10-Year Interim Results From the ESPRIT Registry: Real-World Safety, Effectiveness, and Patient-Reported Outcomes of Adalimumab for Moderate-to-Severe Psoriasis

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OBJECTIVES

- To report the interim safety, effectiveness, and patient-reported outcomes over the registry's initial 10 years

INTRODUCTION

- Originator adalimumab (ADA), a fully human, recombinant, monoclonal antibody directed against tumor necrosis factor-α, is indicated to treat moderate-to-severe chronic plaque psoriasis (Ps) in adults[1]
- ESPRIT is an ongoing, 10-year, international, prospective, observational registry evaluating the long-term safety and effectiveness of originator ADA in routine clinical practice, for adults with moderate-to-severe chronic plaque Ps; it was initiated as a part of postmarketing commitment to the US FDA and EMA (NCT00799877)[2,3]

MATERIALS AND METHODS

STUDY DESIGN AND PATIENTS

- **Enrollment:** 26 September 2008 through 8 November 2012; 13 countries in North America and Europe
- **Treatment:** ADA was dosed according to local product labeling
- **Main Inclusion Criteria:** Adults (≥18 years) with chronic plaque Ps, who had been prescribed ADA according to local product labeling and met 1 of the following
  1. Previously initiated and continued ADA therapy with ≤70 consecutive days off drug
  2. Received initial ADA dose in 1 of 9 pre-registry feeder clinical trials or from an existing prescription outside such a trial
  3. Newly initiated ADA therapy within 4 weeks of registry entry
- **Populations:** *All-treated (All-Rx) Population:* received ≥1 dose of ADA in the registry. *New-prescription (New-Rx) Population:* subset of All-Rx who newly initiated ADA within 4 weeks pre-enrollment in registry

STATISTICAL ANALYSIS

- Descriptive statistics for baseline demographics and patient characteristics. Registry evaluations were at 3 and 6 months post enrollment, and then every 6 months for up to 10 years

MATERIALS AND METHODS (CONTINUED)

- **ADA exposure**
  - *Overall ADA exposure (outside of and within the registry)* was time from initial (first ever) ADA dose to 14 days after the last ADA dose in the registry, excluding the total number of days of treatment interruption (>70 days with no ADA dose, TI) in the registry
  - *Registry ADA exposure* was time from the first ADA dose in the registry to 14 days after the last ADA dose in the registry, excluding the total number TI days
- **Safety**
  - All-TEAEs are defined as treatment-emergent adverse events from the initial (first-ever) ADA dose through 70 days after the last ADA dose in the registry, excluding TIs
  - Cumulative incidence rates (IRs) of All-TEAEs per 100 patient-years (E/100PY) of overall ADA exposure are summarized by periods of overall ADA exposure for All-Rx
  - Standardized mortality ratio (SMR) is the ratio of observed to expected registry treatment-emergent deaths[4]
- **Effectiveness and Patient-Reported Outcomes (collected only in US):** The as-observed achievement of Physician Global Assessment score of clear or minimal disease (PGA 0 or 1) (patients were not necessarily receiving ADA at the time of assessment). Achievement of a Dermatology Life Quality Index score of no effect or a little effect of Ps on quality of life (DLQI 0 or 1)

RESULTS

- The 10-year interim analysis comprises data from previous ADA studies for rollover patients, data retroactively collected pre-registry entry since the initial ADA dose, and data cumulatively collected during the registry from 26 September 2008 through 30 November 2018
- Patients analyzed: 6014 All-Rx (6.4% from pre-registry feeder trials, 51.3% with existing prescriptions, and 2544 [42.3%] New-Rx). The majority (83.6%) were from US (69.6%), and Canadian (14.0%) sites

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RESULTS (CONTINUED)

- Medical history of interest, New-Rx: hypertension (n = 578, 22.7%); hyperlipidemia (n = 301, 11.8%); diabetes mellitus (n = 257, 10.1%); depression (n = 252, 9.9%)

Table 1. Patient Demographics and Disease Characteristics at Registry Entry

	All-Rx, N = 6014	New-Rx, N = 2544
Male, n (%)	3463 (57.6)	1370 (53.9)
Female, n (%)	2551 (42.4)	1174 (46.1)
Race[a,b], n (%)		
White	5243 (87.3)	2215 (87.1)
Black	178 (3.0)	65 (2.6)
Asian	258 (4.3)	105 (4.1)
Other	325 (5.4)	158 (6.2)
Age, years, median (range)	47 (18, 94)	46 (18, 91)
Weight[a], kg, median (range)	87.0 (41.0, 252.0)	87.0 (41.0, 218.0)
BMI[a], kg/m^2, median (range)	29.4 (16.0, 76.8)	29.4 (16.0, 69.9)
Ps family history[a], n (%)	Not analyzed[c]	1065 (42.0)
Ps duration[d], years, median (range)	Not analyzed[c]	13.4 (0, 68)
PGA[a], n (%)		
Clear (0)	731 (12.2)	53 (2.1)
Minimal (1)	1175 (19.6)	141 (5.6)
Mild (2)	1146 (19.1)	313 (12.4)
Moderate (3)	1770 (29.5)	1110 (43.8)
Severe (4)	965 (16.1)	745 (29.4)
Very severe (5)	211 (3.5)	171 (6.8)

