Five-year analysis from the ESPRIT 10-year postmarketing surveillance registry of adalimumab treatment for moderate to severe psoriasis

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Background: ESPRIT is an ongoing, 10-year, observational registry, evaluating long-term safety and effectiveness of adalimumab treatment in routine clinical practice for patients with moderate to severe, chronic plaque psoriasis.

Objectives: Initial 5-year results are reported.

Methods: Two populations were analyzed: the "all-treated" population received 1 or more adalimumab doses in registry, continuing adalimumab treatment from a current prescription or previous study participation, and included the "new-prescription" population initiating adalimumab 4 weeks or earlier preregistry entry.

Results: Data were collected from September 26, 2008, through November 30, 2013, for all-treated (n = 6059), which included new-prescription (n = 2580, 42.6%); median registry exposure was 765 and 677 days, respectively. In all-treated, rate (events per 100 patient-years of total adalimumab exposure [E/100PY]) of serious treatment-emergent adverse events (inside or outside of the registry) was 4.3 E/100PY, serious infection 1.0 E/100PY, malignancies 0.9 E/100PY (nonmelanoma skin cancers 0.6 E/100PY; melanomas <0.1 E/100PY). Standardized mortality ratio was 0.30 (95% confidence interval 0.19-0.44). Physician Global Assessment clear or minimal (effectiveness parameter) was achieved by 57.0% at 12 months and 64.7% at 60 months of treatment.

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Limitations: Observational data are subject to outcome-reporting bias.

Conclusion: No new safety signals were observed with adalimumab treatment during this initial 5-year registry review. Observed number of deaths was below expected. As-observed effectiveness remained stable through 60 months. (J Am Acad Dermatol 2015;73:410-9.)

Key words: adalimumab; adverse events; long-term safety; malignancy; registry; serious infections.

Psoriasis is a chronic, systemic, immune-mediated disease, associated with multiple comorbidities,[1,2] including risk factors for cardiovascular disease and metabolic syndrome (hypertension, diabetes, hyperlipidemia, and obesity) especially in patients with severe psoriasis,[3-6] with an increased risk for myocardial infarction (MI)[7] and psoriatic arthritis.[1,2] Long-term efficacy and/or safety of anti–tumor necrosis factor-alfa agents, including adalimumab, has been demonstrated in moderate to severe psoriasis for up to 5 years in clinical trials and observational registries,[8-13] and in a database analysis across multiple indications of adalimumab (including psoriasis) in patients with up to 12 years of adalimumab exposure.[14] ESPRIT is an ongoing, multicenter, postmarketing, 10-year, international, observational registry (NCT00799877) with the objective of prospectively evaluating long-term safety and effectiveness of adalimumab in patients treated for chronic psoriasis per local product label in routine clinical practice, who are candidates for systemic therapy or phototherapy. Enrollment completed November 8, 2012. The objective of this prespecified analysis was to determine the cumulative, long-term safety and effectiveness of adalimumab over the first 5-year period.

CAPSULE SUMMARY

- Adalimumab has an established safety profile in psoriasis and across different indications.
- Findings from the first 5 years of ESPRIT, a prospective registry of patients with psoriasis treated with adalimumab per local label in daily practice, support the safety of long-term treatment.
- Results afford opportunities for clinician/patient interactions on treatment safety.

METHODS

Eligible patients were adults (≥18 years of age) with chronic plaque psoriasis who had been prescribed adalimumab according to local product labeling, signed an informed consent before collection of registry-related data, and met 1 of the following entry criteria: (1) initiated adalimumab within 4 weeks before entry into the registry; or (2) previously initiated adalimumab and were not off drug more than 70 consecutive days, or previously participated in an adalimumab clinical trial ("feeder trial") sponsored by AbbVie Inc, North Chicago, IL, and were not off drug more than 70 consecutive days after study completion. An independent or central ethics committee, or central or local institutional review board, approved the study. Two registry populations are identified: the all-treated population received at least 1 dose of adalimumab during the registry; the new-prescription population, a subgroup of the all-treated population, received the initial (first-ever) dose within 4 weeks before registry enrollment. The registry design and maximum follow-up schedule are illustrated in Fig 1. Patients are encouraged to remain in the registry but can discontinue at any time. Those who discontinue adalimumab are encouraged to continue in the registry to allow complete collection of safety information.

Adalimumab is dosed according to the local product label. Patients are allowed concomitant therapy for psoriasis in accordance with their physician's usual and customary medical practice; however, concurrent use of anakinra, abatacept, or other biologic agents is prohibited. Patients are allowed to continue in the registry if they were being treated with a systemic psoriasis therapy other than adalimumab. For patients who initiated adalimumab therapy before entering the registry or who continued therapy after completing a feeder trial, the full period between initial dose or the end of the previous study and the start of the registry is considered as exposure time since patients received continuous therapy per protocol inclusion criteria (ie, no more than 70 days off drug).

In this analysis, safety was evaluated throughout the registry for both populations by analysis of adverse events (AEs) that were serious, of special interest, spontaneously reported, or led to registry or registry drug discontinuation. Special-interest AEs were defined as those of most concern during adalimumab treatment or those with higher rates compared with placebo in clinical psoriasis trials, and were analyzed in the first 5 years of the

Abbreviations used:

AE:	adverse event
E/100PY:	events per 100 patient-years of total adalimumab exposure
MI:	myocardial infarction
PGA:	Physician Global Assessment
PY:	patient-years
TB:	tuberculosis
TEAE:	treatment-emergent adverse event

registry. Those reported here are categorized as cardiovascular-related, infection-related, and malignancies. The focus of this report is on treatment-emergent AEs (TEAEs), which were events occurring from initial adalimumab dose through 70 days after last registry dose, excluding events during treatment interruptions. These were analyzed for the all-treated population and for subgroups with different durations of total exposure to adalimumab inside or outside of the registry. Treatment effectiveness was measured by achievement of the Physician Global Assessment (PGA) of 0 (clear) or 1 (minimal) on a 6-point severity scale. Statistical methods for safety and efficacy evaluations are provided in the "Supplementary information" section available at http://www.jaad.org.

RESULTS

Patients

This analysis collected data from September 26, 2008, through November 30, 2013, for 6059 patients in the all-treated population, including 2580 (42.6%) in the new-prescription population. Patients were enrolled in 13 countries. The United States and Canada had a combined enrollment of 5059 (83.5%) patients (Table SI; available at http://www.jaad.org). Upon enrollment completion (November 8, 2012), 6.4% had enrolled from a feeder trial and 51.0% had received their initial dose of adalimumab outside of a feeder trial and more than 4 weeks before entering the registry (Fig 1).

