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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

Invented name: Humira

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/000481/II/0147

Marketing authorisation holder (MAH): AbbVie Ltd.

### Note

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



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## List of abbreviations

AZA – azathioprine  
CD – Crohn's disease  
CS - corticosteroids  
eow - every other week  
ew – every week  
DB – double-blind  
GCP - Good Clinical Practice  
HSTCL – hepatosplenic T-cell lymphoma  
IBD – inflammatory bowel disease  
IMM - immunomodulator  
MP - mercaptopurine  
MTX methotrexate  
NRI – non-responder imputation  
OL – open-label  
PCDAI - Paediatric Crohn's Disease Activity Index  
PIP - Paediatric Investigational Plan  
PY – patient-year  
SC - subcutaneous  
TEAEs – treatment emergent adverse events

# 1. Background information on the procedure

## 1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Ltd. submitted to the European Medicines Agency on 14 October 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIA

Extension of Indication for the treatment of paediatric Crohn's disease to include the treatment of moderately active Crohn's disease for Humira; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial corrections to the Labelling.

The requested variation proposed amendments to the Summary of Product Characteristics and Labelling.

### **Information on paediatric requirements**

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0324/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0324/2013 was completed.

The PDCO issued an opinion on compliance for the PIP P/0324/2013.

### **Information relating to orphan market exclusivity**

#### **Similarity**

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

#### **Scientific advice**

The applicant did not seek Scientific Advice at the CHMP.

## 2. Scientific discussion

### 2.1. Introduction

Humira (adalimumab) is a recombinant, fully human immunoglobulin (IgG1) monoclonal antibody that binds specifically and with high affinity to the soluble and transmembrane forms of tumour necrosis factor (TNF)- $\alpha$  and inhibits the binding of TNF- $\alpha$  with its receptors.

Humira was approved for treatment of adult patients with active Crohn's disease (CD) in 2007. The approved indication is for treatment of moderately to severely active CD, in patients who have not

responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Humira was approved for the treatment of severe active Crohn's disease in paediatric patients in 2012 (EMA/H/C/481/11/88). The approval was based on the results of the pivotal Phase III trial M06-806 and the interim results from the ongoing supportive study M06-807 (cut-off date 30 November 2010). There were no new safety signals during the studies but due to the potentially serious safety profile and limited safety data available in the paediatric population, it was considered appropriate to restrict the treatment indication to subjects having severely active disease only. Humira is presently approved for the treatment of severe active CD disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator (IMM), or who are intolerant to or have contraindications for such therapies.

Study M06-806 was a randomized, double-blind (DB), multicentre paediatric CD study on subjects with moderate to severe CD to evaluate the efficacy, safety, and pharmacokinetics (PK) of induction and maintenance dose regimens of adalimumab. The ongoing open-label (OL) extension, Study M06-807, was initiated in subjects who completed Study M06-806 to study the long-term efficacy, safety, and tolerability of adalimumab.

In this submission the MAH propose to extend the presently approved paediatric indication severely active CD, to include also patients with *moderately* active CD. In addition, the present prerequisite for treatment i.e. inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, is proposed to be changed to patients that could have failed enteral nutrition and *either* corticosteroids *or* immunomodulator (IMM).

## **2.2. Non-clinical aspects**

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

## **2.3. Clinical aspects**

### **2.3.1. Introduction**

#### **GCP**

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
M06-806/ 45/BEL, CAN, CZ, FR, IT, NL, POL, UK, US/ 52 weeks	04 May 2007; Completed 18 May 2010; 192 enrolled/ 186 planned	Randomized, DB, 2 dose regimens, OL induction, DB period with possible OL period	Adalimumab SC injection, OL induction: <sup>a</sup> 160 mg at Wk 0 and 80 mg at Wk 2 (BW ≥ 40 kg); or 80 mg at Wk 0 and 40 mg at Wk 2 (BW < 40 kg); DB maintenance: <sup>a</sup> randomized to LD eow or HD eow at Wk 4: LD = 10 mg (BW < 40 kg) or 20 mg (BW ≥ 40 kg); HD = 20 mg (BW < 40 kg) or 40 mg (BW ≥ 40 kg) eow From Wk 12, option to increase to ew, then OL HD if flare	Safety, efficacy and PK of adalimumab for the induction and maintenance of clinical remission in pediatric subjects with moderate to severe CD	188 subjects randomized LD 95/58, HD 93/66	108/84 14.0 yr (6 – 17 yr)	Moderate to severe CD, failed or could not tolerate conventional therapy for CD. Patients who had lost response/had intolerance to infliximab were eligible to be enrolled	Clinical remission (PCDAI ≤ 10) at Wk 26; external efficacy comparisons with adult Study M02-404; internal comparison HD vs. LD
M06-807/ 31 sites/ BEL, CAN, CZ, POL, UK, US/ 336 weeks <sup>b</sup>	01 May 2008/ Ongoing, data available through 31 Jan 2015/ 100 enrolled/ 130 planned	OL extension study of Study M06-806	Adalimumab SC injection <sup>a</sup> 40 mg eow (BW ≥ 40 kg) or 20 mg eow (BW < 40 kg) or OL dose in Study M06-806 (40 mg ew or 20 mg ew); from Wk 8 option to increase to ew if flare	Long-term safety and efficacy (maintenance of clinical response)	100 entered/ 18 completed <sup>c</sup> / 28 ongoing	52/48, 14.0 years (7 – 17 years)	Moderate to severe CD, successful completion of Study M06-806 through Week 52, responder at any time point during Study M06-806 (achieved at least a 15-point reduction in PCDAI from Baseline)	Maintenance of PCDAI clinical response (PCDAI ≥ 15 points lower than the Study M06-806 Baseline)

BEL = Belgium; CAN = Canada; CZ = Czech Republic; FR = France; IT = Italy; NL = the Netherlands; POL = Poland; UK = United Kingdom; US = United States; BW = body weight; DB = double-blind; CD = Crohn's Disease; ew = every week; eow = every other week; HD = high dose; LD = low dose; OL = open-label; PK = pharmacokinetics; PCDAI = Pediatric Crohn's Disease Activity Index; SC = subcutaneous

- Body weight at Baseline was used to determine the induction dose level. Body weight at Week 4 was used to determine the maintenance dose level. Body weight at Week 52 of Study M06-806 was used to determine the initial dose level in Study M06-807.
- Duration was 336 weeks based on Amendment 6, which was effective at the cutoff date for the present analysis; the current duration is 408 weeks via Amendment 7.
- Eighteen subjects discontinued the study because adalimumab became available in their country. These subjects are listed as "discontinued" and also "completed the open-label extension" (Study M06-807 Third Interim CSR [Appendix 16.2.1.1](#)). Per the protocol, these subjects are considered to have completed.

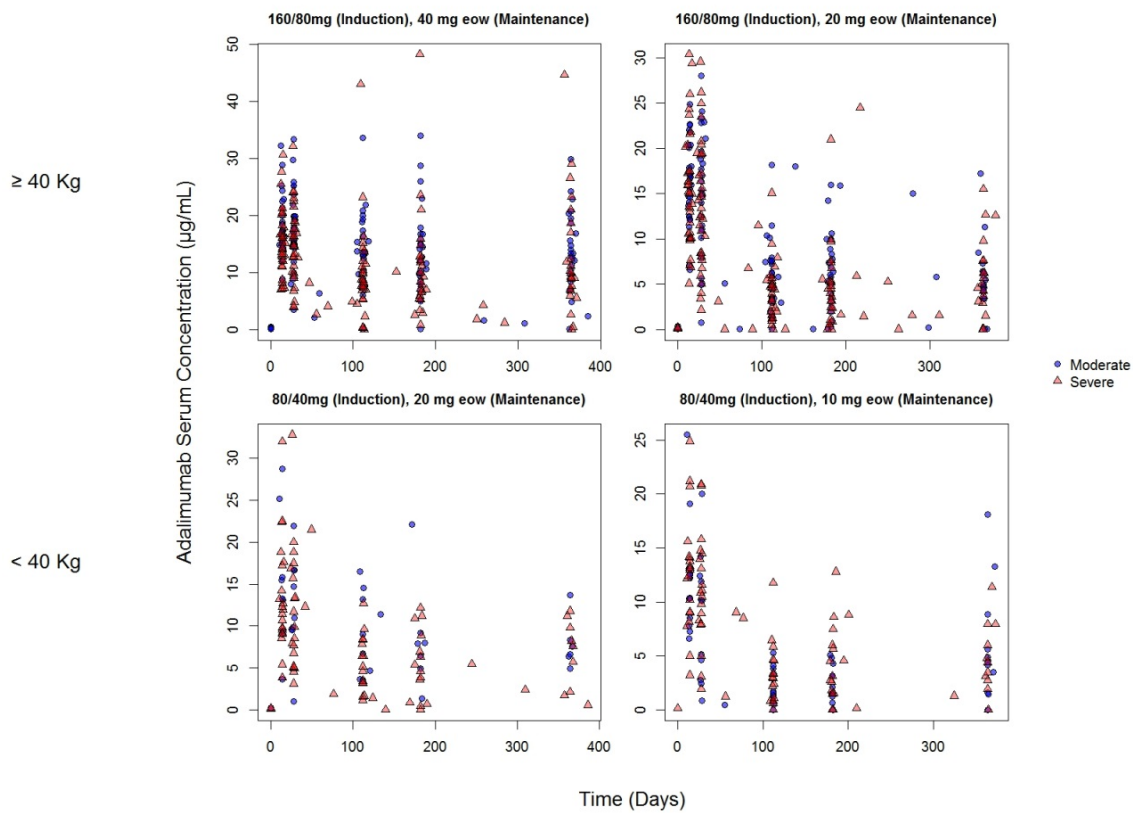
## 2.3.2. Pharmacokinetics

For this submission the MAH has analysed data from study M06-806 in order to identify potential differences on adalimumab pharmacokinetics between patients with moderate (PCDAI < 40) and severe CD (PCDAI ≥ 40). The assessments were performed in the following subgroups:

