18 October 2012
EMA/56352/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Humira

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/000481/II/0088

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1. Introduction

About the product

Adalimumab is a recombinant fully human immunoglobulin (IgG1) monoclonal antibody that binds specifically and with high affinity to the soluble and transmembrane forms of TNF-α and inhibits the binding of TNF-α with its receptors. Adalimumab is approved for the treatment of inflammatory diseases including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), axial spondyloarthritis (AxSpA), plaque psoriasis (Ps), ulcerative colitis (UC) and Crohn's disease (CD).

Problem statement

Crohn's disease is an autoimmune disorder of unknown etiology that primarily involves the bowel. CD may affect any part of the gastrointestinal tract from mouth to anus causing a wide variety of symptoms such as abdominal pain, diarrhoea, vomiting, weight loss, tiredness. The most commonly involved area of the bowel is the small bowel, particularly the distal ileum which is involved in 70% of cases often in combination with colitis. Males and females are equally affected. CD can occur at any age but it is rare in early childhood, tends to peak both in the teens-twenties and in the fifties-seventies. The incidence rates of CD in patients less than 18 years of age range from 1.2 to 4.9 per 100,000 persons in the UK, Europe and North America.

Despite obvious physiologic and development differences, the clinical presentation of CD in the paediatric population is generally similar to that seen in older patients and is heterogeneous with regard to anatomic localisation and clinical severity. The unique aspect of this disease in children is its impact on nutrition and growth, with a potential marked impact on growth retardation.

The general approach to the treatment of CD in children is similar to adults with the goals being induction and maintenance of remission, prevention of relapse and hospitalizations, improved quality of life and avoidance of disease related complications. Restoration and/or preservation of normal growth and pubertal development are additional therapeutic goals. Treatment options are restricted to controlling symptoms, maintaining remission and preventing relapse. The medical armamentarium is similar to adults and includes corticosteroids, immunomodulators (IMMs) such as azathioprine (AZA), 6-mercaptopurine (6-MP) and methotrexate (MTX), aminosalicylates and nutritional therapy. Tumour necrosis factor (TNF) is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation in chronic inflammatory diseases such as CD. Infliximab is a monoclonal antibody directed against TNF-α (anti-TNF therapy) approved in the EU for the treatment of CD in the paediatric and adult population. Surgical treatment may be indicated in cases developing intestinal strictures and/or perianal disease with fistula/and abscess.

Adalimumab is a fully human recombinant anti-TNF monoclonal antibody that has been approved in the EU for the treatment of CD in adults in June 2007.

Scope of the variation

In this submission the MAH applies for a new therapeutic indication for Humira for the treatment of active CD defined as a Paediatric Crohn's Disease Activity Index (PCDAI) score >30 in paediatric patients (6 to 17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid and an immunomodulator or who are intolerant to

or have contraindications for such therapies. Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC were proposed to be updated accordingly as well as the package leaflet.

The initially proposed wording for the indication reads as follows:

Paediatric Crohn's Disease

Humira is indicated for the treatment of active Crohn's disease defined as a Paediatric Crohn's Disease Activity Index (PCDAI) score > 30 in paediatric patients (6 to 17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies.

The following variation application is made in this submission:

Clinical:

Variation requested		**Type**
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one	II

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/141/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/141/2011 was not yet completed as some measures were deferred.

Development programme and compliance with CHMP guidance and scientific advice

The clinical development program for adalimumab in the sought paediatric CD indication includes 2 clinical studies:

- Study M06-806: a pivotal randomized, double-blind (DB) induction and maintenance of clinical remission study
- Study M06-807: an ongoing supportive long-term open-label (OL) extension study (with a data cut-off of 30 November 2010 for the data included in this submission)

Study M06-806 evaluated the efficacy of an OL induction dose regimen and 2 adalimumab maintenance dose regimens (low-dose and high-dose) for the induction and maintenance of clinical remission in paediatric subjects between the ages of 6 and 17 inclusive with moderate to severe CD. Study M06-807 assesses the long-term efficacy and safety of adalimumab in paediatric subjects with moderate to severe CD. Subjects were allowed to enroll in Study M06-807 if they successfully completed Study M06-806 through Week 52.

Compliance with scientific advice

The applicant did not seek scientific advice at the CHMP.

Compliance with CHMP guideline

Guideline on the development of medicinal products for the treatment of Crohn's disease, CPMP/EWP/2284/99 Rev. 1 is applicable for this development. The development program presented was considered in line with this regulatory guideline. The primary endpoint was clinical remission at week 26, defined as PCDAI score <10. The subject population of patients who had failed conventional

treatment (e.g. corticosteroids, AZA or 6-MP) was chosen in line with the approved indication of another anti-TNFα agent together with patients who had lost response or intolerance to infliximab. The open-label part of this trial is meant to provide supportive information on the maintenance of clinical remission.

General comments on compliance with GCP

The clinical trial submitted was performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement that the clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

1.2. Clinical aspects

1.2.1. Clinical pharmacology

1.2.1.1. Pharmacokinetics

1.2.1.1.1. Introduction

In the Phase 3 Study M06-806, adalimumab PK was evaluated in paediatric subjects with moderate to severe CD. In the adult population with moderate to severe CD, adalimumab PK was evaluated in infliximab-naïve subjects following a 4-week induction regimen (Study M02-403) and a 52-week maintenance regimen (Study M02-433) and in subjects who had lost response or were intolerant to infliximab (Study M04-691).

Population PK analysis of adalimumab was performed in the adult (Studies M02-403 and M02-433) as well as paediatric CD population (Study M06-806) using a nonlinear mixed effects modeling (NONMEM) approach. The impact of covariates (such as concomitant immunosuppressant use, anti-adalimumab antibody [AAA] status and body weight) on adalimumab PK was assessed. Finally, the immunogenicity of adalimumab and its potential impact on efficacy and safety was also examined in the above-mentioned studies.

1.2.1.1.2. Study M06-806

This was a multicenter, randomized, double-blind, safety, efficacy and pharmacokinetic study designed to demonstrate the effectiveness of two dosage regimens of adalimumab in the induction and maintenance of clinical remission in paediatric subjects with moderate to severe CD.

Dosing regimens

This study contained 2 dosing periods, a 4-week open-label (OL) induction period and a 48-week double-blind (DB) maintenance period. Subjects who experienced flare or non-response following an 8-week course of double-blinded weekly therapy were switched to open-label weekly therapy. The induction and maintenance doses were dependent on the subject's body weight. In the OL period subjects ≥40 kg received 160 mg and 80 mg adalimumab at Weeks 0 and 2, respectively. Subjects <40 kg received 80 mg and 40 mg at Weeks 0 and 2, respectively. At Week 4, subjects were stratified (according to their body weight at Week 4, responder status and their prior exposure to infliximab) and then randomized 1:1 into high dose (40/20 mg) or low dose (20/10 mg) maintenance treatment groups. The high dose group received either 40 mg adalimumab every other week (eow) (if Week 4 body weight ≥40 kg) or 20 mg adalimumab eow (if Week 4 body weight <40 kg). In the low dose group subject received either 20 mg eow (if Week 4 body weight ≥40 kg) or 10 mg adalimumab sc eow (if Week 4 body weight <40 kg).

Subjects were expected to remain on blinded eow therapy throughout the 48-week study period. However, starting at the Week 12 study visit, subjects who experienced a disease flare (increase in the PCDAI of ≥ 15 points when compared to Week 4 and an absolute PCDAI above 30) or were non-responders (not achieving a decrease in the PCDAI score of at least 15 points when compared to the baseline score for 2 consecutive visits at least 2 weeks apart), were switched from blinded eow dosing to blinded weekly dosing, continuing with the same blinded dose.

A total of 192 paediatric subjects between the ages of 6 and 17 years inclusive were enrolled.

Table 1 Dosing regimens in Study M06-806

	Open Label (OL)		Double Blind (DB)	
			Week 4 – Week 52	
Treatment Groups	Week 0 (Baseline)	Week 2	High-Dose	Low-Dose
≥ 40 kg	160 mg	80 mg	40 mg eow	20 mg eow
< 40 kg	80 mg	40 mg	20 mg eow	10 mg eow

Collection of blood samples

Blood samples were obtained for the measurement of adalimumab concentrations at baseline, Weeks 2, 4, 16, 26 and at Week 52 or early termination (ET) visit. Serum for measurement of anti-adalimumab antibodies (AAA)s were obtained at baseline, Week 16, 26 and Week 52 or ET visit. Blood samples were obtained at baseline for measurement of human anti-chimeric antibody (HACA) to infliximab as well as infliximab drug levels.

Pharmacokinetic data analysis

The PK analysis set used for summary statistics consisted of 178 patients of the total 192 randomized. Adalimumab serum trough concentrations were summarized by treatment groups at each time point using descriptive statistics including number of subjects (N), number of non-missing observations (nnmiss), mean, median, standard deviation, coefficient of variation, minimum, maximum, and geometric mean. Individual subject concentration-time plots and mean concentration-time plots stratified by treatment group were provided.

Analysis of blood samples

Adalimumab concentrations in serum were determined using a validated enzyme-linked immunoadsorbent assay (ELISA) method. Eight (8) subjects had measurable adalimumab concentrations at baseline (Week 0). All 8 subjects had measurable infliximab concentrations at baseline. Since these subjects were adalimumab naïve prior to the beginning of the study and the sampling occurred prior to the first adalimumab dose, the measurable values are likely due to infliximab interference with adalimumab assay.

Serum samples were analyzed for screening and confirmatory AAA assay using a validated double antigen immunoassay. The assay detects antibodies directed against epitopes on the entire adalimumab molecule. The total number of AAA samples received for the entire study was 700. Of the total samples received, 287 samples had adalimumab levels <2 µg/mL and were analyzed for AAA.

Infliximab concentrations in serum were determined using a validated ELISA method. Fifteen (15) subjects out of 117 in the ≥40 kg (160/80 mg) OL treatment group had measurable concentrations of infliximab at baseline. Five (5) subjects out of 65 in the <40 kg (80/40 mg) treatment group had measurable concentrations of infliximab at baseline.

HACA concentrations in serum were qualitatively determined using a validated ELISA method. Twenty-six (26) subjects out of 117 in the ≥40 kg (160/80 mg) OL treatment group were identified as HACA+

at baseline. Seventeen (17) subjects out of 65 in the <40 kg (80/40 mg) treatment group were identified as HACA+ at baseline.

Serum trough concentration

For the induction phase, the mean ± SD serum adalimumab trough concentrations achieved at Week 4 were 15.74 ± 6.55 µg/mL for subjects ≥40 kg (160 mg/80 mg) and 10.56 ± 6.06 µg/mL for subjects <40 kg (80 mg/40 mg). Furthermore, the mean ± SD serum adalimumab trough concentrations across various treatment groups were similar, ranging from 12.1 ± 7.52 to 15.5 ± 6.74 µg/mL at Week 4. During maintenance phase for subjects who stayed on their randomized therapy, the mean ± SD adalimumab trough concentrations at Week 52 were 9.48 ± 5.61 µg/mL and 3.51 ± 2.21 µg/mL for the high-dose (40/20 mg eow) and low-dose (20/10 mg eow) groups, respectively (Table 2). The mean trough concentrations appeared to be maintained in subjects who continued on their randomized adalimumab treatment eow for 52 weeks. For subjects who dose escalated, the mean ± SD serum concentrations of adalimumab at Week 52 were 15.3 ± 11.4 µg/mL (40/20 mg, weekly) and 6.65 ± 3.49 µg/mL (20/10 mg, weekly) for the high-dose and low-dose groups, respectively. Within each treatment group, the mean serum adalimumab trough concentrations in subjects with body weights <40 kg were numerically lower compared to subjects with body weights ≥40 kg. The range of concentrations for the 2 body weight groups tended to overlap.

Table 2 Summary of serum adalimumab trough concentrations (µg/mL) by dose in study M06-806

	Mean ± SD (Min – Max) N_{nmiss}					
Treatment Groups[a]	Week 0	Week 2	Week 4	Week 16	Week 26	Week 52
Double-blind 40/20 mg eow stayed (N = 53)	0.018 ± 0.068 (0.000 – 0.341) 53	16.2 ± 6.07 (3.68 – 32.3) 52	15.5 ± 6.74 (1.02 – 33.4) 50	10.3 ± 4.80 (1.12 – 23.2) 41	10.4 ± 4.26 (4.59 – 23.6) 39	9.48 ± 5.61 (0.000 – 26.6) 39
Double-blind 40/20 mg eow dose escalated to 40/20 mg weekly and then switched to open-label (N = 34)[b]	0.026 ± 0.083 (0.000 – 0.413) 34	14.4 ± 5.97 (3.83 – 30.7) 34	13.1 ± 7.36 (3.13 – 32.2) 33	9.31 ± 9.44 (0.000 – 43.1) 33	11.5 ± 11.8 (0.000 – 48.3) 27	15.3 ± 11.4 (0.000 – 44.7) 22
Double-blind 20/10 mg eow stayed (N = 45)[c]	0.013 ± 0.062 (0.000 – 0.337) 45	14.6 ± 4.77 (6.61 – 24.9) 45	12.4 ± 6.17 (0.735 – 22.9) 43	3.98 ± 2.38 (0.000 – 10.1) 30	3.63 ± 2.50 (0.000 – 8.33) 31	3.51 ± 2.21 (0.000 – 7.62) 29
Double-blind 20/10 mg dose escalated to 20/10 mg weekly (N = 30)[d]	0.006 ± 0.030 (0.000 – 0.164) 29	15.5 ± 6.50 (5.01 – 30.4) 30	13.5 ± 6.92 (1.93 – 28.0) 29	4.34 ± 4.08 (0.000 – 18.2) 29	4.25 ± 3.93 (0.000 – 14.2) 24	6.65 ± 3.49 (2.89 – 15.5) 17
Double-blind 20/10 mg dose escalated to 20/10 mg weekly and then switched to open-label 40/20 mg weekly (N = 16)[e]	0.019 ± 0.041 (0.000 – 0.152) 16	13.4 ± 5.97 (3.22 – 26.0) 16	12.1 ± 7.52 (0.868 – 29.6) 15	4.68 ± 4.14 (0.000 – 15.1) 16	7.59 ± 5.76 (0.000 – 21.0) 14	9.43 ± 5.10 (0.000 – 17.2) 12

Nnmiss = number of non-missing observations
a. Subjects were in open-label induction 160/80 mg for body weight > 40 kg, and 80/40 mg for body weight ≤ 40 kg at Weeks 0/2, then randomized to double-blind treatment groups.
b. Among 34 subjects who dose escalated, 11 subjects switched to open-label. Median (range) week of dose escalation = 18 (12 – 48) weeks. Median (range) week of switching to open-label = 31 (20 – 47) weeks. At Week 26, 1 subject had body weight increase from < 40 kg to ≥ 40 kg; therefore dose was increased from 20 to 40 mg.
c. At Week 26, 3 subjects had body weight increase from < 40 kg to ≥ 40 kg; therefore dose was increased from 10 to 20 mg.
d. Median (range) week of dose escalation = 23 (12–48) weeks.
e. Median (range) week of dose escalation = 12.3 (12–32) weeks and median (range) week of switching to open-label = 26 (20 – 48) weeks. At Week 26, 4 subjects had body weight increase from < 40 kg to ≥ 40 kg; therefore dose was increased from 20 to 40 mg.

Influence of prior infliximab use, HACA and AAA antibodies on the exposure to adalimumab

In the OL group, 59 of 117 subjects who received adalimumab 160/80 mg at Week 0/2 and 28 of 65 who received adalimumab 80/40 mg at Week 0/2 were anti-TNF experienced (infliximab). In the DB group, 43 of 87 subjects in high dose group and 42 of 91 in low dose group were anti-TNF experienced. In the OL induction period, the mean adalimumab trough concentrations were slightly higher in infliximab naïve subjects than in infliximab experienced subjects. The ranges of concentrations tended to overlap. During the double-blind maintenance phase, mean serum adalimumab trough

concentrations in infliximab experienced subjects were numerically lower, except for the 20/10 mg dose group from Week 16 and onwards, but the range of concentrations overlapped.

Table 3 Summary of adalimumab concentrations versus time (First 4 Weeks) for subjects in the open-label induction treatment by previous infliximab treatment status

Open-Label Treatment (N = 192)	Previous Infliximab Treatment	Mean ± SD (Min – Max), N_{nmiss} Week 0	Week 2	Week 4
Dose 160/80 mg at Week 0/2 with body weight ≥ 40 kg (N = 117)	Yes (N = 59)[a]	0.036 ± 0.093 (0.000 – 0.413), 59	15.4 ± 4.96 (6.61 – 30.7), 57	14.0 ± 6.51 (0.735 – 29.6), 56
	No (N = 58)	0.000 ± 0.000 (0.000 – 0.000), 58	17.8 ± 5.45 (6.83 – 32.3), 58	17.2 ± 6.39 (3.50 – 33.4), 54
Dose 80/40 mg at Week 0/2 with body weight < 40 kg (N = 65)	Yes (N = 28)[b]	0.029 ± 0.074 (0.000 – 0.289), 27	10.3 ± 4.66 (3.22 – 22.4), 27	7.94 ± 5.33 (0.868 – 20.9), 26
	No (N = 37)	0.000 ± 0.000 (0.000 – 0.000), 37	13.8 ± 5.88 (3.83 – 32.0), 36	11.7 ± 5.80 (1.93 – 32.8), 35

Nnmiss = number of non-missing observations Note: Ten subjects were excluded from the analysis due to protocol violation. a. Subjects were included as previous infliximab treated due to their measurable HACA concentration at baseline even though they were infliximab-naïve in clinical database.
b. Subject was included as infliximab experienced due to the measurable HACA result at baseline even though the subject was infliximab-naïve in clinical data base.

Table 4 Summary of adalimumab concentrations versus time by dose and prior infliximab use

Treatment	Prior Infliximab Use	Mean ± SD (Min – Max), N_{nmiss} Week 0	Week 2	Week 4	Week 16	Week 26	Week 52
Double-blind 40/20 mg eow stayed (N = 53)	INF- (N = 27)	0.000±0.000 (0.000-0.000), 27	18.8±6.00 (8.78-32.3), 27	18.5±6.71 (7.23-33.4), 25	11.6±5.06 (3.58-23.2), 23	11.3±4.65 (4.59-23.6), 23	10.6±5.61 (0.556-26.6), 23
	INF+ (N = 26)	0.037±0.094 (0.000-0.341), 26	13.4±4.83 (3.68-22.4), 25	12.6±5.43 (1.02-22.5), 25	8.71±4.03 (1.12-17.4), 18	9.14±3.36 (4.96-15.1), 16	7.86±5.37 (0.000-20.7), 16
Double-blind 40/20 mg eow to Weekly and open-label (N = 34)	INF- (N = 17)[a]	0.000±0.000 (0.000-0.000), 17	15.2±6.25 (3.83-27.7), 17	13.6±7.79 (3.13-32.2), 16	10.4±10.2 (0.000-43.1), 17	12.7±13.1 (0.000-48.3), 14	17.6±12.5 (0.000-44.7), 11
	INF+ (N = 17)[b]	0.053±0.113 (0.000-0.413), 17	13.7±5.77 (8.08-30.7), 17	12.7±7.13 (3.90-25.9), 17	8.14±8.78 (0.241-33.6), 16	10.1±10.5 (0.434-34.0), 13	13.0±10.1 (0.426-29.1), 11
Double-blind 20/10 mg eow stayed (N = 45)	INF- (N = 25)	0.000±0.000 (0.000-0.000), 25	14.8±5.06 (6.83-24.9), 25	13.7±4.44 (5.07-22.9), 24	3.98±2.03 (1.23-10.1), 21	3.50±2.21 (0.000-8.33), 22	3.30±1.94 (0.000-6.42), 20
	INF+ (N = 20)	0.029±0.091 (0.000-0.337), 20	14.4±4.49 (6.61-21.8), 20	10.8±7.67 (0.735-22.8), 19	3.98±3.19 (0.000-7.91), 9	3.94±3.23 (0.000-7.39), 9	3.97±2.79 (0.000-7.62), 9
Double-blind 20/10 mg eow to Weekly and open-label (N = 46)	INF- (N = 24)[c]	0.000±0.000 (0.000-0.000), 24	15.8±5.97 (7.13-29.4), 24	13.8±6.91 (1.93-28.0), 23	4.18±3.92 (0.558-18.2), 23	3.98±3.14 (0.000-9.73), 19	7.87±4.55 (2.89-15.9), 14
	INF+ (N = 22)[d]	0.022±0.049 (0.000-0.164), 21	13.7±6.66 (3.22-30.4), 22	12.1±7.32 (0.868-29.6), 21	4.76±4.27 (0.000-15.1), 22	6.97±5.88 (0.000-21.0), 19	7.73±4.36 (0.000-17.2), 15

Nnmiss = Number of non-missing observations; INF- = infliximab naïve; INF+ = infliximab experienced
a. Median (range) week of dose escalation in double-blind = 20 (12-48) weeks. Among the 17 subjects who dose escalated to weekly, 3 of them switched to open-label treatment. The median (range) week of switching to open-label = 33 (27-46) weeks.
b Median (range) week of dose escalation in double-blind = 16 (12-42) weeks. Among the 17 subjects who dose escalated to weekly, 8 of them switched to open-label .treatment. The median (range) week of switching to open-label = 30 (20-47) weeks.
c. Median (range) week of dose escalation in double-blind = 20 (12-48) weeks. Among the 24 subjects who dose escalated to weekly, 4 of them switched to open-label treatment. The median (range) week of switching to open-label = 20 (20-26) weeks.
d. Median (range) week of dose escalation in double-blind = 14 (12-34) weeks. Among the 22 subjects who dose escalated to weekly, 12 of them switched to open-label treatment. The median (range) week of switching to open-label = 29 (20-48) weeks.

In the OL group, 26 of 117 subjects who received adalimumab 160/80 mg and 17 of 65 who received adalimumab 80/40 mg at Week 0/2 were HACA+ at baseline. In the DB group, 23 of 87 subjects in the high dose group and 18 of 91 in low dose group were HACA+ at baseline. Mean serum adalimumab concentrations were numerically lower in HACA+ subjects versus HACA– subjects. Summary statistics of serum trough adalimumab concentrations versus time stratified by dose group and HACA status are presented in the Table below. Mean serum adalimumab concentrations were numerically lower in HACA+ subjects versus HACA- subjects. Individual serum adalimumab trough concentrations in HACA+ subjects were generally within the range of those observed in HACA- subjects making the clinical significance of baseline HACA on serum adalimumab concentrations inconclusive.

