22 March 2018
EMA/CHMP/222491/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Humira

adalimumab

Procedure no: EMEA/H/C/000481/P46/102

Note

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

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1. Introduction

On September 26th the MAH submitted a completed paediatric study for Crohn's disease, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measures.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that this multi-centre, open-label Study (M06-807) 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 is a stand-alone study.

The MAH stated that Study (M06-807) is part of a clinical development program.

The latest interim report for study M06-807 was submitted as part of variation application EMEA/H/C/000481/II/0147, to support the approval of moderately active paediatric Crohn's Disease.

This is a final report for Study M06-807 the OLE of study M06-806 and The Week 52 visit from Study M06-806 was the Baseline Visit in Study M06-807 for subjects entering Study M06-807.

No changes to the product information are proposed by the MAH with this application.

2.2. Information on the pharmaceutical formulation used in the study

Adalimumab, a human monoclonal antibody against tumour necrosis factor, is approved for the treatment of CD in children in over 70 countries globally including the European Union, United States, Canada, Australia, and Switzerland. The product is administered via injection the dose was adjusted to body weight.

The study drug was provided as a subcutaneous injection solution in pre-filled syringes containing adalimumab 40 mg/0.8 mL or adalimumab 20 mg/0.4 mL or in vials containing adalimumab 40 mg/0.8 mL. However, no vials were used in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final report for:

- M06-807 multi-centre, open-label Study (M06-807) 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

2.3.2. Clinical study

Study M06-807

Description

Study M06-807 was a multicentre, one-armed study of adalimumab in paediatric subjects (aged 6 and 17 years, inclusive, with moderate to severe CD at Study M06-806 Baseline) who completed Study M06-806 through Week 52 (the Baseline for Study M06-807). Study M06-806 had enrolled subjects 6 to 17 years of age, inclusive, with moderately to severely active CD who had failed conventional therapy for CD, including subjects who had previously received infliximab and lost response or had intolerance to infliximab. Subjects who entered Study M06-807 from blinded therapy in Study M06-806 initially received open-label adalimumab at a dose dependent on their body weight (40 mg every other week [eow] if weighing ≥ 40 kg at M06-807 Baseline; 20 mg eow if weighing < 40 kg at M06-807 Baseline). Subjects who enrolled from open-label therapy (adalimumab 40 mg every week [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.

Beginning at Week 8, dosing adjustment (dose or dose frequency change) may have been made based on the clinical status of the individual subject: disease flare (eow to ew), body weight increase or decrease (to next higher or lower dose level) or response to treatment (to next lower treatment level). Subjects were seen at specified intervals, and follow-up calls were conducted to inquire about adverse events (AEs) and medications. Subjects continued in the study until adalimumab received country and local (if applicable) regulatory approval for paediatric CD or for a maximum of 408 weeks.

Methods

Objective(s)

Key study objectives were to evaluate:

- Efficacy in reducing disease activity as measured by Pediatric Crohn's Disease Activity Index (PCDAI) remission and response, CDAI (Crohn's Disease Activity Index remission and response (for subjects ≥ 13 years of age at Study M06-807 Baseline), and steroid-free PCDAI remission and CDAI remission
- Efficacy in improving health-related quality of life outcomes as assessed by the IMPACT III questionnaire (for subjects ≥ 10 years of age at Study M06-807 Baseline) and the Work Productivity and Activity Impairment Crohn's Disease – Caregiver (WPAI-CD – Caregiver) questionnaire
- Safety as assessed by reports of AEs and laboratory data.

Study design

The first study visit after Baseline of Study M06-807 (Week 52 of Study M06-806) occurred at Week 4 and was followed by 12-week interval study visits (Week 8 through Week 120), then followed by 24-week interval study visits (Week 144 through 408) and 24-week interval telephone calls to update medications and AEs (Week 156 through Week 396). A 70-day follow-up call was done for any subject who completed or discontinued early from the study. The first subject's first visit in Study M06-807 was 01 May 2008, the last subject's last visit was 07 February 2017, and the last 70-day follow-up call for any subject occurred on 04 April 2017.

Case report forms were the primary data source. For safety evaluations, subjects were asked about AEs at each visit and during phone calls. Adverse events were reported by Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 system organ class and preferred term.

Study population /Sample size

Subjects were enrolled at 31 investigative sites in the US, Canada, and Europe, with the number of subjects entered at each site ranging from 1 to 14.

Baseline Demographics

The intent-to-treat population (same as the safety population) consisted of 100 subjects who received at least 1 dose of adalimumab in Study M06-807. Baseline demographics for these subjects were based on the values from the Baseline of Study M06-806. Approximately half (52%) of all subjects were males, most (93%) were white, and two-thirds were ≥ 13 years old. Mean age was 13.5 ± 2.5 years. Median PCDAI was 40 and median CDAI (in subjects aged ≥ 13 years) was 239.5, indicative of a population with moderate to severe disease activity. Most subjects had CD of the colon (80.0%) and ileum (85.0%).

