 (n=59)	52			
Week 36 (n=55)	53			
Week 48 (n=53)	48			
Week 60 (n=52)	48			
Week 72 (n=50)	45			
Week 84 (n=50)	47			
Week 96 (n=50)	45			
Week 108 (n=49)	47			
Week 120 (n=43)	40			
Week 144 (n=41)	41			
Week 168 (n=35)	34			
Week 192 (n=33)	33			
Week 216 (n=30)	28			
Week 240 (n=29)	28			
Week 264 (n=24)	24			
Week 288 (n=18)	18			
Week 312 (n=15)	15			
Week 336 (n=9)	9			
Week 360 (n=7)	7			
Week 384 (n=1)	1			
Week 408 (n=0)	0			

Notes:

[6] - Subjects ≥ 13 years old at M06-806 entry;rcvd ≥ 1 dose adalimumab;had ≥ 1 non-missing efficacy meas

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects in Steroid-free Pediatric Crohn's Disease Activity Index (PCDAI) remission over time

End point title	Number of subjects in Steroid-free Pediatric Crohn's Disease Activity Index (PCDAI) remission over time
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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. PCDAI corticosteroid-free remission was defined as discontinued corticosteroid use at least 90 consecutive days prior to the respective visit, with a PCDAI ≤ 10 at that visit.

End point type	Secondary
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End point timeframe:

Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384

End point values	Any adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	37 ^[7]			
Units: subjects				
Week 0 (n=37)	23			
Week 4 (n=37)	23			

Week 8 (n=37)	23			
Week 12 (n=37)	20			
Week 24 (n=37)	21			
Week 36 (n=33)	19			
Week 48 (n=32)	19			
Week 60 (n=30)	24			
Week 72 (n=28)	17			
Week 84 (n=29)	19			
Week 96 (n=29)	20			
Week 108 (n=27)	18			
Week 120 (n=25)	19			
Week 144 (n=24)	17			
Week 168 (n=22)	16			
Week 192 (n=19)	15			
Week 216 (n=19)	13			
Week 240 (n=16)	13			
Week 264 (n=13)	11			
Week 288 (n=10)	9			
Week 312 (n=5)	5			
Week 336 (n=3)	2			
Week 360 (n=2)	1			
Week 384 (n=0)	0			

Notes:

[7] - Corticosteroid use at M06-806 entry; rcvd ≥ 1 dose adalimumab; ≥ 1 non-missing efficacy measurement

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects in Steroid-free Crohn's Disease Activity Index (CDAI) remission over time

End point title	Number of subjects in Steroid-free Crohn's Disease Activity Index (CDAI) remission over time
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End point description:

The CDAI includes 8 variables encompassing subject-reported (symptoms, general well-being) and objective (medication usage, laboratory variables, presence of abdominal mass or complications, and weight) variables. Subjects kept track of daily symptoms on a diary card, and the scores were summed for the week. Each item in the CDAI is assigned a specific weight, and the items are totaled to produce the CDAI score. Higher CDAI scores indicate greater disease activity; 0 is the lower limit with no set upper limit. The scale for the score is as follows: < 150 (remission), 150 - 219 (mildly active disease), 220 - 450 (moderately active disease), and > 450 (severely active disease). A CDAI was calculated at each visit for subjects ≥ 13 years old at M06-806 entry. CDAI corticosteroid-free remission was defined as discontinued use at least 90 consecutive days prior to the respective visit and a CDAI < 150 at that visit.

End point type	Secondary
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End point timeframe:

Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384

End point values	Any adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	26 ^[8]			
Units: subjects				
Week 0 (n=26)	21			
Week 4 (n=26)	22			
Week 8 (n=26)	22			
Week 12 (n=26)	20			
Week 24 (n=26)	21			
Week 36 (n=24)	22			
Week 48 (n=24)	22			
Week 60 (n=23)	21			
Week 72 (n=21)	19			
Week 84 (n=22)	20			
Week 96 (n=22)	20			
Week 108 (n=21)	18			
Week 120 (n=18)	16			
Week 144 (n=17)	15			
Week 168 (n=14)	13			
Week 192 (n=12)	11			
Week 216 (n=13)	10			
Week 240 (n=11)	10			
Week 264 (n=8)	8			
Week 288 (n=6)	6			
Week 312 (n=4)	4			
Week 336 (n=3)	2			
Week 360 (n=2)	1			
Week 384 (n=0)	0			

Notes:

[8] - ≥ 13 yrs, corticosteroid use at M06-806 entry;rcvd ≥ 1 dose adalimumab; ≥ 1 non-missing efficacy meas

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Pediatric Crohn's Disease Activity Index (PCDAI) over time

End point title	Mean change from baseline in Pediatric Crohn's Disease Activity Index (PCDAI) over time
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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 baseline value was defined as the last non-missing value on or before the date of the first dose of study drug in Study M06-806. Negative changes indicate reductions (improvement) in disease activity.