At enrollment (baseline), demographics were generally comparable between the 2 populations (Table I). More new-prescription patients had severe

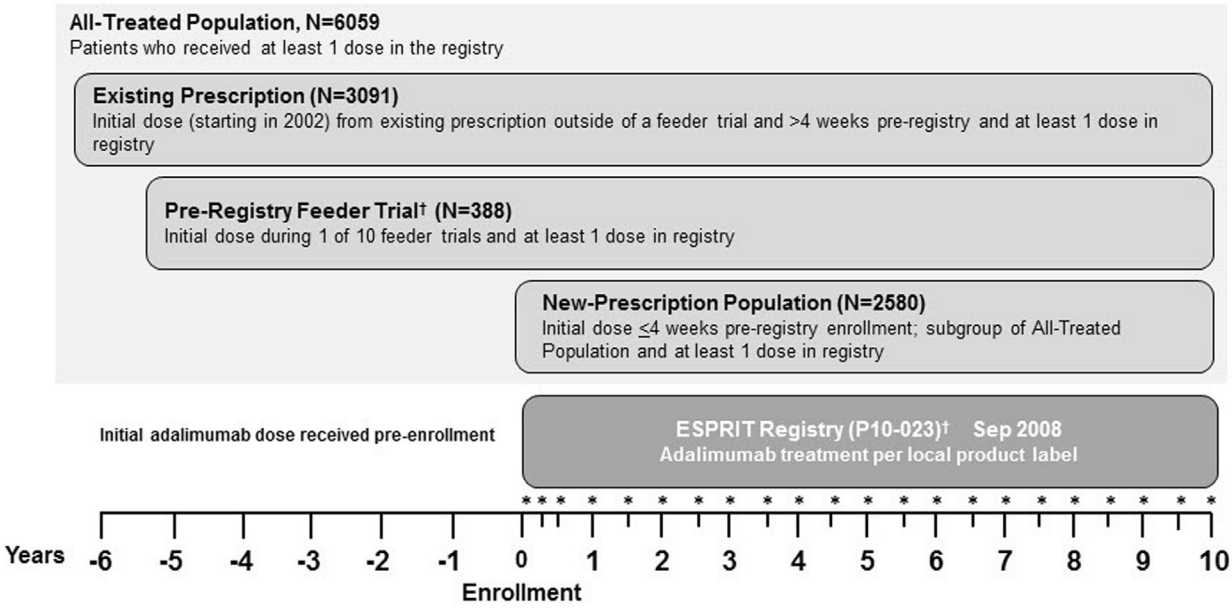


Fig 1. Registry design. Feeder trials included M02-570 (phase III, n = 1, June 2003), M02-538 (phase II, n = 1, June 2003), M03-658 (open-label extension trial [OLE], n = 195, May 2004; included the REVEAL, CHAMPION, M02-538 trials for which the number of patients was counted separately from the OLE's 195 patients), M03-656 (phase III REVEAL, n = 3, December 2004), M04-716 (phase III CHAMPION, n = 2, July 2005), M06-808 (phase III, n = 1, June 2006), M10-060 (BELIEVE, n = 75, November 2007), W10-151 (phase III PRIDE, n = 62, September 2007), M10-238 (phase III PROGRESS, n = 25, January 2008), and M10-405 (phase IV REACH, n = 23, August 2008). *Patients are followed up at regular office visits, at intervals as determined by routine clinical practice or as recommended by national guidelines. Enrolled patients are followed up for up to 10 years, including patients who discontinue adalimumab before 10 years of registry participation, during regular office visits that are determined by routine practice or national guidelines. Registry visits are conducted initially at 3 and 6 months postenrollment, then every 6 months for up to 10 years. †Study start dates are shown.

Table I. Patient demographics, characteristics, and medical history at entry into the registry

	All-treated population, N = 6059 n (%)	New-prescription population, N = 2580 n (%)
Sex		
Male	3493 (57.6)	1395 (54.1)
Female	2566 (42.4)	1185 (45.9)
Race		
White	5234 (87.3)	2230 (87.1)
Black	178 (3.0)	67 (2.6)
Asian	253 (4.2)	105 (4.1)
Other*	331 (5.5)	158 (6.1)
Disease characteristics		
Psoriatic arthritis	†	862 (33.9)
Family history of psoriasis	†	1068 (42.0)
PGA (0-5)‡		
Clear (0)	556 (11.5)	43 (2.0)
Minimal (1)	899 (18.7)	104 (4.9)
Mild (2)	905 (18.8)	251 (11.8)
Moderate (3)	1456 (30.2)	920 (43.4)
Severe (4)	813 (16.9)	649 (30.6)
Very severe (5)	185 (3.8)	154 (7.3)
	Median (range)	**Median (range)**
Age, y	47.0 (18-94)	46.0 (18-91)
Weight, kg	87.0 (41-252) n = 5904	87.0 (41-218) n = 2506
BMI, kg/m^2	29.4 (16-76.8) n = 5883	29.4 (16-69.9) n = 2498
Duration of psoriasis,§ y	†	13.4 (0-68) n = 2543
Medical history¶ in ≥5% of patients and other history of interest		**New-prescription population N = 2580, n (%)**
Cardiovascular-related		
Hypertension		567 (22.0)
Coronary artery disease		48 (1.9)
MI		30 (1.2)
Cardiac arrhythmia		21 (0.8)
Angina		19 (0.7)
CHF		8 (0.3)
CVA		6 (0.2)
Gastrointestinal		
Gastroesophageal reflux disease		162 (6.3)
Inflammatory bowel disease		14 (0.5)
Metabolic		
Hyperlipidemia		295 (11.4)
Diabetes mellitus		244 (9.5)
Hypothyroidism		140 (5.4)
Obesity		46 (1.8)
Infection-related		
TB		27 (1.0)
Malignancy		
Cancer		23 (0.9)
Neurologic and psychiatric		
Depression		245 (9.5)
Anxiety disorder		132 (5.1)

BMI, Body mass index; *CHF*, congestive heart failure; *CVA*, cerebrovascular accident; *MI*, myocardial infarction; *PGA*, Physician Global Assessment; *TB*, tuberculosis.

*Includes American Indian/Alaska Native (all-treated, 0.3%; new-prescription, 0.3%), native Hawaiian or other Pacific Islander (all-treated, 0.7%; new-prescription, 0.9%), multiple races (all-treated, 0.4%; new-prescription, 0.5%), other (all-treated, 4.2%; new-prescription, 4.5%). Missing (all-treated, n = 63; new-prescription, n = 20).

†Not analyzed because not all data were captured in the registry database.

‡Many patients received adalimumab before entering the registry, demonstrated by the number of patients entering the registry with a PGA 0 or 1. Missing data (all-treated, n = 1245; new-prescription, n = 459).

§Calculated from start of registry.

