21 July 2022
EMA/591638/2022
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/P46/125

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	23 May 2022	23 May 2022	☐
☐	CHMP Rapporteur Assessment Report	27 June 2022	15 June 2022	☐
☐	CHMP members comments	11 July 2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	14 July 2022	n/a	☐
☒	CHMP adoption of conclusions:	21 July 2022	21 July 2022	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

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1. Introduction

On 05/06/22, the MAH submitted a final paediatric study report for Humira, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided by the MAH.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study ID P18-835 "**Special drug use-results survey of evaluating safety and effectiveness of Humira in long term treatment in patients with Hidradenitis Suppurativa**" is a standalone study.

2.2. Information on the pharmaceutical formulation used in the study

Adalimumab is a recombinant human monoclonal antibody produced in Chinese Hamster Ovary cells. The product is formulated as a subcutaneous injection to adult and paediatric patients according to the Humira® label.

Adalimumab Humira® was prescribed to patients as per Japan label by a physician with sufficient knowledge and experience in the treatment of Hidradenitis Suppurativa (HS).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- **P18-835** - **Special drug use-results survey of evaluating safety and effectiveness of Humira in long term treatment in patients with Hidradenitis Suppurativa**

Humira® (adalimumab) was approved for the treatment of HS in Japan in February 2019. Study P18-835 was conducted based on the GPSP Ordinance (Good Post-marketing Study Practice; Ministerial Ordinance No. 171 of the Ministry of Health, Labour and Welfare dated December 20, 2004). Due to a limited number of Japanese patients (15 patients) in the Phase 3 clinical study of Humira® in patients with hidradenitis suppurativa (M15-537), the present study was conducted to evaluate safety and effectiveness of Humira® in long-term treatment in Japanese patients.

2.3.2. Clinical study

P18-835 - Special drug use-results survey of evaluating safety and effectiveness of Humira in long term treatment in patients with Hidradenitis Suppurativa

Description

Methods

This was a prospective, non-randomized, unblinded, non-comparative, non-interventional, multi centre Post-Marketing Observational Study (PMOS).

The PMOS was conducted in accordance with Good Post-marketing Study Practice (GPSP), ministerial ordinance of the Ministry of Health, Labour and Welfare (MHLW) of Japan. The ordinance requires that new drugs be confirmed as safe and effective in daily medical practice.

No diagnostic or monitoring procedures were performed in this study other than what would be considered standard of care. The treatment period was aligned with the approved Japan label for Humira® and only data from evaluations conducted routinely as part of daily practice were collected.

To minimize selection bias (e.g., prior medications, prior therapies) which is common practice in PMOS per Japanese regulation, patients who were newly prescribed Humira® for treatment of HS by their physician based on routine clinical practice were included in the study. Patients who had been treated previously with Humira® were excluded. The observational period of the study was 52 weeks from the start of Humira® treatment. None of the study medication prescribed in this study was provided by AbbVie.

Study participants

A total of 80 patients were planned and 84 patients were enrolled in this study from 65 registered survey sites. One patient was excluded from the safety analysis set due to withdrawal of consent. A total of 83 patients were evaluated for safety and all were included in the effectiveness analysis set.

Treatments

Humira® was administered as a subcutaneous injection to adult and pediatric patients according to the dosing schedule shown in Table 1. For adult patients, the first dose of 160 mg was administered at Week 0 (Day 1) given in 1 day or split between 2 consecutive days. The second dose of 80 mg was administered at Week 2 (Day 15). A third dose of 40 mg was administered to 80 patients (96.4%) at Week 4 (Day 29) with subsequent doses administered weekly for the remainder of the observational period. Three patients (3.6%) received a third dose of 80 mg at Week 4 (Day 29) with subsequent doses administered every 2 weeks for the remainder of the observational period.

As with the adult patients, pediatric patients were administered a first dose of 160 mg at Week 0 (Day 1) on the same day or split between 2 consecutive days. The second dose of 80 mg was administered at Week 2 (Day 15) and the third dose of 40 mg was administered beginning at Week 4 (Day 29) and continued weekly for the remainder of the observational period.

