18 May 2017
EMA/CHMP/356790/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Humira

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/000481/II/0159

Note

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

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Assessment Timetable / Steps taken for the assessment

Timetable	Planned dates	Actual dates
Start of procedure:	12 September 2016	12 September 2016
PRAC Rapporteur Assessment Report	14 October 2016	17 October 2016
PRAC members comments	19 October 2016	19 October 2016
Updated PRAC Rapporteur Assessment Report	20 October 2016	n/a
PRAC Outcome	27 October 2016	27 October 2016
CHMP members comments	28 October 2016	28 October 2016
Request for supplementary information	10 November 2016	10 November 2016
Submission of MAH's responses	20 January 2017	16 January 2017
Re-start of procedure:	23 January 2017	23 January 2017
PRAC Rapporteur Assessment Report	24 February 2017	24 February 2017
PRAC members comments	01 March 2017	01 March 2017
Updated PRAC Rapporteur Assessment Report	02 March 2017	n/a
PRAC Outcome	09 March 2017	09 March 2017
CHMP members comments	13 March 2017	13 March 2017
2nd Request for supplementary information	23 March 2017	23 March 2017
Submission of MAH's responses	18 April 2017	7 April 2017
Re-start of procedure:	19 April 2017	19 April 2017
PRAC Rapporteur Assessment Report	24 April 2017	24 April 2017
PRAC members comments	26 April 2017	26 April 2017
Updated PRAC Rapporteur Assessment Report	27 April 2017	n/a
PRAC Outcome	5 May 2017	5 May 2017
CHMP members comments	8 May 2017	8 May 2017
CHMP opinion	18 May 2017	18 May 2017

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1. Background information on the procedure

1.1. Requested type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Ltd. submitted to the European Medicines Agency on 31 August 2016 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of study P06-134: “A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of Humira in Subjects with Moderately to Severely Active Crohn's Disease” in fulfilment of MEA 056.9. The study includes also some paediatric patients and fulfils obligations according to article 46 of the paediatric Regulation (EC) No 1901/2006.

The requested variation proposed no amendments to the Product Information.

1.2. Rationale for the proposed change

The type II variation concerns submission of final study report for the following study: P06-134, A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of Humira in Subjects with Moderately to Severely Active Crohn's Disease.

This registry study was a commitment (MEA 056), undertaken in 2007 following variation EMEA/H/C/000481/II/0033 to amend section 4.1 of the SmPC to include treatment of adult patients with Crohn's Disease.

Additionally, as patients under the age of 18 years were enrolled, this application is being submitted to comply with Article 46 of Regulation (EC) No1901/2006, as amended. Six patients < 18 years old were entered into the registry. Of these 6 patients, 3 patients discontinued; for 1 patient data are available until 2010, and 2 patients who are currently > 18 years old remained in the registry.

2. Overall conclusion and impact on the benefit/risk balance

Study P06-134 is a multicenter, uncontrolled, non-interventional registry involves CD patients being treated with Humira in a routine clinical setting. The participating physicians, with regard to countries and sites, were representative of the gastroenterologists who prescribe Humira to patients with CD in North America, Europe, South Africa, New Zealand, and Australia. Patients receive commercial Humira, which is prescribed per local prescribing information.

The primary objectives were to assess safety, which is the focus of this report, while the effectiveness data collected is not further assessed.

Reported exposure up to 1 year is relatively large with 4385 patients (87.3 %) and up to 2 years 3464 patients (68.9 %). The overall cumulative registry exposure to Humira corresponds to 16,680 patient-years.

According to the protocol, SAEs, AEs of interest, and AEs leading to Humira discontinuation were captured; including serious opportunistic infections (including TB), lymphoma, and other malignancies, immune reactions including lupus/lupus-like illness, CNS demyelinating disorders, congestive heart failure and occurrence of symptomatic intestinal obstruction.

There is no comparison group within the registry, which hampers the possibility for comparative analyses. Nevertheless, it has been shown that the frequencies of AEs in the registry population were not increased compared with the frequencies in the current product information. Further, no new safety signals during the registry have been reported.

Overall, the events observed are as expected based on the clinical trials experience and in line with known class effects for an anti-TNF agent, and with what is reflected in the product information.

In total 285 patients had 356 pregnancy events reported. This is a relatively large number of pregnancies within one study setting. Based on information provided by the MAH concerning the outcome of these pregnancies and follow up data for the newborn children no new safety concern is raised in association with Humira treatment.

Six patients were < 18 years old when entering the study. Of these 6 patients, 3 patients discontinued; for 1 patient data are available until 2010, and 2 patients who are currently > 18 years old remained in the registry. None of these patients experienced an adverse event and based on the data for these patients no conclusions can be drawn for the paediatric population.

The MAH has provided an updated (version 2.0) report with correct statistical subgroup analyses for prior Humira Use and stated that the overall conclusions have not been changed. This is accepted and no further discussions are required.

The benefit-risk balance of Humira remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of study P06-134: “A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of Humira in Subjects with Moderately to Severely Active Crohn's Disease” in fulfilment for MEA 056.9. The study includes also some paediatric patients and fulfils obligations according to article 46 of the paediatric Regulation (EC) No 1901/2006.

is recommended for approval.

The variation leads to no amendments to the Product Information.

4. Scientific discussion

4.1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

Humira was approved for treatment of severe Crohn's disease (CD) in the EU in the spring of 2007 (EMEA/H/C/481/II/33) and for treatment moderately active CD in 2012. As a post-marketing condition the MAH agreed to set up a non-interventional registry evaluating the long-term safety and effectiveness of Humira as used in routine clinical practice in adult patients with moderately to severely active (CD) who are candidates for anti-TNF therapy according to the local product label.

All patients who consented to take part in the registry will be followed for up to 6 years. Interim reports have been submitted yearly. End of data collection for this final report was 04 February 2016, and the final study report was submitted in August 2016.

4.2. Clinical Safety aspects

The primary objective of this registry was to evaluate the long-term safety of adalimumab in adult patients with CD treated as recommended in the local product label. The secondary objective was to evaluate long-term effectiveness in adult patients with CD treated as recommended in the local product label.

4.2.1. Methods – analysis of data submitted

Study P06-134 is a multicenter, uncontrolled, non-interventional registry involves CD patients being treated with Humira in a routine clinical setting. The participating physicians, with regard to countries and sites, were representative of the gastroenterologists who prescribe Humira to patients with CD in North America, Europe, South Africa, New Zealand, and Australia. The patients participating in this registry correspond to the target population in Humira labels in the participating countries. Patients receive commercial Humira, which is prescribed per local prescribing information.

Enrolment for this registry was completed (last patient in) on 14 December 2009. Physicians were free to determine the appropriate therapy for each patient in accordance with the locally approved label. The decision to prescribe Humira was made separately from, and prior to, the decision to enroll the patients in this registry. The physician was to follow the patients during regular office visits at intervals determined by routine clinical practice, or as recommended by national guidelines.

Inclusion:

An adult patient (18 years of age or older) with CD for whom Humira therapy was indicated according to the local product label and who met the following criteria was eligible for participation in this study:

1. Patients enrolled fell into one of the following categories:

*Patients who were newly prescribed Humira therapy (had never been treated with Humira).

*Patients who were current participants in AbbVie sponsored investigational CD trials who were currently receiving Humira and for whom the treating physician made the decision to continue with Humira therapy beyond the duration of the investigational trial.

*Patients who were prior participants in AbbVie sponsored investigational CD trials, and did not have dose interruptions since the last dose of Humira, where the Investigator provided source documentation of dosing information.

*Patients who were currently receiving Humira, as per the local product label, who did not have dose interruptions since the induction dose of Humira where the Investigator provided source documentation of dosing information.

2. Patients willing to consent to data being collected and provided to AbbVie.

3. Patients capable of and willing to give written informed consent and to comply with the requirements of the registry protocol.

Exclusion:

A patient was not eligible for participation if he/she could not be treated in accordance with the local product label.

Discontinuation:

A patient could have withdrawn from the registry at any time without prejudice. If the physician, for any reason, decided it was in the best interest of the patient to discontinue Humira, treatment should have been stopped.

All patients that were unreachable after 3 documented attempts to contact the patient via phone, email, or certified letter, were considered lost to follow-up.

Patients were to be followed for up to 6 years, providing unique long-term safety and effectiveness data on Humira in CD. If treatment with Humira was permanently discontinued for any reason, patients were to be encouraged to remain in the registry. If a patient discontinued the registry, the physician was to offer the patient participation in the direct to HCP process regardless of Humira treatment. Patients who decided to participate in the HCP process were to be asked to sign a Patient Authorization for Use/Disclosure of Data form. Patients who had affirmatively withdrawn their authorization to have their personal health information used or disclosed in connection with the registry were not to be asked to continue in the registry or asked to participate in the HCP process.

