24 June 2021
EMA/CHMP/396886/2021
Human Medicines Division

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/P46/122

Note

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

Table of contents

1. Introduction

On 05 March 2021, the MAH submitted a final study report of a completed paediatric study (P17-164) for Humira (adalimumab), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

Humira in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (JIA), in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

2. Scientific discussion

2.1. Information on the development program

The MAH submitted a final study report for:

Study P17-164 (P46 Study): Prospective Multi-Center Observational Study to Assess Persistence, Adherence and Changes in Disease Activity in the Children Population of Juvenile Arthritis Patients Treated with adalimumab (HUMIRA) in the Routine Clinical Settings in the Russian Federation (PETITE)

2.2. Information on the pharmaceutical formulation used in the study

Humira is approved for two paediatric indications in Russia according to the MAH (polyarticular JIA in patients > 2 years, and enthesitis-related arthritis in patients > 6 years); and was administered according to the Russian product label, which was not provided.

2.3. Clinical aspects

2.3.1. Clinical study

P17-164: Prospective Multi-Center Observational Study to Assess Persistence, Adherence and Changes in Disease Activity in the Children Population of Juvenile Arthritis Patients Treated with adalimumab (HUMIRA) in the Routine Clinical Settings in the Russian Federation (PETITE)

Description

The Study P17-164 was a prospective, non-interventional, product-focused, longitudinal, and multi-center study with no control group designed to assess persistence, adherence, and change in disease activities in children diagnosed with polyarticular Juvenile Idiopathic Arthritis (JIA) according to International League of Associations for Rheumatology (ILAR) criteria treated with adalimumab (Humira) over 48 weeks in routine clinical settings in the Russian Federation.

Methods

Objectives

The primary objective was:

- To assess persistence in patients with polyarticular JIA treated with Humira over 48 weeks.

The secondary objectives of the study were:

1. To assess adherence in patients with polyarticular JIA treated with Humira over 48 weeks.

2. To assess change of disease activity using the 10-joint juvenile arthritis disease activity score (JADAS10) and American College of Rheumatology Pediatric 30, 50, and 70 response criteria (ACR Pedi 30/50/70) and its components* including extra-articular manifestations (EAMs), such as JIA-associated non-infectious uveitis, inflammatory bowel disease, and psoriasis, in patients with polyarticular JIA treated with Humira over 48 weeks.

   * *Information about disease activity based on JADAS10, ACR Pedi 30/50/70, and Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI) was collected from the medical charts if the site and physicians/investigators applied them in the routine medical practice. If physicians/investigators did not apply JADAS10, ACR Pedi 30/50/70, and CHAQ in the routine medical practice, then Unknown/Not Available/Not Applicable checkbox was to be chosen. In this study, AbbVie did not provide any license permission for using JADAS10, ACR Pedi 30/50/70, and CHAQ to investigators nor special training for correct usage of JADAS10, ACR Pedi 30/50/70, and CHAQ. Only routine medical practice data were collected and further analyzed in this post-marketing observational study.*

Study population /Sample size

70 patients were included in this descriptive observational study without any priory sample size justification/calculation. Convenient sampling methods were used for enrollment of patients who attended routine outpatient visits, fulfilled the inclusion/exclusion criteria and had signed patient's informed consent form by the parent or guardian/and by the child (if applicable).

Patient was included in the study if he/she met the following criteria:

1. Aged ≥ 2 and < 18 years.

2. Confirmed diagnosis of polyarticular JIA according to ILAR criteria (International League of Associations for Rheumatology).

3. Planned treatment with HUMIRA according to the local product label and prescription guidelines. Alternatively, subjects assigned to HUMIRA treatment not more than 1 month prior to inclusion can be enrolled.

4. Negative result of tuberculosis (TB) screening procedure and TB specialist permission to start biologic therapy.

5. Patient's informed consent form signed by the parent or guardian/and by the child, if applicable.

Patients meeting any of the following criteria were not included in the study:

1. Has contraindications for the treatment with HUMIRA according to the latest version of the locally approved label.

2. Any biologic drugs taken prior to 3 months of enrolment in the study.

3. Patients treated with any biosimilar version of HUMIRA.

4. Previous participation and dropout from this study.

5. Patients participating in another clinical and/or observational study priory 3 months before the enrolment to this study.

