PASS Information

Title	A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of Humira® (Adalimumab) in Subjects with Moderately to Severely Active Crohn's Disease (CD)
Study Identifier	P06-134
Version Identifier of the Interim Study Report	Final report
Date of Last Version of Interim Study Report	February 2015
EU PAS Register Number	Study not registered.
Active Substance and Medicinal Product	Humira (ATC code L04AB04)
Product Reference	Humira – EU/1/03/256/001-010 & 012-019
Procedure Number	EMEA/H/C/481/MEA/056.9
Marketing Authorisation Holder(s)	AbbVie
Joint PASS	No
Research Question and Objectives	This report provides final cumulative safety data from the CD Humira non-interventional registry (treatment as used in routine clinical practice as recommended in the local product label) in adult patients (18 years of age or older) with moderately to severely active CD, who were candidates for anti-tumor necrosis factor therapy.
Countries of Study	Australia, New Zealand, South Africa, Europe, Canada, and the United States
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Date of Report: 18Aug2016

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1.0 Abstract

Title

A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of Humira® (Adalimumab) in Subjects with Moderately to Severely Active Crohn's Disease (CD)

Keywords

Humira; adult; Crohn's disease; non-interventional; long-term safety

Rationale and Background

This registry, Registry P06-134, as well as the submission of this final report, is part of a postmarketing commitment from AbbVie to the United States (US) Food and Drug Administration and the European Medicines Agency. This postmarketing observational registry was designed to assess 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-tumor necrosis factor therapy as recommended in the local product label. Each patient who consented to take part in the registry was to be followed for up to 6 years. Enrollment for this registry is complete. This final report provides cumulative, long-term safety and effectiveness data from the registry. The data collected in this registry are complementary to data from the preregistration studies of Humira in patients with moderately to severely active CD.

Objectives

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

The study was designed to rule out a doubling of the expected background rate of lymphoma in adult patients with CD treated with Humira in clinical practice.

Study Design

This is a multi-center, uncontrolled, observational registry of adult patients with moderately to severely active CD treated with Humira in a routine clinical practice setting.

Setting

Approximately 450 physicians were expected to participate in this registry by enrolling patients whom they had previously decided to treat with Humira. Of these 450 physicians, approximately 185 were to be included as investigators based on their participation in prior AbbVie-sponsored clinical development studies and 265 physicians were to be included based on their eligible patient population.

Patients and Study Size, Including Dropouts

Approximately 5,000 patients in the US, Canada, the European Union, South Africa, Australia, and New Zealand were to be enrolled. The sources for patients included:

- Patients who were newly prescribed Humira therapy; i.e., patients who 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 received in the trial and 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 and the Investigator provided source documentation of dosing information.

A total of 5061 patients were enrolled in the registry. The data from 36 patients were excluded from the analyses due to non-compliance at a US site. Therefore, the data from 5025 patients were analyzed in this final report. Of note, among the 5025 patients, there were 34 patients with unsigned casebooks in spite of efforts to obtain physician signatures. A sensitivity analysis was performed in which the data from the 4991 patients with signed casebooks was compared with the data of the 5025 patients that included 34 patients with unsigned casebooks. The results of this comparison confirmed that the data from these 34 patients did not significantly alter the overall study results and conclusions.

Overall, a total of 3478/5025 patients (69.2%) in the all treated population discontinued Humira or the registry.

Variables and Data Sources

Included in this final report:

- Serious adverse events (SAEs) and adverse events (AEs) of special interest
- Effectiveness data including: Short Inflammatory Bowel Disease Questionnaire (SIBDQ), Work Productivity and Activity Impairment: Special Health Problem (WPAI:SHP), and Physician's Global Assessment of disease activity (PGA).

Final Registry Results

The database for Registry P06-134 was open and dynamic until database lock, which occurred shortly after the end of data collection on 04 February 2016. Therefore, if new information was received, the event details may have changed from the 7th interim report. In this final report, Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 Lowest Level MedDRA Queries were used without further adjudication.

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 majority of patients (88%) were not prior participants in Humira clinical trials. Prior anti-tumor necrosis factor (TNF) or biologic use was present in 56.8% of patients. Most patients were Caucasian (96.4%), the mean age ± SD was 37.8 ± 12.7 years and 43.1% of patients had ≥ 10 years of disease duration. Participants were encouraged to remain in the registry during interruption or discontinuation of Humira therapy. Some patients who discontinued the registry were re-enrolled to continue their long-term observation, as outlined below.

At the request of the European Medicines Agency (EMA), the registry protocol was amended (Amendment 2; Section 9.1) 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. The process included a revised consent form that allowed information gathering under these circumstances. Active registry participants were re-consented; patients who then discontinued the registry could be contacted by the site for this information. Re-consented patients who were then lost to follow-up had their information submitted by a third-party vendor (ProClinica) to the National Death Index (NDI) database, which has statistics and details on the deaths of US citizens. In addition, sites outside of the US were instructed to search national/regional vital registries when available and allowed by local regulations.

A number of patients discontinued the registry prior to the implementation of Amendment 2. Therefore, they could not give permission for vital status data collection. In an effort to include the data from these patients, AbbVie contacted the sites' Ethics Committees and requested approval to collect their vital status information. However, AbbVie did not request that the sites pursue information on (1) patients who had withdrawn consent because they did not want to be contacted or (2) patients who were lost to follow-up because the site had no information on how to reach them.

If the sites' Ethics Committee granted approval, the site personnel contacted discontinued patients, obtained consent, collected vital status data and entered it into the registry database. The results of vital status collection and the NDI search are included in Section 10.6.3.

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.

A total of 36.9% (1853/5025) of patients reported at least 1 registry treatment-emergent (TE) serious adverse event (SAE). The registry exposure-adjusted SAE rate was 24.8 E/100 PYs.

Registry treatment-emergent adverse events (TEAEs) leading to permanent discontinuation of Humira were reported in 596 patients (11.9%, 4.6 E/100 PYs). Registry TEAEs leading to permanent discontinuation in 296 patients were considered to be possibly or probably related to Humira by the physician.

No patients reported Hepatosplenic T-cell lymphoma (HSTCL), glioblastoma, Merkel Cell carcinoma, Waldenström's macroglobulinemia, reactivation of hepatitis B, progressive multifocal leukoencephalopathy (PML), or Humira administration-related medication errors. Stevens-Johnson syndrome (SJS) and reversible posterior leukoencephalopathy syndrome (RPLS) were reported in 1 patient each as non-treatment-emergent events.

The observed TEAEs of special interest during the registry included:

- 855 patients (17.0%) reported infections (8.0 E/100 PYs).
- 556 patients (11.1%) reported serious infections (4.7 E/100 PYs).
- 1 patient (< 0.1%) reported a Legionella infection (< 0.1 E/100 PYs).
- 19 patients (0.4%) reported an opportunistic infection (0.1 E/100 PYs).
- 9 patients (0.2%) reported oral candidiasis (< 0.1 E/100 PYs).
- 17 patients (0.3%) reported tuberculosis (TB) (0.1 E/100 PYs). Of these, 10 patients (0.2%) reported active TB (< 0.1 E/100 PYs) and 7 patients (0.1%) reported latent TB (< 0.1 E/100 PYs).
- 4 patients (< 0.1%) reported parasitic infection (< 0.1 E/100 PYs).
- 6 patients (0.1%) reported diverticulitis (≤ 0.1 E/100 PYs).
- 116 patients (2.3%) reported malignancy (0.8 E/100 PYs).
- 11 patients (0.2%) reported melanoma (< 0.1 E/100 PYs).
- 10 patients (0.2%) reported lymphoma (< 0.1 E/100 PYs).
- 3 patients (< 0.1%) reported leukemia (< 0.1 E/100 PYs).
- 36 patients (0.7%) reported non-melanoma skin cancer (NMSC) (0.3 E/100 PYs).
- 60 patients (1.2%) reported malignancy other than lymphoma, HSTCL, NMSC, melanoma, and leukemia (0.4 E/100 PYs).
- 29 patients (0.6%) reported systemic lupus erythematosus and lupus-like reactions (0.2 E/100 PYs).
- 1 patient (< 0.1%) reported sarcoidosis (< 0.1 E/100 PYs).
- 30 patients (0.6%) reported allergic reactions (0.2 E/100 PYs); 9 patients reported serious allergic reactions.
- 11 patients (0.2%) reported vasculitis (4 non-cutaneous, 7 cutaneous) (< 0.1 E/100 PYs).
- 13 patients (0.3%) reported myocardial infarction (< 0.1 E/100 PYs).
- 11 patients (0.2%) reported cerebrovascular accident-related AEs (< 0.1 E/100 PYs).

- 3 patients (< 0.1%) reported congestive heart failure-related AEs (< 0.1 E/100 PYs).
- 13 patients (0.3%) reported pulmonary embolism-related AEs (< 0.1 E/100 PYs).
- 4 patients (< 0.1%) reported interstitial lung disease (< 0.1 E/100 PYs).
- 1 patient (< 0.1%) reported primary lateral sclerosis, which is a non-clinially definitive event of ALS but not a diagnosis.
- 27 patients (0.5%) reported intestinal perforation-related AEs (0.2 E/100 PYs).
- 475 patients (9.5%) reported an intestinal stricture-related AE (3.5 E/100 PYs).
- 17 patients (0.3%) reported pancreatitis (0.1 E/100 PYs).
- 92 patients (1.8%) reported worsening and/or new onset of psoriasis (0.6 E/100 PYs).
- 1 patient (< 0.1%) reported erythema multiforme (< 0.1 E/100 PYs).
- 8 patients (0.2%) reported demyelinating disorder-related AEs (< 0.1 E/100 PYs).
- 64 patients (1.3%) reported hematologic events (0.4 E/100 PYs).
- 13 patients (0.3%) reported liver failure or another liver event (< 0.1 E/100 PYs).
- 12 patients (0.2%) reported injection site reactions (0.1 E/100 PYs).

All evaluations of effectiveness showed improvement over time.

Discussion

This completed international registry was conducted in 5025 adult patients with CD who accumulated 16,680 PYs of exposure to Humira, not including the use of Humira prior to registry enrollment in clinical trials or by commercial prescription. Humira was well tolerated; the AEs reported were consistent with the established Humira safety profile. No patients reported HSTCL, glioblastoma, Merkel Cell carcinoma, Waldenström's macroglobulinemia, reactivation of hepatitis B, PML, or Humira administration-related medication errors. SJS and RPLS were reported in 1 patient each as non-treatment-emergent events.

The sample size of this study was calculated to rule out the doubling of the expected rate of lymphoma in patients with moderate to severe CD treated with Humira in clinical practice. The estimated registry background lymphoma rate was based on several assumptions. Firstly, patients with CD not treated with thiopurine were assumed to have a lymphoma rate similar to the general population of 0.0263 E/100 PYs for patients between 15 – 76 years of age according to the SEER 17 Registry database.[9] This rate was sex-adjusted to match the Crohn's disease population, which is approximately 60% female. Secondly, patients with thiopurine treatment would have a lymphoma rate approximately 4 times higher than patients not exposed to thiopurines (0.1052 E/100 PYs, which is 4 times 0.0263 E/100 PYs). Thirdly, 73% of the CD registry patients were assumed to have a history of thiopurine exposure while the remaining 27% of the patients would not have used thiopurines. The assumed background lymphoma rate for the registry population was therefore based on a weighted average of these two lymphoma rates; 0.084 E/100 PYs (73%*0.1052 E/100 PYs + 27%*0.0263 E/100 PYs = 0.084 E/100 PYs).

Calculations yielded that at least 15,180 PYs were required to provide a 90% power to rule out a doubling of the background lymphoma rate of 0.084 E/100 PYs at a 1-sided type I error rate of $\alpha = 5\%$ and the required sample size to gather this amount of PYs with a planned up to 6 years of follow-up per patient was determined by factoring in the estimated attrition rate from the registry. The final Humira registry exposure of 16,680 PYs exceeded the required 15,180 PYs. Furthermore, the final registry sex ratio (57.1% female) and prior thiopurine use (78.2%) were similar to the predicted 60% female and 73% thiopurine exposure used for the estimation of PYs required.

There were 10 treatment-emergent events of lymphoma during the registry. There were no non-treatment-emergent lymphoma events reported. Nine of the 10 patients had prior treatment with thiopurines; 3 of these 9 patients were receiving thiopurine at enrollment and were still being treated with thiopurine at diagnosis. Conversely, 6 of the 9 patients with lymphoma who had prior thiopurine use were not taking thiopurine during registry participation. The 10 lymphoma events were of 7 different types;

2 each of Hodgkin's lymphoma, Non-Hodgkin's lymphoma, and B-cell lymphoma; 1 each of T-cell lymphoma, follicle center lymphoma, metastatic lymphoma and mycosis fungoides. Using the most conservative registry exposure time (16,680 PYs) the registry-exposure adjusted lymphoma rate for these patients with CD was 0.060 E/100 PYs. The upper bound of the 1-sided 95% CI of this rate was 0.102 E/100 PYs, which was below 0.168 E/100 PYs (double the background rate of 0.084 E/100 PYs). Thus, a doubling of lymphoma risk in patients with CD treated with Humira was ruled out. The lymphoma rate adjusted for the overall Humira exposure, including registry and prior clinical trial exposure of 17,765 PYs, was 0.056 E/100 PYs.

A total of 69 deaths were reported; 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. The overall death rate during the registry (N = 63) was 0.38 E/100 PYs based on registry exposure of 16,680 PYs. The treatment-emergent mortality rate in the TREAT registry of infliximab treated patients with CD was 0.58 E/100 PYs based on 14,184 PYs of exposure,[10] which was higher than the rate observed in Registry P06-134, even though the 0.38 E/100 PYs rate from Registry P06-134 described above included deaths that were not treatment-emergent. The Standard Mortality Ratio (SMR) for treatment-emergent deaths in the registry was calculated based on the expected death rate in an age and sex matched adult general population. For details on the SMR calculation see the statistical analysis plan (SAP) Version 2.0 in Annex 4. The registry SMR of 0.88 with 95% CI [0.63, 1.18] was calculated from registry treatment-emergent deaths (N = 43) and the overall Humira exposure, including prior exposure in clinical trials (17,764.7 PYs). The SMR calculated based on treatment-emergent deaths and overall Humira exposure did not exceed 1.00, indicating that the observed death rate was consistent with the expected rate for an age and sex matched adult general population.

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Names and Affiliations of Principal Investigators

The list below includes only physicians who enrolled patients.

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Australia	Local
		Australia	Local
		Australia	Local
		Australia	Local
		Australia	Local
		Australia	Local
		Australia	Local
		Australia	Local
		Australia	Local
		Australia	Local
		Australia	Local
		Australia	Local
		Australia	Local
		Austria	NA
		Austria	NA
		Austria	NA
		Austria	NA
		Austria	NA
		Austria	NA
		Austria	NA
		Austria	NA

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Austria	NA
		Austria	NA
		Austria	NA
		Austria	NA
		Austria	NA
		Austria	NA
		Austria	NA
		Austria	NA
		Austria	NA
		Austria	NA
		Austria	NA
		Belgium	Central
		Belgium	Central
		Belgium	Central
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		Belgium	Central

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Belgium	Central
		Belgium	Central
		Belgium	Central
		Belgium	Central
		Canada	Central
		Canada	Local
		Canada	Local
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Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Canada	Local
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Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Czech Republic	Local
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Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		France	NA
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		Germany	Central

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Germany	Central
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Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Germany	Central
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Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Germany	Central
		Germany	Central
		Greece	Local
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Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Greece	Local
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Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Greece	Local
		Greece	Local
		Greece	Local
		Hungary	Central
		Hungary	Central
		Hungary	Central
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Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Italy	Local
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		Netherlands	NA

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Netherlands	Local
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Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Portugal	Local
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		Slovenia	Local
		South Africa	Central
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		South Africa	Central
		South Africa	Central
		Spain	Central + Local
		Spain	Central + Local

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Spain	Central + Local
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		Spain	Central + Local
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Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Spain	Central + Local
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Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Spain	Central + Local
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Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Spain	Central + Local
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		Spain	Central + Local
		Spain	Central + Local
		Sweden	Central

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		Sweden	Central
		Sweden	Local
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		Sweden	Central
		Sweden	Central
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		Sweden	Central
		Sweden	Central
		Sweden	Central
		United Kingdom	Central + Local
		United Kingdom	Central + Local
		United Kingdom	Central + Local
		United Kingdom	Central + Local
		United Kingdom	Central + Local

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		United Kingdom	Central + Local
		United Kingdom	Central + Local
		United Kingdom	Central + Local
		United Kingdom	Central + Local
		United Kingdom	Central + Local
		United Kingdom	Central + Local
		United Kingdom	Central + Local
		United Kingdom	Central + Local
		United Kingdom	Central + Local
		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Local
		United States	Central
		United States	Local
		United States	Central

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		United States	Central
		United States	Central
		United States	Central
		United States	Local
		United States	Local
		United States	Central
		United States	Central
		United States	Central
		United States	Local
		United States	Central
		United States	Local
		United States	Local
		United States	Local
		United States	Local
		United States	Central
		United States	Central
		United States	Central
		United States	Central

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		United States	Central
		United States	Local
		United States	Central
		United States	Local
		United States	Central
		United States	Local
		United States	Central
		United States	Local
		United States	Local
		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Local
		United States	Local

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Local
		United States	Local
		United States	Central
		United States	Central
		United States	Local
		United States	Loca
		United States	Central
		United States	Local
		United States	Central
		United States	Central
		United States	Central
		United States	Local

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Local
		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Local
		United States	Central
		United States	Local
		United States	Central
		United States	Central
		United States	Central
		United States	Central

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		United States	Central
		United States	Local
		United States	Central
		United States	Central
		United States	Central
		United States	Local
		United States	Central
		United States	Local
		United States	Central
		United States	Local
		United States	Local
		United States	Local
		United States	Local
		United States	Central
		United States	Central
		United States	Central

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		United States	Central
		United States	Local
		United States	Central
		United States	Local
		United States	Local
		United States	Local
		United States	Central
		United States	Local
		United States	Local
		United States	Local
		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Local
		United States	Local
		United States	Central

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		United States	Central
		United States	Local
		United States	Central
		United States	Local
		United States	Local
		United States	Central
		United States	Local
		United States	Central
		United States	Central
		United States	Local
		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Central
		United States	Local

Principal Physician[a]	Site Name	Country	Central or Local IRB/EC[b]
PPD		United States	Central
		United States	Central
		United States	Local
		United States	Local

IRB = internal review board; EC = ethics committee; N/A = not applicable

a. There may be discrepancies in the spelling of physicians' names within this list versus that found in the statistical tables.

b. The central EC for all sites in the United Kingdom was Cambridge East Research Ethics Committee. The central EC for all sites in Spain was Comite Etico de Investigacion Clinica del Hospital Clinic I Provincial de Barcelona.

c. PPD replaced PPD at the conclusion of the registry but the database was not updated to reflect this change.

2.0 List of Abbreviations

6-MP	6-mercaptopurine
AE	Adverse event
ALS	Amyotrophic lateral sclerosis
AZA	Azathioprine
CD	Crohn's disease
CHF	Congestive heart failure
CRF	Case report form
CRO	Contract research organization
CVA	Cerebrovascular accident
DVT	Deep vein thrombosis
E	Events
EC	Ethics committee
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
HCP	Healthcare Provider
HCRU	Health care resource utilization
HSTCL	Hepatosplenic T-cell lymphoma
IgG	Immunoglobulin
ILD	Interstitial lung disease
IMM	Immunomodulator
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MTX	Methotrexate
NDI	National Death Index
NMSC	Non-melanoma skin cancer
PAS	(EU) Post-Authorisation Studies (Register)
PGA	Physician's Global Assessment
PML	Progressive multifocal leukoencephalopathy

PRO	Patient-reported outcome
Ps	Psoriasis
PT	Preferred term
PY	Patient-year
RA	Rheumatoid arthritis
RPLS	Reversible posterior leukoencephalopathy syndrome
SAE	Serious adverse event
SAP	Statistical analysis plan
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SJS	Stevens-Johnson syndrome
SLE	Systemic lupus erythematosus
SMR	Standardized mortality ratio
SOC	System organ class
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
TNF	Tumor necrosis factor
US	United States
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

3.0 Investigators

A list of registry physicians with detailed contact information is presented in Annex 2.

4.0 Other Responsible Parties

AbbVie, working in cooperation with the contract research organization (CRO) Mapi (Lexington, Kentucky [United States; US] and Lyon, France), managed the registry, collected all registry information, and completed all statistical analyses. Mapi was responsible for data management. ProClinica was responsible for recovering vital status on patients. No central laboratories were used.

