


Long-Term Safety and Effectiveness of Adalimumab for Moderate to Severe Psoriasis: Results from 7-Year Interim Analysis of the ESPRIT Registry

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ABSTRACT

Introduction: ESPRIT (NCT00799877) is an ongoing 10-year international prospective observational registry evaluating the long-term safety and effectiveness of originator adalimumab in routine clinical practice for adult

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patients with chronic plaque psoriasis. Herein, we report the long-term safety, effectiveness, and patient-reported outcomes (PROs) following adalimumab treatment over the first 7 years of the ESPRIT registry.

Methods: All treatment-emergent (All-TE) adverse events (AE) since the initial (first ever) dose of adalimumab were assessed. Physician Global Assessment (PGA) and PROs (PROs for US patients only) were evaluated during registry participation.

Results: As of 30 November 2015, 6051 patients in the ESPRIT registry were analyzed, representing 23,660.1 patient-years (PY) of overall adalimumab exposure. The incidence rates for All-TE serious AEs, serious infections, and malignancies were 4.4, 1.0, and 1.0 events per 100 PY (E/100PY), respectively. The standardized mortality ratio for TE deaths in the registry was 0.27 (95% CI 0.18–0.38). During the registry's first 7 years, PGA "clear" or "minimal" was achieved by >50% of patients at each annual visit, and among US patients, the mean improvement from baseline in different PROs was maintained.

Conclusion: No new safety signals were identified during the first 7 years of the registry, and safety was consistent with the known safety profile of adalimumab. The number of TE deaths was below the expected rate. During the registry's first 7 years, most of the patients remained free of All-TE cardiovascular events, serious infections, and malignancy. As-observed

effectiveness of adalimumab and improvements from baseline in PROs were maintained through 7 years of registry participation.

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Keywords: Adalimumab; Cardiovascular events; Effectiveness; Long-term safety; Malignancy; Patient-reported outcomes; Psoriasis; Registry; Serious infections

INTRODUCTION

Psoriasis, a chronic, immune-mediated, inflammatory skin disease, is prevalent in about 2–3% of the world's population [1, 2]. Patients with psoriasis are at a higher risk of developing several comorbidities such as cardiovascular disease, metabolic syndrome, joint disease, depression, and Crohn's disease, resulting in diminished quality of life [3–7]. In addition, patients with psoriasis are at an increased risk for serious infections and certain malignancies compared to the general population [8–10]. Although topical therapies, phototherapy, or conventional systemic non-biologic therapies are most often used as the first line of treatment, the introduction of biologic agents has vastly improved disease management in patients with moderate-to-severe psoriasis [2, 11].

Adalimumab, a fully human recombinant, monoclonal antibody directed against tumor necrosis factor- α (TNF- α), is approved for the treatment of moderate-to-severe chronic plaque psoriasis in adult patients, who are candidates for systemic therapy or phototherapy [12]. Long-term safety and efficacy of adalimumab in patients with moderate-to-severe psoriasis has been demonstrated in clinical trials and observational registries [13–15]. ESPRIT (NCT00799877) is an ongoing 10-year international prospective observational registry evaluating the long-term safety and effectiveness of originator adalimumab prescribed in routine clinical practice according to local product labeling for adult patients with chronic plaque

psoriasis [13]. The objective of this analysis is to report the long-term safety, effectiveness, and PROs following treatment with adalimumab over the first 7 years of the ESPRIT registry.

METHODS

Study Design and Patients

Patient enrollment was initiated on 26 September 2008 and completed on 8 November 2012. As of 30 November 2015, 6066 patients were enrolled in the ESPRIT registry, and 6051 were analyzed. Study sites were located in the USA, Canada, Austria, Czech Republic, Denmark, France, Germany, Greece, Ireland, Netherlands, Spain, Sweden, and UK. Adalimumab was dosed as recommended in the local product label.

Adult patients (≥ 18 years) with chronic plaque psoriasis prescribed adalimumab (Humira[®], Abbvie, Inc.) according to local product labeling and met one of the following criteria—(1) previously initiated on adalimumab therapy and having continued on adalimumab with no more than 70 consecutive days off drug or (2) newly initiated on adalimumab therapy within 4 weeks of registry entry—were eligible to be included in the ESPRIT registry. In patients who previously initiated adalimumab therapy, the initial adalimumab dose was received either in a pre-registry feeder clinical trial sponsored by AbbVie Inc, North Chicago, IL, or from an existing prescription outside of a pre-registry feeder trial. Source documentation of serious adverse events (SAEs), adverse events (AEs) of special interest, and dosing information since the initiation of therapy were provided by the physician. An independent or central ethics committee, or central or local institutional review board, approved the study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Statistical Analyses

This analysis included two patient populations from the registry: (1) the all-treated (All-Rx) population included patients who received at least one dose of adalimumab in the registry; (2) the new-prescription (New-Rx) population, a subpopulation of All-Rx, included patients who newly initiated adalimumab within 4 weeks prior to registry enrollment. The study design and patient populations of the ESPRIT observational registry as of 30 November 2015 are illustrated in Fig. 1. Patients were evaluated at 3 and 6 months post enrollment and then every 6 months for up to 10 years. Patients were

followed at intervals determined by routine clinical practice or as recommended by national guidelines. Safety data were captured throughout the entire study period. Patients who discontinued the registry drug were encouraged to remain in the registry.

