Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for adalimumab

Proprietary Product Name: Humira

Sponsor: AbbVie Pty Ltd

First round CER: October 2013

Second round CER: January 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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List of abbreviations

Abbreviation	Meaning
6-MP	6-mercatopurine
AAA	Anti-adalimumab antibody
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate transaminase
AZA	Azathioprine
BMI	Body mass index
BW	Body weight
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	Confidence interval
DB	Double-blind
eow	Every other week
EU	European Union
Ew	every week, weekly
HACA	Human anti-chimeric antibody
ICH	International Conference on Harmonisation
IgG1	Immunoglobulin
IEC	Independent Ethics Committee
IMM	Immunosuppressant
ITT	Intent-to-Treat
IV	Intravenous

Abbreviation	Meaning
IVRS	Interactive voice response system
JIA	Juvenile idiopathic arthritis
LFT	Liver function test
LOCF	Last observation carried forward
MTX	Methotrexate
NRI	Non-responder imputation
OC	Observed case
OL	Open-label
PCDAI	Paediatric Crohn's Disease Activity Index
PK	Pharmacokinetic
PP	Per-protocol
SC	Subcutaneous(ly)
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF	Tumour Necrosis Factor
US	United States

1. Introduction

At the time of this evaluation report, the following dosage forms and strengths were registered.

Brand		Strength	Presentation	ARTG no
HUMIRA	adalimumab	40mg	vial	95779
HUMIRA	adalimumab	40mg	pre-filled pen	127116
HUMIRA	adalimumab	40mg	pre-filled syringe	95780

Brand		Strength	Presentation	ARTG no
HUMIRA	adalimumab	20mg	pre-filled syringe	155315
HUMIRA	adalimumab	40mg	pre-filled pen	194410
HUMIRA	adalimumab	40mg	pre-filled syringe	194412
HUMIRA	adalimumab	20mg	pre-filled syringe	194411

Adalimumab was registered in 2003 and its indications have been extended to now include: Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease (in adults as shown below), Ulcerative Colitis, and Psoriasis in Australia. The indication for treatment of Crohn's disease in adults was approved in June 2007 following a peer review process.

The UC indication specifies that patients should show a clinical response within 8 weeks of treatment to continue treatment beyond that time. Humira has not been studied in children except for the investigation in polyarticular juvenile idiopathic arthritis.

The only other anti-TNF agent approved for the treatment of Crohn's disease in a paediatric population is infliximab. The paediatric CD indication for infliximab applies to patients aged from 6 to 17 years with moderate to severe CD. The dose regimen for infliximab is based on body-weight (BW) with all age groups with CD receiving the 5 mg/kg each dose, whereas for adalimumab the proposed dose regimen is more coarsely adjusted with the same regimen for all children and adolescents with BW <40 kg and the same regimen for all those with BW greater than or equal to 40 kg. The infliximab dose recommendations also state the following: Available data do not support further infliximab treatment in children and adolescent patients (6-17 years) not responding within 10 weeks to the initial infusion. The sponsor has not proposed a similar limitation for use of adalimumab in CD.

The paediatric clinical development program was discussed with the European Rapporteur (Swedish Medical Products Agency [MPA]) in the context of the presubmission meeting for the adult CD indication on 17 May 2006.

2. Clinical rationale

The sponsor has advised that the clinical development program for adalimumab in paediatric patients with moderate to severe CD was a postmarketing commitment in the US and a Paediatric Investigation Plan commitment in the EU, includes 1 pivotal randomised, double-blind (DB) study, Study M06-806, and an ongoing supportive, long-term, open-label (OL) extension study, Study M06-807.

The only TNF alpha agonist approved for treatment of Crohn's disease in children is infliximab, approved in 2007.

Therapeutic Guidelines notes the following with respect to Crohn's disease in children: The incidence of Crohn's disease in childhood is increasing. In general medical treatment is similar to that for adults, but with a strong emphasis on nutrition to avoid growth failure. Growth impairment is a presenting feature in up to 85% of prepubertal children. This may be due to

disease activity, longstanding inadequate nutrition, or treatment (particularly with corticosteroids). Nutritional supplements are required in most cases to ensure adequate nutrients for catch-up growth. There is a role for 6 to 8 weeks of exclusive enteral nutrition (instead of corticosteroid therapy) to induce remission in children, especially those with small bowel disease. Referral to a dietician is advised.

Osteopenia is usually present at the time of diagnosis of inflammatory bowel disease, due to disease activity and malnutrition. Corticosteroids can exacerbate calcium loss, and a daily calcium supplement (1000 to 1300 mg elemental calcium) may be useful. Vitamin D status should be monitored as these children are frequently deficient, and supplements may be necessary.

Avoid prolonged corticosteroid use in children, and consider other therapies such as exclusive enteral nutrition or infliximab.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- The sponsor's Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.
- 1 pivotal efficacy/safety study to demonstrate safety and efficacy and assess PK of adalimumab administered via SC injection in paediatric subjects (ages 6 to 17) with moderate to severe CD.
- 1 other efficacy/safety study to evaluate long-term maintenance of clinical response, safety, and tolerability of repeated administration of adalimumab in paediatric subjects with CD
- Integrated Summary of Safety from the two submitted studies.

3.2. Paediatric data

The submission included paediatric pharmacokinetic, efficacy and safety data.

3.3. Good clinical practice

The studies were conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki.

4. Pharmacokinetics

The clinical pharmacology and immunogenicity of adalimumab have been characterised in healthy adult subjects as well as in adult subjects with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, UC and CD. The clinical pharmacology and immunogenicity of adalimumab has been examined in studies in paediatric subjects with polyarticular juvenile idiopathic arthritis (JIA) that were included in previous submissions.

4.1. Studies providing pharmacokinetic data

Additional pharmacokinetic data were provided from the pivotal safety and efficacy study included in this submission. Using data from Study M06-806 population pharmacokinetic and adalimumab exposure-PCDAI response models were built using nonlinear mixed effect modelling based on NONMEM 7.12 compiled with the Intel Fortran compiler (Version 11.1). In Study M06-806 subjects the dose regimens consistent with those proposed for registration were given. All doses were given via subcutaneous injection.

- Induction:
  - Subjects with BW greater than or equal to 40 kg: 160 mg at Week 0 and 80 mg adalimumab at Week 2.
  - Subjects with BW < 40 kg: 80 mg at Week 0 and 40 mg adalimumab at Week 2.
- Maintenance:
  - Subjects with BW greater than or equal to 40 kg: low-dose 20 mg eow; high-dose 40 mg eow
  - Subjects with BW < 40 kg: low dose 10 mg eow; high dose 20 mg eow.
  - Subjects who did not respond to their initial maintenance dose or experienced a flare were given the option to dose escalate from eow dosing to ew dosing.