5.0 Milestones

Milestone	Planned Date	Actual Date	Comments
Date of first ethics committee (EC)/institutional review board (IRB) approval	NA	09 August 2007	
Start of data collection	31 August 2007	05 September 2007	First patient enrolled in registry
Last EC/IRB approval	NA	20 May 2009	
End of data collection	15 January 2016	04 February 2016	Last subject last day in the registry
Registration in the European Union Post-Authorisation Studies (EU PAS) Register	NA	NA	
Interim report: (list all) 1st interim report 2nd interim report 3rd interim report 4th interim report 5th interim report 6th interim report 7th interim report	 February 2009 February 2010 February 2011 February 2012 February 2013 February 2014 February 2015	 February 2009 February 2010 February 2011 February 2012 February 2013 February 2014 February 2015	
Final report of study results	August 2016	August 2016	

6.0 Rationale and Background

6.1 Rationale

This registry, Registry P06-134, as well as the submission of this final report, is part of a postmarketing commitment from AbbVie to the US Food and Drug Administration (FDA) and the European Medicines Agency. This postmarketing observational registry was designed to assess the long-term safety and effectiveness of Humira® (adalimumab) as used in routine clinical practice in adult patients with moderately to severely active Crohn's disease (CD) who are candidates for anti-tumor necrosis factor (TNF) therapy according to the local product label. All patients who consented to take part in the registry were followed for up to 6 years. Enrollment for this registry was completed in December 2009. This final report provides cumulative, long-term safety and effectiveness

data from the completed registry. The data collected in this registry are complementary to those from the preregistration studies of Humira in moderately to severely active CD.

6.2 Background

CD encompasses a spectrum of clinical and pathological processes manifested by focal asymmetric, transmural, and occasionally, granulomatous inflammation affecting any segment of the gastrointestinal tract.[1] The prevalence of CD is approximately 140/100,000 in the US and 40 – 140/100,000 in the European Union (EU).[3] The incidence is lower in developing countries. The disease can affect persons of any age and onset is most common in the second and third decades. Males and females are affected equally. The risk for disease is higher in some ethnic groups.[5] There is no medical or surgical cure for CD, thus therapeutic approaches are necessary to control the symptoms, improve the quality of patients' lives, and minimize short and long-term toxicity and complications.[6] Despite the relatively low incidence of the disease, the cost of therapy for these patients has been estimated to be 2 billion dollars annually in the US.[8]

Although no single etiologic agent causes CD, there is evidence of a genetic predisposition as well as a strong association with smoking.[11] Current theories propose environmental factors in genetically predisposed hosts result in an unregulated immune response to protein antigens that are present in normal intestinal microbial flora.
A number of immunologic defects may all contribute to a disease marked by excessive Type 1 T helper (Th1) T-cell response (with increased production of tumor necrosis factor-alpha [TNF-α], interleukin-2 [IL-2], and interleukin-12 [IL-12]).[12]

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. There is considerable evidence for the efficacy of anti-TNF agents in CD.[13,14]

Humira is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Humira production relies on recombinant DNA

technology in a mammalian cell expression system. It consists of 1,330 amino acids and has a molecular weight of approximately 148 kilodaltons.

Humira binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Humira is composed of fully human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Humira binds with high affinity and specificity to soluble TNF-α but not lymphotoxin (TNF-β).

Humira also modulates TNF induced or TNF regulated biological responses. After treatment with Humira, levels of acute phase reactants of inflammation (C-reactive protein and erythrocyte sedimentation rate) and serum cytokines rapidly decrease. Patients treated with Humira usually experience improvement in these laboratory indicators of inflammation.

The FDA first approved Humira for the treatment of patients with rheumatoid arthritis (RA) in the US in December 2002 and by the European Commission for the EU countries in September 2003. As of 31 December 2015, Humira has been approved in over 90 countries for the treatment of inflammatory diseases including RA, juvenile idiopathic arthritis, pediatric enthesitis-related arthritis, psoriatic arthritis, ankylosing spondylitis, axial spondyloarthritis, plaque psoriasis (Ps), pediatric plaque Ps, hidradenitis suppurativa, CD, pediatric CD, and ulcerative colitis. The FDA approved Humira for the treatment of CD on 27 February 2007. In the EU Humira was approved for the treatment of adults with severely active CD on 04 June 2007 and moderately active CD on 30 August 2012. Approval was based on 4 controlled clinical studies that showed that Humira was well tolerated and the pattern and frequency of adverse events (AEs) were comparable to those seen in the other patient populations previously studied.

As of 31 December 2015, Humira has been evaluated in more than 42,000 subjects (> 43,000 patient-years [PYs] of exposure) in clinical trials and patient registries. The estimated cumulative postmarketing patient exposure since the international birth date (31 December 2002) through 31 December 2015 is 4.2 million PYs.

7.0 Objectives

This final report provides a summary of safety and effectiveness data from completed Registry P06-134. Previous reports are shown in Table 1. Each report had a data cutoff date of 01 December each year beginning with the first interim report in 2009. The end of data collection for this final report was 04 February 2016.

Table 1. Study P06-134 Interim Reports

Interim Report Number	AbbVie R&D Number
1	R&D/09/055
2	R&D/09/1355
3	R&D/10/1322
4	R&D/11/1149
5	R&D/12/1079
6	R&D/13/945
7	R&D/14/1176

The primary objective of this registry was to evaluate the long-term safety of Humira in adult patients with CD who were treated as recommended in the local product label. The study was designed to rule out a doubling of the risk of lymphoma in patients treated with Humira from an expected background lymphoma rate. The secondary objective was to evaluate long-term effectiveness of Humira in adult patients with CD who were treated as recommended in the local product label.

8.0 Amendments and Updates

The original protocol and all amendments (described below) are provided in their entirety in Annex 3. Also included in Annex 3 are those administrative changes that were not made part of an amendment (Administrative Change 8 [02 July 2013] clarified the data collection period for pregnancies; Administrative Change 9 [12 August 2014] and Administrative Change 10 [08 June 2015] updated contact information).

Amendment No.	Date	Section of Study Protocol	Reason
1	27 December 2007	Multiple	1. Expanded inclusion criteria to include previous Humira-treated patients. 2. Added pregnancy criterion related to discontinuation and restart of Humira treatment. 3. Clarified dosing in episodic dosing population analysis.
2	29 June 2010	Multiple	1. Changed Rationale and Objective to include adults 18 years of age and older with CD. 2. Added contact information for serious adverse event (SAE) reporting. 3. Extended registry from 5 to 6 years. 4. Updated the change in Medical Monitor and Sponsor address for sites located outside of North America (EU, Australia, New Zealand, and South America). 5. Updated CRO contact information. 6. Added follow-up procedures for patients who discontinued from the registry. 7. Added additional AEs of special interest. 8. Updated informed consent procedures to include re-consent and consent to the healthcare provider process (HCP) process. 9. Updated concomitant medication reporting requirements. 10. Added process for determining vital status at the end of patients' 6 year observational period. 11. Added reporting of seriousness to collection of AEs of special interest. 12. Clarified case report forms (CRFs) with regard to the retrospective AE and HCP paper questionnaires. 13. Included additional statistical sub-analyses for data from retrospective and direct to HCP questionnaires. 14. Clarified analysis of treatment-emergent SAEs and AEs of special interest. 15. Added analysis of observational AEs. 16. Clarified the safety reporting process and updated the safety contact information in the AE and pregnancy reporting sections.

Amendment No.	Date	Section of Study Protocol	Reason
3	18 June 2013	Multiple	1. Updated contact information and removed Good Clinical Practice requirement from the title page. 2. Described when an investigator may become an HCP. 3. Added criteria regarding concomitant medications during interventional clinical trials. 4. Clarified completion of electronic case report form (eCRF) pages for discontinued or lost to follow up patients. 5. Updated the reporting period for SAEs and AEs of special interest to be consistent within the protocol. 6. Clarified event reporting procedures for patients who re-enroll into the registry. 7. Clarified definition of registry completion. 8. Added new safety monitoring requirements. 9. Updated reporting period for AEs of special interest and SAEs. 10. Updated data collection period for pregnancy. 11. Changed Sponsor from Abbott to AbbVie throughout.

9.0 Research Methods

9.1 Study Design

Registry P06-134 is a multi-center, uncontrolled, observational registry of adult patients with moderately to severely active CD treated with Humira in a routine clinical practice setting. Enrollment 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. Note that in some instances the term "investigator" is used in place of "physician" (e.g., statistical tables and corresponding in-text tables). Qualified physician assistants and nurse practitioners from US sites who treated patients with Humira could have enrolled patients into the registry and are also referred to throughout this report as physicians or investigators.

Approximately 5,000 patients in the US, Canada, the EU, South Africa, Australia, and New Zealand were to enroll. Approximately 450 physicians were to participate in this registry. Of this total, approximately 185 physicians were to be included based on participation in prior AbbVie-sponsored clinical development and an additional 265 physicians were included based on their available eligible patient population.

The participating registry physicians are representative of the gastroenterologists who will prescribe, or are prescribing, Humira to patients with CD in North America, Europe, South Africa, New Zealand, and Australia. The patients selected for this registry corresponded to the target population in the Humira labels in the participating countries. The patients received commercial Humira prescribed per their local prescribing information. AbbVie did not provide any medication or therapy for this registry.

Patients who consented to participate in the registry were followed for up to 6 years, including patients who discontinued Humira before 6 years of participation in the registry or had interruptions in Humira therapy. 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 or 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.

The physician was to follow the patient during regular office visits at intervals as determined by routine clinical practice or as recommended by national guidelines. While the physician could have chosen to have the patient return for additional visits during the observation period, data were to be collected only at the intervals that most closely correspond to those in Table 2. However, information related to safety was to be captured at any time. Physicians were to have treated their patients as they would in their routine clinical practice.

Table 2. Schedule of Registry Assessments

Procedure	Study Enrollment	Months[a] 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, and 72	At Time of Reported Event
Informed consent	√		
Demographics[b]	√		
Medical/surgical history (including CD medical/surgical history)[c]	√		
Safety data collection (AEs of special interest/SAEs)[d]	√	√	√
Previous CD medications, prior concomitant medications[e]	√		
Prior and concomitant CD medications	√	√	√
All concomitant medications	√		√
Physician Global Assessment (PGA)	√	√	
Short Inflammatory Bowel Disease questionnaire (SIBDQ)	√	√	
Work Productivity Activity Impairment: Specific Health Problem (WPAI:SHP) Questionnaire	√	√	
Healthcare Resource Utilization (HCRU; Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations Questionnaire)	√	√	
Humira treatment and dosing changes[f]	√	√	
CRF completion	√	√	√

a. Data collection at regular visits closest to time points described.

b. Once the physician determined that the patient was eligible for inclusion, and the patient agreed to be included in the registry, the patient's demographic data, including date of birth, sex, race, and ethnicity were recorded on the electronic CRFs/eCRFs) at the enrollment visit.

c. The physician was to obtain a complete medical and surgical history (CD-related and non-CD-related) including history of tobacco and alcohol use at the enrollment visit. The location of CD, duration of disease, and history of complications related to the disease were to be recorded.

d. SAEs and AEs of special interest were to be collected throughout the registry to 70 days after last dose and through Humira interruptions. For patients who participated in the direct to HCP process and patients who re-enrolled, the registry physician or the patient's current HCP was to document any hospitalizations, surgeries, and any AEs of special interest (HCP process collection was annual).

Table 2. Schedule of Registry Assessments (Continued)

e. All prior medications used to treat CD were to be collected at enrollment, including highest maintained dose, date of administration, length of time on medication, and reason for stopping CD medication. All concomitant medications the patient was receiving at the enrollment visit were to be recorded, including reason for use, duration of use, and dosage. Information on medications taken for CD (including dose changes) and a complete list of all medications taken at the time of an SAE or AE of special interest were to be collected throughout the registry. In addition, for patients aged ≤ 30 with a reported malignancy AE, prior exposure to, or current use of, antineoplastics, or other drugs which have a risk of malignancy as stated in their label and other relevant dosing information to estimate total exposure were to be collected in the source documents and appropriate eCRF pages. At the time of the reported malignancy AE, sites were to be asked if any of the prior and concomitant medications contributed to the event. Any medications used prior to the registry were to be captured on the appropriate eCRF. Information on the reason for use, date(s) of administration including start and end dates, highest maintained dose, dosage information including dose, route and frequency, and reason for stopping the medication were to be collected in the source documents and appropriate eCRF pages. The administration of anakinra (Kineret®) or other biologic agents may not have been given concurrently while participating in the registry. Refer to the local product label for the use of live vaccines while a patient was on Humira. For patients who participated in the HCP process or re-enroll, information about medications to treat CD was to be collected (HCP process collection is annual).

f. The participating physician was to provide the patient a prescription for Humira, along with instructions for appropriate use. At subsequent protocol-defined study visits the physician was to collect the start and stop dates, any dose interruptions, and reason for the dose interruption that may have occurred since the last study visit. The dose, dates of administration, any dose interruptions and the reason for the interruption were captured in the source documents and eCRFs. Dose interruptions for the study were defined as patients missing > 1 dose. The reason(s) for interruptions were captured on the eCRF.

9.2 Setting

This is a multi-center, non-interventional, observational registry of adult patients diagnosed with moderately to severely active CD prescribed and treated in a routine clinical setting with Humira as recommended in the local product label. It was expected that approximately 450 physicians would participate in this registry; of this total approximately 185 physicians were to be included based on participation in prior AbbVie-sponsored clinical development studies with patients participating in clinical trials for Humira and 265 physicians were to be included based on their available eligible patient population.

9.3 Patients

Approximately 5,000 patients in the US, Canada, the EU, South Africa, Australia, and New Zealand were to be enrolled.

A patient informed consent template was provided to registry physicians. Prior to any registry-related data being collected, an informed consent statement was reviewed, signed, and dated by the patient and the person who administered the informed consent. A copy of the signed informed consent form was given to the patient and the original was placed in the patient's medical record.

Inclusion Criteria

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 Criteria

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. Physicians were encouraged to keep patients in the registry for a full 6-year observation period irrespective of future treatment decisions to obtain important and complete safety information. If a patient developed an AE of special interest or SAE while in the registry, they were to be followed throughout the patient's participation in the registry or direct to HCP process until satisfactory resolution or until 70 days following the last registry dose (whichever was longer). Follow-up information received about ongoing SAEs and/or AEs of special interest at the time of registry conclusion were to be reported using postmarketing reporting requirements. If a patient withdrew or was withdrawn from the registry, this information was to be noted, along with the reason for withdrawal, on the Study Completion eCRF. An assessment of the patient's current medical condition was to be completed at the time of withdrawal.

Patients who discontinued from the registry before Year 6 were to be offered the option to participate in a direct to HCP process, as applicable per local regulations. In order to participate in the follow-up process, the patient must have signed a Patient Authorization for Use/Disclosure of Data form.

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.

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.

9.4 Variables

Effectiveness variables included SIBDQ, HCRU, WPAI:SHP, and PGA. Safety variables included SAEs, AEs of special interest, and AEs that led to permanent discontinuation of Humira.

9.5 Data Sources and Measurement

All data associated with this registry were collected and reported electronically (eCRF) via a web address and secure password. Patient self-administered questionnaires were completed on paper forms and submitted to be entered into the database. Patient data collected during visits were to be entered into the visit date that most closely corresponded to the registry-recommended schedule of assessments visits shown in Table 2.

Patients who discontinued from the registry for any reason and signed the authorization for data release for the completion of the HCP questionnaire in the direct to HCP process received their HCP as paper/electronic questionnaires for completion.

A Study Completion eCRF was to be completed for all patients when they completed or terminated participation in the registry, as well as an assessment of their current medical conditions.

9.5.1 Safety Evaluation

An AE was defined as any untoward medical occurrence that occurred during treatment in a patient, but did not necessarily have a causal relationship with their treatment. An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event was considered causally related to the use of the product.

Such an event could result from use of the drug as stipulated in the labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness was considered an AE.

An elective surgery/procedure scheduled to occur during a registry was not considered an AE if the surgery/procedure was being performed for a pre-existing condition and the surgery/procedure had been planned prior to registry entry. However, if the pre-existing condition deteriorated unexpectedly during the registry (e.g., surgery performed earlier than planned), the deterioration of the condition for which the elective surgery/procedure was being done was considered an AE.

SAEs, AEs of special interest (Table 3), and AEs that led to permanent discontinuation of Humira were collected.

Table 3. AEs of Special Interest for Registry P06-134

Infections: nonserious infection, serious infection, legionella, opportunistic infection (excluding oral candidiasis and tuberculosis [TB]), oral candidiasis, TB (active and latent), parasitic infection, diverticulitis
Malignancies: malignancy (including Merkel cell carcinoma, Waldenström's macroglobulinemia, and glioblastoma), lymphoma, non-melanoma skin cancer (NMSC), melanoma, leukemia, other malignancies (except lymphoma, leukemia, NMSC, hepatosplenic T-cell lymphoma [HSTCL]), melanoma), HSTCL, or pediatric/adolescent/young adult malignancy
Immune reactions including lupus-like reaction, systemic lupus erythematosus (SLE), allergic reactions including angioedema/anaphylaxis, Stevens-Johnson Syndrome (SJS), sarcoidosis, vasculitis (cutaneous and non-cutaneous)
Demyelinating disorders (including demyelination, multiple sclerosis, Guillain-Barré syndrome, optic neuritis)
Interstitial lung disease (ILD)
Cardiovascular events: congestive heart failure (CHF), cerebrovascular accident (CVA), myocardial infarction (MI)
Gastrointestinal events: intestinal perforation, intestinal stricture, pancreatitis
Hematologic disorders including pancytopenia
Hepatic events: liver enzyme abnormalities,[a] liver failure and other liver events, reactivation of hepatitis B, autoimmune hepatitis
Injection site reaction
Skin and subcutaneous tissue disorders: erythema multiforme, worsening or new onset of Ps
Pulmonary embolism
Nervous system disorders: progressive multifocal leukoencephalopathy (PML), reversible posterior leukoencephalopathy syndrome (RPLS), amyotrophic lateral sclerosis (ALS)
Humira administration-related medication errors

a. AbbVie does not have the laboratory samples to analyze liver enzyme abnormalities; therefore, they were not collected during this registry unless reported as an AE.

For patients participating in the direct to HCP process, surgeries, hospitalizations, deaths, and events listed as AEs of special interest were collected. The physician assessed and recorded any AE of special interest and/or SAE in detail on the AE eCRF, including the date and time of onset, description, severity, time course, duration and outcome, relationship of the AE to Humira, information specific to the event, final diagnosis/syndrome (if known), and any action(s) taken. For all AEs of special interest, the physician was to pursue and obtain all the above-mentioned information in order to

adequately determine the outcome of the AE and to assess whether it met the criteria for classification as an SAE as well as to determine a causal relationship. Follow-up safety queries were issued to sites 3 times and considered closed after the next scheduled quarterly monitor contact per approval of the medical monitor. In the event of a death, follow-up included an autopsy report, if available, and a death certificate.

If an AE (not limited to AEs of special interest) met any of the following criteria, it was to be reported to AbbVie as a SAE within 24 hours of the site being made aware of the event.

Death of Patient	An event that resulted in the death of a patient.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that resulted in an admission to the hospital for any length of time. This did not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurred while the patient was hospitalized and prolonged the patient's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth or any anomaly that resulted in fetal loss.
Persistent or Significant Disability/Incapacity	An event that resulted in a condition that substantially interfered with the activities of daily living of a patient. Disability was not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not have been immediately life-threatening or resulted in death or hospitalization, but based on medical judgment may have jeopardized the patient and may have required medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events included allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Spontaneous Abortion	Miscarriage experienced by patient.
Elective Abortion	Elective abortion performed on patient.

The physician used the following definitions to rate the severity for any AE of special interest being collected as an endpoint/data point in the registry and for all SAEs.

Mild	The AE was transient and easily tolerated by the patient.
Moderate	The AE caused the patient discomfort and interrupted the patient's usual activities.
Severe	The AE caused considerable interference with the patient's usual activities and may have been incapacitating or life-threatening.

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).

The physician investigator took into account all relevant factors in reporting AEs. As a result, the physician may have reported an event as "not related" or "probably not related" to Humira exposure despite the event being reported as associated with Humira exposure in the label. Other factors were considered in judging causality including patient age, sex, a history of similar events prior to the start of Humira, prior exposure to other medications (biologics, immunomodulators, systemic corticosteroids), environmental exposures to relevant agents (i.e., smoking, alcohol consumption, sun exposure), the natural progression of underlying disease, prior medical history, family history, and start/stop/length of Humira exposure. All these factors may play a role in determining the relationship between the event and Humira use.