Treatments

Treatment with Humira was according to the local product label and prescription guidelines. Humira was prescribed by physician according to the routine clinical practice.

Outcomes/endpoints

Primary Variables

• Humira persistence

(1) Persistence was defined as the time (in days) between the start date of Humira (adalimumab) treatment and the earliest date of discontinuation* of Humira (adalimumab) or drop out of study or lost to follow up. Patients who did not discontinue after 48 weeks follow up period were censored at 48 weeks.

(2) Persistent rate – defined as the probability of patients that are ongoing on treatment at 48 weeks since they started on Humira (adalimumab) using Kaplan-Meier Method.

Humira (adalimumab) discontinuation was defined as the interruption of continual adalimumab therapy for at least 28 days between doses (without prescription of an alternate bDMARD). Periods of less than 28 days between doses were defined as temporary dose delays, not meeting the criteria for a Humira (adalimumab) discontinuation. Also, discontinuation included stopping to participate in the study due to any reason (death, lost to follow-up, discontinuation due to AEs, switching to another treatment, physician decision, others).

Secondary Variables
• Medication adherence over observational study period – the extent to which a patient act in accordance with the prescribed interval and dose of a dosing. The cut-off for the adherence/non-adherence set up for this study at ≥ 80% of timely taking doses.

The measure is based on patient or caregiver/legal representative reported data (patient or caregiver/legal representative diaries).

• Proportion of patients with 30%, 50% and 70% ACR pedi responses at 2, 3, 4 and 5 observational visits. The ACR Pediatric 30, 50, 70 are defined as 30%, 50%, and 70%, improvement respectively in a minimum of three core set criteria with worsening of one variable by no more than 30%.

• Change from baseline in physician overall disease activity measured by of 10 cm VAS – at 2, 3, 4 and 5 observational visits.

• Change from baseline in patient (if appropriate in age) or parent overall well-being measured by 10 cm VAS at 2, 3, 4 and 5 observational visits.

• Change from baseline in Childhood Health Assessment Questionnaire-Disability Index (CHAQ-DI) total score and subscales (disability, discomfort and pain) score at 2, 3, 4 and 5 observational visits.

• Change from baseline in number of joints with active arthritis at 2, 3, 4 and 5 observational visits.

• Change from baseline in number of joints with limited range of motion at 2, 3, 4 and 5 observational visits

• Change from baseline in ESR at 2, 3, 4 and 5 observational visits.

• Change from baseline in JADAS10 at 2, 3, 4 and 5 observational visits.

• Proportion of patient with low diseases activity (defined as a JADAS10 of 1.1 – 2) and moderate disease activity (defined as a JADAS10 of 2.1 – 4.2) based on JADAS10 at baseline, 2, 3, 4 and 5 observational visits.

• Proportion of patients with one, two and etc. missed dosed of HUMIRA and number of missed doses at 2, 3, 4 and 5 observational visits.

• Proportion of patients with any Extra-articular manifestations (EAMs) (JIA-associated non inflectional uveitis, IBD, psoriasis) at baseline, 2, 3, 4 and 5 observational visits.

• Proportion of patients with any comorbidity at baseline, 2, 3, 4 and 5 observational visits.

Statistical Methods

Categorical (qualitative) variables were summarized with the number and proportion of patients in each category. Exact 95% Clopper-Pearson confidence interval for a single proportion for each category was calculated.

For interval (quantitative) variables values on baseline and each visit and change from baseline to each visit were presented with descriptive statistics. Descriptive statistics included number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum and maximum values, and 95% CI for mean or median (as appropriate).

Comparison between baseline and other visits was made using Wilcoxon Signed-Rank Test or the Friedman Test for dependent variables (as appropriate).