Table 5 Summary of adalimumab concentrations versus time by dose and baseline HACA status

		Mean ± SD (Min – Max), N_{nmiss}					
		Week					
		0	2	4	16	26	52
Double-blind 40/20 mg eow stayed (N=52)*	HACA- (N=38)	0.026±0.080 (0.000-0.341), 38	17.9±5.59 (8.78-32.3), 37	17.6±6.23 (7.23-33.4), 35	11.2±4.57 (3.58-23.2), 32	10.9±4.44 (4.59-23.6), 31	10.2±5.45 (0.000-26.6), 30
	HACA+ (N=14)	0.000±0.000 (0.000-0.000), 14	11.8±5.40 (3.68-22.4), 14	10.3±5.30 (1.02-19.9), 14	7.31±4.75 (1.12-17.4), 8	8.55±3.19 (5.25-14.9), 7	8.01±5.80 (2.26-20.7), 8
Double-blind 40/20 mg eow to Weekly & open-label (N=33)*	HACA- (N=24)[a]	0.029±0.092 (0.000-0.413), 24	14.8±5.71 (3.83-27.7), 24	13.8±7.91 (3.13-32.2), 23	10.8±10.7 (0.000-43.1), 23	13.7±12.7 (0.000-48.3), 20	18.0±11.3 (0.000-44.7), 16
	HACA+ (N=9)[b]	0.021±0.064 (0.000-0.193), 9	14.1±7.01 (8.08-30.7), 9	12.3±5.77 (5.07-23.1), 9	5.85±4.55 (0.241-14.3), 9	5.45±4.99 (0.434-13.0), 6	8.07±8.50 (0.426-20.3), 6
Double-blind 20/10 mg eow stayed (N=44)[#]	HACA- (N=34)	0.017±0.071 (0.000-0.337), 34	15.2±4.93 (6.83-24.9), 34	13.7±5.23 (2.47-22.9), 32	4.18±2.23 (0.804-10.1), 26	3.81±2.40 (0.000-8.33), 28	3.77±2.04 (0.000-7.62), 25
	HACA+ (N=10)	0.000±0.000 (0.000-0.000), 10	12.2±3.76 (6.61-18.0), 10	9.01±7.45 (0.735-22.8),10	2.64±3.19 (0.000-7.26), 4	1.95±3.36 (0.000-5.83), 3	1.99±3.45 (0.000-5.98), 3
Double-blind 20/10 mg eow to Weekly & open-label (N=46)	HACA- N=38)[c]	0.013±0.038 (0.000-0.164), 37	15.7±6.02 (7.13-30.4), 38	13.8±6.94 (0.868-29.6), 36	4.69±4.15 (0.000-18.2), 37	5.72±4.93 (0.000-21.0), 31	8.27±4.68 (0.000-17.2), 22
	HACA+ (N=8)[d]	0.000±0.000 (0.000-0.000), 8	10.5±6.39 (3.22-22.7), 8	9.72±7.19 (3.08-23.3), 8	3.39±3.64 (0.000-11.5), 8	4.41±4.95 (0.000-14.2), 7	6.33±3.05 (3.48-11.3), 7

Nnmiss = Number of non-missing observations; * Subjects did not have HACA results in double-blind high dose 40/20 mg eow treatment group. Subjects did not have HACA results in double-blind low dose 20/10 mg eow treatment group.
a Median (range) week of dose escalation in double-blind = 18 (12-48) weeks and median (range) week of switching to open-label = 27 (20-46) weeks. Among the 24 subjects dose escalated to weekly, 6 of them switched to open-label.
b Median (range) week of dose escalation in double-blind = 22 (12-42) weeks and median (range) week of switching to open-label = 37 (28-47) weeks. Among the 9 subjects dose escalated to weekly, 4 of them switched to open-label.
c Median (range) week of dose escalation in double-blind = 18 (12-48) weeks and median (range) week of switching to open-label = 26 (20-48) weeks. Among the 38 subjects dose escalated to weekly, 13 of them switched to open-label.
d Median (range) week of dose escalation in double-blind = 21 (12-32) weeks and median (range) week of switching to open-label = 43 (22-45) weeks. Among the 8 subjects dose escalated to weekly, 3 of them switched to open-label.

The number and percentage of subjects who achieved clinical remission per PCDAI score in Study M06-806 stratified by baseline HACA status were presented. The rate of clinical response and the rate of remission as assessed based on paediatric CDAI score were higher in the infliximab-naïve group than the infliximab-experienced group. However, in the infliximab-experienced group, the rate of clinical remission was comparable or even numerically higher in HACA+ subjects than in HACA– subjects. Overall, these results suggested that the presence of HACA had no significant effect on the efficacy, and the trend of slightly lower adalimumab concentrations in the presence of HACA was not clinically meaningful. However, the numbers are too small to draw definite conclusions.

Table 6 Summary of subjects with clinical remission in PCDAI at Week 26 by prior infliximab use and HACA status at baseline (Non-responder imputation- NRI)

	Number and Percent of Subjects with Remission Per Mayo Score n/N (%)		
	Infliximab Experienced/HACA+	Infliximab Experienced/HACA-	Infliximab Naïve/HACA-
Double-Blind High Dose 40/20 mg eow	3/21 (14.3%)	3/20 (15.0%)	29/51 (56.9%)
Double-Blind Low Dose 20/10 mg eow	4/17 (23.5%)	4/23 (17.4%)	19/54 (35.2%)

The effects of concomitantly-administered immunosuppressants (IMM) on the PK of adalimumab were evaluated. For paediatric subjects with CD in Study M06-806, the median adalimumab clearance (CL/F; post-hoc estimates) values were similar for subjects with IMMs (AZA and MTX, 13.36 mL/h) and those without IMMs (13.54 mL/h). In adults, following longer-term treatment with adalimumab (Study M02-433), neither AZA nor 6-mercaptopurine (6-MP) had statistically significant effects on adalimumab CL/F (P = 0.2135 and 0.0913, respectively). The numbers of subjects on MTX were too small to make conclusions regarding its effects on adalimumab clearance.

Overall, six (6/182, 3.3%) subjects were identified as AAA+ during the study. Two of the AAA+ subjects (2/87, 2.3%) were in the high dose group and they were infliximab naïve and HACA-. Four of the AAA+ subjects (4/91, 4.4%) were randomized to the low dose group. These 4 subjects had prior infliximab experience including two subjects who had measurable HACA at baseline. Among the 43 HACA+ subjects, 2 of them became AAA+ (4.65%, 2/43). These two AAA+ subjects were not on immunosuppressants. Among the 136 HACA- subjects, 4 of them were AAA+ (2.94%, 4/136). Two AAA+ subjects were on immunosuppressants and 2 of the AAA+ subjects were not.

The individual serum adalimumab concentrations, remission status at Week 26 and the concomitant use of immunosuppressants are listed in the Table below. Two of the 6 AAA+ subjects were on a concomitant MTX. Five of the 6 AAA+ subjects had serum concentrations declined to below the limit of detection of the assay during maintenance phase. The 6th subject early terminated the study with serum adalimumab concentration below the limit of detection. There were 2 subjects who achieved remission at Week 26 whereas 4 subjects did not.

An overview of the number and percentage of subjects with adverse events (AEs) stratified by AAA status and the double-blind dose group in Study M06-806. The percentage of AE was fairly comparable between AAA+ and AAA– subjects. No serious infections, malignancy, demyelinating disease AE or death was observed in subjects who developed AAA.

Table 7 Individual adalimumab concentrations (µg/mL), remission status and concomitant use of immunosuppressants for AAA positive subjects

Treatment Group	Week							Week Became AAA+	Remission at Week 26 (NRI)	Remission at Week 26 (LOCF)	Use of Immuno-suppressants
	0	2	4	16	26	52	ET				
Low dose 20/10 mg eow	0	16.7	0.735	NR	NR	NR	0	ET	NA	No	No
	0	10.3	0.868	0	0	0	NR	16	Yes	Yes	Yes
	0	14.7	5.68	0	NR	NR	0	16	NA	No	No
	0	13.6	5.02	0	0	0	NR	52	Yes	Yes	No
High dose 40/20 mg eow	0	7.24	9.36	0	2.92	9.24	NR	16	No	Yes	No
	0	16.8	3.5	0	0	0	NR	16	No	No	Yes

ET = early termination; NRI = Non responder imputation; LOCF = Last observation carry forward; NA = not applicable; NR = No result. Immunosuppressants = methotrexate, 6-mercaptopurine, Azathioprine.
* Subjects early terminated the study before Week 26 due to withdrawn consent and lack of efficacy, respectively.

1.2.1.1.3. Comparison and analyses of results across studies

Induction regimen

The PK of adalimumab during the 4-week induction period was evaluated in 178 paediatric subjects (Study M06-806) with moderately to severely active CD. In the adult population with moderately to severely active CD, adalimumab PK was evaluated in 1) 159 subjects (Study M04-691) who had previously responded to but stopped responding or was intolerant to infliximab and 2) 71 infliximab-naïve subjects (Study M02-403). The serum adalimumab concentrations in adult and paediatric studies at Week 2 and Week 4 are summarized in Table 8.

Table 8 Summary of serum adalimumab concentrations (µg/mL) in paediatric (study M06-806) and adult subjects with Crohn's Disease (Study M02-403 and Study M04-691) at Week 2 and Week 4

			Mean ± SD (Range), N_{nmiss}	
Study	Dose	Infliximab Use	Week 2	Week 4
M06-806	160/80 mg	No (N = 58)	17.8 ± 5.45 (6.83 – 32.3), 58	17.2 ± 6.39 (3.50 – 33.4), 54
M02-403	160/80 mg	No (N = 71)	12.3 ± 3.68 (6.30 – 23.5), 68	12.6 ± 5.25 (0.00 – 12.2), 67
M06-806	160/80 mg	Yes (N = 59)	15.4 ± 4.96 (6.61 – 30.7), 57	14.0 ± 6.51 (0.735 – 29.6), 56
M04-691	160/80 mg	Yes (N=159)	NA	12.6 ± 6.04 (0.00 – 36.4), 149
M06-806	80/40 mg	No (N = 37)	13.8 ± 5.88 (3.83 – 32.0), 36	11.7 ± 5.80 (1.93 – 32.8), 35
M06-806	80/40 mg	Yes (N = 28)	10.3 ± 4.66 (3.22 – 22.4), 27	7.94 ± 5.33 (0.868 – 20.9), 26
M02-403	80/40 mg	No (N = 71)	5.57 ± 2.42 (0.00 – 12.6), 68	5.65 ± 3.06 (0.00 – 14.8), 65

During the induction phase, the mean trough concentrations of adalimumab in adult, infliximab naïve subjects (Study M02-403) were consistent between 2- and 4-weeks for each of the regimens evaluated and were 5.65 and 12.6 µg/mL for the induction doses of 80 mg/40 mg and 160 mg/80 mg given at Week 0/Week 2, respectively. In infliximab-experienced subjects (Study M04-691), the mean serum adalimumab trough concentrations (12.6 µg/mL) were identical to those observed in infliximab-naïve subjects (Study M02-403, 12.6 µg/mL) after administration of adalimumab 160 mg/80 mg at Week 0/Week 2, respectively. In the paediatric population in Study M06-806, the mean serum adalimumab trough concentrations achieved during the induction phase in infliximab naïve subjects were 11.7 and 17.2 µg/mL for the induction doses of 80 mg/40 mg (body weight <40 kg) and 160 mg/80 mg (body weight ≥40 kg) given at Week 0/Week 2, respectively. Similarly, for infliximab-experienced paediatric subjects, the mean serum adalimumab trough concentrations during the induction phase were 7.94 and 14.0 µg/mL for the induction doses of 80 mg/40 mg (body weight <40 kg) and 160 mg/80 mg (body weight ≥40 kg) given at Week 0/Week 2, respectively. The mean adalimumab trough concentrations (Study M06-806) were higher in infliximab naïve subjects than in infliximab experienced subjects, the ranges of concentrations tended to overlap suggesting no effect of prior infliximab use on serum adalimumab concentrations.

Overall, serum adalimumab trough concentrations in children were numerically higher compared to adult patients during the induction regimen period when taking dose group and prior infliximab use into account.

Maintenance regimen

The PK of adalimumab was evaluated during Week 4 to 52 maintenance regimen in paediatric subjects with moderately to severely active CD (Study M06-806) and during a 52-week maintenance regimen in adult subjects with moderately to severely active CD (Study M02-433). Week 4 of Study M02-403 was the baseline visit for Study M02-433. A comparison of the serum adalimumab concentrations in paediatric subjects (Study M06-806) who were administered adalimumab 40/20 mg (high-dose) and 20/10 mg (low-dose) and adult subjects administered 40 mg(Study M02-433) is shown Figure 1 and Table 9.

Figure 1 **Comparison of Mean (SD) serum adalimumab concentrations in paediatric subjects (Study M06-806) and adult subjects with Crohn's disease (Study M02-433)**

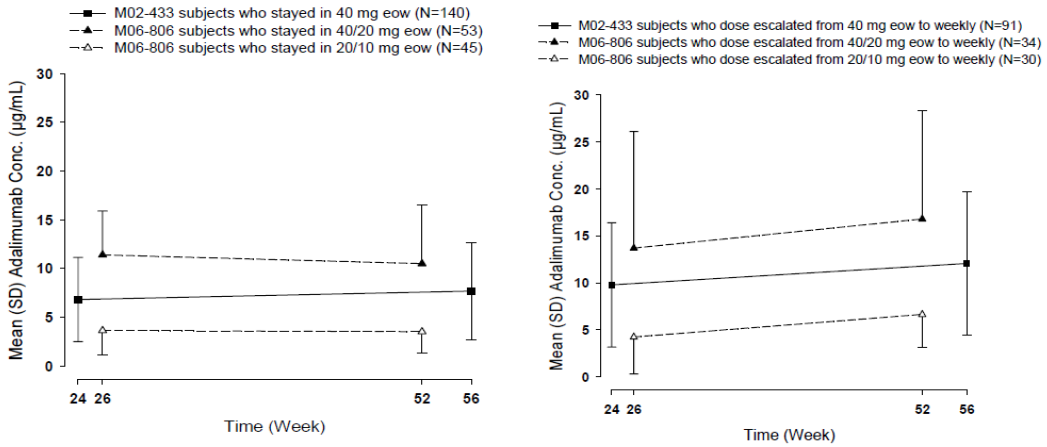


Table 9 **Summary of serum adalimumab concentrations (µg/mL) in paediatric subjects (Study M06-806) and adult subjects (Study M02-433) with Crohn's disease**

		Mean ± SD (Range), N_{nmiss}	
Treatment	**Study**	**Week 24 or Week 26***	**Week 52 or Week 56***
Stayed in Therapy			
Stayed in 40/20 mg eow	M06-806	10.4 ± 4.26 (4.59 – 23.6), 39	9.48 ± 5.61 (0.000 – 26.6), 39
Stayed in 20/10 mg eow	M06-806	3.63 ± 2.50 (0.000 – 8.33), 31	3.51 ± 2.21 (0.000 – 7.62), 29
Stayed in 40 mg eow	M02-433	6.81 ± 4.32 (0.000 – 21.6), 92	7.67 ± 4.97 (0.000 – 21.7), 81
Dose Escalated			
40/20 mg eow to 40/20 mg weekly	M06-806	11.5 ± 11.8 (0.000 – 48.3), 27	15.3 ± 11.4 (0.000 – 44.7), 22
20/10 mg eow to 20/10 mg weekly	M06-806	4.25 ± 3.93 (0.000 – 14.2), 24	6.65 ± 3.49 (2.89 – 15.5), 17
40 mg eow to 40 mg weekly	M02-433	9.79 ± 6.61 (0.00 – 23.58), 72	12.1 ± 7.59 (0.00 – 33.94), 59

Mean serum concentrations of adalimumab in paediatric subjects (Study M06-806) who were administered (and stayed on) adalimumab 40/20 mg eow (high-dose) and 20/10 mg eow (low-dose) with a 40 kg body weight cut-off were 9.5 and 3.5 µg/mL at Week 52, respectively. Mean adalimumab concentrations at Week 52 in paediatric subjects with body weight ≥40 kg were 10.5 µg/mL (40 mg eow) and 3.8 µg/mL (20 mg eow) whereas paediatric subjects with body weight <40 kg had mean serum concentrations of 6.9 µg/mL (20 mg eow) and 2.6 µg/mL (10 mg eow). In the adult population (Study M02-433), the mean serum concentrations were 7.67 µg/mL at Week 56 for subjects that stayed on adalimumab 40 mg eow (DB and OL Phase).

For subjects who dose escalated, the mean serum concentrations of adalimumab at Week 52 were 15.3 µg/mL (40/20 mg, weekly) and 6.7 µg/mL (20/10 mg, weekly) in paediatric subjects and 12.1 µg/mL at Week 56 in the adult population (Study M02-433).

Overall, the mean serum adalimumab trough concentrations achieved during the maintenance phase in paediatric (Study M06-806) patients on 20/10 mg eow (low dose) were lower than those in adult (Study M02-433) patients that stayed on adalimumab 40 mg eow. Conversely, the children receiving 40/20 mg (high dose) during the maintenance phase had higher trough concentrations than adult patients that stayed on adalimumab 40 mg eow. The same order of higher exposure compared to adults for the high dose in children and lower exposure compared to adults for the low in children was observed for the patients that dose escalated to weekly dosing.

1.2.1.1.4. Population pharmacokinetics in paediatric CD

Population PK analyses were performed to estimate adalimumab apparent CL/F and apparent volume of distribution (V2/F) in paediatric subjects from Study M06-806 (N = 189). The final population pharmacokinetic model was a one-compartment model with first order elimination, one exponential term for inter-individual variability on the apparent clearance and a combined residual error model. Statistically significant covariates for clearance included body weight and the presence of AAA, while body weight was a statistically significant covariate for central volume (V2). The median CL/F for all subjects was 11.69 mL/hr. The overall median V2/F was 0.11 L/kg, which indicates that adalimumab mainly resides in the extracellular space. Post-hoc analysis showed that there was 60% difference in the mean CL/F between the first and CL/F were comparable for subjects <13 years of age (10.23 mL/h) compared to subjects ≥ 13 years of age (12.74 mL/h). Median CL/F was about 2.5-fold higher in the AAA+ subjects versus AAA- subjects. However, since only 6 subjects were AAA+ in the current study, the clinical relevance of AAA status can not be determined. Overall, the PK was comparable between adult and paediatric subjects.

In the final population PK model, body weight (WTBS) was a statistically significant covariate on CL/F. In the base model, the estimate of variability (ETA) on clearance was 0.253. Univariate inclusion of WTBS as a covariate led to a reduction in ETA by approximately 11%. This suggested that body weight was a minor factor in determining the total variability in adalimumab pharmacokinetics.

1.2.1.1.5. Population PK/PD analysis in paediatric CD

In addition to the population pharmacokinetic analysis, a pharmacokinetic-pharmacodynamic (PKPD) model was developed in order to describe the relationship between adalimumab exposure and clinical remission, defined as the patient achieving a PCDAI score≤10.

Exposure-Response modeling was conducted using data available from Study M06-806 investigating the relationship of adalimumab exposure with clinical outcome (%Remission). PCDAI scores were used to quantify clinical remission. The drug effect on clinical outcome was incorporated using a maximum inhibitory concentration (Emax) model with the Emax fixed to 1. Two modeling approaches were used to evaluate the exposure-response relationship: 1) Indirect response model and 2) Markov chain model.

Based on the results of goodness-of-fit plots, visual predictive checks and bootstrap evaluation, Markov model described the data more appropriately. The final Markov model included prior infliximab use and concomitant immunosuppressants (AZA, MTX) as covariates on EC50. Based on the Markov analysis, the population estimate of EC50 was 3.41 ng/mL.

1.2.1.1.6. Clinical trial simulations

Clinical trial simulations were conducted to address the following objectives regarding adalimumab treatment of paediatric subjects with CD: 1) to determine if the 160 mg induction dose can be given over multiple days and still provide comparable efficacy as the dose given in a single day; and 2) to determine if the dose-escalation regimen of 40/20 mg eow would provide comparable efficacy as a 20/10 mg ew regimen. Simulations were carried out to determine if the current induction dose regimen could be split over multiple days instead of being given in 1 day and still achieve similar clinical remission. The standard induction dose regimen consisted of a fixed dose of 160 mg (≥40 kg, high-dose) administered at Week 0. The alternative dosing regimen being simulated consisted of the 160 mg induction dose being split over multiple days (i.e., 80 mg on Day 0 and 80 mg on Day 7). This split dosing regimen would provide additional convenience and may be more tolerable for paediatric

subjects. The results predicted that the remission rate would be comparable regardless of whether the induction dose is given in a single day or split over 7 days.

Per the protocol for Study M06-806, subjects who experienced flare during treatment had the option to dose escalate from 20/10 mg eow dosing to 20/10 mg ew dosing starting at Week 12. Simulations were carried out to determine if dose escalation to 40/20 mg eow instead of 20/10 mg ew would provide comparable response as the less frequent dosing may be more acceptable for paediatric subjects. The results indicated that the serum adalimumab concentrations expected following administration of the two regimens during the maintenance period almost completely overlay by Week 52. The remission rate was also similar in both simulated regimens. Thus, the current dose escalation regimen of 20/10 mg ew in the event of flares could be substituted with the more convenient 40/20 mg eow dosing without any loss of serum concentrations and efficacy.

Discussion on pharmacology

Adalimumab PK data were collected in the pivotal maintenance study M06-806. In the current application only trough levels were analysed in Study M06-827 to allow the detection of unexpected changes in clearance, to verify dose-proportionality, to verify the comparability with adult exposure to adalimumab both during induction and maintenance phases and to establish a PK-efficacy relationship. As the PK profile of adalimumab has been characterised in previous submissions this was considered acceptable by the CHMP. Serum trough levels observed from Study M06-806 were compared with results from previous studies in adult CD Study M02-403 for the induction period and compared with results from Study M02-403 and M04-691 for the maintenance period. PK data from study M06-806 were also used for population PK analyses to estimate adalimumab apparent CL/F and apparent volume of distribution (V2/F) in paediatric subjects. In addition a PK/PD analysis was presented to describe the relationship between adalimumab exposure and clinical remission.

Serum adalimumab trough concentrations during the induction phase in adults (Study M02-403 and Study M04-691) showed a similar trend to those in paediatric (Study M06-806) subjects with moderate to severe CD. However a consistently numerically higher serum concentration levels during the induction regimen were observed in children as compared to adults when both dose groups and prior infliximab use are considered. The mean serum adalimumab trough concentrations achieved during the maintenance phase in paediatric subjects (Study M06-806) on 20/10 mg eow (low-dose) were lower than those in adult subjects (Study M02-433) who stayed on adalimumab 40 mg eow. Similar results were observed for paediatric (20/10 mg, weekly) and adult subjects (40 mg, weekly) who dose-escalated from eow to ew dosing. Furthermore, the serum adalimumab trough concentrations in paediatric subjects on 40/20 mg eow (high-dose) were comparable to or lower than those achieved in adult subjects who dose escalated to 40 mg ew. The proposed induction dose in children was 160/80 mg in children ≥40 kg and 80/40 mg in children <40 kg, while the approved recommended dose in adult patients with CD is a 80/40 mg dose. Comparing adalimumab exposure in children and adults at the recommended doses, roughly two- to three-fold higher serum levels will be reached in children compared to adults. In children weighing >40 kg the adalimumab concentration (17.2 µg/ml) is 3-fold higher and in children weighing <40 kg the concentration (11.7 µg/ml) is 2-fold higher than in adults (5.65 µg/ml). Thus the CHMP raised the possibility for supra-therapeutic exposure during the induction phase in children. On the contrary, the recommended maintenance dose of adalimumab in adults is higher than the low maintenance dose of adalimumab in children, leading to a possibility for sub-therapeutic exposure during the maintenance phase with the low dose in children. In particular under the proposed fixed dosing regimen with body weight cut-off at 40 kg, the patients in the lower body weight category seemed to obtain significantly lower trough values than patients in the higher body weight category.

The population PK model identified body weight and positive AAA status as significant covariates on the apparent clearance of adalimumab. However, inclusion of body weight in the model only decreased total inter-individual variability by 11%. The exposure-response model of adalimumab in children with CD may serve as a valuable tool for interpretation and hypothesis generation. However, the disease and the effect of and interactions between treatments with different combinations of drugs are likely to be more complex than the model indicates. Modifications to the dosage regimen as suggested based on the clinical trial simulations would need to be studied in future trials in order to be considered valid. The simulation based evaluation of dosing by body weight raises the concern of under exposure to adalimumab in patients weighing 30 to 40 kg. According to the MAH, the difference in exposure does not lead to any considerable reduction in remission rate. However, as differences between high and low dose groups in observed drop-out and occurrence of dose escalation suggest, under exposure to adalimumab may be a cause of lack of treatment effect and there was a concern that the model does not describe this adequately.

During the procedure, regarding the induction dose of 160/80 mg for those >40 kg and 80/40 for those below <40 kg, the MAH acknowledged that the exposure in children will be unnecessarily high compared to adults. The MAH presented PK and efficacy simulations to evaluate a lower induction dose: 80/40 mg on Weeks 0/2 for subjects ≥40 kg, and 40/20 mg on Weeks 0/2 for subjects <40 kg. The predicted adalimumab trough concentrations at the lower induction dose in paediatric CD subjects were similar to those observed in adult CD subjects (receiving 80/40 mg) and the adalimumab trough concentrations were lower than observed in adult CD subjects who received the induction dose of 160/80 mg. The simulated efficacy result (remission at Week 4) for the low induction dose was comparable to that for the high induction dose. Based on the above, the MAH proposed that subjects receive the lower induction dose (for subjects ≥40 kg: 80 mg at Week 0, followed by 40 mg at Week 2 and for subjects <40 kg: 40 mg at Week 0, followed by 20 mg at Week 2) in the first instance, with the option to receive the initially proposed, higher induction dose (160/80 mg for those ≥40 kg and a dose of 80/40 mg for those <40 kg) if a more rapid response is required, which is similar to the adult CD induction dosing recommendation. This dosing regimen, including the option of the higher induction dose, was endorsed by the CHMP. See efficacy section concerning the discussion on the option of the higher induction dose.