Table 1. Dose administration (table from the Clinical Overview)

Dose Sequence	Administration Week/Day	Dose Administered (mg)[a]		
		Adult		Pediatric
First dose	Week 0/Day 1	160[b]	160	160
Second dose	Week 2/Day 15	80	80	80
Third and all subsequent doses	Week 4/Day 29	40[c]	80[d, e]	40

a. Administered by subcutaneous injection.
b. The 160 mg dose was given in 1 day or split over 2 consecutive days.
c. All subsequent doses were administered weekly.
d. All subsequent doses were administered every 2 weeks.
e. Administered to 3 patients (approved May 2020).

Objective(s)

To evaluate the long-term safety and effectiveness of Humira® in patients with HS in real-world clinical practice in Japan.

Outcomes/endpoints

Primary endpoints

- Incidence of serious infections (Priority survey item)
- Incidence of adverse drug reactions
- Incidence of infections.

Secondary endpoints

- The percentage (%) of patients achieving "Improved" of overall improvement by physician at 12 weeks and 52 weeks.
- The percentage (%) of patients achieving HiSCR at 12 weeks, 24 weeks, and 52 weeks.
- Changes from baseline in CRP at 12 weeks, 24 weeks, and 52 weeks.
- Changes from baseline in Patient's global assessment of skin pain at 12 weeks, 24 weeks, and 52 weeks.
- Changes from baseline in DLQI at 12 weeks and 52 weeks.

Sample size

The sample size is 80 patients.

Randomisation and blinding (masking)

Not applicable since the study is a prospective, non-randomized, unblinded, non-comparative, non-interventional, multi centre Post-Marketing Observational Study.

Statistical Methods

Descriptive statistics were used to describe the demographics and other basic features of the data. Continuous variables were described by the number of valid cases and missing data, mean, standard deviation, median, minimum, and maximum. Categorical variables were described as the total number and percentage per category. Descriptive and exploratory statistical methods were used to analyse the data of the study. All baseline and disease characteristics were summarized for the safety population and effectiveness population.

Statistical significance was determined by two-tailed tests with a significance level of 0.05. If applicable, inferential statistics were performed at a nominal significance level of 0.05 (two-sided).

Missing observations were documented as missing values. All data was analysed on the basis of observed cases.

No sensitivity analyses have been performed.

CHMP comments:

The performed prospective, non-randomized, unblinded, non-comparative, non-interventional, multi centre PMOS was performed in Japan in patients with hidradenitis suppurativa as a formal request by the Ministry of Health, Labour and Welfare. Due to a limited number of Japanese patients in the Phase 3 clinical study of Humira® at the approval of the indication hidradenitis suppurativa, the PMOS was conducted to evaluate safety and efficacy of Humira® in long-term treatment in Japanese patients.

A total of 80 patients were planned and 84 patients were enrolled in this study from 65 registered survey sites. One patient was excluded from the safety analysis set due to withdrawal of consent. A total of 83 patients were evaluated for safety, and all were included in the efficacy analysis set.

Humira® was dosed according to label in both adult and paediatric patients who were exposed to Humira® for the first time. Primary endpoints were incidence of serious infections, incidence of adverse drug reactions and incidence of infections. Secondary endpoints were related to clinical efficacy, change from baseline in CRP, assessment of skin pain and Quality of life. The observational period of the study was 52 weeks from the start of Humira® treatment.

The statistical methods and study design is overall considered adequate for an observational study.

Results

Participant flow

The analysis population of enrolled patients can be seen in the figure below.