The company adjudication of SAE causality assessment regarding Humira exposure is similar to that of the physician. The AbbVie study designated physician and safety team may query the site for more relevant information about an AE in order to provide the most appropriate context for causality assessment. AbbVie thoroughly reviewed the details of all SAEs in depth, including those for deaths, serious infections, and malignancies considered unrelated to Humira, and assessed causality of Humira exposure appropriately. AbbVie's assessments may agree or disagree with those of the investigator.

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.

The SAEs, AEs of special interest, and AEs that led to permanent discontinuation of Humira were reported to AbbVie following the administration of the first commercial dose of Humira or following initial informed consent signing (whichever date was earlier). These AEs were reported throughout the patient's participation in the registry, or direct to HCP process, until satisfactory resolution of the event or 70 days after the patient's last dose of registry drug (whichever period was longer). Follow-up information received on ongoing SAEs and AEs of special interest post-registry was to be reported using standard postmarketing reporting.

Patients remained in the registry and continued to be monitored during Humira treatment interruptions. SAEs and AEs of special interest were collected and queried for changes in CD medications and medical history of the event during registry visits. If Humira treatment was permanently discontinued for any reason, the reason was recorded and the patient was encouraged to remain in the registry for the full 6 years.

Patients who were joining the registry from enrollment in a prior AbbVie Humira study had their ongoing events at the time of registry entry collected.

In the event of an SAE, and/or additionally, any non-serious event of malignancy in patients 30 years of age and younger, whether related to Humira or not, the physician was to notify AbbVie within 24 hours of the physician becoming aware of the event.

Pregnancy in a registry patient must have been reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Pregnancies were collected from the date of the first dose of Humira in the registry through 150 days following the last dose of registry drug or the end of the patient's participation in registry (whichever was longer).

Physicians should have referred to their local prescribing information when making treatment decisions for patients who became pregnant while being treated with Humira in the registry. Patients who became pregnant and interrupted their Humira therapy should have remained in the registry and should have continued to be monitored for new SAEs and AEs of special interest.

All female patients who became pregnant while enrolled in this registry were to be followed from the time the pregnancy was reported until the outcome of the pregnancy was known. Information was collected regarding a pregnancy occurrence in a registry patient and the outcome of the pregnancy.

Pregnancy in a registry patient was not considered an AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly was considered an SAE and was required to be reported to AbbVie within 24 hours of the site becoming aware of the event.

For patients participating in the direct to HCP process, HCPs documented any hospitalizations, surgeries, deaths, and any AE of special interest annually via a paper questionnaire or electronic data capture (EDC). The HCP assessed and recorded the date of onset (if known), event description, use of Humira and other CD medications.

These events were reported to AbbVie from the time of registry consent up to 6 years, irrespective of any treatment interruption, any changes in treatment, or discontinuation of Humira.

9.5.2 Effectiveness Evaluation

This section lists the planned effectiveness measures evaluated during the course of the registry. The results on these effectiveness measures are summarized in Section 10.4. Effectiveness data were not collected during the timeframe that a patient was not participating in the registry.

PGA

The PGA (Protocol Appendix F [Annex 3]) measures the physician's assessment of the patient's current disease activity from 'very good' to 'very bad'.

The PGA was to be calculated at all registry visits starting at study enrollment, if part of the physician's routine clinical assessment. 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):

SIBDQ

The SIBDQ (Protocol Appendix C [Annex 3]) measures the impact of inflammatory bowel disease symptoms on daily life (i.e., health-related quality of life); an increase in score indicates improvement.

WPAI:SHP

The WPAI:SHP (Protocol Appendix E [Annex 3]) evaluates the effect of the patient's CD on ability to work and perform regular activities during the previous 7 days.

HCRU

The HCRU is designed to track the frequency of unscheduled outpatient visits, emergency room visits, or hospitalizations for their CD (Protocol Appendix D [Annex 3]).

9.6 Bias

The list of AEs of special interest was updated, as needed. However, an underestimation of the number of nonserious AEs of special interest in the categories of events that were not included in the list at registry initiation may have occurred.

Effectiveness results should be interpreted considering the following:

- Per registry design, patients who entered the registry may have been newly initiated on Humira shortly before registry entry or may already have been

continuously treated for a longer period. Thus, some patients may have been Humira-naïve at Baseline, while others had been treated with Humira for a period of time at the Baseline effectiveness measurement.

- There might have been a selection bias (especially for later endpoints) if a large proportion of patients who dropped out of the registry did so because they were not improving adequately.

9.7 Study Size

The sample size of this study was calculated to rule out a doubling of the expected rate of lymphoma in patients with moderate to severe CD treated with Humira in clinical practice. The sample size for this registry was determined to be 5,000 patients, a calculation that was based on assumptions as follows:

Firstly, patients with CD not treated with thiopurine were assumed to have a lymphoma rate similar to the general population of 0.0263 events (E)/100 PYs for patients between 15 – 76 years of age according to the SEER 17 Registry database.[9] This rate was sex-adjusted to match the Crohn's disease population, which is approximately 60% female. Secondly, patients with thiopurine treatment would have a lymphoma rate approximately 4 times higher than patients not exposed to thiopurines (0.1052 E/100 PYs, which is 4 times 0.0263 E/100 PYs). Thirdly, 73% of the CD registry patients were assumed to have a history of thiopurine exposure while the remaining 27% of the patients would not have used thiopurines. The assumed background lymphoma rate for the registry population was therefore based on a weighted average of these two lymphoma rates; 0.084 E/100 PYs (73%*0.1052 E/100 PYs + 27%*0.0263 E/100 PYs = 0.084 E/100 PYs).

Calculations yielded that at least 15,180 PYs were required to provide a 90% power to rule out a doubling of the background lymphoma rate of 0.084 E/100 PYs at a 1-sided type I error rate of $\alpha = 5\%$ and the required sample size to gather this amount of PYs with a planned up to 6 years of follow-up per patient was determined by factoring in the estimated attrition rate from the registry.

The final Humira registry exposure of 16,680 PYs exceeded the required 15,180 PYs. Furthermore, the final registry sex ratio (57.1% female) and prior thiopurine use (78.2%) were similar to the predicted 60% female and 73% thiopurine exposure used for the estimation of PYs required.

9.8 Data Transformation

This was an observational study, therefore, data were analyzed as observed. Derivations and calculations for analysis ready datasets are described in the statistical analysis plan (SAP) (Annex 4).

9.9 Statistical Methods

The final SAP Version 2.0 is presented in Annex 4.

9.9.1 Main Summary Measures

See Section 9.9.2.

9.9.2 Main Statistical Methods

The following analysis sets were to be used. All analyses sets excluded patients from Site PPD due to site noncompliance (Section 12.0).

All Treated Population

All treated population is defined as the set of all patients who received at least 1 injection of Humira in the registry.

Episodic Dosing Population

The episodic dosing population consists of patients in the all treated population who:

- discontinued Humira at least once for more than 70 days and received at least 1 dose of Humira after the treatment interruption,
- did not receive any other biologics during the treatment interruption,

- provided data before and after Humira treatment interruption period(s), and
- included safety data collected during the registry only.

Non-Episodic Dosing Population

The non-episodic dosing population consists of all patients in the all treated population excluding patients with treatment interruptions.

Re-Enrollment Safety Population

The re-enrollment safety population consists of all patients who discontinued from the registry due to prior protocol withdrawal criteria (i.e., patients who discontinued Humira therapy) or discontinued for other reasons and re-consented to participation in the registry. This is the population for safety analyses of data collected during the re-enrollment period.

HCP Safety Population

The HCP safety population consists of all patients who declined re-enrollment to participation in the registry or who discontinued from the registry for other reasons and consented to data release for the completion of a simplified HCP questionnaire in the direct to HCP process. This describes the population for safety analyses of data collected from the HCP questionnaire.

Effectiveness Analysis Populations

The effectiveness analysis populations consist of all patients who received at least 1 dose of Humira in the registry and had at least 1 post-enrollment measurement of the respective effectiveness parameter. Only observed effectiveness parameters were to be analyzed. No missing data imputations were to be performed.

9.9.3 Missing Values

This was a postmarketing observational study. No missing data were replaced and all data were included as observed in all presentations.

9.9.4 Sensitivity Analyses

A sensitivity analysis was performed in which the data from the 4991 patients with signed casebooks was compared with the data of the 5025 patients that included 34 patients with unsigned casebooks.

9.9.5 Amendments to the Statistical Analysis Plan

Analyses were conducted as planned in the SAP Version 2.0 (Annex 4). There were no changes in the planned statistical analyses as described in this final SAP.

9.10 Quality Control

Prior to the initiation of the registry, physician and site personnel were provided training on registry protocol. Training included a detailed discussion of the protocol, performance of procedures, paper PRO completion, and eCRF completion. Sites were given a paper PRO and eCRF completion workbook for reference.

Monitoring visits were performed at a subset of the sites. At the visits, a quality assurance check was performed against entries on the paper and eCRF, and a quality assurance check was performed to ensure that the physician was complying with the protocol and local regulations. The monitoring plan detailed how sites were selected for the on-site monitoring visits and what data was to be source data verified during the visit. Throughout the registry, Mapi and AbbVie periodically followed up with the sites to ensure that SAEs and AEs of special interest were being reported.

All registry data were entered via the eCRF except for pregnancy data, which were collected via paper CRFs until October 2014 after which these data were also collected via the eCRF. Only PROs completed by the patients were included via paper CRFs and these were submitted to be entered into the database. All eCRF information was imported directly into the electronic data capture system. Any necessary corrections were made to the database and documented via addenda, queries, source data clarification forms, or an audit trail. A manual review of selected line listings was performed at the end of the

registry. All paper questionnaires (including direct to HCP questionnaire) were to be entered into the database Mapi data management group upon receipt.

10.0 Results

The database for Registry P06-134 was open and dynamic; therefore, event details may have changed from those reported in the 7th interim report if new information was received. Changes may have included intentional updates in EDC: e.g., based upon responses to queries, Medical Dictionary for Regulatory Activities (MedDRA) version upgrade, and others.

In this final report, the Lowest Level MedDRA Queries from MedDRA Version 18.1 were used to evaluate AEs of special interest.

10.1 Participants

Description	Table	Appendix
Summary of analyzable population (all treated)		
By previous CD trial	14.1__1.1	
By geographic location, country, and investigator	14.1__1.2	
Subject populations	14.1__1.3	
By type of practice	14.1__1.4	
Discontinuation of the study or study drug		
Subjects who discontinued the study or study drug (all treated)	14.1__2.1	16.2__1.1
Subjects who discontinued the study or study drug before re-enrollment (re-enrollment population)	14.1__2.2	16.2__1.2
Time to discontinuation from the registry (all treated)	14.1__2.3	
Inclusion/Exclusion criteria		16.2__2.1
Protocol deviations		16.2__2.2
Description	**Figure**	
Kaplan-Meier plot of time to first discontinuation from the registry (all treated)	14.1__2.4	
Kaplan-Meier plot of time to final discontinuation from the registry (all treated)	14.1__2.5	

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). A total of 5061 patients were enrolled in the registry. Thirty-six patients were excluded from the analyses due to non-compliance at a US site; therefore, the total number of patients analyzed in this final report is 5025 (Section 12.0). The first patient enrolled on 05 September 2007 and the last patient enrolled on 14 December 2009. The majority of patients (88.0%) in the registry did not roll over from a prior Humira study (Table 4).

Table 4. Source of Participating Patients (All Treated Patients)

	Number (%) of Patients
Patient Source	**Any Humira N = 5025**
New patients	4424 (88.0)
Study M02-433	31 (0.6)
Study M04-690	171 (3.4)
Study M05-769	43 (0.9)
Study M06-808	39 (0.8)
Study M06-829	238 (4.7)
Study W06-405	79 (1.6)

Cross reference: Table 14.1__1.1

A total of 3478 patients (69.2%) discontinued from the registry or from Humira; the most common reason given was lack of efficacy (Table 5). 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 5. 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.

Cross reference: Table 14.1__2.1

10.2 Descriptive Data

Description	Table	Appendix
Demographic characteristics (all treated)		16.2__4.1
Categorical data	14.1__3.1.1	
Tobacco and alcohol use	14.1__3.1.2	16.2__4.3
Maintenance and induction regimen at enrollment	14.1__3.1.3	
Duration of CD (years)	14.1__3.1.4	
Continuous data	14.1__3.2.1	
Age (years) by subgroups	14.1__3.2.2	
Crohn's disease history (all treated)	14.1__3.3	16.2__4.2.3
Hospitalization history		16.2__4.2.5
Surgeries		16.2__4.4
AEs of special interest history		16.2__4.5.1
Risk factors		16.2__4.5.2

Description	Table	Appendix
Medical history by body system and condition/diagnosis	14.1__3.4	16.2__4.2.1
Prior anti-TNF/biologic use (all treated)	14.1__4.1	16.2__4.2.2 16.2__7.2.5
Concomitant immunosuppressant and systemic corticosteroid use at Baseline (all treated)	14.1__4.2	16.2__4.2.4
Other prior medications by generic name (all treated)	14.1__4.3	16.2__7.4.2
Concomitant medications started during the registry (all treated)	14.1__4.4	16.2__7.4.1
HCP Questionnaire		16.2__4.6
By geographic location (all treated)		
Prior anti-TNF/biologic use	14.1__4.5.1	
Concomitant immunosuppressant and systemic corticosteroid use at Baseline	14.1__4.5.2	
Other prior medications by generic name	14.1__4.5.3	
Concomitant medications started during the registry	14.1__4.5.4	
By type of practice (all treated)		
Prior anti-TNF/biologic use	14.1__4.6.1	
Concomitant immunosuppressant and systemic corticosteroid use at Baseline	14.1__4.6.2	
Other prior medications by generic name	14.1__4.6.3	
Concomitant medication started during the registry	14.1__4.6.4	

Patients who participated in the registry had a mean age of 37.8 years at enrollment and were predominantly white and female (Table 6).

Table 6. 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 (Patients PPD , PPD).

Note: Percentages calculated based on non-missing values.

Cross reference: Table 14.1__3.1.1, Table 14.1__3.2.1

Prior anti-TNF or biologic use and concomitant immunomodulator (IMM) and systemic corticosteroid use at Baseline is presented in Table 7.

Table 7. Summary of Prior Anti-TNF or Biologic Use and Concomitant IMM 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).

Cross reference: Table 14.1__4.1, Table 14.1__4.2

10.3 Outcome Data

See Section 10.4.

10.4 Main Results

Description	Table	Appendix
SIBDQ for each visit		16.2__6.1 16.2__6.4.1 16.2__6.4.2
All treated patients with SIBDQ measurements	14.2__1.1	
By geographic location	14.2__1.2	
By type of practice	14.2__1.3	
By prior use of other anti-TNF/biologic	14.2__1.4	
By prior use of Humira	14.2__1.5	
By prior use of tobacco	14.2__1.6	
By prior use of alcohol	14.2__1.7	
By prior complications due to CD	14.2__1.8	
By CD duration	14.2__1.9	
By age group	14.2__1.10	
By prior participation in Humira CD clinical study	14.2__1.11	
By number of treatment interruptions	14.2__1.12	
Change in SIBDQ from enrollment for each visit		
All treated patients with SIBDQ measurements	14.2__1.13	
By geographic location	14.2__1.14	
By type of practice	14.2__1.15	
By prior use of other anti-TNF/biologic	14.2__1.16	
By prior use of Humira	14.2__1.17	
By prior use of tobacco	14.2__1.18	
By prior use of alcohol	14.2__1.19	
By prior complications due to CD	14.2__1.20	
By CD duration	14.2__1.21	
By age group	14.2__1.22	
By prior participation in Humira CD clinical study	14.2__1.23	
By number of treatment interruptions	14.2__1.24	
Summary of work productivity and activity impairment (WPAI) for each visit		16.2__6.2 16.2__6.5.1 16.2__6.5.2
All treated patients with WPAI measurements	14.2__2.1	
By geographic location	14.2__2.2	

Description	Table	Appendix
By type of practice	14.2__2.3	
By prior use of other anti-TNF/biologic	14.2__2.4	
By prior use of Humira	14.2__2.5	
By prior use of tobacco	14.2__2.6	
By prior use of alcohol	14.2__2.7	
By prior complications due to CD	14.2__2.8	
By CD duration	14.2__2.9	
By age group	14.2__2.10	
By prior participation in a Humira CD clinical study	14.2__2.11	
By number of treatment interruptions	14.2__2.12	
Summary of change in WPAI from enrollment for each visit		
All treated patients with WPAI measurements	14.2__2.13	
By geographic location	14.2__2.14	
By type of practice	14.2__2.15	
By prior use of other anti-TNF/biologic	14.2__2.16	
By prior use of Humira	14.2__2.17	
By prior use of tobacco	14.2__2.18	
By prior use of alcohol	14.2__2.19	
By prior complications due to CD	14.2__2.20	
By CD duration	14.2__2.21	
By age group	14.2__2.22	
By prior participation in a Humira CD clinical study	14.2__2.23	
By number of treatment interruptions	14.2__2.24	
Summary of Physician's Global Assessment (PGA) for each visit		16.2__6.6.1 16.2__6.6.2
All treated patients with PGA measurements	14.2__3.1	
By geographic location	14.2__3.2	
By type of practice	14.2__3.3	
By prior use of other anti-TNF/biologic	14.2__3.4	
By prior use of Humira	14.2__3.5	
By prior use of tobacco	14.2__3.6	
By prior use of alcohol	14.2__3.7	
By prior complications due to CD	14.2__3.8	
By CD duration	14.2__3.9	

Description	Table	Appendix
By age group	14.2__3.10	
By prior participation in a Humira CD clinical study	14.2__3.11	
By number of treatment interruptions	14.2__3.12	
Summary of change in PGA from enrollment for each visit		
All treated patients with PGA measurements	14.2__3.13	
By geographic location	14.2__3.14	
By type of practice	14.2__3.15	
By prior use of other anti-TNF/biologic	14.2__3.16	
By prior use of Humira	14.2__3.17	
By prior use of tobacco	14.2__3.18	
By prior use of alcohol	14.2__3.19	
By prior complications due to CD	14.2__3.20	
By CD duration	14.2__3.21	
By age group	14.2__3.22	
By prior participation in a Humira CD clinical study	14.2__3.23	
By number of treatment interruptions	14.2__3.24	
Analysis of healthcare resource utilization data for each visit (all treated patients)	14.2__4	16.2__6.3

Effectiveness analyses are as observed; that is, patients needed to have an assessment at a time point in order to be counted. Effectiveness data are presented in Table 8 (all treated population – patients with measurements).

Table 8. Mean Change by Visit in SIBDQ, WPAI:SHP, and PGA (All Treated Population – Patients with Measurements) – As Observed

	Patients (All Treated Population [Patients with Measurements]) – As Observed	
Assessment Timepoint (Month)	**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

Table 8. Mean Change by Visit in SIBDQ, WPAI:SHP, and PGA (All Treated Population – Patients with Measurements) – As Observed (Continued)

Assessment Timepoint (Month [Year])	Patients (All Treated Population [Patients with Measurements]) – As Observed	
	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).

Cross reference: Table 14.2__1.13, Table 14.2__2.13, Table 14.2__3.13

10.5 Other Analyses

Not applicable.