Descriptive statistics are presented for baseline patient demographics and disease characteristics. Overall exposure to adalimumab (outside of and within the registry) was calculated as the time from the initial (first ever) adalimumab dose to 14 days after the last adalimumab dose in the registry, excluding the total number of days of treatment interruption in the registry. Registry exposure to adalimumab

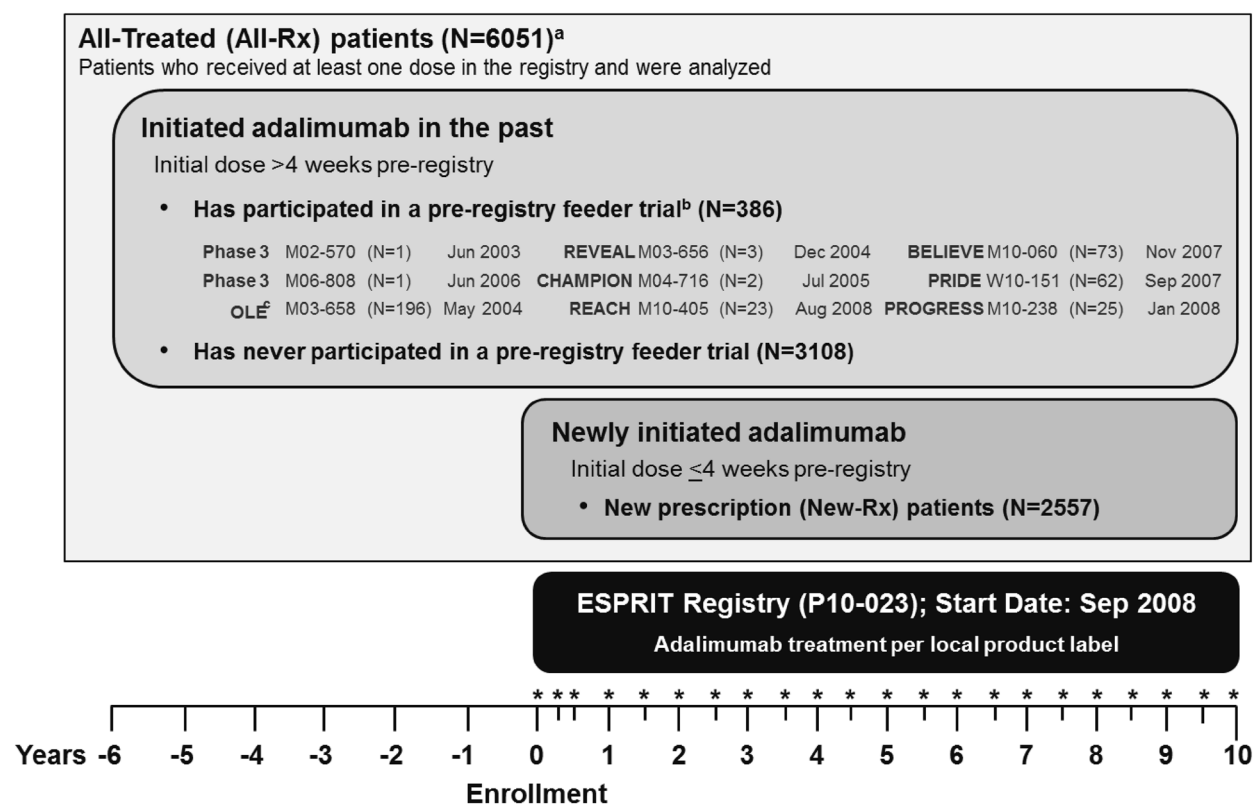


Fig. 1 Study design and patient population of the ESPRIT observational registry. ^aOf the 6066 patients enrolled, 4 had dosing information unavailable in the interim analysis of the database, and 11 patients from one site in the US were excluded from all analyses since the physician was unavailable to confirm the safety information and data in the database. ^bStart dates are shown for clinical trials. ^cREVEAL and CHAMPION were among the feeder trials for the OLE; the number of patients in

these trials were counted separately from OLE’s 196 patients. *Patients were evaluated 3 and 6 months post enrollment and then every 6 months for up to 10 years. Patients were followed at intervals determined by routine clinical practice or as recommended by national guidelines. Safety data are captured during the entire study period. Patients who discontinued the registry drug were encouraged to remain in the registry

(within the registry) was calculated as the time from first adalimumab dose in the registry to 14 days after the last adalimumab dose in the registry, excluding the total number of days of treatment interruption in the registry. A treatment interruption is defined as >70 days without any adalimumab dose. The times to discontinuation from the registry and from the registry drug for the All-Rx and New-Rx populations were analyzed by the Kaplan-Meier method.

All-TE AEs were events occurring from the date of the initial (first ever) adalimumab dose through 70 days (5 half-lives of adalimumab) after the date of the last adalimumab dose in the registry [including AEs retrospectively collected since the initial (first ever) dose of adalimumab and from previous adalimumab studies for rollover patients], excluding AEs occurring during treatment interruptions (defined as >70 days without any adalimumab dose). Incidence rates for All-TEAEs are reported as events per 100 patient years of overall exposure to adalimumab (E/100PY). Incidence rates of All-TE AEs of interest by time of event occurrence in the registry are summarized for the All-Rx patient population. AEs of special interest in this analysis included cardiovascular events, serious infections, and malignancies. Cardiovascular-related AEs of special interest included myocardial infarction (MI), cerebrovascular accident (CVA), or congestive heart failure (CHF). The times to first All-TE cardiovascular event, serious infection, and malignancy were evaluated by the method of Kaplan-Meier. Standardized mortality ratio (SMR) was calculated as the ratio of observed to expected treatment-emergent deaths using the 2006 country-specific World Health Organization (WHO) mortality rates.

Treatment effectiveness was defined as patients achieving Physician's Global Assessment (PGA) of "clear" or "minimal" during registry participation (patients were not necessarily receiving adalimumab at the time of assessment). Patient-reported Dermatology Life Quality index (DLQI) and Work Productivity and Activity Impairment (WPAI) were analyzed during registry participation in US patients

only. The proportion of patients achieving PGA "clear" or "minimal" and change from baseline in DLQI and WPAI scores were calculated for each registry visit in the as-observed population.

RESULTS

Patient Disposition and Baseline Characteristics

Of the 6051 patients (2557 New-Rx patients, 42.3%) included in this 7-year interim analysis of the ESPRIT registry, a majority of patients were from sites in the US (69.5%) and Canada (13.9%). As of 30 November 2015, 4242 (70.1%) All-Rx and 1652 (64.6%) New-Rx patients were continuing in the registry. Among patients continuing in the registry, 3070 (50.7%) All-Rx and 1061 (41.5%) New-Rx patients have not permanently discontinued adalimumab. Of those, 2150 (35.5%) All-Rx and 674 (26.4%) New-Rx patients never interrupted adalimumab treatment for longer than 70 days. The most frequent reason for discontinuation from the registry was being lost to follow-up (14.4 and 19.2% for All-Rx and New-Rx populations, respectively). The reasons for discontinuation from the registry and from the registry drug in greater than 1% of All-Rx patients are listed in Table 1.