Table 1Demographic Data at Baseline of Study M06-806 (ITT Population)

Variable	Any Adalimumab N = 100
Sex, n (%)	
Male	52 (52.0)
Female	48 (48.0)
Race, n (%)	
White	93 (93.0)
Black	3 (3.0)
Other	2 (2.0)
Multi-race	2 (2.0)
Ethnicity, n (%)	
Hispanic or Latino	2 (2.0)
No ethnicity	98 (98.0)
Age (years), n (%)	
< 13	35 (35.0)
≥ 13	65 (65.0)
Age (years)	
Mean ± SD	13.5 ± 2.452
Median (range)	14.0 (7.0 to 17.0)
Weight (kg), n (%)	
< 40	38 (38.0)
≥ 40	62 (62.0)
Weight (kg)	
Mean ± SD	43.75 ± 14.333
Median (range)	42.0 (20.0 to 101.0)
BMI (kg/m^2)	
Mean ± SD	18.19 ± 3.86
Median (range)	17.73 (12.8 to 40.0)
Height (cm)	
Mean ± SD	153.24 ± 14.284
Median (range)	155.0 (122.0 to 185.0)

Table 2 Concomitant IMM and Systemic Corticosteroid Use at Study M06-806 Baseline (ITT Population)

Parameter	Number (%) of Subjects Any Adalimumab N = 100
With IMM	73 (73.0)
With systemic corticosteroid	37 (37.0)
Without IMM and without systemic corticosteroid	12 (12.0)
Without IMM and with systemic corticosteroid	15 (15.0)
With IMM and without systemic corticosteroid	51 (51.0)
With IMM and with systemic corticosteroid	22 (22.0)

Note: IMM includes medications with generic names of AZA, MP, or MTX. Concomitant IMM use at Study M06-806 Baseline was defined as the use of IMMs (AZA, MP, or MTX) if the medication start date was before or equal to adalimumab first dose date and the medication end date was after or equal to adalimumab first dose date.

Treatments

Twenty-seven subjects weighing < 40 kg at Week 52 of Study M06-806 entered Study M06-807. Of these, 21 subjects received adalimumab 20 mg eow and 6 subjects received adalimumab 20 mg ew. Seventy-three subjects weighing ≥ 40 kg at Week 52 of Study M06-806 entered Study M06-807. Of these, 68 subjects received adalimumab 40 mg eow, 4 subjects received adalimumab 40 mg ew, and 1 subject received adalimumab 20 mg ew. Thirty-nine subjects escalated from eow to ew dosing during Study M06-807), and 14 subjects had a weight-based dosage adjustment after Week 8.

Outcomes/endpoints

Paediatric Crohn's Disease Activity Index

The PCDAI (Protocol Appendix G) was calculated at each visit. When completing the PCDAI, the haematocrit, albumin, and ESR values were utilized from the same study visit.

Crohn's Disease Activity Index

At each visit, a CDAI (Protocol Appendix I) was calculated for subjects who were age 13 or older at M06-807 Baseline. The CDAI was calculated utilizing the subject diary and the haematocrit value from the same study visit.

Efficacy Analyses by Subgroup

Subgroup analyses (LOCF and observed case) were performed for the number and percentage of subjects in PCDAI remission/response over time for the following characteristics at Baseline of Study M06-806:

- Age (< 13 years, ≥ 13 years)
- BW (< 40 kg, ≥ 40 kg)
- Prior infliximab use (yes, no)
- Corticosteroid use (yes, no)
- IMM use (yes, no)

Healthcare Resource Utilization:

The Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations Questionnaire (Protocol Appendix N) was to be completed by the site personnel at each visit including unscheduled visits by querying the subject

Patient- and Caregiver-Reported Outcomes:
IMPACT III Questionnaire and Work Productivity and Activity Impairment Questionnaire: Crohn's Disease

Statistical Methods

In general, missing Baseline and safety data were not estimated.

Baseline Value is missing: Subjects were excluded from analysis of change and percent change from Baseline if the Baseline evaluation was missing.

Missing Efficacy and Outcome Evaluations: The following imputation methods were used to impute missing values in the efficacy analyses. In addition, an observed case analysis was performed.

When an endpoint in the study was analysed as observed, no imputation of the missing values was performed.

In the subgroup analysis of efficacy variables, an LOCF analysis was carried out as sensitivity analysis. The following rules were used for the LOCF approach:

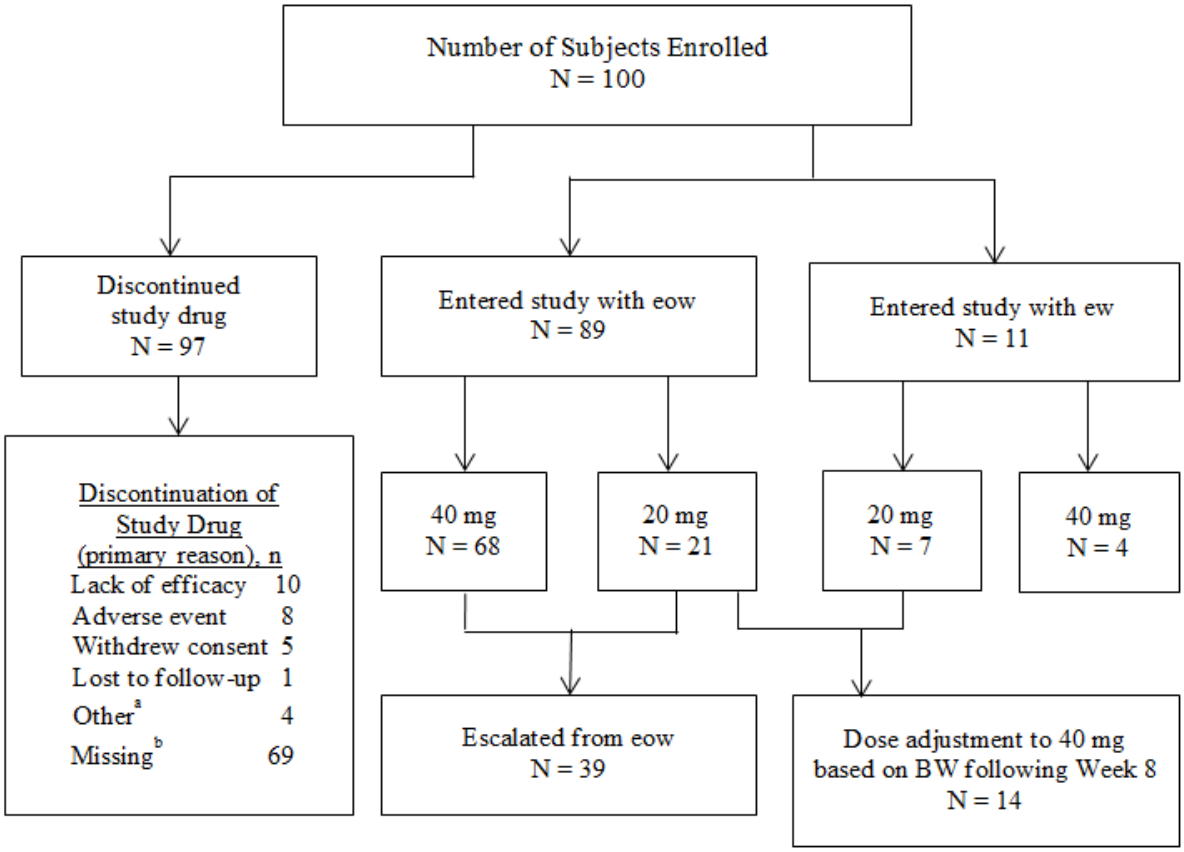
1. Baseline (the Week 52 visit of Study M06-806) and pre-baseline values were not used to impute the missing post-baseline values.