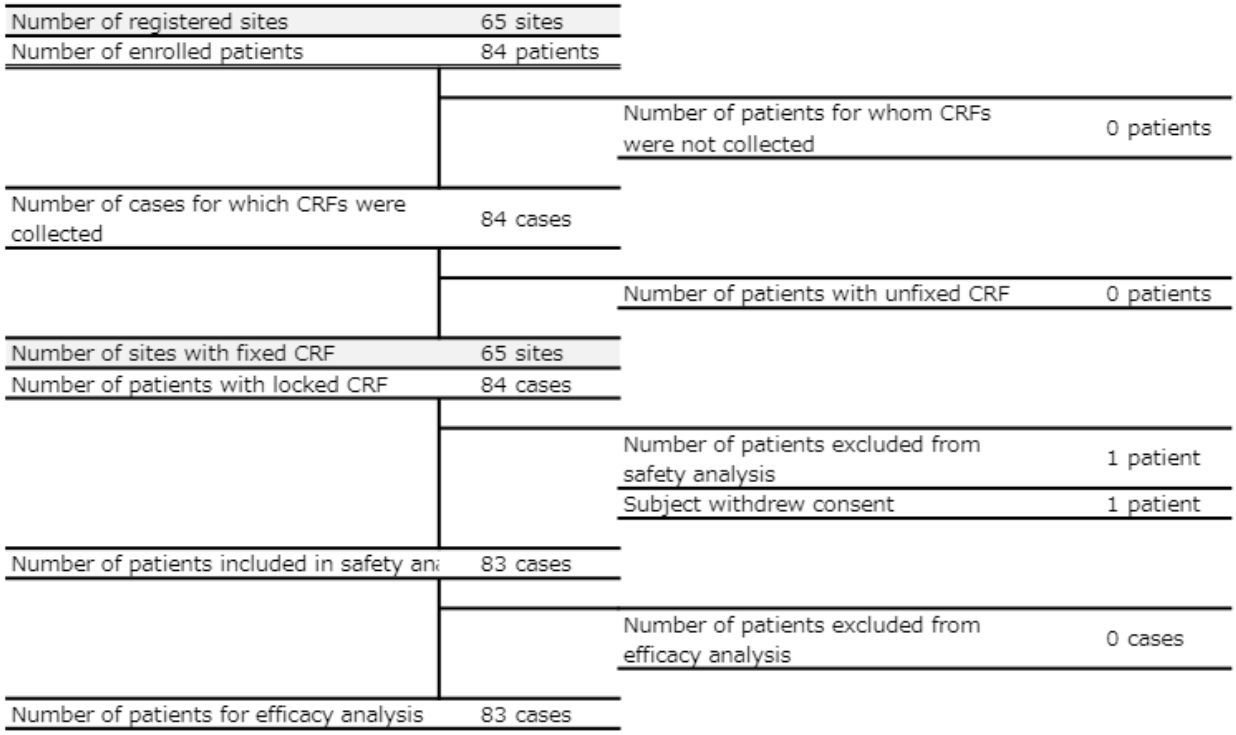

Figure 1. Disposition of patients (from the study report)

Recruitment

Study Period

Enrolment period: From April 23, 2019 to February 14, 2020.

Study period: From March 11, 2019 to May 14, 2021.

Baseline data

Mean age (± SD) of patients in this study was 42.0 ± 15.2 years. Patients < 18 years comprised 4.8% (4/83) of the total patients in the study while patients ≥ 18 to < 65 years comprised 85.5% (71/83) and patients ≥ 65 years comprised 9.6% (8/83). No patients were < 15 years old. The proportion of patients who were male was 78.3% (65/83) and the proportion who were female was 21.7% (18/83). Means for weight and body mass index (BMI) were 78.55 ± 23.21 kg and 26.90 ± 6.76 kg/m^2, respectively.

The mean duration of HS for patients in the study was 12.76 ± 11.14 years. Areas affected by HS lesions were the axilla for 50 patients (60.2%), buttocks for 49 patients (59.0%), the peri-inguinal region for 39 patients (47.0%), the perianal region for 23 patients (27.7%), and the perineum for 17 patients (20.5%). Of the 66 patients with knowledge of HS family history, 60 (72.3%) reported no family history of the disease. Disease severity classified by Hurley classification was I (mild) for 6 patients (3.6%), II (moderate) for 27 patients (32.5%), and III (severe) for 51 patients (61.4%).

Renal impairment was present at baseline in 7 of 83 patients (8.4%) and hepatic impairment was present in an additional 7 (8.4%) patients; no patients had both renal and hepatic impairment.

Number analysed

Table 2. Number of institutions surveyed, and number of patients surveyed (from the study report)

Number of sites with fixed CRF	65
Number of patients with locked CRFs	84
Survey form 1	84
Survey form 2	80
Average number of cases per site *	1.3
Maximum number of cases per site *	3
Minimum number of subjects per site *	1

*: The number of patients fixed in CRF 1.