Results

Recruitment/ Number analysed

A total of 70 patients with polyarticular JIA according to ILAR criteria (22 male and 48 female patients) from 16 clinical sites were included in the study.

Baseline data

Patients enrolled had a median age of 10 years (range: 2 to 17) and were predominantly female (48/70; 68.6%). All patients with recorded values had highly active disease at baseline as defined by a JADAS10 > 4.2. Mean JADAS10 total score at baseline was 22.6. Patients also had high numbers of joints with active arthritis (mean 8.6) and elevated acute phase erythrocyte sedimentation rate (ESR, mean 26.3 mm/h).

The most common diseases in the medical history of patients by system organ class (SOC) were eye disorders (18 patients, 25.7%); gastrointestinal disorders (8 patients, 11.4%); and congenital, familial and genetic disorders (6 patients, 8.6%). The most common diagnosis by preferred term was iridocyclitis (14 patients, 20%).

The most common prior medications were folic acid analogues (29 patients, 41.4%), glucocorticoids (20 patients, 28.6%), and immunosuppressants (16 patients, 22.9%). The most common concomitant drug therapy included folic acid analogs (53 patients, 75.7%) and folic acid and derivatives (14 patients, 20%).

Efficacy results

Persistence in patients with polyarticular JIA treated with Humira over 48 weeks
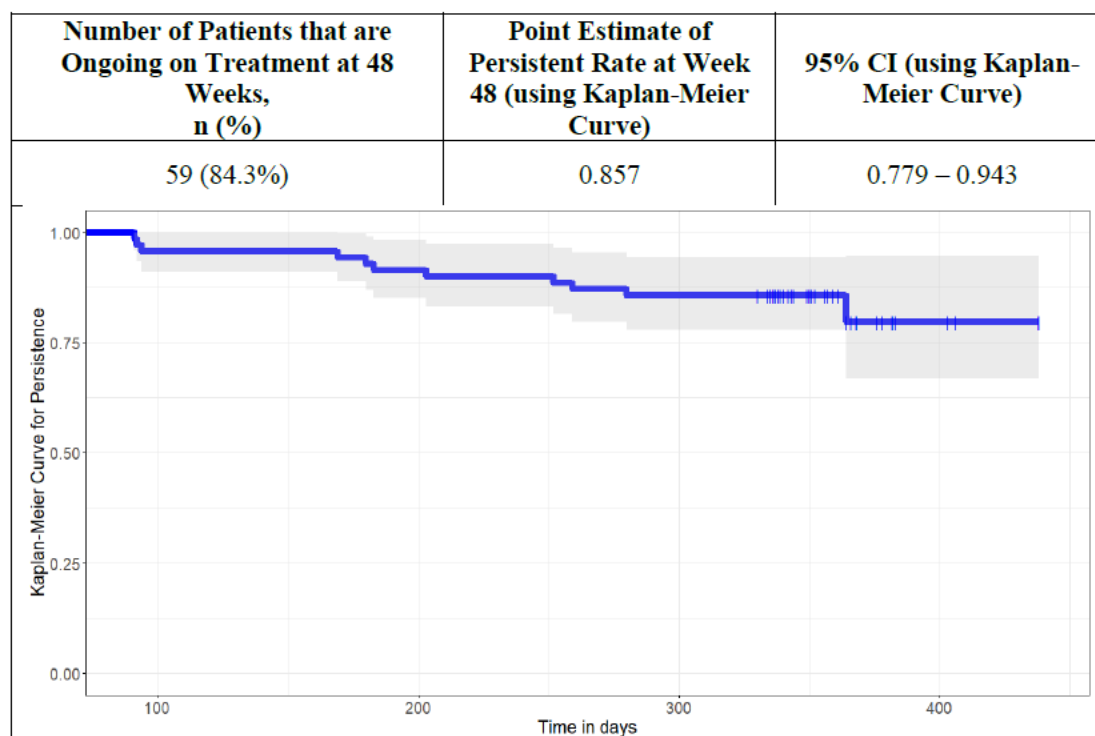
In the enrolled patient population (70 patients), the median duration of therapy with Humira (adalimumab) was 338.5 days (95% confidence interval [CI] 336 – 350 days; range: 91 to 438 days). For patients with persistence who completed the 48-week study (n = 59), the median duration of therapy was 343 days (95% CI 337 – 351 days), and for patients with discontinuation (n = 11) – 183 days (95% CI 92 – 280 days).