End point type	Secondary
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End point timeframe:

Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384

End point values	Any adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	100 ^[9]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 0 (n=100)	-29.95 (± 11.459)			
Week 4 (n=98)	-30.15 (± 11.514)			
Week 8 (n=97)	-30.7 (± 11.415)			
Week 12 (n=96)	-29.19 (± 11.405)			
Week 24 (n=94)	-29.84 (± 11.702)			
Week 36 (n=87)	-30.89 (± 12.354)			
Week 48 (n=82)	-30.73 (± 11.983)			
Week 60 (n=79)	-32.78 (± 10.927)			
Week 72 (n=76)	-31.15 (± 10.404)			
Week 84 (n=74)	-32.94 (± 10.809)			
Week 96 (n=77)	-31.14 (± 11.33)			
Week 108 (n=72)	-33.54 (± 9.538)			
Week 120 (n=67)	-33.36 (± 10.441)			
Week 144 (n=64)	-34.38 (± 9.204)			
Week 168 (n=58)	-32.57 (± 11.273)			
Week 192 (n=55)	-33 (± 13.258)			
Week 216 (n=50)	-31.95 (± 12.344)			
Week 240 (n=46)	-34.18 (± 13.386)			
Week 264 (n=37)	-35 (± 9.242)			
Week 288 (n=29)	-35.95 (± 11.941)			
Week 312 (n=18)	-33.19 (± 14.318)			
Week 336 (n=11)	-35.23 (± 12.013)			
Week 360 (n=8)	-38.75 (± 10.69)			
Week 384 (n=2)	-46.25 (± 22.981)			

Notes:

[9] - ITT population: subjects who rcvd ≥ 1 dose of adalimumab and had ≥ 1 non-missing efficacy measurement

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Crohn's Disease Activity Index (CDAI) over time

End point title	Mean change from baseline in Crohn's Disease Activity Index (CDAI) over time
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End point description:

The CDAI includes 8 variables: subject-reported (symptoms, general well-being) and objective (medication usage, laboratory variables, presence of abdominal mass or complications, and weight) variables. For symptoms scores, subjects kept track of daily symptoms on a diary card, and the scores were summed for the week. Each item in the CDAI is assigned a specific weight, and the items are totaled to produce the CDAI score. Higher CDAI scores indicate greater disease activity; 0 is the lower limit with no set upper limit. The scale for the score is as follows: < 150 (remission), 150 - 219 (mildly active disease), 220 - 450 (moderately active disease) and > 450 (severely active disease). A CDAI was calculated at each visit for subjects who were ≥ 13 years old at Protocol M06-806 entry. The baseline value was defined as the last non-missing value on or before the date of the first dose of study drug in Study M06-806. Negative changes indicate reductions (improvement) in disease activity.

End point type	Secondary
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End point timeframe:

Week 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384

End point values	Any adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	64 ^[10]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 0 (n=64)	-160.8 (± 82.543)			
Week 4 (n=63)	-159.9 (± 79.986)			
Week 8 (n=62)	-164.45 (± 79.272)			
Week 12 (n=61)	-151.34 (± 87.157)			
Week 24 (n=59)	-161.51 (± 84.663)			
Week 36 (n=55)	-173.55 (± 77.358)			
Week 48 (n=53)	-162.08 (± 86.292)			
Week 60 (n=52)	-168.27 (± 82.605)			
Week 72 (n=50)	-165.4 (± 80.038)			
Week 84 (n=50)	-172.68 (± 86.223)			
Week 96 (n=50)	-168.3 (± 79.658)			
Week 108 (n=49)	-171.63 (± 85.19)			
Week 120 (n=43)	-179.14 (± 86.93)			