10.6 Adverse Events and Adverse Reactions

10.6.1 Extent of Exposure

Description	Table	Appendix
Prior adalimumab exposure (all treated – new patients with initial dose date)	14.1__5.1	
Adalimumab exposure during the registry up to first discontinuation (all treated)		
Categorical data	14.1__5.2.1	
Continuous data	14.1__5.2.2	
Adalimumab exposure during the registry up to first discontinuation including adalimumab exposure from previous CD studies (all treated)		
Categorical data	14.1__5.3.1	
Continuous data	14.1__5.3.2	
Adalimumab exposure during re-enrollment period (re-enrollment population)		
Categorical data	14.1__5.4.1	
Continuous data	14.1__5.4.2	
Duration of retrospective period (re-enrollment population)		
Categorical data	14.1__5.5.1	
Continuous data	14.1__5.5.2	
Duration of observation period (all treated)		
Categorical data	14.1__5.6.1	
Continuous data	14.1__5.6.2	
Adalimumab exposure during the registry up to first discontinuation by geographic location – continuous data (all treated)		
US	14.1__5.7.1	
North America other than US	14.1__5.7.2	
Eastern Europe	14.1__5.7.3	
Other European countries	14.1__5.7.4	
Other countries	14.1__5.7.5	
Adalimumab exposure during re-enrollment period by geographic location – continuous data (re-enrollment population)		
US	14.1__5.8.1	
North America other than US	14.1__5.8.2	

Description	Table	Appendix
Eastern Europe	14.1__5.8.3	
Other European countries	14.1__5.8.4	
Other countries	14.1__5.8.5	
Adalimumab exposure during the registry up to first discontinuation by type of practice – continuous data (all treated)		
Clinical research center	14.1__5.9.1	
Group practice	14.1__5.9.2	
Hospital practice	14.1__5.9.3	
Private practice	14.1__5.9.4	
University practice	14.1__5.9.5	
Other	14.1__5.9.6	
Adalimumab exposure during re-enrollment period by type of practice – continuous data (re-enrollment population)		
Clinical research center	14.1__5.10.1	
Group practice	14.1__5.10.2	
Hospital practice	14.1__5.10.3	
Private practice	14.1__5.10.4	
University practice	14.1__5.10.5	
Other	14.1__5.10.6	
Study drug administration information		16.2__5.1 16.2__5.2.1 16.2__5.2.2 16.2__5.3 16.2__5.4

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 (Section 12.0), representing a cumulative exposure to Humira of 17,764.7 PYs including Humira exposure for patients who received it as part of their participation in a previous CD clinical study (Table 9). The cumulative registry exposure to Humira (i.e., not including exposure from previous CD studies) was 16,680.4 PYs. Of note, there were 34 patients with unsigned casebooks. A sensitivity analysis was performed in which the data analysis from the 4991 patients with signed casebooks was compared with the data analysis of the 5025 patients that included 34 patients with unsigned casebooks. The

results of this comparison confirmed that the data from these 34 patients did not significantly alter the overall study results and conclusions. These data are in the statistical listings.

Table 9. 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

Table 9. Extent of Humira Exposure During the Registry up to First Registry Discontinuation Including Exposure from Previous CD Studies (All Treated Patients) (Continued)

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.

Cross reference: Table 14.1__5.3.1

10.6.2 Adverse Events and Adverse Reactions

Description	Table	Appendix
Overview of treatment-emergent adverse events (TEAEs)		16.2__7.1.1 16.2__7.2.2 16.2__7.2.3 16.2__7.2.4 16.2__7.2.6
N (%)		
All treated patients	14.3__1.1.1.1	
Not related to Humira	14.3__1.1.6.1	
Non-episodic dosing population	14.3__1.1.1.3	
Episodic dosing population	14.3__1.1.1.5	
All treated patients including previous feeder studies	14.3__1.1.2.1	
Re-enrollment population, after re-enrollment period	14.3__1.1.3.1	
Per 100 PYs		
All treated patients	14.3__1.1.1.2	
Not related to Humira	14.3__1.1.6.2	
Non-episodic dosing population	14.3__1.1.1.4	
Episodic dosing population	14.3__1.1.1.6	
All treated patients including previous feeder studies	14.3__1.1.2.2	
Re-enrollment population, after re-enrollment period	14.3__1.1.3.2	
Overview of observational AEs		16.2__7.1.1 16.2__7.2.2 16.2__7.2.3 16.2__7.2.4 16.2__7.2.6
N (%)		

Description	Table	Appendix
All treated patients	14.3__1.1.4.1	
All treated patients excluding patients with unsigned casebooks	14.3__1.1.4.3	
Per 100 PYs		
All treated patients	14.3__1.1.4.2	
All treated patients excluding patients with unsigned casebooks	14.3__1.1.4.4	
Overview of retrospectively collected AEs		16.2__7.1.1 16.2__7.2.2 16.2__7.2.3 16.2__7.2.4 16.2__7.2.6
N (%)		
Re-enrollment population	14.3__1.1.5.1	
Per 100 PYs		
Re-enrollment population	14.3__1.1.5.2	
Shift tables of subjects with TEAEs		
N (%)		
Subjects with 1 treatment interruption (episodic dosing population)	14.3__1.1.1.7	
Subjects with 2 treatment interruptions (episodic dosing population)	14.3__1.1.1.8	
TEAEs by primary MedDRA system organ class (SOC) and preferred term (PT)		16.2__7.1.1 16.2__7.2.2 16.2__7.2.3 16.2__7.2.4 16.2__7.2.6
N (%)		
All treated patients	14.3__1.2.1	
By maximum severity	14.3__1.3	
By maximum relationship	14.3__1.4	
At least possibly related	14.3__1.5	
After re-enrollment	14.3__1.6	
Per 100 PYs		
All treated patients	14.3__1.2.2	

Description	Table	Appendix
Retrospectively collected TEAEs by primary MedDRA SOC and PT (re-enrollment population)		16.2__7.1.1 16.2__7.2.2 16.2__7.2.3 16.2__7.2.4 16.2__7.2.6
N (%)	14.3__1.2.3.1	
Per 100 PYs	14.3__1.2.3.2	
By-patient listing of retro AEs (re-enrollment population)	14.3__2.43.1.2	
By-patient listing of other than retro AEs on event coding form (all treated patients)	14.3__2.43.1.4	
Summary of diagnosis during HCP process (HCP population)	14.3__1.2.4	16.2__4.6
By-patient listing of diagnosis during HCP process (HCP population)	14.3__2.43.1.3	
Hematology determinations		16.2__8.1.1 16.2__8.1.2 16.2__8.1.3 16.2__8.1.4 16.2__8.1.5 16.2__8.1.6
Chemistry determinations		16.2__8.2.1 16.2__8.2.2 16.2__8.2.3 16.2__8.2.4 16.2__8.2.5 16.2__8.2.6 16.2__8.2.7 16.2__8.2.8 16.2__8.2.9
Urinalysis determinations		16.2__8.3.1 16.2__8.3.2 16.2__8.3.3

In accordance with the protocol, SAEs, predefined AEs of special interest (Table 3), and AEs leading to Humira discontinuation were the only events specified to be captured in this registry; however, if other AEs were reported, they were also analyzed. The locations of associated data outputs are referenced above. MedDRA Version 18.1 was used.

The analysis sets used for safety are described in Section 9.9.2. Three types of AE analyses have been performed:

- Observational AEs were summarized from the first dose of Humira in the registry through the last contact.
- Registry treatment-emergent SAEs and AEs of special interest were summarized from the day of the first dose of Humira in the registry until 70 days after the last non-missing Humira injection date in the registry.
- All treatment-emergent SAEs and AEs of special interest were summarized from the day of the first recorded dose of Humira until 70 days after the last non-missing Humira injection date. For patients who previously participated in an Abbott- or AbbVie-sponsored CD study, the analysis included data occurring from the first recorded dose of Humira in the previous study (but data from the possible gap between the previous study and registry start was excluded). For patients previously treated with commercial Humira, analysis began from the first dose of Humira in the registry.

For patients who re-enrolled in the registry, safety data based on a retrospective review of their records collected in the retro period (i.e., the period between registry discontinuation and re-enrollment) were analyzed separately.

Additionally, the following sub-type of registry TEAEs was tabulated separately:

- Re-enrollment registry treatment-emergent SAEs and AEs of special interest are summarized from the day of the start of the re-enrollment period until 70 days after the last non-missing Humira injection date in the registry.

Full narratives (Annex 5) are provided for:

- All deaths regardless of treatment emergence and causality assessment
- All malignancies regardless of treatment emergence and causality assessment
- All active TB regardless of treatment emergence and causality assessment
- All treatment-emergent serious infections regardless of causality assessment

- All AEs leading to discontinuation from Humira regardless of treatment emergence and causality assessment

In addition, condensed narratives are presented for all SAEs via additional columns in the in-text by patient listing, when SAEs are presented.

10.6.2.1 Overview of Adverse Events by Subgroups

10.6.2.1.1 Geographic Location

Description	Table
Overview of TEAEs	
By geographic location (all treated patients)	
N (%)	
US	14.3__2.42.7.1.1
North America other than US	14.3__2.42.7.1.2
Eastern Europe	14.3__2.42.7.1.3
Other European countries	14.3__2.42.7.1.4
Other countries	14.3__2.42.7.1.5
Per 100 PYs	
US	14.3__2.42.7.2.1
North America other than US	14.3__2.42.7.2.2
Eastern Europe	14.3__2.42.7.2.3
Other European countries	14.3__2.42.7.2.4
Other countries	14.3__2.42.7.2.5
By geographic location (after re-enrollment, re-enrollment population)	
N (%)	
US	14.3__2.42.7.3.1
North America other than US	14.3__2.42.7.3.2
Eastern Europe	14.3__2.42.7.3.3
Other European countries	14.3__2.42.7.3.4
Other countries	14.3__2.42.7.3.5
Per 100 PYs	
US	14.3__2.42.7.4.1
North America other than US	14.3__2.42.7.4.2

Description	Table
Eastern Europe	14.3__2.42.7.4.3
Other European countries	14.3__2.42.7.4.4
Other countries	14.3__2.42.7.4.5

10.6.2.1.2 Type of Practice

Description	Table
Overview of TEAEs	
By type of practice (all treated patients)	
N (%)	
Clinical research center	14.3__2.42.8.1.1
Group practice	14.3__2.42.8.1.2
Hospital practice	14.3__2.42.8.1.3
Private practice	14.3__2.42.8.1.4
University practice	14.3__2.42.8.1.5
Per 100 PYs	
Clinical research center	14.3__2.42.8.2.1
Group practice	14.3__2.42.8.2.2
Hospital practice	14.3__2.42.8.2.3
Private practice	14.3__2.42.8.2.4
University practice	14.3__2.42.8.2.5
By type of practice (after re-enrollment, re-enrollment population)	
N (%)	
Clinical research center	14.3__2.42.8.3.1
Group practice	14.3__2.42.8.3.2
Hospital practice	14.3__2.42.8.3.3
Private practice	14.3__2.42.8.3.4
University practice	14.3__2.42.8.3.5
Per 100 PYs	
Clinical research center	14.3__2.42.8.4.1
Group practice	14.3__2.42.8.4.2
Hospital practice	14.3__2.42.8.4.3
Private practice	14.3__2.42.8.4.4

Description	Table
University practice	14.3__2.42.8.4.5

10.6.2.1.3 Prior Use of Another Anti-TNF/Biologic

Description	Table
Overview of TEAEs	
By prior use of another anti-TNF/biologic (all treated patients)	
N (%)	
Yes	14.3__2.42.9.1.1
No	14.3__2.42.9.1.2
Per 100 PYs	
Yes	14.3__2.42.9.2.1
No	14.3__2.42.9.2.2
By prior use of another anti-TNF/biologic (after re-enrollment, re-enrollment population)	
N (%)	
Yes	14.3__2.42.9.3.1
No	14.3__2.42.9.3.2
Per 100 PYs	
Yes	14.3__2.42.9.4.1
No	14.3__2.42.9.4.2

10.6.2.1.4 Prior Use of Humira

Description	Table
Overview of TEAEs	
By prior use of Humira (all treated patients)	
N (%)	
Yes	14.3__2.42.10.1.1
No	14.3__2.42.10.1.2
Per 100 PYs	
Yes	14.3__2.42.10.2.1
No	14.3__2.42.10.2.2
By prior use of Humira (after re-enrollment, re-enrollment population)	

Description	Table
N (%)	
Yes	14.3__2.42.10.3.1
No	14.3__2.42.10.3.2
Per 100 PYs	
Yes	14.3__2.42.10.4.1
No	14.3__2.42.10.4.2

10.6.2.1.5 Tobacco Use

Description	Table
Overview of TEAEs	
By tobacco use (all treated patients)	
N (%)	
User	14.3__2.42.11.1.1
Ex-user	14.3__2.42.11.1.2
Non-user	14.3__2.42.11.1.3
Unknown	14.3__2.42.11.1.4
Per 100 PYs	
User	14.3__2.42.11.2.1
Ex-user	14.3__2.42.11.2.2
Non-user	14.3__2.42.11.2.3
Unknown	14.3__2.42.11.2.4
By tobacco use (after re-enrollment, re-enrollment population)	
N (%)	
User	14.3__2.42.11.3.1
Ex-user	14.3__2.42.11.3.2
Non-user	14.3__2.42.11.3.3
Unknown	14.3__2.42.11.3.4
Per 100 PYs	
User	14.3__2.42.11.4.1
Ex-user	14.3__2.42.11.4.2
Non-user	14.3__2.42.11.4.3
Unknown	14.3__2.42.11.4.4

10.6.2.1.6 Alcohol Use

Description	Table
Overview of TEAEs	
By alcohol use (all treated patients)	
N (%)	
Drinker	14.3__2.42.12.1.1
Ex-drinker	14.3__2.42.12.1.2
Non-drinker	14.3__2.42.12.1.3
Unknown	14.3__2.42.12.1.4
Per 100 PYs	
Drinker	14.3__2.42.12.2.1
Ex-drinker	14.3__2.42.12.2.2
Non-drinker	14.3__2.42.12.2.3
Unknown	14.3__2.42.12.2.4
By alcohol use (after re-enrollment, re-enrollment population)	
N (%)	
Drinker	14.3__2.42.12.3.1
Ex-drinker	14.3__2.42.12.3.2
Non-drinker	14.3__2.42.12.3.3
Unknown	14.3__2.42.12.3.4
Per 100 PYs	
Drinker	14.3__2.42.12.4.1
Ex-drinker	14.3__2.42.12.4.2
Non-drinker	14.3__2.42.12.4.3
Unknown	14.3__2.42.12.4.4

10.6.2.1.7 Prior Complications Due to CD

Description	Table
Overview of TEAEs	
By prior complications due to CD (all treated patients)	
N (%)	
Yes	14.3__2.42.13.1.1
No	14.3__2.42.13.1.2

Description	Table
Per 100 PYs	
Yes	14.3__2.42.13.2.1
No	14.3__2.42.13.2.2
By prior complications due to CD (after re-enrollment, re-enrollment population)	
N (%)	
Yes	14.3__2.42.13.3.1
No	14.3__2.42.13.3.2
Per 100 PYs	
Yes	14.3__2.42.13.4.1
No	14.3__2.42.13.4.2

10.6.2.1.8 CD Duration

Description	Table
Overview of TEAEs	
By CD duration (all treated patients)	
N (%)	
< 2 years	14.3__2.42.14.1.1
2 to < 5 years	14.3__2.42.14.1.2
5 to < 10 years	14.3__2.42.14.1.3
≥ 10 years	14.3__2.42.14.1.4
Per 100 PYs	
< 2 years	14.3__2.42.14.2.1
2 to < 5 years	14.3__2.42.14.2.2
5 to < 10 years	14.3__2.42.14.2.3
≥ 10 years	14.3__2.42.14.2.4
By CD duration (after re-enrollment, re-enrollment population)	
N (%)	
< 2 years	14.3__2.42.14.3.1
2 to < 5 years	14.3__2.42.14.3.2
5 to < 10 years	14.3__2.42.14.3.3
≥ 10 years	14.3__2.42.14.3.4

Description	Table
Per 100 PYs	
< 2 years	14.3__2.42.14.4.1
2 to < 5 years	14.3__2.42.14.4.2
5 to < 10 years	14.3__2.42.14.4.3
≥ 10 years	14.3__2.42.14.4.4

10.6.2.1.9 Age Group

Description	Table
Overview of TEAEs	
By age group (all treated patients)	
N (%)	
< 40 years	14.3__2.42.15.1.1
40 to < 60 years	14.3__2.42.15.1.2
≥ 60 years	14.3__2.42.15.1.3
Per 100 PYs	
< 40 years	14.3__2.42.15.2.1
40 to < 60 years	14.3__2.42.15.2.2
≥ 60 years	14.3__2.42.15.2.3
By age group (after re-enrollment, re-enrollment population)	
N (%)	
< 40 years	14.3__2.42.15.3.1
40 to < 60 years	14.3__2.42.15.3.2
≥ 60 years	14.3__2.42.15.3.3
Per 100 PYs	
< 40 years	14.3__2.42.15.4.1
40 to < 60 years	14.3__2.42.15.4.2
≥ 60 years	14.3__2.42.15.4.3

10.6.2.1.10 For Patients who Discontinued the Study or Study Drug

Description	Table
Overview of TEAEs	
For patients who discontinued the study or study drug (all treated patients)	
N (%)	14.3__2.42.16.1
Per 100 PYs	14.3__2.42.16.2

10.6.3 Deaths

Description	Table	Appendix
TEAEs leading to death by primary MedDRA SOC, PT		16.2__7.3.1 16.2__7.3.2
N (%)		
All treated patients		
Registry treatment-emergent	14.3__2.40.1	
All treatment-emergent	14.3__2.40.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.40.3	
By-patient listing of TEAEs leading to death		
All treated patients	14.3__2.43.41.1	
All treated patients during previous feeder studies	14.3__2.43.41.2	
By-patient listing of TEAEs leading to death after re-enrollment (re-enrollment population)	14.3__2.43.41.3	
Standard mortality ratios – treatment-emergent deaths (Humira exposure including previous feeder studies, all treated patients)	14.3__2.41	
By-patient listing of deaths (all patients)	14.3__2.43.42	
By-patient listing of TEAEs leading to death classified as not related to Humira by the Investigator (all treated patients)	14.3__2.43.43.1	
By-patient listing of TE serious infections leading to death (all treated patients)	14.3__2.43.43.2	

At the request of the EMA, the registry protocol was amended (Amendment 2; Section 9.1) 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. The process included a revised consent form that allowed information gathering under

these circumstances. Active registry participants were re-consented; patients who then discontinued the registry could be contacted by the site for this information.

Re-consented patients who were then lost to follow-up had their information submitted by a third-party vendor (ProClinica) to the National Death Index (NDI) database, which has statistics and details on the deaths of US citizens. In addition, sites outside the US were instructed to search national/regional vital registries when available and allowed by local regulations.

A number of patients discontinued the registry prior to the implementation of Amendment 2, therefore, they could not give permission for vital status data collection. In an effort to include the data from these patients, AbbVie contacted the sites' Ethics Committees and requested approval to collect their vital status information. However, AbbVie did not request that the sites pursue information on (1) patients who had withdrawn consent because they did not want to be contacted or (2) patients who were lost to follow-up because the site had no information on how to reach them.

If the sites' Ethics Committee granted approval, the site personnel contacted discontinued patients, obtained consent, collected vital status data and entered it into the registry database. The results of vital status collection and the NDI search are included below.

Six reports of death were obtained in addition to those reported as treatment emergent (N = 43) and non-treatment-emergent (N = 20) during the registry. Of these 6 reports, 5 were provided by the site by follow up on patients who were lost to follow up or discontinued from the registry and 1 was a potential match to a death report in the NDI database. Details on these 6 deaths are shown in Table 10 below.

Table 10. Deaths Identified by Vital Status Requests

Patient Number	Source of Information/Date	Details
PPD	Vital Status eCRF	Kidney Disease/Crohn's Disease
	Vital Status eCRF	Disease of the Heart
	Vital Status eCRF	Sepsis/Malignant Neoplasm
	Vital Status eCRF	Disease of the Heart
	Vital Status eCRF	Nephritis, Nephritic Syndrome and Nephrosis Secondary: Heart Disease
Not provided[a]	National Death Index	Sequelae of stroke not specified as haemorrhage or infarction

a. Subject identifying information was not shared by NDI.

Thus, the total number of deaths reported in the registry population is 69 (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.

The registry treatment-emergent deaths in 43 patients (0.9%; 0.3 deaths/100 PYs of registry exposure) are summarized in Table 11.

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.

Full narratives are provided for all deaths regardless of treatment emergence and causality assessment in Annex 5.

Treatment-emergent standardized mortality ratios (SMRs) were calculated using the country-specific mortality rates through 2006. For details on the SMR calculation see SAP Version 2.0, Annex 4. 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).