In an effort to maximize safety data collection, physicians were asked to do the following:

- Consent and re-enroll patients who were previously discontinued due to protocol withdrawal criteria that were later removed by Protocol Amendment 2 (e.g., patients who had discontinued Humira therapy) or who discontinued for other reasons. Data collection for these patients was to resume via the electronic data report form process. For the period between registry discontinuation and re-enrollment, registry physicians were to report surgeries or hospitalizations, AEs of special interest, and CD-related medication use based on a retrospective review of their patient records.
- For patients who declined re-enrollment or who had discontinued from the registry for other reasons, physicians were requested to obtain the patient's consent to release data for the completion of a simplified HCP questionnaire on an annual basis. The first data collection period captured data from the time of the patient's discontinuation of the registry through the start of the direct to HCP process. The questionnaire focused on the collection of surgeries on hospitalizations, AEs of special interest, and CD-related medication use since registry discontinuation. The registry physician or the patient's current HCP were to complete the questionnaire.

AbbVie took reasonable actions to ascertain vital status at the end of the patient's 6-year observational period. AbbVie made every effort to work through investigational sites to match patients lost to follow-up against the National Death Index (NDI) in the US, national/regional cancer registries and vital registries as were available in other countries and were allowed per local regulations.

Safety variables included: serious adverse events (SAEs), adverse events (AEs) of special interest, and AEs that led to permanent discontinuation of Humira. Effectiveness variables included: Short Inflammatory Bowel Disease Questionnaire (SIBDQ), Work Productivity and Activity Impairment: Special Health Problem (WPAI:SHP) Questionnaire, and Physician's Global Assessment of disease activity (PGA).

4.2.2. Results

Disposition of patients

This completed international registry was conducted in 5025 adult patients with CD who accumulated 16,680 patient-years (PYs) of exposure to Humira, not including the use of Humira prior to registry enrollment in clinical trials or by commercial prescription. The registry enrolled patients who had participated in previous Humira clinical studies as well as new patients (patients who did not previously participate in other clinical studies with Humira). The majority of patients in the registry were new patients (n=4424, 88%), followed by patients in Study M06-829 (n=238, 4.7%), patients in Study M04-690 (n=171, 3.4%), and patients in Study W06-405 (n=79, 1.6%).

Overall, a total of 3478/5025 patients (69.2%) in the all treated population discontinued Humira or the registry. A total of 339 patients who were discontinued re-enrolled in the registry under Protocol Amendment No. 2. Patients who declined re-enrollment were followed for safety information if they agreed to the HCP follow-up process; a total of 9 patients were part of the HCP follow-up process. These 9 patients discontinued the registry or Humira due to 1 or more of the following reasons: AEs, lost to follow-up, protocol violation, lack of efficacy, and 'other' reasons. Patients were considered lost to follow-up if no final disposition could be obtained after 1 year following their last site visit (Table 1).

Table 1. Patient Discontinuation from Registry or Humira (All Treated Patients)

	Number (%) of Patients
	Any Humira N = 5025
Discontinuation due to (all reasons)	3478 (69.2)
AE	288 (5.7)
Withdrew consent	248 (4.9)
Lost to follow-up	876 (17.4)
Protocol violation	26 (0.5)
Administrative reasons	159 (3.2)
Lack of efficacy	1256 (25.0)
Death	55 (1.1)
SAE	386 (7.7)
Other	1037 (20.6)

Note: Data included in this table are per the CRFs and consistent with the reason(s) chosen by the physician. Patients who discontinued the registry or Humira are counted under each reason given for discontinuation; therefore, patients may have been counted more than once in the analysis of discontinuation.

Most patients were Caucasian (96.4%), the mean age ± SD was 37.8 ± 12.7 years (Table 2) and 43.1% of patients had ≥ 10 years of disease duration .

Table 2. Demographic Characteristics (All Treated Patients)

Characteristic	Any Humira N = 5025
Sex, n (%)	
Female	2869 (57.1)
Male	2156 (42.9)
Race, n (%)	
White	4843 (96.4)
Black	98 (2.0)
Asian	18 (0.4)
American Indian/Alaska Native	3 (< 0.1)
Native Hawaiian or other Pacific Islander	0
Other	47 (0.9)
Multi-race	16 (0.3)
Ethnicity, n (%)	
Hispanic or Latino	214 (4.3)
No ethnicity specified	4811 (95.7)
Age[a] (years), n (%)	
< 40	2981 (59.3)
40 to < 60	1717 (34.2)
≥ 60	327 (6.5)
Age[a] (years)	
Mean ± SD	37.8 ± 12.7
Median	36
Range	(13 – 83)[a]

a Age at enrollment: Six patients < 18 years old were entered into the registry

Note: Percentages calculated based on non-missing values.

Prior anti-tumor necrosis factor (TNF) or biologic use was present in 56.8% of patients (Table 3).

Table 1. Summary of Prior Anti-TNF or Biologic Use and Concomitant Immunosuppressant and Systemic Corticosteroid Use at baseline (All Treated Patients)

Prior or Concomitant Medication	Number (%) of Patients Any Humira N = 5025
At least 1 prior anti-TNF/biologic use, n	2852 (56.8)
Infliximab	2785 (55.4)
Certolizumab	249 (5.0)
Natalizumab	49 (1.0)
Ustekinumab	38 (0.8)
Vedolizumab	26 (0.5)
Adalimumab[a]	16 (0.3)
Anti-TNF monoclonal antibody	4 (< 0.1)
Golimumab	16 (0.3)
Investigational drug	1 (< 0.1)
Rituximab	3 (< 0.1)
Tocilizumab	2 (< 0.1)
Concomitant IMM and systemic corticosteroid use at Baseline[b]	
With IMM	1798 (35.8)
With IMM and with systemic corticosteroid	581 (11.6)
With IMM but without systemic corticosteroid	1217 (24.2)
With systemic corticosteroid	1463 (29.1)
With systemic corticosteroid but without IMM	882 (17.6)
Without IMM and without systemic corticosteroid	2345 (46.7)

a. Prior adalimumab use was entered on the Other Medication page rather than the Study Drug Administration page for these 16 patients.

b. IMMs are defined as azathioprine (AZA), 6-mercaptopurine (6-MP), thioguanine, and methotrexate (MTX).

Table 2. Extent of Humira Exposure During the Registry up to First Registry Discontinuation Including Exposure from Previous CD Studies (All Treated Patients)

Duration of Humira Exposure		Number (%) of Patients Total N = 5025
Days	Up to Week	
1 – 183	26	5025 (100.0)
184 – 365	52	4385 (87.3)
366 – 547	78	3874 (77.1)
548 – 729	104	3464 (68.9)
730 – 911	130	3148 (62.6)
912 – 1093	156	2913 (58.0)
1094 – 1275	182	2706 (53.9)
1276 – 1457	208	2507 (49.9)
1458 – 1639	234	2314 (46.0)
1640 – 1821	260	2117 (42.1)
1822 – 2003	286	1908 (38.0)
2004 – 2185	312	1693 (33.7)
2186 – 2367	338	1118 (22.2)
2368 – 2549	364	317 (6.3)
2550 – 2731	390	173 (3.4)
2732 – 2913	416	130 (2.6)
2914 – 3095	442	112 (2.2)
3096 – 3277	468	99 (2.0)
3278 – 3459	494	89 (1.8)
3460 – 3641	520	70 (1.4)
3642 – 3823	546	64 (1.3)
3824 – 4005	572	42 (0.8)
4006 – 4187	598	13 (0.3)
4188 – 4369	624	2 (< 0.1)
PYs	--	17764.7

Note: The duration of exposure is derived from the last Humira dose date (up to first discontinuation from the registry) minus the first Humira dose date plus 14 days minus total days of treatment interruption during the registry. Humira exposure from a previous CD study is included for patients who participated in a previous CD study and received Humira in that study.

The MAH states the following: The Humira registry exposure of 16,680 PYs exceeded the required 15,180 PYs needed to provide 90% power to rule out a doubling of the expected background lymphoma rate of 0.084 events (E)/100 PYs. The expected background lymphoma rate was based on a weighted average of background lymphoma rates of patients with and without prior thiopurine use. The final observed registry exposure-adjusted lymphoma rate was 0.060 E/100 PYs, which is lower than the expected background rate of 0.084 E/100 PYs. The upper bound of the 1-sided 95% confidence interval (CI) of the observed

lymphoma rate was 0.102 E/100 PYs. Since the upper bound of the 1-sided 95% CI fell below 0.168 E/100 PYs (double the assumed background rate of 0.084 E/100 PYs), the registry reached the goal of ruling out a doubling of lymphoma risk in patients with CD treated with Humira.

In accordance with the protocol, SAEs, predefined AEs of special interest, and AEs leading to adalimumab discontinuation are the only events intended to be captured in this registry; however, if spontaneously reported other AEs are captured, they are also analyzed. Adverse events of interest for this registry include reports of serious and opportunistic infections, lymphoma, other malignancies, immune reactions including lupus/lupus-like illness, CNS demyelinating disorders (including Multiple Sclerosis, Guillain Barré syndrome, and optic neuritis) and congestive heart failure.

Deaths

A total of 69 deaths were reported (1.4%; 0.41 deaths/100 PYs of registry exposure). If the exposure of patients in clinical trials prior to entering the registry is used, the death rate is 0.39 E/100 PYs. During registry participation 63 deaths occurred, of which 43 were treatment emergent and 20 were non-treatment emergent, and an additional 6 deaths were reported after patients had discontinued from the registry via above mentioned vital status data collection and National Death Index (NDI) search.