Most patients continued therapy at the end of the study (48 weeks or 336 days). At 48 weeks of follow-up, 59 patients (84.3%) continued therapy with Humira. The probability of patients remains on treatment 48 weeks (point estimate of the persistent rate at Week 48 using the Kaplan-Meier Curve) after commencing Humira (adalimumab) was 0.857 (95% CI 0.779 – 0.943). See (Tables 10.3-2, 10-3.3) below.

Table 10.3-2. Summary of Persistence in Patients with Polyarticular Juvenile Arthritis Treated with HUMIRA for 48 Weeks (Available Data Set, n = 70).

Number of Patients	Number of Patients with Persistence	Number of Patients with Discontinuation	Median	95% CI (using Kaplan-Meier Method)
70	59	11	Median survival not reached	Median survival not reached

Table 10.3-3. Persistent Rate at Week 48 (Available Data Set, n = 70).

Number of Patients that are Ongoing on Treatment at 48 Weeks, n (%)	Point Estimate of Persistent Rate at Week 48 (using Kaplan-Meier Curve)	95% CI (using Kaplan-Meier Curve)
59 (84.3%)	0.857	0.779 – 0.943

Adherence in patients with polyarticular JIA treated with Humira over 48 weeks.

Most patients (64/67 patients with evaluable adherence data, 95.5%) demonstrated high adherence to therapy (≥ 80% of timely taking doses). The mean number of missed doses in the study was 0.239 suggesting that patients follow the recommendations for the adalimumab (Humira) therapy regimen.

Change of disease activity in patients with polyarticular JIA treated with Humira over 48 weeks

Change of disease activity was assessed using the 10-joint juvenile arthritis disease activity score (JADAS10) and ACR Pedi 30/50/70 response criteria and its components including extra-articular manifestations (EAMs), such as JIA-associated non-infectious uveitis, inflammatory bowel disease, and psoriasis.

By Week 12, 58/58 (100%) of patients had achieved at least ACR Pedi 30, with 43/58 (74.1%) achieving ACR Pedi 50, and 18/58 (31.0%) achieving ACR Pedi 70. At Week 48, the proportions of patients achieving ACR Pedi 30, 50, and 70 were 50/50 (100%), 47/50 (94.0%), and 46/50 (92.0%), respectively.

All patients had high disease activity at baseline (JADAS10 > 4.2). At Weeks 12, 24, 36, and 48, the proportion of patients achieving at least low disease, defined as a JADAS10 ≤ 2.0 was 2/63 (3.2%), 9/64 (14.1%), 21/64 (32.8%), and 30/58 (51.7%), respectively. Furthermore, the proportions of patients achieving a classification of inactive disease (defined as a JADAS10 ≤ 1.0) were 2/63 (3.2%), 3/64 (4.7%), 13/64 (20.3%), and 19/58 (32.8%) at Weeks 12, 24, 36, and 48, respectively. The mean JADAS10 total score decreased (improved) during the study: mean values at baseline, Weeks 12, 24, 36, and 48 were 22.649, 11.956, 7.556, 5.041, and 3.179, respectively.

There was a decrease in the number of joints with active arthritis and a decrease in the number of joints with limited range of motion over the course of the study compared to baseline. The mean number of joints with active arthritis as per ACR Pedi at baseline and Weeks 12, 24, 36, and 48 was 8.594, 3.525, 1.78, 1.05, and 0.528, respectively. The mean number of joints with limited range of motion as per ACR Pedi at baseline and Weeks 12, 24, 36, and 48 was 7.594, 4.017, 2.508, 1.717, and 0.981, respectively.