4.2. Summary of pharmacokinetics

In Study, M06-806 blood samples were obtained for the measurement of adalimumab concentrations at Baseline, Week 2, Week 4, Week 16, Week 26 and at Week 52/Early Termination (ET). Serum for measurement of anti-adalimumab antibodies (AAAs) was obtained at Baseline, Week 16, Week 26 and Week 52/ET. Samples were also obtained at Baseline for measurement of human anti-chimeric antibody (HACA) to infliximab as well as infliximab drug levels.

Adalimumab and AAA samples were analysed at Celerion Switzerland AG, Allmendstrasse 32, 8320 Fehraltorf (Switzerland). The lower limit of quantification (LLOQ) for adalimumab was established at 31.25 ng/mL in human serum. The LLOQ for AAA was established at 10 ng/mL in human serum. Serum samples were considered to be positive for AAA (AAA+) if all of the following criteria were met: the measured AAA concentration was > 20 ng/mL and the serum sample was collected within 30 days after an adalimumab dose.

Blood samples for infliximab and HACA assay were collected at Week 0 (Baseline). The sample was obtained immediately prior to dosing. Infliximab and HACA samples were analysed at ALTA Analytical Laboratory, San Diego, CA. The LLOQ for infliximab was established at 20 ng/mL in diluted serum or 40 ng/mL in undiluted serum. HACA assay was a qualitative titration method to detect antibodies to infliximab in human serum against positive controls.

Adalimumab serum trough concentrations were summarised 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. Adalimumab serum trough concentrations were used to estimate adalimumab apparent clearance (CL/F) of 0.283 L/day and 4.80 L for adalimumab apparent volume of distribution of central compartment (V2/F). Inter-individual variability for CL/F was ~46%. Statistically significant covariates for clearance included bodyweight and the presence of AAA, while bodyweight was a statistically significant covariate for central volume (V2/F). Exposure/ response modelling described the time course of adalimumab concentration effect on clinical outcome state transition rates.

Statistically significant covariates on EC50 (half maximal effective concentration) were prior infliximab use and concomitant medications (methotrexate and azathioprine).

The mean adalimumab trough concentrations achieved during the induction phase (Week 0 through Week 4) in which both groups received the appropriate induction dose were similar across treatment groups ranging from 12.1 to 15.5 μg/mL. This compares with a mean of approximately 12 μg/mL in adults with CD given the same regimen. During the maintenance phase, the mean adalimumab trough concentrations were approximately 10 and 4 μg/mL for the high dose group (40/20 mg eow) and low dose group (20/10 mg eow), respectively. This compares with mean steady state trough concentrations in adults with CD receiving 40 mg eow of 6.6μg/mL at Week 24 and 7.2 μg/mL at Week 56. The mean trough concentrations appeared to be maintained in subjects who continued to receive adalimumab treatment eow for 52 weeks. In subjects whose doses were escalated, higher trough concentrations were achieved after dose escalation. Six (6/182, 3.3%) subjects were identified as AAA+ during the study.

During the double-blind maintenance phase, mean serum adalimumab trough concentrations in infliximab experienced subjects were generally lower, but the range of concentrations overlapped.

4.3. Evaluator's overall conclusions on pharmacokinetics

The sponsor is proposing to use the same adalimumab induction regimen for paediatric patients as is currently approved for adults. The adalimumab trough concentration data and modelling suggest that trough concentrations will be similar in adults and paediatric patients and support this induction regimen.

The sponsor has proposed that maintenance dose be determined by severity of disease as well as body weight for children. This is not the approach that was taken for adults or for the other anti-TNF agent (infliximab) (where dosing for adults and children is on a mg/kg basis). It's been proposed that paediatric patients with "moderate" CD receive half the current recommended maintenance dose for adults provided BW is greater than or equal to 40 kg and a quarter of the adult dose if BW is <40 kg. For paediatric patients with "severe" disease the adult maintenance dose regimen is recommended if BW is greater than or equal to 40 kg and half the adult maintenance dose regimen if BW is <40 kg. Reducing the dose interval to weekly resulted in approximately doubling the trough concentration of adalimumab.

The proposed maintenance dose regimens resulted in mean adalimumab trough concentrations that were comparable to those seen in adults given 40 mg eow, with trough levels somewhat higher for those given the high dose regimen and somewhat lower for those given the low dose regimen compared with adults with CD given their recommended dose. Subjects with previous exposure to infliximab generally had reduced trough levels of adalimumab as did subjects who were HACA+. There were only 6 subjects who were AAA+ during the course of the pivotal study. Five of these subjects had serum adalimumab concentrations decline to below the limit of detection of the assay during the maintenance phase. The 6th subject terminated the study early with serum adalimumab concentration below the limit of detection.

5. Pharmacodynamics

No data submitted.

6. Dosage selection for the pivotal studies

Population PK modelling of serum adalimumab concentration data from paediatric subjects with JIA was used to identify doses to be evaluated in the current study in children with CD. A

model based on the JIA population was chosen because the BW range closely paralleled that in a juvenile CD population. PK data obtained from this study was then compared with PK data obtained in the studies of CD in adults.

The results from 2 previously evaluated controlled studies in adults (Study M02-403 and Study M04-691) supported the proposed induction dose regimen of 160 mg at Baseline (Week 0) and 80 mg at Week 2 for adult patients with CD.

The results of the pivotal maintenance trial in adults (Study M02-404), in conjunction with results from Study M02-433,supported a maintenance dose of adalimumab 40 mg eow. The sponsor also indicated the data suggested that patients who lost response to adalimumab at 40 mg eow could be dose-escalated to 40 mg ew with the potential of regaining clinical response.

7. Clinical efficacy

7.1. Paediatric patients with moderate to severe Crohn's disease

7.1.1. Pivotal efficacy studies

7.1.1.1. Study M06-806

A Multicenter, Double-blind Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of the Human Anti-TNF Monoclonal Antibody Adalimumab in Paediatric Subjects with Moderate to Severe Crohn's Disease.

7.1.1.1.1. Study design, objectives, locations and dates

This was a multi-centre, randomised, double-blind, safety, efficacy, and PK study. It assessed the efficacy and safety of two dose regimens of adalimumab in the induction and maintenance of clinical remission in paediatric subjects between the ages of 6 and 17 inclusive, with moderate to severe CD. No control group was included and an historical control (comparison with results from treatment with adalimumab in adults with CD) was used in the analysis of results.

The objective was to demonstrate the safety and efficacy of adalimumab for the induction and maintenance of clinical remission in paediatric subjects with moderate to severe Crohn's disease (CD) and to assess the pharmacokinetics (PK) of adalimumab administered by subcutaneous (SC) injection.

The primary measure of disease severity was the Paediatric Crohn's Disease Activity Index (PCDAI), a validated rating scale to assess the severity of CD in children. Points are accrued based on reported abdominal pain, stool frequency, patient functioning/ well-being, haematocrit, ESR, albumin and body weight (gain or loss). The maximum possible score is 100.

The study was conducted between May 2007 and May 2010 in 45 sites in Belgium, Canada, Czech Republic, France, Italy, The Netherlands, Poland, the United Kingdom, and the United States.