Table 11. Number and Percentage of Patients with Registry TEAEs Leading to Death (All Treated Patients)

MedDRA 18.1 SOC PT	Any Humira N = 5025 n (%)
Any AE leading to death[a]	43 (0.9)
Blood and lymphatic system disorders	
Disseminated intravascular coagulation	1 (< 0.1)
Lymphadenopathy [b]	1 (< 0.1)
Cardiac disorders	
Cardiac arrest	2 (< 0.1)
Myocardial infarction	1 (< 0.1)
Gastrointestinal disorders	
CD	1 (< 0.1)
Functional gastrointestinal disorder	1 (< 0.1)
Ileal stenosis	1 (< 0.1)
General disorders and administration site conditions	
Death	2 (< 0.1)
Multi-organ failure	3 (< 0.1)
Sudden death	2 (< 0.1)
Infections and infestations	
Appendicitis perforated	1 (< 0.1)
Bronchopulmonary aspergillosis	1 (< 0.1)
Endocarditis	1 (< 0.1)
Hepatitis C	1 (< 0.1)
Pneumonia	1 (< 0.1)
Sepsis	1 (< 0.1)
Septic shock	2 (< 0.1)
Staphylococcal sepsis	1 (< 0.1)
Urosepsis	1 (< 0.1)

Table 11. Number and Percentage of Patients with Registry TEAEs Leading to Death (All Treated Patients) (Continued)

MedDRA 18.1 SOC PT	Any Humira N = 5025 n (%)
Injury, poisoning and procedural complications	
Femoral neck fracture	1 (< 0.1)
Pneumothorax traumatic	1 (< 0.1)
Road traffic accident	1 (< 0.1)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	
Adenocarcinoma gastric	1 (< 0.1)
Adenocarcinoma of colon	1 (< 0.1)
Anal cancer	1 (< 0.1)
Breast cancer metastatic	1 (< 0.1)
Cholangiocarcinoma	1 (< 0.1)
Colon cancer metastatic[b]	1 (< 0.1)
Gallbladder cancer metastatic	1 (< 0.1)
Lung adenocarcinoma metastatic	1 (< 0.1)
Lung cancer metastatic	2 (< 0.1)
Lung neoplasm malignant	1 (< 0.1)
Metastases to bone	1 (< 0.1)
Metastatic lymphoma	1 (< 0.1)
Esophageal adenocarcinoma	1 (< 0.1)
Nervous system disorders	
Hemorrhagic stroke	2 (< 0.1)
Ischemic stroke	1 (< 0.1)
Psychiatric disorders	
Completed suicide	1 (< 0.1)
Renal and urinary disorders	
Renal failure	1 (< 0.1)

Table 11. Number and Percentage of Patients with Registry TEAEs Leading to Death (All Treated Patients) (Continued)

MedDRA 18.1 SOC PT	Any Humira N = 5025 n (%)
Respiratory, thoracic and mediastinal disorders	
Pulmonary embolism	1 (< 0.1)
Pneumonia aspiration	1 (< 0.1)
Pulmonary edema	1 (< 0.1)
Vascular disorders	
Arteriosclerosis	1 (< 0.1)
Hypertension	1 (< 0.1)

a. Not included in this table are an additional 20 patients who had non-treatment emergent AEs leading to death (i.e., AE date of onset was > 70 days after the last dose of Humira) so that the total number of deaths in the registry is 63.

b. Lymphadenopathy and colon cancer metastatic were reported as TEAEs leading to death in the same patient.

Note: A registry TEAE is defined as any AE with an onset date on or after the first dose of Humira in the registry and up to 70 days after the last dose of Humira in the registry.

Cross reference: Table 14.3__2.40.1

10.6.4 Other SAEs

Description	Table	Appendix
All treatment-emergent SAEs by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1 16.2__7.2.2 16.2__7.2.3 16.2__7.2.4 16.2__7.2.6 16.2__7.5 16.2__7.6
N (%)		
All treated patients	14.3__2.2.1	
N (%) of patients with at least possibly drug-related registry treatment-emergent SAEs by primary MedDRA SOC and PT (all treated patients)	14.3__2.1.3	
Treatment-emergent at least possibly drug-related SAEs Per 100 PYs by primary MedDRA SOC and PT (all treated patients)	14.3__2.1.4	
N (%) of patients with registry treatment-emergent SAEs by primary MedDRA SOC, PT, and maximum relationship to Humira (all treated patients)	14.3__2.1.1	
Registry treatment-emergent SAEs Per 100 PYs by primary MedDRA SOC, PT, and maximum relationship to Humira (all treated patients)	14.3__2.1.2	
N (%) of patients with at least possibly drug-related all treatment-emergent SAEs by primary MedDRA SOC and PT (all treated patients)	14.3__2.2.2	
By-patient listing of pretreatment SAEs (all patients)	14.3__2.43.1.1	
By-patient listing of treatment-emergent SAEs		
All treated patients	14.3__2.43.2.1	
All treated patients during previous feeder studies	14.3__2.43.2.2	
Re-enrollment population after re-enrollment	14.3__2.43.2.3	

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 registry treatment-emergent SAEs (reported by ≥ 1% of patients) are summarized in Table 12.

Table 12. Number and Percentage of Patients with Registry Treatment-Emergent SAEs in ≥ 1% of Patients and Corresponding E/100 PYs (All Treated Patients)

	Any Humira	
MedDRA 18.1 PT	**N = 5025 n (%)**	**PYs = 16680.4 Events (E/100 PY)**
Any SAE	1853 (36.9)	4129 (24.8)
CD	606 (12.1)	606 (3.6)
Small intestinal obstruction	131 (2.6)	131 (0.8)
Intestinal obstruction	127 (2.5)	127 (0.8)
Anal abscess	119 (2.4)	119 (0.7)
Ileal stenosis	94 (1.9)	94 (0.6)
Anal fistula	84 (1.7)	84 (0.5)
Sub ileus	68 (1.4)	68 (0.4)
Abdominal pain	61 (1.2)	61 (0.4)

Note: A registry TEAE is defined as any AE with an onset date on or after the first dose of Humira in the registry and up to 70 days after the last dose of Humira in the registry.

Cross reference: Table 14.3__2.1.1, Table 14.3__2.1.2

Most registry treatment-emergent SAEs were assessed by the physician as not related or probably not related to Humira; however, 8.4% (422/5025) of patients had at least 1 registry treatment-emergent SAE that was considered possibly or probably related to Humira by the physician. The most frequently reported registry treatment-emergent SAEs considered by the treating physician to be at least possibly related to Humira and reported in ≥ 0.1% of patients are summarized in Table 13. A summary of all treatment-emergent SAEs at least possibly related to Humira including events that occurred in preceding studies is presented in Table 14.3__2.2.2.

Table 13. Number and Percentage of Patients with Registry Treatment-Emergent SAEs Assessed by the Physician as Possibly Related or Probably Related to Humira in ≥ 0.1% of Patients and Corresponding E/100 PYs (All Treated Patients)

	Any Humira	
MedDRA 18.1 PT	**N = 5025 n (%)**	**PYs = 16680.4 Events (E/100 PY)**
Any at least possibly drug-related SAE	422 (8.4)	627 (3.8)
CD	45 (0.9)	49 (0.3)
Pneumonia	26 (0.5)	26 (0.2)
Anal abscess	20 (0.4)	24 (0.1)
Intestinal obstruction	15 (0.3)	16 (< 0.1)
Small intestinal obstruction	13 (0.3)	17 (0.1)
Sepsis	11 (0.2)	11 (< 0.1)
Cellulitis	11 (0.2)	11 (< 0.1)
Herpes zoster	8 (0.2)	8 (< 0.1)
Pyrexia	9 (0.2)	9 (< 0.1)
Abdominal abscess	9 (0.2)	10 (< 0.1)
Anal fistula	7 (0.1)	7 (< 0.1)
Ileal stenosis	7 (0.1)	7 (< 0.1)
Intestinal stenosis	6 (0.1)	6 (< 0.1)
Urinary tract infection	7 (0.1)	7 (< 0.1)
Lupus-like syndrome	6 (0.1)	6 (< 0.1)
Subcutaneous abscess	6 (0.1)	7 (< 0.1)
Staphylococcal infection	6 (0.1)	6 (< 0.1)
Sub ileus	6 (0.1)	6 (< 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 and up to 70 days after the last dose of Humira in the registry.

Cross reference: Table 14.3__2.1.3, Table 14.3__2.1.4

10.6.5 Adverse Events of Special Interest

In this section, AEs of special interest have been analyzed in a manner consistent with the presentation of safety in other documents for Humira (i.e., Humira IB Edition 22.1). The AEs of special interest categories include infections, malignancies, immune reactions,

demyelinating disorders, cardiovascular events, and others. A detailed list of all AEs of special interest included in this registry is provided in Table 3.

No patients reported HSTCL, glioblastoma, Merkel Cell carcinoma, Waldenström's macroglobulinemia, reactivation of hepatitis B, PML, or Humira administration-related medication errors. SJS (Section 10.6.5.3.3) and RPLS (Section 10.6.5.13.2) were reported in 1 patient each as non-treatment-emergent events. These events are described in more detail in the sections that follow.

10.6.5.1 Infections

10.6.5.1.1 Nonserious and Serious Infections

Description	Table	Appendix
Treatment-emergent infection by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.4.1	
All treatment-emergent	14.3__2.4.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.4.3	
Treatment-emergent serious infection by primary MedDRA SOC, PT, and maximum relationship to Humira		
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.5.1	
All treatment-emergent	14.3__2.5.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.5.3	
Registry treatment-emergent serious infection by concomitant IMM use (all treated patients)		
N (%)	14.3__2.42.1.1	
Per 100 PYs	14.3__2.42.1.2	
Registry treatment-emergent infection by concomitant IMM use by primary MedDRA SOC and PT (all treated patients)		
N (%)	14.3__2.42.1.3	
Per 100 PYs	14.3__2.42.1.4	
Registry treatment-emergent infection by concomitant immunosuppressant and corticosteroid use at Baseline by primary MedDRA SOC and PT (all treated patients: CD duration < 2 years)		
N (%)	14.3__2.42.17.1	
Per 100 PYs	14.3__2.42.17.2	

Description	Table	Appendix
Registry treatment-emergent infection by concomitant immunosuppressant and corticosteroid use at Baseline by primary MedDRA SOC and PT (all treated patients: CD duration 2 to < 5 years)		
N (%)	14.3__2.42.17.3	
Per 100 PYs	14.3__2.42.17.4	
Registry treatment-emergent infection by concomitant immunosuppressant and corticosteroid use at Baseline by primary MedDRA SOC and PT (all treated patients: CD duration 5 to < 10 years)		
N (%)	14.3__2.42.17.5	
Per 100 PYs	14.3__2.42.17.6	
Registry treatment-emergent infection by concomitant immunosuppressant and corticosteroid use at Baseline by primary MedDRA SOC and PT (all treated patients: CD duration ≤ 10 years)		
N (%)	14.3__2.42.17.7	
Per 100 PYs	14.3__2.42.17.8	
Registry treatment-emergent serious infection by concomitant IMM and corticosteroid use by primary MedDRA SOC and PT (all treated patients)		
N (%)	14.3__2.42.2.1	
Per 100 PYs	14.3__2.42.2.2	
Registry treatment-emergent infection by concomitant IMM and corticosteroid use by primary MedDRA SOC and PT (all treated patients)		
N (%)	14.3__2.42.2.3	
Per 100 PYs	14.3__2.42.2.4	
By-patient listing of treatment-emergent infection		
All treated patients	14.3__2.43.4.1	
All treated patients during previous feeder studies	14.3__2.43.4.2	
By-patient listing of treatment-emergent infection after re-enrollment (re-enrollment population)	14.3__2.43.4.3	
By-patient listing of treatment-emergent serious infection		
All treated patients	14.3__2.43.5.1	
All treated patients during previous feeder studies	14.3__2.43.5.2	
By-patient listing of treatment-emergent serious infection after re-enrollment (re-enrollment population)	14.3__2.43.5.3	

Description	Table	Appendix
By-patient listing of treatment-emergent serious infection classified as not related to Humira by Investigator (all treated patients)	14.3__2.43.43.3	
By-patient listing of treatment-emergent serious infection leading to death (all treated patients)	14.3__2.43.43.4	

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 Humira by the physician. The only serious infection reported by ≥ 1% of patients was anal abscess (2.4%; Table 12); all other serious infections were reported by 0.9% or fewer patients. Ten patients had registry treatment-emergent serious infections that resulted in death (Table 14). With the exception of Patient PPD , 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.

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Serious Infections in Patients Receiving Concomitant Corticosteroids and/or IMM Therapy at Baseline

Serious infections were reported by a statistically significantly (at an α level of 5%) higher proportion of the following subsets of patients: patients receiving Humira with IMM (6-MP, AZA, or MTX) compared to Humira without IMM, with or without corticosteroids (12.6% versus 10.2%, $P = 0.010$). Compared to patients receiving Humira without IMM and without corticosteroids (9.6% of whom experienced serious infections), the following groups had statistically significantly higher proportions of patients experiencing serious infections: patients receiving Humira with IMM and without corticosteroids (12.7% versus 9.6%, $P = 0.007$) and patients receiving Humira with IMM and with corticosteroids (12.6% versus 9.6%, $P = 0.039$). In patients receiving Humira without IMM, there was a higher proportion of serious infections reported by patients receiving Humira with corticosteroids compared to Humira without corticosteroids (11.7% versus 9.6%, $P = 0.090$); however, this difference was not statistically significant. The registry exposure-adjusted rate of serious infections was higher in all 3 subsets of patients receiving combination IMM and/or corticosteroid therapy with Humira (6.4, 4.8, and 5.0 E/100 PYs, respectively), versus 4.2 E/100 PYs for Humira without corticosteroids and without IMM (Table 15).

Table 15. Summary of Patients with Registry Treatment-Emergent Serious Infections by Concomitant IMM and Corticosteroid Use at Baseline (All Treated Patients)

	Humira Without IMM	Humira With IMM	Humira Without IMM		Humira With IMM	
	With or Without Corticosteroids (Reference Group)	With or Without Corticosteroids	Without Corticosteroids (Reference Group)	With Corticosteroids	Without Corticosteroids	With Corticosteroids
	N = 3227 PYs = 10421.6	N = 1798 PYs = 6258.8	N = 2345 PYs = 7968.3	N = 882 PYs = 2453.3	N = 1217 PYs = 4338.1	N = 581 PYs = 1920.7
P values (versus respective reference group, fisher's exact test)		0.010		0.090	0.007	0.039
Number (%) of patients with serious infections	329 (10.2)	227 (12.6)	226 (9.6)	103 (11.7)	154 (12.7)	73 (12.6)
Number of serious infection events (E/100 PYs)	489 (4.7)	303 (4.8)	332 (4.2)	157 (6.4)	207 (4.8)	96 (5.0)

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.

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

Cross reference: Table 14.3__2.42.1.1, Table 14.3__2.42.1.2, Table 14.3__2.42.2.1, Table 14.3__2.42.2.2

10.6.5.1.2 Opportunistic Infections (Excluding Oral Candidiasis and TB)

Description	Table	Appendix
Treatment-emergent opportunistic infection excluding oral candidiasis and TB by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.10.1	
All treatment-emergent	14.3__2.10.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.10.3	
By-patient listing of treatment-emergent opportunistic infection excluding oral candidiasis and TB		
All treated patients	14.3__2.43.10.1	
All treated patients during previous feeder studies	14.3__2.43.10.2	
By-patient listing of treatment-emergent opportunistic infection excluding oral candidiasis and TB after re-enrollment (re-enrollment population)	14.3__2.43.10.3	

Nineteen patients (0.4%) experienced 21 registry treatment-emergent opportunistic infections (excluding oral candidiasis and TB), for a registry exposure-adjusted event rate of 0.1 E/100 PYs. Fifteen patients had events that the physician considered at least possibly related to Humira. Thirteen patients had serious opportunistic infections, and 5 of these patients discontinued Humira due to their event (Table 16). The possible contribution of prior anti-TNF use or current IMM or steroid use is shown as well as additional risk factors for infection of diabetes and smoking.

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10.6.5.1.3 Oral Candidiasis

Description	Table	Appendix
Treatment-emergent oral candidiasis by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.39.1	
All treatment-emergent	14.3__2.39.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.39.3	
By-patient listing of treatment-emergent oral candidiasis		
All treated patients	14.3__2.43.40.1	
All treated patients during previous feeder studies	14.3__2.43.40.2	
By-patient listing of treatment-emergent oral candidiasis after re-enrollment (re-enrollment population)	14.3__2.43.40.3	

Nine patients (0.2%) experienced registry treatment-emergent oral candidiasis. The registry exposure-adjusted event rate was < 0.1 E/100 PYs. Six patients had events that the physician considered possibly or probably related to Humira. One event of oral candidiasis was serious (Patient PPD and led to interruption of Humira.

10.6.5.1.4 TB

Description	Table	Appendix
Treatment-emergent TB by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.38.1.1	
All treatment-emergent	14.3__2.38.1.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.38.1.3	

Description	Table	Appendix
Treatment-emergent active TB by primary MedDRA SOC, PT, and maximum relationship to Humira		
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.38.2.1	
All treatment-emergent	14.3__2.38.2.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.38.2.3	
Treatment-emergent latent TB by primary MedDRA SOC, PT, and maximum relationship to Humira		
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.38.3.1	
All treatment-emergent	14.3__2.38.3.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.38.3.3	
By-patient listing of treatment-emergent TB		
All treated patients	14.3__2.43.39.1.1	
All treated patients during previous feeder studies	14.3__2.43.39.1.2	
By-patient listing of treatment-emergent TB after re-enrollment (re-enrollment population)	14.3__2.43.39.1.3	
By-patient listing of treatment-emergent active TB		
All treated patients	14.3__2.43.39.2.1	
All treated patients during previous feeder studies	14.3__2.43.39.2.2	
By-patient listing of treatment-emergent active TB after re-enrollment (re-enrollment population)	14.3__2.43.39.2.3	
By-patient listing of treatment-emergent latent TB		
All treated patients	14.3__2.43.39.3.1	
All treated patients during previous feeder studies	14.3__2.43.39.3.2	
By-patient listing of treatment-emergent latent TB after re-enrollment (re-enrollment population)	14.3__2.43.39.3.3	

Seventeen patients (0.3%) reported registry treatment-emergent TB (active or latent). The registry exposure adjusted event rate was 0.1 E/100 PYs. Of the 17 patients with TB, 10 patients had active TB (0.2%; < 0.1 E/100PYs) and 7 had latent TB (0.1%; < 0.1 E/100 PYs).

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. Eight of the 10 patients received TB treatment; no treatment information was available for the remaining 2 patients. 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).

A listing of patients with serious registry treatment-emergent TB, which only occurred in patients with active TB, is provided in Table 17. Full narratives are provided in Annex 5 for all active TB regardless of treatment emergence and causality assessment.


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10.6.5.1.5 Legionella Infection

Description	Table	Appendix
Treatment-emergent legionella infection by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.23.1	
All treatment-emergent	14.3__2.23.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.23.3	
Listing of treatment-emergent legionella infection		
All treated patients	14.3__2.43.23.1	
All treated patients during previous feeder studies	14.3__2.43.23.2	
By-patient listing of treatment-emergent legionella infection after re-enrollment (re-enrollment population)	14.3__2.43.23.3	

One patient (< 0.1%) reported a registry treatment-emergent Legionella infection (< 0.1 E/100 PYs). This 1 event, with a description of Legionella chest infection, was reported as an SAE on Day 1532, resolved on Day 1688, resulted in interruption of study drug, and was considered by the physician to be moderate in severity and possibly related to Humira.

10.6.5.1.6 Parasitic Infections

Description	Table	Appendix
Treatment-emergent parasitic infection by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.11.1	
All treatment-emergent	14.3__2.11.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.11.3	
Listing of treatment-emergent parasitic infection		
All treated patients	14.3__2.43.11.1	
All treated patients during previous feeder studies	14.3__2.43.11.2	
By-patient listing of treatment-emergent parasitic infection after re-enrollment (re-enrollment population)	14.3__2.43.11.3	

Four patients (< 0.1%) experienced a registry treatment-emergent parasitic infection (< 0.1 E/100 PYs). Patient PPD experienced pythium insidiosum of the right eye on Day 1340. The event lasted for 117 days, was severe, serious, and considered possibly related to Humira by the physician. Humira was discontinued as a result of the event. Patient PPD experienced a positive Giardia test on Day 1851. The event lasted for 20 days, was nonserious, mild, and considered probably not related to Humira by the physician. Patient PPD experienced cryptosporidiosis on Day 2180. The event lasted for 11 days, was mild, nonserious, and considered possibly related to Humira by the physician. Patient PPD experienced enterobiasis on Day 1897. The event lasted for 29 days, was mild, nonserious, and considered probably not related to Humira by the physician.

10.6.5.1.7 Diverticulitis

Description	Table	Appendix
Treatment-emergent diverticulitis by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.19.1	
All treatment-emergent	14.3__2.19.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.19.3	
Listing of treatment-emergent diverticulitis		
All treated patients	14.3__2.43.19.1	
All treated patients during previous feeder studies	14.3__2.43.19.2	
By-patient listing of treatment-emergent diverticulitis after re-enrollment (re-enrollment population)	14.3__2.43.19.3	

Six patients (0.1%) reported 7 registry treatment-emergent events of diverticulitis. The registry exposure-adjusted event rate was < 0.1 E/100 PYs. Events in 5 patients were reported as SAEs, 1 event resulted in discontinuation of Humira, and 1 event was considered by the physician to be possibly related to Humira (Table 18).