[a]Missing data (n): Race; All-Rx (10), New-Rx (1). Weight; All-Rx (111), New-Rx (56). BMI; All-Rx (130), New-Rx (56). Ps family history (7). PGA; All-Rx (16), New-Rx (11). [b]Percentages calculated on non-missing values. Not analyzed as not all data were captured in the registry database. [c]Calculated at registry entry. ADA, adalimumab; All-Rx, all-treated population; New-Rx, new prescription population; BMI, body mass index; PGA, Physician Global Assessment; Ps, psoriasis.

- Patient disposition as of 30 November 2018:
  - Discontinued registry: 3138 (52.2%) All-Rx/1491 (58.6%) New-Rx. Major reasons: lost to follow-up (21.4%/27.6%) and withdrawal of consent (11.5%/11.0%)
  - Ongoing in registry: 2870 (47.7%) All-Rx/1048 (41.2%) New-Rx, of whom 1447 (24.1%) All-Rx/414 (16.3%) New-Rx have not permanently discontinued ADA and have never interrupted ADA treatment for >70 days
  - Prematurely discontinued ADA: 4106 (68.3%) All-Rx/1986 (78.1%) New-Rx. Major reasons: lack of efficacy (24.6%/30.3%) and lost to follow-up (21.7%/27.9%)

ADA EXPOSURE

- The 6014 All-Rx patients represented 28161.0 PY of overall ADA exposure. Median duration (days) of exposure and range for All-Rx: Overall ADA exposure was 1387.5 (14–5891); Registry ADA exposure was 1006.5 (14–3669)

SAFETY

- The IR (E/100PY) for All-TEAEs (All-Rx) was 22.5 overall. IR for events of special interest were relatively stable over time on ADA **(Table 2** and **Figure 1)**

Table 2. Incidence Rates of All-TEAEs of Interest by Periods of Overall ADA Exposure (All-Rx)