7.1.1.1.2. Inclusion and exclusion criteria

- The major 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).

- 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.

The major exclusion criteria referred to concomitant treatments for CD. Infliximab was required to be discontinued greater than or equal to 8 weeks before Baseline. Previous use of any other anti-TNF medication, including previous adalimumab use, was prohibited. Cyclosporine, tacrolimus, and mycophenolate mofetil were prohibited within 4 weeks prior to Baseline. Subjects taking Kineret (anakinra) were required to discontinue use 2 days prior to Baseline. Subjects with any prior exposure to Tysabri (natalizumab) were excluded.

7.1.1.1.3. Study treatments

All subjects received an open-label induction regimen, dependent on their body weight at baseline.

- Subjects with BW greater than or equal to 40 kg: 160 mg at Week 0 and 80 mg adalimumab at Week 2.
- Subjects with BW < 40 kg: 80 mg at Week 0 and 40 mg adalimumab at Week 2.

At Week 4, subjects were randomised 1:1 to one of 2 maintenance treatment groups (low-dose or high-dose). Subjects with BW greater than or equal to 40 kg: low-dose 20 mg eow; high-dose 40 mg eow. Subjects with BW < 40 kg: low dose 10 mg eow; high dose 20 mg eow. Subjects who did not respond to their initial maintenance dose were given the option to dose escalate from eow dosing to ew dosing.

Subject BW taken at Week 26 was to be used to readjust the maintenance dosing regimen for subjects whose BW had increased from < 40 kg to greater than or equal to 40 kg during the study.

Subjects were to continue their doses of AZA, 6-MP, and MTX and doses were to remain stable throughout the study. IMM therapy was to be discontinued at or after Week 26 at the investigator's discretion if the subject met the clinical response criterion. IMM therapy could not be reinstituted once discontinued. Subjects were to continue their doses of growth hormone and doses were to remain stable throughout the study.

Prednisone less than or equal to 40 mg/day and greater than or equal to 10 mg/day (or equivalent) was permitted provided subjects were on stable doses for at least 2 weeks prior to Baseline. Budesonide less than or equal to 9 mg/day was permitted provided subjects were on stable doses for at least 2 weeks prior to Baseline. Starting at Week 4, subjects who met the definition of clinical response (defined as a PCDAI decrease of greater than or equal to 15 points compared to Baseline) began a corticosteroid taper.

If the subject experienced a flare (defined as an increase in the PCDAI of greater than or equal to 15 points when compared to Week 4 and an absolute PCDAI >30) or loss of response (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), the corticosteroid dose could be increased to a maximal dose equivalent to the dose used at Baseline. Reductions in concomitant therapy were allowed for CD treatment-related toxicities assessed as moderate to severe in the opinion of the investigator.

7.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome was clinical remission at Week 26, defined as PCDAI score less than or equal to 10.

The primary efficacy outcome for external comparison was the PCDAI clinical remission at Week 26 in the ITT population. The external efficacy comparison was to compare data from the current paediatric study to data from the adult CD study, Study M02-404.

The primary efficacy outcome for internal comparison was to be the proportion of subjects who were in clinical remission at Week 26, as measured by the PCDAI in the ITT population. The internal primary analysis was to be the comparison of high-dose versus low-dose with respect to the primary efficacy outcome for internal comparison.

The major secondary efficacy endpoints (ranked) were:

1. Proportion of subjects in PCDAI clinical remission at Week 52.
2. Proportion of subjects in PCDAI clinical response at Week 26.
3. Proportion of subjects in PCDAI clinical response at Week 52.
4. Proportion of subjects in PCDAI clinical remission at Week 26 who were Week 4 responders.
5. PCDAI clinical remission at Week 4.
6. Proportion of subjects receiving corticosteroids at Baseline who had discontinued corticosteroids for at least 90 consecutive days prior to Week 26 and were in PCDAI clinical remission at Week 26.
7. Change from Baseline in z-score for height velocity at Week 26.
8. Change from Baseline in total IMPACT III scores at Week 26.

Secondary endpoints No. 4 and No. 5 are external comparisons of the paediatric and adult data; all other comparisons are internal comparisons of subjects in the High-Dose and Low-Dose treatment groups. Additional analyses were conducted after the study blind was broken including an analyses to compare the proportion of subjects in PCDAI clinical remission/clinical response (at Week 26 and Week 52) during the eow and ew double-blind maintenance phase.

7.1.1.1.5. Randomisation and blinding methods

All subjects were centrally randomised using an IVRS. Before the study initiation, the telephone number and call-in directions for the IVRS were provided to each site. This call-in provided information on the subject's stratification status to the IVRS. The assigned randomisation number determined the treatment assignment during the double-blind period. Abbott, the investigator, site study personnel, and subject were to remain blinded to treatment received (that is, high- or low-dose adalimumab) during the blinded phase of the study.

7.1.1.1.6. Analysis populations

The primary population for all efficacy analyses was the ITT population, defined as all randomised subjects who received at least one dose of DB study medication. Results were also presented for the per-protocol (PP) population, which excluded all subjects with major protocol deviations and violations. Safety evaluations/analyses were based on the safety population, defined as all subjects who received at least one dose of adalimumab. The safety set was analysed as treated, according to treatment the subject actually received.

7.1.1.1.7. Sample size

Sample size was calculated assuming an expected week 26 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 that is 82 subjects per group was expected to provide 80% statistical power to detect the difference between the high and low dose treatment groups based on a 2-sided chi-square test with a significance level of 0.05. To allow for a pre-randomisation dropout rate / withdrawal rate of 10%, approximately 186 subjects were expected to be enrolled to provide approximately 164 randomised subjects. The study was stratified at Week 4 by body weight, responder status (Yes or No), and prior infliximab use (Yes or No) in order to ensure a balance of treatment groups across these adalimumab dose groups.

7.1.1.1.8. Statistical methods

All statistical tests were to be two-sided and conducted at an alpha level of 0.05, unless otherwise stated. Centre effects were not to be included in any analysis since there were not enough subjects per treatment within each centre for a meaningful analysis. The primary external efficacy comparisons were to be determined 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 the ITT population (n = 260) contained zero.

The extended Cochran-Mantel-Haenszel (CMH) test was used for the primary analysis, adjusting for strata (Week 4 response status [No, Yes] and prior infliximab experience Adalimumab [No, Yes]). The treatment–by-strata interaction was tested using Breslow-Day test at 10% significance level. ITT subjects were analysed on the observed case (OC) data with NRI and LOCF for imputed data. Failure or non-responder imputation (NRI) was used for imputed binary endpoints. Subjects who prematurely discontinued the study, switched from DB eow to ew dosing, who discontinued DB eow treatment before the scheduled evaluation of clinical remission, or who did not have a relevant PCDAI score (and/or CDAI score for subjects greater than or equal to 13 years of age) were to be considered to have not achieved clinical remission (denoted as NRI).