Physician assessment of overall disease activity measured by 10 cm visual analog scale (VAS) decreased (improved) over the course of the study with a mean change from baseline of −5.875 cm at Week 48. Similarly, patient (if appropriate in age) or parent assessment of overall well-being measured by 10 cm VAS decreased (improved) during the study with a mean change from baseline of −5.946 cm at Week 48.

Disability as measured by CHAQ-DI showed improvements over baseline through Week 48 in patients with recorded values including improvements for individual disability assessment parameters dressing, arising, eating, walking, hygiene, reach, grip, activities, discomfort and pain, and general evaluation.

Treatment with Humira did not appear to influence the presence of extra-articular manifestations (EAMs) of JIA. The proportions of patients with EAMs of juvenile idiopathic arthritis (JIA-associated non-inflectional uveitis, IBD, psoriasis) remained almost unchanged during the study. However, it should be noted that this study did not assess whether these EAMs had improved during the course of the study.

CHMP's comment:

Results of the primary and secondary outcome measures were summarised by the MAH which included assessment of persistence in patients with polyarticular JIA treated with Humira over 48 weeks (primary objective); and assessment of adherence and change of disease activity using the JADAS10 and ACR Pedi 30/50/70 and its components including extra-articular manifestations (EAMs), in patients with polyarticular JIA treated with Humira over 48 weeks (secondary objectives).

Persistence is defined as the time between the start date of Humira treatment and the earliest date of discontinuation of Humira, or drop out of study, or lost to follow up. Humira discontinuation was defined as the interruption of continual adalimumab therapy for at least 28 days between doses (without prescription of an alternate bDMARD). Periods of less than 28 days between doses were defined as temporary dose delays, not meeting the criteria for a Humira discontinuation.

The most common reason for discontinuation was more than 28 days between doses (5 patients, 45.5% of patients with discontinuation). According to the MAH, the remaining reasons for discontinuation of therapy (including switching to another therapy or the ineffectiveness of adalimumab) account for less than half of the cases of discontinuation of therapy. There were not patients who discontinued the study by physician decision according to completion form. However, it is not clear to the PRAC Rapporteur if the reason for Humira discontinuation was due to AE in any cases.

Overall, the MAH concluded that the patients are highly persistent and compliant with the prescribed therapy; and adalimumab is an effective disease-modifying biological agent from the point of view of evaluating the use of adalimumab in routine pediatric practice and in clinical trials in Russia.

The efficacy results have not been reviewed in detail since the focus/scope for this P46 is safety in paediatric patients with polyarticular JIA. However, it is agreed that a great majority of the included

patients remained on the Humira therapy throughout the study, which indicates efficacy of Humira as well as good tolerability in the studied population (polyarticular JIA patients).

Safety results

The study recorded a total of 4 AE's, all of which were serious adverse events (SAEs), and all occurred in the same female patient: 2 severe SAEs (PT 10014581 Encephalitis and PT 10046980 Varicella) and 2 moderate SAEs (PT 10003591 Ataxia (ataxic syndrome) and PT 10061281 Meningeal disorder (meningeal symptoms)).

Table 10.6-2. Summary of Adverse Events – Frequency.

Parameter	Number of Patients		Number of AEs
	N	%	
Adverse Events (AEs)	1	1.4	4
Serious Adverse Events (SAEs)	1	1.4	4
Adverse Event of Special Interest (AESI)	0	0	0
No Reasonable Possibility AEs	1	1.4	4
Reasonable Possibility AEs	0	0	0
Discontinued from the Study due to AEs	0	0	0

Table 10.6-4. Number of Patients with SAEs by Maximum Severity by System Organ Class and Preferred Term (according to MedDRA 23.1).