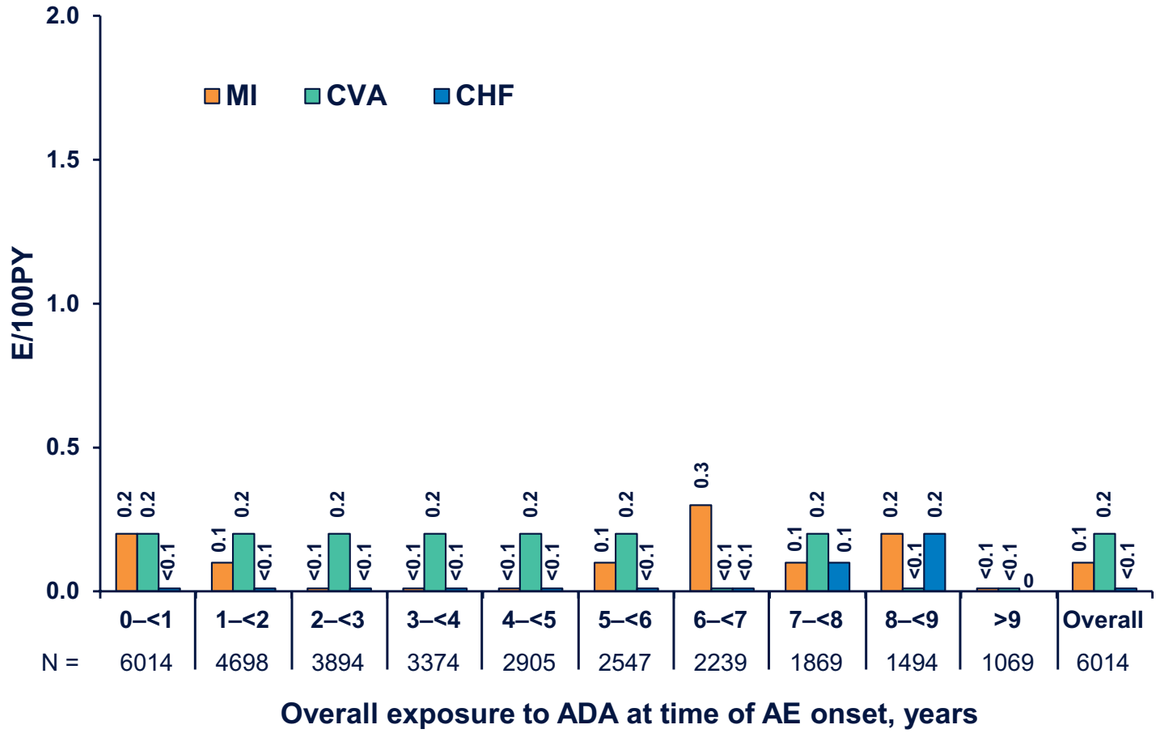
AE of Interest, E (E/100PY)	Years N = PY =	Overall ADA exposure at the onset of AE (years) 0–<1[a] 6014 5299.9	1–<2 4698 4257.4	2–<3 3894 3615.1	3–<4 3374 3135.7	4–<5 2905 2718.0	5–<6 2547 2386.9	6–<7 2239 2064.5	7–<8 1869 1678.4	8–<9 1494 1302.6	>9[b] 1069 1702.5	Overall 6014 28161.0
AE		1744 (32.9)	936 (22.0)	877 (24.3)	767 (24.5)	497 (18.3)	370 (15.5)	329 (15.9)	293 (17.5)	213 (16.4)	306 (18.0)	6332 (22.5)
AE leading to ADA d/c		164 (3.1)	78 (1.8)	59 (1.6)	50 (1.6)	42 (1.5)	22 (0.9)	27 (1.3)	14 (0.8)	16 (1.2)	18 (1.1)	490 (1.7)
Serious AE		253 (4.8)	184 (4.3)	183 (5.1)	153 (4.9)	139 (5.1)	95 (4.0)	87 (4.2)	82 (4.9)	66 (5.1)	79 (4.6)	1321 (4.7)
Oral candidiasis		7 (0.1)	1 (<0.1)	1 (<0.1)	0	0	0	0	1 (<0.1)	0	1 (<0.1)	11 (<0.1)
Active tuberculosis		3 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)	0	1 (<0.1)	1 (<0.1)	0	8 (<0.1)
Opportunistic infection, other[c]		1 (<0.1)	0	0	0	1 (<0.1)	0	2 (<0.1)	1 (<0.1)	0	0	5 (<0.1)
Any malignancy		56 (1.1)	45 (1.1)	42 (1.2)	38 (1.2)	44 (1.6)	31 (1.3)	31 (1.5)	30 (1.8)	21 (1.6)	21 (1.2)	359 (1.3)
Lupus-like reactions and systemic lupus		6 (0.1)	0	0	4 (0.1)	0	0	0	0	0	0	10 (<0.1)
Demyelinating disorder		2 (<0.1)	0	2 (<0.1)	0	0	1 (<0.1)	0	0	0	0	5 (<0.1)
Serious infection		64 (1.2)	41 (1)	41 (1.1)	28 (0.9)	33 (1.2)	20 (0.8)	15 (0.7)	15 (0.9)	17 (1.3)	21 (1.2)	295 (1.0)
Injection site reaction		60 (1.1)	1 (<0.1)	0	1 (<0.1)	0	0	1 (<0.1)	0	0	0	63 (0.2)
AE leading to death		8 (0.2)	12 (0.3)	6 (0.2)	7 (0.2)	4 (0.1)	6 (0.3)	8 (0.4)	4 (0.2)	6 (0.5)	1 (<0.1)	62 (0.2)

[a]The AEs collected from rollover patients during feeder studies most likely occurred in the first years of overall ADA exposure. A closer AE documentation in feeder studies is expected compared with registry and retroactive collections of AEs for patients who initiated ADA therapy outside of an AbbVie clinical trial pre-registry. [b]Patients with ≥9 years overall ADA exposure are a selected subgroup from the overall population who had longest ADA exposure and potentially had a longer duration of disease. [c]Excluding oral candidiasis and tuberculosis. All-TEAE, All treatment-emergent adverse event; All-Rx, all-treated population; ADA, adalimumab; E, event; PY, patient year; AE, adverse event; d/c, discontinuation.