¶Medical history at enrollment was summarized only for the new-prescription population.

or very severe disease (37.9% vs 20.7% all-treated population). More all-treated patients had baseline PGA of 0 or 1 (30.2% vs 6.9% new-prescription population), most likely occurring because many of the all-treated population received adalimumab longer than 4 weeks before registry entry. Baseline comorbidities for the new-prescription population included risk factors for cardiovascular disease (Table I).

Patients were observed for 17,739.8 patient-years (PY) (first to last day in the registry), and exposed to adalimumab during the registry for 13,639.0 PY. Total patient exposure was 19,242.8 PY. Exposure to adalimumab during and outside of the registry is shown in Table II. Registry discontinuation rates were 10.6% and 13.1% for the all-treated and new-prescription populations, respectively (Table SII; available at http://www.jaad.org). At the time of data cutoff for the registry's first 5 years, 76.5% and 69.2% of the all-treated and new-prescription populations, respectively, had not permanently discontinued adalimumab. Of patients continuing in the registry, 85.6% and 79.6% in the all-treated and new-prescription populations, respectively, were continuing adalimumab. The most frequent reason for discontinuation from the registry was lost to follow-up (3.6% and 4.5% for all-treated and new-prescription populations, respectively) (Table SII). Time to discontinuation of adalimumab within the registry is illustrated in Fig 2, *A*. Patients were eligible to reinitiate adalimumab after any interruption.

Table II. Duration of patient exposure to adalimumab in ESPRIT

	Subgroups with different durations of total exposure to adalimumab, N			
	≤1 y	>1-3 y	>3-5 y	>5 y
Total adalimumab exposure (during or outside of registry)*				
All-treated population,† N = 6059	953	2029	2109	968
New-prescription population,‡ N = 2580	724	1037	815	4
Adalimumab exposure during registry§				
All-treated population,† N = 6059	1301	2617	2136	5
New-prescription population,‡ N = 2580	726	1037	813	4

*Calculated as the date of the last dose minus the date of the initial dose plus 14 d, minus the total days of treatment interruptions during the registry.
†Included 388 patients from previous AbbVie clinical trials and 3091 with existing prescriptions.
‡Subgroup of all-treated population who entered the registry with new prescriptions.
§Calculated as the date of the last dose minus the date of the first dose in the registry plus 14 d, minus the total days of treatment interruptions during the registry.

Table III. Incidence rates for treatment-emergent adverse events (all-treated population)

	Subgroups with different durations of total exposure to adalimumab, events (E/100PY)				
	≤1 y	>1-3 y	>3-5 y	>5 y	Overall, events (E/100PY)
	PY = 493.4 N = 953	PY = 3999.9 N = 2029	PY = 8506.6 N = 2109	PY = 6242.9 N = 968	PY = 19,242.8 N = 6059
TEAEs					
Any TEAE	280 (56.7)	612 (15.3)	988 (11.6)	2393 (38.3)	4273 (22.2)
TEAE leading to death	8 (1.6)	10 (0.3)	7 (<0.1)	2 (<0.1)	27 (0.1)
Serious TEAEs overview					
Any serious TEAE	116 (23.5)	219 (5.5)	325 (3.8)	167 (2.7)	827 (4.3)
Any serious infection	30 (6.1)	58 (1.5)	64 (0.8)	36 (0.6)	188 (1.0)
Serious TEAEs by ≥20 events overall					
Cellulitis*	8 (1.6)	9 (0.2)	4 (<0.1)	5 (<0.1)	26 (0.1)
Pneumonia†	4 (0.8)	5 (0.1)	9 (0.1)	6 (0.1)	24 (0.1)
MI‡	5 (1.0)	4 (0.1)	8 (0.1)	3 (<0.1)	20 (0.1)
SCC§	0	2 (0.1)	11 (0.1)	7 (0.1)	20 (0.1)
TEAEs leading to registry discontinuation					
Any TEAE	34 (6.9)	19 (0.5)	17 (0.2)	4 (<0.1)	74 (0.4)
TEAEs by ≥5 events overall					
MI	1 (0.2)	2 (<0.1)	1 (<0.1)	1 (<0.1)	5 (<0.1)
TEAEs leading to registry drug discontinuation					
Any TEAE¶	149 (30.2)	125 (3.1)	100 (1.2)	14 (0.2)	388 (2.0)
TEAEs by ≥5 events overall					
MI‡	3 (0.6)	3 (<0.1)	1 (<0.1)	1 (<0.1)	8 (<0.1)
Drug hypersensitivity	4 (0.8)	0	1 (<0.1)	0	5 (<0.1)
Bronchitis	1 (0.2)	5 (0.1)	1 (<0.1)	0	7 (<0.1)
Cellulitis‖	3 (0.6)	3 (<0.1)	1 (<0.1)	0	7 (<0.1)
Pneumonia#	2 (0.4)	5 (0.1)	4 (<0.1)	0	11 (0.1)
Arthralgia	2 (0.4)	2 (<0.1)	1 (<0.1)	0	5 (<0.1)
Headache	4 (0.8)	2 (<0.1)	0	0	6 (<0.1)
Psoriasis	13 (2.6)	17 (0.4)	8 (<0.1)	1 (<0.1)	39 (0.2)

Some patients were exposed to adalimumab up to 6 y before entering the registry (Fig 1).
E/100PY, Events per 100 patient-years of total adalimumab exposure; *MI*, myocardial infarction; *PY*, patient-year; *SCC*, squamous cell carcinoma; *TEAE*, treatment-emergent adverse event.
*Includes cellulitis, and anorectal, staphylococcal, external-ear, infusion-site, and periorbital cellulitis.
†Includes pneumonia, and atypical, lobar, legionella, and aspiration pneumonias.
‡Includes MI and acute MI.
§Includes SCC and SCC of skin.
¶Events not coded (n = 6).
‖Includes cellulitis and anorectal cellulitis.
#Includes pneumonia, pneumonia mycoplasmal, atypical pneumonia, and pneumonia aspiration.