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10.6.5.2 Malignancy

Description	Table	Appendix
Treatment-emergent malignancy by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1 16.2__7.3.2 16.2__7.7
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.6.1.1	
All treatment-emergent	14.3__2.6.1.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.6.1.3	
Treatment-emergent pediatric/young adult malignancy by primary MedDRA SOC, PT, and maximum relationship to Humira (patients with age ≤ 30 years at the first registry dose among all treated patients)		
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.6.1.4	
All treatment-emergent	14.3__2.6.1.5	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.6.1.6	
Registry treatment-emergent malignancy by concomitant immunosuppressant use at Baseline by primary MedDRA SOC and PT (all treated patients)		
N (%)	14.3__2.42.3.1	
Per 100 PYs	14.3__2.42.3.2	
Registry treatment-emergent malignancy by concomitant immunosuppressant and corticosteroid use at Baseline by primary MedDRA SOC and PT (all treated patients)		
N (%)	14.3__2.42.4.1	
Per 100 PYs	14.3__2.42.4.2	
By-patient listing of treatment-emergent malignancy		
All treated patients	14.3__2.43.6.1.1	
All treated patients during previous feeder studies	14.3__2.43.6.1.2	
By-patient listing of treatment-emergent malignancy after re-enrollment (re-enrollment population)	14.3__2.43.6.1.3	
By-patient listing of treatment-emergent malignancy classified as not related to Humira by Investigator (all treated patients)	14.3__2.43.43.2	

Description	Table	Appendix
By-patient listing of treatment-emergent pediatric/young adult malignancy		
Patients with age ≤ 30 years at the first registry dose among all treated patients	14.3__2.43.6.5.1	
Patients with age ≤ 30 years at the first registry dose among all treated patients during previous feeder studies	14.3__2.43.6.5.2	

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 the physician considered at least possibly related to Humira. Full narratives are provided in Annex 5 for all malignancies regardless of treatment emergence and causality assessment.

10.6.5.2.1 Lymphoma

Description	Table	Appendix
Treatment-emergent lymphoma by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1 16.2__7.3.2 16.2__7.7
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.6.2.1	
All treatment-emergent	14.3__2.6.2.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.6.2.3	
Registry treatment-emergent lymphoma by concomitant immunosuppressant use at Baseline by primary MedDRA SOC and PT (all treated patients)		
N (%)	14.3__2.42.5.1	
Per 100 PYs	14.3__2.42.5.2	
Registry treatment-emergent lymphoma by concomitant immunosuppressant and corticosteroid use at Baseline by primary MedDRA SOC and PT (all treated patients)		
N (%)	14.3__2.42.6.1	
Per 100 PYs	14.3__2.42.6.2	
By-patient listing of treatment-emergent lymphoma		
All treated patients	14.3__2.43.6.2.1	
All treated patients during previous feeder studies	14.3__2.43.6.2.2	
By-patient listing of treatment-emergent lymphoma after re-enrollment (re-enrollment population)	14.3__2.43.6.2.3	

Ten patients (0.2%) reported 10 registry treatment-emergent lymphomas, for an overall lymphoma event rate of 0.060 E/100 PYs. These 10 lymphomas include 1 event from Patient 415003, whose event was not retrieved as lymphoma since it was not part of the Lowest Level MedDRA query for lymphoma within the MedDRA version 18.1 used for this report. All events of lymphoma were considered serious; all patients discontinued Humira due to lymphoma, including Patient PPD who died of metastatic cancer lymphoma. The events were considered possibly or probably related to Humira by the physician for 6 of the 10 patients. The events that the physician considered probably not

related or not related to Humira may have been due to limited exposure to study drug prior to onset of the event, the presence of the event prior to initiation of study drug, or to the presence of confounding factors (i.e., concurrent use of IMMs, and family history of malignancy). Prior or current IMM use is a known factor in the risk of lymphoma. Nine of these 10 patients had prior use of IMM and 3 of the 9 were taking IMM at registry enrollment and at the time of the lymphoma diagnosis. A listing of all patients with registry treatment-emergent lymphoma is provided in Table 19. Full narratives are provided in Annex 5 for all malignancies regardless of treatment emergence and causality assessment.

The upper bound of the 1-sided 95% CI for the registry-exposure adjusted rate of lymphoma in the registry (0.060 E/100 PYs) was 0.102 E/100 PYs and fell below 0.168 E/100 PYs (double the expected rate of 0.084 E/100 PYs). This confirms that the registry reached the goal of ruling out a doubling of lymphoma risk in patients with CD treated with Humira. The lymphoma rate adjusted for the overall Humira exposure, including registry and prior clinical trial exposure of 17,764.7 PYs, was 0.056 E/100 PYs.

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Table 19. Listing of Patients with Registry Treatment-Emergent Lymphoma (All Treated Patients) (Continued)

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 PPD 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.

Cross reference: Table 14.3__2.43.6.2.1, Table 14.3__2.43.6.4.1

10.6.5.2.2 Hepatosplenic T-Cell Lymphoma (HSTCL)

Description	Table	Appendix
Treatment-emergent HSTCL by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1 16.2__7.3.2 16.2__7.7
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.7.1	
All treatment-emergent	14.3__2.7.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.7.3	
By-patient listing of treatment-emergent HSTCL		
All treated patients	14.3__2.43.7.1	
All treated patients during previous feeder studies	14.3__2.43.7.2	
By-patient listing of treatment-emergent HSTCL after re-enrollment (re-enrollment population)	14.3__2.43.7.3	

There were no reported cases of HSTCL.

10.6.5.2.3 Non-Melanoma Skin Cancer (NMSC)

Description	Table	Appendix
Treatment-emergent NMSC by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1 16.2__7.3.2 16.2__7.7
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.6.3.1	
All treatment-emergent	14.3__2.6.3.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.6.3.3	
By-patient listing of treatment-emergent NMSC		
All treated patients	14.3__2.43.6.3.1	
All treated patients during previous feeder studies	14.3__2.43.6.3.2	
By-patient listing of treatment-emergent NMSC after re-enrollment (re-enrollment population)	14.3__2.43.6.3.3	

Thirty-six (0.7%) patients had 49 registry treatment-emergent events of 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 Humira discontinuation. Nineteen of the 36 patients had events of NMSC that the physician considered possibly or probably related to Humira. The events that were considered 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 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). A listing of all patients with registry treatment-emergent NMSC is provided in Table 20. Full narratives are provided in Annex 5 for all malignancies regardless of treatment emergence and causality assessment.

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10.6.5.2.4 Melanoma

Description	Table	Appendix
Treatment-emergent melanoma by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1 16.2__7.3.2 16.2__7.7
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.9.1	
All treatment-emergent	14.3__2.9.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.9.3	
By-patient listing of treatment-emergent melanoma		
All treated patients	14.3__2.43.9.1	
All treated patients during previous feeder studies	14.3__2.43.9.2	
By-patient listing of treatment-emergent melanoma after re-enrollment (re-enrollment population)	14.3__2.43.9.3	

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 Humira due to melanoma. A listing of patients with registry treatment-emergent melanoma is provided in Table 21. Full narratives are provided in Annex 5 for all malignancies regardless of treatment emergence and causality assessment.

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10.6.5.2.5 Leukemia

Description	Table	Appendix
Treatment-emergent leukemia by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1 16.2__7.3.2 16.2__7.7
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.8.1	
All treatment-emergent	14.3__2.8.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.8.3	
By-patient listing of treatment-emergent leukemia		
All treated patients	14.3__2.43.8.1	
All treated patients during previous feeder studies	14.3__2.43.8.2	
By-patient listing of treatment-emergent leukemia after re-enrollment (re-enrollment population)	14.3__2.43.8.3	

Among the category of leukemia AEs, 3 patients (< 0.1%) had 3 registry treatment-emergent events of acute myeloid leukemia, for an overall leukemia rate of < 0.1 E/100 PYs. All events of leukemia were considered serious and resulted in discontinuation of Humira (Table 22). All 3 were considered possibly related to Humira by the physician. Full narratives are provided in Annex 5 for all malignancies regardless of treatment emergence and causality assessment.


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10.6.5.2.6 Other Malignancies, Excluding Lymphoma, HSTCL, Leukemia, NMSC, and Melanoma

Description	Table	Appendix
Treatment-emergent malignancy other than lymphoma, HSTCL, leukemia, NMSC, or melanoma by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1 16.2__7.3.2 16.2__7.7
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.6.4.1	
All treatment-emergent	14.3__2.6.4.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.6.4.3	
By-patient listing of malignancy other than lymphoma, HSTCL, leukemia, NMSC, or melanoma		
All treated patients	14.3__2.43.6.4.1	
All treated patients during previous feeder studies	14.3__2.43.6.4.2	
By-patient listing of treatment-emergent malignancy other than lymphoma, HSTCL, leukemia, NMSC, or melanoma after re-enrollment (re-enrollment population)	14.3__2.43.6.4.3	

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.

Twenty-two patients had registry treatment-emergent malignancies other than lymphoma, HSTCL, leukemia, NMSC, and melanoma that the physician considered possibly or

probably related to Humira (Table 23). Full narratives are provided in Annex 5 for all malignancies regardless of treatment emergence and causality assessment.

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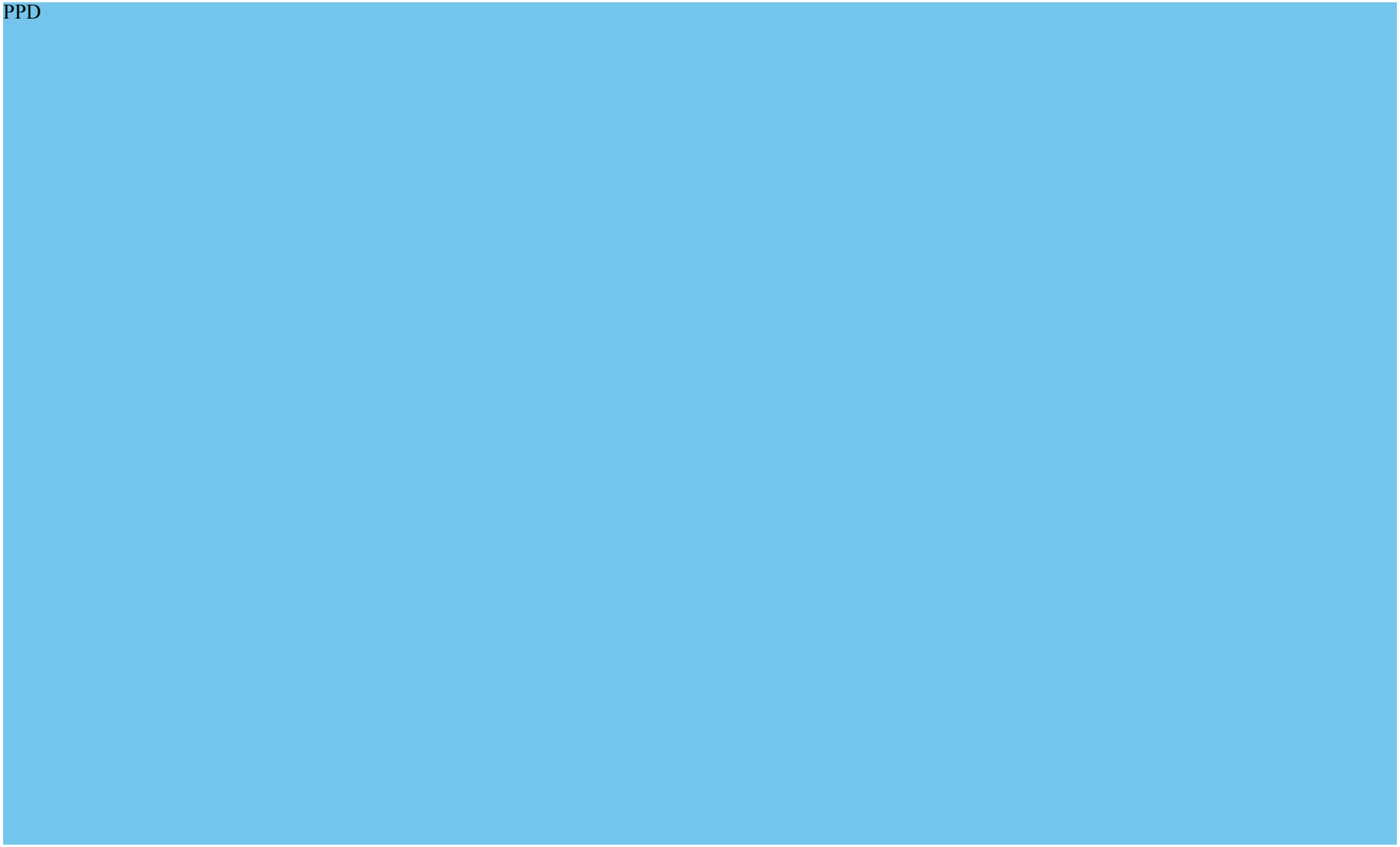

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10.6.5.3 Immune Reactions

10.6.5.3.1 Lupus-Like Reactions and SLE

Description	Table	Appendix
Treatment-emergent lupus-like reactions and SLE by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.13.1	
All treatment-emergent	14.3__2.13.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.13.3	
By-patient listing of treatment-emergent lupus-like reactions and SLE		
All treated patients	14.3__2.43.13.1	
All treated patients during previous feeder studies	14.3__2.43.13.2	
By-patient listing of treatment-emergent lupus-like reactions and SLE after re-enrollment (re-enrollment population)	14.3__2.43.13.3	

Twenty-nine patients (0.6%) had a registry treatment-emergent events 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.[2,4] Lupus-like syndrome is an event usually related to medication use, including Humira, 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 Humira due to the event, and 26 patients had events that the physician considered at least possibly related to Humira (Table 24).

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10.6.5.3.2 Allergic Reaction Including Angioedema/Anaphylaxis

Description	Table	Appendix
Treatment-emergent allergic reactions by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.14.1	
All treatment-emergent	14.3__2.14.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.14.3	
By-patient listing of treatment-emergent allergic reactions		
All treated patients	14.3__2.43.14.1	
All treated patients during previous feeder studies	14.3__2.43.14.2	
By-patient listing of treatment-emergent allergic reactions after re-enrollment (re-enrollment population)	14.3__2.43.14.3	

Thirty patients (0.6%) had 37 registry treatment-emergent allergic reactions for a total registry exposure-adjusted event rate of 0.2 E/100 PYs; 6 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 (Table 25); all serious events resolved. Two of the 9 patients had 2 allergic reactions. Two patients with serious events had events that the physician considered at least possibly related to Humira. Two patients had serious allergic reaction-related events leading to discontinuation of Humira.

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10.6.5.3.3 Stevens-Johnson Syndrome (SJS)

Description	Table	Appendix
Treatment-emergent SJS by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.29.1	
All treatment-emergent	14.3__2.29.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.29.3	
By-patient listing of treatment-emergent SJS		
All treated patients	14.3__2.43.29.1	
All treated patients during previous feeder studies	14.3__2.43.29.2	
By-patient listing of treatment-emergent SJS after re-enrollment (re-enrollment population)	14.3__2.43.29.3	

No patient reported registry treatment-emergent SJS. One patient (< 0.1%) had a non-treatment-emergent AE of SJS (Table 14.3__1.1.4.1). This patient developed SJS 87 days after the last dose of Humira, which was discontinued due to lack of efficacy. The event was attributed by the PI to pantoprazole at the time of diagnosis.

10.6.5.3.4 Vasculitis

Description	Table	Appendix
Treatment-emergent vasculitis by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.17.1.1	
All treatment-emergent	14.3__2.17.1.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.17.1.3	
Treatment-emergent cutaneous vasculitis by primary MedDRA SOC, PT, and maximum relationship to Humira		
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.17.2.1	
All treatment-emergent	14.3__2.17.2.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.17.2.3	
Treatment-emergent non-cutaneous vasculitis by primary MedDRA SOC, PT, and maximum relationship to Humira		
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.17.3.1	
All treatment-emergent	14.3__2.17.3.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.17.3.3	
By-patient listing of treatment-emergent vasculitis		
All treated patients	14.3__2.43.17.1.1	
All treated patients during previous feeder studies	14.3__2.43.17.1.2	
By-patient listing of treatment-emergent vasculitis after re-enrollment (re-enrollment population)	14.3__2.43.17.1.3	
By-patient listing of treatment-emergent cutaneous vasculitis		
All treated patients	14.3__2.43.17.2.1	
All treated patients during previous feeder studies	14.3__2.43.17.2.2	
By-patient listing of treatment-emergent cutaneous vasculitis after re-enrollment (re-enrollment population)	14.3__2.43.17.2.3	
By-patient listing of treatment-emergent non-cutaneous vasculitis		
All treated patients	14.3__2.43.17.3.1	

Description	Table	Appendix
All treated patients during previous feeder studies	14.3__2.43.17.3.2	
By-patient listing of treatment-emergent non-cutaneous vasculitis after re-enrollment (re-enrollment population)	14.3__2.43.17.3.3	

Eleven patients (0.2%) had 12 registry treatment-emergent events compatible with vasculitis, for an overall registry exposure-adjusted event rate of < 0.1 E/100 PYs. Four patients had vasculitis-related registry TEAEs that were non-cutaneous and 7 patients had vasculitis-related registry TEAEs that were cutaneous. Of the 11 patients, 7 patients had events that the physician considered at least possibly related to Humira. Five patients had events that were serious, and 6 patients had events that led to discontinuation of Humira. A listing is presented by patient in Table 26.

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10.6.5.3.5 Sarcoidosis

Description	Table	Appendix
Treatment-emergent sarcoidosis by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.34.1.1	
All treatment-emergent	14.3__2.34.2.1	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.34.3.1	
By-patient listing of treatment-emergent sarcoidosis		
All treated patients	14.3__2.43.34.1	
All treated patients during previous feeder studies	14.3__2.43.34.2	
By-patient listing of treatment-emergent sarcoidosis after re-enrollment (re-enrollment population)	14.3__2.43.34.3	

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.

Patient 613019, a 44-year-old white male, had a serious event of pulmonary sarcoidosis on Day 808 that resolved on Day 814. The physician assessed the event as moderate in severity and probably not related to Humira. Humira was not discontinued in this patient.

10.6.5.4 Demyelinating Disorders

Description	Table	Appendix
Treatment-emergent demyelinating disorder by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.15.1	
All treatment-emergent	14.3__2.15.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.15.3	
By-patient listing of treatment-emergent demyelinating disorder		
All treated patients	14.3__2.43.15.1	
All treated patients during previous feeder studies	14.3__2.43.15.2	
By-patient listing of treatment-emergent demyelinating disorder after re-enrollment (re-enrollment population)	14.3__2.43.15.3	

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 patients had serious events and 6 patients had events that the physician considered at least possibly related to Humira. Six events resulted in discontinuation of Humira (Table 27). There were no events of Guillain-Barré syndrome reported in the registry. One event of optic neuritis was reported in the registry.

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10.6.5.5 Interstitial Lung Disease (ILD)

Description	Table	Appendix
Treatment-emergent ILD by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.32.1	
All treatment-emergent	14.3__2.32.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.32.3	
By-patient listing of treatment-emergent ILD		
All treated patients	14.3__2.43.32.1	
All treated patients during previous feeder studies	14.3__2.43.32.2	
By-patient listing of treatment-emergent ILD after re-enrollment (re-enrollment population)	14.3__2.43.32.3	

Four patients (< 0.1%) reported 4 registry treatment-emergent events related to ILD, for a registry exposure-adjusted event rate of < 0.1 E/100 PYs. Two events were reported as SAEs. Three patients had events that the physician considered at least possibly related to Humira (Table 28).

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10.6.5.6 Cardiovascular Events

10.6.5.6.1 Myocardial Infarction (MI)

Description	Table	Appendix
Treatment-emergent MI by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.24.1	
All treatment-emergent	14.3__2.24.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.24.3	
By-patient listing of treatment-emergent MI		
All treated patients	14.3__2.43.24.1	
All treated patients during previous feeder studies	14.3__2.43.24.2	
By-patient listing of treatment-emergent MI after re-enrollment (re-enrollment population)	14.3__2.43.24.3	

Thirteen patients (0.3%) had 14 registry TEAEs of MI, for an overall registry exposure-adjusted event rate of < 0.1 E/100 PYs. All events were SAEs, 6 patients had events that led to discontinuation of Humira, 2 patients had events that the physician considered possibly related to Humira, and 1 patient (Patient PPD) had a fatal event (Table 29). Risk factors for MI such as a history of smoking, coronary artery disease, or hypertension are included in the table.