Testing for statistical significance for the major secondary endpoints was to be based on the hypotheses associated with the fixed a priori order of the endpoints listed above, using the hierarchical stepwise closed testing procedure to control the overall significance level at 0.05. The major secondary endpoints that were of the binary type were analysed in the same way as the primary analysis, using the CMH test. The *P* value and a 95% CI were to be provided for the difference in proportions between the two treatment groups. Major secondary endpoints that were of the continuous type were analysed as change from Baseline, and compared between the two treatment groups via analysis of covariance (ANCOVA), with treatment group as a factor and adjusted for the Baseline covariates (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 provided. Descriptive statistics were provided for demographic, efficacy, and safety parameters. Continuous variables were summarised by the number of observations, mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum. Discrete variables were summarised by counts and percentages.

In order to describe the total clinical response (or remission) at Week 52 including the dose escalation portion of the study, a modified NRI (mNRI) imputation method was utilized in a post hoc analysis: the mNRI imputation method considered all missing response (or remission) values as non-response (or non-remission). Subjects who dose escalated to adalimumab 40 mg weekly were considered as responders (or remitters) or non-responders (or non-remitters) according to their observed response (or remission) status after the dose escalation during the DB ew period.

7.1.1.1.9. Major protocol violations/deviations

The original protocol had 5 amendments, 4 administrative letters, and 1 country specific Amendment (for France). The most important amendment was made on 21 in August 2007. As one of a 21 major protocol amendments the following changes were made:

Changes were made to clarify the wording of the pre-specified endpoints, to include additional endpoints (time to steroid-free PCDAI clinical remission, change from Baseline in CRP level), and in one instance, to change a pre-specified endpoint (from average median corticosteroid dose to 'change from Baseline in corticosteroid dose') so as to make them more concise and more closely in line with the clinical objectives of the study. The primary endpoint was revised so it would clearly refer to PCDAI clinical remission in the ITT population. Similarly, the

secondary endpoints were revised to specifically refer to PCDAI clinical remission and PCDAI clinical response in order to clearly distinguish them from CDAI measurements (since both PCDAI- and CDAI-based remission, were being measured in the study). Endpoints involving DB period were clarified to read as 'DB eow' period. As a result of the clarifications, changes, and additions noted in the above paragraph, it became necessary to also implement corresponding clarifications and revisions in the analysis descriptions and the analysable populations to reflect those changes. Additionally, statistical sections of the protocol were synchronised with the SAP.

Additional subgroup analyses were conducted after completion of the study when the blind was broken. These included a comparison of the high-dose group to the low-dose group based on prior infliximab use for the primary, major secondary variables, and PCDAI clinical remission/clinical response (at Week 26 and Week 52) for subjects who were responders at Week 4.

Mean PCDAI score at baseline was 40.76 (Range 30 – 62.5) for the low-dose group and 41.34 (Range 25.0 – 62.5) for the high-dose group. CDAI, CRP and ESR results were similar in the two treatment groups. Median bone age at baseline was 13.6 years in both dose groups. Median Z score for height velocity was -1.25 (R: -7.3 to 12.2) for the low dose and 0 (R: -7.3 to 16.1) for the high dose group.

Approximately 44% of subjects had used infliximab previously. Almost all subjects who had previously received infliximab had an initial response, but 80.7% of those 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. Over half (62.2%) of all subjects reported IMM use at Baseline and 37.8% of all subjects reported systemic corticosteroid use at Baseline. IMM included azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX), thioguanine, cyclosporin and tacrolimus. Prednisone, azathioprine, mesalazine, and methotrexate were the most frequently reported prior medications; each medication was taken by greater than or equal to 20% of all subjects.

7.1.1.1.1. Results for the primary efficacy outcome

A total of 52/188 (27.7%) of all randomised subjects were in remission at Week 4. Subjects were then randomised to high (n= 93) or low dose (n=95) adalimumab treatment.

The external comparison for the primary efficacy outcome is shown in Table 1 below.

Table 1. Proportion of subjects in PCDAI Clinical Remission at Week 26.

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 = Pediatric 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.

Thus for the primary efficacy outcome external comparison, the study was a success in that the 95% CI for the difference in remission rates at Week 26 crossed 0 (or better) for the overall use of adalimumab in the paediatric population and for each dose regimen assessed (high-dose and

low dose). Adalimumab performed better in the paediatric CD population than in the adult population.

For the internal efficacy comparison, the difference in remission rates at Week 26 between low dose and high dose adalimumab did not reach statistical significance. Remission rates at Week 26 were 38.7% (high dose) and 28.4% (low dose), p = 0.075.

Although the primary internal comparison for the primary efficacy outcome did not reach statistical significance the sponsor produced the planned subgroup analyses for the primary efficacy outcome, some of which did reach statistical significance. For the subgroup of infliximab naïve subjects remission rates at Week 26 were 56.9% (high dose) and 35.2% (low dose), p= 0.026. Overall (for subjects given either dose regimen) 46% of infliximab naïve subjects were in remission at Week 26 compared with 18% infliximab experienced subjects. For infliximab experienced subjects the remission rate at Week 26 did not increase with increased adalimumab dose. Of infliximab experienced subjects who had not achieved remission at Week 4 only 2/19 (10.5%) achieved remission at Week 26. This compares with 3/14 (21.4%) infliximab naïve subjects who were not in remission at Week 4 but who went on to remission at Week 26.

Similar results were obtained from the LOCF and PP analyses (NRI and LOCF). Remission status at Week 4 and prior exposure to infliximab were strong predictors of remission status at Week 26 for both the high and low dose adalimumab groups.

Of the 95 subjects randomised to low dose treatment 48 (50.5%) were switched from eow to ew treatment compared with 35/93 (37.6%) who were randomised to high dose treatment.

7.1.1.1.2. Results for other efficacy outcomes

The first (remission at Week 52) and second (response at Week 26) ranked secondary endpoints did not show statistically significant differences between the high and low dose adalimumab groups. The third ranked secondary endpoint was response at Week 52. 28.4% subjects given low dose and 41.9% given high dose adalimumab had a clinical response at Week 52. The p value was reported as 0.038. Given that secondary endpoints were ranked and the higher ranked endpoints did not show a statistically significant difference the subsequent comparisons cannot be considered valid and the inclusion of p-values associated with descriptions of the between group differences for subsequent endpoints is not appropriate. They're discussed below without statistical comparisons in order to explore appropriate limits on adalimumab dosing in paediatric patients with moderate to severe CD.

Response at Week 4 appears to be predictive of remission rate at Week 26 for any dose of adalimumab. For subjects who responded at Week 4 the remission rate for the combined dose groups at Week 26 was 37.4% that is if treatment is continued in subjects who have not had a response at Week 4 an additional 15.2% of patients with CD can be expected to have achieved remission at Week 26. The remission rate at Week 52 was 23.2% for the low dose group and 33.3% for the high dose group. The response rate at Week 52 was 28.4% for the low dose and 41.9% for the high dose. No difference in terms of increased height velocity or quality of life measures between the high and low dose treatments was apparent. QOL was assessed using IMPACT III, a QOL questionnaire specifically developed and validated for paediatric patients with inflammatory bowel disease.