Table IV. Incidence rates for treatment-emergent adverse events of special interest (all-treated population)

	Subgroups with different durations of total exposure to adalimumab, events (E/100PY)				
	≤1 y	>1-3 y	>3-5 y	>5 y	Overall, events (E/100PY)
TEAEs of special interest	PY = 493.4 N = 953	PY = 3999.9 N = 2029	PY = 8506.6 N = 2109	PY = 6242.9 N = 968	PY = 19,242.8 N = 6059
Cardiovascular-related					
CVA	2 (0.4)	5 (0.1)	10 (0.1)	9 (0.1)	26 (0.1)
CHF	2 (0.4)	3 (<0.1)	6 (<0.1)	1 (<0.1)	12 (<0.1)
MI	5 (1.0)	4 (0.1)	8 (<0.1)	3 (<0.1)	20 (0.1)
Malignancies					
Malignancy	15 (3.0)	33 (0.8)	76 (0.9)	54 (0.9)	178 (0.9)
Lymphoma	0	0	2 (<0.1)	0	2 (<0.1)
HSTCL	0	0	0	0	0
NMSC	4 (0.8)	15 (0.4)	50 (0.6)	43 (0.7)	112 (0.6)
Leukemia	0	0	0	0	0
Melanoma	4 (0.8)	1 (<0.1)	3 (<0.1)	2 (<0.1)	10 (<0.1)
Malignancy, other*	7 (1.4)	17 (0.4)	21 (0.2)	10 (0.2)	55 (0.3)
Infection-related					
Infection	69 (14.0)	215 (5.4)	337 (4.0)	864 (13.8)	1485 (7.7)
Oral candidiasis	0	5 (0.1)	0	3 (<0.1)	8 (<0.1)
Opportunistic infection†	0	0	1 (<0.1)	0	1 (<0.1)
Active TB	0	2 (<0.1)	1 (<0.1)	0	3 (<0.1)
Latent TB	1 (0.2)	7 (0.2)	4 (<0.1)	3 (<0.1)	15 (<0.1)

Some patients were exposed to adalimumab up to 6 y before entering the registry (Fig 1).
CHF, Congestive heart failure; *CVA*, cerebrovascular accident; *E/100PY*, events per 100 patient-years of total adalimumab exposure; *HSTCL*, hepatosplenic T-cell lymphoma; *MI*, myocardial infarction; *NMSC*, nonmelanoma skin cancer; *PY*, patient-year; *TB*, tuberculosis; *TEAE*, treatment-emergent adverse event.
*Excluding melanoma, lymphoma, HSTCL, NMSC, or leukemia.
†Excluding oral candidiasis and TB.

Safety

This analysis focusses on TEAEs for the all-treated population. Rates of observational AEs and registry TEAEs of special interest are provided in the "Supplemental information" section and Table SIII (available at http://www.jaad.org).

The rate of serious TEAEs was 4.3 events per 100 PY of total adalimumab exposure (E/100PY) (Table III); the most common was infection (1.0 E/100PY), and no patterns across any exposure categories were identified. The rates for TEAEs leading to discontinuation from the registry or from registry drug overall were 0.4 E/100PY and 2.0 E/100PY, respectively (Table III). Rates of AEs leading to registry and registry drug discontinuation decreased across subgroups with different duration of total exposure to adalimumab treatment (Table III). The rate of events leading to death regardless of causality was 0.1 E/100PY (Table SIV; available at http://www.jaad.org). The most common event leading to death was MI (<0.1 E/100PY).

Cardiovascular-related TEAEs of special interest included cerebrovascular accident (0.1 E/100PY), MI (0.1 E/100PY), and congestive heart failure (<0.1 E/100PY) (Table IV). The overall incidence rate for malignancy was 0.9 E/100PY (<0.1 E/100PY for each of melanoma and lymphoma, and 0.6 E/100PY for nonmelanoma skin cancer) and 0.3 E/100PY for other malignancies (Table IV). The overall incidence rate of infections was 7.7 E/100PY (<0.1 E/100PY for each of oral candidiasis, active tuberculosis [TB], latent TB, and opportunistic infection other than oral candidiasis or TB) (Table IV). The times to the first occurrence of TEAEs of special interest are illustrated in Fig 2, *B*.

The standardized mortality ratio was similar for the all-treated (0.30 [95% confidence interval 0.19-0.44]) and the new-prescription (0.33 [95% confidence interval 0.17-0.60]) populations (Fig 3). The number of observed deaths was below the expected age-, sex-, and country-matched population.

Effectiveness

In both populations, PGA 0 or 1 was achieved by over 50% of patients at years 1 and 2, and generally over 60% at years 3 to 5 of their registry participation (Fig 4, *A*). The percentage of patients within each group achieving PGA 0 or 1 increased across the 5 years, with a slight decrease at year 4 in the new-prescription

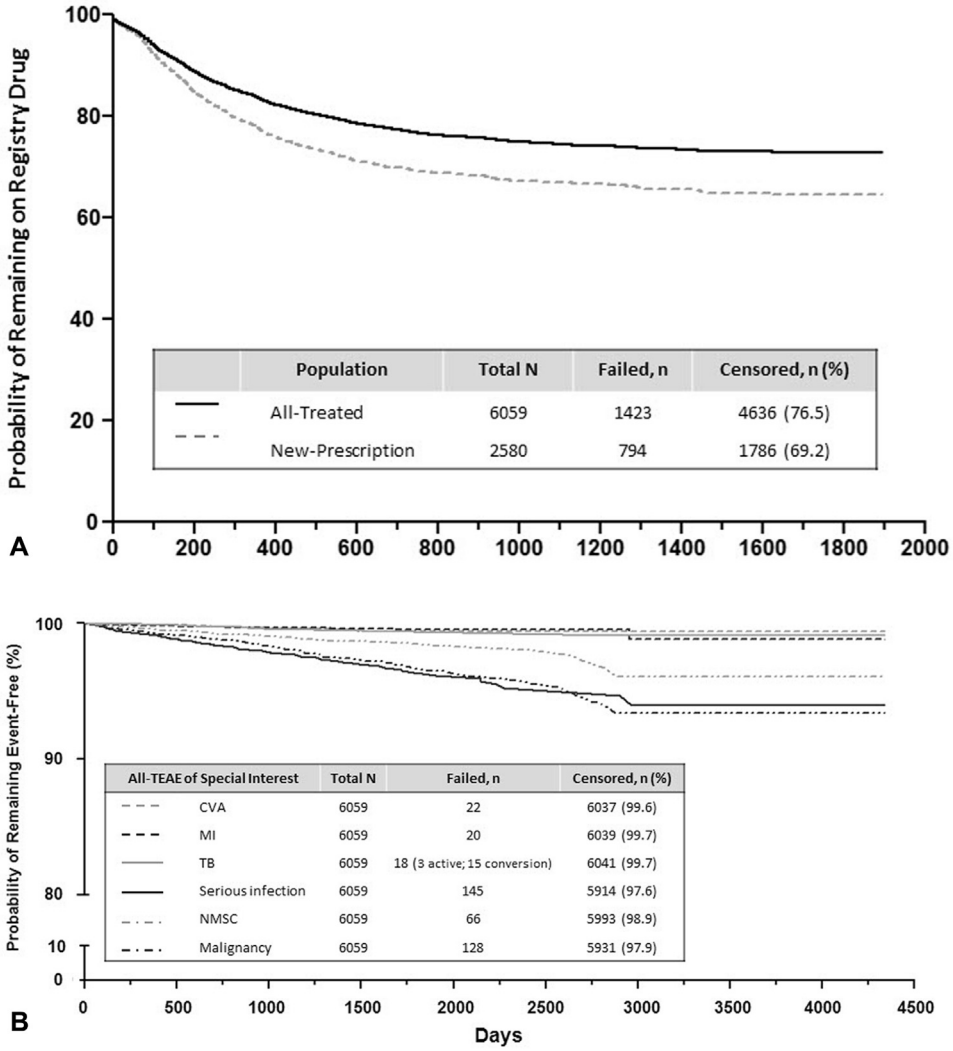


Fig 2. Kaplan-Meier plots: continuation on registry drug (**A**) and time to occurrence of first treatment-emergent adverse event (*TEAE*) of special interest (all-treated population) (**B**). *CVA*, Cerebrovascular accident; *MI*, myocardial infarction; *NMSC*, nonmelanoma skin cancer; *TB*, tuberculosis.

population. Over 50% of the new-prescription population with or without psoriatic arthritis achieved PGA 0 or 1 for psoriasis at years 1 to 4 (Fig 4, *B*).