In the registry, treatment-emergent deaths were reported in 43 patients (0.9%; 0.3 deaths/100 PYs of registry exposure). Registry TEAEs leading to death in 9 of the 43 patients were considered possibly related to Humira by the physician (< 0.1 E/100 PYs) and included staphylococcal sepsis, urosepsis, anal cancer, breast cancer metastatic, gall bladder cancer metastatic, lung cancer metastatic, lung neoplasm malignant, metastases to bone, and esophageal adenocarcinoma. All other registry TEAEs leading to death were assessed by the physician as probably not related or not related to Humira.

At the request of the EMA, the registry protocol was amended to provide a process for gathering vital status data on patients who became lost to follow up or discontinued the registry prior to the full 6 years of observation time. Additional 6 cases reported after discontinuation had the cause of death including kidney disease/Crohn's disease (n=1), disease of the heart (n=2), sepsis/malignant neoplasm (n=1), nephritis, nephritic syndrome and nephrosis / secondary: heart disease (n=1), sequelae of stroke not specified as haemorrhage or infarction (n=1).

Treatment-emergent standardized mortality ratios (SMRs) were calculated using the country-specific mortality rates through 2006. These SMRs were calculated including Humira exposure for patients who received it as part of their participation in a previous CD clinical study. The SMR was 1.04 (95% confidence interval [CI] [0.63, 1.62]) for females (19 deaths, 9577.8 PYs), 0.78 (95% CI [0.50, 1.16]) for males (24 deaths, 8186.9 PYs), and 0.88 (95% CI [0.63, 1.18]) overall (43 deaths, 17,764.7 PYs).

Other serious adverse events

A total of 36.9% (1853/5025) of patients reported at least 1 registry treatment-emergent SAE. The registry exposure-adjusted SAE rate is 24.8 E/100 PYs. The most frequently reported treatment-emergent SAEs assessed as (reported by ≥ 1% of patients) were Crohn’s disease (n=606, 12.1 %), small intestinal obstruction (n=131, 2.6 %), intestinal obstruction (n=127, 2.5 %), anal abscess (n=119, 2.4 %), ileal stenosis (n=94, 1.9 %), anal fistula (n=84, 1.7 %) and sub ileus and abdominal pain (n=68, 1.4 % and n=61, 1.2 %, respectively).

The majority of treatment-emergent SAEs were not related or probably not related to the use of adalimumab. Four hundred twenty two patients (8.4 %) had treatment-emergent SAEs that were considered at least possibly or probably related to adalimumab by the physician. The most frequently reported SAEs at least possibly or probably related, were Crohn’s disease (n=45), pneumonia (n=26), anal abscess (n=20), intestinal obstruction (n=15), small intestinal obstruction (n=13), sepsis (n=11),

cellulitis (n=10), pyrexia (n=9), herpes zoster (n=8), abdominal abscess (n=9), anal fistula (n=7), ileal stenosis (n=7), intestinal stenosis (n=6), urinary tract infection (n=7), subcutaneous abscess (n=6), staphylococcal infection (n=6), sub ileus (n=6), and lupus-like syndrome (n=6), sub ileus (n=6).

Adverse events of special interest

Infections

A total of 855 patients (17.0%) reported 1333 registry treatment-emergent infections, for a registry exposure-adjusted rate of 8.0 E/100 PYs. The most frequently reported infections included anal abscess (2.6%), herpes zoster (1.1%), pneumonia (1.0%), abdominal abscess (0.9%), nasopharyngitis (0.9%), urinary tract infection (0.9%), and gastroenteritis (0.7%). Most patients with registry treatment-emergent infections were assessed by the physician as not related or probably not related to Humira; 380/5025 of patients had registry treatment-emergent infections that were at least possibly related to Humira by the physician (including 2 patients with events having an unknown relationship to study drug).

A total of 556 patients (11.1%) reported 792 registry treatment-emergent *serious infections*, for a registry exposure-adjusted rate of 4.7 E/100 PYs, with 212 patients having events considered at least possibly related to adalimumab by the physician. The only serious infection reported by ≥ 1% of patients was anal abscess (2.4%); all other serious infections were reported by 0.9% or fewer patients. Ten patients had registry treatment-emergent serious infections that resulted in death. With the exception of one patient, who was found dead at home, the other 9 patients had other relevant clinical information besides Humira exposure that may have contributed to the serious infection leading to death.

Serious infections were reported by a statistically significantly higher proportion of the subjects of patients receiving adalimumab plus corticosteroids, patients receiving adalimumab plus immunosuppressants (6-MP, AZA, or MTX) and patients receiving adalimumab plus immunosuppressants and corticosteroids compared with adalimumab monotherapy.

Nineteen patients (0.4%) experienced 21 registry treatment-emergent *opportunistic infections* (excluding oral candidiasis and TB). Fifteen patients had events that were considered by the physician to be at least possibly related to adalimumab.

Thirteen patients had serious opportunistic infections, and 5 of these patients discontinued adalimumab due to their event, see

Table 5.

Table 3. Listing of Patients with Registry Treatment-Emergent Serious Opportunistic Infections (Excluding Oral Candidiasis and TB) (All Treated Patients)

Age/Sex/ Race	Onset Day[a]	End Day[a]	PT	Severity	Physician Assessment of Relationship to Humira	SAE? (Y/N)	Discontinued Humira Due to Event? (Y/N)	Current Steroids or IMMs (Y/N)/ Prior Anti-TNFs (Y/N)	Diabetes (Y/N)/ Smoker (Y/N/Former)
55/M/W	1771	1778	Fungaemia	Moderate	Possibly related	Y	N	Y/Y	Y/N
75/M/W	1134 (13)	1155	Candida pneumonia	Moderate	Possibly related	Y	Y	Y/Y	N/Former
66/M/W	436	438	Esophageal candidiasis	Severe	Not related	Y	N	Y/Y	Y/N
29/M/W	1327	1362	*Pneumocystis jirovecii* pneumonia	Severe	Probably related	Y	Y	Y/N	N/Y
47/F/W	1508[b]	1573	Esophageal candidiasis	Moderate	Possibly related	Y	N	N/Y	N/Y
44/M/W	555	575	Varicella zoster pneumonia	Severe	Possibly related	Y	N	N/Y	N/Y
45/M/W	861	875	Esophageal candidiasis	Moderate	Probably related	Y	N	N/Y	N/Y
64/M/W	200 (43)	211	Cytomegalovirus colitis	Moderate	Not related	Y	N	Y/N	N/N
26/M/W	981	1034[b]	Herpes esophagitis	Moderate	Probably related	Y	N	N/Y	N/Y
31/M/W	10	27	*Pneumocystis jirovecii* pneumonia	Severe	Possibly related	Y	N	Y/N	N/Former
73/M/W	1447	1479	Bronchopulmonary aspergillosis	Severe	Not related	Y	Y	Y/Y	N/N
37/M/W	21 (15)	29	Esophageal candidiasis	Mild	Possibly related	Y	Y	N/N	N/Y
24/M/B	1633	1648	*Pneumocystis jirovecii* pneumonia	Severe	Probably related	Y	Y	N/Y	N/N

a. The number of days since the first Humira injection in the registry. Numbers in parentheses indicate days after the last dose of Humira.
b. Date is estimated.
Note: A registry TEAE is defined as any AE with an onset date on or after the first dose of Humira in the registry until 70 days after the last non-missing Humira injection date in the registry.

Nine patients (0.2%) experienced registry treatment-emergent *oral candidiasis* and seventeen patients (0.3%) reported registry treatment-emergent *tuberculosis* (*TB*) (active TB n=10 and latent TB n=7). Of the 10 patients with active TB, all events were serious. None of these patients had received TB prophylaxis prior to the event of active TB. All but 3 patients discontinued Humira due to active TB. All but 1 patient had events that the physician considered possibly or probably related to Humira. Six of the 10 events of active TB occurred in patients in endemic areas (3 events in Spain, 2 in Portugal, and 1 in South Africa) and 4 events did not (1 event each in Austria, Czech Republic, France, and New Zealand). Four of these 10 patients also had risk factors such as visiting an endemic region or living with a person with active TB.

Of the 7 patients with latent TB, none of the patients had a serious event. All 7 patients received TB prophylaxis. One patient had a negative TB test result prior to receiving Humira in the registry. TB test results prior to receiving Humira are unknown for the other 6 patients. Five of the 7 patients with latent TB interrupted Humira; for the remaining 2 patients, no action was taken. For 5 of the 7 patients with latent TB, the events were considered by the physician to be possibly or probably related to Humira. One event of latent TB occurred in an endemic area (Spain) and 6 events did not (3 in US, 1 in Belgium, 1 in Slovenia, and 1 in Australia).

Malignancies

A total of 116 patients (2.3%) reported 134 registry treatment-emergent *malignancies*, for an overall malignancy event rate of 0.8 E/100 PYs. Fifty-three patients had events that were considered by the physician as at least possibly related to adalimumab.

