Amsterdam, 23 July 2020
EMA/495296/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Humira

International non-proprietary name: adalimumab

Procedure no.: EMEA/H/C/000481/P46 119

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact Telephone +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

On 6th of April 2020, the MAH submitted a completed paediatric study for Humira, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This study was part of a postmarketing commitment from AbbVie to the French Health Authority (HAS: Haute Autorité de Santé).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study P15-759 is assessing long-term effectiveness of adalimumab for treating children and adolescents with Crohn's disease in real life conditions – LEA.

2.2. Information on the pharmaceutical formulation used in the study

Humira is approved for several paediatric indications and was administered in accordance with the product label.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted final report for:

- Study P15-759: Assessing Long-term Effectiveness of Adalimumab for treating children and adolescents with Crohn's disease in real life conditions - LEA

Crohn's disease (CD) is a relapsing-remitting inflammatory bowel disease involving potentially any part of the digestive tract and potentially associated with extra-intestinal manifestations involving joints, skin, eyes, or liver. During relapses, symptoms associate abdominal pain, diarrhoea often with mucus and blood, ano-perineal involvement, and sometimes systemic manifestations. Fatigue, weight loss, anorexia, and fever are frequently reported. CD may be complicated by intestinal obstructions, fistulae, abscesses, anal fissures, malnutrition, malabsorption, peritonitis, digestive haemorrhages. Patients with extensive colitis are at high risk of dysplasia and cancer, especially in case of cholangitis.

In paediatric patients, the reported incidence rates of CD ranges from 0.1 to 13.9 per 100,000 persons internationally (Benchimol 2011). There are phenotypic characteristics unique to pediatric CD, including a greater propensity for disease extension (Levine 2011). Beside intestinal and extra-intestinal manifestations, growth failure and pubertal delay are specific to children and adolescents with CD, involving up to 30% of children and challenging their quality of life (Hensley 1987, Molinari 2002).

CD therapies aim to reach sustained, steroid-free remission, with mucosal healing and enhancement of growth and pubertal development of paediatric patients. Apart from enteral nutritional therapy, oral corticosteroid, and amino salicylates, anti-TNF treatments are indicated for inducing and maintaining remission in paediatric patients with chronically active luminal CD despite prior optimized immunomodulator therapy and in children with active steroid-refractory CD. Anti-TNF therapy should be considered early in the treatment plan for severe extra-intestinal manifestations (Ruemmele 2014). In particular, adalimumab, a fully human recombinant anti-TNF monoclonal antibody containing only

human peptide sequences, demonstrated efficacy and tolerability in a previous interventional study conducted in 192 children and adolescents with active CD (IMAGINE 1, Hyams 2012).

IMAGINE1 was the pivotal clinical study leading to the approval of the paediatric Crohn's indication. After receiving open-label induction therapy with adalimumab, at week 4 subjects were randomised to either low-dose adalimumab (10 mg eow [<40 kg] or 20 mg [≥40 kg]) or high-dose adalimumab (20 mg [<40 kg] or 40 mg [≥40 kg] eow). Study endpoints were assessed at week 26,

In a retrospective non-interventional study conducted in 36 CD children receiving adalimumab, an improvement in linear growth was shown after 6 months in 42% of patients, especially in those entering remission regardless of the steroid sparing effect (Malik 2012). However, long-term outcomes were only available in CD adults treated with adalimumab (up to Week240 in the IMAGINE2 extension study, Faubion 2017) and no data were available in treated pediatric patients.

2.3.2. Clinical study

Clinical study number and title

P15-759: Assessing Long-term Effectiveness of Adalimumab for treating children and adolescents with Crohn's disease in real life conditions - LEA

Description

This was a French prospective, non-interventional, multicenter study conducted in pediatric patients who started adalimumab treatment with for CD in real-life conditions.

Methods

Objectives

At the time of the protocol writing, the primary objective of this study was to evaluate long-term effectiveness of adalimumab in paediatric patients starting a treatment for CD in real-life conditions, namely to describe the time to loss of clinical benefit in a time to event approach. Main secondary objectives were to describe growth and pubertal development and to describe long-term safety. The patients were to be followed for up to 10 years.