DISCUSSION

In this analysis of the first 5 years of the ESPRIT registry, psoriasis-related comorbidities observed at baseline included inflammatory bowel disease, psoriatic arthritis, and other cardiovascular-related conditions including cerebrovascular accident, congestive heart failure, and MI, plus risk factors for cardiovascular disease (hypertension, diabetes, and hyperlipidemia).

Safety

Observed AEs in the first 5 years of this registry are consistent with the adalimumab safety profile and no new safety signals were observed. Historically, AEs of special interest after treatment with anti–tumor necrosis factor agents, include serious infections, malignancies, reactivation of TB,[14-20] and development or worsening of congestive heart failure.[21,22] Conflicting reports make any risk of lymphoma development difficult to assess as this risk has also been associated with pre-existing psoriasis and systemic inflammation, ie, up to a 2-fold increased risk in the psoriatic population at baseline.[15,23]

Across the subgroups of patients with different durations of total exposure to adalimumab in this analysis, incidence rates of any TEAE and infection decreased as time of total exposure to adalimumab increased up to 5 years. The subgroup with more than 5 years of total adalimumab exposure was more likely

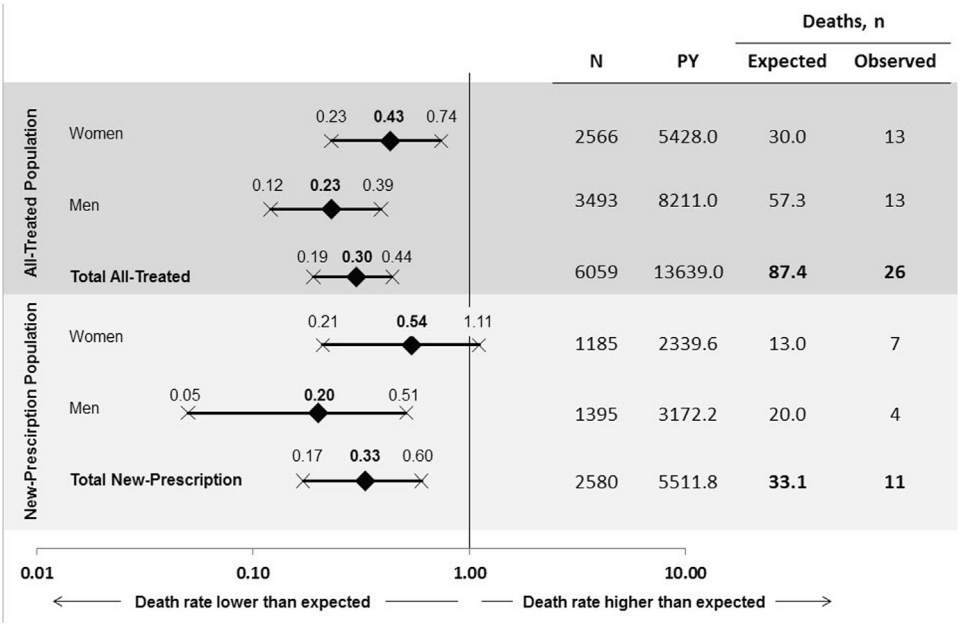


Fig 3. Standardized mortality, overall and by sex. *PY*, Patient-years of exposure.

to report AEs occurring before the registry after long exposure to adalimumab. As total exposure to adalimumab increased, rates also generally decreased after 1 year of total exposure for the TEAEs of special interest and remained stable thereafter, except rates for malignancies, which slightly increased after 3 years, and rates for nonmelanoma skin cancer, which generally increased slightly, although did not reach the level of the less than or equal to 1 year category rate. Incidence rates for any TEAE that led to registry or registry drug discontinuation decreased as total exposure increased. Generally, decreased rates of AEs with increased exposure to adalimumab were also reported in clinical trial populations treated long-term.[10,11,14]

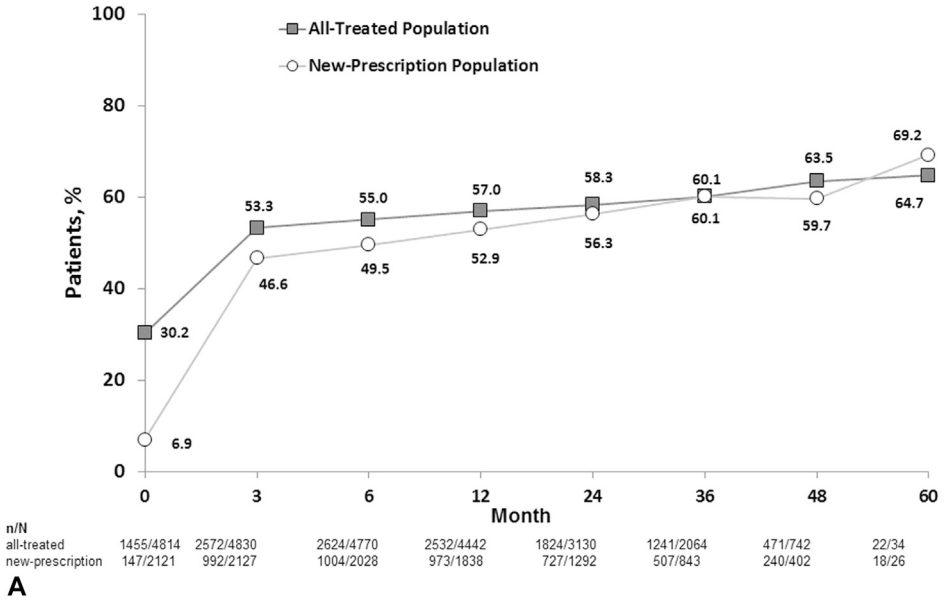
In this analysis, rates of any serious TEAE and serious TEAEs of special interest were low, and rates of serious TEAEs and serious infections decreased with increasing adalimumab exposure. In another observational registry of patients with psoriasis treated with an anti–tumor necrosis factor agent, the cumulative incidence proportions of serious TEAEs and serious infections increased with increasing exposure to drug over 3 years of the registry.[24] In that registry, rates of serious AEs (5.18 E/100PY) and serious infections (1.46 E/100PY) were similar to rates observed in the current analysis. The number of observed deaths in the current analysis (all-treated population, 0.8%) was lower than would be expected in the general population, and deaths caused by TEAEs (0.1 E/100PY) declined as exposure to adalimumab increased.