Patient demographics and disease characteristics at registry entry (baseline) were generally comparable between the All-Rx and New-Rx populations (Table 2). The majority of patients were white and younger than 65 years; 58 and 54% of All-Rx and New-Rx patients, respectively, were male. At registry entry, a greater proportion of New-Rx patients had severe or very severe disease (36.2% vs. 19.7% for All-Rx population), as assessed by PGA, most likely because a majority of patients in the All-Rx population had received adalimumab longer than 4 weeks before registry entry. The most prevalent comorbidities observed among New-Rx patients were hypertension (22.2%), hyperlipidemia (11.5%), diabetes mellitus (9.7%), and depression (9.7%).

Table 1 Reasons for discontinuation from the registry and from the registry drug (All-Rx and New-Rx patient population)

Reason for discontinuation (in >1% patients)	All-Rx (n = 6051) n (%)	New-Rx (n = 2557) n (%)
From registry ^a , any reason	1809 (29.9)	905 (35.4)
Lost to follow-up	874 (14.4)	491 (19.2)
Lack of efficacy	89 (1.5)	56 (2.2)
Withdrew consent	355 (5.9)	156 (6.1)
Death	70 (1.2)	25 (1.0)
Non-compliance	86 (1.4)	49 (1.9)
Other	333 (5.5)	116 (4.5)
From registry drug ^b , any reason	2981 (49.3)	1496 (58.5)
AE	170 (2.8)	87 (3.4)
SAE or SAE of interest	101 (1.7)	40 (1.6)
Lost to follow-up	399 (6.6)	226 (8.8)
Lack of efficacy	1101 (18.2)	610 (23.9)
Intolerance	44 (0.7)	35 (1.4)
Withdrew consent	117 (1.9)	59 (2.3)
Other	445 (7.4)	220 (8.6)
Unknown reason	668 (11.0)	268 (10.5)

All-Rx all-treated patient population, New-Rx new prescription patient population, AE adverse event, SAE serious adverse event

^a Reasons for registry discontinuations in $\leq 1\%$ of patients were AE, intolerance, patient moved, SAE or SAE of interest, satisfactory improvement, pregnancy, or unknown reasons

^b Reasons for registry drug discontinuations in $\leq 1\%$ of patients were intolerance, patient death, satisfactory improvement, or required additional therapy

The median duration of overall exposure to adalimumab was 1398 (14–4798) days and 714 (14–2581) days for the All-Rx and New-Rx patient population, respectively. The median duration of registry exposure to adalimumab was 1132 (14–2581) days and 714 (14–2581) days for the All-Rx and New-Rx patient population, respectively. The number of patients according to duration of overall exposure to adalimumab and registry exposure to adalimumab is shown in Fig. 2. The time to discontinuation from the registry and from the registry drug (adalimumab) in the All-Rx and New-Rx patients is shown in Fig. 3.

Safety

This analysis included 6051 All-Rx patients representing 23,660.1 PY of overall exposure to adalimumab. An overview of incidence rates (E/100PY) of All-TEAEs in All-Rx patients by the duration of overall exposure to adalimumab at the time of onset of AE is presented in Table 3. The incidence rate of All-TE serious AEs was 4.4 E/100 PY of overall exposure to adalimumab; the most common All-TE serious AE was serious infection (1.0 E/100 PY). All-TE serious AEs with incidence of ≥ 20 events overall were cellulitis (31 events, 0.1 E/100 PY), pneumonia (29

Table 2 Patient demographics and disease characteristics at registry entry (All-Rx and New-Rx patient population)

Demographic or characteristic	All-Rx (<i>n</i> = 6051)	New-Rx (<i>n</i> = 2557)
Sex, <i>n</i> (%)		
Male	3489 (57.7)	1380 (54.0)
Female	2562 (42.3)	1177 (46.0)
Race ^a , <i>n</i> (%)		
White	5268 (87.3)	2223 (87.1)
Black	178 (2.9)	65 (2.5)
Asian	259 (4.3)	106 (4.2)
American Indian/Alaska native	16 (0.3)	7 (0.3)
Native Hawaiian or other Pacific Islander	40 (0.7)	25 (1.0)
Other	253 (4.2)	115 (4.5)
Multi-race	22 (0.4)	12 (0.5)
Psoriatic arthritis, <i>n</i> (%)	Not analyzed ^b	867 (34.0) ^c
Family history of psoriasis, <i>n</i> (%) [*]	Not analyzed ^b	1067 (41.9) ^d
PGA ^e , <i>n</i> (%)		
Clear	731 (12.1)	53 (2.1)
Minimal	1177 (19.5)	141 (5.5)
Mild	1149 (19.1)	310 (12.2)
Moderate	1781 (29.6)	1118 (44.0)
Severe	973 (16.2)	749 (29.5)
Very severe	213 (3.5)	172 (6.8)
Age, years, median (range)	47.0 (18–94)	46.0 (18–91)
Weight, kg, median (range)	87.0 (41–252) ^f	86.0 (41–218) ^g
BMI, kg/m ² , median (range)	29.4 (16–77) ^h	29.4 (16–70) ⁱ
Duration of psoriasis ^j , years, median (range)	Not analyzed ^b	13.4 (0–68) ^k
Medical history in ≥5% of patients and other history of interest		New-Rx (<i>n</i> = 2557)
Cardiovascular, <i>n</i> (%)		
Hypertension		568 (22.2)
Coronary artery disease		51 (2.0)
Myocardial infarction		30 (1.2)
Cardiac arrhythmia		21 (0.8)
Angina		19 (0.7)
Congestive heart failure		8 (0.3)
Cerebrovascular accident		6 (0.2)

Table 2 continued

Medical history in $\geq 5\%$ of patients and other history of interest	New-Rx ($n = 2557$)
Gastrointestinal, n (%)	
Gastroesophageal reflux disease	165 (6.5)
Inflammatory bowel disease	14 (0.5)
Metabolic	
Hyperlipidemia	295 (11.5)
Diabetes mellitus	249 (9.7)
Hypothyroidism	142 (5.6)
Obesity	48 (1.9)
Infections	
Tuberculosis	28 (1.1)
Malignancy	
Cancer	24 (0.9)
Neurologic and psychiatric	
Depression	247 (9.7)
Anxiety disorder	133 (5.2)