- Induction dose of 160 mg on Week 0 and 80 mg on Week 2 (160/80 mg) followed by 40 mg eow maintenance dose up to 52 weeks;
- Induction doses of 160/80 mg followed by 20 mg eow maintenance dose up to 52 weeks;
- Induction dose of 80 mg on Week 0 and 40 mg on Week 2 (80/40 mg) followed by 20 mg eow maintenance dose up to 52 weeks;
- Induction doses of 80/40 mg followed by 10 mg eow maintenance dose up to 52 weeks.

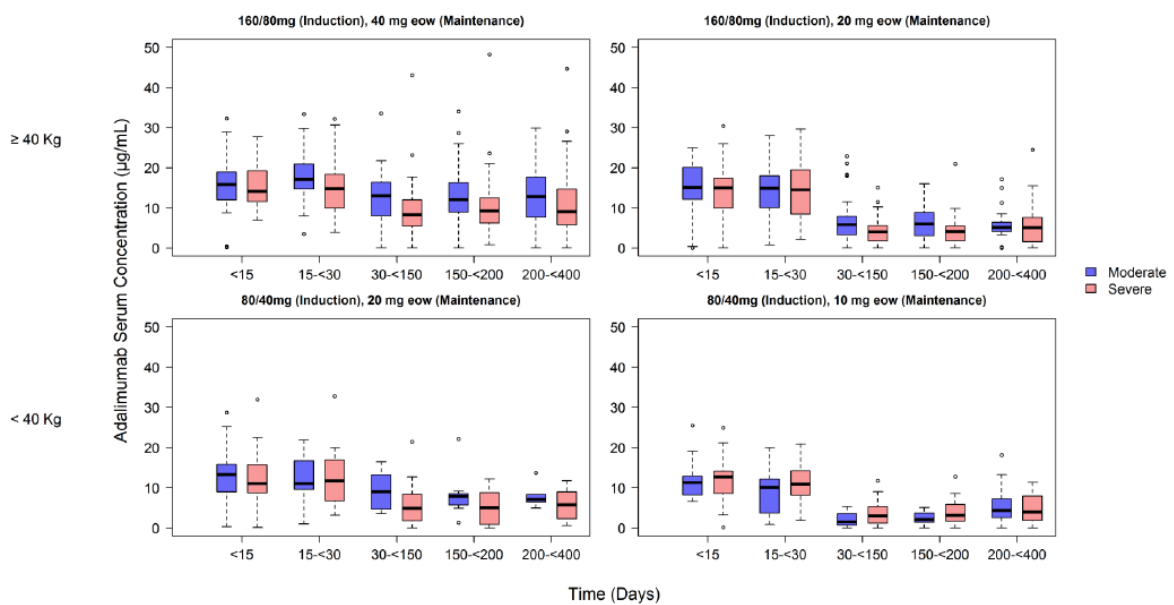
Within each treatment group, adalimumab trough concentrations were compared between paediatric subjects with moderate (PCDAI < 40) and severe CD (PCDAI ≥ 40). Observed adalimumab serum concentrations over time in paediatric subjects with moderate versus severe CD in each treatment group are provided in **Figure 1**.

**Figure 1 Observed Trough Serum Adalimumab Concentrations Over Time in Paediatric Subjects with CD by Disease Severity at Baseline in Each Treatment Group in Study M06-806**



There were no apparent differences in the observed adalimumab concentrations within each treatment group between paediatric subjects with moderate and severe CD.

**Figure 2. Observed Trough Serum Adalimumab Concentrations in Pediatric Subjects with CD by Disease Severity at Baseline and Time Interval in Each Treatment Group in Study M06-806**



### **Population Pharmacokinetic modelling**

The pharmacokinetics of adalimumab in paediatric subjects with CD was characterized using population PK methods. The previously developed population pharmacokinetic model was used to compare moderate and severe paediatric CD populations. The clearance and volume of distribution values in individual subjects, post-hoc predicted by the population pharmacokinetic model, were used to compare the estimates of pharmacokinetic parameters in subjects with moderate CD versus severe CD. Within each treatment group, the ranges of apparent clearance and apparent volume of distribution in subjects with moderate CD were comparable with the ranges observed in paediatric subjects with severe CD (data not shown).

For this assessment, the disease severity was also tested as a categorical covariate (moderate = 0 and severe = 1) on both CL/F and V2/F in the base model [one compartment with extravascular absorption, detailed in PK/PD report (R&D/10/1498)], separately. The individual data from Study M06-806 was used for this assessment. The decrease in objective function values was not statistically significant ( $< 3.84$  drop in the objective function,  $\chi^2$  distribution,  $P > 0.05$ , degrees of freedom = 1) from the base model without disease severity as a covariate. Therefore, the values of pharmacokinetic parameters are not influenced by the disease severity.

#### **2.3.3. Discussion on clinical pharmacology**

The range of observed adalimumab serum trough concentrations in paediatric subjects with moderate CD in each treatment group was comparable with the range of observed concentrations in paediatric subjects with severe CD. Within each treatment group, the range of individual CL/F and V2/F estimated by population PK model in paediatric subjects with moderate CD was comparable with the range observed in paediatric subjects with severe CD. The disease severity as a categorical covariate on CL/F and V2/F did not show significant impact on the pharmacokinetic estimates.

#### **2.3.4. Conclusions on clinical pharmacology**

The data supplied show no major differences in adalimumab concentrations between patients with moderate and severe CD.

### **2.4. Clinical efficacy**

#### **2.4.1. Dose response study**

No new studies have been performed for the present application which is considered acceptable. The approved dose for the treatment of paediatric patients with CD is 40 mg at Week 0 followed by 20 mg at Week 2 and every other week (eow) thereafter for patients  $< 40$  kg, and 80 mg at Week 0 followed by 40 mg at Week 2 and eow thereafter for paediatric patients  $\geq 40$  kg. In case there is a need for a more rapid response to therapy, the regimen 80 mg at Week 0 and 40 mg at Week 2 can be used for patients  $< 40$  kg, and the regimen 160 mg at Week 0 and 80 mg at Week 2 can be used for paediatric patients  $\geq 40$  kg. Patients who experience insufficient response may increase their dosing frequency to every week (ew).

#### **2.4.2. Main studies**

The assessment of efficacy in the sought extension of the indication is based on the pivotal phase III clinical trial M06-806 and interim results of the ongoing supportive study M06-807 (cut-off date 31 January 2015).