Ten patients (0.2%) reported 10 registry treatment-emergent *lymphomas*, for an overall lymphoma event rate of < 0.1 E/100 PYs, see Table 6.

Table 4. Listing of Patients with Registry Treatment-Emergent Lymphoma (All Treated Patients)

Age/Sex/ Race	Onset Day[a]	End Day[a]	PT	Severity	Physician Assessment of Relationship to Humira	SAE? (Y/N)	Discontinued Humira Due to Event? (Y/N)	Prior or Current IMM Use (Y/N)/Approx. # Yrs of Exposure	Prior Anti-TNF Use (Y/N)	Smoker (Y/N/ Former)	Family History of Cancer (Y/N)
58/M/W	221	249	Metastatic lymphoma	Severe	Not related	Y	Y	Y/11	N	Former	N
57/M/W	1621	1797[c]	Non-Hodgkin's lymphoma	Severe	Possibly related	Y	Y	Y/6	N	Y	Y
56/F/W	1555	2135[b]	B-cell lymphoma	Severe	Possibly related	Y	Y	Y/< 1	N	Y	Y
26/M/W	947	1075[b]	Mycosis fungoides	Severe	Possibly related	Y	Y	N	N	Y	N
43/F/W	1232	2369[b]	Hodgkin's disease	Severe	Probably related	Y	Y	Y/1	Y	N	N
33/M/W	638	931[b]	Follicle centre lymphoma, follicular grade I, II, III	Severe	Possibly related	Y	Y	Y/1	N	Former	N
37/M/W	996	2185[b]	B-cell lymphoma	Severe	Possibly related	Y	Y	Y/2	Y	Y	N
59/M/W	678 (20)	811	T-cell lymphoma	Severe	Probably not related	Y	Y	Y/7 UNK	Y	N	UNK
48/M/W	887 (5)	1215	Hodgkin's disease	Severe	Probably not related	Y	Y	Y/8	Y	Y	UNK
41/M/W	268 (3)	276	Non-Hodgkin's lymphoma	Moderate	Probably not related	Y	Y	Y/6	N	N	N

a. The number of days since the first Humira injection in the registry. Numbers in parentheses indicate days after the last dose of Humira.

b. Ongoing as of this day.

c. Date is estimated.

Notes: A registry TEAE is defined as any AE with an onset date on or after the first dose of Humira in the registry until 70 days after the last non-missing Humira injection date in the registry.

Patient 415003 had metastatic lymphoma that was not retrieved as lymphoma since it was not part of the Lowest Level MedDRA query for lymphoma within MedDRA version 18.1 used for this report. Therefore, this event was classified as a malignancy other than lymphoma, HSTCL, NMSC, melanoma, and leukemia in the source tables.

Thirty-six patients (0.7%) had 49 registry treatment-emergent events of *non-melanoma skin cancer* (*NMSC*), for an overall NMSC event rate of 0.3 E/100 PYs. 29 treatment-emergent events were basal cell carcinoma, 9 treatment-emergent events were squamous cell carcinoma of the skin, 7 treatment-emergent events were squamous cell carcinoma, 2 treatment-emergent events were Bowen's disease, 1 TEAE was carcinoma in situ of skin, and 1 TEAE was squamous cell carcinoma of vulva. Four of the events of NMSC resulted in adalimumab discontinuation. Nineteen of the 36 patients had events of NMSC that the physician considered possibly or probably related to adalimumab. The events that were considered probably not related or not related to adalimumab by the physician may have been due to limited exposure to study drug prior to onset of the event, the presence of the events prior to initiation of study drug, or due to the presence of confounding factors (i.e., history of sun exposure, smoking, IMM use, and personal or family history of malignancy, especially skin cancer).

Eleven patients (0.2%) reported a registry treatment-emergent melanoma. The registry exposure-adjusted event rate was < 0.1 E/100 PYs. All but 1 patient, who had an in situ skin melanoma, had events that were serious. Six patients had melanoma that the physician considered possibly or probably related to Humira. Five patients had melanoma that the physician considered probably not related to Humira that may have been due to limited exposure to study drug prior to onset of the event or presence of confounding factors, such as history of sun exposure, concurrent use of other IMMs, and prior history of skin disorders. Five patients discontinued adalimumab due to melanoma.

There were 3 patients with events of *leukemia*. The events were serious and resulted in discontinuation of the treatment and were assessed as being possibly related to adalimumab.

Sixty patients (1.2%) reported a registry treatment-emergent malignancy other than lymphoma, HSTCL, leukemia, NMSC, and melanoma. The registry exposure adjusted event rate was 0.4 E/100 PYs. Six patients reported PTs of breast cancer (0.1%), 3 patients (< 0.1%) each had PTs of adenocarcinoma of colon and prostate cancer, and 2 patients (< 0.1%) each had PTs of anal cancer, carcinoid tumor, colon cancer metastatic, lung adenocarcinoma, non-small cell lung cancer, renal cell carcinoma, lung cancer metastatic, small intestine adenocarcinoma, and testis cancer; all other malignancies were reported in 1 patient. No treatment-emergent events of glioblastoma, Merkel Cell carcinoma, or Waldenström's macroglobulinemia were reported. For 20 patients the events were considered as possibly or probably related to adalimumab.

Immune reactions

Twenty-nine patients (0.6%) had a registry treatment-emergent event of *lupus-like reaction and SLE*, a category that includes 10 patients (0.2%) with events of SLE, 17 patients (0.3%) with events of lupus-like syndrome and 2 patients (< 0.1%) with cutaneous lupus erythematosus. Overall, most patients were females (23 of 29) and 18 of the 23 female patients were 50 years of age or younger, which is consistent with the epidemiology of lupus. Lupus-like syndrome is an event usually related to medication use, including adalimumab, and may resolve on discontinuation of the medication. The registry exposure-adjusted event rate was 0.2 E/100 PYs. Eight events were reported as SAEs, 25 patients discontinued adalimumab due to the event, and 26 patients had events that the physician considered at least possibly related to adalimumab.

During the registry period there have been 30 patients (0.6%) with 37 registry treatment-emergent *allergic reactions* for a total registry exposure-adjusted event rate of 0.2 E/100 PYs. Six patients had events that were possibly related per the physician and 11 patients had events considered by the physician to be probably related. Nine patients had serious events (including anaphylactic reaction and asthma), of which all resolved. Two patients had serious allergic reaction-related events leading to discontinuation of adalimumab.

Eleven patients (0.2%) had 12 treatment-emergent events compatible with *vasculitis.* Four patients had vasculitis that was non-cutaneous and 7 patients had vasculitis that was cutaneous (registry exposure-adjusted event rate of < 0.1 E/100 PYs). Of the 11 patients, 7 patients had events that were considered by the physician to be at least possibly related to adalimumab (including Behcet's syndrome, hypersensitivity vasculitis, polyarteritis nodosa, Henoch-Schönlein purpura). Five patients had events that were serious and 6 patients had events that led to discontinuation of adalimumab.

One patient (< 0.1%) reported a registry treatment-emergent event of *sarcoidosis*, for a registry exposure-adjusted event rate of < 0.1 E/100 PYs.

Eight patients (0.2%) had 8 registry treatment-emergent *demyelinating disorder* AEs for an overall registry exposure-adjusted event rate of < 0.1 E/100 PYs. Six events were serious and 6 events were considered to be possibly or probably related to adalimumab. Six events resulted in discontinuation of adalimumab (including multiple sclerosis). There were no events of Guillain-Barré syndrome reported in the registry. One event of optic neuritis was reported in the registry.

Four patients (< 0.1%) reported 4 registry treatment-emergent events related to *Interstitial Lung Disease (ILD)*, for a registry exposure-adjusted event rate of < 0.1 E/100 PYs. Two events were reported as serious and three patients had events that the physician considered at least possibly related to adalimumab.

Cardiovascular Events

There have been thirteen patients with 14 events of *myocardial infarction* (MI). All events were SAEs, 2 patients had events that led to discontinuation of adalimumab, 2 patients had events that were considered by the physician to be possibly related, and 1 patient had a fatal event.

Eleven patients (0.2%) had 12 registry TEAEs compatible with CVA, for an overall registry exposure-adjusted event rate of < 0.1 E/100 PYs. All events were serious and 3 events were fatal. Two patients had events (CVA, cerebral infarction) that the physician considered possibly or probably related to adalimumab.

Three patients (< 0.1%) had 3 registry treatment-emergent CHF-related AEs, for an overall registry exposure-adjusted event rate of < 0.1 E/100 PYs. Two events were serious and the physician considered them not related to adalimumab; 1 of these events, pulmonary edema, was fatal. The third event was nonserious, considered by the physician as possibly related to adalimumab, and did not lead to discontinuation from adalimumab.

Gastrointestinal Events

Twenty-seven events of *intestinal perforation* were reported. Nine patients had an intestinal perforation: 6 had large intestine perforation; 5 had small intestinal perforation, 2 each had diverticular perforation, jejunal perforation, and ileal perforation; and 1 had appendicitis perforated. All but 1 was considered serious. Six patients discontinued Humira due to an intestinal perforation event. One event was considered possibly related and 1 event was probably related to adalimumab.