Percentages calculated on non-missing values

All-Rx all-treated patient population, *New-Rx* new prescription patient population, *PGA* physician's global assessment, *BMI* body mass index

^a Missing data: *All-Rx*: $n = 15$; *New-Rx*: $n = 4$

^b Not analyzed because not all data were captured in the registry database

^c Missing data: *New-Rx*: $n = 7$

^d Missing data: *New-Rx*: $n = 9$

^e Many patients had received adalimumab prior to entering the registry, demonstrated by the number of patients entering the registry with a *PGA* of clear or minimal (missing data: *All-Rx*: $n = 27$; *New-Rx*: $n = 14$)

^f $n = 5927$

^g $n = 2497$

^h $n = 5909$

ⁱ $n = 2492$

^j Calculated at registry entry

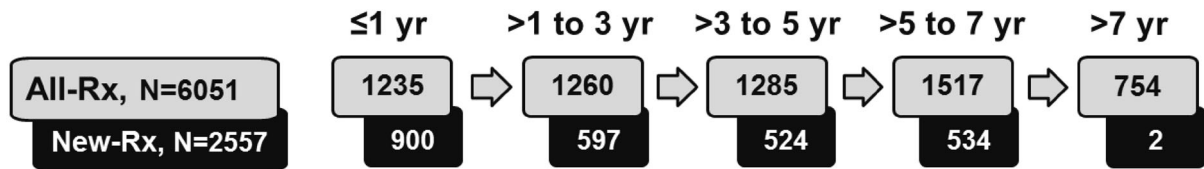
^k $n = 2548$

events, 0.1 E/100 PY), and myocardial infarction (22 events, <0.1 E/100 PY). The rate of *All-TE* AEs leading to discontinuation of adalimumab was 1.7 E/100 PY overall, and the rates either decreased or remained stable over time. The incidence rate for *All-TE* AEs leading to death regardless of causality in the *All-Rx* population was 0.1 E/100 PY; the most common event

leading to death was myocardial infarction (five events, <0.1 E/100 PY).

The incidence rates of *All-TE* inflammatory bowel disease [Crohn's disease, four events (two patients with documented history of Crohn's disease); ulcerative colitis, two events] and depression (34 events) were <0.1 E/100 PY and 0.1 E/100 PY, respectively. Incidence rates for

Number of patients based on their overall exposure to ADA (outside of and within the registry)



Number of patients based on their registry exposure to ADA (within the registry)

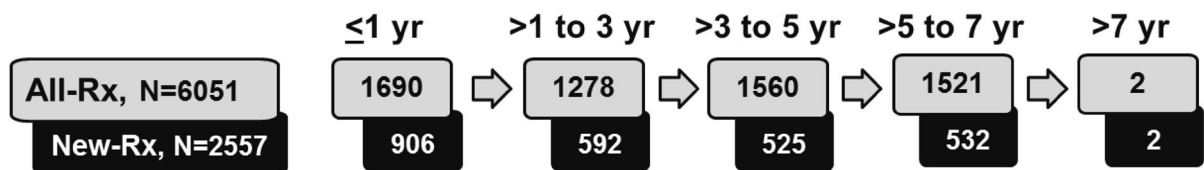


Fig. 2 Number of patients based on duration of adalimumab exposure (All-Rx and new-Rx patient population). Overall exposure to adalimumab (outside of and within the registry) was calculated as the time from the initial (first ever) adalimumab dose to 14 days after the last adalimumab dose in the registry, excluding the total number of days of treatment interruption in the registry. Registry exposure to adalimumab (within the registry) was

calculated as the time from the first adalimumab dose in the registry to 14 days after the last adalimumab dose in the registry, excluding the total number of days of treatment interruption (defined as >70 days without any adalimumab dose) in the registry. ADA adalimumab; All-Rx all-treated patient population, New-Rx new prescription patient population

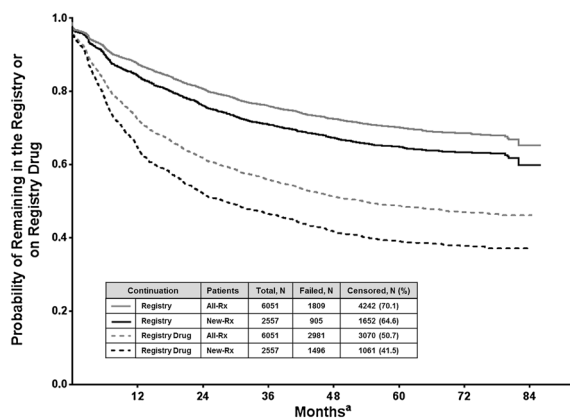


Fig. 3 Kaplan-Meier plots of time to discontinuation from the registry and from the registry drug (adalimumab) (All-Rx and New-Rx patient populations). ^aTime of observation (first day to last day of registry participation) was used for time to registry discontinuation; registry exposure to adalimumab was used for time to registry drug discontinuation. All-Rx all-treated patient population, New-Rx new prescription patient population

All-TE hyperlipidemia (12 events), diabetes mellitus (21 events), hypothyroidism (7 events), and obesity (4 events) were <0.1 E/100 PY each. The incidence rates of arthritis (16 events), psoriatic arthritis (44 events), rheumatoid arthritis (4 events), and myalgia (23 events) were <0.1, 0.1, 0.2, <0.1, and <0.1 E/100 PY, respectively.

An overview of incidence rates (E/100 PY) for All-TE cardiovascular events, serious infections, and malignancies in All-Rx patients by the duration of overall exposure to adalimumab at the time of onset of the AE is shown in Fig. 4. All-TE cardiovascular events, serious infections, and malignancies were the primary causes of 8, 1, and 12 deaths (<0.1 E/100PY, each), respectively.