## Study M06-806

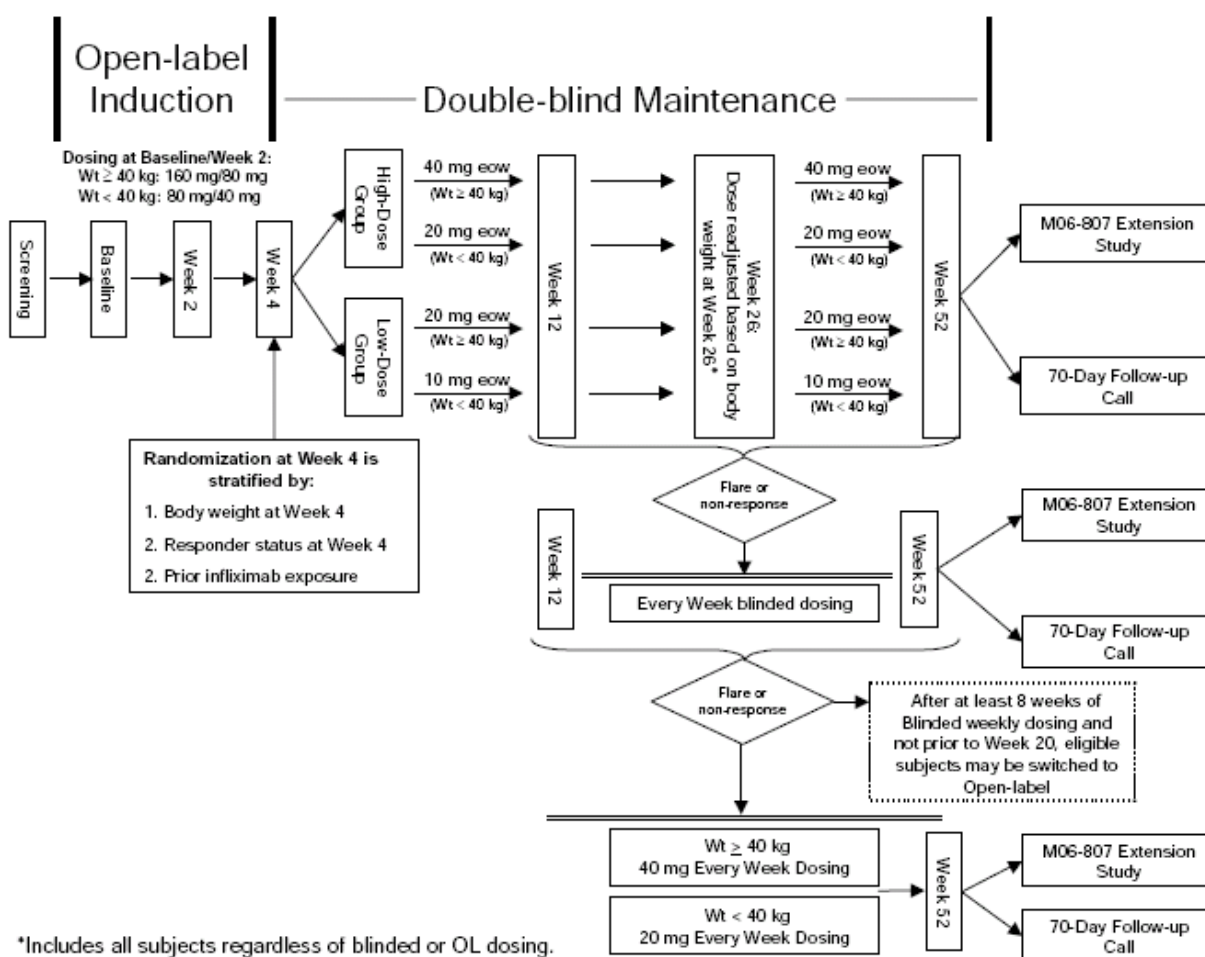
A multicenter, double-blind study to evaluate the efficacy, safety and pharmacokinetics of the human anti-TNF monoclonal antibody adalimumab in paediatric subjects with moderate to severe Crohn's disease

Methods

## Study 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.

**Figure 3. Schematic design of studies M06-806 and M06-807**



## Methods

### Study participants

#### Study M06-806

Paediatric patients with moderate to severe Crohn's diseases (PCDAI > 30), with confirmed CD by endoscopic or radiological evaluation, were recruited in the US and in EU. The patients had failed previous conventional therapy.

### 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 azathioprine (AZA) or 6-mercaptopurine (6-MP), or methotrexate (MTX).
- 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.

### Study M06-807

Enrolled patients had successfully completed study M06-806 through week 52 .i.e. being responder at any time during the study period and fulfilling all inclusion criteria and none of the exclusion criteria.

### ***Treatments***

#### Study M06-806

The patients received open-labelled induction therapy at weeks 0 and 2. The dosing regimen was dependent on the individual's weight. Patients that had a body weight  $\geq 40$  kg received 160 and 80 mg adalimumab 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  $\geq 15$  points compared to baseline) and previous infliximab therapy.

Patients that were randomized to the high dose group received either 40 mg or 20 mg every other week (eow) depending on weight ( $\geq 40$ / $<40$  kg). Corresponding figures for the low dose group were 20 mg or 10 mg eow depending on weight ( $\geq 40$ / $<40$  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, could patients that were non-responders (not having a decrease in PCDAI  $\geq 15$  points compared to baseline for 2 consecutive visits) or experienced worsening of Crohn's disease (increase in the PCDAI of  $\geq 15$  points from week 4 or PCDAI > 30) be switched to blinded treatment every week (ew) 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  $\geq 40$  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 was to be discontinued at week 26 for patients in clinical response.

#### Study M06-807

All patients received OL therapy based on their body weight. For patients that ended the previous study on DB treatment received 40 mg ( $\geq 40$  kg) or 20 mg (< 40 kg) eow, corresponding to high dose treatment arm. The higher dose was 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  $\geq 15$  points compared to the previous visit) were switched to ew treatment on the same dose.

### **Objectives**

#### Study M06-806

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

For the present application, subgroup analyses of data according to disease severity at baseline of Study M06-806 (PCDAI  $< 40$  defined as moderately active CD and  $\geq 40$  severely active CD) have been performed. In addition, to evaluate efficacy and safety for subjects who failed to respond to or did not tolerate either IMM or corticosteroids but not both, data have been analysed by prior use of IMM only or corticosteroids only.

#### Study M06-807

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 participated in, and successfully completed, study M06-806 through week 52.

### **Outcomes/endpoints**

#### Study M06-806

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

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, 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 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 adults PCDAI clinical remission at Week 4, for external comparison with OL induction at week 4 for all subjects in adults
- 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

Response was defined as decrease from baseline in PCDAI score  $\geq 15$  points.

#### Study M06-807

Efficacy evaluations for this interim analysis are based on the proportion of patients in clinical remission defined as PCDAI  $\leq 10$  and clinical response defined as CDAI  $\geq 15$  points lower than at baseline of study M06-806.

### ***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  $\geq 13$  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  $\geq 15$  points from the baseline score.

### ***Blinding (masking)***

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***

For the present application, PCDAI were summarized by baseline disease severity and by prior use of corticosteroids only or IMM only (before the first dose of adalimumab). IMMs were defined as medications with generic names of azathioprine, mercaptopurine or MT

### ***Results***

#### **Participant flow**

The disposition of patients is shown in **Table 1**.

**Table 1. Disposition of All Subjects in Studies M06-806 and M06-807 Through 31 January 2015 by Study M06-806 Baseline PCDAI (All Enrolled Subjects)**

Disposition	Adalimumab, N		All Subjects
	PCDAI < 40	PCDAI ≥ 40	
Received at least 1 dose of open-label induction treatment	82	110	192
Randomized to double-blind treatment	80	108	188
Completed Study M06-806	61	63	124
Enrolled in Study M06-807	49	51	100
Treated	49	51	100
Discontinued <sup>a</sup>	40	32	72
Ongoing	9	19	28
Primary reason for discontinuation from Study M06-806 or M06-807 <sup>b</sup>	n (%) <sup>c</sup>	n (%) <sup>c</sup>	n (%) <sup>c</sup>
All reasons	61 (74.4)	79 (71.8)	140 (72.9)
Adverse event	10 (12.2)	25 (22.7)	35 (18.2)
Withdrew consent	7 (8.5)	8 (7.3)	15 (7.8)
Lost to follow-up	4 (4.9)	2 (1.8)	6 (3.1)
Protocol violation	5 (6.1)	3 (2.7)	8 (4.2)
Death	0	0	0
Lack of efficacy	20 (24.4)	27 (24.5)	47 (24.5)
Administrative reasons	1 (1.2)	1 (0.9)	2 (1.0)
Other <sup>a</sup>	14 (17.1)	13 (11.8)	27 (14.1)
Missing	0	0	0

- a. Includes 18 subjects who discontinued from Study M06-807 because Humira was approved in their country. These subjects are listed as "discontinued" and also "completed the open-label extension" (Study M06-807 Third Interim CSR Appendix 16.2 1.1. Per the protocol, these subjects are considered to have completed.
- b. For subjects with no primary reason for discontinuation entered and with only 1 reason checked, the available reason was used as the primary reason for discontinuation.
- c. Denominator for PCDAI < 40 = 82; denominator for PCDAI ≥ 40 = 110; denominator for All Subjects = 192.

## **Recruitment**

### Study M06-806

The first patients' first visit: 04 May 2007

Last patients last visit: 18 May 2010

### Study M06-807

Interim results, cut-off date 31 January 2015

## **Baseline data**

Demographic characteristics are shown in Table 2.