Effectiveness

Adalimumab treatment for psoriasis showed increasing observed effectiveness across the first 5 years of ESPRIT, even though at entry into the registry, some patients had received varying durations of adalimumab treatment and therefore, may have had clear to minimal disease severity at baseline. Long-term efficacy results may be affected by patient discontinuation that was due to poor efficacy. The majority of patients continuing in the registry after the first 5 years continued treatment with adalimumab. Patients with psoriatic arthritis experienced a similar degree of increasing effectiveness for psoriasis across the first 5 years; however, because psoriatic arthritis was patient-reported and not necessarily diagnosed previously by a rheumatologist, this result should be interpreted with caution.

Population differences

Despite the fact that the all-treated population likely had a longer exposure to adalimumab at entry to the registry compared with the new-prescription population, and that the portion of this group originating from a feeder trial may have had to meet more feeder-trial entry requirements than patients entering the registry outside of a feeder trial, the adalimumab safety and treatment-effectiveness profiles were similar for both populations. In addition, similar percentages of patients in both populations stayed in the registry and on adalimumab during the registry's first 5 years. These important observations suggest that the effectiveness and safety profiles of adalimumab are similar for patients



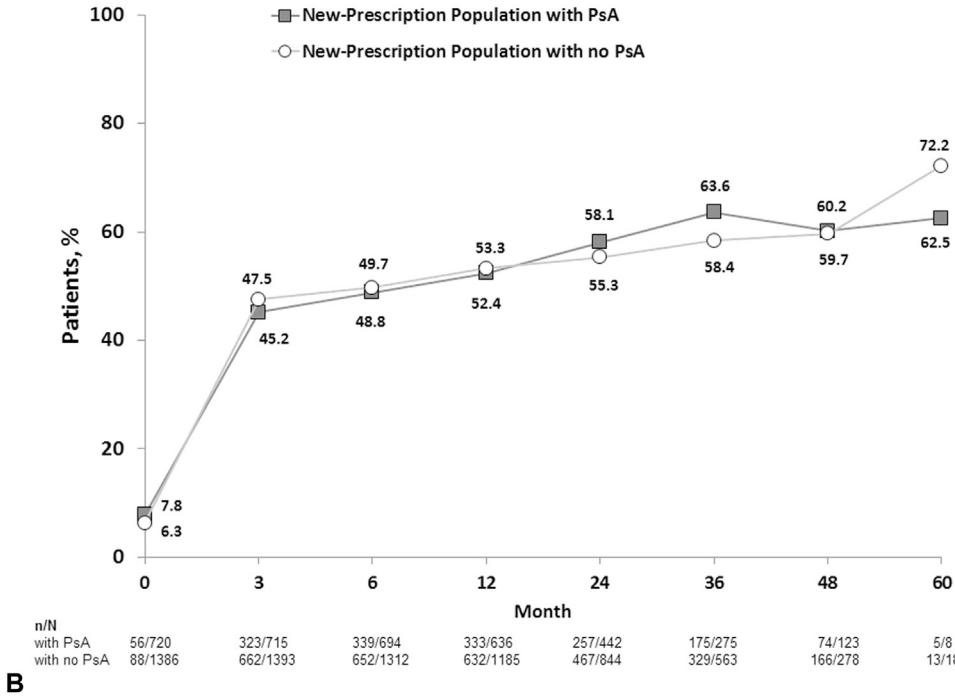


Fig 4. Proportion of observed (not necessarily on drug at the time of this assessment) patients achieving Physician Global Assessment 0 or 1: all-treated and new-prescription populations (**A**) and new-prescription population (**B**) by presence or absence of psoriatic arthritis (*PsA*). *n*, Number of patients with Physician Global Assessment 0 or 1 at the respective visit; *N*, number of patients with data at the respective visit.

whether treated in the physician's office or in controlled, clinical trials.

Limitations

Observational data are subject to outcome-reporting bias. At entry into the registry, some patients were adalimumab-naïve. For patients with long-term adalimumab treatment before registry enrollment, the total exposure-adjusted incidence rate of TEAEs may be underestimated, and lower PGA scores at registry entry may have affected efficacy results.

Conclusions

During the first 5 years of the ongoing, postmarketing ESPRIT registry, adalimumab continued to be

well tolerated in the vast majority of this large population of adults with chronic plaque psoriasis, and no new safety signals were identified. Safety was comparable with previous adalimumab clinical trials and postmarketing surveillance. Based on this analysis, the known safety profile of adalimumab remains unchanged. Adalimumab demonstrated continued effectiveness over the registry's first 5 years.

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SUPPLEMENTAL INFORMATION

Methods

Physician Global Assessment (PGA) 0 indicates clear or no plaque elevation or scaling accompanied by erythema of diffuse pink/red coloration. Physician Global Assessment 1 indicates minimal or plaque elevation possible but difficult to ascertain, scaling consisting of surface dryness and some white coloration; up to moderate erythema (up to definite red coloration).

Statistical analysis

As this was an analysis of a postmarketing observational registry, no missing data were replaced and outliers are included in the analyses. The observational period was the number of days from registry enrollment to last day in the registry. Descriptive statistics are presented for demographic and baseline characteristics. Effectiveness was measured by the proportion of patients achieving PGA 0 or 1, analyzed as observed during registry participation by descriptive statistics (patients were not necessarily taking adalimumab at the time of an assessment; they may have been taking a topical or a different systemic treatment or no treatment at all).

Adverse events (AEs) occurring between the period of a patient's first-ever adalimumab dose or the end of a feeder trial and the start of the registry were collected retroactively. Incidence rates of AEs are reported as events per 100 patient-years of total adalimumab exposure (E/100PY). A serious AE was any event that was fatal, was life-threatening, required hospital admission or prolonged hospitalization, was a congenital anomaly, resulted in a persistent or significant disability, required medical/surgical intervention to prevent a serious outcome, or was a spontaneous or an elective abortion. Serious AEs of special interest and AEs leading to adalimumab discontinuation were analyzed as observational AEs, treatment-emergent AEs (TEAEs), and registry TEAEs. Observational AEs and registry TEAEs are described below.