Week 144 (n=41)	-181.53 (± 78.99)			
Week 168 (n=35)	-175.05 (± 80.965)			
Week 192 (n=33)	-172.42 (± 76.381)			
Week 216 (n=30)	-173.13 (± 78.588)			
Week 240 (n=29)	-184.46 (± 94.114)			
Week 264 (n=24)	-186.42 (± 75.396)			
Week 288 (n=18)	-197.11 (± 88.029)			
Week 312 (n=15)	-199 (± 77.184)			
Week 336 (n=9)	-240.33 (± 97.395)			
Week 360 (n=7)	-224.86 (± 89.025)			
Week 384 (n=1)	-458 (± 0)			

Notes:

[10] - Subjects ≥ 13 years old at M06-806 entry;rcvd ≥ 1 dose adalimumab;had ≥ 1 non-missing efficacy meas

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) were collected from the time of study drug administration in Protocol M06-806 until 70 days after the last dose of study drug in Protocol M06-807 (up to 470 weeks).

Adverse event reporting additional description:

TEAEs and TESAEs are defined as any adverse event (AE) or serious adverse event (SAE) with an onset date that is after the first dose of study drug until 70 days after the last dose of study drug and were collected whether elicited or spontaneously reported by the participant.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Any adalimumab
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Reporting group description:

Adalimumab was administered via subcutaneous injection. Dosage was based on body weight and clinical status, and ranged from 10, 20, or 40 mg every other week to 20 or 40 mg every week.

Serious adverse events	Any adalimumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 100 (48.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Heart rate irregular			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Bone contusion			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Facial bones fracture			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Lymphadenitis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis ulcerative			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Crohn's disease			

subjects affected / exposed	25 / 100 (25.00%)		
occurrences causally related to treatment / all	0 / 36		
deaths causally related to treatment / all	0 / 0		
Faecal volume increased			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal pain			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ileal perforation			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileal stenosis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine perforation			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			

subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal stenosis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Pelvic fluid collection			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Schizoaffective disorder			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Somatic symptom disorder			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Systemic lupus erythematosus			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cystitis viral			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes virus infection			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Impetigo			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic abscess			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Perirectal abscess				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Salmonellosis				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal abscess				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth abscess				

subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Yersinia infection			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Any adalimumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 100 (98.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	13 / 100 (13.00%)		
occurrences (all)	15		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 100 (18.00%)		
occurrences (all)	24		
Injection site pain			
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	23		
Injection site reaction			

subjects affected / exposed occurrences (all)	16 / 100 (16.00%) 34		
Pain subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 8		
Pyrexia subjects affected / exposed occurrences (all)	20 / 100 (20.00%) 35		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	5 / 100 (5.00%) 5		
Seasonal allergy subjects affected / exposed occurrences (all)	8 / 100 (8.00%) 10		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	7 / 100 (7.00%) 18		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	20 / 100 (20.00%) 34		
Dyspnoea subjects affected / exposed occurrences (all)	5 / 100 (5.00%) 5		
Epistaxis subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 12		
Nasal congestion subjects affected / exposed occurrences (all)	12 / 100 (12.00%) 17		
Oropharyngeal pain subjects affected / exposed occurrences (all)	27 / 100 (27.00%) 48		
Rhinitis allergic			

subjects affected / exposed occurrences (all)	5 / 100 (5.00%) 6		
Rhinorrhoea subjects affected / exposed occurrences (all)	7 / 100 (7.00%) 13		
Sinus congestion subjects affected / exposed occurrences (all)	7 / 100 (7.00%) 10		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 7		
Insomnia subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 6		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 6		
Antinuclear antibody positive subjects affected / exposed occurrences (all)	5 / 100 (5.00%) 6		
C-reactive protein increased subjects affected / exposed occurrences (all)	15 / 100 (15.00%) 15		
Red blood cell sedimentation rate increased subjects affected / exposed occurrences (all)	8 / 100 (8.00%) 9		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 8		
Procedural pain subjects affected / exposed occurrences (all)	9 / 100 (9.00%) 9		
Cardiac disorders			