The time to first All-TE occurrence of myocardial infarction, cerebrovascular accident, congestive heart failure, serious infection, malignancy, lymphoma, or non-melanoma skin cancer in the All-Rx patient population is

Table 3 Incidence rates of All-TE AE of interest by time of event occurrence (All-Rx patient population)

AE of interest E (E/100PY)	Overall exposure to ADA at the onset of AE (years)							Overall	
	0-<1 ^a	1-<2	2-<3	3-<4	4-<5	5-<6	6-<7		≥7 ^b
N	6051	4820	4069	3561	2891	2276	1570	765	6051
PY	5401.4	4403.5	3804.2	3246.5	2572.4	1945.9	1176.7	1109.5	23660.1
AE	1712 (31.7)	911 (20.7)	852 (22.4)	726 (22.4)	413 (16.1)	236 (12.1)	142 (12.1)	168 (15.1)	5160 (21.8)
AE leading to d/c of ADA	168 (3.1)	71 (1.6)	59 (1.6)	43 (1.3)	37 (1.4)	10 (0.5)	14 (1.2)	7 (0.6)	409 (1.7)
Serious AE	245 (4.5)	182 (4.1)	182 (4.8)	142 (4.4)	121 (4.7)	65 (3.3)	44 (3.7)	54 (4.9)	1035 (4.4)
Serious infection	64 (1.2)	44 (1.0)	43 (1.1)	28 (0.9)	30 (1.2)	17 (0.9)	10 (0.8)	11 (1.0)	247 (1.0)
Oral candidiasis	7 (0.1)	1 (<0.1)	1 (<0.1)	0	0	0	0	0	9 (<0.1)
Active tuberculosis	3 (<0.1)	1 (<0.1)	1 (<0.1)	0	1 (<0.1)	0	0	0	6 (<0.1)
Opportunistic infection, other ^c	1 (<0.1)	0	0	0	1 (<0.1)	0	1 (<0.1)	0	3 (<0.1)
Malignancy	53 (1.0)	44 (1.0)	40 (1.1)	36 (1.1)	30 (1.2)	15 (0.8)	12 (1.0)	17 (1.5)	247 (1.0)
Congestive heart failure	3 (<0.1)	1 (<0.1)	2 (<0.1)	3 (<0.1)	1 (<0.1)	0	1 (<0.1)	0	11 (<0.1)
Lupus-like reactions and systemic lupus ^d	6 (0.1)	0	0	2 (<0.1)	0	0	0	0	8 (<0.1)
Demyelinating disorder	2 (<0.1)	0	2 (<0.1)	0	0	1 (<0.1)	0	0	5 (<0.1)
AE leading to death	8 (0.1)	8 (0.2)	4 (0.1)	5 (0.2)	2 (<0.1)	0	2 (0.2)	2 (0.2)	31 (0.1)

All-TE AE all treatment-emergent adverse event, All-Rx all-treated patient population, AE adverse event, ADA adalimumab, d/c discontinuation

^a The AEs collected from rollover patients during feeder studies most likely occurred in the first years of overall exposure to adalimumab. A closer AE documentation in feeder studies is expected compared with registry AE collection and retrospective collection of AEs for patients who initiated adalimumab therapy outside of an AbbVie clinical trial before the registry

^b Patients with ≥7 years of overall exposure to adalimumab are a selected subgroup from the overall population who had the longest exposure to adalimumab and potentially had a longer duration of disease

^c Excluding oral candidiasis and tuberculosis

^d There were no reports of drug-induced lupus among seven patients with lupus-like reactions and systemic lupus during the registry