Discontinuation of study

The most common reasons for discontinuation were "hospital transfer or missed visits" and "improvement of symptoms."

Table 3. Discontinuation of study (patients analysed for safety) (from the study report)

Item	Safety Patients analyzed (%)
Number of subjects	83
Number of discontinued subjects	36 (43.4)
Reason for discontinuation * 1	36 (100.0)
Onset of adverse event * 2	5 (13.9)
For surgery for hidradenitis suppurativa * 2	4 (11.1)
Symptom improvement * 2	10 (27.8)
UNSAT. RESPONSE * 2	5 (13.9)
Pregnancy (females only) * 2	0 (0.0)
Economic reasons * 2	0 (0.0)
Withdrawal of consent * 2	0 (0.0)
Transfer to another hospital or no visit * 2	14 (38.9)
Other * 2	1 (2.8)
Reason for discontinuation unknown/not specified	0 (0.0)

*1: The denominator of the proportion was the number of discontinued subjects.
*2: Multiple choices allowed

Efficacy results

The clinical efficacy was evaluated in the study by assessment of overall improvement by the treating physician. A total of 74 of 83 patients (89.2%) were assessed as responders based on this measure. The response rate was ≥ 89% at all time points, suggesting that the effectiveness of Humira is maintained over the long-term. The three patients who were treated with 80 mg/week after the third dose of 40 mg were assessed as responders at Week 12 and Week 52.

An evaluation of the response rate by age category showed that 90.7% of patients (68/75) aged ≥ 15 to < 65 years (which included the 4 paediatric patients aged ≥ 15 and < 18 years) and 75.0% of patients (6/8) ≥ 65 years were assessed as responders.

The changes from baseline in abscess count and number of inflammatory nodules (AN count) showed statistically significant decreases ($p<0.0001$) at all time points (Weeks 12, 24 and 52, and the final assessment). The proportion of patients who achieved an AN count of 0, 1 or 2 (number, 95% confidence interval) was 73.3% (11/15, 44.9 ~ 92.2), 53.3% (8/15, 26.6 ~ 78.7) and 73.3% (11/15, 44.9 ~ 92.2) at 12, 24 and 52 weeks after the start of treatment, respectively. The proportion of patients who achieved HiSCR was 86.7% (13/15, 59.5 ~ 98.3), 66.7% (10/15, 38.4 ~ 88.2), and 66.7% (10/15, 38.4 ~ 88.2) at Weeks 12, 24 and 52, respectively. In summary, the proportion of patients who achieved an AN count of 0, 1, or 2 was maintained at approximately 50% after Week 12. Similarly, the proportion of patients who achieved HiSCR was ≥ 50% at all time points and remained ≥ 60% after Week 24.

Table 4. Overall improvement rate (from the study report)

Analysis population: efficacy analysis population

Item	Week 12 of	Week 52 of	At the final
Number of subjects	81	47	83
Effective	76 (93.8)	44 (93.6)	74 (89.2)
No	4 (4.9)	2 (4.3)	8 (9.6)
Unassessable	1 (1.2)	1 (2.1)	1 (1.2)

Changes from baseline in CRP, patient global assessment of skin pain, Numeric Rating Scale (NRS) 30 response rate, and DLQI score also showed statistically significant decreases at all time points (data not shown). The NRS 30 response rate was ≥ 75% at all time points.

Safety results

A total of 39 AEs were reported by 21 patients (25.3%) and 19 ADRs were reported by 10 patients (12.0%). Seven serious AEs were reported in 4 patients (4.8%) and 5 serious ADRs in 2 patients (2.4%). Five patients (13.9%) discontinued from the study due to an AE.

A total of 11 patients (13.3%) reported AEs of infections and infestations. ADRs with an incidence of ≥ 2% by System Organ Class (MedDRA version 24.0) were infections and infestations (6.0%), skin and subcutaneous tissue disorders (3.6%), and hepatobiliary disorders (2.4%). In patients who discontinued treatment due to AEs, 13 AEs were reported by 5 patients and 11 ADRs were reported by 4 patients.