Regarding the maintenance dose there was evidence that patients with a body weight ≥30 kg and <40 kg had a significantly lower (approximately half) exposure to adalimumab during the maintenance phase compared to patients in all other weight groups. This group had also lower observed remission rate at week 26 (see efficacy). These facts implied that the cut-off for weight based dosing was suboptimal for achieving similar exposure in different weight groups. As performed in support for the additional higher induction dose, further analyses were conducted for the maintenance dose in patients with severe paediatric CD. See efficacy section concerning the discussion on the higher maintenance dose.

In patients with previous experience of infliximab and/or with HACA at baseline, exposure to adalimumab was generally lower compared to non-infliximab experienced patients. A measure analysis of variance (ANOVA) was performed on the serum adalimumab trough concentrations at Week 2 through Week 52 to examine the difference between subjects with and without previous infliximab treatment as well as HACA+ and HACA– subjects. The difference in adalimumab trough concentrations between the infliximab experienced and naïve subjects was not statistically significant in any groups ($p \geq 0.1465$) except in the adalimumab high-dose group without dose escalation ($p = 0.0045$). For those subjects in the adalimumab high-dose group without dose escalation, the trough concentrations of adalimumab were lower in infliximab-experienced subjects than those in infliximab-naïve subjects with estimates of 8.04 and 11.54 µg/mL, respectively. The trough adalimumab concentrations of adalimumab in HACA+ subjects were lower than those in HACA– subjects in the high-dose group (7.50

versus 11.25 µg/mL for subjects with dose escalation; 6.80 versus 11.23 µg/mL for subjects without dose escalation). The trough adalimumab concentrations of adalimumab in HACA+ subjects and HACA– subjects were not significantly different in the low-dose group.

Exposure to adalimumab was considerably lower in children with detectable amounts of AAA. Since only 41% of the samples collected for analysis of AAA were actually analysed, the clinical implication of this finding remain uncertain.

Conclusion on pharmacology

With the proposed, studied induction dose the adalimumab concentration in children was considerably higher than in adults treated with 80/40 mg. In infliximab-naïve children weighing ≥40 kg treated with 160/80 mg, the mean adalimumab concentration was approximately 3-fold higher and in infliximab-naïve children weighing <40 kg treated with 80/40 mg the concentration was 2-fold higher than in adults treated with 80/40 mg. Hence, the initially proposed induction dose in children was considered unnecessarily high and additional simulations towards a lower induction dose were conducted as described below. In the maintenance period, compared to adult patients with CD, children receiving the low dose of adalimumab have a lower exposure to adalimumab and children receiving the high dose have a higher exposure than seen in adult patients. This indicated that neither of the dose levels produced an exposure in children that was comparable to the exposure in adult patients. Under the proposed dosing regimen with body weight cut-off at 40 kg, the patients in the lower body weight category obtained significantly lower trough values than patients in the higher body weight category.

Additional simulations were conducted and showed that a lower induction dose (80/40 mg on Weeks 0/2 for subjects ≥40 kg, and 40/20 mg on Weeks 0/2 for subjects <40 kg) would provide comparable PK and efficacy to the induction dose examined in Study M06-806. Therefore the CHMP concluded that the induction dose should be reduced at 80/40 mg, thus achieving generally the same exposure as in adult patients. This modification of the posology is based on the assumption of linear PK in the studied dose range and a similar exposure-response relationship in adults and children. The CHMP considered acceptable to consider that there are no significant differences in the exposure-response relationship between adults and children.

ANOVA analysis shows that in the adalimumab high-dose group without dose escalation, the trough concentrations of adalimumab were significantly lower in infliximab-experienced subjects than in those naïve (p=0.0045). ANOVA analysis shows also that serum adalimumab trough concentrations were significantly lower in HACA+ subjects than in those HACA- (for subjects included in the high-dose group with or without dose escalation). The rate of clinical response and the rate of remission as assessed based on the PCDAI score were higher in the infliximab-naïve group than the infliximab experienced group. However, in the infliximab experienced group, the rate of clinical remission was comparable or even numerically higher in HACA+ subjects than in HACA– subjects. These results suggested that the presence of HACA had no significant effect on the efficacy and the trend of lower adalimumab concentrations in the presence of HACA was not clinically meaningful. However, the numbers are too small to draw definite conclusions. Overall, in patients with previous experience of infliximab and/or with HACA at baseline, exposure to adalimumab was generally lower compared to non-infliximab experienced patients. Exposure to adalimumab was considerably lower in children with detectable amounts of AAA. The number of AAA+ subjects in each treatment group was too small to make definitive conclusion about the impact of immunogenicity on efficacy and safety of adalimumab.

1.2.2. Clinical efficacy

1.2.2.1. Introduction

The assessment of efficacy in the sought indication is based on the pivotal randomised Phase III trial M06-806 and the interim results from one ongoing supportive study M06-807 (cut-off date November 2010).

1.2.2.2. Dose response studies

No dose response studies have been performed to support the present variation. In order to identify the lowest effective dose with regard to potential safety concerns, the low-dose treatment group was added to the protocol. Concerning the adult CD development, the two studies M02-403 and M04-691 were performed in order to evaluate adalimumab as induction therapy for moderate to severe CD and further for evaluation of maintenance, the pivotal Study M02-404 and the extension study Study M02-433 were performed. According to the MAH, the previously performed studies in adult patients with CD (studies M02-403 and M04-691) support the proposed induction dose while the results of studies M02-404 in combination with M02-433 support the proposed maintenance dose. The dosing selected for study M06-806 was further based on population PK modelling of serum adalimumab concentration data from paediatric subjects with juvenile idiopathic arthritis.

1.2.2.3. Main study

Study M06-806

A multicenter, double-blind study to evaluate the efficacy, safety and pharmacokinetics of the human anti-TNF monoclonal antibody adalimumab in paediatric subjects with moderate to severe Crohn's disease.

Methods

- **Study participants**

Paediatric patients with moderate to severe CD (PCDAI >30), with confirmed CD by endoscopic or radiological evaluation. The patients had failed previous conventional therapy. Patients that previously had been treated with infliximab should have lost response or had discontinued the treatment due to intolerance.

The main inclusion criteria were:

• Males and females between the ages of 6 and 17 inclusive, prior to baseline dosing.

• Subjects with a diagnosis of CD for greater than 12 weeks prior to screening, confirmed by endoscopy or radiologic evaluation.

• PCDAI >30 despite concurrent treatment with an oral corticosteroid, and/or AZA or 6-MP or MTX as defined below:

- Oral corticosteroid – prednisone ≥10 mg/day or equivalent, but not exceeding 40 mg, with a stable dose for at least 2 weeks prior to baseline.

- AZA or 6-MP - AZA dose of ≥1.5 mg/kg/day or 6-MP dose of ≥1 mg/kg/day rounded to the nearest available tablet formulation, or a dose that was the highest tolerated for the subject, in the opinion of the investigator for at least 8 weeks prior to baseline with a stable dose for at least 4 weeks prior to baseline.

- MTX dose of ≥5 mg once ew, either SC, intramuscularly (IM), or orally for subjects whose bw was ≥ 20 kg, or a dose that was the highest tolerated for the subject, in the opinion of the investigator (for example due to leucopoenia, elevated liver enzymes, nausea, etc.) for at least 8 weeks prior to baseline with a stable dose for at least 4 weeks prior to baseline.

- MTX dose of 0.2 mg/kg, up to 5 mg, once ew, either SC, IM, or orally for subjects whose BW was <20 kg, or a dose that is the highest tolerated for the subject, in the opinion of the investigator (for example, due to leucopoenia, elevated liver enzymes, nausea, etc.) for at least 8 weeks prior to baseline with a stable dose for at least 4 weeks prior to baseline.

- Concurrent therapy not required for subjects who within the past 2 years in the opinion of the investigator had not responded to or could not tolerate systemic corticosteroids, AZA, 6-MP, or MTX as defined below:

  ○ Corticosteroids:

    - Failed to successfully respond to corticosteroids, or

    - Medical complications and/or AEs from corticosteroids that, in the judgment of their physician, precluded their use (e.g. psychosis, uncontrolled diabetes, osteoporosis, or osteonecrosis).

  ○ AZA, 6-MP, or MTX:

    - Failed to successfully respond to these drugs, or

    - Medical complications and/or AEs that, in the judgment of their physician, precluded their use (e.g. allergic reaction, pancreatitis, elevated liver enzymes, hepatitis, or leukopenia).

• For subjects who had previously received infliximab, must have had an initial response and then discontinued use due to a loss of response or must have discontinued use due to intolerance to the medication.

<u>The main exclusion criteria were:</u>

- History of cancer or lymphoproliferative disease other than a successfully and completely treated cutaneous squamous cell or basal cell carcinoma or carcinoma–in-situ of the cervix.
- History of listeria, histoplasmosis, chronic or active hepatitis B infection, human immunodeficiency virus (HIV) infection, any immunodeficiency syndrome, central nervous system (CNS) demyelinating disease or active tuberculosis (TB) (receiving treatment or not receiving treatment), severe infections such as sepsis and opportunistic infections.
- Subject with a current diagnosis of ulcerative colitis or indeterminate colitis as determined by the investigator and Medical Monitor.
- Subject with symptomatic known obstructive strictures.
- Subject who had surgical bowel resections within the past 24 weeks of the Baseline visit or planned any resection at any time point while enrolled in the study.
- Subject with an ostomy or ileo-anal pouch (subjects with a previous ileo-rectal anastomosis were not excluded.)
- Subject who had short bowel syndrome as determined by the investigator.
- Subject who previously used infliximab within 8 weeks of baseline.

- Subject who previously used infliximab and had not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction to infliximab.
- Previous treatment with any other anti-TNF agent except infliximab.
- Received previous treatment with adalimumab or previous participation in an adalimumab clinical study.

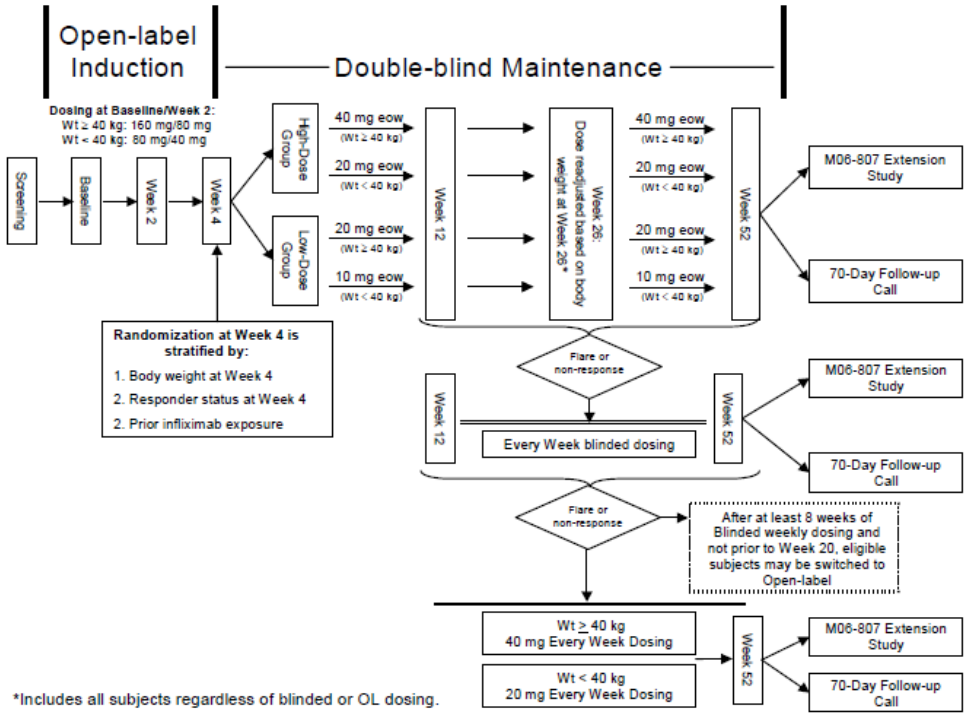
- **Treatments**

The patients received open-labelled induction therapy at weeks 0 and 2. The dosing regimen was dependent on the individual's weight. Patients with a body weight ≥40 kg received 160 and 80 mg and patients <40 kg, 80 and 40 mg at baseline and at week 2. At week 4, patients were randomized 1:1 to a low or high dose maintenance group. They were stratified according to clinical responder status (decrease in PCDAI of ≥15 points compared to baseline), previous infliximab therapy and body weight at Week 4. Patients that were randomized to the high dose group received either 40 mg or 20 mg every other week (eow) depending on weight (≥40/<40 kg). Corresponding figures for the low dose group were 20 mg or 10 mg eow depending on weight (≥40/<40 kg).

The treatment was expected to continue for 48 weeks. At week 26 readjustment were performed of dosing in relation to weight. At week 12 or thereafter, patients who were non-responders (not having a decrease in PCDAI ≥15 points compared to baseline for 2 consecutive visits) or experienced worsening of CD (increase in the PCDAI of ≥15 points from week 4 or PCDAI >30) could be switched to blinded treatment every week on the same dose. Patients continuing to be non-responders or if the disease worsened after 8 week of treatment could thereafter (i.e. at or after week 20) receive open-labelled therapy (20 mg for patients <40 kg and 40 mg for those ≥40 kg).

Patients on concomitant corticosteroids and who achieved clinical response at week 4 were starting a tapering scheme for the corticosteroid, at that same time-point. Concomitant immunosuppressive treatment may be discontinued at or after week 26 for patients in clinical response. The study design is shown in Figure 2.

Figure 2 Schematic study designs



- **Objectives**

The objective of the study was to demonstrate the efficacy and safety of adalimumab and to assess the PK of adalimumab administered by SC injection in paediatric subjects with moderate to severe CD.

- **Outcomes / endpoints**

The primary efficacy endpoint was the proportion of patients being in clinical remission at week 26 (PCDAI score ≤10).

The internal primary analysis was the comparison of high-dose versus low-dose and for external comparison data from the current paediatric study was compared with adult data from Study M02-404, using a conversion factor.

Secondary endpoints included two groups. The first group consisted of ranked hierarchically endpoints that were tested by a step down procedure. The second group contained all non-ranked endpoints. The ranked secondary endpoints were:

- proportion of patients in PCDAI clinical remission at week 52
- proportion of subjects in PCDAI clinical response at week 26.
- proportion of subjects in PCDAI clinical response at week 52.
- proportion of subjects in PCDAI clinical remission at Week 26 who were week 4 responders, for external comparison with modified ITT data from adult Study M02-404.
- PCDAI clinical remission at Week 4, for external comparison with OL induction at week 4 for all subjects in adult Study M02-404.
- proportion of subjects receiving corticosteroids at baseline who have discontinued corticosteroids for at least 90 consecutive days prior to week 26 and are in PCDAI clinical remission at week 26.

- change from baseline in "z-score" for height velocity at week 26.
- change from baseline in total IMPACT III scores at week 26.

- **Sample size**

Assuming an expected clinical remission rate of 20% in the low-dose adalimumab group and 40% in the high-dose adalimumab group, a total sample size of 164 subjects (i.e. 82 subjects per group) was to provide a power of 80% based on a 2-sided chi-square test with a significance level of 0.05. To allow for a pre-randomization dropout rate/withdrawal rate of 10%, approximately 186 subjects were expected to be enrolled (i.e. take the first dose of adalimumab). At least 80 subjects were to be ≥13 years old at baseline.

- **Randomisation**

All subjects who met entry criteria were given the induction regimen and were at Week 4 centrally randomized 1:1 to high-dose or low-dose maintenance treatment. At randomisation subjects were stratified by their Week 4 responder status, prior infliximab exposure and by body weight at Week 4. Clinical response (at Week 4) was defined as decrease in PCDAI ≥15 points from the baseline score.

- **Blinding**

The MAH, the investigator, site study personnel and patients remained blinded to each patient's treatment throughout the study. Unblinding was available in case of medical emergency.

- **Statistical methods**

Efficacy:

The primary internal comparison was between high-dose and low-dose adalimumab with respect to the primary efficacy endpoint, proportion of subjects in clinical remission at week 26. The extended Cochran-Mantel-Haenszel (CMH) test was used, adjusting for Week 4 response status and prior infliximab experience. The treatment–by-strata interaction was tested using Breslow-Day test at 10% significance level. Fisher's exact test was to be used as an alternative method if the CMH test failed. The point estimates for the proportion of subjects who achieved PCDAI clinical remission in each treatment group and the difference in proportions between the groups were provided together with the p-value and 95% CIs for the difference.

For binary efficacy endpoints, missing values were handled using NRI i.e. subjects who prematurely discontinued the study, or who switched from DB eow to ew dosing, or who discontinued DB eow treatment before the scheduled evaluation of clinical remission, or did not have the relevant PCDAI score (and/or CDAI score for subjects ≥13 years of age) were considered in the analysis to have not achieved clinical remission or clinical response. In addition, LOCF was used for both binary and continuous endpoints. For LOCF, the subject's last non-missing value in the study while receiving DB eow study medication was used in the analysis.

Analyses of the primary endpoint was to be performed based on the ITT and PP analysis sets using both LOCF and NRI with the primary analysis being based on ITT using NRI.

Due to the absence of a placebo control group, external comparisons were performed comparing data from this paediatric study to data from the adult CD Study M02-404 (pivotal maintenance study performed in adults). The primary comparisons were based on the 95% CI for the difference in remission rates at Week 26 between the paediatric Study M06-806 and the adult Study M02-404.

Study M06-806 was to be considered successful if the 95% CI for the difference between the adjusted paediatric PCDAI-based remission rate and the Week 26 CDAI-based remission result for Study M02-404 (adalimumab 40 mg eow ITT population) contained zero. A Conversion factor using CDAI and PCDAI data was used to calculate the adjusted PCDAI clinical remission rate in Study M06-806 and allowed for a comparison to the CDAI clinical remission for ITT data in adults Study M02-404.

The major secondary endpoints that were of the binary type were to be analyzed in a similar manner as the primary analysis using the CMH test for internal comparisons. Analysis in the ITT population using NRI was to be considered primary for inferential purpose. Major secondary endpoints that were of the continuous type were to be analyzed as change from baseline, and compared between the 2 treatment groups via analysis of covariance (ANCOVA), with treatment group as a factor and the baseline of the corresponding endpoint (prior infliximab use and week 4 response status as covariates). The estimated treatment mean difference, p-values, and 95% CI for the treatment difference were to be provided. Analysis was conducted in the ITT population, and the Observed Case (OC) analysis considered primary for inference. Based on a hierarchical stepwise closed testing procedure, 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 efficacy endpoints were statistically significant at 0.050.

Safety:

Adverse events, laboratory data, and vital signs were the primary safety parameters in this study. All safety comparisons were performed within the safety population (or the Safety analysis set). Between treatments comparisons were performed only for the TEAEs and SAEs during the DB eow period, using Fisher's exact test. Other safety variables, such as laboratory data and vital signs, were described by statistical characteristics. Shift tables from baseline to DB period were provided to cross-classify subjects from baseline to DB period in each treatment group by the presence of clinically significant laboratory test values.

Results

- Participant flow

A total of 192 subjects received at least one dose of adalimumab and participated in the 4-week OL induction period of the study. Of these, 188 subjects participated in the DB Maintenance period. A greater proportion of subjects in the high-dose treatment group (71.0%) who entered the maintenance period completed the study compared to the proportion of subjects in the low-dose treatment group (61.1%). A lower proportion of subjects in the high-dose treatment group reported lack of efficacy as a primary reason for discontinuation of the maintenance period compared with subjects in the low-dose treatment group.

Figure 3 Participant flow

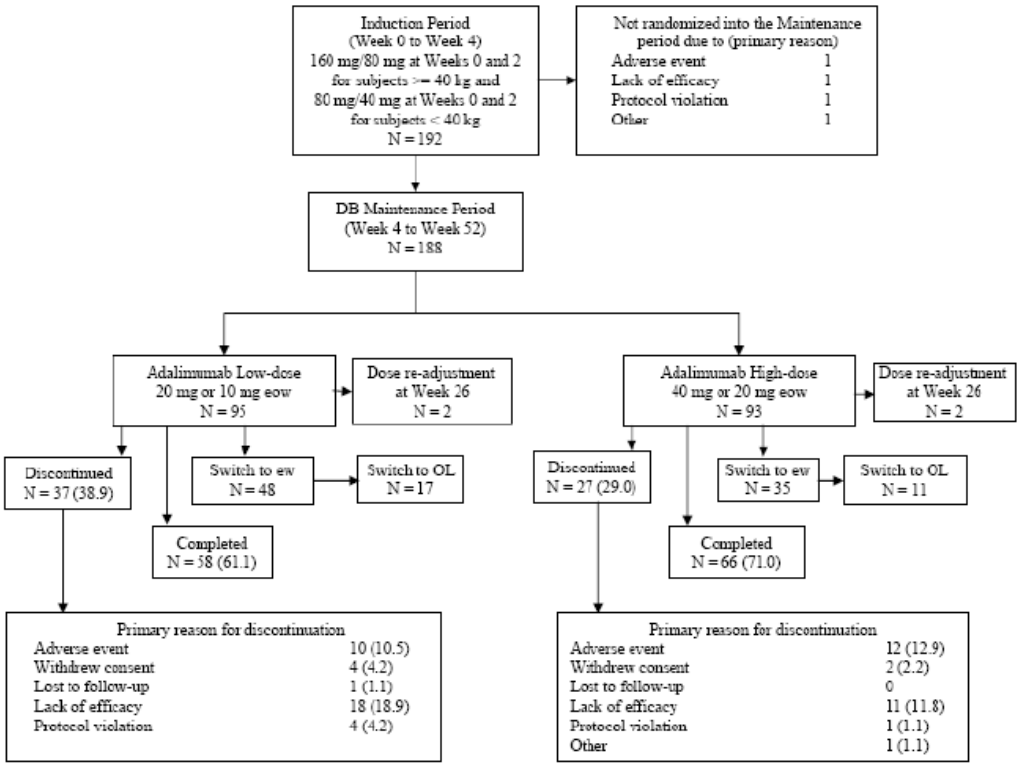


Table 10 Number of patients who completed weeks 26 and 52 (ITT)

	N/n (%) of Subjects	
Completed Visit Treatment	Low-Dose Adalimumab 20 mg or 10 mg eow	High-Dose Adalimumab 40 mg or 20 mg eow
Week 26	N = 77	N = 75
on DB eow	49 (63.6)	55 (73.3)
on DB ew	19 (24.7)	17 (22.7)
on OL ew	9 (11.7)	3 (4.0)
Week 52[a]	N = 58	N = 66
on DB eow	30 (51.7)	41 (62.1)
on DB ew	16 (27.6)	18 (27.3)
on OL ew	12 (20.7)	7 (10.6)

Among subjects who completed Week 26, a greater proportion of subjects in the high-dose treatment group were on DB eow at Week 26 compared to the proportion of subjects in the low-dose treatment groups. A greater proportion of subjects completed Week 26 on OL ew in the low-dose treatment group compared to the high-dose group. Among subjects who completed Week 52, a greater proportion of subjects in the high-dose group were on DB eow compared to the low-dose group. A greater proportion of subjects in the low-dose group who completed Week 52 were on OL ew adalimumab compared to the high-dose group. Per Protocol results were similar.

- **Conduct of the study**

There were 5 protocol amendments. The main purpose of amendment 1 was to clarify procedure and safety issues and to update the exclusion criteria. Amendment 2 concerned update and clarifications of withdrawal, inclusion & exclusion criteria. Additional clarifications regarding withdrawal of patients with flares and on exclusion criteria were made for a country specific amendment. In amendment 3, update in accordance with the country specific amendment was performed and also an update regarding the

management of patients with a positive *Clostridium difficile* stool assay. Amendment 4 concerned stopping rules and a clarification regarding temporary suspension of enrolment. Further, a number of updates were introduce to address feedback from the FDA and these concerned e.g. primary endpoint will be analyzed and compared with externally (adult CD data from study M02-404), change of order of secondary endpoints, comparisons performed between the paediatric and adult populations also for a secondary endpoint. A number of updates were included in amendment 5. The major issues were clarifications regarding the external comparisons using adult CD data that should be performed for the primary and some of the major secondary endpoints.

- **Baseline data**

The majority of subjects were male, white, and ≥13 years old. There were no statistically significant differences observed between the treatment groups. Similar results were observed for the PP and Safety analysis sets.