There were 475 patients that had treatment-emergent event compatible with *intestinal stricture,* see Table 7. Intestinal strictures are part of the natural progression of CD. The registry exposure adjusted event rate was 3.5 E/100 PYs. The most frequently reported events of intestinal stricture were intestinal obstruction, small intestinal obstruction, and ileal stenosis. Forty-five patients had intestinal stricture events that the physician considered at least possibly related to adalimumab.

Table 7. Number (%) of Patients with Registry Treatment-Emergent Intestinal Stricture (All Treated Patients)

	Any Humira
MedDRA 18.1 PT	N = 5025 n (%)
Any intestinal stricture AE	475 (9.5)
Intestinal obstruction	134 (2.7)
Small intestinal obstruction	130 (2.6)
Ileal stenosis	105 (2.1)
Intestinal stenosis	46 (0.9)
Large intestinal stenosis	44 (0.9)
Anastomotic stenosis	16 (0.3)
Small intestinal stenosis	23 (0.5)
Large intestinal obstruction	9 (0.2)
Jejunal stenosis	6 (0.1)
Duodenal stenosis	2 (< 0.1)
Gastrointestinal stenosis	1 (< 0.1)

Note: A registry TEAE is defined as any AE with an onset date on or after the first dose of Humira in the registry until 70 days after the last non-missing Humira injection date in the registry.

Seventeen patients (0.3%) had 20 registry treatment-emergent *pancreatitis* events. All events were reported as SAEs, and events in 3 patients were considered possibly related to adalimumab.

Injection Site Reactions

Twelve patients had registry treatment-emergent injection site reactions (0.2%; 0.1 E/100 PYs). All events were nonserious and the physician considered them at least possibly related to adalimumab. Events of injection site reaction led to discontinuation of adalimumab in 2 patients; events of injection site rash, injection site induration, and injection site inflammation led to discontinuation of adalimumab in 1 patient each.

Hematologic Disorders (Including Pancytopenia)

Sixty-four patients (1.3%) had a total of 71 registry treatment-emergent *hematologic disorders including pancytopenia*, for a registry exposure-adjusted rate of 0.4 E/100 PYs. Fifty-five patients had anemia, 3 patients each had leukopenia and thrombocytopenia, 2 patients each had neutropenia and neutropenic sepsis, and 1 each had febrile bone marrow aplasia, pancytopenia (serious, probably not related), and hemoglobin decreased. Events in 4 patients were considered by the physician to be at least possibly related to adalimumab.

Hepatic Events

Thirteen patients (0.3%) had 16 registry treatment-emergent *liver failure or other liver events*, for an overall registry exposure-adjusted event rate of < 0.1 E/100 PYs. Nine events were serious, 2 led to discontinuation of adalimumab, 1 was considered by the physician to be possibly related to adalimumab, and 3 were considered by the physician to be probably related to adalimumab. One patient reported registry treatment-emergent autoimmune hepatitis.

Skin and Subcutaneous Tissue Disorders

Ninety-two patients (1.8%) had 96 registry treatment-emergent events compatible with *worsening or new onset of Psoriasis*. Eight events were reported as serious and 36 events led to discontinuation of adalimumab. Events in 86 patients were considered to be possibly or probably related to adalimumab by the physician.

Pulmonary Embolism

Thirteen patients (0.3%) reported 13 registry TEAEs of *pulmonary embolism*, for a registry exposure-adjusted event rate of < 0.1 E/100 PYs. One event was fatal. One event was considered by the physician to be possibly related to adalimumab; all events were reported as serious. Two patients discontinued adalimumab due to the event.

No patients reported registry treatment-emergent *HSTCL, SJS, glioblastoma, Merkel Cell carcinoma, Waldenström's macroglobulinemi, autoimmune hepatitis, reactivation of hepatitis B, RPLS, PML,* or *Humira administration-related medication errors*.

Adverse events leading to premature discontinuation of adalimumab

A total of 596 patients (11.9 %) in the registry had experienced AEs leading to premature discontinuation of adalimumab. The majority of AEs concerned Crohn's disease (n=132, 2.5 %). Overall, 296 patients had registry TEAEs leading to discontinuation that were considered possibly or probably related to the registry drug.

MAH's summary of the safety data

No new safety signals have been observed during the registry. In this final report, 36 patients were excluded from the analyses due to non-compliance at a US site; therefore, the total number of patients analyzed in this report is 5025, representing a cumulative exposure to Humira of 17,765 PYs including

Humira exposure for patients who received it as part of their participation in a previous CD clinical study. The cumulative registry exposure to Humira (i.e., not including exposure from previous CD studies) is 16,680 PYs which exceeded the needed 15,180 PYs of exposure in order to rule out a doubling of the expected background rate of lymphoma in adult patients with CD treated with Humira in clinical practice.

By comparison, the total adalimumab exposure in previous years of the registry was as follows:

- Year 1 reported through 30 November 2008 (R&D/09/055) was 1,491.6 PYs
- Year 2 reported through 01 December 2009 (R&D/09/1355) was 5,362.8 PYs
- Year 3 reported through 01 December 2010 (R&D/10/1322) was 9,249.0 PYs
- Year 4 reported through 01 December 2011 (R&D/11/1149) was 10,579.6 PYs
- Year 5 reported through 01 December 2012 (R&D/12/1079) was 14,425.3 PYs
- Year 6 reported through 01 December 2013 (R&D/13/945) was 15,007.1 PYs
- Year 7 reported through 01 December 2014 (R&D/14/1176) was 16,533.6 PYs
- Year 8 (the final year) reported through 04 February 2016 was 17,764.7 PYs

The expected background lymphoma rate of 0.084 E/100 PYs was based on a weighted average of background lymphoma rates of patients with and without prior thiopurine use was. The final observed registry-exposure adjusted lymphoma rate was 0.060 E/100 PYs, which is lower than the expected background rate of 0.084 E/100 PYs. The upper bound of the 1-sided 95% CI of the registry-exposure adjusted rate of lymphoma was 0.1017 E/100 PYs. Since the upper bound of the 1-sided 95% CI fell below 0.168 E/100 PYs (double the assumed background rate of 0.084 E/100 PYs), the registry reached the goal of ruling out a doubling of lymphoma risk in patients with CD treated with Humira.

In general, the types and frequency of AEs noted in the registry were similar to those observed in the Humira CD clinical trials, with many of the events reflecting the underlying disease state in this treatment refractory population. A total of 36.9% of all patients experienced 1 or more registry treatment-emergent SAE (1853 of 5025 patients; 24.8 E/100 PYs). The most frequently reported registry treatment-emergent SAEs considered by the treating physician to be at least possibly related to Humira were: CD (45 patients, 0.9%); pneumonia (26 patients, 0.5%); anal abscess (20 patients, 0.4%); intestinal obstruction (15 patients, 0.3%); small intestinal obstruction (13 patients, 0.3%); sepsis and cellulitis (each 11 patients, 0.2%); pyrexia (9 patients, 0.2%); abdominal abscess (9 patients, 0.2%); herpes zoster (8 patients, 0.2%); anal fistula, ileal stenosis, and urinary tract infection (each 7 patients, 0.1%); and subcutaneous abscess, staphylococcal infection, sub ileus, lupus-like syndrome, and intestinal stenosis (each 6 patients, 0.1%). All other events were reported by 5 or fewer patients (< 0.1%).

Forty-three patients had registry TEAEs leading to death (0.3 deaths/ 100 PYs). An additional, 26 patients had non treatment-emergent AEs leading to death (i.e., AE date of onset was > 70 days after the last dose of Humira); of these 26 patients, 20 patients were reported as part of the registry, 5 patients were reported following vital status requests, and 1 patient was reported following an NDI database search. Thus, the total number of deaths in the registry is 69 (1.4%; 0.41 deaths/100 PYs of registry exposure). The SMR calculated based on treatment-emergent deaths and overall Humira exposure (0.88; 95% CI 0.63, 1.18) did not exceed 1.00, indicating that the observed death rate was consistent with expected rate for an age and sex matched adult general population.

Adverse events of special interest:

<u>Infections</u>

- A total of 855 patients (17.0%) reported 1333 registry treatment-emergent infections, for a registry exposure-adjusted rate of 8.0 E/100 PYs.

- Serious infections were reported by 556 patients (11.1%; 4.7 E/100 PYs), with 212 patients having events considered at least possibly related to adalimumab. The most frequently reported serious infection was anal abscess (2.4%); this type of infection is expected in a CD population.
- The frequency of serious infections was influenced by concomitant treatment with corticosteroids and immunosuppressants (6-MP, AZA, or MTX).

Opportunistic Infections

- Opportunistic infections (excluding oral candidiasis and TB) were reported in 19 patients (0.4%, 0.1 E/100 PYs), with 15 patients reporting events that were considered at least possibly related to adalimumab. Nine patients had oral candidiasis, 10 patients had serious events of active TB (0.2%; < 0.1 E/100 PYs) and 7 patients had latent TB (0.1%; < 0.1 E/100 PYs).
- Other infections were rare; 1 patient (< 0.1%, < 0.1 E/100 PYs) reported a treatment-emergent case of Legionella infection, 4 patients (< 0.1%, < 0.1 E/100 PYs) reported a registry treatment-emergent parasitic infection, and 6 patients (0.1%, < 0.1 E/100 PYs) reported registry treatment-emergent diverticulitis.