Considering the limited number of inclusions during the planned 2-year period (n= 62 versus 200 expected) and in agreement with French Health Authorities, the study discontinued prematurely on 14/10/2019, with very few follow-up medical visits after 12 months. Consequently, analysis focused on the baseline characteristics of paediatric patients who started treatment with adalimumab for Crohn's disease, the use of adalimumab and safety data collected until Month 12 (M12). Exploratory objectives aimed to describe available effectiveness data and evolution of treated patient productivity.

Study design

This was a French prospective, non-interventional, multicenter study conducted in paediatric patients who started adalimumab treatment for CD in real-life conditions. Follow-up visits, treatments, procedures and diagnostic methods were at the sole discretion of the participant physicians. Data to be documented in a dedicated eCRF were those closest to the following time-windows: baseline, 3, 6 and 12 months after, and then every year until the end of the study. At each study visit, physicians asked patients to fulfil a "paper" questionnaire on their productivity (at school or work whichever was applicable).

The initially planned study duration was 12 years (inclusions:2 years; follow-up: 10 years). Considering the limited number of enrolled patients at the end of the inclusion period, the study was prematurely discontinued at that time.

Study population /Sample size

Inclusion criteria

- Patient aged between 6 and 17 years old
- Suffering from Crohn's disease
- Adalimumab-naive patient (a patient having received an anti-TNF other than adalimumab may enter the study)
- Starting a treatment with adalimumab
- Guardian capable of and willing to grant authorization for use/disclosure of data collected and patient able to comply with the requirements of the study protocol

Exclusion criteria

- Patients with a history of treatment with adalimumab
- Patients enrolled in a concomitant interventional clinical trial

Study size

Around 200 included children and adolescents starting adalimumab for CD were initially expected over a 2-year period; 62 were enrolled during this time with none of them being excluding from analysis.

Analysis population

Safety population: all included patients with at least one injection of adalimumab were included in the Safety population.

Full Analysis Set (FAS) Population: all the patients included in the Safety population and meeting all the inclusion and non-inclusion criteria were included in this population.

Treatments

The use of adalimumab was considered as in accordance with the product label in the following conditions:

Patient Weight	Initiation of Adalimumab	Treatment Maintenance
< 40 kg	40 mg at Week 0 and 20 mg at Week 2 (or 80 mg at Week 0 and 40 mg at Week 2 in case of a need for a more rapid response)	20 mg every other week (or 20 mg every week in case of insufficient response)
≥ 40 kg	80 mg at Week 0 and 40 mg at Week 2 (or 160 mg at Week 0 and 80 mg at Week 2 in case of a need for a more rapid response)	40 mg every other week (or 40 mg every week or 80 mg every other week in case of insufficient response)

Outcomes/endpoints

Considering the changes in study conduct as described above, the planned analyses related to the long-term outcomes of adalimumab were not performed.

The following analysis were carried out:

- Baseline characteristics of eligible patients, medical history, CD characteristics, and prior CD treatments
- Modalities of the use of adalimumab (number and percentage of patients with each drug regimen during the initial and the maintenance treatment periods, treatment duration, number and percentage of patients with temporary discontinuation(s), number and percentage of patients with permanent discontinuation with reasons, concomitant treatments for CD and other diseases)
- Number and percentage of patients with at least one serious adverse event(SAE), with at least one adverse event of special interest(AESI), with at least one serious AESI, with at least one SAE (AESI, serious AESI) leading to permanent discontinuation of treatment, with at least one SAE (AESI, serious AESI) leading to death(and detailed adverse events); causal relationship with adalimumab and outcomes.

Exploratory effectiveness variables were as follows: growth and puberty data, CD activity, imaging and laboratory data (at each follow-up visit until M12).

Data from the work productivity questionnaire completed by patients at each follow-up visit until M12 were other exploratory variables.