SOC by MedDRA version 23.1	PT level by MedDRA version 23.1 (Diagnosis or Symptom)	Severity	Number of Patients		Number of AEs
			N	%	
10021881 Infections and infestations	10014581 Encephalitis (encephalitis)	Severe	1	1.4	1
	10046980 Varicella (varicella)		1	1.4	1
10029205 Nervous system disorders	10003591 Ataxia (ataxic syndrome)	Moderate	1	1.4	1
	10061281 Meningeal disorder (meningeal symptoms)		1	1.4	1

For all reported adverse events, there was no reasonable possible association with the use of adalimumab (Humira). The patient experienced varicella with an onset date of 31 October 2019 followed by encephalitis, ataxia, and meningeal disorder on 06 November 2019. Humira was discontinued due to the events, and the 4 SAEs resolved on 21 November 2019. The investigator attributed the SAEs of encephalitis, ataxia, and meningeal disorder to the SAE of varicella. For the SAE of varicella, the investigator reported no reasonable possible association with the use of Humira; an alternate etiology was not provided.

Overall, Humira treatment of patients with polyarticular JIA throughout the study was well tolerated.

CHMP's comment:

A total of 4 serious adverse events (SAEs) were recorded and all of them occurred in the same female patient; which included 2 severe SAEs (preferred terms: encephalitis and varicella) and 2 moderate SAEs (preferred terms: ataxia (ataxic syndrome) and meningeal disorder (meningeal symptoms)). According to the MAH, there was no reasonable possible association with the use of adalimumab (Humira) for all the reported adverse events. The investigator attributed the SAEs of encephalitis,

ataxia, and meningeal disorder to the SAE of varicella. For the SAE of varicella, the investigator reported no reasonable possible association with the use of Humira.

It is known that the risk of infections is increased during Humira treatment including serious infections / opportunistic infections. SAE of varicella was reported before, e.g. varicella was reported in 7 serious cases involving patients aged < 18 years treated with adalimumab in PSUSA EMEA/H/C/PSUSA/00000057/201612. The MAH concluded that no new safety signals or unexpected trends were identified during this study. No updates to the product information have been proposed by the MAH as part of this Article 46 submission.

The overall risk for serious infections including opportunistic infections are well covered in the SmPC for adalimumab. The PRAC Rapporteur considers that no new or unexpected findings were identified in the MAH's presentation of data (Study P17-164). It is however noted that there is unclearness in methodology regarding collecting/registering AEs. No non-serious AEs were presented in the study report. Absence of non-serious AEs in this study population is not very likely and it is assumed that the non-serious AEs were not recorded.

Conclusions as provided by the MAH

This prospective, multicenter, observational study demonstrated high compliance and persistence of therapy in routine clinical practice, which supports the conclusion that Humira is convenient to use in the treatment of patients with polyarticular JIA. The results of this study regarding the effects of therapy on the manifestations of JIA in children are consistent with the published data. No new safety signals or unexpected trends were identified during this study. The benefit-risk of adalimumab is unchanged and no update to the Summary of Product Characteristics has been proposed as a result of the data obtained during this study.

2.3.2. Discussion on clinical aspects

The MAH submitted a final study report of a completed paediatric study (P17-164) for Humira (adalimumab), in accordance with Article 46 of Regulation (EC) No1901/2006.

The Study P17-164 was a prospective, non-interventional, product-focused, longitudinal, and multi-center study with no control group. The study was conducted in order to assess persistence, adherence, and change in disease activities in children diagnosed with polyarticular JIA according to ILAR criteria treated with adalimumab (Humira) over 48 weeks in routine clinical settings in the Russian Federation. Treatment with Humira was according to the local product label and prescription guidelines, and it should be noted that these are not available to the PRAC Rapporteur. However, it is assumed that the posology was in accordance with the EU label. Humira was prescribed by physician according to the routine clinical practice. Only routine medical practice data were collected and further analyzed in this study. It is noted that there is unclearness in methodology regarding collecting/registering AEs, see further discussion below.

A total of 70 patients with polyarticular JIA according to ILAR criteria (22 male and 48 female patients) from 16 clinical sites were included in the study (11 patients did not complete the study; 59 patients fully completed participation in accordance with the protocol). Patients enrolled had a median age of 10 years (range: 2 to 17) and were predominantly female (48/70; 68.6%). All patients with recorded values had highly active disease at baseline.