From Week 16 onwards higher remission rates are reported in the high dose compared to the low dose group. Differences between the high and low dose regimens are small but consistently favour the higher dose. Both prior infliximab use and the presence of HACA were associated with reduced remission rates.

Six subjects were found to be AAA+ during the study. Of these, 2 were on a concomitant immunosuppressant (methotrexate). Five of the 6 AAA+ subjects had serum concentrations decline to below the limit of detection of the assay during maintenance phase. The 6th subject

terminated the study early with a serum adalimumab concentration below the limit of detection. Two of these subjects (12903 and 31001) achieved remission at Week 26 whereas 4 subjects did not.

Remission at Week 4 was a strong predictor of remission at Week 26 regardless of dose or prior infliximab exposure. For the low dose group only 2 subjects who were not in remission at Week 4 achieved remission at Week 26. For the high dose group 3 subjects who were not in remission at Week 4 were in remission at Week 26.

A total of 26.8% of subjects who were taking systemic corticosteroids at Baseline discontinued corticosteroids for greater than or equal to 90 consecutive days prior to Week 26 and achieved PCDAI clinical remission at Week 26.

Across the two dose groups 20 subjects who had not achieved a clinical response were dose escalated. Of these subjects at Week 52, 7 had attained a clinical response and 5 clinical remission. 63 subjects were dose escalated after achieving a clinical response, for those subjects 36 (57%) were in clinical response at Week 52 and 15 (24%) were in clinical remission. Of the 117 subjects who were taking immunosuppressives at baseline 14/117 (12%) had discontinued immunosuppressants and were in remission at Week 52.

7.1.1.2. Study M06-807

7.1.1.2.1. Study design, objectives, locations and dates

Study 807 was a multi-centre, open-label study of adalimumab to evaluate the efficacy and long-term safety and tolerability of repeated administration of adalimumab in paediatric subjects with Crohn's disease who demonstrated a clinical response in Study M06-806 through to Week 52.

It was conducted at 31 sites in the US, Canada, and Europe from May 2008. An interim report with data cut-off 30 November 2010 was included in the submission.

7.1.1.2.2. Inclusion and exclusion criteria

The major criteria for inclusion were:

- Subject must have had successfully enrolled in and completed Protocol M06-806 through Week 52.
- Subject 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).

7.1.1.2.3. Study treatments

All subjects were on OL maintenance therapy during this study. Subjects who enrolled from blinded therapy in Study M06-806 received OL therapy at a dose dependent on their body weight as assessed at baseline of this study. Subjects who weighed greater than or equal to 40 kg at Baseline were to receive adalimumab 40 mg every other week (eow), while subjects who weighed < 40 kg at Baseline were to receive adalimumab 20 mg eow that is all subjects were to receive the high dose regimen.

Beginning at Week 8, subjects who had a disease flare may have been switched to every week (ew) treatment at the same dose of adalimumab received while on eow treatment. A disease flare was defined as an increase in the Paediatric Crohn's Disease Activity Index (PCDAI) of greater than or equal to 15 points when compared to the PCDAI score obtained at the previous visit.

The higher dose of 40 mg was used to maintain blinding in Study M06-806. Subjects who enrolled into the study from OL therapy (adalimumab 40 mg ew or 20 mg ew) in Study M06-806 continued to receive the same dose they were receiving at the Week 52 visit of Study M06-806. Subjects who developed a flare while receiving ew therapy or had a PCDAI score greater than or

equal to 15 points higher than baseline at any time during this study could have been discontinued from the study at the discretion of the investigator. Beginning from Week 8, the dose of adalimumab may have been increased to 40 mg, at the discretion of the investigator, for subjects whose body weight increased from < 40 kg to greater than or equal to 40 kg from the Baseline visit.

Reductions in concomitant therapy were allowed for CD treatment-related toxicities (e.g. leukopenia, anaemia, neuropathy) of Grade 3 or higher. Subjects were allowed to decrease prednisone (or equivalent) and budesonide if qualifications were met. The duration of the study could last up to 264 weeks (approximately 5 years). Subjects who complete, or who early terminate from the study are to be contacted 70 days after their last dose of study drug to obtain information on any ongoing and new adverse events (AEs).

This study was planned to conclude approximately 12 weeks after adalimumab received country and local (if applicable) regulatory approval for paediatric Crohn's disease.

7.1.1.2.4. Efficacy variables and outcomes

There was no primary efficacy variable as Study M06-807 is an extension of Study M06-806, whose primary efficacy variable was the proportion of subjects who were in clinical remission at Week 26, as measured by the PCDAI in the (ITT) population. In Study M06-807, efficacy was evaluated based on the proportion of subjects who maintained PCDAI clinical response at each visit. Clinical response was defined as a PCDAI score greater than or equal to 15 points lower than the Study M06-806 Baseline score.

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. Other measures of disease activity being assessed in this study were summarised, including 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).

7.1.1.2.5. Randomisation and blinding methods

This was an open label study and subjects were not randomised or blinded.

7.1.1.2.6. Analysis populations

The ITT population, consisting of all subjects who received at least one dose of adalimumab in Study M06-807 and also had at least one non-missing efficacy measurement during the study was the population used for efficacy analyses. The Safety population, consisting of all subjects who received at least one dose of adalimumab in Study M06-807 was used for safety analyses.

7.1.1.2.7. Sample size

Subjects who successfully completed Study M06-806 through Week 52 may have been eligible to participate in this study. It was expected that approximately 70% (130) of subjects from Study M06-806 would enrol in this study.

7.1.1.2.8. Statistical methods

Descriptive statistics only were determined for each visit, based on observed data. An additional summary was to be provided for the last visit, using the last observation carried forward (LOCF).

7.1.1.2.9. Major protocol violations/deviations

Three subjects had deviations related to receipt of concomitant treatments. None of the protocol deviations were deemed to have had a notable effect on the safety outcomes of the study.

7.1.1.2.10. Baseline data

Data from 100 subjects were available. Only 24 subjects were receiving the low dose regimen (20/10 mg eow) at Week 52, 19 with BW greater than or equal to 40 kg and 5 with BW <40 kg. A total of 29/100 had prior infliximab experience, 73 were taking concomitant immunosuppressants and 37 were taking concomitant corticosteroid. Twenty-two were taking both immunosuppressant and corticosteroid and 12 were taking neither concomitant immunosuppressant or corticosteroid.

7.1.1.2.11. Results for efficacy outcomes

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

The sponsor reported 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 assessed achieved PCDAI clinical remission (defined as PCDAI score less than or equal to 10) at each visit.

7.1.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

Not applicable.

7.1.2. Evaluator's conclusions on clinical efficacy for paediatric Crohn's disease

No assessment of different induction doses was performed so the efficacy of any alternative induction regimen would be speculative, based on PK data alone. The evaluator recommends that the proposed weight-based induction regimen be accepted.