**Table 2. Demographic Characteristics by Disease Severity at Baseline (ITT Analysis Set)**

Characteristic	PCDAI < 40 N = 80	PCDAI ≥ 40 N = 108
<b>Sex, n (%)</b>		
Male	41 (51.3)	64 (59.3)
Female	39 (48.8)	44 (40.7)
<b>Race, n (%)</b>		
White	70 (87.5)	96 (88.9)
Black	3 (3.8)	8 (7.4)
Asian	0	3 (2.8)
Multi-race	3 (3.8)	0
Other	4 (5.0)	1 (0.9)
<b>Age (years)</b>		
Mean ± SD	14.0 ± 2.42	13.4 ± 2.53
Median (range)	14.0 (7, 17)	13.0 (6, 17)
<b>Weight (kg)</b>		
Mean ± SD	47.5 ± 14.06	43.8 ± 16.22
Median (range)	44.5 (20, 81)	41.0 (19, 120)
<b>Height (cm)</b>		
Mean ± SD	156.7 ± 13.95	152.9 ± 15.13
Median (range)	160.0 (124, 185)	154.0 (106, 184)
<b>Z-score for height velocity</b>	N = 77	N = 107
Mean ± SD	-0.14 ± 3.449	-0.88 ± 4.030
Median (range)	0.00 (-6.4, 12.2)	-1.55 (-7.4, 16.1)
<b>IMPACT III score</b>	N = 77	N = 104
Mean ± SD	118.20 ± 16.069	112.04 ± 17.965
Median (range)	119.0 (73, 157.0)	113.5 (67, 151.0)
<b>CRP (mg/dL)</b>	N = 78	N = 108
Mean ± SD	1.80 ± 2.858	2.79 ± 3.133
Median (range)	0.65 (0.0, 16.8)	1.76 (0.0, 14.4)

PCDAI ranged from 25.0 to 37.5 among subjects with moderate CD (the lower value was a protocol deviation, as the inclusion criteria required a PCDAI > 30), with a median of 35. In subjects with severe disease, median PCDAI was 45, and values ranged from 40.0 to 62.5

Location of CD and duration of disease were similar between subjects with moderate and severe disease. While the proportions of subjects with draining cutaneous or perianal fistulas was somewhat higher in the subjects with severe disease, a clinically relevant percentage of subjects with moderate disease (15%) had at least 1 fistula in both the draining cutaneous and perianal fistula categories.

### **Numbers analysed**

For Study M06-806, the ITT Analysis Set was defined as all randomized subjects who received at least 1 dose of double-blind study drug (N = 188). For Study M06-807, the ITT Analysis Set was defined as all subjects who received at least one dose of adalimumab in Study M06-807 (N = 100).

For this submission two subgroups have been defined:

- By baseline disease activity: moderately active Crohn's disease (PCDAI < 40) and severely active Crohn's disease (PCDAI ≥ 40). This analysis allows for the evaluation of efficacy and safety for paediatric subjects with moderate CD (n = 82 and n = 80 for Safety and ITT Analysis Set,

respectively) separately from subjects with severe CD (n = 110 and n = 108 for Safety and ITT Analysis Set, respectively).

- By prior use of IMM only or CS only: Prior use of IMM only is defined as use of 6-MP, AZA, and/or MTX without CS before the first dose of study drug. Prior use of CS only is defined as use of CS without IMM before the first dose of study drug. This analysis allows for the evaluation of efficacy and safety for subjects who failed to respond to either IMM or CS but not both (n = 61 and n = 58 for Safety and ITT Analysis Set, respectively) before initiating adalimumab therapy.

### Outcomes and estimation

#### Study M06-806

#### Primary endpoint

Results for the primary efficacy endpoint in the total population in study M06-806 is shown in **Table 3**.

**Table 3. 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	Adalimumab High-Dose	All Adalimumab	Difference <sup>a</sup>	95% CI <sup>b</sup>	P value
		20 mg or 10 mg eow n/N (%)	40 mg or 20 mg eow n/N (%)				
Yes	Total	8/41 (19.5)	7/42 (16.7)	15/83 (18.1)	-2.85	-19.40, 13.71	0.736 <sup>c</sup>
	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 <sup>c</sup>
	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 <sup>d</sup>

eow = every other week; ITT = intent-to-treat; LOCF = last observation carried forward; NRI = non-responder imputation; PCDAI = Pediatric Crohn's Disease Activity Index; PP = Per Protocol

- Difference is between the Low- and High-Dose treatment groups.
- The CI was based on normal approximation.
- The P value is based on the chi-square test (or Fisher's exact test if  $\geq 20\%$  of the cells have expected cell count  $< 5$ ).
- 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.

In the subgroup with no previous infliximab use there was a larger proportion of patients in remission in the high dose group in comparison with the low dose group (low dose 19/54 (35 %), high dose 29/51 (57 %),  $P= 0.026$ ).

For the present submission, for patients with moderate disease at baseline, 40 % were in in clinical remission at week 26 (PCDAI score  $< 10$ ). The corresponding figure for patients with severe disease was 29 %.

#### Secondary endpoints

For the highest ranked secondary endpoint, proportion of patients in clinical remission at week 52 was 36 % in patients with moderate disease and 22 % in patients with severe disease.

The result from the remaining ranked secondary endpoints in subgroups with moderate or severe CD is shown in **Table 4**.

**Table 4. Additional Ranked Secondary Efficacy Endpoints by Disease Severity at Baseline (Study M06-806, ITT Population)**

<b>Ranked Secondary Endpoints</b>	<b>PCDAI &lt; 40 N = 80</b>	<b>PCDAI ≥ 40 N = 108</b>
Response at Week 26 (NRI), n/N (%)	47/80 (58.8)	54/108 (50.0)
Response at Week 52 (NRI), n/N (%)	35/80 (43.8)	31/108 (28.7)
Remission at Week 26 for subjects who were responders at Week 4 (NRI), n/N (%)	28/61 (45.9)	30/94 (31.9)
Remission at Week 4 (NRI), n/N (%)	22/80 (27.5)	30/108 (27.8)
Remission at Week 26 and discontinued corticosteroids for ≥ 90 days, for subjects using corticosteroids at Baseline (NRI), n/N (%)	7/26 (26.9)	12/45 (26.7)
Change from Baseline in Z-scores for height velocity at Week 26 (OC), mean	N = 55 1.92 ± 3.375	N = 74 2.35 ± 5.622
Change from Baseline in total IMPACT III scores at Week 26 (OC), mean ± SD	N = 47 26.12 ± 19.027	N = 57 23.98 ± 16.187

NRI = Nonresponder imputation

Note: Remission is defined as PCDAI ≤ 10. Response is defined as a decrease from Study M06-806 Baseline in PCDAI ≥ 15.

Remission and response in subgroups of children that had previously failed either corticosteroids or IMM is presented in Tables 5 and 6.

**Table 5. Remission (NRI) at Weeks 4, 26, and 52 by Prior IMM Use Only or CS Use Only (ITT Analysis Set)**

<b>Visit</b>	<b>All Subjects N = 188</b>	<b>Subjects Who Used Prior IMM Only or Prior CS Only<sup>a</sup> N = 58</b>
Week 4	52 (27.7)	19 (32.8)
Week 26	63 (33.5)	22 (37.9)
Week 52	53 (28.2)	24 (41.4)

a. Includes subjects who had previously failed to respond to either IMM treatment or to CS treatment; excludes subjects who were previously treated with both IMM and CS, as well as 2 subjects who, in violation of protocol criteria, had never received either IMM or CS.

Note: Medications with a start date prior to the first study drug administration date regardless of medication end date. In case medication start date or first study drug administration date was missing, the medication was counted as prior medication.



**Table 6. Response (NRI) at Weeks 4, 26, and 52 by Prior IMM Use Only or CS Use Only (ITT Analysis Set)**

Visit	All Subjects N = 188	Subjects Who Used Prior IMM Only or Prior CS Only <sup>a</sup> N = 58
Week 4	155 (82.4)	49 (84.5)
Week 26	101 (53.7)	35 (60.3)
Week 52	66 (35.1)	25 (43.1)

a. Includes subjects who had previously failed to respond to either IMM treatment or to CS treatment; excludes subjects who were previously treated with both IMM and CS, as well as 2 subjects who, in violation of protocol criteria, had never received either IMM or CS.

Note: Medications with a start date prior to the first study drug administration date regardless of medication end date. In case medication start date or first study drug administration date was missing, the medication was counted as prior medication.

For patients failing previous treatment with IMM or corticosteroids (but not both), a larger proportion achieved remission and response at week 26 and 52 as compared with the total group of patients.

#### Study M06-807

Of the 100 patients entering the open-labelled extension study there were 28 patients remaining (cut-off date January 2015). There were 9 patients with PCDAI < 40 and 19 with PCDAI ≥ 40 remaining.

At baseline of the study after one year treatment in Study M06-806, 67 % of the patients (67/100) were in remission (defined as PCDAI ≤ 10) and 95 % (95/100) were in response (defined as a decrease in PCDAI of at least 15 since baseline of study M06-806). Of patients remaining in the study a large proportion continued to be in remission and response at the different time-points.

#### **Supportive studies**

During the procedure the MAH was requested to discuss adalimumab monotherapy in children who are candidates for systemic therapy without necessarily being non-responders to other systemic therapies. This question was posed to obtain more insight into what is known about the potential risks and benefits of initiating adalimumab early in the treatment of paediatric Crohn's patients rather than leaving this option for later stages.