Malignancies

- The frequency of and types of malignancies observed were similar to what is already known about Humira treatment. Registry treatment-emergent malignancy was reported in 116 patients (2.3 %, 0.8 E/100 PYs); 36 of these patients had events of NMSC (0.7%, 0.3 E/100 PYs). Among the 116 patients with malignancies, the physician considered the events in 53 of the patients to be at least possibly related to Humira. Other causes included confounding factors, including the concurrent use of IMMs.
- Registry treatment-emergent lymphoma was reported in 10 patients (0.2%, < 0.1 E/100 PYs), leukemia in 3 patients (< 0.1%, < 0.1 E/100 PYs), and melanoma in 11 patients (0.2%, < 0.1 E/100 PYs).
- Registry treatment-emergent malignancies other than lymphoma, HSTCL, leukemia, NMSC, and melanoma were reported in 60 patients (1.2%, 0.4 E/100 PYs).

Immune Reactions

- Registry treatment-emergent immune reaction AEs occurred infrequently; allergic reactions were reported in 30 patients (0.6%, 0.2 E/100 PYs); registry treatment-emergent SLE and lupus-like syndrome were reported in 29 patients (0.6 %, 0.2 E/100 PYs); and registry treatment-emergent vasculitis was reported in 11 patients (0.2%, < 0.1 E/100 PYs)
- One patient reported a registry treatment-emergent event of sarcoidosis.

Cardiovascular Events

- Registry treatment-emergent CHF was reported in 3 patients (< 0.1%, < 0.1 E/100 PYs); registry treatment-emergent MI was reported in 13 patients (0.3 %, < 0.1 E/100 PYs); and registry treatment-emergent CVA was reported in 11 patients (0.2 %, < 0.1 E/100 PYs).

Gastrointestinal Events

- Registry treatment-emergent intestinal perforation was reported in 27 patients (0.5%, 0.2 E/100 PYs); registry treatment-emergent intestinal stricture was reported in 475 patients (9.5%, 3.5 E/100 PYs); and registry treatment-emergent pancreatitis was reported in 17 patients (0.3%, 0.1 E/100 PYs). The majority of these events were considered by the physician to not be related to Humira.

Hematologic Disorders

- Registry treatment-emergent hematologic disorders including pancytopenia were reported in 64 patients (1.3%, 0.4 E/100 PYs).

Hepatic Events

- Registry treatment-emergent liver events were reported in 13 patients (0.3%, < 0.1 E/100 PYs); 9 events were serious.

Injection Site Reactions

- Twelve patients had registry treatment-emergent injection site reactions (0.2%; 0.1 E/100 PYs).

Skin and Subcutaneous Tissue Disorders

- Erythema multiforme was reported in 1 patient (< 0.1%, < 0.1 E/100 PYs) and was considered probably not related to the treatment.
- Worsening or new occurrence of psoriasis was reported in 92 patients (1.8%, 0.6 E/100 PYs), with 86 events considered at least possibly related to adalimumab.

Demyelinating Disorders

- Demyelinating disorders were reported in 8 patients (0.2%, < 0.1 E/100 PYs), with the events in 6 patients considered to be possibly or probably related to adalimumab.

ILD

- ILD was reported in 4 patients (< 0.1%, < 0.1 E/100 PYs); 3 events were considered at least possibly related to adalimumab.

Pulmonary Embolism

- Pulmonary embolism was reported in 13 patients (0.3 %, < 0.1 E/100 PYs), one event was considered at least possibly related.

MAH's elucidation on the assessment of causality

Despite events of death, including infection-related death, serious infection, and malignancies being associated with Humira exposure in the label, there were a number of these events in Registry P06-134 that were considered not related by the physician.

The physician used the following definitions for any AE of special interest that was collected as an endpoint in the registry and for all SAEs, to assess the relationship of the AE to the use of Humira. For all SAEs and AEs of special interest with a possible or probable causal relationship to Humira, follow-up by the physician was required until the event or its sequelae resolved or stabilized at a level acceptable to the physician:

Probably Related: An AE had a strong temporal relationship to pharmaceutical product or recurred on re-challenge and another cause of event was unlikely or significantly less likely.

Possibly Related: An AE had a strong temporal relationship to the pharmaceutical product and another cause of event was equally or less likely compared to the potential relationship to drug.

Probably Not Related: An AE had little or no temporal relationship to the pharmaceutical product and/or a more likely other cause of event existed.

Not Related: An AE was due to an underlying or concurrent illness or effect of another drug and was not related to the pharmaceutical product (e.g., had no temporal relationship to drug or had a much more likely other cause of event).

If an investigator's causality opinion of an event was "possibly," "probably not," or "not related" to Humira, the investigator was required to provide an "other" cause of SAE.

In order to assess whether physician assessments of causality were appropriate, the rates of Humira registry TEAEs that were considered not related were compared to pooled placebo TEAEs, which may closely represent the baseline rates seen in CD patients, see Table 8.

Table 8. Comparison of Registry P06-134 TEAEs Assessed as Not Related by the Physician and Pooled Placebo TEAEs

	Pooled Placebo Data Across 7 CD Studies[a,b] N = 217[c]		Registry P06-134 TEAEs Assessed as Not Related[d] N = 5025	
	% of Patients	E/100 PYs	% of Patients	E/100 PYs
Serious infection	5.6	8.3	3.7	2.0
All malignancies	0.9	1.61	0.5	0.2
Deaths	0.5	0.8	0.4	0.2
Infection-related deaths	0.5	0.8	< 0.1	< 0.1

a. Placebo data pooled primary safety data across 7 CD trials.[10]
b. With or without concomitant conventional therapy.
c. N = 161 for serious infection for placebo.
d. Physician assessment.

According to the MAH, the data suggest that the Humira non-related TEAEs are being appropriately assessed, as the rates are even less than observed in the pooled placebo patients and suggest that not all events are related to Humira despite being associated with exposure in the label.

The MAH is further stating that reasons for considering events for patients as probably not related or not related to Humira by the physician may have been due to limited exposure to study drug prior to onset of the event, the event being pre-existing prior to initiation of study drug, or to the presence of confounding factors (i.e., history of sun exposure, concurrent use of other IMMs, and family history of malignancy).

Other Information

A US site was discontinued from the registry following the discovery of non-compliance issues. At the time of discontinuation, 36 patients were enrolled at this site. There was no impact on the further conduct of the registry.

A total of 285 patients had 356 pregnancy events during the registry. There were 10 sets of twins during the registry; each was counted as a single pregnancy. Of the 356 pregnancy events, 288 were live births, 26 were spontaneous abortions, 5 were lost to follow-up, 16 were elective abortions, 7 were ectopic pregnancies, 2 were stillbirths, and in 12 cases, the patient did not provide outcome information on the pregnancy. Of the 356 pregnancy events, 69 were medically significant (as indicated in the data listings) and 7 had birth defects noted.

MAH's conclusion

Compared with the prior registry interim report (August 2015) there were no new reports of lymphoma and the rates of events of interest show little to no change. In addition, as of 31 December 2015, 3,861 Crohn's disease study participants in company trials had accrued a total of 4,256.3 PYs of exposure time.

In this completed postmarketing registry, Humira was well-tolerated in adult patients with moderately to severely active CD. No new safety signals were observed. The lymphoma rate in the registry was observed following sufficient patient exposure and observation time to rule out a doubling of lymphoma in patients with CD treated with Humira. Safety data are comparable to those observed in previous Humira clinical trials and postmarketing surveillance. Based on these final registry results, the known safety profile of Humira remains unchanged.

Rapporteur's conclusion concerning safety

The final study report is submitted from the registry in Crohn's disease, which was agreed when variation EMEA/H/C/481/II/33, for the indication Crohn's disease, was given a positive opinion in 2007. A number of interim reports from this study have been assessed since its initiation. Reported exposure up to 1 year

is relatively large with 4385 patients (87.3 %) and up to 2 years 3464 patients (68.9 %). The overall cumulative registry exposure corresponds to 16,680 patient's years.

According to the protocol, SAEs, AEs of interest, and AEs leading to discontinuation of Humira are the only events intended to be captured in the registry. Adverse events of interest include serious opportunistic infections (including TB), lymphoma, and other malignancies, immune reactions including lupus/lupus-like illness, CNS demyelinating disorders (including Multiple Sclerosis, Guillain Barré syndrome, and optic neuritis), congestive heart failure and occurrence of symptomatic intestinal obstruction.

In the latest interim reports, the MAH was asked to provide pertinent information from narratives with a short conclusion for all fatal cases, serious infections and malignancies classified as not being related to the treatment with adalimumab. This was presented by the MAH. There is no comparison group within the registry, which hampers the possibility for comparative analyses. Nevertheless, it has been shown that the frequency of non-related TEAEs in the registry population were less than those observed in the pooled placebo patient groups. Thus, this suggests that not all events in these categories are related to Humira treatment, despite being reported as associated with exposure in the label.