Paediatric patients with CD given the proposed dose regimens appear in the cross study comparison to adult patients with CD to have better outcomes in terms of remission at Week 26 regardless of whether they received the high or low dose maintenance regimen. No statistically significant difference was apparent between the high and low dose maintenance regimens for the internal primary efficacy analysis. This suggests the low dose treatment should be the recommended maintenance dose regimen. Prescribers should be advised of the extent of reduced response/ remission rates in patients with prior infliximab experience.

The lack of a placebo group for within study comparisons, while understandable, results in a lack of internal reference which is important for a disease which is known to vary in its severity over time irrespective of treatment. The responses and remissions shown in subjects who were AAA+ and had adalimumab levels below the limit of quantification suggest that responses and remissions would have occurred in subjects given placebo (in addition to their usual treatment). Due to the absence of a placebo group it is not possible to estimate the NNT for one patient to derive a clinical response or remission.

There was no planned analysis of efficacy of the high dose maintenance regimen by severity of disease, though the sponsor is proposing paediatric dose regimen based on disease severity that is the high dose regimen for severe disease and the low dose regimen for moderate disease. The statistical analysis plan did not provide for assessment of remission/response rates based on severity of disease at baseline. Any subsequent analysis would be post-hoc and its statistical significance would be limited by its status as an exploratory endpoint in a study in which the primary efficacy comparison (between high and low dose regimens) did not reach statistical significance. I do not consider that there has been sufficient examination of the effect of dose on efficacy stratified by disease severity for it to be supported as part of the dose regimen.

Differences in secondary efficacy endpoints between the high and low dose regimen were generally quite small, particularly for subjects with prior exposure to infliximab. Most of the statistical analyses of secondary endpoints could not be validated due to lack of statistically significant results for the first ranked secondary endpoint. Although this is a major limitation to

interpretation of the data it is likely that clinical response or remission at Week 4, no prior experience of infliximab and AAA are predictors of subsequent response to adalimumab, regardless of whether the high or low dose regimen is used. In the study around ¼ of subjects taking systemic corticosteroids at baseline were able to stop them for at least 90 days and achieve remission at Week 26 of treatment and 12% of subjects taking immunomodulators at baseline were able to cease them and achieve remission at Week 52. The extent of reduced likelihood of remission should be adequately described in the Clinical Trials section of the PI, particularly for those subgroups least likely to benefit from treatment. I do not recommend continuing treatment in patients who have not responded to the induction dose regimen. To support continuing use, the evaluator considers a placebo-controlled comparison is required.

There is no restriction on continued use of adalimumab in adults with CD who have predictors of poor subsequent response however consideration should be given to advising prescribers to cease treatment in paediatric patients who have not responded after receiving the induction regimen, particularly if those patients have prior infliximab exposure. It is not clear how long the trial of initial treatment should be from the data presented.

It is notable that for infliximab, paediatric patients aged from 6 to 17 years with moderate to severe Crohn's disease the recommended dose regimen is the same as the adult dose regimen with the additional statement that available data do not support further infliximab treatment in children and adolescent patients (6-17 years) not responding within 10 weeks to the initial infusion.

At commencement of the OL extension study subjects taking low dose adalimumab could be increased to higher doses. Those who were taking ew regimens at the high dose continued. The sponsor has not proposed long term use of the higher dose for patients with moderate Crohn's disease and there is no analysis of efficacy of the low dose regimen beyond 52 weeks.

From the descriptive data supplied it not possible to determine whether there is a loss of response over time due to the high loss of subjects from the extension study (M06-807). That study did show that subjects who continued treatment continued to respond. The extent of withdrawals from this study and reasons for withdrawal were not apparent in the interim study report. Persistence of efficacy in paediatric subjects with CD is likely to require post-market assessment.

8. Clinical safety

8.1. Studies providing evaluable safety data

Studies M06-806 and its OL extension, Study Mo6-807provided evaluable safety data. A data cut-off date of 30 November 2010 applied to the Study M06-807 which is ongoing.

Subject disposition was provided in a combined analysis in the Safety Summary for the submission.

8.2. AEs of special interest

- Allergic reactions related AEs
- Injection site reactions related AEs
- Opportunistic infections (excluding TB)
- Congestive heart failure
- Demyelinating diseases

- Lupus-like syndrome
- Hepatic related AEs
- Malignant AE
- Lymphomas
- Non-melanoma skin cancers (NMSC)
- Malignancies (excluding lymphomas and NMSC)
- Malignancies (including lymphomas, excluding NMSC)
- Infectious AEs
- Serious infectious AEs
- Haematological event
- Cutaneous vasculitis
- Diverticulitis
- Intestinal perforations
- Intestinal stricture
- Interstitial lung disease (ILD)
- Stevens-Johnson syndrome
- Pancreatitis
- Hepatosplenic T-cell lymphoma (HSTCL)
- Leukaemia
- Melanoma
- ALT (alanine transaminase) elevation
- Cerebrovascular accident (CVA)
- Myocardial infarction (MI)
- Worsening/new onset of psoriasis
- Pulmonary embolism
- Erythema multiforme

8.3. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.4. Patient exposure

Across both studies a total of 192 paediatric subjects with CD were exposed to at least 1 dose of adalimumab as of 30 November 2010. Cumulative exposure was 258.9 patient years (PYs). Of these subjects, 115 (59.9%) had > 12 months of adalimumab exposure and 91 (47.4%) had > 18 months of adalimumab exposure. The median exposure was 434 days (range, 14 to 1,184 days). The proportion of subjects decreased over time due to discontinuations, but primarily because the study is still ongoing and most subjects have not been exposed to study drug for longer durations at the cut-off date.

The majority of study subjects received dose escalation as shown in Table 2 below. Twenty-four subjects received the low dose without escalation for a mean (SD) of 691.1 ± 209.22 treatment days.

Table 2. Extent of Exposure (dose escalation and no dose escalation sets).