Palpitations subjects affected / exposed occurrences (all)	5 / 100 (5.00%) 5		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 10 37 / 100 (37.00%) 100 8 / 100 (8.00%) 13		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Lymphadenectomy subjects affected / exposed occurrences (all)	8 / 100 (8.00%) 9 5 / 100 (5.00%) 6 7 / 100 (7.00%) 10		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	5 / 100 (5.00%) 5		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Anal fissure subjects affected / exposed occurrences (all)	24 / 100 (24.00%) 57 15 / 100 (15.00%) 26 9 / 100 (9.00%) 10		

Constipation			
subjects affected / exposed	15 / 100 (15.00%)		
occurrences (all)	25		
Crohn's disease			
subjects affected / exposed	24 / 100 (24.00%)		
occurrences (all)	48		
Diarrhoea			
subjects affected / exposed	26 / 100 (26.00%)		
occurrences (all)	41		
Dyspepsia			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	6		
Haematochezia			
subjects affected / exposed	8 / 100 (8.00%)		
occurrences (all)	12		
Malpositioned teeth			
subjects affected / exposed	6 / 100 (6.00%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	19 / 100 (19.00%)		
occurrences (all)	49		
Rectal haemorrhage			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	5		
Toothache			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	10		
Vomiting			
subjects affected / exposed	22 / 100 (22.00%)		
occurrences (all)	39		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	7		
Alopecia			

subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	7		
Dry skin			
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	10		
Eczema			
subjects affected / exposed	8 / 100 (8.00%)		
occurrences (all)	11		
Erythema			
subjects affected / exposed	6 / 100 (6.00%)		
occurrences (all)	8		
Psoriasis			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	6		
Rash			
subjects affected / exposed	15 / 100 (15.00%)		
occurrences (all)	25		
Urticaria			
subjects affected / exposed	8 / 100 (8.00%)		
occurrences (all)	13		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 100 (21.00%)		
occurrences (all)	36		
Back pain			
subjects affected / exposed	14 / 100 (14.00%)		
occurrences (all)	25		
Joint swelling			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	6		
Muscle spasms			
subjects affected / exposed	8 / 100 (8.00%)		
occurrences (all)	11		
Myalgia			

subjects affected / exposed	9 / 100 (9.00%)		
occurrences (all)	10		
Pain in extremity			
subjects affected / exposed	9 / 100 (9.00%)		
occurrences (all)	9		
Infections and infestations			
Bronchitis			
subjects affected / exposed	11 / 100 (11.00%)		
occurrences (all)	18		
Conjunctivitis			
subjects affected / exposed	9 / 100 (9.00%)		
occurrences (all)	11		
Ear infection			
subjects affected / exposed	10 / 100 (10.00%)		
occurrences (all)	15		
Eye infection			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	5		
Gastroenteritis			
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	9		
Gastroenteritis viral			
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	7		
Herpes zoster			
subjects affected / exposed	8 / 100 (8.00%)		
occurrences (all)	9		
Impetigo			
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	9		
Influenza			
subjects affected / exposed	15 / 100 (15.00%)		
occurrences (all)	23		
Oral herpes			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	6		

Otitis media			
subjects affected / exposed	8 / 100 (8.00%)		
occurrences (all)	11		
Pharyngitis			
subjects affected / exposed	20 / 100 (20.00%)		
occurrences (all)	48		
Pharyngitis streptococcal			
subjects affected / exposed	14 / 100 (14.00%)		
occurrences (all)	20		
Pneumonia			
subjects affected / exposed	8 / 100 (8.00%)		
occurrences (all)	9		
Respiratory tract infection viral			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	5		
Rhinitis			
subjects affected / exposed	10 / 100 (10.00%)		
occurrences (all)	20		
Sinusitis			
subjects affected / exposed	17 / 100 (17.00%)		
occurrences (all)	33		
Staphylococcal infection			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	7		
Tonsillitis			
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	8		
Upper respiratory tract infection			
subjects affected / exposed	31 / 100 (31.00%)		
occurrences (all)	60		
Urinary tract infection			
subjects affected / exposed	14 / 100 (14.00%)		
occurrences (all)	19		
Viral infection			
subjects affected / exposed	18 / 100 (18.00%)		
occurrences (all)	21		

Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	39 / 100 (39.00%) 88		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2008	Amendment 1 • Updated Inclusion Criterion #2 to clarify that subject must be responder during Study M06-806. • Amended the stopping rules as follows: The rate of possibly related SAEs or higher, on a per subject per year basis in excess of 0.45, was changed to the proportion of SAEs, possibly related or higher, on a per subject basis in excess of 0.20. • Changed overall rate, in excess of 0.09 infectious SAEs on a per subject per year basis to the overall proportion of infectious SAEs in excess of 0.20 on a per subject basis. • Changed the protocol paragraph with text "If either of these criteria is met, no new enrollment will occur until the Data Monitoring Committee (DMC) or the Sponsor Steering Committee makes their recommendations" to "If either of the above criteria is met, the DMC will meet within 2 weeks to consider whether or not to recommend a temporary suspension of enrollment." • Removed Section 12.2 re: publication. • Administrative Changes: - Updated approvals from other indications to reflect the most current data available. - Updated Safety Hotline address and contact information for AE reporting. - Updated to add reference for current guidelines for treatment of latent TB to reference list. - Appendix C (Documents Required Prior to Initiation of the Study): updated to reflect current regulatory requirements. - Appendix D (Responsibilities of the Clinical investigator): updated to reflect current regulatory requirements. - Appendix E (Centers for Disease Control [CDC] Treatment of Tuberculosis Infection [Preventive Therapy]): updated with current guidelines for treatment of latent TB. - Appendix H (PCDAI User's Guide and Guideline for Reference Weight and Height): updated to clarify from Wk 48 to Wk 72 and from post Wk 72, using height from Wk 48. - Appendix L (Excluded Medications): updated to state any previous anti TNF medication except infliximab before Study M06-806 - Appendix M (Day 70 Phone Call): updated faxing contact info.
26 August 2010	Amendment 2 • Added blood sample collections for adalimumab concentration and AAA assays. • Changed the stopping criteria for study based on discussion and recommendation by the DMC members. • Added subject visits through Week 264 and provided for study to continue until local regulatory approval. • Incorporated Administrative Changes 3 through 6 into this protocol. • Added a new required template for protocol signatories (Appendix B).
14 December 2010	Amendment 3 • Included an interim analysis. • Clarified that the x-ray for bone age was not to be performed at the unscheduled visit. • Added a statement allowing the investigator to omit the x-ray for bone age and the determination of serum bone markers if the subject was no longer growing.

29 June 2011	Amendment 4 Allowed dose and frequency decrease in subjects who responded well to treatment, allowed dose adjustment due to weight loss, and added 10 mg eow dosage.
03 January 2012	Amendment 5 Added in regular TB testing in response to the US Food and Drug Administration required labeling change based on cases of reactivation of TB/occurrence or new TB infections in patients receiving Humira. The US package insert now says retest should be done "periodically" during therapy, without specifying the interval. Based on the actual US package insert and on literature search, annual TB rescreening was implemented as a reasonable interval.
12 April 2013	Amendment 6 - Added subject visits through Week 336 to extend the study. - Section 3.0, Section 5.2.3.1, and Section 6.5 were revised to include additional anti-TNF information per Humira standards, and provided background information about enhanced data collection to understand the risks of malignancy in subjects 30 and younger. - Section 5.2.3.2 Concomitant Therapy was revised to allow immunosuppressant to be started or restarted during the study. In addition, a sentence regarding the use of therapeutic enemas, suppositories and TPN was added to encourage the investigator to discuss with the Medical Monitor prior to use. - In Section 5.2.3.4 Prohibited Medication, the use of therapeutic enemas and suppositories was removed. - Section 5.3.1.1 Study Procedures (Outcomes): A clarification on the completion procedure of the WPAI-CD Caregiver was added. - Section 5.3.2.1 Collection of samples for analysis: A clarification on collecting samples for subjects who require switching or change dose was added. - Section 5.5.2.1 Packaging and Labeling was revised. - Section 6.6 Pregnancy: The verbiage regarding the pregnancy registry was removed, as the registry is closed to Humira subjects and is only enrolling in the comparator (non-Humira) arm. - Incorporated Administrative Change 7 into this protocol.
26 May 2015	Amendment 7 - Added subject visits through Week 408 (approximately 8 years) to extend the study and provide for study to continue until local regulatory approval. - Added the Complaint and Product Complaint definition to Sections 6.0, 6.2.1, and 6.2.2 as well as the reporting requirements for Product Complaints. - Updated Section 8.1.5, Interim Analysis. - Incorporated Administrative Changes 8 and 9 into this protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28129288>