With regards to efficacy, no data in patients are available from the M06-806 and 807 studies that would represent this proposed target population, based on the inclusion criteria that were used. All patients were already pretreated with immunomodulators and/or corticosteroids and approximately one-half of all patients had also failed prior infliximab. Almost all patients continued systemic immunosuppressants and/or corticosteroids into the study as concomitant treatments. In addition, the characteristics of the children included in the studies most likely differ from children at an earlier stage of disease, and therefore it is not obvious that the results can be extrapolated to an early setting.

Some data can be obtained from a published study in adult patients of infliximab monotherapy, azathioprine monotherapy and the two drugs combined in adults with moderate to severe Crohn's disease who failed first-line therapy; infliximab monotherapy showed significantly higher rates of CS free remission and mucosal healing at Week 26 than azathioprine monotherapy, although the greatest efficacy was seen with combination therapy. Following subgroup analyses, the authors discussed that future prospective studies may show that measurement of CRP and endoscopy may identify those patients who are the most likely to have a greater response to infliximab monotherapy or combination therapy as compared to azathioprine monotherapy (Colombel JF et al, N Engl J Med. 2010;362:1383-95).

The RISK study (Walters TD, et al, *Gastroenterology*. 2014;146(2):383-91) is an ongoing observational research program in paediatric patients with CD diagnosed from 2008 through 2012 at paediatric gastroenterology centers in North America. The authors used propensity score methodology to compare the efficacy of early therapies (within 3 months after diagnosis), comparing early anti-TNFalpha monotherapy (68 subjects of whom 67 received infliximab, 1 adalimumab), early immuno monotherapy (248 subjects) and no early immunotherapy (236 subjects). However, patients could receive various other treatments (corticosteroids, mesalamine, enteral nutrition). Most patients (60-85%) received CS during the first 3 months.

It was concluded that early anti-TNFalpha monotherapy compared with early IM monotherapy was associated with significantly improved overall clinical outcomes in terms of CS-free clinical remission and linear growth during the first year. The authors also examined the question of whether patients who failed IM and then went on to anti-TNFalpha monotherapy between 3 and 12 months (n=47) had similar outcomes to patients receiving anti-TNFalpha in the first 3 months (n=68), which showed higher CS and surgery-free remission at 1 year in the early anti-TNFalpha group.

In the discussion, the authors cite some limitations related to the observational nature of the study, lack of data on mucosal improvement or healing, lack of protocol-based dosing, among others, concluding that further data will be required to best identify children most likely to benefit from early treatment with an anti-TNFalpha therapy.

### **2.4.3. Discussion on clinical efficacy**

#### **Design and conduct of clinical studies**

Paediatric patients with moderate to severe active Crohn's diseases (PCDAI > 30), with confirmed CD by endoscopic or radiological evaluation, were included in the pivotal study. The patients had active disease in spite of concomitant treatment with an oral corticosteroid, and/or azathioprine (AZA) or 6-mercaptopurine (6-MP), or methotrexate (MTX). The primary endpoint was clinical remission at week 26. The study design and conduct has been previously assessed as appropriate (Humira-H-C-481-II-0082).

For the present submission new analyses have been performed in order to evaluate the efficacy in subgroups of patients with moderate or severe disease at baseline. Further, the efficacy has been evaluated in subgroups of patients who failed or did not tolerate prior treatment with IMM only or corticosteroids only.

#### **Efficacy data and additional analyses**

In general, the effect of adalimumab in patients with moderate disease was higher than in patients with severe disease. In comparison with the effect in the total group, higher responses were also observed for patients that had previously failed either corticosteroids or IMM (but not both). The CHMP considered that the respective groups exerted similar efficacy by providing a breakout of the results for remission and response for only prior IMM users, only CS users, users of both IMM and CS and the overall population, respectively.

Results from the ongoing extension study support continuous benefit for patients that initially responded to the treatment although the clinical relevance of the results is not fully apparent since the majority of patients have discontinued from the study.

In the course of the procedure, the MAH was requested to discuss also the benefit-risk of adalimumab monotherapy in children who are candidates for systemic therapy without necessarily being non-responders to other systemic therapies, i.e., without having an inadequate response to current or prior systemic therapy with immunomodulators and/or corticosteroids. However, due to the inclusion criteria in the pediatric CD studies (Studies M06-806 and M06-807), no data are available on the efficacy in this target population from these studies. A recent consensus guideline (ECCO/ESPGHAN) on the medical management of pediatric Crohn's disease (Ruemmele FM, et al *J Crohns Colitis*. 2014;8(10):1179-207)

states that anti-TNF therapy as primary induction therapy may be considered for selected children with high risk for poor outcome, citing ongoing studies of the Porto IBD working group aimed to establish more precise predictors of poor outcome in children as clear criteria mandating treatment escalation have so far not been fully defined yet.

Thus, even though data from the RISK study indicate that first line systemic treatment with anti-TNF-alpha therapy may be more efficient compared to IM, currently there seems to be uncertainties with respect to what patient groups that may benefit. Also, a direct comparison to corticosteroids is not addressed by the RISK study as most patients were treated with concomitant CS.

#### 2.4.4. Conclusions on the clinical efficacy

The results of the pivotal study M06-806 have previously been accepted to be supportive of the effect of adalimumab in the treatment of active CD in children. At the time of the approval of the paediatric CD indication, the indication was only granted for patients with severe disease due to the limited safety data available.

Efficacy is supported also for patients with moderate disease and for patients that have previously failed either corticosteroids or IMMs.

### 2.5. Clinical safety

#### Introduction

Treatment with adalimumab is associated with potentially serious adverse events that include serious infections, risk of lymphoproliferative disorders or malignancies including HSTCL.

The present safety analysis set is presented for several safety populations:

- the safety population from study M06-806 (n=192) (all patients receiving at least one dose of adalimumab during the study)

- the any adalimumab analysis set, that includes all patients that received at least one dose of adalimumab in study M06-806 (n=192). Safety data are available from baseline of the pivotal study through last available observation in Study M06-806/Study M06-807.

- the safety population from study M06-807 (n=100) (patients that received at least one dose of adalimumab during the study M06-807).

#### Patient exposure

##### Study M06-806

The exposure during the maintenance phase in the Study M06-806 is presented in Table 7.

**Table 7. Extent of Exposure During Double-Blind Maintenance Period by Disease Severity at Baseline (Safety Analysis Set)**

	PCDAI < 40 N = 80	PCDAI ≥ 40 N = 108
Duration (days), mean ± SD	217.5 ± 128.51	182.6 ± 123.29
Total number of injections, mean ± SD	15.4 ± 9.15	12.9 ± 8.82
Total dose (mg), mean ± SD	416.3 ± 324.45	336.1 ± 303.91
Patient-years of exposure	47.6	54.0

Exposure to adalimumab during the 4-week open-label induction period was of similar extent in the disease severity subgroups. During the double-blind maintenance period, mean duration of exposure was greater among subjects with moderate disease than subjects with severe disease. This difference is

attributable to the higher completion rate in Study M06-806 for patients with moderate disease (61/80 [76.3%]) compared to those with severe disease (63/108 [58.3%]) based on the higher rate of AEs leading to discontinuation in the severe disease subgroup.

#### Study M06-807

Mean exposure to adalimumab since the first dose in Study M06-806 was 1631.9 ± 706.67 days (approximately 4.5 years), for a total of 446.8 patient-years of exposure. Since the start of Study M06-807, 52 subjects had at least 208 weeks (4 years) of exposure to adalimumab as of the 31 January 2015 data cut-off.

#### Studies M06-806 and M06-807

For an overview of the total extent of the exposure see Table 8.

**Table 8. Extent of Exposure Through 31 January 2015 by Study M06-806**

**Baseline PCDAI (Study M06-806 and Study M06-807, Any Adalimumab Analysis Set)**

<b>Duration of Exposure</b>	<b>PCDAI &lt; 40 N = 82 N (%)</b>	<b>PCDAI ≥ 40 N = 110 n (%)</b>	<b>All Subjects N = 192 n (%)</b>
1549 – 1639 days (up to Week 234)	27 (32.9)	30 (27.3)	57 (29.7)
1640 – 1730 days (up to Week 247)	27 (32.9)	28 (25.5)	55 (28.6)
1731 – 1821 days (up to Week 260)	26 (31.7)	26 (23.6)	52 (27.1)
1822 – 1912 days (up to Week 273)	26 (31.7)	26 (23.6)	52 (27.1)
1913 – 2003 days (up to Week 286)	22 (26.8)	25 (22.7)	47 (24.5)
> 2003 days	22 (26.8)	25 (22.7)	47 (24.5)
<b>Number treated</b>	<b>82</b>	<b>110</b>	<b>192</b>
<b>Total number of patient years</b>	<b>235.3</b>	<b>262.8</b>	<b>498.1</b>

Notes: Includes Study M06-806 and Study M06-807.