Statistical Methods

Statistical analyses were performed using SAS® software (version 9.2 or higher), by the CRO in charge of statistics. The SAP was finalized before the data base lock performed on January 14, 2020.

All parameters were summarized in tables including the following descriptive statistics:

- Quantitative variables: number of available data, missing data, mean, standard deviation, median, quartiles (Q) 1 and 3, and range, with associated 95% confidence interval (CI) if relevant,
- Qualitative variables: number of available data, missing data, frequency, and percentage for each modality, with associated 95% CI if relevant.

Main Statistical Methods

Baseline Characteristics

Patients were described for all baseline data in the FAS Population [patient characteristics including growth and puberty data, smoking and alcohol status, medical history, CD characteristics and activity (wPCDAI; Harvey-Bradshaw Index, HBI; Simple Endoscopic Score for Crohn's Disease, SES-CD), medical imaging and laboratory findings, and prior CD treatments], using descriptive statistics.

Use of Adalimumab

The reasons for adalimumab initiation and the modalities of the use of adalimumab during the study were described in the FAS Population[drug regimens during the initial and the maintenance treatment periods, treatment duration, temporary discontinuations (number per patient, duration, reasons) permanent discontinuations (reasons), concomitant CD treatments], using descriptive statistics.

The proportions of patients with adalimumab used in conformity with its label at treatment start and during the maintenance period were described.

Patients' follow-up duration was also described in the FAS Population.

Adverse Events

SAEs, AESIs and serious AESIs were described in the Safety Analysis (with causal relationship with adalimumab and outcomes), using descriptive statistics. Additional nonserious and non-AESIs spontaneously reported by investigators were also described. Patients' follow-up duration was also described in the Safety Population.

Exploratory Efficacy Analysis

Growth and puberty data, CD activity (wPCDAI, HBI, and SES-CD indexes), medical imaging, and laboratory data were described at each follow-up visit, with absolute and relative changes from baseline (apart from medical imaging data).

The number and percentage of patients with improvement in the wPCDAI score was described from baseline to each follow-up visit, as well as the number and percentage of patients with fistula remission. The proportion of patients with mucosal healing was also described at each visit, using the SES-CD index.

Other Exploratory Analysis

Data from the productivity questionnaire completed by patients were described at each visit.

Missing Values

Partial dates were managed as usual. Other missing data were not replaced.

Sensitivity Analyses

No sensitivity analysis was performed.

Amendments to the Statistical Analysis Plan

Not applicable.

Quality Control

Participant centers were instructed on the protocol, the functionality and handling of the eCRF, and the requirement to maintain source documents for each patient in the study.

A comprehensive data validation program using front-end checks in the eCRF validated the data. Automated checks for data consistency were implemented, discrepancies had to be solved by the researcher in the eCRF before the module could be completed.

Follow-up on eCRF data for medical plausibility was done by a company mandated by AbbVie (ICTA). The principal investigator of each site finally reviewed the eCRFs for completeness and accuracy of available data and provided his/ her electronic signature and date to eCRFs as evidence thereof.

Continuous monitoring of the study and frequent site telephone contacts were performed by a company mandated by AbbVie (ICTA).

Results

Recruitment/ Number analysed

During the 2-year inclusion period, 62 patients were enrolled. First patient entered the study on September 24, 2017 and last inclusion was performed on August 07, 2019; last patient last visit was on October 14, 2019.

Considering that all these 62 patients had at least one injection of adalimumab from inclusion and met all the selection criteria, all the 62 enrolled patients entered the Safety and the FAS population (no exclusion from analyses).