2. Missing values after Study Day 1 were imputed using the latest non-missing values after Day 1 and prior to the missing value.

Results

A total of 97 (97.0%) subjects discontinued study drug. The primary reason was not indicated for 69 subjects; for 36 of these subjects, the investigative site indicated that the subject had discontinued study drug because Humira had become commercially available (received regulatory approval for paediatric CD) in their country. Those subjects were considered to have completed the study. For other subjects, 1 or more reasons for discontinuation of study drug were recorded (Figure below).

Figure 1 Subject Disposition



a. Other reasons include the following: planned bowel resection surgery (2 subjects), consulted outside physician (1 subject), and loss of response to study medication (1 subject).

b. Thirty-six subjects discontinued study drug because Humira was approved in their country (primary reason listed as "missing" on the CRF); these subjects were considered study completers. Other subjects who were missing a primary reason for study drug discontinuation had 1 or more of the following reasons recorded: lack of efficacy (8), withdrawal of consent (6), AE (5), lost to follow-up (4), subject transitioned to adult care (4), protocol violation (2), administrative reasons (2), subject was in remission (1); and subject discontinued from the study/did not want to return for ET visit (1). Other reasons include the following: planned bowel resection surgery (2 subjects), consulted outside physician (1 subject), and loss of response to study medication (1 subject).

Assessor's comment:

The applicant should describe in more detail the data with different cut-offs with regard to time in study for individual patients (for example patients exposed for > 2, > 4 and > 6 years) to facilitate the interpretation of data and describe the efficacy and safety data. See RSI

Recruitment / Number analysed

Baseline data

Table 3 Disease Activity at Baseline of Study M06-806 (ITT Population)

Parameter	Any Adalimumab N = 100
PCDAI	
N	100
Mean ± SD	40.10 ± 6.656
Median (range)	40.0 (25.0 – 62.5)
CDAI[a]	
N	64
Mean ± SD	244.55 ± 85.085
Median (range)	239.50 (75.0 – 470.0)
hs-CRP (mg/dL)	
N	98
Mean ± SD	2.27 ± 2.837
Median (range)	1.14 (0.0 – 14.4)
hs-CRP (mg/dL), n (%)	
< 1	45 (45.9)
≥ 1	53 (54.1)
Missing	2
ESR (mm/HR)	
N	97
Mean ± SD	32.36 ± 21.499
Median (range)	28.0 (1.0 – 135.0)

a. In subjects ≥ 13 years old.
Note: Percentages calculated on non-missing values. Baseline is defined as the last non-missing value on or before the first dose date of Study M06-806.

Table 4 Infliximab History at Baseline of Study M06-806 (ITT Population)

	Number (%) of Subjects
	Any Adalimumab N = 100
Prior infliximab use	
Yes	29/100 (29.0)
No	71/100 (71.0)
Initial response to infliximab	
Yes	28/29 (96.6)
No	1/29 (3.4)[a]
Loss of response to infliximab	
Yes	20/29 (69.0)
No	9/29 (31.0)[b]
Reaction to infliximab	
Yes	12/29 (41.4)
Acute	8/12 (66.7)
Delayed	4/12 (33.3)
No	17/29 (58.6)
Loss of response and reaction	
Yes	4/29 (13.8)
No	25/29 (86.2)

a) Subject (nr redacted) had an acute reaction to infliximab
b) All 9 subjects had reactions to infliximab
Note: infliximab history is from Study M06 806. Percentages calculated based on non-missing values.

Table 5 Concomitant IMM and Systemic Corticosteroid Use at Study M06-806 Baseline (ITT Population)

Parameter	Number (%) of Subjects Any Adalimumab N = 100
With IMM	73 (73.0)
With systemic corticosteroid	37 (37.0)
Without IMM and without systemic corticosteroid	12 (12.0)
Without IMM and with systemic corticosteroid	15 (15.0)
With IMM and without systemic corticosteroid	51 (51.0)
With IMM and with systemic corticosteroid	22 (22.0)

Note: IMM includes medications with generic names of AZA, MP, or MTX. Concomitant IMM use at Study M06-806 Baseline was defined as the use of IMMs (AZA, MP, or MTX) if the medication start date was before or equal to adalimumab first dose date and the medication end date was after or equal to adalimumab first dose date.