The standardized mortality ratio (ratio of observed to expected registry treatment-emergent deaths) was calculated using the most recent country-specific World Health Organization mortality through 2006. A ratio of less than 1.0 indicates an observed death rate below expected in an age-, sex-, and country-matched population. Confidence intervals were calculated using Byar approximation.

Patient exposure to adalimumab

Total exposure to adalimumab was calculated as the date of last adalimumab dose minus date of initial adalimumab dose plus 14 days minus total days of treatment interruption during the registry. For TEAEs by exposure category, the TEAE did not occur at these time points. They represent TEAEs within or outside of the registry reported by patients who had been exposed to adalimumab for the time periods indicated by the exposure category. Total exposure is based on the initial dose, whether occurring in or outside of the registry, and was analyzed in increments up to 1, more than 1 to 3, more than 3 to 5, and more than 5 years. Registry exposure was calculated as the date of the last adalimumab dose minus the date of the first adalimumab dose in the registry plus 14 days minus the total days of treatment interruption. The time to a patient's discontinuation of adalimumab was analyzed using Kaplan-Meier methodology.

The median duration of total exposure was 1118 days (range 14-4352) and 680 days (range 14-1892) for the all-treated and new-prescription populations, respectively; median exposure in registry was 765 days (range 14-1892) and 677 days (range 14-1892) for the all-treated and new-prescription populations, respectively; and during feeder trials was 953.0 days (N = 377). Approximately 50% (56.7% and 47.6% all-treated and new-prescription populations, respectively) had neither permanently stopped nor interrupted adalimumab treatment for more than 70 days (Table SII).

Time to discontinuation

Time to registry discontinuation was defined as the last contact minus first day in the registry plus 1 if the patient discontinued from the registry, otherwise the patient was censored at the cutoff date plus 1 day. Time to registry drug discontinuation was defined as the date of last adalimumab dose in the registry minus the first adalimumab dose in the registry plus 1 minus total days of treatment interruptions during the registry if the patient permanently discontinued the registry or the registry drug. If still on drug in the registry, the patient was censored at the cutoff date plus 1 day, adjusting the time since the first adalimumab dose in the registry for total days of treatment interruptions during the registry.

Time to first TEAE

Time to first TEAE (or registry TEAE) was defined as the date of first occurrence of the event minus the initial adalimumab dose (or first adalimumab dose in the registry), plus 1 minus the total number of days of treatment interruptions during the registry if the patient had an event. If the patient permanently discontinued the registry or registry drug without having a TEAE, the patient was censored at the last

adalimumab dose plus 70 days, adjusting the time since the initial adalimumab dose (or first adalimumab dose in the registry) for total days of treatment interruptions during the registry. If the patient was still on drug in the registry without a TEAE, the patient was censored at the cutoff date plus 1 day, adjusting the time since the initial adalimumab dose (or first adalimumab dose in the registry) for total days of treatment interruptions during the registry.

Observational AEs and registry TEAEs

See Table SIII. Observational AEs were events occurring from first registry day through last contact irrespective of treatment duration, and were analyzed for the all-treated and new-prescription populations. The incidence rate of the all-treated population with serious AEs was 5.5 E/100PY of observation, serious infections 1.2 E/100PY, and AEs leading to registry drug discontinuation 2.2 E/100PY. Incidence rates for the new-prescription population were 5.4 E/100PY for serious AEs, 1.2 E/100PY for serious infections, and 2.5 E/100PY for AEs leading to registry drug discontinuation. Fifty deaths (observational) were reported during the first 5 years of the registry; 2 of these patients had not received a registry drug and were not part of the all-treated population and 21 patients were of the new-prescription population. For 6 patients, causes of death that were possibly or probably related to adalimumab as determined by the investigator were arrhythmia, staphylococcal infection, staphylococcal sepsis, metastatic breast cancer, squamous cell carcinoma of the lung, and pneumonia aspiration.

Registry TEAEs were events occurring from first registry adalimumab dose through 70 days after last registry dose, excluding events during treatment interruptions, and were analyzed for only the all-treated population.

Table SI. Patient enrollment

Country	All-treated population, N = 6059 n (%)	New-prescription population, N = 2580 n (%)
United States	4217 (69.6)	1969 (76.3)
Canada	842 (13.9)	144 (5.6)
Germany	158 (2.6)	87 (3.4)
France	132 (2.2)	64 (2.5)
Czech Republic	112 (1.8)	37 (1.4)
Greece	101 (1.7)	53 (2.1)
The Netherlands	104 (1.7)	41 (1.6)
Spain	106 (1.7)	91 (3.5)
United Kingdom	91 (1.5)	10 (0.4)
Austria	85 (1.4)	65 (2.5)
Denmark	87 (1.4)	14 (0.5)
Ireland	21 (0.3)	2 (<0.1)
Sweden	3 (<0.1)	3 (0.1)

Table SII. Patient disposition

Reasons	Registry,* n (%)		Registry drug,† n (%)	
	All-treated population N = 6059	New-prescription population N = 2580	All-treated population N = 6059	New-prescription population N = 2580
Continuing	5416 (89.4)	2243 (86.9)	4636 (76.5)‡	1786 (69.2)‡
Discontinued	643 (10.6)	337 (13.1)	780 (12.9)‡	457 (17.7)‡
No dose discontinuation or interruption§	n/a	n/a	3438 (56.7)	1228 (47.6)
Reasons for discontinuation				
AE	25 (0.4)	14 (0.5)	108 (1.8)	62 (2.4)
Lost to follow-up	221 (3.6)	117 (4.5)	146 (2.4)	89 (3.4)
Lack of efficacy	74 (1.2)	49 (1.9)	639 (10.5)	385 (14.9)
Withdrew consent	190 (3.1)	93 (3.6)	80 (1.3)	44 (1.7)
Other	83 (1.4)	38 (1.5)	268 (4.4)	150 (5.8)

Reasons for discontinuation are listed by ≥1% of the all-treated population across discontinuation categories.
AE, Adverse event; *n/a*, not applicable.
*Reasons in ≤1% of patients were AE, intolerance, patient death, serious AE, satisfactory improvement, noncompliant, pregnancy. Data missing (all-treated population, n = 21; new-prescription population, n = 8).
†Reasons in ≤1% of patients were intolerance, patient death, serious AE, required additional therapy. Data missing (all-treated population, n = 149; new-prescription population, n = 56).
‡Among patients who have not yet discontinued the registry.
§Patients who neither permanently stopped adalimumab treatment nor interrupted adalimumab treatment for >70 d.