Table 11 Demographic characteristics (ITT)

Demographic Characteristic	Low-Dose Adalimumab 20 mg or 10 mg eow N = 95	High-Dose Adalimumab 40 mg or 20 mg eow N = 93	All Adalimumab N = 188	*P* value
Sex, n (%)				0.883[b]
Male	54 (56.8)	51 (54.8)	105 (55.9)	
Female	41 (43.2)	42 (45.2)	83 (44.1)	
Race, n (%)				0.656[b]
White	85 (89.5)	81 (87.1)	166 (88.3)	
Black	6 (6.3)	5 (5.4)	11 (5.9)	
Asian	0	3 (3.2)	3 (1.6)	
American Indian/Alaska Native	0	0	0	
Native Hawaiian or other Pacific Islander	0	0	0	
Multi-race	2 (2.1)	1 (1.1)	3 (1.6)	
Other	2 (2.1)	3 (3.2)	5 (2.7)	
Ethnicity, n (%)				1.000[b]
Hispanic or Latino	1 (1.1)	1 (1.1)	2 (1.1)	
No ethnicity	94 (98.9)	92 (98.9)	186 (98.9)	
Age (years), n (%)				0.649[b]
< 13 years	35 (36.8)	31 (33.3)	66 (35.1)	
≥ 13 years	60 (63.2)	62 (66.7)	122 (64.9)	
Age (years)				0.636[a]
Mean ± SD	13.5 ± 2.47	13.7 ± 2.52	13.6 ± 2.49	
Median (range)	14.0 (6 to 17)	14.0 (7 to 17)	14.0 (6 to 17)	
Weight (kg), n (%)				
< 40 kg	35 (36.8)	32 (34.4)	67 (35.6)	0.762[b]
≥ 40 kg	60 (63.2)	61 (65.6)	121 (64.4)	
Weight (kg)				0.404[a]
Mean ± SD	44.4 ± 13.96	46.3 ± 16.79	45.3 ± 15.41	
Median (range)	43.0 (19 to 81)	44.0 (19 to 120)	43.0 (19 to 120)	
BMI (kg/m^2)				0.266[a]
Mean ± SD	18.20 ± 3.500	18.88 ± 4.836	18.54 ± 4.217	
Median (range)	17.31 (12.8 to 30.5)	18.31 (13.5 to 43.5)	17.85 (12.8 to 43.5)	
Height (cm)				0.921[a]
Mean ± SD	154.4 ± 15.29	154.6 ± 14.20	154.5 ± 14.72	
Median (range)	156.0 (106 to 185)	156.0 (111 to 183)	156.0 (106 to 185)	
Nicotine use,[c] n (%)				0.497[b]
User	2 (2.1)	0	2 (1.1)	
Ex-user	1 (1.1)	0	1 (0.5)	
Non-user	92 (96.8)	93 (100)	185 (98.4)	
Alcohol use,[c] n (%)				0.719[b]
Drinker	3 (3.2)	4 (4.3)	7 (3.7)	
Ex-drinker	1 (1.1)	1 (1.1)	2 (1.1)	
Non-drinker	91 (95.8)	88 (94.6)	179 (95.2)	

BMI = body mass index; eow = every other week; ITT = intent-to-treat; SD = standard deviation
a. The *P* value for differences among treatment groups from one-way ANOVA.
b. The *P* value is based on Fisher's exact test to compare high-dose and low-dose treatment groups.
c. Ex-users and non-users were combined for analysis of nicotine, and ex-drinkers and non-drinkers were combined for analysis of alcohol. A subject may have been a user of one type of nicotine, an ex-user of another type of nicotine, and a non-user of another type of nicotine. A subject is counted in the category closest to user.
Percentages are calculated on non-unknown values. Note: Percentages calculated on non-missing values.

The greatest proportion of subjects at baseline had CD of the colon and ileum. Although a greater proportion of subjects in the low-dose treatment group had CD of the anus/perianal area and jejunum at baseline, this was not clinically significant. Results were similar for PP and safety analysis set data.

Table 12 Crohn's Disease location at baseline (ITT)

	Number (%) of Subjects	
CD Location	Low-Dose Adalimumab 20 mg or 10 mg eow N = 95	High-Dose Adalimumab 40 mg or 20 mg eow N = 93
Anal/perianal	30 (31.6)	24 (25.8)
Colon	77 (81.1)	77 (82.8)
Gastroduodenum	35 (36.8)	32 (34.4)
Ileum	75 (78.9)	70 (75.3)
Jejunum	11 (11.6)	3 (3.2)
Rectum	32 (33.7)	29 (31.2)
Other	10 (10.5)	12 (12.9)

CD = Crohn's disease; eow = every other week; ITT = intent-to-treat.
Note: A subject can have multiple CD locations

There were no differences between the treatment groups concerning draining cutaneous fistulas. There were no major differences between the groups regarding the medical history at baseline. The most commonly reported conditions included anaemia, skin disorders and drug allergies or reactions.

Table 13 Baseline disease activity (ITT)

Parameter	Low-Dose Adalimumab 20 mg or 10 mg eow N = 95	High-Dose Adalimumab 40 mg or 20 mg eow N = 93	All Adalimumab N = 188	*P* value
PCDAI score				0.570[a]
N	95	93	188	
Mean ± SD	40.76 ± 6.774	41.34 ± 7.210	41.05 ± 6.980	
Median (range)	40.00 (30.00 – 62.5)	40.0 (25.00 – 62.5)	40.0 (25.00 – 62.5)	
CDAI score				0.024[a]
N	60	62	122	
Mean ± SD	243.02 ± 73.085	279.31 ± 99.399	261.46 ± 88.979	
Median (range)	245.5 (80 – 432)	263.5 (75 – 470)	254.5 (75 – 470)	
CRP mg/dL				0.553[a]
N	94	92	186	
Mean ± SD	2.24 ± 2.492	2.51 ± 3.544	2.38 ± 3.053	
Median (range)	1.31 (0 – 12.4)	1.16 (0 – 16.8)	1.21 (0 – 16.8)	
CRP (mg/dL), n (%)				0.883[b]
< 1 mg/dL	41 (43.6)	42 (45.7)	83 (44.6)	
≥ 1 mg/dL	53 (56.4)	50 (54.3)	103 (55.4)	
Missing	1	1	2	
ESR				0.090
N	94	91	185	
Mean ± SD	30.29 ± 17.457	35.70 ± 25.142	32.95 ± 21.693	
Median (range)	27.50 (1.0 – 86.0)	30.00 (1.0 – 135.0)	29.00 (1.0 – 135.0)	

ANOVA = analysis of variance; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; SD = standard deviation eow = every other week; ITT = intent-to-treat; PCDAI = Paediatric Crohn's Disease Activity Index; a. The *P* value for differences among treatment groups from one-way ANOVA. b. The *P* value is based on Fisher's exact test to compare high-dose and low-dose treatment groups. Note: Percentages calculated on non-missing values.

No statistically significant differences were observed between treatment groups in mean baseline PCDAI score or CRP. Mean ESR was higher in the high-dose treatment group compared to the low-dose treatment group; however, statistical significance was not observed. The high-dose treatment group had a statistically significantly higher CDAI score at baseline than did the low-dose treatment group.

Results for the PP analysis set were similar. However, for both groups the scores were within the range for moderately active disease (220-450).

Table 14 Concomitant immunosuppressant and systemic corticosteroid use at baseline (ITT)

	Number (%) of Subjects		
	Low-Dose Adalimumab 20 mg or 10 mg eow N = 95	High-Dose Adalimumab 40 mg or 20 mg eow N = 93	All Adalimumab N = 188
With IMM[a]	57 (60.0)	60 (64.5)	117 (62.2)
With IMM[b]	57 (60.0)	60 (64.5)	117 (62.2)
With systemic corticosteroid	38 (40.0)	33 (35.5)	71 (37.8)
Without IMM[b] and without systemic corticosteroid	20 (21.1)	15 (16.1)	35 (18.6)
Without IMM[b] and with systemic corticosteroid	18 (18.9)	18 (19.4)	36 (19.1)
With IMM[b] and without systemic corticosteroid	37 (38.9)	45 (48.4)	82 (43.6)
With IMM[b] and with systemic corticosteroid	20 (21.1)	15 (16.1)	35 (18.6)

Between treatment groups, concomitant IMM and systemic corticosteroid use at baseline was numerically similar. Over half (62.2%) of all subjects reported IMM use at baseline and 37.8% of all subjects reported systemic corticosteroid use at baseline. A total of 18.6% of subjects reported at baseline that they did not take IMMs together with systemic corticosteroids at baseline while 18.6% of subjects reported taking both. More subjects reported taking IMMs without systemic corticosteroids than subjects who reported taking no IMMs with systemic corticosteroids (43.6% versus 19.1%, respectively). The most frequently prior medication taken by at least 20 % of the patients were prednisone, azathioprine, mesalazine and methotrexate.

Table 15 Infliximab history (ITT analysis set)

	Number (%) of Subjects			
	Low-Dose Adalimumab 20 mg or 10 mg eow N = 95	High-Dose Adalimumab 40 mg or 20 mg eow N = 93	All Adalimumab N = 188	*P* value[a]
Prior infliximab use				0.883
Yes	41 (43.2)	42 (45.2)	83 (44.1)	
No	54 (56.8)	51 (54.8)	105 (55.9)	
Initial response to infliximab				0.494
Yes	40 (97.6)	42 (100)	82 (98.8)	
No	1 (2.4)	0	1 (1.2)	
Loss of response to infliximab				1.000
Yes	33 (80.5)	34 (81.0)	67 (80.7)	
No	8 (19.5)	8 (19.0)	16 (19.3)	
Reaction to infliximab				0.817
Yes	13 (31.7)	15 (35.7)	28 (33.7)	
Acute	6 (46.2)	12 (80.0)	18 (64.3)	
Delayed	7 (53.8)	3 (20.0)	10 (35.7)	
No	28 (68.3)	27 (64.3)	55 (66.3)	
Loss of response and reaction				1.000
Yes	7 (17.1)	7 (16.7)	14 (16.9)	
No	34 (82.9)	35 (83.3)	69 (83.1)	

eow = every other week; ITT = intent-to-treat. a. The *P* value is based on Fisher's exact test.
Note: Percentages calculated based on non-missing values.

No statistically significant difference was observed between treatment groups for infliximab history. Approximately 44% of subjects had used infliximab previously. Almost all subjects who previously took infliximab had an initial response, but 80.7% of subjects experienced a loss of response to infliximab.

Approximately one-third (33.7%) of subjects experienced a reaction to infliximab, and 16.9% had both a loss of response and reaction to previous infliximab use. Results were similar for the PP analysis set.

- **Numbers analysed**

The populations analysed were the ITT analysis that included all randomized patients who received at least one dose of DB adalimumab. The PP analysis included all patients in the ITT analysis with no major protocol deviations. The safety analysis – included all patients that received at least one dose of adalimumab.

Table 16 Analysis sets

	Number of Subjects			
	Induction Phase	Maintenance Phase		
Analysis Set	N	Low-Dose Adalimumab 20 mg or 10 mg eow	High-Dose Adalimumab 40 mg or 20 mg eow	All Adalimumab
Intent-to-Treat	188	95	93	188
Per Protocol	178	91	87	178
Safety	192	95	93	192[a]

eow = every other week. a. Four subjects were not randomized into the maintenance period.

- **Outcomes and estimation**

Primary endpoint

The primary endpoint was clinical remission at Week 26, defined as PCDAI score ≤10. For the primary endpoint, external and internal comparisons were performed. The external comparison compared the adjusted PCDAI-based remission rate at Week 26 to the CDAI-based clinical remission in adult maintenance Study M02-404. The purpose of the external comparison was to demonstrate the efficacy of adalimumab in the paediatric population by comparing the paediatric and adult data, because there was no placebo arm in the paediatric study. The internal comparison was between randomized treatment groups (high-dose versus low-dose) by NRI and LOCF for the both ITT and PP analysis sets, and was performed to evaluate dose.

The results of the primary external analysis demonstrated that the low-dose treatment group was efficacious, with rate of clinical remission at Week 26 comparable to that of the adult study based the 95% CI. The results also demonstrated that the high-dose treatment and overall treatment with adalimumab (low-dose and high-dose treatment groups combined) were efficacious, with rate of clinical remission at Week 26 exceeding the remission rate in the adult study based on the lower bound of the 95% CI.

Table 17 External comparison of the proportion of patients in adjusted PCDAI clinical remission at week 26 (NRI, ITT)

Adalimumab	N	Proportion of Subjects in Remission[a]	Difference[b]	95% CI[c]
Study M02-404 (40 mg eow [ITT])	260	33.46	--	--
Study M06-806 Low-Dose	95	44.66	11.20	–0.33, 22.73
Study M06-806 High-Dose	93	46.77	13.31	1.66, 24.96
Study M06-806 Overall	188	46.17	12.71	3.56, 21.86

CI = confidence interval; eow = every other week; ITT = intent-to-treat; NRI = non-responder imputation; PCDAI = Paediatric Crohn's Disease Activity Index. a. For Study M02-404, the proportion of subjects in remission is based on CDAI clinical remission on ITT analysis and for Study M06-806, the proportion of subjects in remission is based on the adjusted PCDAI clinical remission.
b. Difference is between Study M06-806 adalimumab dose group and Study M02-404 (40 mg eow [ITT]). c. The CI is based on normal approximation.

In subjects ≥13 years old, the overall CDAI remission rate in Study M06-806 at Week 26 was 50.8% for all subjects (55.0% of low-dose subjects and 46.8% high-dose subjects) compared to 33.5% for Study M02-404. At Week 52, in subjects ≥13 years old the overall CDAI clinical remission rate was 36.1% (35.0% of low-dose subjects and 37.1% of high-dose subjects) compared to 29.2% for Study M02-404. The proportions of subjects ≥13 years old in CDAI clinical remission at Week 26 and at Week 52 and their comparison to Study M02-404 demonstrated the efficacy of adalimumab in this paediatric population as well.

Table 18 External comparisons: proportions of subjects ≥13 years of age at baseline in CDAI remission at Week 26 and at Week 52 – NRI (Study M06-806, ITT)

Adalimumab	N	Proportion of Subjects in CDAI Remission (%)	Difference[a]	95% CI[b]
CDAI Remission at Week 26				
Study M02-404 (40 mg eow [ITT])	260	33.46	--	--
Study M06-806 Low-Dose	60	55.00	21.54	7.71, 35.37
Study M06-806 High-Dose	62	46.77	13.31	–0.37, 26.99
Study M06-806 Overall	122	50.82	17.36	6.79, 27.92
CDAI Remission at Week 52[c]				
Study M02-404 (40 mg eow [ITT])	260	29.23	--	--
Study M06-806 Low-Dose	60	35.00	5.77	–7.51, 19.04
Study M06-806 High-Dose	62	37.10	7.87	–5.37, 21.10
Study M06-806 Overall	122	36.07	6.83	–3.32, 16.99

CDAI = Crohn's Disease Activity Index; eow = every other week; ITT = intent-to-treat; NRI = non-responder Imputation. a. Difference is between Study M06-806 adalimumab dose group and Study M02-404 (40 mg eow [ITT]). Subjects in Study M06-806 were ≥ 13 years of age. b. The CI is based on normal approximation. c. Week 52 in Study M06-806 was compared to Week 56 in Study M02-404.

Internal comparison of PCDAI clinical remission at Week 26 between the low-dose and the high-dose treatment groups (ITT analysis set) demonstrated that a greater proportion of subjects in the high-dose treatment group achieved PCDAI clinical remission at Week 26 compared with the low-dose treatment group, although the difference between the treatment groups did not reach statistical significance (*P* = 0.075). Results for ITT LOCF and PP analysis were similar. The proportions of subjects in PCDAI clinical remission at Week 26 were higher for those subjects without prior infliximab use with a statistically significant difference (ITT overall comparison *P* = 0.026) in favor of the high-dose treatment group compared to the low-dose treatment group (56.9% versus 35.2%, respectively).

Table 19 Primary internal comparison of the proportion of patients in PCDAI clinical remission at week 26 (NRI, ITT)

Prior Infliximab Use	Week 4 Response Status	Adalimumab Low-Dose 20 mg or 10 mg eow n/N (%)	Adalimumab High-Dose 40 mg or 20 mg eow n/N (%)	All Adalimumab n/N (%)	Difference[a]	95% CI[b]	*P* value
Yes	Total	8/41 (19.5)	7/42 (16.7)	15/83 (18.1)	–2.85	–19.40, 13.71	0.736[c]
	Yes	7/32 (21.9)	6/32 (18.8)	13/64 (20.3)	--	--	--
	No	1/9 (11.1)	1/10 (10.0)	2/19 (10.5)	--	--	--
No	Total	19/54 (35.2)	29/51 (56.9)	48/105 (45.7)	21.68	3.05, 40.31	0.026[c]
	Yes	18/48 (37.5)	27/43 (62.8)	45/91 (49.5)	--	--	--
	No	1/6 (16.7)	2/8 (25.0)	3/14 (21.4)	--	--	--
Overall		27/95 (28.4)	36/93 (38.7)	63/188 (33.5)	10.29	–3.14, 23.71	0.075[d]

eow = every other week; ITT = intent-to-treat; LOCF = last observation carried forward; NRI = non-responder imputation; PCDAI = Paediatric Crohn's Disease Activity Index; PP = Per Protocol. a. Difference is between the low- and high-dose treatment groups.

b. The CI was based on normal approximation. c. The *P* value is based on the chi-square test (or Fisher's exact test if ≥ 20% of the cells have expected cell count < 5). d. The *P* value is from the CMH test adjusted for prior infliximab use and response status at Week 4. Note: NRI and LOCF were used for missing PCDAI.

Subgroup analyses

Subgroup analyses (NRI) were performed using sex, age, race, baseline weight, CRP, IMM/steroid and AZA/6-MP/MTX use at baseline. In general the proportion of patients in PCDAI clinical remission at Week 26 was larger in the high dose group. Within the low-dose group, a higher rate of PCDAI clinical remission was noted in males and in subjects ≥13 years old. Within each of the low- and high-dose treatment groups, the rate of clinical remission was greater among subjects who weighed ≥40 kg at baseline, and among subjects with CRP <1.0 mg/dL. When weight groups were examined by 10 kg intervals of weight at Week 4 in an additional analysis, the highest rate of PCDAI clinical remission was observed in the ≥70 kg group among subjects in the low-dose group (66.7%) and in the ≥40 kg to <50 kg group among subjects in the high-dose group (48.3%). However, the number of subjects in the pertinent subgroups was small. By analysis of IMM/steroid use at baseline, the greatest proportion of subjects overall who achieved PCDAI clinical remission at Week 26 were those who had previously taken IMM only at baseline. LOCF analysis demonstrated similar results.

Table 20 Subgroup analysis of the proportion of patients in PCDAI clinical remission at week 26 - NRI (ITT Analysis Set)

Subgroup	Adalimumab Low-Dose 20 mg or 10 mg eow n/N (%)	Adalimumab High-Dose 40 mg or 20 mg eow n/N (%)	Adalimumab Overall n/N (%)
Sex			
Male	13/41 (31.7)	17/42 (40.5)	30/83 (36.1)
Female	14/54 (25.9)	19/51 (37.3)	33/105 (31.4)
Age group			
< 13 years	6/35 (17.1)	12/31 (38.7)	18/66 (27.3)
≥ 13 years	21/60 (35.0)	24/62 (38.7)	45/122 (36.9)
Race category			
White	26/85 (30.6)	31/81 (38.3)	57/166 (34.3)
Non-White	1/10 (10.0)	5/12 (41.7)	6/22 (27.3)
Baseline weight category			
< 40 kg	9/35 (25.7)	11/32 (34.4)	20/67 (29.9)
≥ 40 kg	18/60 (30.0)	25/61 (41.0)	43/121 (35.5)
Week 4 weight group in 10 kg intervals (post hoc analysis)			
< 30 kg	4/11 (36.4)	3/11 (27.3)	7/22 (31.8)
≥ 30 kg to < 40 kg	2/20 (10.0)	7/18 (38.9)	9/38 (23.7)
≥ 40 kg to < 50 kg	9/30 (30.0)	14/29 (48.3)	23/59 (39.0)
≥ 50 kg to < 60 kg	6/16 (37.5)	7/17 (41.2)	13/33 (39.4)
≥ 60 kg to < 70 kg	2/12 (16.7)	4/11 (36.4)	6/23 (26.1)
≥ 70 kg	4/6 (66.7)	1/7 (14.3)	5/13 (38.5)
CRP group			
< 1.0 mg/dL	13/41 (31.7)	17/42 (40.5)	30/83 (36.1)
≥ 1.0 mg/dL	14/53 (26.4)	18/50 (36.0)	32/103 (31.1)
Missing	0/1	1/1 (100)	½ (50.0)
IMM/[a]steroid use at Baseline			
IMM only	10/37 (27.0)	22/45 (48.9)	32/82 (39.0)
IMM and steroid	6/20 (30.0)	4/15 (26.7)	10/35 (28.6)
Steroid only	5/18 (27.8)	7/18 (38.9)	12/36 (33.3)
No IMM or steroid	6/20 (30.0)	3/15 (20.0)	9/35 (25.7)
AZA/6-MP/MTX use at Baseline			
Yes	16/57 (28.1)	26/60 (43.3)	42/117 (35.9)
No	11/38 (28.9)	10/33 (30.3)	21/71 (29.6)

6-MP = 6-mercaptopurine, AZA = azathioprine, CRP = C-reactive protein; eow = every other week; IMM = immunosuppressant; ITT = intent-to-treat; MTX = methotrexate; NRI = non-responder imputation; PCDAI = Paediatric Crohn's Disease Activity Index

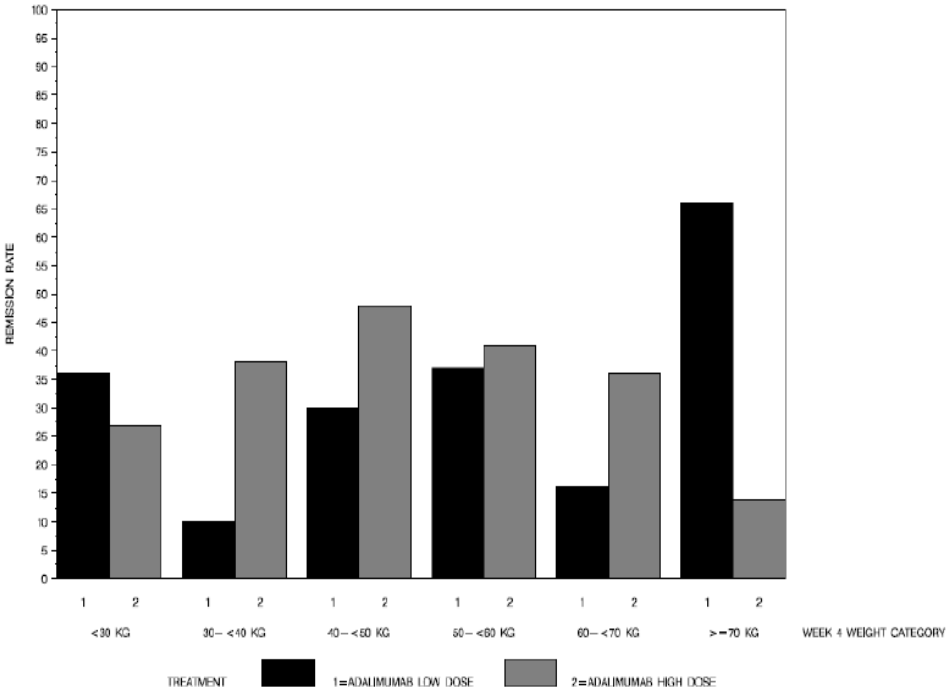
a. IMM use is defined according to the project convention for adalimumab studies. This includes medications with generic names of azathioprine, mercaptopurine, methotrexate, thioguanine, ciclosporin, or tacrolimus. Note, no subject took thioguanine, ciclosporin, or tacrolimus at baseline.

Note: Non-responder imputation was used for missing PCDAI.

PCDAI clinical remission by dose group and Week 4 weight in intervals of 10 kg is shown in Figure 4. When weight groups were examined by 10 kg intervals of weight at Week 4, a greater proportion of subjects in the low-dose treatment group who were <30 kg and ≥70 kg achieved PCDAI clinical

remission at Week 26 than subjects in the high-dose group. This trend was reversed for 10 kg weight intervals from ≥30 kg to <70 kg.