	Adalimumab			
	Subjects Who Dose Escalated, Dose Escalation Set			
Exposure to Study Drug	Prior to Dose Escalation N = 115	Post Dose Escalation N = 115	Overall N = 115	No Dose Escalation Set N = 77
Duration of treatment (days)				
Mean ± SD	237.1 ± 172.98	319.7 ± 251.26	557.2 ± 285.83	396.0 ± 353.05
Median (min – max)	197.0 (82 – 996)	266.0 (21 – 1021)	575.0 (111 – 1141)	351.0 (14 – 1184)
Total number of injections				
Mean ± SD	19.7 ± 12.59	35.3 ± 29.57	55.0 ± 29.44	31.2 ± 25.30
Median (min – max)	16.0 (7 – 75)	29.0 (3 – 140)	50.0 (11 – 147)	27.0 (1 – 86)
Average monthly number of injections				
Mean ± SD	71.76 ± 29.455	94.71 ± 38.773	82.52 ± 30.241	94.10 ± 48.436
Median (min – max)	65.00 (27.7 – 136.6)	80.00 (32.0 – 266.7)	74.48 (30.0 – 158.7)	85.82 (1.0 – 320.0)
Duration of Exposure		n (%)		
1 – 15 days	115 (100)	115 (100)	115 (100)	77 (100)
16 – 29 days	115 (100)	115 (100)	115 (100)	74 (96.1)
30 – 57 days	115 (100)	112 (97.4)	115 (100)	73 (94.8)
58 – 85 days	115 (100)	101 (87.8)	115 (100)	59 (76.6)
86 – 113 days	92 (80.0)	90 (78.3)	115 (100)	50 (64.9)
114 – 141 days	76 (66.1)	87 (75.7)	114 (99.1)	49 (63.6)
142 – 169 days	66 (57.4)	77 (67.0)	109 (94.8)	47 (61.0)
170 – 197 days	62 (53.9)	74 (64.3)	104 (90.4)	45 (58.4)
198 – 225 days	57 (49.6)	72 (62.6)	101 (87.8)	45 (58.4)
226 – 253 days	47 (40.9)	67 (58.3)	97 (84.3)	44 (57.1)
254 – 281 days	42 (36.5)	61 (53.0)	93 (80.9)	43 (55.8)
282 – 309 days	40 (34.8)	52 (45.2)	90 (78.3)	42 (54.5)
310 – 337 days	37 (32.2)	42 (36.5)	87 (75.7)	39 (50.6)
338 – 365 days	33 (28.7)	40 (34.8)	85 (73.9)	39 (50.6)
366 – 456 days	9 (7.8)	38 (33.0)	83 (72.2)	32 (41.6)
457 – 547 days	8 (7.0)	30 (26.1)	67 (58.3)	28 (36.4)
548 – 638 days	6 (5.2)	24 (20.9)	63 (54.8)	28 (36.4)
639 – 729 days	5 (4.3)	19 (16.5)	46 (40.0)	23 (29.9)
730 – 820 days	2 (1.7)	10 (8.7)	31 (27.0)	16 (20.8)
821 – 911 days	2 (1.7)	5 (4.3)	23 (20.0)	12 (15.6)
912 – 1002 days	2 (1.7)	3 (2.6)	15 (13.0)	8 (10.4)
1003 – 1093 days	0	2 (1.7)	9 (7.8)	5 (6.5)
1094 – 1184 days	0	0	4 (3.5)	4 (5.2)
Total number of patient years	74.7	100.7	175.4	83.5

Max = maximum; min = minimum; SD = standard deviation

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

8.5. Adverse events

8.5.1. All adverse events (irrespective of relationship to study treatment)

Approximately 96% of subjects (185 of 192 subjects) experienced greater than or equal to 1 treatment-emergent AE (TEAE), with an incidence of 844.0 events/100 PYs. TEAE considered at least possibly related to study drug were reported by 107/192 (55.7%) subjects. SAEs were reported in 40.1% of subjects.

There were no fatal AEs and no subjects died on study. Infectious AEs were the most frequently reported AE of special interest; 136 subjects (70.8%) had greater than or equal to 1 infectious AE. The rate of serious infectious AEs was 8.9%.

8.5.2. Treatment-related adverse events (adverse drug reactions)

An overview of TEAEs is shown below:

Table 3. Treatment related adverse events.

	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 Adalimumab Set N = 192 PYs = 258.9	
Treatment-Emergent AE Category	**n (%)**	**E (E/100 PYs)**
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

8.5.3. Deaths and other serious adverse events

No deaths occurred during the trial. The most frequent serious TEAEs were related to the gastrointestinal system.

8.5.4. Discontinuation due to adverse events

Of the 192 subjects assessed for safety 49 had TEAE leading to discontinuation. The most frequent reason for discontinuation was CD (n=37).

8.5.5. Laboratory tests

8.5.5.1. Liver function

12 subjects had hepatic enzyme abnormalities, 8 (4.2%) had elevated ALT (4.2%) and 2 (1%) had elevated AST. None were serious.

8.5.5.2. Kidney function

Not relevant.

8.5.5.3. Other clinical chemistry

Not relevant.

8.5.6. Haematology

Haematological events were reported as follows.

Table 4. Haematological events.

Preferred Term	Any Adalimumab Set N = 192 n (%)
Any hematologic related AE	23 (12.0)
Anaemia	12 (6.3)
Leukopenia	8 (4.2)
White blood cell count decreased	3 (1.6)
Neutropenia	1 (0.5)
Pancytopenia	1 (0.5)

Notes: Includes Study M06-806 and Study 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 November 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.

8.6. Post-marketing experience

This indication received marketing authorisation in the EU in 2012, with no new signals or trends identified for the patient population since then. Post-marketing data were not included in the submission.

8.7. Safety issues with the potential for major regulatory impact

The safety issues of most concern for adalimumab are serious infections and malignancies. In adolescents with CD there have been reports of lymphoma, including hepatosplenic T cell lymphoma. While there were no reports of these events in these studies the sample and follow-up time were quite restricted for these rare adverse events.

Table 5. Unwanted immunological events.

Preferred Term	Any Adalimumab Set N = 192 n (%)
Any allergic reaction related AE	15 (7.8)
Hypersensitivity	7 (3.6)
Urticaria	5 (2.6)
Drug hypersensitivity	1 (0.5)
Eye swelling	1 (0.5)
Eyelid oedema	1 (0.5)
Lip swelling	1 (0.5)
Swelling face	1 (0.5)
Upper airway obstruction	1 (0.5)

8.8. Other safety issues

8.8.1. Safety related to drug-drug interactions and other interactions

The proportion of subjects who had serious infections, and the incidence rate in E/100 PY, were slightly higher (but not statistically significant) in subjects with concomitant immunomodulator use (9.9%, 8.0 E/100 PY versus 7.0%, 5.9 E/100 PY).

8.8.2. Injection site reactions

Injection site reactions were reported by 38 (19.8%) of subjects. None were serious.

8.8.3. Opportunistic infections

Two subjects developed opportunistic infections. One subject developed disseminated histoplasmosis that led to study drug discontinuation. Another subject developed Aeromona infection. The event resolved after 17 days and the subject did not discontinue study drug due to the event. In the Dose Escalation Set, no subjects reported opportunistic infection related AEs.

8.9. Evaluator's overall conclusions on clinical safety

No new safety issues have been identified in these two studies. The number of paediatric subjects assessed was quite limited and insufficient to determine the extent of risk of rare serious adverse events such as malignancies and severe opportunistic infections. The proposed dose regimen does not appear to have resulted in a clinically significant increased risk of adverse events compared with use in adults given their recommended dose regimen however, longer term safety will require post-market assessment.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of adalimumab in the proposed usage are:

- Adalimumab provides another treatment option for those patients who are already taking optimised conventional therapy for CD but who have had insufficient response.
- It is suitable for patients who did not respond to or lost response to infliximab and for patients who were intolerant of infliximab, though the probability of a treatment response is considerably reduced compared to infliximab naïve patients.