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10.6.5.6.2 Cerebrovascular Accident (CVA)

Description	Table	Appendix
Treatment-emergent CVA by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.25.1	
All treatment-emergent	14.3__2.25.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.25.3	
By-patient listing of treatment-emergent CVA		
All treated patients	14.3__2.43.25.1	
All treated patients during previous feeder studies	14.3__2.43.25.2	
By-patient listing of treatment-emergent CVA after re-enrollment (re-enrollment population)	14.3__2.43.25.3	

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 that the physician considered possibly or probably related to Humira (Table 30). Risk factors for CVA such as smoking, hypertension and coronary artery disease are included in the table.

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10.6.5.6.3 Congestive Heart Failure (CHF)

Description	Table	Appendix
Treatment-emergent CHF by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.31.1	
All treatment-emergent	14.3__2.31.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.31.3	
By-patient listing of treatment-emergent CHF		
All treated patients	14.3__2.43.31.1	
All treated patients during previous feeder studies	14.3__2.43.31.2	
By-patient listing of treatment-emergent CHF after re-enrollment (re-enrollment population)	14.3__2.43.31.3	

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 (Table 31). Two events were serious and the physician considered them not related to Humira; 1 of these events, pulmonary edema, was fatal. The third event was nonserious, considered by the physician as possibly related to Humira, and did not lead to discontinuation from Humira.

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10.6.5.7 Gastrointestinal Events

10.6.5.7.1 Intestinal Perforation

Description	Table	Appendix
Treatment-emergent intestinal perforation by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.20.1	
All treatment-emergent	14.3__2.20.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.20.3	
By-patient listing of treatment-emergent intestinal perforation		
All treated patients	14.3__2.43.20.1	
All treated patients during previous feeder studies	14.3__2.43.20.2	
By-patient listing of treatment-emergent intestinal perforation after re-enrollment (re-enrollment population)	14.3__2.43.20.3	

Twenty-seven patients (0.5%) had 27 registry treatment-emergent events compatible with intestinal perforation, with an exposure adjusted event rate of 0.2 E/100 PYs. Four of these events occurred in the setting of an endoscopy and 3 of these events occurred during a surgical procedure. Nine patients (0.2%) had an intestinal perforation: 6 (0.1%) had large intestine perforation; 5 (< 0.1%) had small intestinal perforation, 2 (< 0.1%) each had diverticular perforation and jejunal perforation, and 1 (< 0.1%) each had ileal perforation, rectal perforation, and appendicitis perforated. All but 1 event 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 Humira (Table 32).

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10.6.5.7.2 Intestinal Stricture

Description	Table	Appendix
Treatment-emergent intestinal stricture by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.21.1	
All treatment-emergent	14.3__2.21.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.21.3	
By-patient listing of treatment-emergent intestinal stricture		
All treated patients	14.3__2.43.21.1	
All treated patients during previous feeder studies	14.3__2.43.21.2	
By-patient listing of treatment-emergent intestinal stricture after re-enrollment (re-enrollment population)	14.3__2.43.21.3	

A total of 475 patients (9.5%) had a registry treatment-emergent event compatible with intestinal stricture (Table 33). 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 Humira.

Table 33. Number (%) of Patients with Registry Treatment-Emergent Intestinal Stricture (All Treated Patients)

MedDRA 18.1 PT	Any Humira 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.

Cross reference: Table 14.3__2.21.1

10.6.5.7.3 Pancreatitis

Description	Table	Appendix
Treatment-emergent pancreatitis by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.33.1	
All treatment-emergent	14.3__2.33.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.33.3	
By-patient listing of treatment-emergent pancreatitis		
All treated patients	14.3__2.43.33.1	
All treated patients during previous feeder studies	14.3__2.43.33.2	
By-patient listing of treatment-emergent pancreatitis after re-enrollment (re-enrollment population)	14.3__2.43.33.3	

Seventeen patients (0.3%) had 21 registry treatment-emergent pancreatitis events, reflecting a registry exposure-adjusted event rate of 0.1 E/100 PYs. None of the events could be attributed to alcoholism or alcohol abuse by patient history, although the majority of cases included exposure to a variety of medications that may have contributed to the risk of pancreatitis including azathioprine. Six of the 21 events were due to or suspected to be due to the presence of gallstones. All events were reported as SAEs, and there were events in 3 patients that the physician considered possibly related to Humira (Table 34).

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10.6.5.8 Hematologic Disorders (Including Pancytopenia)

Description	Table	Appendix
Treatment-emergent hematologic disorders including pancytopenia by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.16.1	
All treatment-emergent	14.3__2.16.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.16.3	
By-patient listing of treatment-emergent hematologic disorders including pancytopenia		
All treated patients	14.3__2.43.16.1	
All treated patients during previous feeder studies	14.3__2.43.16.2	
By-patient listing of treatment-emergent hematologic disorders including pancytopenia after re-enrollment (re-enrollment population)	14.3__2.43.16.3	

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 (1.1%) had anemia, 3 (< 0.1%) patients each had leukopenia and thrombocytopenia, 2 (< 0.1) patients each had neutropenia and neutropenic sepsis, and 1 (< 0.1%) each had febrile bone marrow aplasia (severe, not related) and pancytopenia (moderate, probably not related). Events in 4 patients were considered by the physician to be at least possibly related to Humira (Table 35).

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10.6.5.9 Hepatic Events

10.6.5.9.1 Liver Failure and Other Liver Events

Description	Table	Appendix
Treatment-emergent liver failure and other liver event by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.22.1	
All treatment-emergent	14.3__2.22.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.22.3	
By-patient listing of treatment-emergent liver failure and other liver event		
All treated patients	14.3__2.43.18.1	
All treated patients during previous feeder studies	14.3__2.43.18.2	
By-patient listing of treatment-emergent liver failure and other liver event after re-enrollment (re-enrollment population)	14.3__2.43.18.3	
Treatment-emergent autoimmune hepatitis by primary MedDRA SOC, PT, and maximum relationship to Humira		
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.34.1.2	
All treatment-emergent	14.3__2.34.2.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.34.3.2	
By-patient listing of treatment-emergent autoimmune hepatitis		
All treated patients	14.3__2.43.35.1	
All treated patients during previous feeder studies	14.3__2.43.35.2	
By-patient listing of treatment-emergent autoimmune hepatitis after re-enrollment (re-enrollment population)	14.3__2.43.35.3	

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. Relevant risk factors included primary sclerosing cholangitis, fatty liver, opioid/drug abuse, chronic hepatic cytolysis, and/or cholelithiasis. One patient had a benign liver cyst and another patient had a diagnosis of nodular regenerative hyperplasia. Nine events were serious,

2 led to discontinuation of Humira, 1 was considered by the physician to be possibly related to Humira, and 3 were considered by the physician to be probably related to Humira (Table 36).

One patient reported registry treatment-emergent autoimmune hepatitis.

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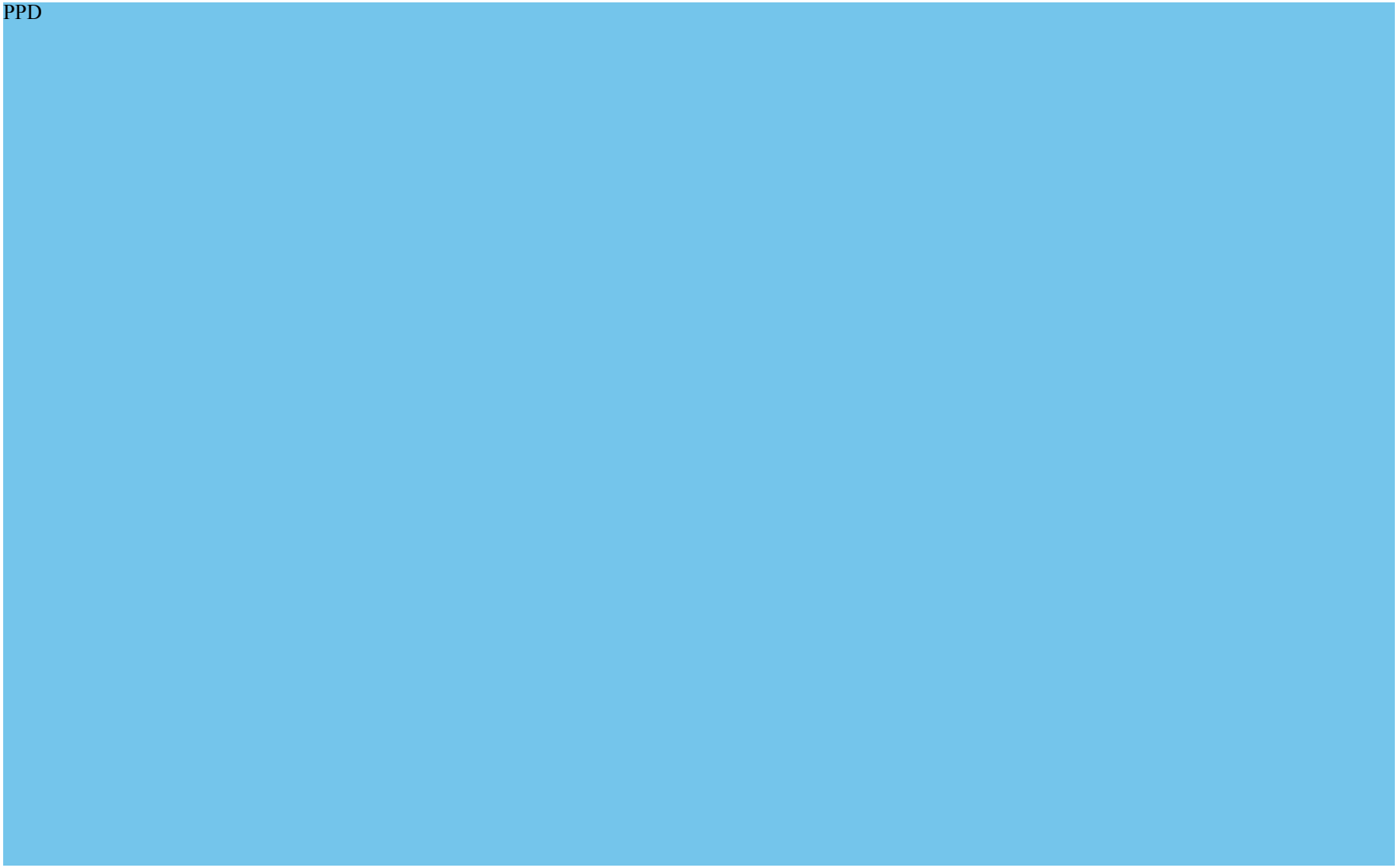

10.6.5.9.2 Reactivation of Hepatitis B

Description	Table	Appendix
Treatment-emergent reactivation of hepatitis B by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.18.1	
All treatment-emergent	14.3__2.18.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.18.3	
By-patient listing of treatment-emergent reactivation of hepatitis B		
All treated patients	14.3__2.43.22.1	
All treated patients during previous feeder studies	14.3__2.43.22.2	
By-patient listing of treatment-emergent reactivation of hepatitis B after re-enrollment (re-enrollment population)	14.3__2.43.22.3	

No patient reported a registry treatment-emergent reactivation of hepatitis B.

10.6.5.10 Injection Site Reactions

Description	Table	Appendix
Treatment-emergent injection site reactions by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.12.1	
All treatment-emergent	14.3__2.12.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.12.3	
By-patient listing of treatment-emergent injection site reactions		
All treated patients	14.3__2.43.12.1	
All treated patients during previous feeder studies	14.3__2.43.12.2	
By-patient listing of treatment-emergent injection site reactions after re-enrollment (re-enrollment population)	14.3__2.43.12.3	

Twelve patients (0.2%) had 22 registry treatment-emergent injection site reactions, for a registry exposure-adjusted event rate of 0.1 E/100 PYs. All events were nonserious and

the physician considered them at least possibly related to Humira. Events of injection site reaction led to discontinuation of Humira in 2 patients; events of injection site rash, injection site induration, and injection site inflammation led to discontinuation of Humira in 1 patient each.

10.6.5.11 Skin and Subcutaneous Tissue Disorders

10.6.5.11.1 Erythema Multiforme

Description	Table	Appendix
Treatment-emergent erythema multiforme by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.30.1	
All treatment-emergent	14.3__2.30.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.30.3	
By-patient listing of treatment-emergent erythema multiforme		
All treated patients	14.3__2.43.30.1	
All treated patients during previous feeder studies	14.3__2.43.30.2	
By-patient listing of treatment-emergent erythema multiforme after re-enrollment (re-enrollment population)	14.3__2.43.30.3	

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

Patient PPD, a 39-year-old white female, had a nonserious event of erythema multiforme on Day 453 that resolved on Day 473. The patient was treated with betamethasone; hydrocortisone was an ongoing treatment at the onset of the event. The physician assessed the event as moderate in severity and probably not related to Humira. Humira was not discontinued in this patient.

10.6.5.11.2 Worsening/New Onset of Ps

Description	Table	Appendix
Treatment-emergent worsening/new onset of Ps by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.27.1	
All treatment-emergent	14.3__2.27.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.27.3	
By-patient listing of treatment-emergent worsening/new onset of Ps		
All treated patients	14.3__2.43.27.1	
All treated patients including during feeder studies	14.3__2.43.27.2	
By-patient listing of treatment-emergent worsening/new onset of Ps after re-enrollment (re-enrollment population)	14.3__2.43.27.3	

Ninety-two patients (1.8%) had 96 registry treatment-emergent events compatible with worsening or new onset of Ps, for an overall registry exposure-adjusted event rate of 0.6 E/100 PYs. Twenty of the 92 patients had a history of Ps. Sixty nine patients (1.4%) had events of Ps, 19 (0.4%) had dermatitis psoriasiform, 3 (< 0.1%) had pustular Ps, and 2 (< 0.1%) had guttate Ps. Eight patients reported registry treatment-emergent serious events and 36 patients had events that led to discontinuation of Humira.
Eighty-six patients had events that the physician considered possibly or probably related to Humira. A listing by patient of registry treatment-emergent serious events compatible with worsening or new onset of Ps is presented in Table 37.

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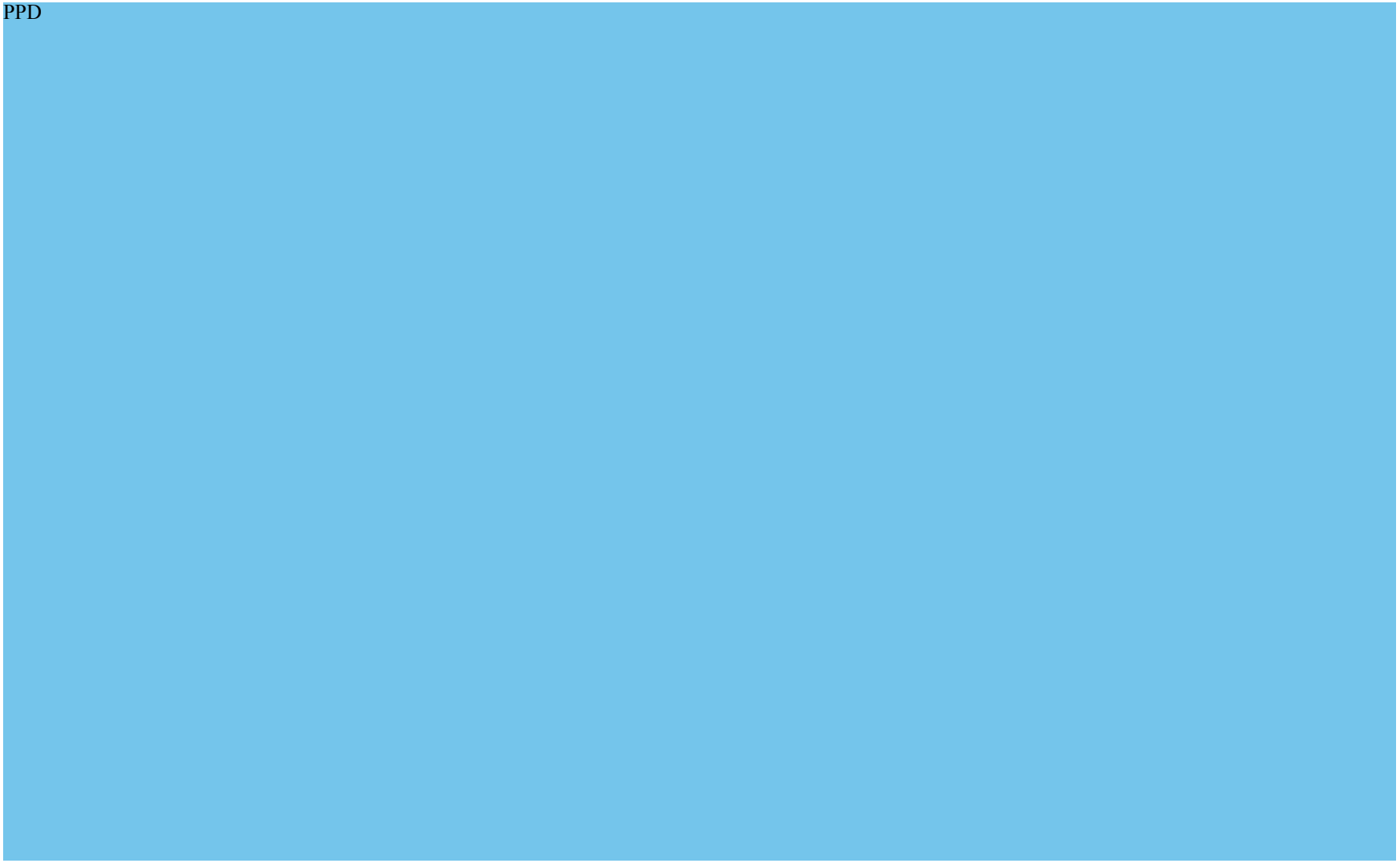
10.6.5.12 Pulmonary Embolism

Description	Table	Appendix
Treatment-emergent pulmonary embolism by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.26.1	
All treatment-emergent	14.3__2.26.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.26.3	
By-patient listing of treatment-emergent pulmonary embolism		
All treated patients	14.3__2.43.26.1	
All treated patients during previous feeder studies	14.3__2.43.26.2	
By-patient listing of treatment-emergent pulmonary embolism after re-enrollment (re-enrollment population)	14.3__2.43.26.3	

Thirteen patients (0.3%) reported 13 registry TEAEs of pulmonary embolism, for a registry exposure-adjusted event rate of < 0.1 E/100 PYs (Table 38). One event was fatal. One event was considered by the physician to be possibly related to Humira; all events were reported as serious. Two patients discontinued Humira due to the event.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10.6.5.13 Nervous System Disorders

10.6.5.13.1 ALS

Description	Table	Appendix
Treatment-emergent ALS by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.37.1	
All treatment-emergent	14.3__2.37.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.37.3	
By-patient listing of treatment-emergent ALS		
All treated patients	14.3__2.43.38.1	
All treated patients during previous feeder studies	14.3__2.43.38.2	
By-patient listing of treatment-emergent ALS after re-enrollment (re-enrollment population)	14.3__2.43.38.3	

One registry TEAE of ALS was captured by the Lowest Level MedDRA Query search criteria. However, this patient reported an event of primary lateral sclerosis, a rare upper motor neuron disease of voluntary muscles, which is a non-clinically definitive event of ALS; therefore, clinically this patient did not have a diagnosis of ALS. The physician considered the event as probably not related to Humira and the patient did not discontinue Humira treatment after the event.

10.6.5.13.2 RPLS

Description	Table	Appendix
Treatment-emergent RPLS by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.36.1	
All treatment-emergent	14.3__2.36.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.36.3	
By-patient listing of treatment-emergent RPLS		
All treated patients	14.3__2.43.37.1	
All treated patients during previous feeder studies	14.3__2.43.37.2	
By-patient listing of treatment-emergent RPLS after re-enrollment (re-enrollment population)	14.3__2.43.37.3	

No patient reported a registry treatment-emergent event of RPLS. One patient (< 0.1%) had an observational AE of RPLS (Table 14.3__1.1.4.1). This patient (Patient PPD) was reported as having experienced RPLS approximately 3 months after discontinuing Humira therapy. The patient's symptoms of headache, altered consciousness, hypertension, hypercalcemia, seizure, and acute renal failure followed a complication of surgery performed 3 months prior for CD progression. The surgical complication resulted in bilateral hydronephrosis from ureteral obstruction and lead to acute renal failure. The patient was successfully treated with dialysis and was recovering in a rehabilitation center at last contact.