Table SIII. Incidence rates of observational adverse events and registry treatment-emergent adverse events

	Observational adverse events		Registry TEAEs
	All-treated population, N = 6059 PY of observation = 17,739.8 Events (E/100PY)	New-prescription population, N = 2580 PY of observation = 7777.6 Events (E/100PY)	All-treated population, N = 6059 PY of exposure = 13,639.0 Events (E/100PY)
Events of special interest			
Any event*	2487 (14.0)	960 (12.3)	2046 (15.0)
Any event leading to registry drug discontinuation	399 (2.2)	195 (2.5)	385 (2.8)
Any event leading to death	51 (0.3)	22 (0.3)	26 (0.2)
Cardiovascular-related			
MI	22 (0.1)	10 (0.1)	17 (0.1)
CVA	31 (0.2)	16 (0.2)	23 (0.2)
CHF	16 (<0.1)	6 (<0.1)	12 (<0.1)
Malignancy-related			
Malignancy	192 (1.1)	72 (0.9)	151 (1.1)
Lymphoma	3 (<0.1)	0	2 (<0.1)
HSTCL	0	0	0
NMSC	111 (0.6)	44 (0.6)	88 (0.6)
Leukemia	0	0	0
Melanoma	10 (<0.1)	4 (<0.1)	10 (<0.1)
Malignancy other†	69 (0.4)	24 (0.3)	52 (0.4)
Infection-related			
Infections	817 (4.6)	278 (3.6)	700 (5.1)
Oral candidiasis	3 (<0.1)	1 (<0.1)	3 (<0.1)
Opportunistic infection‡	2 (<0.1)	0	1 (<0.1)
Latent TB	20 (0.1)	8 (0.1)	14 (0.1)
Active TB	3 (<0.1)	3 (<0.1)	3 (<0.1)
Serious events; ≥10 events in any population			
Any serious adverse event§	977 (5.5)	418 (5.4)	758 (5.6)
Serious infection	212 (1.2)	90 (1.2)	175 (1.3)
Angina‖	13 (<0.1)	9 (0.1)	¶
CHF	11 (<0.1)	4 (<0.1)	¶
MI#	22 (0.1)	10 (0.1)	¶
Cellulitis**	30 (0.2)	17 (0.2)	¶
Pneumonia††	28 (0.2)	9 (0.1)	¶
Urinary tract infection	10 (<0.1)	3 (<0.1)	¶
Basal cell carcinoma	11 (<0.1)	3 (<0.1)	¶
SCC‡‡	18 (0.1)	11 (0.1)	¶
CVA	16 (<0.1)	9 (0.1)	¶
Depression	11 (<0.1)	5 (<0.1)	¶
Renal failure§§	11 (<0.1)	4 (<0.1)	¶
Psoriasis	15 (<0.1)	4 (<0.1)	¶

CHF, Congestive heart failure; *CVA*, cerebrovascular accident; *E/100PY*, events per 100 patient-years of observation/total adalimumab exposure; *HSTCL*, hepatosplenic T-cell lymphoma; *MI*, myocardial infarction; *NMSC*, nonmelanoma skin cancer; *PY*, patient-year; *SCC*, squamous cell carcinoma; *TB*, tuberculosis; *TEAE*, treatment-emergent adverse event.

*During the first 5 y of the registry, there was no reported reactivation of hepatitis B, HSTCL, leukemia, Stevens-Johnson syndrome, erythema multiforme–related adverse events, cutaneous vasculitis, amyotrophic lateral sclerosis, reversible posterior leukoencephalopathy syndrome, progressive multifocal leukoencephalopathy, adalimumab administration medication error, Merkel cell carcinoma, Waldenström macroglobulinemia, or glioblastoma.

†Malignancy other than lymphoma, HSTCL, leukemia, NMSC, or melanoma.

‡Excluding oral candidiasis and TB.

§Events not coded: observational, all-treated population (n = 25); observational, new-prescription population (n = 14).

¶Registry serious TEAEs were not summarized.

‖Includes angina unstable and angina pectoris.

#Includes MI and acute MI.

**Includes for all-treated: cellulitis, and anorectal, staphylococcal, external-ear, infusion-site, and periorbital cellulitis; and for new-prescription: cellulitis, and staphylococcal and periorbital cellulitis.

††Includes for all-treated: pneumonia, and atypical, lobar, legionella, and aspiration pneumonias; and for new-prescription: pneumonia, and staphylococcal and aspiration pneumonias.

‡‡Includes SCC and SCC of skin.

§§Includes renal failure and acute renal failure.

Table SIV. All treatment-emergent adverse events leading to death (all-treated population)

	Subgroups with different durations of total exposure to adalimumab, events (E/100PY)				
	≤1 y	>1-3 y	>3-5 y	>5 y	Overall events (E/100PY)
	PY = 493.4 N = 953	PY = 3999.9 N = 2029	PY = 8506.6 N = 2109	PY = 6242.9 N = 968	PY = 19,242.8 N = 6059
Any TEAE leading to death*	8 (1.6)	10 (0.3)	7 (<0.1)	2 (<0.1)	27 (0.1)
Arrhythmia	0	1 (<0.1)	0	0	1 (<0.1)
Cardiac arrest	0	0	1 (<0.1)	0	1 (<0.1)
Cardiac failure acute	0	1 (<0.1)	0	0	1 (<0.1)
CHF	1 (0.2)	0	0	0	1 (<0.1)
MI	0	2 (<0.1)	1 (<0.1)	1 (<0.1)	4 (<0.1)
Death†	2 (0.4)	1 (<0.1)	1 (<0.1)	1 (<0.1)	5 (<0.1)
Staphylococcal infection	1 (0.2)	0	0	0	1 (<0.1)
Staphylococcal sepsis	1 (0.2)	0	0	0	1 (<0.1)
Road traffic accident	1 (0.2)	0	0	0	1 (<0.1)
Breast cancer metastatic	0	1 (<0.1)	0	0	1 (<0.1)
Metastatic gastric cancer	0	0	1 (<0.1)	0	1 (<0.1)
Metastatic neoplasm	0	1 (<0.1)	0	0	1 (<0.1)
Papillary thyroid cancer	0	1 (<0.1)	0	0	1 (<0.1)
Sarcoma	0	1 (<0.1)	0	0	1 (<0.1)
Small cell lung cancer	0	0	1 (<0.1)	0	1 (<0.1)
Squamous cell carcinoma of lung	0	1 (<0.1)	0	0	1 (<0.1)
Subarachnoid hemorrhage	0	0	1 (<0.1)	0	1 (<0.1)
COPD	0	0	1 (<0.1)	0	1 (<0.1)
Pneumonia aspiration	1 (<0.1)	0	0	0	1 (<0.1)

CHF, Congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *E/100PY*, events per 100 patient-years of total adalimumab exposure; *MI*, myocardial infarction; *PY*, patient-year; *TEAE*, treatment-emergent adverse event.

*Not coded 1 event (<0.1 E/100PY) in ≤1 y total exposure category.

†Includes death and sudden death.