Exposure is defined as the date of the last adalimumab dose minus the date of the first adalimumab dose + 14 days in Study M06-806. If the first adalimumab dose date occurred in Study M06-807, a between-studies dosing gap > 14 days is excluded.

The overall exposure at the cut-off date for the present submission was 498 PYs as compared with the exposure in the original submission that was 259 PYs.

### **Adverse events / Serious Adverse events**

#### Study M06-806

During the open-labelled induction period there were no major differences between the rate of AEs in patients with moderate and severe disease although the number of patients with infections were higher in patients with moderate CD (22 %, 18/82) than in those with severe CD (8 %, 9/110). There were 2 serious infections in children with moderate disease (Yersinia infection and viral infection).

There were 4 additional SAEs, two in the moderate CD group (IBD flare, relapse of CD) and two in patients with severe CD (CD exacerbation, irregular heart rate (with no clinically significant finding on ECG and Holter monitor tests)).

Adverse events during the maintenance period are presented in Table 9.

**Table 9. Overview of Treatment-Emergent Adverse Events During Double-Blind Maintenance Period by Disease Severity at Baseline Among Subjects Who Received at Least One Dose of Double-Blind Study Drug (Safety Analysis Set)**

Treatment-Emergent AE Category	PCDAI < 40 N = 80, PYs = 47.6		PCDAI ≥ 40 N = 108, PYs = 54.0		All Subjects N = 188, PYs = 101.6	
	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)
Any AE	69 (86.3)	458 (962.2)	98 (90.7)	513 (950.0)	167 (88.8)	971 (955.7)
Any AE at least possibly drug-related <sup>a</sup>	38 (47.5)	117 (245.8)	38 (35.2)	104 (192.6)	76 (40.4)	221 (217.5)
Any severe AE	12 (15.0)	15 (31.5)	18 (16.7)	26 (48.1)	30 (16.0)	41 (40.4)
Any SAE	12 (15.0)	12 (25.2)	29 (26.9)	32 (59.3)	41 (21.8)	44 (43.3)
Any AE leading to discontinuation of study drug	5 (6.3)	5 (10.5)	22 (20.4)	28 (51.9)	27 (14.4)	33 (32.5)
Any infectious AE	46 (57.5)	103 (216.4)	57 (52.8)	96 (177.8)	103 (54.8)	199 (195.9)
Any serious infectious AE	2 (2.5)	2 (4.2)	6 (5.6)	6 (11.1)	8 (4.3)	8 (7.9)
Any malignancy AE	0	0	0	0	0	0
Any opportunistic infection related AE (excl. TB) <sup>b</sup>	0	0	2 (1.9)	2 (3.7)	2 (1.1)	2 (2.0)
Any hepatic related AE	3 (3.8)	3 (6.3)	6 (5.6)	8 (14.8)	9 (4.8)	11 (10.8)
Any allergic reaction related AE	5 (6.3)	6 (12.6)	3 (2.8)	5 (9.3)	8 (4.3)	11 (10.8)
Any hematologic related AE	5 (6.3)	8 (16.8)	8 (7.4)	8 (14.8)	13 (6.9)	16 (15.7)
Deaths <sup>c</sup>	0	0	0	0	0	0

a. As assessed by the investigator.

b. Opportunistic infections were *Aeromonas* infection and *Histoplasmosis disseminata*, the latter of which was serious and resulted in study drug discontinuation; both events resolved with treatment.

c. Includes non-treatment emergent deaths.

Note: Treatment-emergent adverse event is defined as any AE with an onset date on or after the first double-blind adalimumab dose and prior to double-blind ew or open-label dose and up to 70 days after the last dose of study drug if subject discontinued prematurely from the double-blind ew phase.

The rate of AEs leading to discontinuation, SAEs, and serious infections was lower in patients with moderate disease as compared with patients with severe disease. The majority of SAEs were related to CD (27%).

Patients that had failed either corticosteroids or IMM treatment had similar rates of AEs, SAEs (including infections) as the overall study population.

No deaths or malignancies were reported.

#### Study M06-807

Among patients that continued to Study M06-807 (n=100) forty-eighth percent (48.0%) reported SAEs, the most frequent of which were CD (worsening or flare) (24.0%) and anal abscess (3.0%). All other SAEs were reported by one or two patients each. One patient had an SAE of systemic lupus erythematosus; the investigator considered the event probably related to study drug, and the subject was discontinued from the study. Two subjects with a history of anaemia had SAEs of anaemia during the study; both events resolved and the subjects continued in the study. One subject with a history of hepatitis who was receiving concomitant MTX experienced an SAE of hepatitis which the investigator considered probably not related to study drug; the event resolved and the subject continued in the study. Three subjects had intestinal stricture-related SAEs (small intestinal stenosis, ileal stenosis, and colonic stenosis), and two subjects had intestinal perforation-related SAEs (ileal perforation, large intestine perforation); none of these events were considered related to the study drug by the investigator. No malignancies or deaths were reported.

#### Studies M06-806 and M06-807

Treatment-emergent AEs are defined as new events that began on or after the first dose of adalimumab in Study M06-806 up to either 70 days after the last dose or until the interim analysis cut-off date (31 January 2015).

The rate of AEs from baseline of Study M06-806 to the end of Study M06-807 (interim report) is presented in Table 10.

**Table 10. Overview of Treatment-Emergent Adverse Events by Study M06-806 Baseline PCDAI (Study M06-806 and Study M06-807, Any Adalimumab Analysis Set)**

Treatment-Emergent AE Category	PCDAI < 40 N = 82, PYs = 235.3		PCDAI ≥ 40 N = 110, PYs = 262.8		All Subjects N = 192, PYs = 498.1	
	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)
Any AE	81 (98.8)	1433 (609.0)	108 (98.2)	1466 (557.8)	189 (98.4)	2899 (582.0)
AE at least possibly drug-related <sup>a</sup>	52 (63.4)	319 (135.6)	64 (58.2)	299 (113.8)	116 (60.4)	618 (124.1)
Severe AE	23 (28.0)	46 (19.5)	43 (39.1)	71 (27.0)	66 (34.4)	117 (23.5)
SAE	38 (46.3)	77 (32.7)	54 (49.1)	87 (33.1)	92 (47.9)	164 (32.9)
AE leading to discontinuation of study drug	18 (22.0)	21 (8.9)	43 (39.1)	57 (21.7)	61 (31.8)	78 (15.7)
SAE leading to discontinuation of study drug	13 (15.9)	14 (5.9)	25 (22.7)	25 (9.5)	38 (19.8)	39 (7.8)
SAE at least possibly drug-related <sup>a</sup>	7 (8.5)	9 (3.8)	6 (5.5)	6 (2.3)	13 (6.8)	15 (3.0)
Fatal AE	0	0	0	0	0	0
Deaths <sup>b</sup>	0	0	0	0	0	0

a. As assessed by the investigator.

a. Includes non-treatment-emergent deaths.

Note: Treatment-emergent AE 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 most frequently reported AEs (reported by ≥ 20 %) were CD worsening/flare, headache, upper respiratory tract infection, nasopharyngitis, diarrhoea, oropharyngeal pain, abdominal pain, vomiting, pyrexia, arthralgia and cough.

The most frequently reported AEs that were considered to be possibly or probably related to adalimumab were injection site reaction, viral upper respiratory tract infection, headache, sinusitis, and upper respiratory tract infection. All Herpes zoster events considered possibly or probably related to the study drug were mild or moderate in severity and resolved with treatment.

An overview of SAEs considered as probably related or possibly related is presented in Table 11.

**Table 11. Listing of Subjects with Serious Adverse Events Possibly or Probably Related to Study Drug as of 31 January 2015 Including Data from Both Study M06-806 and Study M06-807 (Safety Population)**

A = Asian; B = black; D/C = discontinuation; eow = every other week; ew = weekly; F = female; IV = intravenous; M = male; NPO = oral nutrition prohibited; PR = probably related; PS = possibly related; SAE = serious adverse event; W = white

- a. Age at Screening for Study M06-806.
- b. Day relative to the first dose of adalimumab in Study M06-806. Numbers in parentheses indicate number of days after last dose of adalimumab.
- c. Hosp. = hospitalization or prolongation of hospitalization; Med/surg. = important medical or surgical intervention.
- d. Relationship as assessed by the investigator.
- e. SAE led to discontinuation from study drug.