The time to onset of AEs was variable and there was no trend toward an increased incidence of delayed AEs with long-term use. No ADRs were observed in the 3 patients treated with 80 mg/2 weeks after the third dose.

The outcomes of ADRs were death (1 event in 1 patient), recovering (2 events in 1 patient), and recovered (16 events in 8 patients). One patient with an outcome of fatality was included in the safety specification. This patient was a male in his 70s with a complication of "intellectual disability". The patient experienced "liver disorder" 65 days after the start of this drug and died 299 days after the onset. Humira® was continued after the onset of the event but was discontinued on Day 97 because the patient "changed hospital or did not visit the hospital". The physician assessed the event to be unrelated to Humira®, but the company considered that the relationship could not be ruled out because the event occurred after the administration of this drug, although it was difficult to evaluate due to lack of detailed information. An evaluation of key survey items and safety evaluation items found that there were no events requiring additional measures.

Safety was also evaluated in patients with renal or hepatic impairment; no factor requiring special measures was found. Pregnant women were not included in this PMOS.

Table 5. Incidence of AEs (from the study report)

	Adverse events	Serious adverse events	Adverse drug reactions	Serious adverse drug reactions
Number of subjects	83	83	83	83
Number of patients with events	21	4	10	2
Number of events	39	7	19	5
Incidence	25.3	4.8	12.0	2.4
Type of adverse event	Number of subjects with adverse events by type (incidence)			
Infections and infestations	11 (13.3)	2 (2.4)	5 (6.0)	1 (1.2)
Abscess	2 (2.4)	1 (1.2)	0 (0.0)	0 (0.0)
Ulcer	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
Folliculitis	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
Nasopharyngitis	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
Skin infection	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
Subcutaneous abscess	2 (2.4)	1 (1.2)	1 (1.2)	1 (1.2)
Incision site abscess	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
Abscess limb	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)
Staphylococcal infection	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)
Cardiac disorders	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)
Cardiac failure	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Asthma	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)

	Adverse events	Serious adverse events	Adverse drug reactions	Serious adverse drug reactions
Number of subjects	83	83	83	83
Gastrointestinal disorders	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
Abdominal pain	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
Haematochezia	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
Hepatobiliary disorders	4 (4.8)	1 (1.2)	2 (2.4)	1 (1.2)
Hepatic function abnormal	3 (3.6)	0 (0.0)	1 (1.2)	0 (0.0)
Liver disorder	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)
Skin and subcutaneous tissue disorders	7 (8.4)	0 (0.0)	3 (3.6)	0 (0.0)
Eczema	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Eczema asteatotic	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Erythema	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
hidradenitis	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	2 (2.4)	0 (0.0)	1 (1.2)	0 (0.0)
Rash	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
seborrheic dermatitis	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis psoriasiform	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
Back pain	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
General disorders and administration site condition	2 (2.4)	0 (0.0)	1 (1.2)	0 (0.0)
Pyrexia	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
nodulus	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase increased	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increased	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Product issue	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)
Device occlusion	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)

MedDRA/J version (24.0)

Paediatric Data

There were 4 children aged 15 years to < 18 years enrolled in this study. No children were < 15 years of age. Among the paediatric patients (< 18 years old), no AEs were reported. No safety and effectiveness analyses were performed with the data collected from these patients. Paediatric data are summarized for each subject in the table below.

Table 6. Summary of Paediatric Data (table from the Clinical Overview)

	Case numbers			
	1	2	3	4
Baseline disease characteristics				
Duration of disease (years)	4	2.5833	3.4167	3
Family history (presence or absence)	no	unknown	no	no
Affected sites	axillary, gluteal, inguinofemoral	inguinofemoral, perianal	axillary	axillary, perimammary, gluteal
Hurley classification[a]	II	II	I	II
Past history	no	no	no	no
Humira treatment status	continuing	discontinuation	discontinuation	continuing
Reason for discontinuation	-	symptom relief	symptom relief	-
Effectiveness				
Physician global assessment[b]				
Week 12	effective	no	effective	effective
Week 52	effective	-	-	effective
Final assessment	effective	effective	effective	effective
Achieved HiSCR (Hidradenitis Suppurativa Clinical Response)				
Week 12	not done	-	achievement	achievement
Week 52	not done	not done	-	achievement
Final at assessment	not done	not done	achievement	achievement

BMI = body mass index.

a. Disease severity staging: I = mild; II = moderate.

b. This was an assessment of overall improvement of the patient as judged by the treating physician.