Figure 4 PCDAI clinical remission at week 26 by week 4 body weight



Secondary endpoints

Study M06-806 included 8 ranked secondary variables that were tested in hierarchical order.

In general, there were no statistically significant differences between the groups in subgroups with or without prior infliximab treatment for secondary ranked endpoints. However, for the endpoint 3 (PCDAI clinical response at Week 52), there was a statistically significant larger proportion of patients in clinical response in the high dose group compared to the low dose group. Although the difference between groups was not significant, the change from baseline in "z" score for height velocity and in IMPACT III score was statistically significant in both the low-dose and high-dose treatment groups.

A total of 28.2% of all subjects achieved PCDAI clinical remission at Week 52. No statistically significant difference was observed between the dose groups using NRI. Similar results were observed for subjects with prior infliximab use and subjects without prior infliximab use. The proportions of subjects in PCDAI clinical remission at Week 52 were higher for those without prior infliximab use compared to those with infliximab use; however, there were no statistically significant differences observed between treatment groups by with or without prior infliximab use. Similar results were observed for ITT LOCF data.

A total of 53.7% of all subjects achieved PCDAI clinical response (decrease from baseline in PCDAI score ≥15 points) at Week 26. No statistically significant difference was observed between the two dose groups using NRI. However, in an additional analysis by Week 4 response status and prior infliximab use, Week 4 responders with prior infliximab use in the high-dose group had a statistically significantly higher response rate at Week 26 (56.3%) compared to that of the low-dose group (31.1%) (P = 0.044). Results from the ITT LOCF analysis were similar to the overall results. A greater proportion of infliximab-naïve subjects were in PCDAI response at Week 26 compared to those with

prior infliximab use; however, there were no statistically significant differences observed between treatment groups by with or without prior infliximab use.

A total of 35.1% of all subjects achieved PCDAI clinical response at Week 52. A statistically significantly greater proportion of subjects in the high-dose treatment group (41.9%) achieved PCDAI clinical response at Week 52 than did subjects in the low-dose treatment group (28.4%) using NRI. Results for ITT LOCF data did not yield a statistically significant difference between treatment groups. For subjects without prior infliximab use, the proportions of subjects in PCDAI clinical response at Week 52 demonstrated a statistically significant difference (p = 0.026) in favor of the high-dose treatment group. Among Week 4 responders without prior infliximab use, a greater proportion of subjects in the high-dose treatment group achieved clinical response at Week 52 compared to the low-dose treatment group (P = 0.018).

Table 21 Summary of results of ranked secondary endpoints (ITT, NRI and LOCF)

	Number (%) of Subjects		
Ranked Secondary Endpoint[a]	**Low-Dose N = 95**	**High-Dose N = 93**	***P* value[b,c]**
1. PCDAI clinical remission at Week 52	22 (23.2)	31 (33.3)	0.100
2. PCDAI clinical response at Week 26	46 (48.4)	55 (59.1)	0.073
3. PCDAI clinical response at Week 52	27 (28.4)	39 (41.9)	0.038
	M06-806	**M02-404 mITT[d] Set N = 172**	
	N **%**	**%**	**95% CI[e]**
4. PCDAI clinical remission at Week 26 for subjects who were responders at Week 4[f]		39.53	
Overall	155 52.02		1.75, 23.22
High-Dose	75 54.00		1.03, 27.90
Low-Dose	80 49.34		–3.36, 22.98
	M06-806 N = 192	**M02-404 Overall N = 854**	
5. PCDAI clinical remission at Week 4[f]	55.63	25.29	22.73, 37.95
	Low-Dose N = 38	**High-Dose N = 33**	***P* value[b,c]**
6. PCDAI clinical remission at Week 26 and discontinued corticosteroids for ≥ 90 days, for subjects using corticosteroids at Baseline	9 (23.7)	10 (30.3)	0.329
7. Change from Baseline in "z"-scores for height velocity at Week 26[h]	2.64 ± 4.142	1.75 ± 5.288	0.481
Within-group *P* value[i]	< 0.001	0.008	
	Mean ± SD		
	Low-Dose N = 90	**High-Dose N = 86**	***P* value[b,g]**
8. Change from Baseline in total IMPACT III scores at Week 26	17.20 ± 20.195	18.33 ± 19.691	0.847
Within-group *P* value[i]	< 0.001	< 0.001	

LOCF = last observation carried forward; mITT = modified intent-to-treat;
PCDAI = Paediatric Crohn's Disease Activity Index
a. Listed in rank order, as indicated by the number preceding each endpoint variable.
b. low-dose versus high-dose is an internal comparison.
c. *P* value is from CMH test adjusted for prior infliximab use and response status at 4 weeks.
d. mITT refers to Week 4 responders in Study M02-404 randomized to 40 mg eow.
e. The CI was based on normal approximation.
f. Adjusted PCDAI; only the percent remission was converted and compared in the external analysis.
g. The *P* value is from ANCOVA model with treatment as a factor, adjusted for the baseline value, and the strata (response status at Week 4 and prior infliximab experience).
h. Z scores were set to zero for a female above 14.5 years of age or a male above 17.5 years of age. Older subjects default to zero for the height velocity score as they are generally done growing and therefore there is no more height velocity.
i. *P* value is from paired t-test for change from baseline within each treatment group

There were no statistically significant differences between the treatment groups for the majority of the non-ranked secondary endpoints.

Clinical remission rates were compared between Study M06-806 and Study M02-404 across the duration of the study (Week 4 for all enrolled subjects and Weeks 26 and 52 for both the ITT and mITT populations). Based on the external comparison, adalimumab treatment in the paediatric population (Study M06-806) resulted in clinical remission rates that were comparable to or exceeded those in the adult population (Study M02-404), as evidenced by 95% CIs that contained zero or whose lower bound was greater than zero at all time points and in all analysis populations.

A total of 48 subjects (50.5%) in the low-dose treatment group and 35 subjects (37.6%) in the high-dose treatment group dose escalated from blinded eow dosing to blinded ew dosing; the difference between groups was not statistically significant. Among subjects who dose escalated, clinically meaningful rates of clinical remission and response were observed at Week 52 (clinical remission: 18.8% [low-dose] and 31.4% [high-dose]; clinical response: 47.9% and 57.1%, respectively). The differences between treatment groups were not statistically significant.

Similar proportions of subjects in the low-dose and high-dose treatment groups successfully discontinued corticosteroid use at Week 26 (65.8% and 84.8%; *P* = 0.066) and Week 52 (60.5% and 69.7%; *p*= 0.420). The rate of discontinuation of IMMs at Week 52 was also similar between the 2 dose groups (29.8% and 30.0%; *P* = 0.983). Among subjects who discontinued corticosteroids or IMMs during the study, no statistically significant differences in PCDAI clinical remission rates between the Low-Dose and High-Dose treatment groups were observed.

Supportive study

Study M06-807

A multi-center, open-label study of the human anti-TNF monoclonal antibody adalimumab to evaluate the efficacy and the long-term safety and tolerability of repeated administration of adalimumab in paediatric subjects with Crohn's disease who have demonstrated a clinical response in the M06-806 study.

Methods

- **Study Participants**

Paediatric patients who enrolled subjects in Study M06-806 participate in the study. At the cut-off date (30 November 2010), 100 patients have been enrolled. Enrolled patients have successfully completed study M06-806 through week 52 .i.e. being responder at any time during the study period and are fulfilling all inclusion criteria and none of the exclusion criteria.

The main inclusion criteria were:

- Patients must have had successfully enrolled in and completed Protocol M06-806 through Week 52.
- Patients must have been a responder at any time point during Study M06-806 (defined as having achieved at least a 15-point reduction in PCDAI from baseline).
- Patients that was judged to be in acceptable medical condition, as determined by the Principal Investigator, based upon results of clinical and laboratory evaluations conducted throughout the preceding CD study, Study M06-806.

The main exclusion criteria were:

- For any reason, the patient was considered by the investigator to be an unsuitable candidate for continuing therapy in the Study M06-807.
- Patients having abnormal laboratory or other test results that in the opinion of the investigator would make the subject unsuitable to participate in this study.
- Patients with a history of cancer or lymphoproliferative disease other than a successfully and completely treated cutaneous squamous cell or basal cell carcinoma or carcinoma in situ of the cervix.
- Patients with a history of listeriosis, histoplasmosis, chronic or active hepatitis B infection, human immunodeficiency virus infection, any immunodeficiency syndrome, CNS demyelinating disease, or active TB (receiving treatment or not receiving treatment). Ongoing severe infections such as sepsis and opportunistic infections were exclusionary.
- Patient with known symptomatic obstructive strictures.
- Patient who was planning surgical bowel resection at any time point while enrolled in the study.
- Patient who had short bowel syndrome as determined by the investigator.
- Patient who was receiving total parenteral nutrition.

- **Treatments**

All patients are receiving OL therapy based on their body weight. For patients that ended the previous study on DB treatment receive 40 mg (≥40kg) or 20 mg (<40kg) eow. Only the higher dose has been used in order not to break the blind in study M06-806. Patients that were enrolled while on OL therapy continued to receive the same dose they were receiving at the week 52 visit of Study M06-806.

From week 8 or after patients with flares (PCDAI increase of ≥15 points compared to the previous visit) will be switched to ew treatment on the same dose. Patients with flares can discontinue the study at any time and patients with increased bw from baseline may receive an increased dose (from week 8).

The study duration will be approximately 5 years. Patients that complete the study or are terminating early will be contacted after 70 days after the last dose of adalimumab to gather information on adverse events.

Concomitant CD related treatments were not supposed to be adjusted until after week 8 (unless the patient's safety was at risk). After week 8 decreases were allowed at the investigators medical judgement. CD related therapies (except for IMM) could also be initiated or re-started.

- **Objectives**

The objective of the study was to evaluate the long-term maintenance of clinical response, safety and tolerability of repeated administration of adalimumab in paediatric subjects with CD who successfully completed study M06-806 through week 52 and who met all of the inclusion and none of the exclusion criteria of this study.

- **Outcomes/endpoints**

Efficacy evaluation for the interim analysis was based on the proportion of patients in clinical response at each visit (PCDAI ≥15 points lower than at baseline of study M06-806). Further efficacy measures were: CDAI scores, IMPACT III scores, WPAI-CD Caregiver, z-score for height velocity, bone x-ray, serological markers of bone metabolism and healthcare resource utilization (unscheduled outpatient visits).

Safety endpoints were: adverse events, physical examination, vital signs and laboratory data were assessed throughout the study.

- **Sample size**

It was expected that approximately 70 % of the patients from study M06-806 would be enrolled.

- **Randomisation**

This ongoing study has an OL design.

- **Statistical methods**

Efficacy:

Summary statistics were to be provided for each visit. An additional summary was to be provided for the last visit, using the LOCF. That is, the subject's last non-missing, post-baseline value (i.e. post-Week 52 Study M06-806 double-blind value) was to be carried forward to the last visit.

Safety:

Treatment-emergent and post-treatment AEs were to be summarized. An overview of TEAEs including AEs of special interest, such as AEs leading to death and AEs leading to premature discontinuation, AEs by preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity were to be summarized.

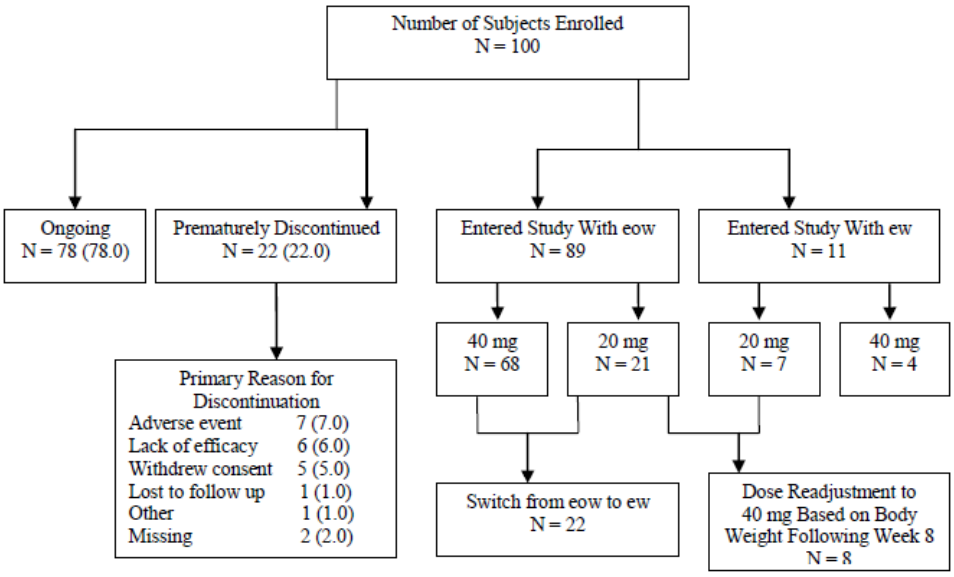
TEAEs were defined as new events that began either on or after the first dose of the study drug and within 70 days after the last dose of the study drug. Adverse events with missing or unknown severity were to be categorized as severe. Adverse events with missing or unknown relationship to study drug were to be categorized as probably related. Adverse events that were reported more than 70 days after last study injection were to be excluded from the summaries.

For laboratory parameters, the normal range was to be used and all values outside the normal range were to be flagged and listed. Additionally, descriptive statistics for the mean change from baseline to minimum value, maximum value and final value during the study were to be calculated. Shift tables were to be provided to cross-classify and tabulate subjects' value from baseline to final value by the presence of clinically significant laboratory results. Each subject's baseline value and final value were to be flagged in reference to the normal range and also categorized as clinically non-significant (Common Toxicity Criteria [CTC] grade <3) or clinically significant (CTC grade ≥3).

Results

- **Participant flow**

Figure 5 **Disposition of patients (Study M06-807), left side: reasons for discontinuations, right side: treatments**



ew = every week; eow = every other week

- **Conduct of the study**

There were 3 amendments. Amendment No 1 concerned an update of the inclusion criteria, amendment of the stopping rules as well as a number of administrative changes. In amendment 2, blood sample collections for adalimumab concentration and AAA assays were added. The stopping criteria for study were changed. Amendment No 3 contained a correction and clarification and also included an interim analysis.

- Baseline data

Table 22 Demographic characteristics (ITT)

Variable	Any Adalimumab N = 100
Sex, n (%)	
Male	52 (52.0)
Female	48 (48.0)
Race, n (%)	
White	93 (93.0)
Black	3 (3.0)
Other	2 (2.0)
Multi-race	2 (2.0)
Ethnicity, n (%)	
Hispanic or Latino	2 (2.0)
No ethnicity	98 (98.0)
Age (years), n (%)	
< 13	35 (35.0)
≥ 13	65 (65.0)
Age (years)	
Mean ± SD	13.5 ± 2.45
Median (range)	14.0 (7.0 to 17.0)
Weight (kg), n (%)	
< 40	38 (38.0)
≥ 40	62 (62.0)
Weight (kg)	
Mean ± SD	43.8 ± 14.33
Median (range)	42.0 (20.0 to 101.0)
BMI (kg/m^2)	
Mean ± SD	18.2 ± 3.86
Median (range)	17.7 (12.8 to 40.0)
Height (cm)	
Mean ± SD	153.2 ± 14.28
Median (range)	155.0 (122.0 to 185.0)
Nicotine use,[a] n (%)	
User	0
Ex-user	1 (1.0)
Non-user	99 (99.0)
Alcohol use,[a] n (%)	
Drinker	3 (3.0)
Ex-drinker	1 (1.0)
Non-drinker	96 (96.0)

BMI = body mass index; ITT = intent-to-treat; SD = standard deviation
a. Ex-users and non-users were combined for analysis of nicotine and ex-drinkers and non-drinkers were combined for analysis of alcohol. A subject may be a user of one type of nicotine, an ex-user of another type of nicotine and a non-user of another type of nicotine. A subject will be counted in the category closest to user. Percentages calculated on non-unknown values. Notes: baseline is defined as the baseline for Study M06-806. Demographic data are from Study M06-806.

Table 23 Baseline disease activity

Parameter	Any Adalimumab N = 100
PCDAI score	
N	100
Mean ± SD	40.10 ± 6.656
Median (range)	40.0 (25.0 to 62.5)
CDAI score[a]	
N	64
Mean ± SD	244.55 ± 85.085
Median (range)	239.5 (75.0 to 470.0)
CRP (mg/dL)	
N	98
Mean ± SD	2.27 ± 2.837
Median (range)	1.14 (0.0 to 14.4)
CRP (mg/dL), n (%)	
< 1	45 (45.9)
≥ 1	53 (54.1)
Missing	2
ESR (mm/HR)	
N	97
Mean ± SD	32.36 ± 21.499
Median (range)	28.0 (1.0 to 135.0)

There were 29 % of the patients that had been treated with infliximab in the past. All but one patient responded initially and the response was later lost in 69 % and 41 % had acute or delayed reaction to infliximab.

- **Numbers analysed**

The safety a analyses were conducted on data from the first dose of adalimumab in Study M06-806 through the data cut-off date (30 November 2010) using the Safety Population (N = 100), which consists of all subjects who received at least 1 dose of adalimumab during Study M06-807.

- **Outcomes and estimation**

For the interim analysis, the efficacy for the ITT population was evaluated by number and percent of subjects with clinical remission, response (as per CDAI and PCDAI scores) and summary of the CDAI and PCDAI scores over time.

With the exception of Week 12 and Week 24, over 65% of subjects achieved PCDAI clinical remission (defined as PCDAI score ≤10) at each visit. A total of 100% (5 subjects) of subjects achieved PCDAI clinical remission at Week 108. At the final visit included in this interim analysis where at least 10% of subjects were observed (Week 96) 83% of subjects achieved clinical remission. A trend toward an increasing proportion of subjects experiencing clinical remission was observed over time.

Table 24 Proportion of patients in PCDAI clinical remission over time (observed case) (ITT)

	n/N (%) of Subjects
Visit in Study M06-807	**Any Adalimumab**
Week 0	67/100 (67.0)
Week 4	65/98 (66.3)
Week 8	67/96 (69.8)
Week 12	60/96 (62.5)
Week 24	59/94 (62.8)
Week 36	51/77 (66.2)
Week 48	39/55 (70.9)
Week 60	35/41 (85.4)
Week 72	20/30 (66.7)
Week 84	15/20 (75.0)
Week 96	10/12 (83.3)
Week 108	5/5 (100)

ITT = intent-to-treat; PCDAI = Paediatric Crohn's Disease Activity Index
Notes: Clinical remission is defined as PCDAI score ≤ 10 points.
Data cutoff was 30 November 2010.

At least 90% of subjects achieved PCDAI clinical response (defined as a subject who had a PCDAI score that was at least 15 points lower than Study M06-806 baseline score) at each visit. At the final visit included in this interim analysis where at least 10% of subjects were observed (Week 96; 11 subjects) 92% of subjects achieved clinical response. A total of 100% (5 subjects) of subjects achieved PCDAI clinical response at Week 108.

Table 25 Proportion of patients in PCDAI clinical response over time (observed case) (ITT)

	n/N (%) of Subjects
Visit in Study M06-807	Any Adalimumab
Week 0	95/100 (95.0)
Week 4	90/98 (91.8)
Week 8	91/96 (94.8)
Week 12	87/96 (90.6)
Week 24	88/94 (93.6)
Week 36	72/77 (93.5)
Week 48	50/55 (90.9)
Week 60	40/41 (97.6)
Week 72	29/30 (96.7)
Week 84	18/20 (90.0)
Week 96	11/12 (91.7)
Week 108	5/5 (100)

ITT = intent-to-treat; PCDAI = Paediatric Crohn's Disease Activity Index
Notes: Clinical response is defined as a decrease from Study M06-806 baseline in PCDAI score of at least 15 points. Data cutoff was 30 November 2010.

There was a mean decrease of 28.6 points in the PCDAI score from Study M06-806 baseline to Study M06-807 Week 108 (LOCF), indicating clinical response per PCDAI score over time (Study M06-807 CSR Table 23). Among subjects who had reached later visits as of the interim analysis cutoff date, there was a sustained mean decrease from baseline in PCDAI score (observed and LOCF) over time.

Among subjects who were ≥13 years of age at Study M06-806 baseline, there was a trend toward an increasing proportion of subjects who experienced CDAI clinical remission (defined as a CDAI score <150) over time (Week 0 to Week 108). Clinical remission rates ranged from 78.6% at Week 84 to 100% at Weeks 60, 72, 96 (the final visit included in the interim analysis where at least 10% of subjects ≥13 years old were observed) and 108.

The proportion of subjects ≥13 years old who achieved clinical response (defined as a decrease from Study M06-806 baseline in CDAI score ≥70 points) ranged from 71.4% at Week 96 to 100% at Week 108.

Discussion on clinical efficacy

The clinical development program for adalimumab in paediatric patients with moderate to severe CD included a pivotal randomized, OL induction and BD maintenance study (Study M06-806) and a supportive long-term, OL extension study (Study M06-807). Study M06-806 is complete and Study M06-807 is currently ongoing. A data cut-off of 30 November 2010 was used for the data included. This program is in line with the CHMP guideline on the development of new medicinal products for the treatment of Crohn's disease CPMP/EWP/2284/99 Rev. 1.

Design and conduct of clinical studies

The pivotal study M06-806 was initiated with a 4-week OL treatment with two induction doses (160/80 mg or 80/40 mg) depending on weight. At week 4 the patients were stratified according to clinical response and previous infliximab treatment and were randomised to the high dose (40 mg or 20 mg eow depending on weight) or the low dose (20 mg or 10 mg eow depending on weight) maintenance treatment group.

The efficacy of adalimumab in Study M06-806 was not assessed against a placebo group due to ethical considerations. This was considered acceptable by the CHMP as a placebo arm would have been not ethically acceptable as infliximab is known to be effective in this indication. Instead, results were evaluated by external comparisons between Study M06-806 and the adult Study M02-404, the pivotal maintenance study performed in adult subjects with moderate to severe CD. Although the study design

could have included a comparator arm, the inclusion of two different dose levels allow for within study comparisons for the assessment of efficacy. In addition a large number of subjects for this type of study in children have been studied.

In general the choice of the primary and secondary endpoints were appropriate according to the CHMP guideline CPMP/EWP/2284/99 Rev. 1. In order to make external comparison feasible between the paediatric population of study M06-806 and the adult population of study M02-404, the MAH introduced the concept of an "adjusted PCDAI" calculated by means of a conversion factor (CF). This approach allowing comparability between PCDAI and CDAI in the two patient populations was considered acceptable. Overall study M06-806 is consistent with the CHMP guideline (CPMP/EWP/2284/99 Rev. 1) with respect to various aspects such as the objectives, patients' population selection, efficacy variables including choice of primary and secondary endpoints, study duration, sample size calculation, blinding, eligibility criteria, evaluation of induction and maintenance treatment in the same study. The study M06-807 was open-labelled, with the main focus to follow safety and maintenance of effect in subjects who had responded during the initial study period. The results from this study are supportive.

Efficacy data and additional analyses

Study M06-806

The primary endpoint was clinical remission at Week 26, defined as PCDAI score ≤10. For the primary endpoint, internal (high/low dose) and external (adults/paediatric CD patients) comparisons were performed. The internal comparison of PCDAI values at Week 26 between the low-dose and the high-dose treatment groups demonstrated that the proportion of subjects who achieved PCDAI clinical remission at Week 26 was not significantly different between treatment groups. In the internal comparison, a larger proportion of patients in the high dose group (38.7%) were in remission as compared to the low dose group (28.4%), the overall difference was 10.29%.

In the subgroup of infliximab naïve patients there was a significantly greater difference between the groups in remission rates i.e. high dose group 29/51 (56.9%) and low dose group 19/54 (35.2%), the difference being approximately 22 % (p = 0.026). For prior infliximab treated patients the remission rates were lower with no difference between treatment groups (19.5% and 16.7% in the low and high dose group, respectively). The observed lower exposure of adalimumab in these patients might account for the inferior response in this group. Furthermore, the vast majority of those patients had lost response to infliximab previously. How many of those who had neutralising antibodies to infliximab is not known, but this group may also contain subjects not responding adequately to inhibition of TNF, and it is thus not unexpected that they will be more difficult to treat adequately with another anti-TNF agent.