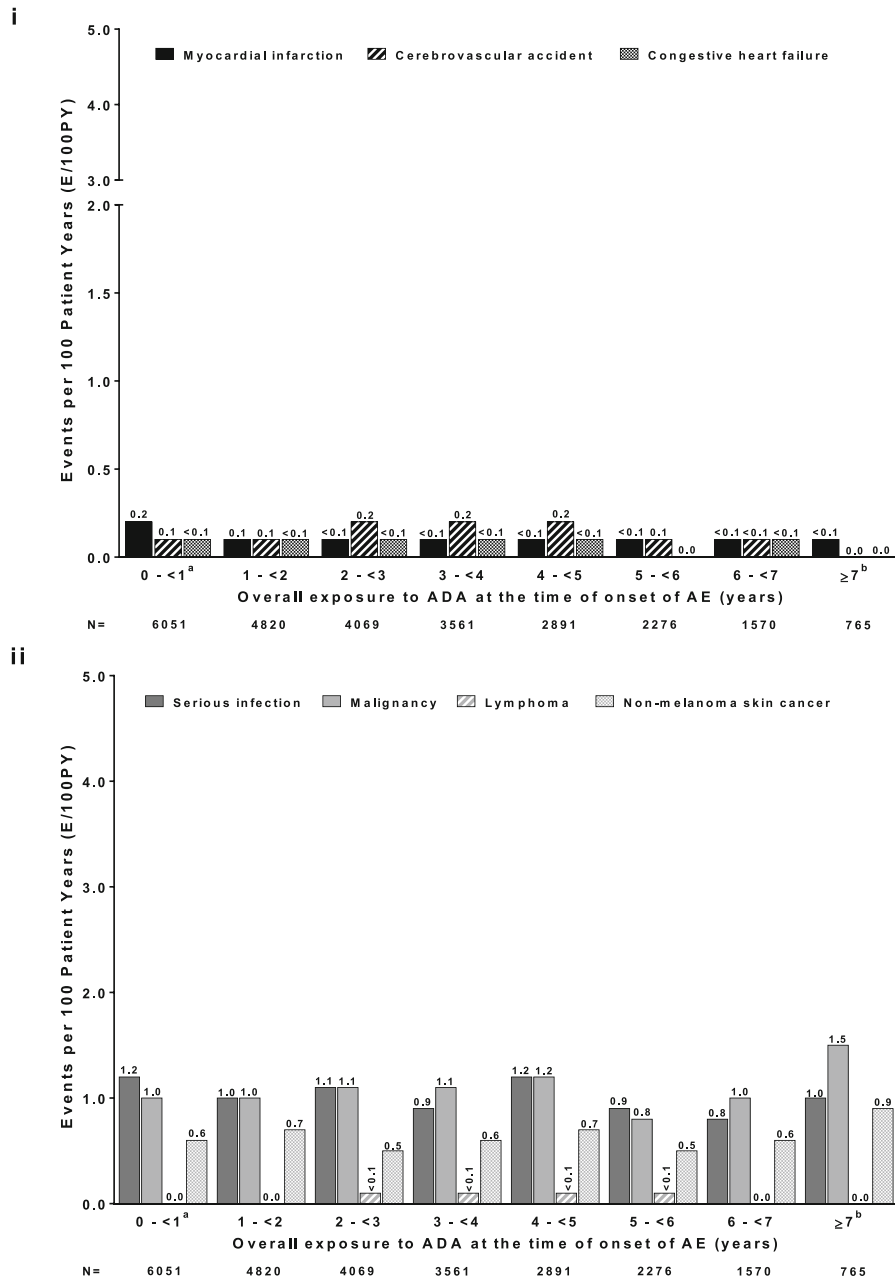


Fig. 4 Incidence rates of All-TE cardiovascular events (1) and serious infections and malignancies (2) by time of event occurrence (All-Rx patient population). ^aThe AEs collected from rollover patients during feeder studies most likely occurred in the first years of overall exposure to adalimumab. A closer AE documentation in feeder studies is expected compared with registry AE collection and retroactive collection of AEs for patients who initiated adalimumab therapy outside of an AbbVie clinical trial

before the registry. ^bPatients with ≥7 years of overall exposure to adalimumab are a selected subgroup from the overall population who had the longest exposure to adalimumab and potentially had a longer duration of disease. *All-TE AE* all treatment-emergent adverse event, *All-Rx* all-treated patient population, *MI* myocardial infarction, *CVA* cerebrovascular accident, *CHF* congestive heart failure, *SI* serious infection, *NMSC* non-melanoma skin cancer, *ADA* adalimumab, *AE* adverse event

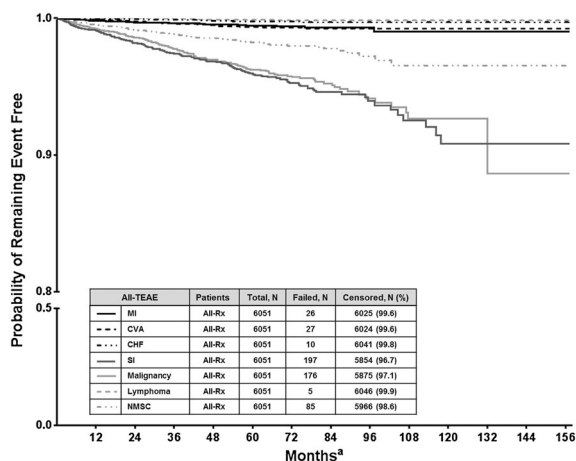


Fig. 5 Time to first all-TE AE of interest (All-Rx patient population). ^aOverall exposure to adalimumab (outside of and within the registry). *All-TE AE* all treatment-emergent adverse event, *All-Rx* all-treated patient population, *MI* myocardial infarction, *CVA* cerebrovascular accident, *CHF* congestive heart failure, *SI* serious infection, *NMSC* non-melanoma skin cancer

shown in Fig. 5. Through 30 November 2015, 99.6%, 99.6%, 99.8%, 96.7%, and 97.1% of patients remained free of All-TE myocardial infarction, cerebrovascular accident, congestive heart failure, serious infections, and malignancies, respectively. The standardized mortality ratio was 0.27 (95% CI 0.18–0.38) for All-Rx and 0.28 (95% CI 0.14–0.50) for New-Rx, indicating that the observed number of deaths in the ESPRIT registry was below expected for the age-, sex- and country-matched population (Fig. 6).

Effectiveness and Patient-Reported Outcomes

During the first 7 years of registry participation, over 50% of All-Rx and New-Rx patients achieved PGA “clear” or “minimal” (Fig. 7, patient numbers were small at 84 months). However, patients were not necessarily receiving adalimumab at the time of assessment. The proportions of All-Rx and New-Rx patients achieving PGA “clear” or “minimal” were similar at each time point and generally increased through 7 years.

Among US patients who reported DLQI data, mean baseline DLQI scores were 7.6 (95% CI

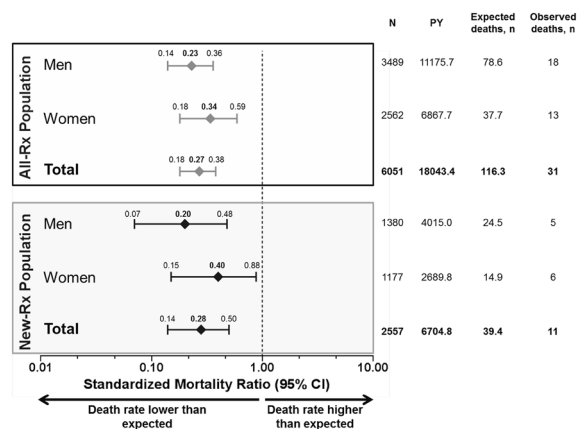


Fig. 6 Standardized mortality ratios (SMR)^a, overall and by gender (All-Rx and new-Rx patient population). ^aSMR was calculated as the ratio of observed to expected treatment-emergent deaths using the 2006 country-specific World Health Organization (WHO) mortality rates. *All-Rx* all-treated patient population, *New-Rx* new prescription patient population, *PY* patient years, *CI* confidence intervals

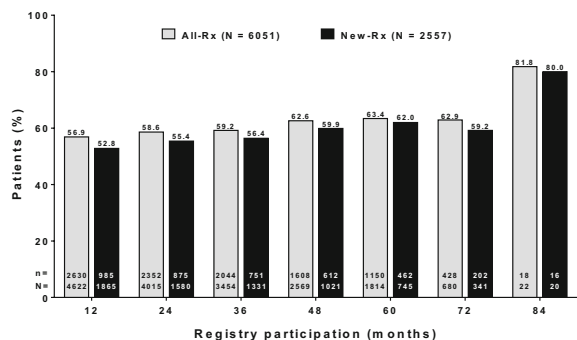


Fig. 7 Proportion of patients (as observed) achieving PGA “clear” or “minimal” (All-Rx and new-Rx patient population). Patients were not necessarily receiving adalimumab at the time of PGA assessment. Only a few selected patients left at 84 months. *PGA* physician’s global assessment, *All-Rx* all-treated patient population, *New-Rx* new prescription patient population