Efficacy results

Approximately two-thirds or more of subjects were in PCDAI clinical remission (PCDAI ≤ 10) at each visit and approximately 90% of subjects or more achieved PCDAI clinical response (PCDAI ≥ 15 points lower than the Study M06-806 Baseline) at each visit. Analyses by age group (< 13 versus ≥ 13 years), body weight group (< 40 versus ≥ 40 kg), prior infliximab use, baseline corticosteroid use, and baseline IMM use, showed high rates of PCDAI remission and response for adalimumab across all subgroups.

Among subjects ≥ 13 years of age at Study M06-806 Baseline, approximately 90% or more of subjects achieved CDAI clinical remission (CDAI < 150) or CDAI clinical response (CDAI ≥ 70 points lower than the Study M06-806 Baseline) at each visit. Among subjects who had been receiving systemic corticosteroids at Study M06-806 Baseline, approximately two-thirds were in steroid-free (for ≥ 90 days) PCDAI remission, and among subjects who were at least 13 years old at Study M06-806 Baseline, over three-quarters were in steroid-free CDAI remission at entry into Study M06-807. These rates were sustained throughout Study M06-807.

Rates of concomitant immunosuppressant-free remission among subjects who had been receiving concomitant immunosuppressant at Baseline of Study M06-806 and had discontinued their IMM use increased over time.

Patient- and caregiver-reported quality of life outcomes reflected the control of disease activity achieved with adalimumab treatment, as demonstrated by the decrease in the impact of the disease on quality of life of the children and by the decreases in work time missed, impairment while working, and overall work impairment for children caregivers who were employed and the decrease in daily activity impairment for all children caregivers.

Assessor's comment:

Efficacy data in this OLE study is difficult to interpret especially since it is not known for how long each patient stayed in the study. However, there are no data that points to a higher disease activity over time. The most common reason for discontinuation of study is that commercial adalimumab (Humira) became available in the study subjects country. Eighteen of 100 subjects discontinued due to loss of efficacy, which is a figure in line with earlier data. However, as the study is not randomised, descriptive data could be assessed also with few patients staying in the study to the end provided the subjects' exposure time is known.

Safety results

Safety results of Study M06-807 included 52-week exposure in Study M06-806. Mean exposure to adalimumab (N = 100) since the first dose in Study M06-806 was 1719.7 ± 806.92 days (approximately 4.7 years), for a total of 470.8 PYs of exposure. Maximum exposure for any subject was 3220 days (approximately 8.8 years).

No deaths were reported. The safety profile of adalimumab with longer-term treatment in paediatric subjects with CD was similar to that observed in 52-week Study M06-806, and no new safety signals were observed.

Approximately half of all subjects (48.0%) reported serious adverse events (SAEs), the most frequent of which were CD (25.0%) and anal abscess (3.0%); all other SAEs were reported by 1 or 2 subjects each. Twenty subjects (20.0%) discontinued study drug due to AEs. Most SAEs and events leading to discontinuation were attributable to a worsening or complication of the underlying CD.

Table 6 Overview of Adverse Events Including Data from Both Study M06-806 and Study M06-807 (Safety Population)

	Adalimumab N = 100 PYs = 470.8	
Subjects with:	**n (%)**	**E (E/100 PY)**
Any AE	100 (100)	2316 (491.9)
AE at least possibly drug-related[a]	79 (79.0)	495 (105.1)
Severe AE	28 (28.0)	51 (10.8)
SAE	48 (48.0)	103 (21.9)
AE leading to discontinuation of study drug	20 (20.0)	25 (5.3)
SAE leading to discontinuation of study drug	10 (10.0)	11 (2.3)
SAE at least possibly drug-related[a]	10 (10.0)	12 (2.5)
Fatal AE	0	0
Deaths[b]	0	0

E = events; E/100 PY = events per 100 patient-years (incidence)

a. As assessed by the investigator.

b. Includes non-treatment-emergent deaths.

Note: Events with unknown severity and relationship to study drug are counted as severe and drug-related, respectively. Analysis excludes data from subjects from Study M06-806 who did not enter Study M06-807.

Table 7 Adverse Events Reported by ≥ 10% of Subjects Including Data from Both Study M06-806 and Study M06-807

	Adalimumab N = 100 PYs = 470.8	
MedDRA Preferred Term[a]	n (%)	E (E/100PY)
Any AE	100 (100)	2287 (511.9)
Crohn's disease[b]	49 (49.0)	108 (22.9)
Viral upper respiratory tract infection	39 (39.0)	88 (18.7)
Headache	37 (37.0)	100 (21.2)
Upper respiratory tract infection	32 (32.0)	62 (13.2)
Diarrhoea	26 (26.0)	41 (8.7)
Oropharyngeal pain	27 (27.0)	48 (10.2)
Abdominal pain	25 (25.0)	64 (13.6)
Vomiting	22 (22.0)	39 (8.3)
Pyrexia	21 (21.0)	38 (8.1)
Arthralgia	21 (21.0)	37 (7.9)
Cough	20 (20.0)	34 (7.2)
Pharyngitis	20 (20.0)	48 (10.2)
Fatigue	19 (19.0)	25 (5.3)
Nausea	19 (19.0)	50 (10.6)
Viral infection	19 (19.0)	22 (4.7)
Sinusitis	18 (18.0)	34 (7.2)
Abdominal pain upper	16 (16.0)	27 (5.7)
Constipation	16 (16.0)	29 (6.2)
Injection site reaction	16 (16.0)	35 (7.4)
C-reactive protein increased	15 (15.0)	15 (3.2)
Influenza	15 (15.0)	23 (4.9)
Rash	15 (15.0)	25 (5.3)
Back pain	14 (14.0)	25 (5.3)
Pharyngitis streptococcal	14 (14.0)	20 (4.2)
Urinary tract infection	14 (14.0)	19 (4.0)

	Adalimumab N = 100 PYs = 470.8	
MedDRA Preferred Term[a]	n (%)	E (E/100PY)
Skin papilloma	13 (13.0)	15 (3.2)
Nasal congestion	12 (12.0)	17 (3.6)
Bronchitis	11 (11.0)	18 (3.8)
Anaemia	10 (10.0)	14 (3.0)
Ear infection	10 (10.0)	15 (3.2)
Pneumonia	10 (10.0)	13 (2.8)
Rhinitis	10 (10.0)	20 (4.2)

a. Listed by decreasing frequency.

b. Worsening or flare of underlying disease.