No new safety signals during the registry have been reported by the MAH. The reported incidence rates obtained from the registry are in general not higher than those described in the current SmPC for Humira. The incidence of serious infections was 4 per 100 PYs in the SmPC (section 4.8) while it was 4.7 per 100 PYs in the registry data. Based on the ongoing and completed clinical trial data, the observed rate of non-melanoma skin cancers is given as 0.96 per 100 PYs in the SmPC, while it is reported as 0.3 per 100 PYs in the registry. Rate for lymphomas is 0.13 per 100 PYs in the SmPC while it was reported as <0.1 per 100 PYs in the registry. The rate of other malignancies is given as 0.85 per 100 PYs in the SmPC while it was reported as 0.4 per 0.4 per 100 PYs in the registry.

Overall, the events observed are as expected based on the clinical trials experience and in line with known class effects for an anti-TNF agent, and with what is reflected in the product information.

In total 285 patients had 356 pregnancy events reported. This is a relatively large number of pregnancies within one study setting. The MAH has been asked to provide follow up data for the newborn children with a a discussion about the outcomes for the reported cases. Based on the provided outcome data no safety concerns can be concluded in association with adalimumab in pregnancy.

Six patients were < 18 years old when entering the study. Of these 6 patients, 3 patients discontinued; for 1 patient data are available until 2010, and 2 patients who are currently > 18 years old remained in the registry. The data for these patients were not presented separately from the adult data. A summary of these subjects were presented by the MAH in their response so that none of these patients had AEs. The requested summary is provided however, no conclusions can be drawn for the paediatric population based on this limited data.

4.3. Clinical Efficacy aspects

The secondary objective was to evaluate long-term effectiveness of Humira in adult patients with CD treated as recommended in the local product label.

4.3.1. Methods – analysis of data submitted

Effectiveness variables included: Short Inflammatory Bowel Disease Questionnaire (SIBDQ), Work Productivity and Activity Impairment: Special Health Problem (WPAI:SHP) Questionnaire, and

Physician's Global Assessment of disease activity (PGA). The following assessments were to be collected as part of the PGA:

*General well-being,

*Abdominal pain,

*Diarrhea,

*Blood in stool,

*Abdominal mass, and

*CD-related complications.

The following are patient-reported outcomes (PROs):

*The SIBDQ measures the impact of inflammatory bowel disease symptoms on daily life (i.e., health-related quality of life); an increase in score indicates improvement.

*The WPAI:SHP evaluates the effect of the patient's CD on ability to work and perform regular activities during the previous 7 days.

The following outcomes were also collected:

*The Healthcare Resource Utilization (HCRU) is designed to track the frequency of unscheduled outpatient visits, emergency room visits, or hospitalizations for their CD.

4.3.2. Results

The MAH briefly states that, data were analyzed for patients with evaluations of effectiveness at/after 12 weeks from first treatment in the registry before the first treatment interruption and at/after 12 weeks after resumption of Humira after the last treatment interruption. In general, values for SIBDQ, WPAI, and Physician's Global Assessment were broadly similar for assessments performed prior to and after the treatment interruption(s).

Table 9. Mean Change by Visit in SIBDQ, WPAI:SHP, and PGA (All Treated Population – Patients with Measurements) – As Observed

Assessment Timepoint (Month)	Patients (All Treated Population [Patients with Measurements]) – As Observed N	Mean Change from Enrollment
SIBDQ total score		
Month 12	1712	4.98
Month 24	1319	4.20
Month 36	1139	5.01
Month 48	969	5.51
Month 60	837	5.45
Month 72	748	5.41
PGA		
Month 12	3335	–1.63
Month 24	2856	–1.63
Month 36	2629	–1.84
Month 48	2403	–1.91
Month 60	2162	–2.00
Month 72	1983	–2.08
WPAI:SHP Absenteeism		
Month 12	829	–4.92
Month 24	612	–3.02
Month 36	507	–5.62
Month 48	436	–3.93
Month 60	368	–3.22
Month 72	303	–3.89
WPAI:SHP Presenteeism		
Month 12	914	–8.00
Month 24	697	–7.04
Month 36	577	–9.84
Month 48	493	–8.09
Month 60	418	–8.21
Month 72	361	–8.03

Assessment Timepoint (Month [Year])	N	Mean Change from Enrollment
WPAI:SHP Overall Work Impairment		
Month 12	821	–9.48
Month 24	605	–7.95
Month 36	498	–11.78
Month 48	435	–9.15
Month 60	365	–8.14
Month 72	300	–9.33
WPAI:SHP Activity Impairment		
Month 12	1665	–10.93
Month 24	1286	–9.75
Month 36	1095	–10.07
Month 48	944	–10.14
Month 60	817	–10.78
Month 72	718	–11.13

Notes: All patients were to have been assessed with the WPAI:SHP questionnaire but the first 3 questions (absenteeism, presenteeism, and overall work impairment) pertained to employment and were only answered by employed patients.

Data are analyzed as observed during registry participation (i.e., patients are not necessarily on registry drug at the time of assessment).

4.3.3. Discussion

The effectiveness results are provided as descriptive data in tables and no further discussion is made by the MAH for the efficacy parameters listed as secondary outcome measures. Given the nature of these data, they are not further evaluated within this report.

5. Request for supplementary information

5.1. Other concerns

Clinical aspects:

1. It is stated that 6 patients under the age of 18 years were enrolled and this application was submitted to comply with Article 46 of Regulation (EC) No1901/2006, as amended. However, no separate description of the safety data is provided for this age group. The MAH is requested to provide a descriptive summary of the data available for these paediatric patients.

2. In total 285 patients had 356 pregnancy events reported. This is a relatively large number of pregnancies within one study setting. The MAH has only provided brief information about these cases. The pregnancy experience should be further elaborated on, including if there are follow up data for the newborn children. Further, a discussion about the outcomes for the reported cases should be provided.

6. Assessment of the responses to the request for supplementary information

Other concerns

Clinical aspects

Question 1
It is stated that 6 patients under the age of 18 years were enrolled and this application was submitted to comply with Article 46 of Regulation (EC) No1901/2006, as amended. However, no separate description of the safety data is provided for this age group. The MAH is requested to provide a descriptive summary of the data available for these paediatric patients.

Summary of the MAH's response

Six patients under the age of 18 (one 13-year-old patient, one 15-year-old patient, and four 17-year-old patients) were enrolled in registry Study P06-134. Of these patients, 3 were female, 3 were male, and all had disease duration of less than 2 years. Regarding prior and concomitant medication use, 1 patient had prior use of infliximab, 4 patients used immunosuppressants concurrently at registry enrollment (2 of them in combination with a systemic corticosteroid), and 1 additional patient used systemic corticosteroids at registry enrollment. Four of the 6 patients prematurely discontinued from the registry or discontinued the registry drug: 2 because of lack of efficacy and 2 because of protocol violation. One of the 2 patients who prematurely discontinued because of protocol violation additionally indicated "Other," and specified "protocol deviation: subject was less than 18 years old and ineligible for enrollment." The median duration of exposure to adalimumab during the registry for these patients was 449 days, and

median duration of observation in the registry was 487 days. None of the 6 patients had an adverse event reported during the registry.

Assessment of the MAH's response

The data related to 6 patients under the age of 18 does not generate any safety conclusions as 4 prematurely discontinued from the registry due to lack of efficacy (2) and protocol violation (2). Accordingly, only two patients remained in the study and none had adverse events. The requested summary is provided however, no conclusions can be drawn for the paediatric population based on this limited data.

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 2

In total 285 patients had 356 pregnancy events reported. This is a relatively large number of pregnancies within one study setting. The MAH has only provided brief information about these cases. The pregnancy experience should be further elaborated on, including if there are follow up data for the newborn children. Further, a discussion about the outcomes for the reported cases should be provided.

Summary of the MAH's response

With reference to the apparently large number of pregnancies in this study, this should be considered in the context of the long individual patient follow-up (up to 6 years) in a routine clinical practice setting, the large number of women enrolled (2869), and the fact that inflammatory bowel disease (IBD) disproportionally affects women of childbearing age.

Of the 356 pregnancies reported during the registry, 288 were live births, 26 were spontaneous abortions, 5 were lost to follow-up, 16 were elective abortions, 7 were ectopic pregnancies, 2 were stillbirths, and in 12 cases, the patient did not provide outcome information on the pregnancy. Of the 356 pregnancy events, 69 were considered to be medically significant by the Investigator.

Of the 69 pregnancies considered to be medically significant by the Investigator, the outcomes of the pregnancies were as follows: 60 live births (including 3 sets of twins) and 12 fetal deaths (7 spontaneous abortions, 2 stillbirths, 2 elective abortions, and 1 ectopic pregnancy).