7.4–7.8) and 10.9 (95% CI 10.5–11.2) in All-Rx (*n* = 4084) and New-Rx (*n* = 1887) patient populations, respectively. The mean change from baseline in DLQI scores was at least –3.1 in All-Rx patients and –5.5 in New-Rx patients (Fig. 8). The improvements in DLQI scores from baseline were maintained through the first 7 years of the registry. Among US patients,

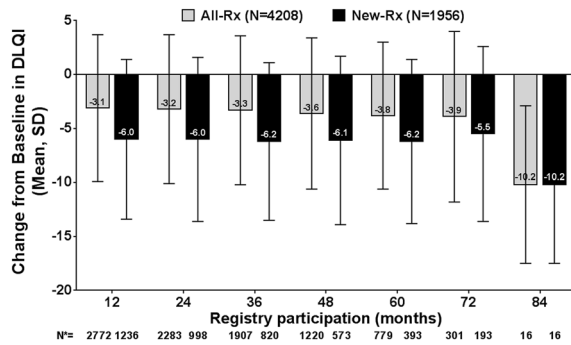


Fig. 8 Change from baseline (as observed) in DLQI scores^a (All-Rx and new-Rx patient population, US patients only). ^aDecrease in DLQI scores denotes improvement. *N** number of patients in as-observed population for respective visit; only a few selected patients left at 84 months. *PGA* physician's global assessment, *All-Rx* all-treated patient population, *New-Rx* new prescription patient population

improvements in total work productivity impairment (TWPI), total activity impairment (TAI), presenteeism, and absenteeism were observed during the first 7 years of the ESPRIT registry (Fig. 9). The improvements in WPAI scores from baseline were maintained through the first 7 years of the registry.

DISCUSSION

During the first 7 years of the ESPRIT registry, no new or unexpected safety signals were observed with adalimumab treatment, and the safety was consistent with the known safety profile of adalimumab. The safety results from the ESPRIT registry were similar to those from the integrated safety analysis of the adalimumab clinical trials in psoriasis and across indications [14–16]. At registry entry, baseline characteristics were similar between All-Rx and New-Rx populations with the exception of greater disease severity in the New-Rx population, which could be attributed to a majority of patients in the All-Rx population receiving adalimumab for longer than 4 weeks at baseline and therefore having better disease control at registry entry. The most frequently reported psoriasis-related comorbidities at enrollment were hypertension, hyperlipidemia,

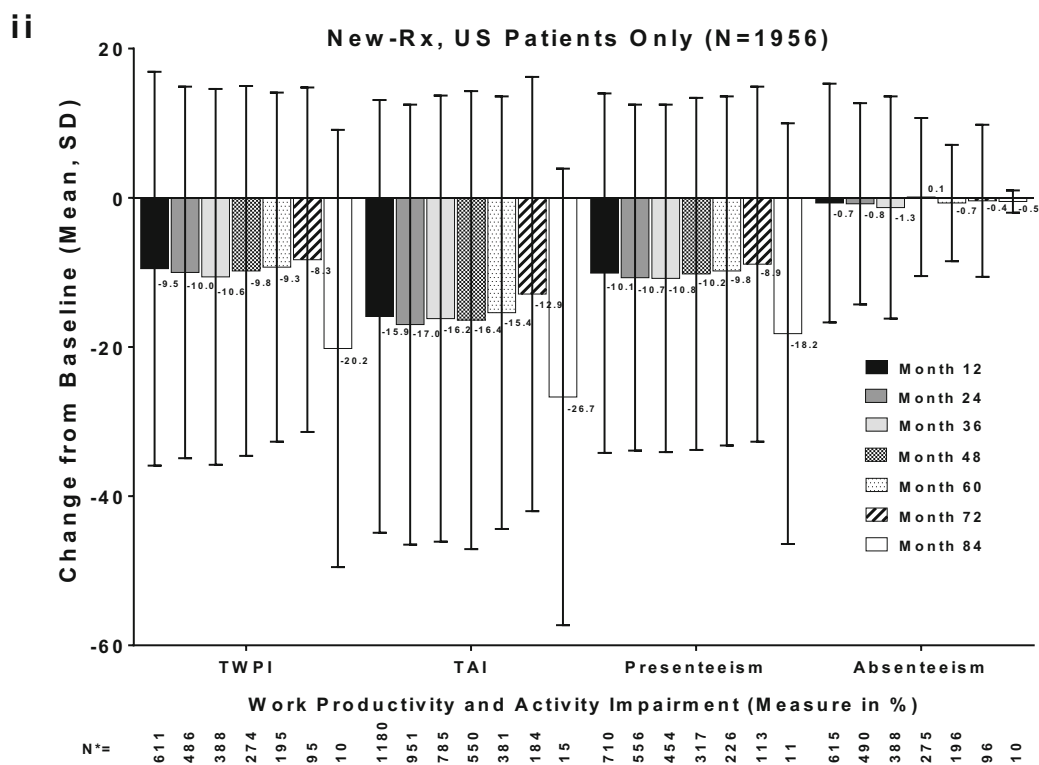
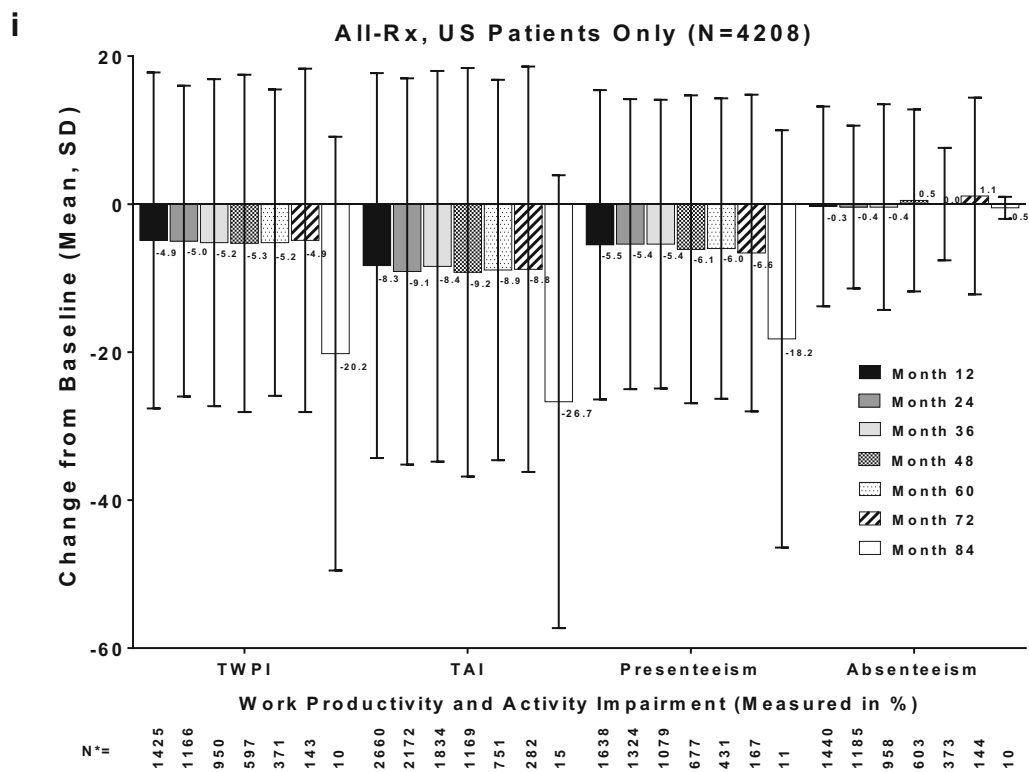
Fig. 9 Change from baseline (as observed) in WPAI scores^a (All-Rx and New-Rx patient population, US patients only). ^aDecrease in WPAI subscores denotes improvement. *N** = number of patients in as-observed population for respective visit; only a few selected patients left at 84 months. *WPAI* work productivity and activity impairment, *TWPI* total work productivity impairment, *TAI* total activity impairment, *presenteeism* impairment while working, *All-Rx* all-treated patient population, *New-Rx* new prescription patient population