Table 8 Adverse Events Possibly or Probably Related to Study Drug Reported by ⩾ 5% of Subjects Including Data from Both Study M06-806 and Study M06-807 (safety population)

MedDRA Preferred Term[a]	Adalimumab N = 100 n (%)
Any AE	79 (79.0)
Injection site reaction	16 (16.0)
Viral upper respiratory tract infection	12 (12.0)
Headache	8 (8.0)
Sinusitis	8 (8.0)
Upper respiratory tract infection	8 (8.0)
Injection site pain	7 (7.0)
Pharyngitis streptococcal	7 (7.0)
Herpes zoster	6 (6.0)
Urinary tract infection	6 (6.0)
Antinuclear antibody positive	5 (5.0)
Nausea	5 (5.0)
Abdominal pain	5 (5.0)
Pneumonia	5 (5.0)
Skin papilloma	5 (5.0)
Pyrexia	5 (5.0)

a. Listed by decreasing frequency.

Table 9 Listing of Subjects with Serious Adverse Events Possibly or Probably Related to Study Drug Including Data from Both Study M06-806 and Study M06-807 (Safety Population)

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

PR = probably related; PS = possibly related

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 Events Leading to Discontinuation

Twenty subjects (20.0%) discontinued from the study due to AEs . Most events were attributable to a worsening or a complication of the underlying CD. Four subjects reported more than 1 AE leading to discontinuation. Events leading to discontinuation were serious for 10 subjects (Crohn's disease in 6

subjects, pelvic fluid collection and pyrexia in 1 subject, and SLE, subcutaneous abscess, and ileal stenosis in 1 subject each).

Among AEs of special interest (AESIs), infections (including 26 serious infections) accounted for approximately one-fourth of all reported AEs (595/2316 events). Injection site reactions accounted for approximately 3% of all AESIs reported; other AESI categories accounted for 1% or less of the AESI total.

Adverse Events of Special Interest

No malignancies (including lymphoma, nonmelanoma skin cancer, hepatosplenic T-cell lymphoma, melanoma, and leukemia), opportunistic infections excluding oral candidiasis, active tuberculosis, legionella infections, demyelinating disorders, vasculitis (cutaneous and noncutaneous), Stevens-Johnson syndrome, sarcoidosis, myocardial infarction, cerebrovascular accident, congestive heart failure, pulmonary embolism, interstitial lung disease, diverticulitis, erythema multiforme, amyotrophic lateral sclerosis, progressive multifocal leukoencephalopathy, reversible posterior leukoencephalopathy syndrome, reactivation of hepatitis B, autoimmune hepatitis, or Humira administration-related medication errors were reported.

Table 10 Overview of Adverse Events of Special Interest Including Data from Both Study M06-806 and Study M06-807 (Safety Population)

	Adalimumab N = 100 PYs = 470.8	
Subjects with:	**n (%)**	**E (E/100 PY)**
Any AE	100 (100)	2316 (491.9)
Infection	95 (95.0)	595 (126.4)
Serious infection	18 (18.0)	26 (5.5)
Oral candidiasis	4 (4.0)	7 (1.5)
Latent TB	2 (2.0)	2 (0.4)
Parasitic infection	1 (1.0)	1 (0.2)
Injection site reaction	26 (26.0)	70 (14.9)
Allergic reaction including angioedema/anaphylaxis	17 (17.0)	23 (4.9)
Lupus-like reaction and SLE	1 (1.0)	1 (0.2)
Hematologic disorder including pancytopenia	16 (16.0)	24 (5.1)
Intestinal perforation	2 (2.0)	2 (0.4)
Intestinal stricture	5 (5.0)	6 (1.3)
Pancreatitis	1 (1.0)	1 (0.2)
Worsening/new onset of psoriasis	5 (5.0)	6 (1.3)
Liver failure and other liver events	1 (1.0)	1 (0.2)

Infection

The majority of subjects reported at least 1 AE of infection during the study. The most frequently reported infections (≥ 20% of subjects) were viral upper respiratory tract infection and upper respiratory tract infection. Most infections were nonserious, mild or moderate in severity, easily manageable within a short timeframe, and did not require interruption or discontinuation of adalimumab.

Eighteen subjects (18.0%) in Study M06-807 reported serious infections during Study M06-806 and Study M06-807. Six of the subjects reported serious infections that represent common complications

related to CD (anal abscess in 3 subjects, abdominal abscess, pelvic abscess, and perirectal abscess in 1 subject each).

Table 11 Serious Infections Including Data from Both Study M06-806 and Study M06-807 (Safety Population)

MedDRA Preferred Term[a]	Adalimumab N = 100 n (%)
Any serious infection	18 (18.0)
Anal abscess	3 (3.0)
Gastroenteritis	2 (2.0)
Pneumonia	2 (2.0)
Subcutaneous abscess	2 (2.0)
Abdominal abscess	1 (1.0)
Cystitis viral	1 (1.0)
Herpes virus infection	1 (1.0)
Impetigo	1 (1.0)
Pelvic abscess	1 (1.0)
Perirectal abscess	1 (1.0)
Peritonitis	1 (1.0)
Salmonellosis	1 (1.0)
Sinusitis	1 (1.0)
Staphylococcal abscess	1 (1.0)
Tonsillitis	1 (1.0)
Tooth abscess	1 (1.0)
Upper respiratory tract infection	1 (1.0)
Viral infection	1 (1.0)
Yersinia infection	1 (1.0)

a. Listed by decreasing frequency.