Table 1. Patient disposition (n=62)

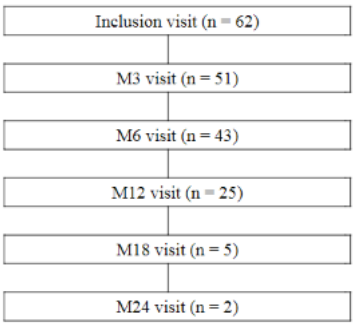
		Total N = 62
Enrolled patients		62
FAS population		62 (100.0%)
Safety population		62 (100.0%)
Premature discontinuation	N	62
	No	0 (0.0%)
	Yes	62 (100.0%)
Reason for premature discontinuation	N	62
	Change of investigator	0 (0.0%)
	Withdrawal of consent	0 (0.0%)
	Lost to follow-up	2 (3.2%)
	Non-compliance with the procedures of the study	0 (0.0%)
	Death	0 (0.0%)
	Other	60 (96.8%)
Other reason for premature discontinuation	N	60
	Patient of age and no longer followed in pediatrics	1 (1.7%)
	Premature termination of the study by the sponsor	58 (96.7%)
	Primary failure to adalimumab	1 (1.7%)

Mainly due to the early study termination, the number of patients at each follow-up visit decreases over time (

Figure 1). Considering the low number of patients with a medical visit at M18 (n = 5, 8%) and M24 (n= 2, 3%), only data available until the M12 follow-up visit were taken into account for analysis.

Four patients (4/62, 6%) did not fulfil the study due to other reasons than the early study termination.

Figure 1. Patient visits



Baseline data

The mean age of paediatric patients was 13±3 years at inclusion (Table 2), ranging from 6 to 17 years according to the product label for paediatric CD. The majority of them were females (60%) and lived in urban area (74%). All patients had never smoked at inclusion and one of them was consuming alcohol. A growth delay was diagnosed in 18/54 patients (33%).

Table 2. Baseline Sociodemographic Characteristics (n = 62)

		Total N = 62
Age at inclusion (years)	N	62
	Missing values	0
	Mean ± SD	12.9 ± 2.7
	Median	13.0
	Q1; Q3	11.0; 15.0
	Min; Max	6.0; 17.0
Gender	N	62
	Missing values	0
	Male	25 (40.3%)
	Female	37 (59.7%)

Apart from CD, 47% of patients had past or concomitant diseases and 23% at least one concomitant disease at the time of inclusion [mainly as respiratory, thoracic and mediastinal disorders (7%, asthma for all) and congenital, familial and genetic disorders (5%)]. Family history of IBD was reported in 19% of cases.

The mean age of patients was 12±3 years at CD diagnosis. At this time, according to the Paris classification, the main CD locations were ileocolonic (44%) and colonic (32%), and the most reported phenotype was the non-stricturing and non-penetrating one (90%).

At inclusion, the median disease duration from first CD symptoms was 1.5 year (range: 0.1; 9.1). At least one past or ongoing CD complication was reported in 52% of patients, mainly as anal fissures (31%), stenosing lesions (13%) or perineal fistulae (10%). At inclusion, 27% of patients had at least one CD complication, including 13% of patients with anal fissures and/or 10% with stenosing lesion. At least one past or ongoing extra-intestinal manifestation was observed in 26% of patients, mainly as acute peripheral rheumatisms (16%) and erythema nodosum (7%). At inclusion, 11% of patients had at least one extra-intestinal manifestation, including acute peripheral rheumatism (5%) and erythema nodosum (5%).

Distal ileum and left colon (transverse – left – sigmoid – rectum) were the most locations affected by CD (in 71% and 41% of the cases, respectively). Stenosis and intraperitoneal abscess were reported in 4 and 1 patients, respectively.

At inclusion, the mean wPCDAI score was 32.1± 24.0; it was 3.7± 4.1 for the HBI, and 12.6± 8.0 for the SES-CD. According to the wPCDAI, the proportions of the patients with moderate (score: [40; 57.5]), severe (score ≥ 57.5), and then moderate-to-severe (score ≥ 40) disease activity were 17%, 17%, and 35%, respectively. According to the HBI, the proportions of the patients with moderate (score: [8; 16]), severe (score > 16), and then moderate-to-severe (score > 16) disease activity were 14%, 0%, and 14%, respectively. In the other hand, using SES-CD,59%, 24%, and 83% of patients had moderate (score: [7; 15]), severe (score > 15), and then moderate-to-severe (score > 7) endoscopic activity respectively at inclusion. The majority of patients had CRP value > 10 mg/L (59%), and high fecal calprotectin value (≥ 100 µg/L: 81%, ≥ 250 µg/L: 71%).