- It is more conveniently administered than infliximab, being administered via subcutaneous injection without the need for administration in a clinic (as is the case for infliximab)
- Regardless of the maintenance dose used in the pivotal study 54% of subjects had achieved a clinical response at Week 26 and 35% at Week 52. Clinical remission was achieved by 33.5% at Week 26 and by 28% at Week 52. Small increases in response and remission rates were seen if subjects who were dose escalated were included in the assessment of response and remission. This is a clinically significant benefit, though the benefits are greater for those without prior infliximab experience, or AAA, and who had an initial response to the induction regimen.

9.2. First round assessment of risks

The risks of adalimumab in the proposed usage are:

- The optimal dose regimen for paediatric patients with CD has not been adequately explored. Unlike infliximab the proposed dose regimen does not take BW into account on a mg/kg basis, but rather on the broad categorisation of <40 kg and greater than or equal to 40 kg.
- The effect of long term exposure in terms of persistence of effect and long term safety is unclear and requires as a minimum, some form of post-marketing assessment.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of adalimumab is unfavourable given the proposed usage, but would become favourable if the changes recommended are adopted.

10. First round recommendation regarding authorisation

In the absence of exploration of alternative induction dose regimens in a clinical study the proposed induction dose regimen is accepted, however, patients who have not achieved a clinical response to the induction regimen should not continue treatment. A robust demonstration of continued benefit for these patients has not been provided and given the risks of continued treatment it is not acceptable to continue to expose patients to a treatment with potential for life-threatening side effects when the extent of benefit is known to be reduced but is otherwise unclear.

The proposed higher dose maintenance regimen has not been shown to be statistically superior to the low dose regimen. Therefore the low dose regimen of 20 mg eow for patients with BW greater than or equal to 40 kg and 10 mg eow for patients with BW <40 kg should be adopted. There is insufficient evidence to support increasing dosing to weekly in patients who lose response or who fail to respond to initial treatment regimens. Consideration could be given to implementing the high dose regimen in patients with severe disease who have responded to the induction regimen.

11. Clinical questions

11.1. Pharmacokinetics

The EMA approved a 40/20 mg/kg induction dose regimen for patients with BW <40 kg and 20mg/10 mg for patients with BW greater than or equal to 40 kg. Are there any data or modelling to support these regimens?

11.2. Pharmacodynamics

Not applicable.

11.3. Efficacy

1. The SPC includes a statement that *Continued therapy should be carefully considered in a subject not responding by Week 12.* The basis for that statement is not clear. Are there any data to show clinical response and remission rates for subjects who did not achieve clinical response prior to Week 12 in Study M06-806?
2. For Study M06-806 a subgroup analysis of efficacy results by baseline severity (PCDAI scores <40 for moderate disease and greater than or equal to 40 for severe disease) has been included in the draft PI. This analysis could not be located in the submission. Please indicate where in the submission this analysis is located, or submit the analysis.
3. For Study M06-807: This study was planned to conclude approximately 12 weeks after adalimumab received country and local (if applicable) regulatory approval for paediatric Crohn's disease. Given the EMA has approved this indication is this study still ongoing? If so when is the next interim report anticipated?
4. Are there any maintenance data beyond 52 weeks for the 20 mg/ 10 mg eow dose regimen for paediatric subjects?
5. For Study M06-807: Please provide data on the number of subjects who withdrew from this study and the reasons for withdrawal.
6. What was the basis for the restricting the indication to patients with severe CD in the EU? Were subgroup analyses of response and/ or remission by disease severity performed? If so please submit these analyses.

11.4. Safety

Not applicable.

12. Second round evaluation

12.1. Pharmacokinetics

The sponsor has responded to the question on PK data for the induction dose regimen recommended in the EU by providing an exposure-efficacy analysis to justify the regimen proposed for Australia. That analysis was based on data from Study M06-806. Patients were categorised into quartiles (Q1 to Q4) based on observed Week 4 serum adalimumab trough concentrations (following induction dosing) and Week 26 PCDAI remission rates (the primary efficacy endpoint) were compared. The results suggested a relationship between adalimumab exposure following the induction dose and the percentage of patients experiencing clinical remission at Week 26.

This post-hoc analysis show a positive correlation between adalimumab trough levels at Week 4 (2 weeks after receiving the second induction dose) and subsequent clinical remission at Week 26. Given it has previously been demonstrated that there is a positive relationship between dose and serum concentration it is reasonable to assume that remission rates at 26 weeks would be lower for patients given the lower dose induction regimen that is the standard regimen approved in the EU. The EU dose recommendations also allow for the induction dose regimen proposed for Australia if a rapid response is needed.

12.2. Efficacy

The sponsor provided analyses by clinical response at Weeks 4, 8 and 12. Results from these analyses are reproduced below and provide strong support for not continuing treatment beyond 12 weeks in patients who do not have a clinical response at Week 12. There is a clinically significant proportion of patients who while not exhibiting a clinical response at Week 4 subsequently do show a clinical response at Week 26 and/ or Week 52. The difference in subsequent response and remission rates between the Week 8 and Week 12 nonresponders is less pronounced.

Results by baseline disease severity with severe CD at baseline, as defined by PCDAI greater than or equal to 40, the adalimumab High-Dose was substantially more effective than the Low-Dose for both response and remission at Week 52. In patients with moderate disease at baseline (PCDAI < 40), efficacy was similar in the High-Dose and Low-Dose groups at Week 52. These results support the proposed higher dose for patients with more severe disease.

The open maintenance study (M06-807) is ongoing. The currently projected date for the last patient to complete the study is October 2016. No further interim reports are planned.

Maintenance data for the 10mg EOW (low dose) maintenance regimen for patients with BW <40kg are available only to 52 weeks.

There were only 100 patients enrolled in the open maintenance study and 46 of these had withdrawn prior to the cut-off date for the interim report. Nine of the 46 had withdrawn due to lack of efficacy. Of note the reason for discontinuation was absent for 19 patients. This study is not adequate to assess the extent of ongoing (that is beyond 12 months) efficacy from maintenance treatment with adalimumab in paediatric patients with CD.

The European indication for paediatric CD was restricted to patients with severe disease by request of the EMA because of considerations regarding potential serious AEs (SAEs) in patients with moderate disease. The sponsor does not agree with this restriction and has not proposed it for Australia.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions the following issues have been clarified:

The longer term clinical response and remission rates in patients who do not show a clinical response at Week 4 is significant. Very few individuals would receive benefit from continuing treatment if they have not achieved a clinical response at their Week 12 assessment.

The proposed higher maintenance dose regimen for patients with severe disease is supported by the post-hoc analyses of clinical remission and response rates by baseline disease severity.

13.2. Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks are unchanged from those identified.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of adalimumab, given the proposed usage, is favourable.

14. Second round recommendation regarding authorisation

Amendments previously recommended to the PI and CMI have not been implemented. This evaluator recommends these be implemented or a justification for not implementing the amendments be provided by the sponsor.

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