Intestinal Perforation

Two subjects (2.0%) had events of intestinal perforation during Study M06-807:

- Subject aged 15 years old at Study M06-806 Baseline with CD involving the ileum, experienced an SAE of ileal perforation (reported term: spontaneous perforation of ileum secondary to Crohn's disease) on Day 2019. The subject was discontinued from the study and hospitalized for surgery; the event resolved in 5 days. The investigator considered the event to be not related to study drug.
- Subject aged 16 years old at Study M06-806 Baseline with a medical history of fistula, experienced an SAE of large intestine perforation on Day 2099, and the subject continued in the study. The subject was hospitalized for surgery, and the event resolved in 376 days. The investigator considered the event not related to study drug.

Intestinal Stricture

- Subject aged 14 years old at Study M06-806 Baseline, experienced an SAE of small intestinal stenosis on Day 905 of adalimumab treatment. The subject was treated (medication and surgery), the event resolved in 10 days, and the subject continued in the study. The investigator considered the event probably not related to study drug.
- Subject aged 11 years old at Study M06-806 Baseline, experienced a nonserious gastrointestinal wall thickening and ileal stenosis on Day 2480. The subject was treated with medication and continued in the study; the events were ongoing at the last evaluation of the study. The investigator considered the events probably not related to study drug.
- Subject aged 14 years old at Study M06-806 Baseline with a CD-related history of internal fistula, experienced an SAE of ileal stenosis on Day 691 of adalimumab treatment. Study drug was discontinued, the subject was treated (medication and surgery), and the event resolved in 17 days. The investigator considered the event probably not related to study drug.
- Subject aged 12 years old at Study M06-806 Baseline, experienced an SAE of large intestinal (colonic) stenosis (reported as progression of stenosis – sigmoideum CD) on Day 1099 of adalimumab treatment. The subject was treated with medication and the event resolved in 163 days. The subject continued in the study. The investigator considered the event probably not related to study drug.
- Subject aged 14 years old at Study M06-806 Baseline, experienced a nonserious event of ileal stenosis on Day 2432. Study drug was discontinued; the event was ongoing as of the last evaluation of the study. The investigator considered the event possibly related to study drug.

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

Assessor's comment:

The safety profile of adalimumab in this OLE is consistent of the safety profile as described in the SmPC. No new safety signals have been identified. There were 5 cases of stricture in the study. However, this does not seem to be a higher frequency than reported in epidemiological studies as described in Levine et al (IBD Volume 17, Number 6, June 2011).

2.3.3. Discussion on clinical aspects

This study evaluated the long-term safety and efficacy of adalimumab for the induction and maintenance of clinical response, safety, and tolerability of adalimumab in paediatric subjects with CD who participated in and completed Study M06-806.

However, the MAH should provide further information on the exposure time in the study expressed as patient years.

MAH discussion

The long-term efficacy of adalimumab in Study M06-807 in this paediatric population was demonstrated by the high proportion of subjects with sustained response and remission as per PCDAI and CDAI over time.

Approximately two-thirds or more of subjects achieved PCDAI clinical remission (defined as PCDAI ≤ 10) at each visit. Approximately 90% or more of subjects achieved PCDAI clinical response (defined as PCDAI at least 15 points lower than Study M06-806 Baseline) at each visit. Approximately 90% or more of subjects achieved CDAI clinical remission (defined as CDAI < 150) or CDAI clinical response (analysed only for subjects ≥ 13 years of age and defined as a decrease from Study M06-806 Baseline in CDAI ≥ 70 points) at each visit.

Safety results reported in this CSR, which includes 52-week Study M06-806 plus exposure from Study M06-807, did not indicate any safety concerns with long-term adalimumab treatment in paediatric subjects with CD. No deaths were reported. Most SAEs and events leading to discontinuation were related to the underlying CD. The safety profile and event rates between subgroups by disease severity were generally comparable. No malignancies (including lymphoma, NMSC, HSTCL, melanoma, and leukaemia), opportunistic infections other than latent TB, legionella infections, demyelinating disorders, vasculitis, SJS, sarcoidosis, MI, CVA, CHF, PE, ILD, diverticulitis, erythema multiforme, ALS, PML, RPLS, reactivation of hepatitis B, autoimmune hepatitis, or Humira administration-related medication errors were reported. No new safety signals were identified.

MAH Conclusion

The final efficacy results from open-label Study M06-807 demonstrated that adalimumab treatment, after 52 weeks of treatment in Study M06-806, was effective in achieving long-term maintenance of remission and response in paediatric subjects (aged 6 to 17 years) with moderately to severely active CD who had failed conventional therapy for CD, including subjects who had previously received infliximab and lost response or had intolerance to infliximab. The long-term safety profile of adalimumab in paediatric subjects with CD, including data from both Study M06-806 and Study M06-807, was generally consistent with the safety profile observed in the 52-week Study M06-806; no new safety signals were identified.

Assessor's comment:

Considering the open label design and uncertainties with regard to exposure time for each patient the efficacy data is difficult to interpret. The mean exposure in the study was approximately 4.7 years and thus, at least some patients had indeed a long term exposure within the study. The MAH should describe the data in more detail as outlined above. Please see the RSI.

3. Rapporteur's overall conclusion and recommendation

The applicant has with this submission presented the final report of study M06-807 which was an OLE study to Study M06-806, in paediatric subjects (aged 6 to 17 years) with moderately to severely active CD who had failed conventional therapy for CD, including subjects who had previously received infliximab and lost response or had intolerance to infliximab. There was an interim report of this study submitted as part of variation application EMEA/H/C/000481/II/0147, to support the approval of moderately active paediatric Crohn's Disease in 2016.