Using the work productivity questionnaire completed at inclusion, 4 patients (7%) did not attend school due to CD. Two patients (4%) went to school as part-time due to CD, and 30 patients (56%) missed school for a total of 5 days or more over the 6 last months.

Prior and concomitant therapies

The majority of patients (73%) received at least one previous CD treatment, mainly as azathioprine (39%), corticosteroids (31%), and/or infliximab (27%), as well as enteral nutrition (37%). In 66% of patients, at least one CD treatment was prescribed in combination with adalimumab during the study period, mainly as azathioprine (44%) and/or corticosteroids (31%). Two patients (3%) underwent at least one surgery for CD before inclusion and the same number had surgery during the study period.

Use of adalimumab

Adalimumab was mainly prescribed as second-line treatment, after failure of conventional treatment or first anti-TNF (24% and 16% of patients, respectively), and in the case of poor tolerability of current treatment (11%) or contra-indication of conventional therapy (5%). It was used as anti-TNF of first intention in 27% of patients.

As planned by the investigators, compliance to the adalimumab label was observed for the majority of patients: 74% at treatment initiation, 68% at maintenance therapy, and 56% at both times. Similar compliance was observed during follow-up (in 80% of patients at M3, 83% at M6, 80% at M12, and 79% at all times).

During patient follow-up (median duration: 6.7 months; range: 0.0; 21.8), 7 patients (11%) stopped adalimumab permanently, mainly due to the lack (n = 2) or loss of efficacy (n = 2), and to related AE (n = 2). The few temporary treatment discontinuations (3 patients, 5%) were due to infections (n = 2) and/or patient poor observance (n = 2).

Efficacy results

Between treatment start and M6, CD activity decreased by wPCDAI (decrease of at least 37.5) in 27% of patients (7/26). wPCDAI remission (score <12.5) was reached at M3 and M6 in 70% (23/33) and 73% (22/30) of patients, respectively (Table 3.).

Table 3. wPCDAI Evolution Over the Study Period

		Inclusion (N = 62)	M3 (N = 51)	M6 (N = 43)	M12 (N = 25)
wPCDAI score	N	52	33	30	19
	Missing values	10	18	13	6
	Mean ± SD	32.1 ± 24.0	12.6 ± 16.4	11.0 ± 16.4	3.3 ± 6.6
	Median	30.0	10.0	7.5	0.0
	Q1; Q3	10.0; 50.0	0.0; 17.5	0.0; 15.0	0.0; 7.5
	Min; Max	0; 88	0; 73	0; 70	0; 25
Absolute change from inclusion	N		29	26	16
	Missing values		22	17	9
	Mean ± SD		−13.0 ± 27.2	−19.4 ± 32.4	−32.7 ± 29.8
	Median		−15.0	−16.3	−25.0
	Q1; Q3		−25.0; 0.0	−42.5; 2.5	−55.0; −6.3
	Min; Max		−75; 63	−78; 60	−88; 3
Relative change from inclusion	N		27	25	16
	Missing values		24	18	9
	Mean ± SD		−0.2 ± 1.5	−0.3 ± 1.5	−0.7 ± 0.4
	Median		−0.6	−0.9	−1.0
	Q1; Q3		−1.0; 0.0	−1.0; 0.0	−1.0; -0.6
	Min; Max		−1.0; 6.3	−1.0; 6.0	−1.0; 0.3
Improvement in CD activity*	N		29	26	16
	Missing values		22	17	9
	No		24 (82.8%)	19 (73.1%)	9 (56.3%)
	Yes		5 (17.2%)	7 (26.9%)	7 (43.8%)

* wPCDAI score having decreased of at least 37.5 from inclusion.