The external comparison compared the adjusted PCDAI-based remission rate at Week 26 to the CDAI-based clinical remission in adult maintenance Study M02-404. The results of the primary external analysis demonstrated that the low-dose treatment group was efficacious, with rate of clinical remission at Week 26 comparable to that of the adult study based the 95% CI. The results also demonstrated that the high-dose treatment and overall treatment with adalimumab (low-dose and high-dose treatment groups combined) were efficacious, with rate of clinical remission at Week 26 exceeding the remission rate in the adult study based on the lower bound of the 95% CI with a difference in PCDAI of +13.31 and +12.71, respectively. External comparisons of CDAI clinical remission at Week 26 and at Week 52 for subjects ≥13 years of age at baseline showed a trend towards a greater response to adalimumab at both time point in this paediatric population compared to that of the adult Study M02-404.

For the induction treatment, the proposed induction dose in children was 160/80 mg in children weighing ≥40 kg and 80/40 in mg children weighing <40 kg, while the approved recommended dose in adult patients with CD is the 80/40 mg regime. Exposure in children during the induction phase was estimated to be approximately 2- to 3-fold higher than in adults when comparing the initially proposed paediatric induction doses with the approved adult induction doses of 80/40 mg. As no known differences in exposure-response between children and adults would require a higher exposure in children than in adults to obtain similar response, the CHMP considered that the proposed induction dose in children was unnecessarily high. The MAH acknowledged this and therefore proposed that the induction dose should be reduced by 50%, thus achieving generally the same exposure as in adult patients. This modification of the posology is based on the assumption of linear PK in the studied dose range and a similar exposure-response relationship in adults and children. See section pharmacology for further details. The CHMP considered that there was no significant impact on efficacy of a reduced induction as there are no important differences in the exposure-response relationship between adults and children. Based on the above, the CHMP agreed that subjects receive a lower induction dose (for subject ≥ 40 kg: 80/40 mg at Week 0 and Week 2 respectively and for subject <40 kg: 40/20 mg at Week 0 and Week 2 respectively).

The option of a higher induction dose (160/80 mg for those ≥40 kg and a dose of 80/40 mg for those <40 kg) for those patients who may need a more rapid response was further discussed. The MAH has presented induction data from adults (study M02-403) showing that there is a relationship between exposure and the rate of response/remission. A higher serum concentration of adalimumab was associated with a higher degree of response or remission at week 4. A similar trend was shown for children using data from study M06-806 for both the whole group of children and in the subgroup with more severe disease. Severe disease was defined as a PCDAI score >40 and was based on the median baseline PDCAI score in the study. The efficacy was further demonstrated to be comparable in groups with different body weight presented across body weight tertiles. There were no patient characteristics that could be identified that predicted the need for a higher induction dose but the MAH argued that patients with more severe disease could benefit the most from a rapid response, likewise as the approved recommendation for adults. Further, the treatment will be restricted to children with severe disease and the proposed higher induction doses (160 mg/80 mg or 80 mg/40 mg depending on weight) are the doses that have been evaluated in the pivotal study. Finally, data from adults and children with CD show that higher exposure of adalimumab is associated with an increased rate of response/remission after 4 weeks. The proposed higher induction dose that will be used at the discretion of the clinician has been evaluated in the pivotal study and there were no major safety concerns revealed during the induction period.

To conclude, considering the potential serious safety profile of adalimumab, it is reasonable that the induction doses should generally be as low as possible as mentioned above. At the same time, as a rapid response could be of major importance for the more seriously affected children the option of a higher induction dose is acknowledged by the CHMP. The higher doses evaluated in the study can be used (160/80 mg for those ≥40 kg and a dose of 80/40 mg for those <40 kg). Overall, the proposed dosing regimen for induction therapy is endorsed since exposure in children during induction phase is comparable to adult exposure and these doses have been studied in the paediatric study.

Concerning the maintenance dose, based on the observed exposures adalimumab in children, the possibility of a sub-therapeutic exposure especially with the low dose in children was raised. Additional analyses on data from the children with CD showed that the higher maintenance dose (40 mg/20 mg depending on body weight ≥/<40 kg) was associated with higher response/remission rates at week 52, in particular in the subgroup of children with severe disease defined as baseline PCDAI ≥40. There were no major differences regarding safety between groups of children receiving the high or low adalimumab dose. There was slight increased incidence of infectious AEs noted in the adalimumab high

dose group compared with the low dose group (60.2% versus 49.5%, respectively); however, by E/100 PY analysis, the high-dose treatment group has a lower rate of infections (181 E/100PYs versus 213 E/100 PYs). The MAH's new proposal for the maintenance dose was therefore 40 mg eow for patients ≥40 kg and 20 mg eow for those <40 kg. This implies that the risk of lower exposure and lower efficacy seen with the initially proposed low dose in children ≥30 kg - <40 kg is avoided. Thus, these dose regimens were agreed by the CHMP.

For patients experiencing an insufficient response, the proposal involved an increased dosing to 40 mg ew for children ≥40 kg. This was accepted by the CHMP, as this was evaluated in the paediatric studies and showed a higher response/remission rate. For children <40 kg, it was suggested to increase the dose by giving 40 mg eow, to maintain eow dosing and thereby reducing the number of injections these smaller children would have to take. The CHMP acknowledged the intention to reduce the injections burden in smaller children. However, this proposal involved a different dosing than what was used in the studies: in both the pivotal and the extension studies, non-responders were switched to ew treatment with the same dose as eow. A possible patient benefit by reducing the frequency of injections was not considered sufficient to outweigh the potential safety risk of a higher expected Cmax. Therefore it was concluded that for children <40 kg who are experiencing insufficient response the studied dose of 20 mg ew should be recommended as increased dosing.

The proportion of Week 4 non-responders with response at Weeks 26 and 52 was high (27.3% and 24.2% respectively). However, the proportion of Week 8 and Week 12 non-responders with remission at Week 26 or Week 52 was limited based on a non-escalated dosing regimen. If there is a lack of response or flare at Week 12, this is an appropriate time point to consider dose-escalation. Approximately 50% of subjects who were non-responders had dose-escalated from eow to ew adalimumab. A total of 24.1% subjects who switched from eow to ew dosing due to flare or non-response were in clinical remission at Week 52, which shows the further benefit for non-responders to dose-escalate. Overall, further benefit can be gained non-responders to dose escalate to the high-dose. The majority of subjects in Study M06-806 dose-escalated as early as Week 12 per the study design. Thus dose escalation beyond Week 12 may be of limited value. Continued therapy should be carefully considered in a subject not responding by Week 12, which is clearly stated in the SmPC.

Concerning the secondary endpoints, numerically there were more patients in clinical remission or who showed clinical response in the high dose group as compared with the low dose group. Irrespectively of endpoint (response or remission) and also time point (week 26 or week 52) the difference between the dose groups was approximately 10% i.e. the same magnitude as seen in the primary analysis. Only for the clinical response at week 52 the difference was statistically significant. No claims can hence be made as these endpoints were ranked and tested in hierarchical order (i.e. 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 efficacy endpoints were statistically significant).

During the procedure the MAH clarified that the majority of subjects (36/63 subjects, 57%) receiving adalimumab were in PCDAI clinical remission at Week 26 and maintained remission through Week 52. A similar percentage of subjects who received adalimumab high-dose or low-dose in Study M06-806 were in PCDAI clinical remission at Week 26 and maintained remission through Week 52. Fourteen percent (14%, 17/125 subjects) of subjects who were not in PCDAI clinical remission at Week 26 reached clinical remission at Week 52. A similar number of subjects who received adalimumab high-dose and low-dose in Study M06-806 were not in PCDAI clinical remission at Week 26 but reached remission at Week 52. Per mNRI analysis for subjects who had their dose regimen adjusted due to flare or non-response, a high percentage of subjects in both the adalimumab low-dose and high-dose groups had PCDAI clinical remission at Week 26 and maintained remission through Week 52. Among subjects who were in PCDAI clinical remission at Week 52, approximately one-third of these subjects were not in PCDAI clinical remission at Week 26 for both high-dose and low-dose groups in Study M06-

806, thus a substantial proportion were able to achieve remission at Week 52 with continued therapy. In addition, a total of 24.1% of subjects who switched from eow to ew dosing due to flare or non-response were in clinical remission at Week 52, which shows the benefit for non-responders to dose escalate. A substantial proportion of subjects were in remission at Week 52 irrespective of Week 26 remission status. Thus there was no plateau of effect at Week 26 and therapy should be continued beyond this time point.

For prior infliximab treated and naïve patients in clinical response at week 4, the differences between the treatment groups in remission rates were approximately 9 % and 19 %, respectively at week 52. At week 52, 20 % of patients that had previously been treated with infliximab were in remission (16% and 25 % in the low and high dose group, respectively) and for infliximab-naïve patients the corresponding figure was 36 % (27% and 47% in the low and high dose groups, respectively).

Efficacy results stratified by concomitant baseline therapy (IMM or corticosteroids) supported a better efficacy of high dose adalimumab in patients taking IMM at baseline (i.e. clinical remission at week 26, 43.3% with IMM group and 30.3% without IMM group). IMM use at baseline did not impact clinical efficacy in the low dose adalimumab. Corticosteroids use at baseline did not influence efficacy results in low dose adalimumab group but the non-use at baseline was associated with a better efficacy in high dose adalimumab. In both cases sample sizes in each group are small.

The majority of subjects were able to discontinue systemic corticosteroids during the study. A higher proportion of subjects in the high-dose group were able to discontinue systemic corticosteroid than that in the low-dose group at both Week 26 and Week 52 (i.e. week 26 high dose group 84.8% versus low dose group 69.7%). Of subjects who were on corticosteroids at baseline, 30.3% in the high-dose treatment group and 23.7% in the low-dose treatment group discontinued corticosteroids for ≥90 consecutive days prior to Week 26 and achieved PCDAI clinical remission at Week 26. The proportions of subjects in PCDAI clinical remission at Week 26 who were receiving corticosteroids at baseline and had discontinued corticosteroids for at least 90 days prior to Week 26 were substantially higher for those without prior infliximab use.

Study M06-807

Although the study has an OL design, weakening the clinical relevance of the observed data, the CHMP acknowledged that results showed a large proportion of subjects achieving clinical response and remission as per PCDAI and CDAI scores over time as well as a sustained decrease in PCDAI and CDAI scores over time. These results support a long-term efficacy of adalimumab in this paediatric population. A trend toward an increasing proportion of subjects who experienced PCDAI clinical remission was observed over time (Week 0 to Week 108). Over 62% of subjects achieved PCDAI clinical remission (defined as PCDAI score ≤10) at each visit. At least 90% of subjects achieved PCDAI clinical response (defined as a subject who had a PCDAI score that was at least 15 points lower than Study M06-806 baseline score) at each visit. There was a mean decrease of 28.6 points in the PCDAI score from Study M06-806 baseline to Week 108 (LOCF), indicating clinical response per PCDAI score over time. There was a sustained mean decrease from baseline in PCDAI score over time. A similar proportion of subjects who used concomitant IMMs at Study M06-807 baseline were in PCDAI clinical response and remission over time compared to subjects who did not use IMMs.

Conclusion on clinical efficacy

Treatment of paediatric subjects with adalimumab showed, in the internal comparison, that a larger proportion of patients in the high dose group (38.7%) were in remission as compared to the low dose group (28.4%), the overall difference was 10.29%. In the subgroup of infliximab naïve patients there was a statistically significant difference between the remission rates in the low and high dose group

(observed difference of 22% week 26). There is therefore a clinical benefit of adalimumab in the treatment of paediatric Crohn's disease. The external comparison showed that treatment of paediatric subjects with adalimumab resulted in clinical remission and response rates at Weeks 26 and 52 that were comparable to the results observed in the pivotal study supporting the approved indication of adalimumab for the treatment of moderate to severe CD in adults. In addition, an external comparison of CDAI clinical remission at Week 26 and at Week 52 for subjects ≥13 years of age at baseline demonstrated the comparable or greater efficacy of adalimumab in the paediatric population compared to that of the adult Study M02-404.

The choice of both induction and maintenance dose of adalimumab in children was questioned with a risk of supra-therapeutic exposure during the induction phase and of sub-therapeutic exposure during the maintenance phase. A revised lower induction dose to 80/40 mg at Week 0/2 for patients above 40 kg and 40/20 at Week 0/2 for those below 40 kg was endorsed by the CHMP as the exposure response is considered to be similar in adults and children and it is not motivated to use the initially proposed dose in children giving rise to an absolute 2-3-fold higher exposure than what is approved in adults. Patients with severe disease can in some situations benefit from a rapid response, and thus an option for a higher induction dose, as already approved in adults, is acknowledged. The data supporting the higher induction dose of 160/80 mg at Week 0/2 for patients above 40 kg or 80/40 mg at Week 0/2 for those below 40 kg were robust. The CHMP recognised that allowing for two options for induction provides the clinicians flexibility and allows for the optimization of patient care. This approach is also consistent with adult CD approved recommendations. To reduce the risk of lower exposure and efficacy observed during the maintenance period a revised higher maintenance dose to 40 eow for patients above 40 kg and 20 eow for those below 40 kg was endorsed by the CHMP as data showed that they were associated to higher response/remission rate at week 52. Patients with an insufficient response should be given the option to dose escalate to 40 ew for patients above 40 kg and 20mg ew for those below 40 kg as these studied dose showed a higher response/remission rate.

In Study M06-806, clinical remission and response rates were higher at Week 26 and 52 in anti-TNF-naïve subjects compared with anti-TNF-experienced subjects. Among anti-TNF-experienced subjects, remission and response were also observed and appeared to correlate with clinical response at Week 4.

The data presented demonstrated that adalimumab is a beneficial treatment alternative for the induction and maintenance of clinical remission in paediatric patients with CD who have failed conventional therapy or who are intolerant to or have contraindications for such therapies. Subjects may also have previously lost response or been intolerant to infliximab. Although efficacy was attenuated in subjects with prior infliximab use, effect also observed in the adult, data showed that adalimumab offers an alternative in those paediatric CD patients left with no other pharmacologic treatment options.

Taken together, efficacy data from the pivotal clinical study, supported by the interim results from the ongoing open-label extension study, demonstrate that treatment with adalimumab is an efficacious, treatment for the induction and maintenance of remission in paediatric subjects with severe, active CD who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies.

1.2.3. Clinical safety

1.3. Introduction

The safety of adalimumab in paediatric CD was determined using data from the two clinical studies: Study M06-806, which is complete and Study M06-807 (the OL extension study) which is ongoing. A

data cut-off date of 30 November 2010 has been applied to the ongoing OL extension Study. Safety evaluations were based on assessments of treatment-emergent AEs (TEAEs), physical examination results, vital sign and laboratory data. Safety results were presented for the OL Induction period and the DB Maintenance period of Study M06-806. For the combined analysis of studies M06-806 and M06-807, the following analyses set were presented:

- Any adalimumab set (N = 192): includes all subjects who received at least one dose of adalimumab in Study M06-806 or Study M06-807. This is the primary safety analysis set to evaluate the safety of all subjects who were exposed to any adalimumab.
- Dose escalation set (N = 115): includes all subjects who dose-escalated from eow to ew dosing in Study M06-806 or Study M06-807 or subjects who were in low-dose group at Week 52 in Study M06-806 and switched to higher dose in Study M06-807.
- No dose escalation set (N = 77): includes all subjects who did not have dose-escalation in Study M06-806 or Study M06-807.
- Low dose eow Set (N = 24): includes all subjects who completed Study M06-806 on eow dosing in the low dose group and rolled over to receive higher OL eow dosing in Study M06-807.

1.4. Patient exposure

Across both studies a total of 192 paediatric subjects with CD have been exposed to at least 1 dose of adalimumab as of 30 November 2010, for a cumulative exposure of 258.9 patient-years (PYs). Of these subjects, 115 (59.9%) have >12 months of adalimumab exposure; 91 (47.4%) have >18 months of adalimumab exposure and 8 (4.2%) have >36 months of adalimumab exposure. The median exposure was 434 days. Among subjects who had dose escalation during Study M06-806/ M06-807, the median exposure was 197 days prior to dose escalation and 266 days after the dose escalation. For subjects who did not have dose escalation during Study M06-806/ M06-807, the median exposure was 351 days. Among subjects in the low dose eow set, the median exposure to adalimumab was 635 days.

1.5. Adverse events

Induction period - Study M06-806

During the OL induction period 52.6 % of the patients reported any AEs. The frequency of AEs was slightly higher among subjects receiving the 160/80 mg induction dose than those receiving the 80/40 mg dose (55.3% versus 47.8% respectively). Almost all events were mild or moderate in severity.

Twenty-seven subjects (14.1%) reported an infection. Most infections were common, self-limited and easily medically-managed. Viral upper respiratory tract infections and upper respiratory tract infections were the most frequently reported treatment-emergent infections in the 2 groups combined. Two subjects reported serious infections, but no subjects reported an opportunistic infection or TB. Twenty-two subjects (11.5%) reported an injection site reaction. injection site pain (12 [6.3%]) and injection site reaction (10 [5.2%]) were 2 TEAEs reported frequently (≥5% of subjects). Three subjects experienced hematologic-related AEs, 1 of which was considered possibly related to study drug. One subject experienced an allergic reaction that was considered not related to study drug.

Ten (5.2%) subjects reported one severe AE. The severe TEAEs included defecation urgency, fecal incontinence, gastritis, adverse drug reaction, injection site pain, injection site reaction, pain, headache, and migraine. Severe CD was reported by 3 subjects.

The frequency of possibly or probably related AEs was higher in subjects receiving the 160/80 mg induction dose (23.6% versus 14.5%, respectively). Overall 20.3 % were considered to be at least possibly related to the study drug. The most frequently reported (>1% of subjects) TEAEs possibly related to study drug were injection site pain, injection site reaction, viral respiratory tract infection, and fatigue. One subject prematurely discontinued due to an AE.

Table 26 Proportion of patients with TEAEs by induction regimen – OL induction period (Study M06-806)

	80/40 mg Induction Doses (Subjects < 40 kg at Baseline) N = 69 n (%)	160/80 mg Induction Doses (Subjects ≥ 40 kg at Baseline) N = 123 n (%)
Any adverse event	33 (47.8)	68 (55.3)
At least possibly drug-related[a]	10 (14.5)	29 (23.6)
Severe adverse event	3 (4.3)	7 (5.7)
Serious adverse event	2 (2.9)	4 (3.3)
Leading to discontinuation of study drug	1 (1.4)	0
At least possibly drug-related serious adverse event[a]	0	0
Infectious adverse event	8 (11.6)	19 (15.4)
Serious infections	1 (1.4)	1 (0.8)
Malignancies	0	0
Lymphomas	0	0
Non-melanoma skin cancer (NMSC)	0	0
Malignancies (excluding NMSC and lymphomas)	0	0
Malignancies (including lymphomas, excluding NMSC)	0	0
Injection site reactions	7 (10.1)	15 (12.2)
Opportunistic infections	0	0
Congestive heart failure	0	0
Demyelinating disease	0	0
Hepatic-related adverse events	0	0
Allergic reactions	0	1 (0.8)
Lupus-like syndrome	0	0
Hematologic-related adverse events	1 (1.4)	2 (1.6)
Fatal adverse event	0	0
Deaths[b]	0	0

a. As assessed by the investigator. b. Includes non-treatment-emergent deaths. Note: A TEAE is any AE with an onset date on or after the first induction dose and prior to DB dose and up to 70 days after the last dose of study drug if subject discontinued prematurely from the Induction period. Events with unknown severity are counted as severe. Events with unknown relationship to study drug are counted as drug-related.

Maintenance period - Study M06-806

A greater proportion of subjects in the high-dose treatment group (92.5%) reported at least 1 TEAE compared with the low-dose treatment group (85.3%). The most frequently reported AE in both the low-dose and high-dose treatment groups was Crohn's disease, representing a flare or worsening of the underlying disease. For CD events, the low- and high-dose treatment groups had 30 events (71.6 events/100 PYs) and 23 events (59.1 events/100 PYs), respectively. These events were mild to moderate in intensity in the majority of subjects (21/30 subjects in the low-dose treatment group and 19/23 in the high-dose treatment group). In the low-dose treatment group, the most frequently reported AEs other than CD were headache, nasopharyngitis, upper respiratory tract infection (URI) and vomiting; all other AEs were reported by <10% of subjects. In the high-dose treatment group, headache, URI, pyrexia, and nausea were reported in >10% of subjects. The overall AE profile was generally comparable between the low-dose and high-dose treatment groups. No statistically significant difference was observed between the treatment groups in the proportions of TEAEs. Most subjects experienced TEAEs that were mild to moderate in severity. The proportion of subjects,

approximately 10%, who reported an injection site reaction was similar between treatment groups. Similar proportions of subjects in each treatment group reported hepatic-related TEAEs. The incidence rate of hematologic-related AEs was considerably lower in the low-dose treatment group (10.5 versus 20.3 E/100 PY); additionally, 3 of the 4 subjects in the low-dose treatment group reporting hematologic AEs were taking concomitant azathioprine or 6 mercaptopurine, which have known potential for hematologic effects. Allergic reactions were substantially less frequent in the low-dose treatment group (6.3 versus 14.8 E/100 PY, a difference of approximately 135%). There were no cases of tuberculosis, malignancy, congestive heart failure, demyelinating disease or lupus-like syndrome reported during the DB Maintenance period.

A greater proportion of subjects in the high-dose treatment group reported an infection compared to subjects in the low-dose treatment group (60.2% versus 49.5%, respectively); however, by E/100 PY analysis, the high-dose treatment group has a lower rate of infections (181.1 E/100PYs versus 212.6 E/100 PYs). Most subjects reported an infection that was non-serious. Most infections were common, self-limited, and easily medically-managed. The most frequently reported infections were upper respiratory tract infection and nasopharyngitis. Six subjects in the low-dose and 7 subjects in the high-dose treatment groups weighing <30 kg reported infectious AEs. However, a greater proportion of subjects weighing <30 kg reported upper respiratory tract infection and nasopharyngitis, compared with the proportion of subjects weighing ≥30 kg at Week 4 who reported upper respiratory tract infection and nasopharyngitis. In subjects weighing ≥30 kg at Week 4, a greater proportion of subjects in the high-dose treatment group reported ≥1 TEAE. Proportions of subjects reporting specific events were similar for the high- and low-dose treatment group subjects.

A greater proportion of subjects in the high-dose treatment group had at least 1 severe TEAE compared to the low-dose treatment group (20.4% versus 11.6%, respectively). By events per 100 PY analysis, the trend was similar.

The differences between dose groups were most apparent in subjects whose Week 4 BW was <40 kg or ≥40 kg. A greater proportion of subjects <40 kg at Week 4 in the high-dose treatment group reported severe, serious TEAEs, and infectious TEAEs, as well as TEAEs leading to discontinuation. The low- and high-dose treatment group AE profiles were similar for subjects weighing ≥40 kg at Week 4. A greater proportion of subjects <30 kg at Week 4 in the high-dose treatment group reported severe, serious, infectious TEAEs, as well as TEAEs leading to discontinuation. A greater proportion of subjects ≥30 kg at Week 4 in the high-dose treatment group reported infectious TEAEs; otherwise, the low- and high-dose treatment group AE profiles were similar for subjects weighing ≥30 kg at Week 4.

Similar proportions of events in the low-dose and high-dose treatment groups were considered at least possibly related to study drug. The most frequently reported TEAEs possibly or probably related to study drug were injection site reaction and headache. Approximately 40% of subjects in both the low-dose and the high-dose treatment groups reported events considered possibly or probably study drug-related. The exposure-adjusted rate of possibly or probably related AEs was nominally higher in the low-dose treatment group (231.6/100 PY versus 205.2/100 PY, respectively, a difference of approximately 13%).