In this OLE no new safety concerns have been identified.

The benefit/risk for Humira in the use in paediatric subjects aged 6-17 years in moderate to severe CD is considered to remain unchanged. However, the MAH should describe the data in a more structured way as described in the RSI below.

☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide description of the additional clarifications requested per study as part of this procedure. (see section “Additional clarification requested”)

4. Additional clarification requested

The applicant should present data on patient exposure expressed as patient years in study and a Kaplan-Mayer plot. In addition efficacy data should be presented by exposure time subgroups (for example patients exposed for > 2, > 4 and > 6 years).

5. Responses to the RSI

MAH Response:

Tables depicting the requested exposure criteria and efficacy data are provided and displayed below. As shown in the supplemental tables provided, efficacy was consistent across exposure groups.

Table 12 Study Drug Exposure in Study M06-807 – Part 2 (Intent-to-Treat Population)

DURATION OF EXPOSURE	ANY ADALIMUMAB (N=100) n (%)
0 - 1 (PATIENT-YEARS)	100 (100)
1 - 2 (PATIENT-YEARS)	82 (82.0)
2 - 3 (PATIENT-YEARS)	75 (75.0)
3 - 4 (PATIENT-YEARS)	61 (61.0)
4 - 5 (PATIENT-YEARS)	51 (51.0)
5 - 6 (PATIENT-YEARS)	38 (38.0)
6 - 7 (PATIENT-YEARS)	14 (14.0)
> 7 (PATIENT-YEARS)	2 (2.0)

NUMBER TREATED	100
PATIENT-YEARS	371.2

Table 13 Proportion of Subjects Who Were in PCDAI Clinical Remission Over Time (Observed Case and LOCF) by Patient-Years Group (Intent-to-Treat Population)

VISIT		ANY ADALIMUMAB PATIENT-YEARS GROUP > 2 PATIENT-YEARS n/N (%)		ANY ADALIMUMAB PATIENT-YEARS GROUP > 4 PATIENT-YEARS n/N (%)		ANY ADALIMUMAB PATIENT-YEARS GROUP > 6 PATIENT-YEARS n/N (%)	
WEEK 0	(OBSERVED)	55/75	(73.3)	37/51	(72.5)	10/14	(71.4)
WEEK 4	(OBSERVED)	55/75	(73.3)	41/51	(80.4)	11/14	(78.6)
	(LOCF)	55/75	(73.3)	41/51	(80.4)	11/14	(78.6)
WEEK 8	(OBSERVED)	55/75	(73.3)	39/51	(76.5)	12/14	(85.7)
	(LOCF)	55/75	(73.3)	39/51	(76.5)	12/14	(85.7)
WEEK 12	(OBSERVED)	50/75	(66.7)	38/51	(74.5)	8/14	(57.1)
	(LOCF)	50/75	(66.7)	38/51	(74.5)	8/14	(57.1)
WEEK 24	(OBSERVED)	49/75	(65.3)	34/51	(66.7)	11/14	(78.6)
	(LOCF)	49/75	(65.3)	34/51	(66.7)	11/14	(78.6)
WEEK 36	(OBSERVED)	53/73	(72.6)	36/50	(72.0)	11/14	(78.6)
	(LOCF)	53/75	(70.7)	36/51	(70.6)	11/14	(78.6)
WEEK 48	(OBSERVED)	53/73	(72.6)	38/50	(76.0)	11/13	(84.6)
	(LOCF)	55/75	(73.3)	39/51	(76.5)	12/14	(85.7)
WEEK 60	(OBSERVED)	57/72	(79.2)	40/49	(81.6)	11/14	(78.6)
	(LOCF)	58/75	(77.3)	41/51	(80.4)	11/14	(78.6)
WEEK 72	(OBSERVED)	48/72	(66.7)	39/49	(79.6)	12/14	(85.7)
	(LOCF)	51/75	(68.0)	41/51	(80.4)	12/14	(85.7)
WEEK 84	(OBSERVED)	54/72	(75.0)	39/48	(81.3)	12/14	(85.7)
	(LOCF)	57/75	(76.0)	42/51	(82.4)	12/14	(85.7)
WEEK 96	(OBSERVED)	54/75	(72.0)	42/51	(82.4)	13/14	(92.9)
	(LOCF)	54/75	(72.0)	42/51	(82.4)	13/14	(92.9)

NOTE: LOCF - LAST OBSERVATION CARRIED FORWARD WAS USED FOR MISSING ASSESSMENTS.
CLINICAL REMISSION IS DEFINED AS PCDAI SCORE <= 10 POINTS.