HBI remission (score <5) was reached at M3 and M6 in 96% (48/50) and 98% (39/40) of patients, respectively.

Improvement in CRP value was also observed during follow-up [≤ 10 mg/L: 41% at inclusion (20/49), 85% at M3 (40/47), and 77% at M6 (26/34)].

Regarding the evolution of patient work productivity between inclusion and M6, the proportion of patients with missed school for a total of 5 days over this period decreased from 57% (30/53) to 22% (7/32).

Safety results

Only AESIs and SAEs were required to be reported by investigators after the first adalimumab injection.

From inclusion and during patient follow-up (median duration: 6.7 months; range:0.0; 21.8), at least one AE was reported in 13 patients (21%, 18 events reported) and 7 patients (11%) experienced at least one AE assessed as related to adalimumab (9 related AEs including 4 CD flares or digestive ulcers). At least one SAE was reported in 10 patients (16%, 12 SAEs reported) and 5 patients (8%) experienced at least one SAE related to adalimumab (6 related SAEs with the preferred terms: CD, colitis ulcerative, ileal ulcer, drug-induced liver injury, malnutrition, and arthralgia).

Five AEs reported in 5 patients (8%) led to treatment discontinuation. Among these 5 AEs, 4 events were assessed as related to adalimumab (CD, drug-induced liver injury, malnutrition, and arthralgia).

One patient (2%) experienced one serious AESI related to adalimumab (probable drug-induced hepatitis) that led to treatment discontinuation.

No malignancy or fatal AE was reported.

Discussion as provided by the MAH

Currently there is limited French real-world data on paediatric patients starting adalimumab for CD. The LEA study was set up to close this data gap. Due to the limited number of included patients (n = 62), the study discontinued prematurely, and only exploratory effectiveness analysis was performed until M12. Finally, the LEA study mainly aimed to describe the characteristics of treated CD paediatric patients, as well as the use and the safety profile of adalimumab.

The characteristics of paediatric patients included in the LEA study were broadly similar to previous non-French interventional and observational studies. At adalimumab start, only 35% of patients had moderate-to-severe disease activity at inclusion by wPCDAI (moderate: 17%; severe: 17%), whereas 39% were mild and 27% were inactive. However, moderate-to-severe endoscopic activity was observed in most patients (83%; moderate: 59%; severe; 24%) using SES-CD, with high CRP (60% > 10mg/L) and high faecal calprotectin (80% ≥ 100 µg/L; 70% ≥ 250 µg/L) which indicate an active disease.

Adalimumab was mainly prescribed as second-line treatment, after failure of conventional treatment (24%) or first anti-TNF (16%), and in the case of poor tolerability of current treatment (11%) or contra-indication of conventional therapy (5%). Treated patients were aged between 6 and 17 years according to the product label for paediatric CD. In the majority of the cases, adalimumab regimens were in accordance with the product label at initiation and maintenance therapy.

Adalimumab was well tolerated with a low number of SAEs and 8% of patients discontinuing treatment prematurely for safety reasons. No new safety signals were detected.

In addition, our findings tend to confirm in a real-life setting the efficacy of adalimumab in CD children and adolescents as CD activity decreased by wPCDAI (at least 37.5) in 27% of patients. wPCDAI remission (score< 12.5) and HBI remission (score <5) were reached at M3 in 70%and 96% of cases, respectively, and at M6 in 73% and 98% of patients. CRF decrease was also observed after adalimumab initiation (≤ 10 mg/L: from 41% at inclusion to 85% at M3 and 77% at M6).

Overall, considering the lack of French data in paediatric CD patients treated with adalimumab, the present study provides new information in this context, both reassuring on the use and on the safety profile of adalimumab.

2.3.3. Discussion on clinical aspects

Humira was approved in 2012 for the treatment of paediatric patients (from 6 years of age) with moderately to severely active Crohn's disease. Study P15-759 was a postmarketing commitment from AbbVie to the French Health Authority (HAS: Haute Autorité de Santé).