Efficacy results

The primary objective of this study was to assess persistence in patients with polyarticular JIA treated with Humira over 48 weeks. Persistence is defined as the time between the start date of Humira treatment and the earliest date of discontinuation of Humira, or drop out of study, or lost to follow up. Humira discontinuation was defined as the interruption of continual adalimumab therapy for at least 28 days between doses (without prescription of an alternate bDMARD). Persistent rate is defined as the probability of patients that are ongoing on treatment at 48 weeks since they started on Humira using Kaplan-Meier method.

In the enrolled patient population (70 patients), the median duration of therapy with Humira (adalimumab) was 338.5 days (95% confidence interval [CI] 336 – 350 days). For patients with persistence who completed the 48-week study (n = 59), the median duration of therapy was 343 days (95% CI 337 – 351 days). Most patients continued therapy at the end of the study (48 weeks or 336 days). At 48 weeks of follow-up, 59 patients (84.3%) continued therapy with Humira. The probability of patients remains on treatment 48 weeks (point estimate of the persistent rate using the Kaplan-Meier Curve) after commencing Humira (adalimumab) was 0.857 (95% CI 0.779 – 0.943).

The most common reason for discontinuation was more than 28 days between doses (5 patients, 45.5% of patients with discontinuation). According to the MAH, the remaining reasons for discontinuation of therapy (including switching to another therapy or the ineffectiveness of adalimumab) account for less than half of the cases of discontinuation of therapy. However, it is not clear to the PRAC Rapporteur if the reason for Humira discontinuation was due to AE in any cases.

The secondary outcome measures included assessment of adherence and 95.5% patients (64/67 polyarticular JIA patients with evaluable adherence data) demonstrated adherence to Humira therapy (≥ 80% of timely taking doses). Results of change of disease activity in patients with polyarticular JIA treated with Humira over 48 weeks (JADAS10 and ACR Pedi 30/50/70 and its components including EAMs) were also summarised by the MAH.

Overall, the MAH concluded that the patients are highly persistent and compliant with the prescribed therapy; and adalimumab is an effective disease-modifying biological agent from the point of view of evaluating the use of adalimumab in routine pediatric practice and in clinical trials in Russia.

The efficacy results have not been reviewed in detail since the focus/scope for this P46 is safety in paediatric patients with polyarticular JIA. However, it is agreed that a great majority of the included patients remained on the Humira therapy throughout the study, which indicates efficacy of Humira as well as good tolerability in the studied population (polyarticular JIA patients).

Safety results

A total of 4 serious adverse events (SAEs) were recorded and all of them occurred in the same female patient; which included 2 severe SAEs (PT: encephalitis and varicella) and 2 moderate SAEs (PT: ataxia and meningeal disorder). The investigator attributed the SAEs of encephalitis, ataxia, and meningeal disorder to the SAE of varicella. For the SAE of varicella, the investigator reported no reasonable possible association with the use of Humira.

It is known that the risk of infections is increased during Humira treatment including serious infections/opportunistic infections. SAE of varicella has been previously reported.

The overall risk for serious infections including opportunistic infections are well covered in the SmPC for adalimumab. The PRAC Rapporteur considers that no new or unexpected findings were identified in

the MAH's presentation of data (Study P17-164). However, it should be noted that there is unclearness in methodology regarding collecting/registering AEs. No non-serious AEs were presented in the study report. Absence of non-serious AEs in this study population is not very likely and it is assumed that the non-serious AEs were not recorded.

No updates to the product information have been proposed by the MAH as part of this Article 46 submission, which is endorsed.

3. Rapporteur's overall conclusion and recommendation

No new data has evolved from the final study report (P17-164) that has any influence on the benefit-risk balance of Humira (adalimumab) in the treatment of patients with polyarticular JIA. It is noted that only one patient out of 70 is reported to have experienced an infection which is not very likely, and it is assumed that the AE recording has not been complete. However, the safety profile of adalimumab in children is well characterized, and this issue is not further pursued. The results indicating high persistence rate on the drug further supports the conclusion that Humira was well tolerated.

No further actions are required.

☒ **Fulfilled - No regulatory action required.**

☐ **Not fulfilled:**