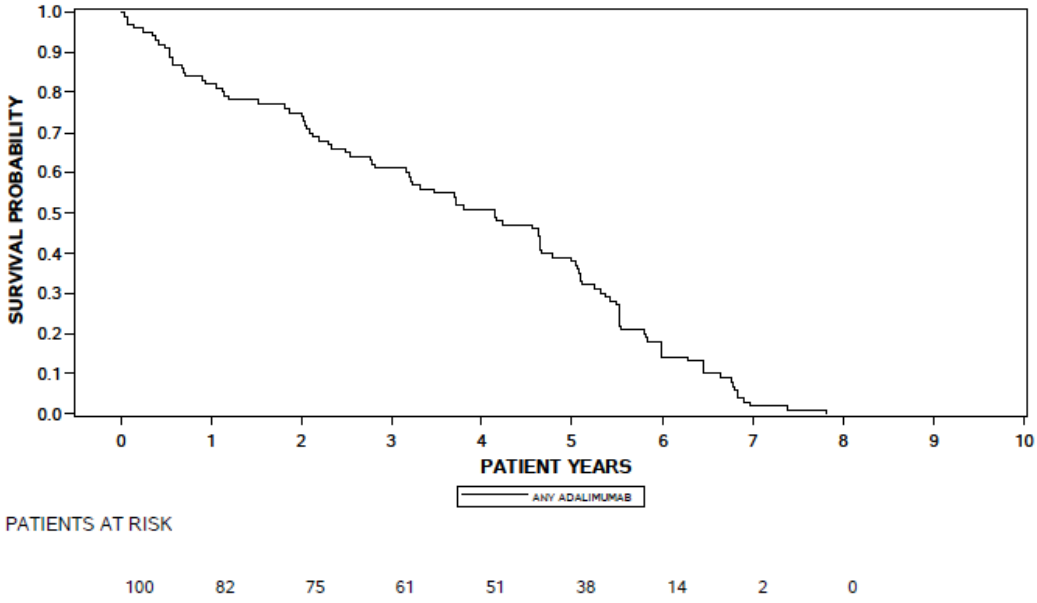
VISIT	ANY ADALIMUMAB PATIENT-YEARS GROUP > 2 PATIENT-YEARS n/N (%)	ANY ADALIMUMAB PATIENT-YEARS GROUP > 4 PATIENT-YEARS n/N (%)	ANY ADALIMUMAB PATIENT-YEARS GROUP > 6 PATIENT-YEARS n/N (%)
WEEK 108 (OBSERVED)	54/72 (75.0)	40/49 (81.6)	12/14 (85.7)
(LOCF)	56/75 (74.7)	42/51 (82.4)	12/14 (85.7)
WEEK 120 (OBSERVED)	52/67 (77.6)	43/50 (86.0)	12/13 (92.3)
(LOCF)	57/75 (76.0)	43/51 (84.3)	12/14 (85.7)
WEEK 144 (OBSERVED)	51/64 (79.7)	44/51 (86.3)	12/14 (85.7)
(LOCF)	57/75 (76.0)	44/51 (86.3)	12/14 (85.7)
WEEK 168 (OBSERVED)	44/58 (75.9)	40/48 (83.3)	9/13 (69.2)
(LOCF)	55/75 (73.3)	43/51 (84.3)	10/14 (71.4)
WEEK 192 (OBSERVED)	44/55 (80.0)	41/50 (82.0)	11/13 (84.6)
(LOCF)	53/75 (70.7)	41/51 (80.4)	11/14 (78.6)
WEEK 216 (OBSERVED)	36/50 (72.0)	36/50 (72.0)	11/13 (84.6)
(LOCF)	49/75 (65.3)	37/51 (72.5)	12/14 (85.7)
WEEK 240 (OBSERVED)	37/46 (80.4)	37/46 (80.4)	11/14 (78.6)
(LOCF)	52/75 (69.3)	40/51 (78.4)	11/14 (78.6)
WEEK 264 (OBSERVED)	31/37 (83.8)	31/37 (83.8)	9/12 (75.0)
(LOCF)	52/75 (69.3)	40/51 (78.4)	11/14 (78.6)
WEEK 288 (OBSERVED)	24/29 (82.8)	24/29 (82.8)	11/13 (84.6)
(LOCF)	52/75 (69.3)	40/51 (78.4)	12/14 (85.7)
WEEK 312 (OBSERVED)	14/18 (77.8)	14/18 (77.8)	9/12 (75.0)
(LOCF)	52/75 (69.3)	40/51 (78.4)	11/14 (78.6)
WEEK 336 (OBSERVED)	8/11 (72.7)	8/11 (72.7)	8/11 (72.7)
(LOCF)	52/75 (69.3)	40/51 (78.4)	11/14 (78.6)

NOTE: LOCF - LAST OBSERVATION CARRIED FORWARD WAS USED FOR MISSING ASSESSMENTS.
CLINICAL REMISSION IS DEFINED AS PCDAI SCORE <= 10 POINTS.

VISIT	ANY ADALIMUMAB PATIENT-YEARS GROUP > 2 PATIENT-YEARS n/N (%)	ANY ADALIMUMAB PATIENT-YEARS GROUP > 4 PATIENT-YEARS n/N (%)	ANY ADALIMUMAB PATIENT-YEARS GROUP > 6 PATIENT-YEARS n/N (%)
WEEK 360 (OBSERVED)	7/8 (87.5)	7/8 (87.5)	7/8 (87.5)
(LOCF)	53/75 (70.7)	41/51 (80.4)	12/14 (85.7)
WEEK 384 (OBSERVED)	2/2 (100)	2/2 (100)	2/2 (100)
(LOCF)	53/75 (70.7)	41/51 (80.4)	12/14 (85.7)
WEEK 408 (LOCF)	53/75 (70.7)	41/51 (80.4)	12/14 (85.7)

The MAH has also provided tables for patients with clinical response which are not depicted in this updated AR.

Table 14 KAPLAN-MEIER PLOT OF STUDY DRUG EXPOSURE IN M06-807 (INTENT-TO-TREAT POPULATION)



5.1. Assessment of response to RSI

The MAH has provided data as was requested. Approximately half of the patients had at least between 4-5 years of drug exposure in Study M06-807. Very few patients were treated for more than 6 years, which in part may be explained by the fact that there were patients that crossed over to commercially available adalimumab. This supplementary information provided by the MAH is acknowledged and accepted as an answer. The data submitted seems reassuring considering the duration of exposure. There seems to be no unexpected changes with regard to efficacy. The exposure data facilitates the interpretation of the safety data as well. No new safety concerns were identified.

Answer accepted. Issue resolved.

5.2. Updated conclusion

☒ **Fulfilled:**

No regulatory action required.