Table 27 Overview of the frequency and incidence of TEAEs per 100 PYs during double-blind every other week or every week dosing

	Low-Dose Adalimumab 20 or 10 mg				High-Dose Adalimumab 40 or 20 mg			
	eow N = 95 PYs = 47.5		ew N = 48 PYs = 14.9		eow N = 93 PYs = 54.1		ew N = 35 PYs = 12.1	
Subjects with:	**n (%)**	**E (E/100 PY)**	**n (%)**	**E (E/100 PY)**	**n (%)**	**E (E/100 PY)**	**n (%)**	**E (E/100 PY)**
Any adverse event	81 (85.3)	464 (976.8)	38 (79.2)	117 (785.2)	86 (92.5)	507 (937.2)	28(80.0)	132 (1090.9)
At least possibly drug related[a]	37 (38.9)	110 (231.6)	14 (29.2)	30 (201.3)	39 (41.9)	111 (205.2)	10 (28.6)	25 (206.6)
Severe adverse event	11 (11.6)	14 (29.5)	7 (14.6)	8 (53.7)	19 (20.4)	27 (49.9)	9 (25.7)	13 (107.4)
SAE	19 (20.0)	20 (42.1)	7 (14.6)	8 (53.7)	22 (23.7)	24 (44.4)	9 (25.7)	13 (107.4)
Leading to discontinuation of study drug	12 (12.6)	13 (27.4)	6 (12.5)	6 (40.3)	15 (16.1)	20 (37.0)	5 (14.3)	7 (57.9)
Any at least possibly drug-related SAEs[a]	2 (2.1)	2 (4.2)	0	0	1 (1.1)	1 (1.8)	0	0
Infectious AEs	47 (49.5)	101 (212.6)	15 (31.3)	20 (134.2)	56 (60.2)	99 (181.1)	16 (45.7)	24 (198.3)
Serious infections	3 (3.2)	3 (6.3)	0	0	5 (5.4)	5 (9.2)	3 (8.6)	4 (33.1)
Malignancies	0	0	0	0	0	0	0	0
Lymphomas	0	0	0	0	0	0	0	0
NMSC	0	0	0	0	0	0	0	0
Malignancies (excluding NMSC and lymphomas)	0	0	0	0	0	0	0	0
Malignancies (including lymphomas, excluding NMSC)	0	0	0	0	0	0	0	0
Injection site reactions	10 (10.5)	24 (50.5)	1 (2.1)	8 (53.7)	9 (9.7)	25 (46.2)	4 (11.4)	7 (57.9)
Opportunistic infections (excluding TB)	1 (1.1)	1 (2.1)	0	0	1 (1.1)	1 (1.8)	0	0
Congestive heart failure	0	0	0	0	0	0	0	0
Demyelinating disease	0	0	0	0	0	0	0	0
Hepatic-related adverse event	5 (5.3)	6 (12.6)	0	0	4 (4.3)	5 (9.2)	1 (2.9)	1 (8.3)
Allergic reactions	2 (2.1)	3 (6.3)	0	0	6 (6.5)	8 (14.8)	1 (2.9)	1 (8.3)
Lupus-like syndrome	0	0	0	0	0	0	0	0
Hematologic-related AEs	4 (4.2)	5 (10.5)	1 (2.1)	1 (6.7)	9 (9.7)	11 (20.3)	3 (8.6)	3(24.8)
Fatal AEs	0	0	0	0	0	0	0	0
Deaths[b]	0	0	0	0	0	0	0	0

AE = adverse events, SAE = serious adverse event; eow = every other week, ew = every week, E/100 PY = events per 100 patient years; NMSC = non-melanoma skin cancer; TB = tuberculosis

a. As assessed by investigator. b. Includes non-treatment-emergent deaths.

Note: A TEAE during the eow DB Maintenance Period is any AE with an onset date on or after the first DB dose and prior to the earliest time of the DB ew dose in Study M06-806, the first study drug in Study M06-807, or up to 70 days after the last dose of study drug if subject discontinued prematurely or completed the study while receiving the eow DB study drug. A TEAE during the ew DB Maintenance Period is any AE with an onset date on or after the first ew DB dose and prior to OL dose or up to 70 days after the last dose of study drug if subject discontinued prematurely from the DB ew period. Events with unknown severity are counted as severe. Events with unknown relationship to study drug are counted as drug-related.

Table 28 Proportion of patients with TEAEs, by week 4 weight category (<40 kg, ≥40 kg) and dose group - eow DB maintenance period (safety analysis set, study M06-806)

	DB Adalimumab eow, n (%)			
	Weight < 40 kg		Weight ≥ 40 kg	
	10 mg dose N = 31	20 mg dose N = 29	20 mg dose N = 64	40 mg dose N = 64
Any adverse event	24 (77.4)	26 (89.7)	57 (89.1)	60 (93.8)
At least possibly drug-related[a]	11 (35.5)	9 (31.0)	26 (40.6)	30 (46.9)
Severe adverse event	4 (12.9)	9 (31.0)	7 (10.9)	10 (15.6)
Serious adverse event	4 (12.9)	10 (34.5)	15 (23.4)	12 (18.8)
Leading to discontinuation of study drug	3 (9.7)	8 (27.6)	9 (14.1)	7 (10.9)
At least possibly drug-related SAE[a]	0	0	2 (3.1)	1 (1.6)
Infectious adverse event	14 (45.2)	19 (65.5)	33 (51.6)	37 (57.8)
Serious infections	1 (3.2)	2 (6.9)	2 (3.1)	3 (4.7)
Malignancies	0	0	0	0
Lymphomas	0	0	0	0
NMSC	0	0	0	0
Malignancies (excluding NMSC and lymphomas)	0	0	0	0
Malignancies (including lymphomas, excluding NMSC)	0	0	0	0
Injection site reactions	2 (6.5)	1 (3.4)	8 (12.5)	8 (12.5)
Opportunistic infections, excluding TB	0	0	1 (1.6)	1 (1.6)
Congestive heart failure	0	0	0	0
Demyelinating disease	0	0	0	0
Hepatic-related adverse events	0	0	5 (7.8)	4 (6.3)
Allergic reactions	1 (3.2)	0	1 (1.6)	6 (9.4)
Lupus-like syndrome	0	0	0	0
Hematologic-related adverse events	1 (3.2)	3 (10.3)	3 (4.7)	6 (9.4)
Fatal AEs	0	0	0	0
Deaths[b]	0	0	0	0

AE = adverse event; NMSC = non-melanoma skin cancer; SAE = serious adverse event; TB = tuberculosis;
a. As assessed by the investigator. b. Includes non-treatment-emergent deaths.
Note: A TEAE during the eow DB Maintenance Period is any AE with an onset date on or after the first DB dose and prior to the earliest time of the DB ew dose in Study M06-806, the first study drug in Study M06-807, or up to 70 days after the last dose of study drug if subject discontinued prematurely or completed the study while receiving the eow DB study drug. Events with unknown severity are counted as severe. Events with unknown relationship to study drug are counted as drug-related.

Dose escalation and no dose escalation sets

Subjects who experienced a flare or worsening of CD or were inadequate responders while receiving blinded eow therapy had the option to dose-escalate to blinded ew therapy. A total of 48 subjects (50.5%) in the low-dose treatment group escalated from blinded eow dosing to blinded ew dosing.

The overall incidence of TEAEs was similar before and after dose escalation. Before dose escalation, a greater proportion of reported AEs were possibly or probably drug-related, as well as injection site-related AEs. After dose escalation, there was a greater proportion of severe AEs, SAEs, AEs leading to discontinuation and SAEs leading to discontinuation.

The majority of TEAEs were infectious AEs, and the proportions were similar before and after dose escalation (56.5% and 55.7%, respectively). The incidence of serious infectious AEs increased <1% after dose escalation (5.2% before dose escalation versus 6.1% after dose escalation). The incidence of TEAEs was also similar between the dose escalation and no dose escalation analysis sets. The incidence of infectious AEs and infectious SAEs were higher in the no dose escalation set.

In the dose escalation set, there were fewer events (14 subjects with 3 subjects reporting severe CD) reported prior to dose escalation versus after dose escalation (26 subjects with 17 subjects reporting severe CD). The occurrence of severe events in the dose escalation set was similar to the any adalimumab set. Injection site reaction and injection site pain were the most frequently reported events assessed as possibly or probably related to study drug prior to dose escalation; pyrexia was the

most frequently reported TEAE assessed as possibly or probably related to study drug in the post-dose escalation group.

Low dose eow Set

Subjects in the low dose eow Set switched from the low dose eow period in Study M06-806 to the high dose eow period in Study M06-807. During the low dose eow period in Study M06-806, approximately 92% of subjects (22 of 24 subjects) experienced ≥1 TEAE. Approximately 46% of subjects (11 of 24 subjects) reported a TEAE that was possibly or probably related to study drug and approximately 8% of subjects reported ≥1 SAE. Infectious AEs were the most frequently reported AE; approximately 83% of subjects (20 of 24 subjects) had ≥1 infectious AE.

When subjects received high-dose eow study drug in Study M06-807, fewer subjects experienced TEAEs compared to the period when they received low-dose study drug in Study M06-806. Approximately 83% of subjects (20 of 24 subjects) experienced ≥1 TEAE. Approximately 29% of subjects (7 of 24 subjects) reported a TEAE that was possibly or probably related to study drug and no subjects reported an SAE. Infectious AEs were the most frequently reported AE of special interest; approximately 63% of subjects (15 of 24 subjects) had ≥1 infectious AE. There were no serious infections reported in the low dose eow set.

Any adalimumab Set

Approximately 96% of subjects (185 of 192 subjects) experienced ≥1 TEAE, with an incidence of 844.0 events/100 PYs. More than 50% of subjects (107 of 192; 55.7%) reported a TEAE that was possibly or probably related to study drug and 40.1% of subjects reported ≥1 SAE. Infectious AEs were the most frequently reported AE; 136 subjects (70.8%) had ≥1 infectious AE. The rate of serious infectious AEs was low (8.9%). Crohn's disease flare was a frequently reported TEAE, occurring in 46.4% of subjects. This represents a flare or worsening of the disease. Headache was reported by approximately 25% of subjects; upper respiratory tract infection was reported by approximately 20% of subjects nasopharyngitis, oropharyngeal pain, and pyrexia were each reported by approximately 16% of subjects. Other TEAEs reported by ≥10% of subjects were abdominal pain, nausea, diarrhoea, vomiting, cough, injection site reaction, abdominal pain upper, arthralgia, and constipation. TEAEs assessed as severe were reported by 59 subjects in the any adalimumab set; 126 subjects had mild or moderate events. Thirty-one subjects reported severe CD; all other severe events occurred in ≤3 subjects. Injection site reaction (21 subjects [10.9%]) and injection site pain (14 subjects [7.3%]) were the most frequently reported events possibly or probably related to study drug.

Table 29 Overview of treatment-emergent adverse events (any adalimumab set)

	Any Adalimumab Set N = 192 PYs = 258.9	
Treatment-Emergent AE Category	**n (%)**	**E (E/100 PYs)**
Any AE	185 (96.4)	2185 (844.0)
Any AE at least possibly drug-related[a]	107 (55.7)	479 (185.0)
Any severe AE	59 (30.7)	99 (38.2)
Any serious AE	77 (40.1)	113 (43.6)
Any AE leading to discontinuation of study drug	49 (25.5)	64 (24.7)
Any SAE leading to discontinuation of study drug	30 (15.6)	30 (11.6)
Any SAE at least possibly drug-related[a]	9 (4.7)	9 (3.5)
Any infectious AE	136 (70.8)	444 (171.5)
Any serious infectious AE	17 (8.9)	19 (7.3)
Any malignant AE	0	0
Any lymphomas AE	0	0
Any non-melanoma skin cancers (NMSC) AE	0	0
Any malignant AE (excl. lymphomas and NMSC)	0	0
Any malignant AE (incl. lymphomas and excl. NMSC)	0	0
Any opportunistic infections (excl. TB)	2 (1.0)	2 (0.8)
Any demyelinating disease AE	0	0
Any hepatosplenic T-cell lymphoma AE	0	0
Any leukemia AE	0	0
Any melanoma AE	0	0
Any injection site reaction AE	38 (19.8)	98 (37.9)
Any lupus-like syndrome AE	1 (0.5)	1 (0.4)
Any allergic reaction related AE	15 (7.8)	22 (8.5)
Any hematologic related AE	23 (12.0)	28 (10.8)
Any cutaneous vasculitis related AE	0	0
Any diverticulitis related AE	0	0
Any intestinal perforations related AE	0	0
Any intestinal stricture related AE	3 (1.6)	3 (1.2)
Any hepatic related AE	12 (6.3)	14 (5.4)
Any elevated ALT levels related AE	8 (4.2)	9 (3.5)
Any myocardial infarction related AE	0	0
Any cerebrovascular accident related AE	0	0
Any pulmonary embolism related AE	0	0
Any psoriatic condition worsening AE	3 (1.6)	3 (1.2)
Any Stevens-Johnson syndrome related AE	0	0
Any erythema multiforme related AE	0	0
Any congestive heart failure related AE	0	0
Any interstitial lung disease related AE	0	0
Any pancreatitis related AE	1 (0.5)	1 (0.4)
Any fatal AE	0	0
Deaths	0	0

AE = adverse event; ALT = alanine aminotransferase; E = events; E/100 PYs = events per 100 patient years; NSMC = non-melanoma skin cancer; PY = patient year; SAE = serious adverse event; TB = tuberculosis
a. Assessed by the investigator. Note: Includes Studies M06-806 and M06-807.
Note: Treatment-emergent adverse event (TEAE) is defined as any AE with an onset date on or after the first adalimumab dose and up to 70 days after the last dose of adalimumab. The last available dose date on or before 30 Nov 2010 was used if a subject was still ongoing in Study M06-807. AEs with an onset date more than 70 days during the gap between studies were excluded.

1.6. Serious adverse events, deaths and other significant events

Serious adverse events

During the OL induction period of Study M06-806, 6 (3.1%) patients had serious TEAEs requiring hospitalisation. None were considered to be possibly or probably related to study drug. Among the 6 subjects, 2 subjects received the 80/40 mg induction doses and 4 subjects received the 160/80 mg induction doses. In the low dose group there were 2 reports, heart rate irregular and viral infection. In the high dose group the serious TEAEs were Crohn's disease (n=2), Yersinia infection and IBD flare. In 3 cases the SAEs led to discontinuation of the study drug. All 3 received the 160/80 mg induction doses**.** No subject reported an opportunistic infection, malignancy, CHF, demyelinating disease, TB, lupus-like syndrome, or a hepatic related event during the induction period.

Of subjects who received at least 1 DB dose, approximately 20% in each treatment group reported at least 1 serious TEAE. Most subjects reported serious TEAEs that were infections or GI-related. The

most frequently reported TEAE was CD (flare or worsening). No statistically significant difference was observed between treatment groups. Three subjects had serious TEAEs that were considered possibly or probably related to study drug (Bartholin's abscess, pancreatitis acute and histoplasmosis disseminated). Eight subjects reported serious infections during the eow DB Maintenance period (3 subjects in the low-dose treatment group and 5 subjects in the high-dose treatment group). Six (6) of the 8 events were considered to be probably not related or not related to study drug.

The rates of SAEs overall and SAEs considered possibly or probably related to study drug were comparable between the two treatment groups. Serious infections were notably less frequent in the low-dose treatment group (6.3 versus 9.2 E/100 PY, 46% difference approximately).

Table 30 Proportion of subjects with serious TEAEs by descending frequency in high-dose treatment group - eow DB maintenance period (safety analysis set)

	Adalimumab, n (%)	
	Low-Dose 20 mg or 10 mg eow N = 95	High-Dose 40 mg or 20 mg eow N = 93
Any serious adverse event	19 (20.0)	22 (23.7)
Crohn's disease	15 (15.8)	12 (12.9)
Anemia	0	4 (4.3)
Small intestinal obstruction	0	1 (1.1)
Abdominal abscess	0	1 (1.1)
Anal abscess	0	1 (1.1)
Gastroenteritis	0	1 (1.1)
H1N1 influenza	0	1 (1.1)
Histoplasmosis disseminated	0	1 (1.1)
Psychosomatic disease	0	1 (1.1)
Pancreatitis acute	1 (1.1)	0
Bartholin's abscess	1 (1.1)	0
Scarlet fever	1 (1.1)	0
Tooth abscess	1 (1.1)	0
Facial bones fracture	1 (1.1)	0

Note: A TEAE is defined as any AE with an onset date on or after the first DB dose and prior to the earliest time of the DB ew dose in Study M06-806, the first study drug in Study M06-807, or up to 70 days after the last dose of study drug if subject discontinued prematurely or completed the study while receiving the eow DB study drug.

In the dose escalation set, CD flare was reported in lower percentage of subjects prior to dose escalation (8 of 115), with anemia reported in 2 subjects and all other SAEs reported in only 1 subject each than the percentage reported for CD flare following dose escalation (25 of 115), with anal abscess and tachycardia reported in 2 subjects each and all other SAEs reported in only 1 subject each. SAEs possibly or probably related to study drug were reported by 2 subjects prior to dose escalation versus 5 subjects following dose escalation.

In the any adalimumab set, any SAE was reported in 77 patients (40.1%) and CD flare was the most common SAE (52 subjects 27.1%).
The following SAEs: anemia, abdominal abscess, anal abscess, tachycardia, gastritis and small intestinal obstruction were each reported in more than 1 subject and all other SAEs were reported in only 1 subject. Nine subjects had SAEs that were possibly or probably related to study drug and 3 subjects discontinued study drug and 6 had prior exposure to infliximab. The SAEs were: histoplasmosis disseminated, systemic lupus erythematosus, staphylococcal abscess, Bartolini's abscess, CD, Herpes virus infection, pancreatitis acute, small intestinal obstruction, lymphadenitis.

Deaths

There were no deaths in Study M06-806 and in Study M06-807.

Adverse events of special interest

Adverse events of special interest were analyzed according to the list of identified and potential risk in the adalimumab Risk Management Plan. No treatment-emergent malignancies, demyelinating diseases, cutaneous vasculitis, diverticulitis, intestinal perforation, myocardial infarction, CVA, pulmonary embolism, Stevens-Johnson syndrome, erythema multiforme, CHF and or interstitial lung disease AEs were reported during Studies M06-806 and M06-807 (data cut-off 30 November 2010).

Infections

Overall, 71 % of the patients had an infection (any adalimumab set), the majority were upper respiratory tract infection (19.3%) or nasopharyngitis (16.1%). In 17 of the patients, the infectious adverse event was reported as serious (abdominal abscess (n=3), anal abscess n=2), the remaining events occurred in 1 patient each). Four subjects had serious infections that were assessed as possibly or probably related to study drug. Four patients discontinued due to a serious infection (one case was considered as probably related to the study drug). Two subjects reported opportunistic infection (excluding TB). In the dose escalation set, infections were reported by 65/115 (56.5%) subjects prior to dose escalation and 64/115 (55.7%) subjects following dose escalation. Serious infections were reported by 6/115 (5.2%) subjects prior to dose escalation and 7/115 (6.1%) subjects following dose escalation.

Injection site reaction-related events

Overall 38 subjects (19.8%) reported this event. In the any adalimumab set, the most frequently reported events were injection site reaction (10.9%) and injection site pain (7.3%). All injection site related TEAEs were assessed as probably related to study drug. In the dose escalation set, injection site reaction were reported by 15/115 (13.0%) subjects prior to dose escalation and 6/115 (5.2%) subjects following dose escalation.

Allergic reaction related

In the any adalimumab set, 15 subjects (7.8%) experienced allergic reaction (7 subjects had hypersensitivity reactions and 5 subjects had urticaria). The remaining events occurred in 1 subject each. Three events of urticaria were considered as possibly or probably related to the study drug. The remaining events were considered not related or probably not related to study drug. In the dose escalation set, allergic reaction were experienced by 5.2% subjects prior to dose escalation and 4.3% subjects following dose escalation.

Hematologic-related events

In the any adalimumab set, 23 subjects (12.0%) experienced hematologic related events of whom 6.3% experienced anaemia and 8 4.2% leukopenia. One event of anemia, 4 events of leukopenia, 3 events of white blood cell count decreased, and 1 event each of pancytopenia and neutropenia were considered possibly related; and 1 event of leukopenia was considered probably related to study drug. The remaining events were considered not related or probably not related to study drug. In the dose escalation set, hematologic events were experienced by 6.1% of subjects prior to dose escalation and 6.1% of subjects following dose escalation. Ten subjects experienced increases from Common Toxicity Criteria (CTC) Grade <3 hemoglobin values to Grade ≥3 values and increases in neutrophil and lymphocyte values to ≥ Grade 3 were experienced by 7 subjects each. Some subjects' hematology values decreased from ≥ CTC Grade 3 to <CTC Grade 3.

Hepatic-related events:

In the any adalimumab set, 8 subjects (4.2%) experienced ALT increased, events in 4 subjects were assessed as possibly related to study drug, and events in 3 subjects were assessed as probably not related to study drug. There were no serious events or discontinuations due to these events.

Intestinal Strictures: in the any adalimumab set, 3 subjects (1.6%) experienced intestinal stricture related TEAEs.

Psoriatic condition worsening

In the any adalimumab set, 3 subjects (1.6%) experienced psoriatic condition worsening TEAEs, all of which were considered probably related to study drug.

Pancreatitis

An event of acute pancreatitis possibly related to study drug occurred on DB treatment with 20 mg adalimumab (low dose).

Lupus-like syndrome:

One patient suffered from serious systemic lupus erythematosus during Study M06-807. The event was severe and probably related to the study drug.

Table 31 Summary of treatment-emergent serious adverse events (any adalimumab set)

System Organ Class MedDRA Preferred Term	Any Adalimumab Set N = 192 n (%)
Any SAE	77 (40.1)
Blood and Lymphatic System Disorders	
Anemia	4 (2.1)
Iron deficiency anemia	1 (0.5)
Lymphadenitis	1 (0.5)
Cardiac Disorders	
Tachycardia	2 (1.0)
Ear and Labyrinth Disorders	
Vertigo	1 (0.5)
Gastrointestinal Disorders	
Crohn's disease	52 (27.1)
Gastritis	2 (1.0)
Small intestinal obstruction	2 (1.0)
Abdominal pain upper	1 (0.5)
Inflammatory bowel disease	1 (0.5)
Oesophagitis	1 (0.5)
Pancreatitis acute	1 (0.5)
Rectal haemorrhage	1 (0.5)
Small intestinal stenosis	1 (0.5)
General Disorders and Administration Site Conditions	
Fatigue	1 (0.5)
Pyrexia	1 (0.5)
Hepatobiliary Disorders	
Hepatitis	1 (0.5)
Infections and Infestations	
Abdominal abscess	3 (1.6)
Anal abscess	2 (1.0)
Bartholin's abscess	1 (0.5)
Device related sepsis	1 (0.5)
Gastroenteritis	1 (0.5)
H1N1 influenza	1 (0.5)

Herpes virus infection	1 (0.5)
Histoplasmosis disseminated	1 (0.5)
Pneumonia	1 (0.5)
Scarlet fever	1 (0.5)
Sinusitis	1 (0.5)
Staphylococcal abscess	1 (0.5)
Tooth abscess	1 (0.5)
Viral infection	1 (0.5)
Yersinia infection	1 (0.5)
Injury, Poisoning and Procedural Complications	
Facial bones fracture	1 (0.5)
Upper limb fracture	1 (0.5)
Investigations	
Heart rate irregular	1 (0.5)
Musculoskeletal and Connective Tissue Disorders	
Systemic lupus erythematosus	1 (0.5)
Nervous System Disorders	
Dizziness	1 (0.5)
Syncope	1 (0.5)
Psychiatric Disorders	
Psychosomatic disease	1 (0.5)
Psychotic disorder	1 (0.5)

SAE = serious adverse event. Note: Includes Studies M06-806 and M06-807. TEAE is defined as any AE with an onset date on or after the first adalimumab dose and up to 70 days after the last dose of adalimumab. The last available dose date on or before 30 Nov 2010 was used if a subject was still ongoing in Study M06-807. Adverse events with an onset date more than 70 days during the gap between studies were excluded.

Possibly or probably related

In the any adalimumab set, in 107 of 192 subjects (55.7%) events were assessed as possibly or probably related of which injection site reaction (10.9%) and injection site pain (7.3%) as the most frequently reported.

In the dose escalation set, a lower percentage of events was assessed as possibly or probably related (54 of 115 subjects, 47.0% prior to dose escalation versus 42 of 115 subjects, 36.5% following dose escalation). In this set, injection site reaction and injection site pain (prior to dose escalation) and pyrexia (post-dose escalation) were the most frequently reported events assessed as possibly or probably related to study drug.

1.7. Laboratory findings

Haematology

In study M06-806 there were overall minor, not statistically significant, changes in haematology variables with the exception for platelet counts that declined in both dosing groups, in particular in the high-dose group. There were overall 23 patients with hematologic related TEAEs, the most common events were anaemia (n=12) and leukopenia (n=8). Of all events, 11 were possibly or probably related to the study drug.