	Age (Years)/Sex/Race <sup>a</sup>	Treatment Group	Onset Day <sup>b</sup>	Duration	Preferred Term	Severity	Reason Serious <sup>c</sup>	Relationship to Study Drug	Relevant Prior and Concomitant Medication
<b>Study M06-806</b>									
	14/M/A	20 mg eow	221	5 days	Pancreatitis acute	Moderate	Hosp.	PS	Prior infliximab, prednisone, AZA, MTX
<b>Study M06-807</b>									
	14/F/W	20 mg eow	1247 1565	3 days 15 days	Pneumonia Cystitis viral	Severe Severe	Hosp. Hosp.	PS PS	Prior 6-MP, prednisone; concomitant AZA
	13/M/W	40 mg eow	386 (7)	9 days	Colitis ulcerative	Severe	Hosp.	PR	Prior infliximab, prednisone, AZA, concomitant AZA
	14/F/W	40 mg eow	534	>134 days	Systemic lupus erythematosus <sup>d</sup>	Severe	Med/surg.	PR	Prior and concomitant AZA and prednisone
	11/F/W	40 mg eow	983	34 days	Lymphadenitis	Moderate	Hosp.	PS	Prior infliximab, prednisone, MTX, 6-MP, concomitant 6-MP, MTX
	7/M/W	10 mg eow	616 2329	4 days 76 days	Staphylococcal abscess Subcutaneous abscess <sup>e</sup>	Mild Moderate	Hosp.; Med/surg. Hosp.; Med/surg.	PR PR	Prior prednisone; concomitant mesalazine, AZA, metronidazole
	12/F/W	20 mg eow	1056	6 days	Pneumonia	Moderate	Hosp.	PS	Prior infliximab, prednisone, AZA, concomitant mesalazine, MTX
	13/M/W	10 mg eow	852	22 days	Subcutaneous abscess	Moderate	Hosp.	PS	Prior and concomitant AZA, mesalazine
	14/M/W	10 mg eow	628	64 days	Herpes virus infection	Moderate	Hosp.	PS	Prior infliximab, concomitant mesalazine, AZA, prednisone
	16/F/B	40 mg eow	740	9 days	Tonsillitis	Moderate	Hosp.	PS	Prior infliximab, prednisolone; concomitant AZA

A = Asian; B = black; D/C = discontinuation; eow = every other week; ew = weekly; F = female; IV = intravenous; M = male; NPO = oral nutrition prohibited; PR = probably related; PS = possibly related; SAE = serious adverse event; W = white

- a. Age at Screening for Study M06-806.
- b. Day relative to the first dose of adalimumab in Study M06-806. Numbers in parentheses indicate number of days after last dose of adalimumab.
- c. Hosp. = hospitalization or prolongation of hospitalization; Med/surg. = important medical or surgical intervention.
- d. Relationship as assessed by the investigator.
- e. SAE led to discontinuation from study drug.

### Adverse event of special interest

Twenty-four categories of AEs of special interest due to presumed or identified risks associated with the immunomodulating mechanism of action of adalimumab or with the underlying disease have been specifically examined. An overview is shown in Table 12

**Table 12. Overview of Treatment-Emergent Adverse Events of Special Interest by Study M06-806 Baseline PCDAI (Study M06-806 and Study M06-807, Any Adalimumab Analysis Set)**

Treatment-Emergent AE Category	PCDAI < 40 N = 82, PYs = 235.3		PCDAI ≥ 40 N = 110, PYs = 262.8		All Subjects N = 192, PYs = 498.1	
	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)	n (%)	E (E/100 PYs)
Any infectious AE	64 (78.0)	329 (139.8)	80 (72.7)	348 (132.4)	144 (75.0)	677 (135.9)
Any serious infectious AE	12 (14.6)	19 (8.1)	12 (10.9)	14 (5.3)	24 (12.5)	33 (6.6)
Lymphoma	0	0	0	0	0	0
Non-melanoma skin cancer (NMSC)	0	0	0	0	0	0
Malignant AE (excl. NMSC and lymphomas)	0	0	0	0	0	0
Opportunistic infection (excl. TB)	2 (2.4)	5 (2.1)	6 (5.5)	6 (2.3)	8 (4.2)	11 (2.2)
Demyelinating disease	0	0	0	0	0	0
Any malignant AE	0	0	0	0	0	0
Any malignant AE (including lymphomas, excluding NMSC)	0	0	0	0	0	0
Hepatosplenic T-cell lymphoma	0	0	0	0	0	0
Leukemia	0	0	0	0	0	0
Melanoma	0	0	0	0	0	0
Injection site reaction related AE	21 (25.6)	38 (16.1)	21 (19.1)	67 (25.5)	42 (21.9)	105 (21.1)
Lupus-like syndrome	0	0	1 (0.9)	1 (0.4)	1 (0.5)	1 (0.2)
Allergic reaction related AE	14 (17.1)	37 (15.7)	22 (20.0)	37 (14.1)	36 (18.8)	74 (14.9)
Hematologic related AE	9 (11.0)	14 (5.9)	21 (19.1)	25 (9.5)	30 (15.6)	39 (7.8)
Cutaneous vasculitis	0	0	0	0	0	0
Diverticulitis related AE	0	0	0	0	0	0
Intestinal perforation related AE	1 (1.2)	1 (0.4)	1 (0.9)	1 (0.4)	2 (1.0)	2 (0.4)
Intestinal stricture related AE	4 (4.9)	4 (1.7)	2 (1.8)	2 (0.8)	6 (3.1)	6 (1.2)
Hepatic related AE	1 (1.2)	1 (0.4)	0	0	1 (0.5)	1 (0.2)
Elevated ALT levels related AE	4 (4.9)	4 (1.7)	5 (4.5)	6 (2.3)	9 (4.7)	10 (2.0)
Myocardial infarction related AE	0	0	0	0	0	0
Cerebrovascular accident related AE	0	0	0	0	0	0
Pulmonary embolism related AE	0	0	0	0	0	0
Psoriatic condition and worsening AE	3 (3.7)	3 (1.3)	3 (2.7)	4 (1.5)	6 (3.1)	7 (1.4)
Stevens-Johnson syndrome related AE	0	0	0	0	0	0
Erythema multiforme related AE	0	0	0	0	0	0
Congestive heart failure related AE	0	0	0	0	0	0
Interstitial lung disease related AE	0	0	0	0	0	0
Pancreatitis related AE	1 (1.2)	1 (0.4)	0	0	1 (0.5)	1 (0.2)

ALT = alanine aminotransferase; TB = tuberculosis

Note: Treatment-emergent AE 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.

## Laboratory findings

No safety concerns have been revealed. Results from the third interim report of Study M06-807 show that there were no major changes in clinical chemistry parameters, urinalysis, and haematology parameters that were of relevance from a safety perspective.

## Discontinuation due to adverse events

Overall the discontinuation rate due to adverse events was 22 % (18/82) for patients with moderate CD as compared with (39 % 43/110) for patients with severe disease. The majority of discontinuations were associated with the underlying disease.

## Post marketing experience

As of 31 December 2014, the estimated postmarketing adalimumab exposure in patients < 18 years of age is 95,206 PYs worldwide. The MAH provided a summary of safety from the STRIVE registry in patients with pJIA and the CAPE registry in patients with paediatric CD. In the latter registry, however, only 11 patients have been enrolled as of 28 February 2015. Enrolment in the STRIVE registry is complete with 543 treated patients in the Humira group (two-thirds in combination with MTX) and 303 patients in the MTX treatment group. Rates of treatment-emergent AEs were generally fairly similar between the



treatment groups. Also malignancies and several other AESI, such as cardiovascular events, are more likely observed in the adult patients than in the paediatric patient population. Overall, the post marketing safety data was consistent with the known safety profile of adalimumab in the paediatric population.

### **2.5.1. Discussion on clinical safety**

The safety profile of adalimumab in the treatment of paediatric moderately active Crohn's disease seems to be similar to that for severely active disease. No new safety concerns have been identified. The well-established safety profile of adalimumab is characterized by the risk of infections, and also by more rare events as demyelination and malignancies (including HSTCL).

In general, paediatric patients with moderate CD, experienced overall higher exposure-adjusted rate of AEs and SAEs at least possibly related to the study drug compared to patients with severe CD. However, discontinuations, SAEs, and serious infections were more common in patients with severe disease than in those with moderate disease. Worsening of CD was the most common adverse event and also the most common reason for discontinuations.

Patients that had failed either corticosteroids or IMM treatment had similar rates of AEs, SAEs (including infections) as the overall study population. To identify the different contribution of IMM or corticosteroids the MAH provided an overview of AEs separately for those subjects with prior IMM, and those subjects with prior CS use and those who were treated with both showing a similar safety profile between these group of patients.

The MAH provided a brief overview of post-marketing data from the respective paediatric indications which did not reveal any new safety concerns. However, a long-term non-interventional registry is already included in the RMP and was initiated in 2014 to assess safety and efficacy of adalimumab in paediatric patients with moderately to severely active Crohn's disease (study P11-292, EMEA/H/C/481 MEA 080). Patients will be followed for up to 10 years.

### **2.5.2. Conclusions on clinical safety**

There were no unexpected safety signals revealed during the study periods and post marketing. There were no major differences regarding adverse reactions between paediatric patients with moderately and severely active Crohn's disease. As outlined in the RMP interim reports on the ongoing registry P-11-292 adalimumab in paediatric patients with moderately to severely active Crohn's disease will be submitted annually to continue monitoring in particular safety in this population.