diabetes mellitus, and depression. Although the All-Rx patient population had longer overall exposure to adalimumab compared with New-Rx population, similar proportions of patients continued in the registry and received adalimumab.

The incidence rates of All-TE AEs by the duration of overall exposure to adalimumab at the time of onset of AE generally remained stable over 7 years in the ESPRIT registry. Intolerance to initial adalimumab therapy and subsequent discontinuations most likely occurred during the first year of adalimumab. In addition, patients with ≥ 7 years of overall exposure to adalimumab are a selected subgroup from the overall population who had the longest exposure to adalimumab and potentially had a longer duration of disease.

Patients with moderate-to-severe psoriasis may have an elevated background risk of cardiovascular events, serious infections, and malignancies compared with general population [3, 6, 8, 9, 17, 18]. Although some studies have reported increased risk of serious infections or malignancies, particularly lymphoma in psoriasis patients treated with TNF- α antagonists, significantly increased risks have not been identified in other studies of TNF- α antagonists [19–22]. In addition, patients with psoriasis receiving TNF- α antagonists have been found to be at reduced risk for cardiovascular events [23–27].

Incidence rates of treatment-emergent cardiovascular events, serious infections, and malignancies in the ESPRIT registry were consistent with rates observed in the adalimumab clinical trials, and there was no cumulative effect for up to >7 years of total adalimumab



exposure. As of 30 November 2015, most of the patients (>96%) remained free of All-TE cardiovascular events, serious infections, or malignancies. The observed incidence rates in the ESPRIT registry were within ranges of published rates of cardiovascular events, serious infections, and malignancies in psoriasis patients not receiving biologic treatment (0.6–1.5 E/100 PY, 0.3–2.1 E/100 PY, and 0.5–2.0 E/100 PY, respectively [10, 21, 28–32]) and consistent with the expected rate in the psoriasis population treated with TNF- α antagonists [21, 22, 33]. The number of observed treatment-emergent deaths in the ESPRIT registry was below the expected rate for the age-, sex-, and country-matched general population. This lower risk could be partly due to patient selection bias as patients at a higher risk of mortality probably tended to be not enrolled into the registry.

As-observed effectiveness of adalimumab either increased or remained stable through 7 years of the ESPRIT registry, even though some patients may have entered the registry with PGA score of “clear” or “minimal,” having received adalimumab treatment for longer than 4 weeks. Since the registry was designed to understand the long-term effectiveness of adalimumab outside of a controlled trial setting and even when adalimumab was stopped, the results may be confounded by patients not necessarily receiving adalimumab at the time of assessment and discontinuations due to lack of efficacy. During the first 7 years of the ESPRIT registry, improvements in DLQI and WPAI scores were maintained in both patient populations.

Some of the limitations of this analysis are the lack of a control group for comparison and that observational data are subject to outcome-reporting bias. At registry entry, some patients did not have previous exposure to adalimumab. In addition, at the time of assessment of effectiveness and PROs, patients were not necessarily receiving adalimumab. The overall exposure-adjusted incidence rates of All-TE AEs may be underestimated in patients who were receiving adalimumab long-term prior to registry entry.

CONCLUSIONS

In summary, no new safety signals were observed with adalimumab treatment in the first 7 years of the ESPRIT registry. Safety data were consistent with the known safety profile of adalimumab from prior clinical trials and postmarketing surveillance. The number of treatment-emergent deaths in the registry was below the expected rate for the comparable general population. The majority of patients remained free of treatment-emergent cardiovascular events, serious infection, or malignancy for up to 7 years of overall registry exposure to adalimumab. As-observed effectiveness of adalimumab and improvement from baseline in PROs remained stable through 7 years of the registry.

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Compliance with Ethics Guidelines. An independent or central ethics committee, or central or local institutional review board, approved the study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study

Data Availability. Qualified researchers may request access to the study datasets from AbbVie via the process defined on AbbVie.com under Clinical Trial Data and Information Sharing.

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