10.6.5.13.3 PML

Description	Table	Appendix
Treatment-emergent PML by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.35.1	
All treatment-emergent	14.3__2.35.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.35.3	
By-patient listing of treatment-emergent PML		
All treated patients	14.3__2.43.36.1	
All treated patients during previous feeder studies	14.3__2.43.36.2	
By-patient listing of treatment-emergent PML after re-enrollment (re-enrollment population)	14.3__2.43.36.3	

No patient reported registry treatment-emergent PML.

10.6.5.14 Humira Administration-Related Medication Errors

Description	Table	Appendix
Treatment-emergent Humira administration-related medication error by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.28.1	
All treatment-emergent	14.3__2.28.2	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.28.3	
By-patient listing of treatment-emergent Humira administration-related medication error		
All treated patients	14.3__2.43.28.1	
All treated patients during previous feeder studies	14.3__2.43.28.2	
By-patient listing of treatment-emergent Humira administration-related medication error after re-enrollment (re-enrollment population)	14.3__2.43.28.3	

No patients reported registry treatment-emergent Humira administration-related medication errors.

10.6.5.15 AEs Leading to Discontinuation

10.6.5.15.1 Adverse Events Leading to Premature Humira Discontinuation

Description	Table	Appendix
TEAEs leading to discontinuation of Humira by primary MedDRA SOC, PT, and maximum relationship to Humira		16.2__7.1.1
N (%) (all treated patients)		
Registry treatment-emergent	14.3__2.3.1	
All treatment-emergent	14.3__2.3.3	
Per 100 PYs (all treated patients)		
Registry treatment-emergent	14.3__2.3.2	
By-patient listing of TEAEs leading to discontinuation of Humira		
All treated patients	14.3__2.43.3.1	
All treated patients including during feeder studies	14.3__2.43.3.2	
Re-enrollment population after re-enrollment	14.3__2.43.3.3	

A total of 596 patients (11.9%) experienced registry TEAEs leading to permanent discontinuation of Humira, with 132 events of CD as the most common event overall. A summary of events experienced by 2 or more patients is provided in Table 39. The registry exposure-adjusted event rate for AEs leading to Humira discontinuation was 4.6 E/100 PYs. A total of 296 patients had registry TEAEs leading to discontinuation that the physician considered possibly or probably related to Humira (Table 14.3__2.3.1). Full narratives are provided for all AEs leading to discontinuation of Humira regardless of treatment emergence and causality assessment (Annex 5).

Table 39. Number and Percentage of Patients with Registry TEAEs Leading to Discontinuation of Humira in 2 or More Patients by Primary MedDRA SOC and PT (All Treated Patients)

MedDRA 18.1 SOC PT	Any Humira N = 5025 n (%)
Any AE	596 (11.9)
Blood and lymphatic system disorders	
Anemia	2 (< 0.1)
Lymphadenitis	2 (< 0.1)
Cardiac disorders	
Tachycardia	2 (< 0.1)
Eye disorders	
Vision blurred	2 (< 0.1)
Gastrointestinal disorders	
CD	132 (2.6)
Intestinal obstruction	16 (0.3)
Ileal stenosis	16 (0.3)
Small intestinal obstruction	13 (0.3)
Sub ileus	9 (0.2)
Large intestinal stenosis	9 (0.2)
Anal fistula	8 (0.2)
Colitis	6 (0.1)
Enterocolonic fistula	5 (< 0.1)
Abdominal pain	4 (< 0.1)
Diarrhea	4 (< 0.1)
Anal stenosis	3 (< 0.1)
Enterocutaneous fistula	3 (< 0.1)
Intestinal fistula	3 (< 0.1)
Large intestinal obstruction	3 (< 0.1)
Small intestinal stenosis	3 (< 0.1)
Intestinal stenosis	3 (< 0.1)
Fistula of small intestine	3 (< 0.1)
Large intestine perforation	2 (< 0.1)

Table 39. Number and Percentage of Patients with Registry TEAEs Leading to Discontinuation of Humira in 2 or More Patients by Primary MedDRA SOC and PT (All Treated Patients) (Continued)

MedDRA 18.1 SOC PT	Any Humira N = 5025 n (%)
Gastrointestinal disorders (continued)	
Abdominal adhesions	2 (< 0.1)
Anorectal disorder	2 (< 0.1)
Anorectal stenosis	2 (< 0.1)
Colitis ulcerative	2 (< 0.1)
Colon dysplasia	2 (< 0.1)
Gastrointestinal inflammation	2 (< 0.1)
Rectal hemorrhage	2 (< 0.1)
Enteritis	2 (< 0.1)
Intestinal perforation	2 (< 0.1)
Vomiting	2 (< 0.1)
General disorders and administration site conditions	
Pyrexia	7 (0.1)
Drug intolerance	2 (< 0.1)
Injection site reaction	2 (< 0.1)
Infections and infestations	
Abdominal abscess	8 (0.2)
Anal abscess	12 (0.2)
Pneumonia	10 (0.2)
Folliculitis	6 (0.1)
Septic shock	3 (< 0.1)
TB	3 (< 0.1)
Urinary tract infection	3 (< 0.1)
Upper respiratory tract infection	3 (< 0.1)
Cellulitis	3 (< 0.1)
Herpes zoster	3 (< 0.1)
Pulmonary tuberculosis	3 (< 0.1)
Abscess intestinal	2 (<0.1)

Table 39. Number and Percentage of Patients with Registry TEAEs Leading to Discontinuation of Humira in 2 or More Patients by Primary MedDRA SOC and PT (All Treated Patients) (Continued)

MedDRA 18.1 SOC PT	Any Humira N = 5025 n (%)
Infections and infestations (continued)	
Ear infection	2 (< 0.1)
Pelvic abscess	2 (< 0.1)
Perirectal abscess	2 (< 0.1)
Peritonitis	2 (< 0.1)
Pneumocystis jirovecii pneumonia	2 (< 0.1)
Staphylococcal infection	2 (< 0.1)
Viral infection	2 (< 0.1)
Injury, poisoning and procedural complications	
Intestinal anastomosis complication	3 (< 0.1)
Musculoskeletal and connective tissue disorders	
Lupus-like syndrome	16 (0.3)
Arthralgia	15 (0.3)
Systemic lupus erythematosus	7 (0.1)
Myalgia	6 (0.1)
Fistula	3 (< 0.1)
Arthritis	3 (< 0.1)
Polyarthritis	2 (< 0.1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	
Malignant melanoma	5 (< 0.1)
Acute myeloid leukemia	3 (< 0.1)
Breast cancer	3 (< 0.1)
Adenocarcinoma of colon	2 (< 0.1)
Anal cancer	2 (< 0.1)
Hodgkin's disease	2 (< 0.1)
Basal cell carcinoma	2 (< 0.1)
Lung adenocarcinoma	2 (< 0.1)
Non-Hodgkin's lymphoma	2 (< 0.1)

Table 39. Number and Percentage of Patients with Registry TEAEs Leading to Discontinuation of Humira in 2 or More Patients by Primary MedDRA SOC and PT (All Treated Patients) (Continued)

	Any Humira
MedDRA 18.1 SOC PT	**N = 5025 n (%)**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps) (continued)	
Skin papilloma	2 (< 0.1)
Squamous cell carcinoma of skin	2 (< 0.1)
Nervous system disorders	
Headache	7 (0.1)
Neuropathy peripheral	5 (< 0.1)
Paraesthesia	4 (< 0.1)
Demyelination	3 (< 0.1)
Multiple sclerosis	2 (< 0.1)
VIIth nerve paralysis	2 (< 0.1)
Pregnancy, puerperium, and perinatal conditions	
Abortion spontaneous	2 (< 0.1)
Renal and urinary disorders	
Renal failure	3 (< 0.1)
Acute kidney injury	2 (< 0.1)
Reproductive system and breast disorders	
Female genital tract fistula	4 (< 0.1)
Respiratory, thoracic and mediastinal disorders	
Dyspnea	2 (< 0.1)
Pulmonary embolism	2 (< 0.1)
Skin and subcutaneous tissue disorders	
Psoriasis	28 (0.6)
Rash	10 (0.2)
Dermatitis psoriasiform	7 (0.1)
Eczema	6 (0.1)
Dermatitis	5 (< 0.1)
Alopecia	4 (< 0.1)
Erythema	3 (< 0.1)

Table 39. Number and Percentage of Patients with Registry TEAEs Leading to Discontinuation of Humira in 2 or More Patients by Primary MedDRA SOC and PT (All Treated Patients) (Continued)

MedDRA 18.1 SOC PT	Any Humira N = 5025 n (%)
Skin and subcutaneous tissue disorders (continued)	
Cutaneous lupus erythematosus	2 (< 0.1)
Dermatitis allergic	2 (< 0.1)
Hypersensitivity vasculitis	2 (< 0.1)
Pustular psoriasis	2 (< 0.1)
Skin reaction	2 (< 0.1)
Vascular disorders	
Vasculitis	2 (< 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 and up to 70 days after the last dose of Humira in the registry.

Cross reference: Table 14.3__2.3.1

10.6.6 CD-Related Registry TEAEs

CD-related registry TEAEs were considered to be events of CD, fistula, and abscess and were taken from the MedDRA SOCs of 'Gastrointestinal Disorders' and 'Infections and Infestations.' A summary of patients with CD-related registry TEAEs is presented in Table 40. The majority of patients with CD, a fistula, or a gastrointestinal abscess had events that the physician considered not related or probably not related to Humira.

Table 40. Number and Percentage of Patients with CD-Related Registry TEAEs (All Treated Patients)

MedDRA 18.1 PT	Any Humira N = 5025 n (%)
CD[a]	687 (13.7)
Fistulae[a]	
Anal fistula	97 (1.9)
Enterocutaneous fistula	24 (0.5)
Intestinal fistula	14 (0.3)
Enterocolonic fistula	8 (0.2)
Colonic fistula	8 (0.2)
Fistula of small intestine	8 (0.2)
Enterovesical fistula	5 (< 0.1)
Gastrointestinal fistula	4 (< 0.1)
Gastric fistula	1 (< 0.1)
Esophageal fistula	1 (< 0.1)
Abscesses[b]	
Anal abscess	133 (2.6)
Abdominal abscess	44 (0.9)
Rectal abscess	23 (0.5)
Abscess	21 (0.4)
Abscess intestinal	19 (0.4)
Perirectal abscess	16 (0.3)
Abdominal wall abscess	3 (< 0.1)
Retroperitoneal abscess	2 (< 0.1)
Peritoneal abscess	1 (< 0.1)

a. From the MedDRA SOC 'Gastrointestinal Disorders.'

b. From the MedDRA SOC 'Infections and Infestations.'

Note: A registry TEAE is defined as any AE with an onset date on or after the first dose of Humira in the registry and up to 70 days after the last dose of Humira in the registry.

Cross reference: Table 14.3__1.4

11.0 Discussion

11.1 Key Results

11.1.1 Summary of Interim Safety Data

This report provides cumulative safety data for completed Registry P06-134 for Humira in patients with moderately to severely active CD. A total of 5061 patients were enrolled in 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.

By comparison, the total 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

Exposure-adjusted event rates provided in the text throughout this report account for registry exposure to Humira only and do not include exposure from previous CD studies. No new safety signals were observed during the registry.

Of note, there were an additional 34 patients with unsigned casebooks in spite of efforts to obtain physician signatures. A sensitivity analysis was performed in which the data analysis from the 4991 patients with signed casebooks was compared with the data

analysis of the 5025 patients that included 34 patients with unsigned casebooks. The results of this comparison confirmed that the data from these 34 patients did not significantly alter the overall study results and conclusions.

The study reached a total enrollment of 5025 patients with a total Humira registry exposure of 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. 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%).

A total of 43 treatment-emergent deaths (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.

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

One event each of SJS and RPLS were reported as non-treatment-emergent events. One patient developed SJS 87 days after the last dose of Humira, which was discontinued due to lack of efficacy. The event was attributed by the investigator to pantoprazole at the time of diagnosis. Another patient was reported as having experienced RPLS approximately 3 months after discontinuing adalimumab therapy. The patient's symptoms of headache, altered consciousness, hypertension, hypercalcemia, seizure, and acute renal failure followed a complication of surgery performed 3 months prior for CD progression. The surgical complication, resulting in bilateral hydronephrosis from ureteral obstruction, led to acute renal failure. The patient was successfully treated with dialysis and was recovering in a rehabilitation center at last contact. The role of Humira in the appearance of these 2 events appears to be unlikely given the alternate etiologies present and the timing of Humira discontinuation prior to the events.

Other TEAEs of special interest are summarized as follows:

<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 registry treatment-emergent infections were reported by 556 patients (11.1%; 4.7 E/100 PYs), with 212 patients having events considered at least possibly related to Humira by the physician. The most frequently reported serious infection was anal abscess (2.4%); this type of infection is expected in a CD population.
- When evaluated without regard to corticosteroids, serious infections were reported more frequently in patients receiving Humira with IMM (6-MP, AZA, or MTX) compared to Humira without IMM (12.6% versus 10.2%, $P = 0.010$). When considered without regard to concomitant IMM use, there was a higher proportion of serious infections reported by patients receiving Humira with corticosteroids compared to Humira without corticosteroids (11.7% versus 9.6%, $P = 0.090$); however, this difference was not statistically significant. Compared to patients receiving Humira without IMM and without corticosteroids (9.6% of whom experienced serious infections), the following groups had statistically significantly higher proportions of patients experiencing serious infections: patients receiving Humira with IMM and without corticosteroids (12.7% versus 9.6%, $P = 0.007$) and patients receiving Humira with IMM and with corticosteroids (12.6% versus 9.6%, $P = 0.039$).

Other Infections

- Registry treatment-emergent opportunistic infections (excluding oral candidiasis and TB) were reported in 19 patients (0.4%, 0.1 E/100 PYs) and 9 patients (0.2%; < 0.1 E/100 PYs) reported registry treatment-emergent oral candidiasis.
- Seventeen patients (0.3%) reported registry treatment-emergent TB (active or latent) (0.1 E/100 PYs); 10 patients had active TB (0.2%; < 0.1 E/100 PYs) and 7 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).

Selected 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).

Other Events

- Registry treatment-emergent erythema multiforme was reported in 1 patient (< 0.1%, < 0.1 E/100 PYs); registry treatment-emergent worsening or new occurrence of Ps was reported in 92 patients (1.8%, 0.6 E/100 PYs), in whom the majority of which (86 patients) had events that were considered by the physician at least possibly related to Humira. Registry treatment-emergent demyelinating disorders were reported in 8 patients (0.2%, < 0.1 E/100 PYs); registry treatment-emergent ILD was reported in 4 patients (< 0.1%, < 0.1 E/100 PYs); and registry treatment-emergent pulmonary embolism was reported in 13 patients (0.3%, < 0.1 E/100 PYs).

While events of death, including infection-related death, serious infection, and malignancies are reported as associated with Humira exposure in the label, a number of these events in Registry P06-134 were considered by the physician to be not related to Humira. Other factors besides Humira use at the time of event were considered in the causality assessment as explained in Section 9.5.1. In order to assess whether physician assessments of causality were appropriate, the rates of Humira registry treatment-emergent serious infection, malignancy and death TEAEs that the physician considered not related were compared to TEAEs reported with pooled placebo data from 7 adalimumab clinical trials, which may represent the baseline rates seen in patients with CD (Table 41). The data suggest that the Humira non-related TEAEs were appropriately assessed, as the rates of TEAEs considered to be "not related" to Humira in the registry are lower than those observed in the pooled placebo patients. This suggests that not all events in these categories are related to Humira treatment, despite being reported as associated with exposure in the label.

Table 41. 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	4.8	1.9
All malignancies	0.9	1.61	0.7	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.[15]

b. With or without concomitant conventional therapy.

c. N = 161 for serious infection for placebo.

d. Physician assessment.

Cross reference: Table 14.3__1.1.6.1, Table 14.3__1.1.6.2, Table 14.3__2.40.1, Table 14.3__2.40.3

11.2 Limitations

Limitations of the study include:

Some variables (e.g., HCRU data), were only available when they were part of the physician's site routine care. These variables may be missing since not all physicians followed the same methodology for routine care.

The duration between Humira initiation and the registry measures varied depending on the timing of Humira start relative to enrollment in the registry (Section 9.6). Some patients had considerable exposure to Humira and some were Humira-naïve at the time of baseline effectiveness measurements. This may have biased baseline effectiveness results, and ultimately affected effectiveness outcomes.

The list of AEs of special interest to Humira was updated, as needed. There may have been an underestimation of nonserious AEs of special interest, especially for those categories, such as lupus/lupus-like illness and demyelinating disorders, which were not in the list at registry initiation.

Events collected during the retrospective and HCP periods were summarized separately.

11.3 Interpretation

No new safety signals were detected through this registry. The AEs noted in the study were consistent with the safety profile of Humira and support a favorable benefit/risk profile of Humira treatment.

11.4 Generalisability

As this registry was observational in nature, the scope of the findings are to be interpreted in the proper context. Overall the registry findings support the effectiveness of Humira in a large adult CD population and a favorable benefit-risk profile supporting the widespread application of Humira for this indication.

12.0 Other Information

A US site (PPD) 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.

- Subject PPD gave birth to a male infant (3 kg and 48.26 cm) with a left ureteral anomaly.
- Subject PPD had an elective abortion as a result of the baby being diagnosed with Down Syndrome at 3 months gestation.
- Subject PPD gave birth to a male infant (3.2 kg and 52 cm) with cerebral paresis.
- Subject PPD gave birth to a female infant (1.8 kg and 45 cm) with pulmonary valve stenosis, tricuspideal insufficiency, and low birth weight.
- Subject PPD gave birth to a male infant with esophageal atresia.
- Subject PPD prematurely gave birth to 2 infants at 30 weeks gestation; 1 infant (0.37 kg and length unknown) died after a few seconds and the other infant (0.48 kg and length unknown) died after 14 days. No congenital anomalies were reported.

13.0 Conclusion

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

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

The study was designed to rule out a doubling of the expected background rate of lymphoma in adult patients with CD treated with Humira as in clinical practice.

The study reached a total enrollment of 5025 patients with a Humira registry exposure of 16,680 PYs that exceeded the required 15,180 PYs. The final registry exposure-adjusted lymphoma rate was 0.060 E/100 PYs, with an upper bound of the 1-sided 95% CI of 0.102 E/100 PYs that fell below double the estimated background lymphoma rate of 0.168 E/100 PYs (2 times the assumed background lymphoma rate of 0.084 E/100 PYs). This confirms that the registry reached the goal of ruling out a doubling of lymphoma risk in patients with CD treated with Humira.

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.

The highly selective nature of clinical trials for patients with specific characteristics, which may reject those with prior use of some medications and certain comorbid conditions, is an important difference between the CD clinical trials and this registry. Registries allow for longer observation periods than clinical trials. In spite of these caveats, the adverse event rates per 100 PYs in this registry showed a high degree of similarity to the event rates per 100 PYs calculated from the combined data from all of AbbVie's CD Humira treatment clinical trials as presented in Humira IB Ed 22.1. The serious TEAE rates were similar; a registry-exposure adjusted treatment-emergent SAE rate was 24.8 E/100 PYs and the all CD trials treatment-emergent SAE rate was 36.1 E/100 PYs. The rates of serious infection were also similar; 4.7 E/100 PYs in this registry and 6.7 E/100 PYs in all CD trials. The rate of lymphoma was < 0.1 E/100 PYs in both sources. Malignancy rates, excluding lymphoma, HSTCL, MNSC, melanoma and leukemia were 0.4 E/100 PYs for this registry and 0.5 E/100 PYs for all CD trials. The

rate of intestinal stricture, an event in the natural progression of CD, was lower in the registry (3.5 E/100 PYs) than all CD trials (6.1 E/100 PYs). All other registry event rates were similar to clinical trial rates. In spite of the differences between the patient populations in trials and a registry, event rates from short-term observation periods do not reflect long term risk. No new risks or known risks were identified as having long term latency in this registry.

Therefore, the registry safety experience is consistent with the current overall safety profile of Humira use in patients with moderately to severely active CD, and no new safety signals were identified.

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.

14.0 References

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Appendices

Document Approval

Study P06134 - A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of Humira (Adalimumab) in Subjects with Moderately to Severely Active Crohn's Disease (CD) - Final

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