Of the 69 pregnancies considered to be medically significant by the Investigator:
- There were 7 cases in which the infant/fetus had a congenital anomaly; 5 were live births and 2 resulted in elective abortions. Of the 5 infants born with congenital anomalies, there were no neonatal deaths.
- In addition to the congenital anomaly cases, there were 5 pregnancies that resulted in 6 live births in which a medically significant event was reported for the infant. Of these 6 live births, 3 infants (including one set of twins) died a few seconds, 2 weeks, and 6 weeks after birth.
- There were 47 pregnancies with live births in which a medically significant event was reported only for the mother. There were no maternal deaths reported as a result of pregnancy during this study.
- There were 12 fetal death cases: 7 spontaneous abortions, 2 stillbirths, 2 elective abortions, and 1 ectopic pregnancy.

Discussion

Congenital Anomalies

Of the 356 pregnancies, there were 7 cases with a congenital anomaly (5 were live births and 2 resulted in elective abortions). In the case of the infant with oesophageal atresia the mother discontinued adalimumab about 2 years prior to conception, and thus causality to study drug is temporally implausible. In the case of the fetus withDown's syndrome a chromosomal abnormality, causality to study drug is biologically implausible. In addition, the case of the infant with cerebral palsy was likely secondary to anoxia caused by maternal uterine rupture and thus should not be attributed to study drug.

In the remaining 4 pregnancies coincident with adalimumab therapy in this registry, there were 2 cardiac and 2 urinary tract anomalies reported. All 4 pregnant women had prior or concomitant exposure to azathioprine, 6-mercaptopurine, and/or mycophenolate, which are all considered to have teratogenic potential.

The possibility of developing congenital malformations has been linked more to ulcerative colitis (UC) than CD; however, whether IBD in general is associated with a higher risk of congenital anomalies remains controversial. In addition, in a meta-analysis performed to assess adverse pregnancy outcomes with anti-TNF use, it was found that anti-TNF-α therapy did not increase the risk of adverse pregnancy outcomes, including preterm birth, low birth weight (LBW) or congenital anomalies when compared with disease-matched controls. Furthermore, the risk of congenital anomalies with anti-TNF use was not increased when published prevalence data were compared with data for the general population. In the general population, the rate of birth defects (congenital anomaly or other conditions present at birth) varies in reports from different regions using a variety of surveillance methodology. In the US, birth defects affect about 3% of the 4 million infants born annually. The European Surveillance of Congenital Anomalies (EUROCAT) registry, a principal source of information of congenital anomalies in Europe, has reported a total prevalence of congenital malformations of 26.1 per 1,000 births from 2008 to 2012. After excluding those with chromosomal anomalies, the reported rate was 21.6 per 1,000 births. In EUROCAT, about 81% of cases were live births, 2% were fetal deaths/stillbirths from 20 weeks, and 17% of all cases resulted in termination of pregnancy due to fetal anomaly.

In a large Eurofetus study including malformations detected during pregnancy and found at birth, the most common malformations were those of the musculoskeletal system, heart and large vessels, and urinary system (all reporting over 20% of the total number of 4,615 malformations recorded in 3,686 fetuses or babies) followed by the central nervous system (16%).

Given the most common malformations in the general population are cardiac and urinary, the birth defects reported in adalimumab-exposed pregnancies in CD Registry P06-134 are consistent with those reported in the US and worldwide general population.

Infant Events

There were 5 pregnancies (6 live births) that contained infant medically significant events. In the case of the infant who developed a pneumothorax , the mother discontinued adalimumab over 1 year prior to conception, and thus a temporal relationship to study drug is implausible.

There were 3 infant deaths. In all 3 cases, the infants were born premature. There was a set of twins born at 29 weeks gestation both with very low birth weight. The twin with a birth weight of 13 oz. died a few seconds after birth, and the twin with a birth weight of 17 oz. died 2 weeks after birth. Twin pregnancy is at higher risk for premature birth. LBW and prematurity are major contributors to infant mortality. The presence of IBD during pregnancy has been shown to adversely affect pregnancy outcomes, including increased rate of preterm births, spontaneous abortions, and a higher probability of undergoing a

caesarean section. Infants born to mothers with IBD are more likely to be LBW or small for gestational age. In the general population, the risk of death increases with increasing immaturity (i.e., decreasing birth weight and gestational age). In the yearly analysis from the National Center for Health Statistics (NCHS), which links all births and infant deaths (through the first year of age) in the US, birth weight less than 500 g was associated with a mortality rate of 85% within the first year of life. LBW is the most common risk factor for mortality around the world.
In the report of the infant with necrotizing enterocolitis who died 6 weeks after birth, the infant was born premature at 27 weeks gestation. The incidence of necrotizing enterocolitis is inversely correlated to gestational age and birth weight10 and thus, premature infants are known to be at increased risk of developing necrotizing enterocolitis.

In the case of the infant with poor growth and fetal distress, the fetus had the umbilical cord wrapped 2 times around its neck, which was the likely cause of the events. In the remaining case of the infant with hypoxia at birth, the hypoxia was noted to be transient and resolved quickly.

Maternal Events
There were 47 pregnancies resulting in live births that contained medically significant events reported only for the mother. In 8 cases, the mother discontinued adalimumab over 6 months prior to conception and thus a temporal relationship is implausible.

Two infections were reported. The first case was post-partum endometritis in which the mother discontinued adalimumab during first trimester, the temporal relationship between the drug and post-partum infection is possible; however, the infection occurred approximately 6 months after discontinuation of adalimumab. The infection more likely can be attributed to the "difficult delivery." The second case of infection was a maternal urinary tract infection, which is a common event during pregnancy.

In the remaining cases, the maternal medically significant events reported (including caesarean section, breech presentation, maternal fever, preeclampsia, HELLP syndrome [hemolysis, elevated liver enzymes, low platelet count], CD flare, and vaginal tear) can be attributed to the pregnancy and/or underlying disease.

Fetal Death Cases
The outcomes of the 12 fetal death cases were the following: 7 spontaneous abortions, 2 stillbirths, 2 elective abortions, and 1 ectopic pregnancy. The 2 elective abortions were described with the congenital anomaly cases. In one case of stillbirth, the mother discontinued adalimumab over 1 year prior to conception and thus a temporal relationship is implausible.

One infection was reported in stillbirth case. This was a case of hydrops fetalis due to parvovirus infection confirmed in the placenta post mortem. B19 infection during pregnancy may be asymptomatic or more severe and associated with fetal loss or hydrops fetalis. It is known that adalimumab can cross the placenta and thus a temporal relationship cannot be ruled out; however, pregnant women lacking antibodies to the virus are as susceptible as any other immunocompetent adult to B19 infection. Thirty-five to 53% of pregnant women have pre-existing immunoglobulin G (IgG) to the virus, indicating immunity from a prior infection. The incidence of acute B19 infection in pregnancy is 3.3% to 3.8%; this risk varies among different occupational groups (higher rates in schoolteachers, day care workers and homemakers).

Conclusions of the Applicant:

Review of the data and pregnancy outcomes from CD Registry P06-134 following maternal exposure to adalimumab indicated no new safety concerns.

Assessment of the MAH's response

Two cardiac and two urinary tract anomalies were reported among congenital anomalies occurred during adalimumab exposure. The MAH argues that in all cases mothers had prior or concomitant exposure to other drugs with teratogenic potential including azathioprine, 6-mercaptopurine, and/or mycophenolate. Only one case of fetal pulmonary valve stenosis, tricuspideal insufficiency, low birth weight and maternal preeclampsia was reported to be probably related by the Investigator.

None of the other cases of fetal or maternal medical importance were reported to be related to adalimumab exposure or had events that could be suspected related to study drug.

The conclusion of the MAH is endorsed.

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

7. 2nd Request for supplementary information

The MAH has recently (14 March 2017) informed the assessment team of the following:

It has recently been brought to MAH's attention that the subgroup statistical analyses for "Prior Humira Use: Yes/No" for effectiveness and safety did not correctly classify all rollover patients as Humira-experienced. This error resulted in lower effectiveness results in the subgroup "Prior Humira Use: No," as this group erroneously included the rollover patients who had already improved at registry enrollment, as they had been on Humira for a longer period. The affected statistical tables are being rerun and will be included in the appendices of the updated report (version 2.0). The MAH believes that the overall conclusions in this report have not changed from those provided in P06-134 final report, version 1.0 as subgroup analyses were not discussed, but as this error has only just come to light, we need to assess fully and confirm that this is the case.
The MAH is aware that the CHMP member comments were due yesterday and that CHMP opinion is due next week, however the MAH would like to request time to review the subgroup analyses and provide an updated report. Therefore, in this circumstance the MAH would like to suggest that the opinion next week is delayed and this be addressed in a 2nd RSI. The MAH apologize for the inconvenience caused.

The Rapporteur agrees with the MAH proposal and a further RSI is proposed.

8. Assessment of the responses to the 2nd request for supplementary information

Response from the Applicant:

Evaluation of the revised statistical outputs for "Prior Humira Use: Yes/No" for effectiveness and safety do not change the overall effectiveness and safety conclusions provided in the Study P06-134 final report,

Version 1.0. A revised report, Version 2.0, includes the revised statistical outputs and is hereby submitted with this Request for Supplementary Information.

Assessment of the Applicant's response:

As the overall conclusions have not been changed the revision is not discussed in detail and is accepted.