Study P15-759 was a French prospective, non-interventional, multicenter study conducted in paediatric patients who started adalimumab treatment with for CD in real-life conditions.

Methods

The original primary objective was to evaluate long-term effectiveness of adalimumab in paediatric patients starting a treatment for CD. Considering the limited number of patients included (n= 62 versus 200 expected) and in agreement with French Health Authorities, the study discontinued prematurely on 14/10/2019, with very few follow-up medical visits after 12 months. Consequently, analysis focused on the baseline characteristics and safety data collected until Month 12 (M12). Exploratory objectives aimed to describe available effectiveness data and evolution of treated patient productivity.

Included patients were adalimumab-naïve Crohn's patients aged 6-17 years. Adalimumab was administered in accordance with the SmPC.

Baseline characteristics and other variables were summarised using descriptive statistics.

Results

During the 2-year inclusion period (2017-2019), 62 patients were enrolled and achieved at least one injection of adalimumab. The mean age was 13±3 years at inclusion, ranging from 6 to 17 years. Detailed baseline disease characteristics were presented.

From an efficacy point of view, CD activity decreased by wPCDAI (decrease of at least 37.5) in 27% of patients (7/26) between treatment start and month 6. wPCDAI remission (score <12.5) was reached at month 3 and month 6 in 70% (23/33) and 73% (22/30) of patients, respectively. HBI remission (score <5) was reached at month 3 and month 6 in 96% (48/50) and 98% (39/40) of patients, respectively.

Regarding safety, from inclusion and during patient follow-up (median duration: 6.7 months; range: 0.0; 21.8), at least one AE was reported in 13 patients (21%, 18 events reported) and 7 patients (11%) experienced at least one AE assessed as related to adalimumab (9 related AEs including 4 CD flares or digestive ulcers). At least one SAE was reported in 10 patients (16%, 12 SAEs reported) and 5 patients (8%) experienced at least one SAE related to adalimumab (6 related SAEs with the preferred terms: CD, colitis ulcerative, ileal ulcer, drug-induced liver injury, malnutrition, and arthralgia).

Five AEs reported in 5 patients (8%) led to treatment discontinuation. Among these 5 AEs, 4 events were assessed as related to adalimumab (CD, drug-induced liver injury, malnutrition, and arthralgia).

One patient (2%) experienced one serious AESI related to adalimumab (probable drug-induced hepatitis) that led to treatment discontinuation. Narrative was provided and based on the information provided, causality with Humira is considered likely. Liver failure is described in the SmPC and this does not constitute any new safety signal. The risk for liver injury is captured in the ongoing registry study on paediatric CD, listed as a category 3 study in the RMP (P11-292). This observational 10-year study aims to enrol approximately 800 paediatric patients with moderately to severely active CD treated with Humira and approximately 500 patients treated with non-biologic immunomodulating therapy. Interim reports are provided every second year, with final report due in 2028. One of the AESIs to be studied is “hepatic events: liver enzyme abnormalities, liver failure and other liver events, reactivation of hepatitis B and autoimmune hepatitis”. In the latest MEA (080.6) in October 2018, only 1 case in the control group reported an event of hepatitis. To conclude, although this case is of concern it does not constitute a new safety signal for Humira, and the risk is continuously followed through additional PhV activities.

No malignancy or fatal AE was reported.

To conclude, the study provided some interesting efficacy and safety data, but the initial purpose could not be fulfilled due to recruiting difficulties.

3. CHMP overall conclusion and recommendation

Although the initial aim of the study could not be fulfilled due to recruiting difficulties, the study includes some interesting data on the disease characteristics in paediatric patients treated with Humira, as well as some efficacy outcomes confirming the efficacy of Humira in the current population. More importantly, there are also some, although limited, safety data. Among these are one case of drug-induced hepatitis where causality with Humira is considered likely. This is a known safety issue with Humira treatment and it does not constitute any new safety signal. The risk for hepatic events in paediatric CD patients is continuously followed through a registry study listed in the RMP. No further actions are currently needed.

☒ Fulfilled:

No regulatory action required.