### **2.5.3. PSUR cycle**

The PSUR cycle remains unchanged.

## **2.6. Risk management plan**

No new RMP version is submitted with this application which is considered acceptable. The pharmacovigilance plan lists already a post authorisation follow up (registry) on safety and effectiveness of adalimumab in paediatric patients with moderately to severely active CD and results are reported annually and the safety specification includes also paediatric CD, in an appropriate way. With respect to the risk minimisation plan, the MAH already has an education program in place.

## 2.7. Update of the Product information

As a consequence of this new indication, sections 4.1 and 4.2, 4.8 and 5.1 of the SmPC have been updated as follows:

The following amendment to the existing paediatric CD indication wording is proposed (new text **bolded** and underlined):

### 4.1 Therapeutic indications

#### Paediatric Crohn's Disease

Humira is indicated for the treatment of **moderately to severely** active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, **and** a corticosteroid and **/or** an immunomodulator, or who are intolerant to or have contraindications for such therapies.

### 4.2 Posology and method of administration

#### Paediatric Crohn's disease patients < 40 kg:

The recommended Humira induction dose regimen for paediatric patients with **moderately to severely active** Crohn's disease is 40 mg at Week 0 followed by 20 mg at Week 2.

#### Paediatric Crohn's disease patients ≥ 40 kg:

The recommended Humira induction dose regimen for paediatric patients with **moderately to severely active** Crohn's disease is 80 mg at Week 0 followed by 40 mg at Week 2.

### 4.8 Undesirable effects

#### Malignancies and lymphoproliferative disorders

No malignancies were observed in 249 paediatric patients with an exposure of 655.6 patient years during Humira trials in patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis). In addition, no malignancies were observed in 192 paediatric patients with an exposure of ~~258.9~~ **498.1** patient years during ~~a Humira trial~~s in paediatric patients with Crohn's disease. No malignancies were observed in 77 paediatric patients with an exposure of 80.0 patient years during a Humira trial in paediatric patients with chronic plaque psoriasis.

#### Section 5.1 Pharmacodynamic Properties

**One hundred patients (n=100) from the Paediatric CD Study continued in an open-label long-term extension study. After 5 years of adalimumab therapy, 74.0% (37/50) of the 50 patients remaining in the study continued to be in clinical remission, and 92.0% (46/50) of patients continued to be in clinical response per PCDAL.**

**In patients with moderately to severely active paediatric Crohn's disease, the rate of anti-adalimumab antibody development in patients receiving adalimumab was 3.3%.**

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet

has been submitted by the applicant and has been found acceptable because there were no proposed changes to the package leaflet.

### **3. Benefit-Risk Balance**

#### ***Benefits***

##### **Beneficial effects**

Adalimumab has been approved for the treatment of adult severe Crohn's disease since 2007 and for moderate CD in adults and paediatric severe CD since 2012. The approval of the paediatric indication was based on data from the pivotal study M06-806 that was performed on children 6 to 17 years of age with moderate to severe CD (defined as PCDAI >30 points). The children and adolescents had failed previous conventional treatments, i.e. failed enteral nutrition therapy a corticosteroid and/or an immunomodulator. There was also a subpopulation included that had failed or were intolerant to previous treatment with infliximab.

A clinically relevant effect of Humira in the treatment of paediatric Crohn's disease has been shown in the pivotal study for up to 12 months. Post-hoc analyses of the data from the pivotal study do not reveal any differences in the rates of clinical remission and response between patients with moderate and severe paediatric Crohn's disease. Furthermore results from the ongoing extension study support continuous benefit for patients that initially responded to the treatment although the clinical relevance of the results is not fully apparent since the majority of patients have discontinued from the study.

##### **Uncertainty in the knowledge about the beneficial effects**

The majority of patients included in the open-labelled extension study have discontinued. Thus, data in support of long-term efficacy of the treatment is limited. Further data on effectiveness in paediatric Crohn's disease is generated post authorisation within an ongoing registry as outlined in the RMP which is considered appropriate.

#### ***Risks***

##### **Unfavourable effects**

There were no unexpected safety signals revealed during the study periods and post marketing. The safety profile of adalimumab is associated with potential serious adverse events including increased risk of infections, risk of lymphoproliferative disorders or malignancies.

There were minor differences between paediatric patients with moderate and severe disease in the rate of adverse events. The differences identified concerned a higher rate of AEs and SAEs at least possibly related to the study drug in the subgroup with moderate disease activity at baseline. However, in the subgroup of patients with severe disease activity there were higher rates of severe AEs, SAEs and AEs leading to discontinuation of the study drug.

The MAH provided an overview of AEs separately for those subjects with prior IMM, and those subjects with prior CS use and those who were treated with both showing a similar safety profile.

##### **Uncertainty in the knowledge about the unfavourable effects**

Long-term data from paediatric patients being treated with adalimumab for Crohn's disease is still limited. As outlined in the RMP a dedicated registry is performed to generate more safety data also in the paediatric population.

## Effects Table

**Table 1. Effects Table for adalimumab in the treatment of paediatric patients with moderate and severe Crohn's Disease (data cut-off:31 January 2015)**

Effect	Short Description	Unit	Adalimumab		Uncertainties	References
			Moderate CD	Severe CD	Strength of evidence	
<b>Favourable Effects</b>						
Remission week 26	PCDAI score ≤ 10	%	40	29	Effects maintained up to week 52 with 36% and 22% of moderate and severe patients in remission	<b>Study M06-806</b>
Effect	Short description	Unit	Adalimumab Moderate CD	Severe CD	Uncertainties Strength of evidence	References
<b>Unfavourable Effects</b>						
Infections	Any	E/100 PYs	139.8	132.4	Other risks observed with adalimumab use in other indications, such as malignancies may also apply in paediatric Crohn's	Studies M06-806 and M06-807
	Serious					
	Opportunistic (excl. TB)		8.1	5.3		
		2.1	2.3			
Intestinal stricture		E/100 PYs	1.7	0.8		
Allergic reactions		E/100 PYs	15.7	14.1		

Abbreviations: CD: Crohn's disease, PCDAI : Paediatric Crohn's Disease Activity Index TB: Tuberculosis, E: Events, PY: Patient years

## **Benefit-Risk Balance**

### **Importance of favourable and unfavourable effects**

The treatment options available for paediatric patients with Crohn's disease comprise apart from anti-TNF treatment, corticosteroids and immunomodulators such as AZA / 6-MP. Particularly for growing children, long-term use of corticosteroids is associated with serious safety concern, and thus a possibility to taper such treatment is an important goal. Further, AZA/6-MP is associated with serious adverse events as well. Recent data more and more support a primary role of those treatments for the development of HSTCL. Thus, there is a need for additional treatment options for children with CD. Adalimumab is considered a valuable option for treatment of patients with moderate and severe paediatric CD.

### **Benefit-risk balance**

A clinically relevant effect of adalimumab in induction and maintenance of clinical remission and response has been demonstrated in the paediatric population with Crohn's disease of both moderate and severe activity.

No new safety concerns have been revealed from post authorisation experience and there are no major differences in the safety profile at between patients with different degree of disease activity. Long-term data are still limited and a non-interventional follow-up registry as outlined in the RMP will provide further structure insight post authorisation.

### **Discussion on the Benefit-Risk Balance**

Treatment with adalimumab has been shown to induce and maintain remission and response in paediatric patients with active Crohn's disease up to 12 months. When the indication in severely active disease was granted the effect had been considered to be of clinical relevance. Presented post-hoc analyses show that there are no differences in response between patients with moderate and severe CD or between patients failing either corticosteroids or IMM only compared to the total population.

In the initial approval for the treatment of the paediatric CD patients (EMA/H/C/000481/II/0088), the claim to include moderate disease in the indication was not accepted because of the limited long-term safety experience with adalimumab.

There were no new safety signals during the studies and based on post marketing experience the safety profile of adalimumab can today be considered as being well established. The risks related to serious infections and malignancies including HSTCL, as well as other types of serious events, are considered balanced with current risk minimisation measures. Long-term data are still limited but addressed by a non-interventional follow-up registry as outlined in the RMP.

Furthermore also conventional therapy for CD include disadvantages such as affecting growth in the case of corticosteroids as well as a risk of malignancies associated with the use of immunomodulators. Adalimumab is therefore considered an option for the treatment of paediatric patients with moderately active Crohn's disease.

## **4. Recommendations**

### **Outcome**

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

<b>Variation accepted</b>		<b>Type</b>	<b>Annexes affected</b>
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIA

Extension of Indication for the treatment of paediatric Crohn's disease to include the treatment of moderately active Crohn's disease for Humira; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial corrections to the Labelling.

The variation leads to amendments to the Summary of Product Characteristics and Labelling.

### ***Paediatric data***

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0324/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.