CHMP comments:

The mean age of patients included in the study was 42.0 ± 15.2 years. Four individuals were between 15 and 18 years of age, while the majority (86%) were between 19-65 years of age. Males were in majority although females are more commonly affected by HS. Means for weight and BMS were 78.55 ± 23.21 kg and 26.90 ± 6.76 kg/m^2, respectively. The mean duration of the disease was 12.76 ± 11.14 years. Disease severity classified by Hurley classification was I (mild) for 6 patients (3.6%), II (moderate) for 27 patients (32.5%), and III (severe) for 51 patients (61.4%). Renal and liver impairment were present in 7 of 83 patients, no patient had both renal and hepatic impairment.

36 patients discontinued the study. The most common reasons for discontinuation were "hospital transfer or missed visits" and "improvement of symptoms."

Clinical efficacy was evaluated in the study by assessment of overall improvement by the treating physician. 74 of 83 patients (89.2%) were assessed as responders based on this measure. The response rate was ≥ 89% at all time points investigated including at the last observation (week 52), suggesting that the clinical efficacy of Humira® is maintained over long-term. There was no

difference in response rates between the different aged groups included in the study. Changes in the other secondary endpoints investigated also showed statistically significant results at all time points investigated.

Primary endpoints were incidence of serious infections, incidence of adverse drug reactions and incidence of infections. A total of 11 patients (13.3%) reported AEs of infections and infestations. ADRs with an incidence of ≥ 2% by System Organ Class (MedDRA version 24.0) were infections and infestations (6.0%), skin and subcutaneous tissue disorders (3.6%), and hepatobiliary disorders (2.4%). One patient with an outcome of fatality was included in the safety specification. This patient was a male in his 70s with a complication of "intellectual disability". The patient experienced "liver disorder" 65 days after the start of this drug and died 299 days after the onset. Humira® was continued after the onset of the event but was discontinued on Day 97 because the patient "changed hospital or did not visit the hospital". The physician assessed the event to be unrelated to Humira®, but the company considered that the relationship could not be ruled out because the event occurred after the administration of Humira®, although it was difficult to evaluate due to lack of detailed information. This view is supported by the assessor.

No factor requiring special measures was found in safety evaluations of patients with renal or hepatic impairment.

There were 4 children aged 15 years to < 18 years enrolled in this study. No children were < 15 years of age. Among the paediatric patients (< 18 years old), no AEs were reported. No safety and efficacy analyses were performed with data collected from these patients which is acceptable considering the limited number of patients included. The overall clinical efficacy and safety profile of Humira® in this very limited patient group resemble that of the adult population.

2.3.3. Discussion on clinical aspects

The results of this observational study support the clinical safety and efficacy of Humira® used in treatment of patients, also in the very limited population of four individuals < 18 years of age with HS in routine daily practice in Japan. The study population was examined in an actual clinical setting, without any strict selection criteria; thus, the results of this PMOS study are considered to reflect the actual situation of patients with HS in Japan. The response rate based on physician global assessment was ≥ 89% at all time points. Hidradenitis Suppurativa showed improvement also in other endpoints. Response rates were similar across age groups (≥ 15 to < 65 years: 90.7%; ≥ 65years: 75%). Similar efficacy was also shown in patients with renal or hepatic impairment.

Safety and clinical efficacy were also demonstrated in the 4 paediatric patients enrolled in this study. No AEs or ADRs were reported in these 4 paediatric patients over the duration of the study.

The safety results were consistent with the currently documented safety profile of the product, as described in the label. The benefit-risk of adalimumab is unchanged and no update to the Summary of Product Characteristics has been proposed because of these data.

3. CHMP overall conclusion and recommendation

No new findings of clinical efficacy and safety were observed in the performed Post-Marketing Observational Study. The MAH has not suggested any update to the Summary of Product Characteristics based on the performed study, a view which is supported by the CHMP.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

None.