Clinical chemistry

Overall, shifts to CTC grade ≥ 3 were observed for 1 or 2 patients for each analysis.

Liver function test

Three patients had persistent potentially clinically significant ALT values; all other potentially clinically significant liver function test values had returned to normal by the final value. Two patients had maximum values in ALT of ≥5 × ULN but <8 × ULN, and 1 patient experienced maximum ALT value to ≥8 × ULN which subsequently decreased <8 × ULN. One subject experienced a maximum AST value of ≥5 × ULN but <8 × ULN. Alkaline phosphatase and total bilirubin levels did not exceed 3 × ULN in any subjects.

1.8. Immunological events

Overall, six (6/182, 3.3%) subjects were identified as AAA+ during the study. The number of AAA+ patients was too small to make definitive conclusion on the impact of immunogenicity on efficacy or safety. Forty-one % of samples were analysed for AAA.

1.9. Discontinuations due to AEs

Forty-nine patients discontinued the studies (any adalimumab set). Crohn's disease was the major reason for the discontinuations (n= 34).

1.10. Observation related to safety

Analyses were performed to assess whether there was any impact of prior use of anti-TNF agents or concomitant corticosteroids and immunomodulators use at baseline on the AE profile of adalimumab.

Prior Infliximab Use

Among subjects previously treated with infliximab, subjects in the low-dose treatment group reported a substantially lower incidence of AEs (891.0 versus 1030.2 E/100 PY), severe AEs (51.3 versus 95.5 E/100 PY), AEs leading to discontinuation (25.6 versus 75.4 E/100 PY), infections (217.9 versus 185.9 E/100 PY) and serious infections (6.4 versus 15.1 E/100 PY) compared with the high-dose treatment group. Among infliximab naïve subjects, the AE profiles were similar for the low-dose and high-dose treatment groups.

Among subjects with prior infliximab use in the any adalimumab set, 96.5% of subjects experienced at least 1 TEAE. More than half of subjects with prior infliximab use (52.9%) reported a TEAE that was possibly or probably related to study drug, and 48.2% of subjects reported at least 1 SAE. No fatal AEs were reported and no subjects died. Infectious AEs were the most frequently reported AE of special interest.

Safety of adalimumab in subjects with concomitant immunomodulator or corticosteroid use

The proportion of subjects in the any adalimumab set who had serious infections, and the incidence rate in E/100 PY, were slightly higher in subjects with concomitant IMM use (9.9%, 8.0 E/100 PY versus 7.0%, 5.9 E/100 PY). The proportion of subjects who reported serious infections, as well as the incidence rate in E/100 PY, were greatest in the subgroup of subjects who used both IMMs and CSs (20.0%, 13.7 E/100 PY), and was smallest in subjects who used neither type of drug concomitantly (5.7%, 5.0 E/100 PY); however, the numbers and proportions of subjects in each subgroup who reported serious infections were very small.

Discussion on clinical safety

Study M06-806

Data from the studies M06-806 and M06-807 support the safety of adalimumab in paediatric patients (6 to 17 years of age) with active CD (PCDAI score >30) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies. The safety of adalimumab throughout the studies was monitored and assessed by AEs, physical examination, laboratory data, and vital signs.

During the initial OL phase 52.6% of all subjects reported at least 1 TEAE. Injection site pain (6.3%) and injection site reaction (5.2%) were reported frequently. Approximately 14 % of subjects reported an infection. Viral upper respiratory tract and upper respiratory tract were the most frequently reported infections. Almost all events were mild or moderate and 5.2% subjects reported severe TEAEs. Six (3.1%) subjects reported an SAE; none were considered related to study drug. There were more reports of TEAEs in children ≥40 kg receiving adalimumab 160/80 mg compare to the children <40 kg receiving adalimumab 80/40 mg. The events that were more frequently assessed as possibly related to study drug were in children ≥40 kg receiving adalimumab 160/80 mg (14.5% in the 80/40mg and 23.6% in the 160/80mg group). The most frequently reported TEAEs possibly related were injection site pain, injection site reaction, viral respiratory tract infection and fatigue. A total of 20.3% of subjects reported a TEAE that was considered possibly or probably related to adalimumab. During the procedure the MAH presented a summary of TEAEs for subjects who received adalimumab 80/40 mg and 160/80 mg during the OL induction period by previous infliximab. The occurrence of TEAEs during the OL induction period was not influenced by the adalimumab dose and infliximab treatment. No specific safety pattern was observed during the first 4 week of the study with respect to previous infliximab use. The MAH also presented a summary of TEAEs for subjects who received adalimumab 160/80 mg (≥40 kg) and 80/40 mg (<40 kg) during the OL induction period by IMM use at baseline. No clear influence was noted in the occurrence of TEAEs during OL period by adalimumab dose and IMM or corticosteroids use.

During the DB period there were more TEAEs reported in the high-dose treatment group (92.5% vs 85.3%). The most frequently reported TEAEs were CD (flare or worsening), headache, nasopharyngitis, and upper respiratory tract infection. No statistically significant difference was observed between treatment groups for any TEAE. There were more patients with severe AEs, serious AEs and infectious AEs in the high-dose group in particular in children <40 kg. Approximately one fourth of all patients discontinued due to adverse events, the largest proportion was in the group of patients <40 kg receiving the higher dose. The proportion of severe AEs, serious AEs and infectious AES were approximately 20 %, 24 % and 60 % in the high dose group with corresponding figures for the low dose group 12 %, 20 % and 50 % approximately. For patients <40kg receiving the high dose i.e. 20 mg the proportion of these events were larger than for the other groups (31 %, 34.5 % and 65.5 %).

The rate of any AE (89.7% versus 77.4%), SAE (34.5% versus 12.9%), severe AE (31.0% versus 12.9%), AE leading to discontinuation of study drug (27.6% versus 9.7%), infectious AE (65.5% versus 45.2%), and serious infections (6.9% versus 3.2%) was higher for those subjects who weighed <40 kg receiving adalimumab 20 mg (high-dose) versus those receiving 10 mg (low-dose). The number of subjects in subjects who weighed <40 kg and escalated from adalimumab 20 mg eow to 20 mg ew in either Study M06-806 or Study M06-807 is low (N = 15). Adverse events did not increase with dose escalation, thus this is a reasonable option for those that may require it. Although he number of patient were limited the data do not indicate that the numbers of AEs increase with increased dosing in children receiving 20 mg ew.

Slightly less than half of the subjects (44%) who were enrolled in the DB maintenance phase (from week 12 to week 52) experienced a flare or non-response and were switched to ew regimen (dose escalation). The overall incidence of AEs was similar before and after dose escalation. After dose escalation there was a greater proportion of severe AEs, SAEs and AEs & SAEs leading to discontinuation. Infections and serious infection were lower in the escalation set.

During the procedure the MAH showed that subjects using concomitant IMMs at baseline experienced a generally higher proportion of TEAEs following dose escalation. Overall, the concomitant use of IMM at baseline, negatively influenced the safety profile of adalimumab in subjects with post dose escalation TEAE (i.e. SAEs with IMM 34.9% versus without IMM 26.9%, infectious AEs with IMM 65.1% versus

without IMM 44.2%, serious infectious AEs with IMM 9.5% versus without IMM 1.9%). TEAE occurrence prior to dose escalation was not influenced by IMM use. Although dose escalation and IMM use led to a higher occurrence of TEAEs such as infectious AEs, the CHMP noted that these AEs were in the majority of cases not serious. Thus, dose escalation is still associated with a manageable adalimumab safety profile. In the dose escalation set, the CHMP noted that CD flare was reported in a higher percentage of subjects following dose escalation. The MAH clarified that dose escalation was probably the consequence of worsening which was later reported as flare.

During the procedure it was clarified that of the low-dose subjects who switched to ew blinded dosing, approximately 79% reported at least 1 TEAE during the eow dosing period. Importantly, SAEs, infections and serious infections did not increase with dose escalation. Thus, allowing subjects in the low-dose group to dose-escalate does not pose any significant safety risks.

Taking in to account the any adalimumab set the most frequently TEAEs were CD, headache, nausea, and upper respiratory tract infection. Most of these events were mild or moderate and 27.1% were considered severe. The most frequently (≥3% of subjects) reported TEAEs possibly related to study drug were injection site reaction and injection site pain. Approximately a third reported at least 1 serious TEAE. Most reported serious TEAEs that were infections or GI-related. The most frequently reported was CD. No statistically significant differences were observed for subgroup analyses of concomitant IMM use and concomitant IMM use and corticosteroid use. There were no malignancies reported and no cases of AEs related to demyelinating diseases, cutaneous vasculitis, diverticulitis, intestinal perforation, myocardial infarction.

No new safety concerns were identified in the analysis of clinical laboratory parameters or vital signs.

Among subjects with prior infliximab use in the any adalimumab set, 96.5% of subjects experienced ≥1 TEAE. More than half of subjects with prior infliximab use (52.9%) reported a TEAE that was possibly or probably related to study drug, and 48.2% of subjects reported ≥1 SAE.

In order to further characterize the long-term safety profile in a clinical real setting the MAH presented a planned paediatric Crohn's disease registry program Study P11-282. This program is a long-term non-interventional registry to assess safety and effectiveness of Adalimumab in paediatric patients with moderately to severely active CD. The primary objective of this registry is to evaluate long-term safety of adalimumab in paediatric patients with moderately to severely active CD. The secondary objective of this registry is to evaluate the long-term effectiveness of adalimumab in patients with moderately to severely active CD. In addition, the impact of treatment interruptions on the safety and effectiveness of Humira will be evaluated. Approximately 500 patients aged 6 to 17 years in the US, Europe and Australia will be enrolled. The proposed registry is aimed at collecting safety information for a period of 10 years as described in the RMP.

The MAH will continue safety surveillance in ongoing programs in children and adolescents, including those with malignancies as specified in the current approved adalimumab Risk Management Plan; this includes the extension of the current educational program to include paediatricians treating paediatric CD.

Study M06-807

Safety results from the study demonstrated that adalimumab is generally safe and well tolerated for up to 2 years of treatment. Overall, 96.0% of subjects reported 1 or more AEs. There have been no deaths reported during this study. Approximately one-third of subjects (33.0%) reported SAEs, half of which (16.0%) were related to worsening or flare of CD. Seven subjects (7.0%) discontinued from the study due to AEs, including 2 subjects with SAEs of CD (worsening or flare) and 1 subject with an SAE of systemic lupus erythematosus. The majority of SAEs were considered to be probably not related to study drug. The most frequently reported AEs possibly or probably related to study drug was injection

site reaction. The MAH will continue collect long-term safety and efficacy data from Study M06-807 for up to 5 years and will provide the final CSR to the Agency by November 2015 as detailed in the RMP.

Conclusion on clinical safety

There is no new safety signal identified in the paediatric clinical development program submitted. Adalimumab has a well characterised safety profile in several authorised indications, including adult CD. Data submitted in this application confirm the known safety profile observed with the approved indications. Overall, the safety profile of adalimumab in the treatment of paediatric CD was considered to be similar to that of other approved indications.

Events more related to the underlying disease i.e. worsening of CD (adverse events and serious adverse events), were reported and represented the most common reported adverse events leading to adalimumab discontinuation. Infections, mainly upper respiratory tract infection and nasopharyngitis, were also reported frequently. These events were mild to moderate in intensity in the majority of subjects. Two cases of opportunistic inspection were reported. No case of tuberculosis was reported. The proportion of infections was similar before and after dose escalation. Injection site reaction and injection site pain were the most frequently reported events possibly or probably related to adalimumab. The overall AE profile was similar between the high- and low-dose treatment groups but a greater proportion of subjects <40 kg at Week 4 in the high-dose treatment group reported severe, serious events, infections as well as events leading to discontinuation. The dominating serious adverse events were also Crohn's disease flares or worsening followed by infections.

The CHMP noted that there were 3 cases of psoriatic worsening condition as well as a case of lupus like syndrome that were reported during the study. Both events are already known risks addressed in the RMP and reflected in the product information.

During the DB period, there were a larger proportion of patients with previous infliximab use that had severe and serious AEs while the opposite was true for infectious AEs.

Treatment with adalimumab is connected with several serious risks i.e. increased risk of infections and the potential risk of lymphoproliferative disorders or malignancies, including hepatosplenic T-cell lymphoma. More rare potential safety concerns include risk for demyelination. All these risks are already addressed in the adalimumab product information as well as in the RMP. No malignancies have been observed in the studies presented. Nevertheless, in view of the younger age and expected longer disease and treatment duration in the CD paediatric population these safety concerns warrant structured post marketing long-term follow-up in the form of a paediatric registry as described in the RMP. The MAH will also continue to collect long-term safety data from Study M06-807 for up to 5 years as detailed in the RMP.

Although there were no new safety signals identified during the study period, the knowledge on the safety profile of adalimumab associated with potential serious adverse events together with the concerns related to malignancy and HSTCL should be taken into account in view of the younger age, expected longer disease and treatment duration in the paediatric population. Taken together, the CHMP requested to revise the indication to include only the most severely ill patients; excluding patients with a moderate active disease; this was accepted by the MAH.

Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure which included a risk minimisation plan.

Table 32 Extract from the summary of the risk management plan

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important missing information		
Long-term pedCD data beyond 2 years	Routine pharmacovigilance activities. Long-term open-label study (Study M06-807) and 10-year registry (P11-292).	Information on clinical data is included in the Clinical Trials section of the SmPC with the addition of the pedCD indication. Clinical data up to 108 weeks exposure is available.

The below pharmacovigilance activity in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
10-year paediatric Crohn's disease registry program study P11-282	Protocol submission by Q1-2013

The following additional risk minimisation activities beyond those included in the product information were required:

- The MAH should ensure that paediatricians handling gastroenterology are also included in the existing educational program described in the RMP.

The program has been designed to educate prescribing physicians, including gastroenterologists, dermatologists, rheumatologists and paediatricians on measures to help prevent reactivation of TB under adalimumab treatment. The educational programme also addresses the safety profile and related risks with adalimumab treatment with special focus on serious infections including opportunistic infections, CHF, demyelinating disorders and malignancies.

Annex II was updated to remove the outdated information that JIA is a new recent indication. As all the adalimumab prescribers specialists are not listed in Annex II, it is considered not necessary to add the term of "paediatricians handling gastroenterology" in Annex II.

2. Overall conclusion and benefit-risk assessment

Benefits

Beneficial effects

Adalimumab has been approved for the treatment of severe adult Crohn's disease since 2007. The submitted pivotal study M06-806 has been performed in children/adolescents (6 –17 years of age) with moderate to severe Crohn's disease (PCDAI >30 points). All patients had failed previous conventional therapy and a subgroup of patients had been previously treated with infliximab and subsequently had lost response or was intolerant to infliximab. All patients received initial OL treatment dependent on weight (160/80 mg for those >40 kg, 80/40 mg for those <40 kg) during the initial 4-week period. After 4 weeks, approximately 80% of the patients were in clinical response. Patients were randomized at week 4 to a high and low dose maintenance group. The high dose group received 40 mg or 20 mg eow depending on weight (≥40/<40 kg) and the low dose group, 20 mg or 10 mg eow depending on weight.

The primary efficacy endpoint, the proportion of patients in remission (PDCAI ≤ 10) at week 26, was evaluated by internal (high/low dose) and external comparisons (adults/paediatric CD patients). The

internal comparison of PCDAI values at Week 26 between the low-dose and the high-dose treatment groups demonstrated that the proportion of subjects who achieved PCDAI clinical remission at Week 26 was not significantly different between treatment groups. In the internal comparison, a larger proportion of patients in the high dose group (38.7%) were in remission as compared to the low dose group (28.4%), the overall difference was approximately 11%. Generally secondary endpoints supported this effect. In the subgroup of infliximab naïve patients there was a greater difference between the groups in remission rates, i.e. high dose group 29/51 (57%) and low dose group 19/54 (35%), the difference being approximately 22%. For prior infliximab treated patients the remission rates were lower with no difference between treatment groups (20% and 18% in the low and high dose group, respectively). The observed lower exposure of adalimumab in these patients might account for the inferior response in this group. Furthermore, the vast majority of those patients had lost response to infliximab previously. This group may also contain subjects not responding adequately to inhibition of TNF, and it is thus not unexpected that they as well as those who had lost response to infliximab can be more difficult to treat adequately with another anti-TNF agent.

Adalimumab treatment led to discontinuation of corticosteroids for ≥90 days prior to achieve clinical remission at week 26 in roughly 27% of subjects.

After completion of the pivotal study, patients who had been a responder at any time during the study could participate in the open-labelled ongoing follow-up study. Results showed a large proportion of subjects achieving clinical response and remission as per PCDAI and CDAI scores over time as well as a sustained decrease in PCDAI and CDAI scores over time. After almost one year of treatment there were 55 patients who had reached the 48 week assessment of the OL study. Of these patients, 50/55 (91%) were in clinical response and 39/55 (71%) were also in clinical remission. These results support a long-term efficacy of adalimumab in this paediatric population.

Uncertainty in the knowledge about the beneficial effects

Comparing the serum adalimumab concentration in children and adults, higher serum levels were reached in children during the induction phase compared with adults given induction treatment. However, during maintenance treatment, lower levels were observed in the subgroup of children who received the lower maintenance dose. This raised uncertainties with regard to the dosing regimen. For the induction dose simulated efficacy results suggested that a lower induction dose (80/40 mg on Weeks 0/2 for subjects ≥40 kg, and 40/20 mg on Weeks 0/2 for subjects <40 kg) was comparable to the higher, initially proposed dose without exposing children to unnecessarily high adalimumab concentrations. Therefore this induction dose was endorsed by the CHMP with the option to receive the initially proposed, higher induction dose (160/80 mg for those ≥ 40 kg and a dose of 80/40 mg for those <40 kg) if a more rapid response is required, which is similar to the adult CD induction dosing recommendation. New analyses also showed that the higher maintenance dose (40 mg/20 mg depending on body weight ≥/<40 kg) was associated with higher response/remission rates at week 52, in particular in the subgroup of children with severe disease. There were no major differences regarding safety between groups of children receiving the high or low adalimumab dose. For patients experiencing an insufficient response, an increased dosing to 40 mg ew for children ≥40 kg and 20 mg ew for children <40 kg was agreed by the CHMP based on the observed data from Study M06-806.

Due to the design of study M06-806 there is limited data on the efficacy of dose-escalation in patients that are non-responders at week 8 and 12. The majority of subjects in Study M06-806 dose-escalated as early as Week 12 per the study design. Thus dose escalation beyond Week 12 may be of limited value. Continued therapy should be carefully considered in a subject not responding by Week 12 so that patients are not exposed to adalimumab for prolonged periods. This cut-off of 12 weeks is used for other approved indications for Humira i.e. polyarticular juvenile idiopathic arthritis and is also

recommended for adult CD. The recommendation to re-consider the treatment if there is no response by week 12 was considered appropriate by the CHMP.

Risks

Unfavourable effects

There were no new safety signals observed during the study period. The observed safety events were consistent with the well-characterised adalimumab safety profile. Events more related to the underlying disease i.e. worsening of CD (adverse events and serious adverse events), were frequently reported. They also represented the most common reported adverse events leading to adalimumab discontinuation.

There were no malignancy cases in the study. The use of concomitant IMM and biological therapy for long period of time is an important safety concern since it is established that the risk of AEs occurrence, e.g. risk for hepatosplenic T lymphoma, is increased in patients treated with both IMM and anti-TNF agent. In the study, there are data from both monotherapy and combination therapy. Although there was higher response rates in the high dose group for those on combination therapy, given the risk for HSTCL it is justified not to include combination therapy as a recommendation in the SmPC. The SmPC includes already information on the risk with combination of AZA/6-MP and adalimumab for development of HSTCL, which is adequate to address this concern.

Uncertainty in the knowledge about the unfavourable effects

Treatment with adalimumab is connected with several serious risks i.e. increased risk of infections and the potential risk of lymphoproliferative disorders or malignancies, including hepatosplenic T-cell lymphoma. More rare potential safety concerns include risk for demyelination. All these risks are already addressed in the adalimumab product information as well as in the RMP. Based on the data analysed in this application this is considered sufficient at the present time. No malignancies have been observed in the studies presented. Nevertheless, in view of the younger age and expected longer disease and treatment duration in the CD paediatric population these safety concerns warrant to include only the most severely ill patients in the indication excluding patients with a moderate active disease. Also it warrants a structured post marketing long-term follow up in the form of a 10-year paediatric Crohn's disease registry program (Study P11-282) as described in the RMP. The primary objective of this registry is to evaluate long-term safety of adalimumab in paediatric patients with active CD. The MAH will also continue collect long-term safety and efficacy data from Study M06-807 for up to 5 years as described in the RMP.

Balance

Importance of favourable and unfavourable effects

In the internal comparison, a larger proportion of patients in the high dose group (38.7%) were in remission as compared to the low dose group (28.4%), the overall difference was approximately 11%. Generally secondary endpoints supported this effect. In the subgroup of infliximab naïve patients there was a greater difference between the groups in remission rates, i.e. high dose group 29/51 (57%) and low dose group 19/54 (35%), the difference being approximately 22%. There is therefore a demonstrated clinical benefit of adalimumab in the treatment of paediatric Crohn's disease.

Recommendations from an expert meeting held in 2006, when the same indication was discussed for infliximab highlighted the importance of primary nutrition therapy in the treatment of paediatric CD. Treatments with adalimumab as well as other alternatives (corticosteroids and IMM) for paediatric CD

are associated with potentially serious adverse events. The disadvantages with steroid treatment in young individuals with effects on growth and bone structure is well characterised and also the increased risk for infections. The safety profile for AZA/6-MP is also serious with increased risks of bone marrow suppression, malignancy / lymphoproliferation, hepatic events and pancreatitis. Recent data support a primary role of those treatments for the development of HSTCL. Main safety concerns for treatment with adalimumab are the increased risk of infections and the potential risk of lymphoproliferative disorders or malignancies including HSTCL. More rare potential safety concerns include risk for demyelination. Thus, the safety of adalimumab in comparison with the safety of alternatives for the treatment of CD is of clinical relevance. Thus, there is a need for additional treatment options for children with more severe CD. The safety profile of adalimumab can be serious, but adalimumab can be considered a valuable alternative for children not responding adequately to these other therapies, including primary nutrition therapy, or when they are not tolerated.

Benefit-risk balance

In the internal comparison, a larger proportion of patients in the high dose group (38.7%) were in remission as compared to the low dose group (28.4%), the overall difference was approximately 11%. Generally secondary endpoints supported this effect. In infliximab naïve patients at week 26, there was a statistically significant and clinically relevant difference between the low and high dose treatment groups, which is considered sufficiently supportive of efficacy. The induction dose in children has been aligned with the approved induction dose in adults. This is reasonable based on the assumption of linear pharmacokinetics in the studied dose range and a similar exposure-response in adults and children. Translation of efficacy data observed in adult CD patients to paediatric CD patients is considered adequate. The aetiology and clinical manifestation of CD in adult and paediatric patients as well as the treatment management of the condition and treatment response are considered to be similar. The proposal for an option to use the higher induction dose in case of need for a more rapid response has been further discussed and is considered adequate. For the maintenance dosing the high dose regimen should be used and thereby the observed low exposure and lower effect in the subgroup of children ≥30 kg - <40 kg will be avoided.

Although there were no new safety signals identified during the study period, the knowledge on the safety profile of adalimumab associated with potential serious adverse events together with the concerns related to malignancy and HSTCL should be taken into account in view of the younger age, expected longer disease and treatment duration in the paediatric population. Taken together, the CHMP considered justified to include only in the indication the most severely ill patients and therefore excluding patients with a moderate active disease; the MAH agreed.

Overall, based on the available efficacy data and the extensive knowledge about the safety profile of adalimumab, the benefit/risk balance of adalimumab is considered positive for the treatment of severe, active Crohn's disease in paediatric subjects (6 to 17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies.

3. Conclusion

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore does recommend, by consensus, the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**
C.I.6 Change(s) to therapeutic indication(s)	Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication for the treatment of severe, active Crohn's disease in paediatric subjects (6 to 17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies. Sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated accordingly as well as the Package leaflet and Annex II.

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/141/2011 and the results of these studies are reflected in the SmPC and, as appropriate, the package leaflet.