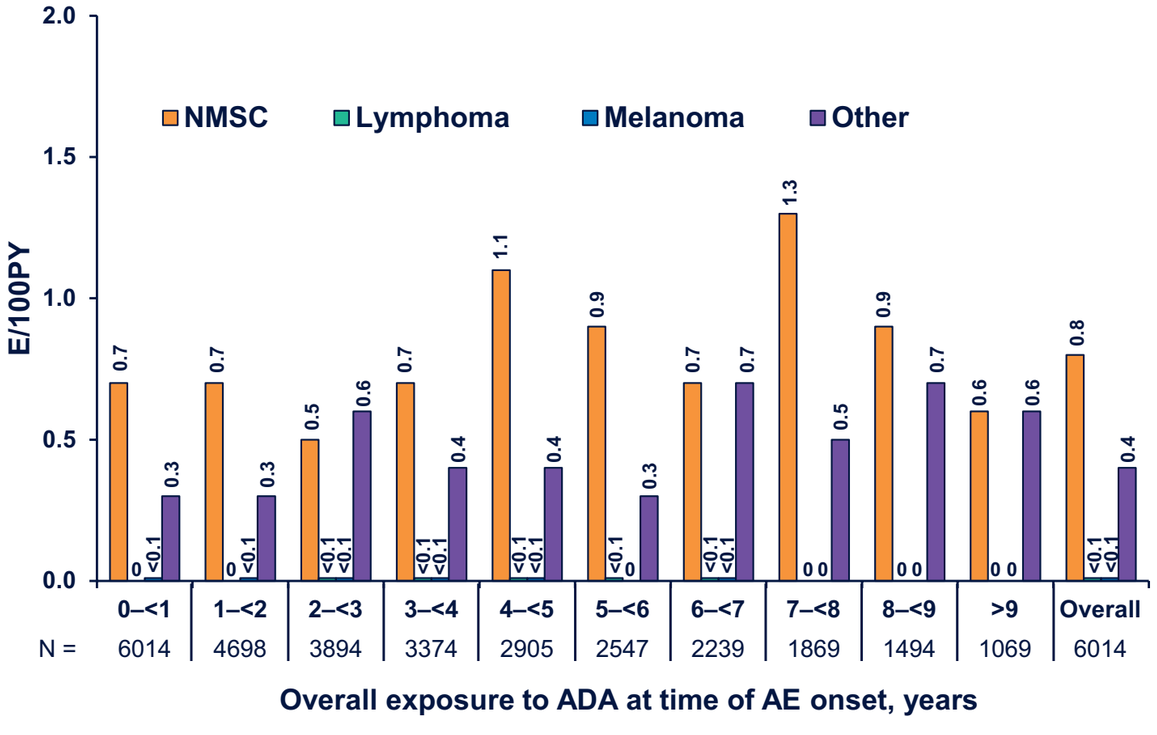
RESULTS (CONTINUED)

Figure 1. Incidence Rates for CV and Malignancy All-TEAEs (E/100PY) by Time of Event Occurrence (All-Rx)

A. CV-related Events



B. Malignancy Events



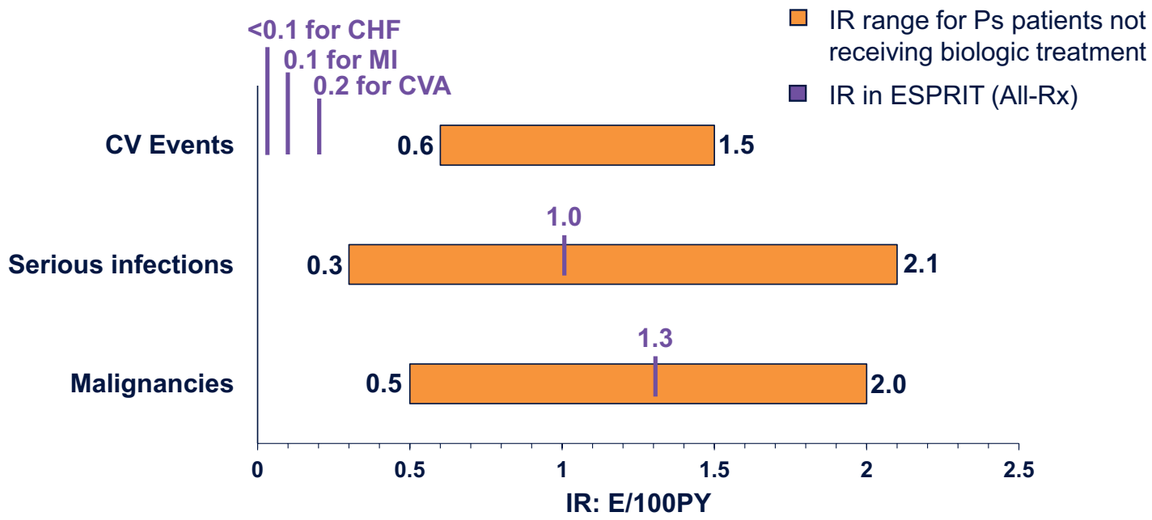
1 TEAE of leukemia was reported at ≥9 years, and 3 overall (<0.1 E/100PY); not shown in graph. "Other" indicates other than NMSC, lymphoma, melanoma, leukemia. CV, cardiovascular; MI, myocardial infarction; CVA, cerebrovascular accident; CHF, congestive heart failure; ADA, adalimumab; AE, adverse event; NMSC, non-melanoma skin cancer.

RESULTS (CONTINUED)

- The reported IRs are within range of published IRs of CV events, serious infections, and malignancies in Ps patients not receiving biologic treatment **(Figure 2)**

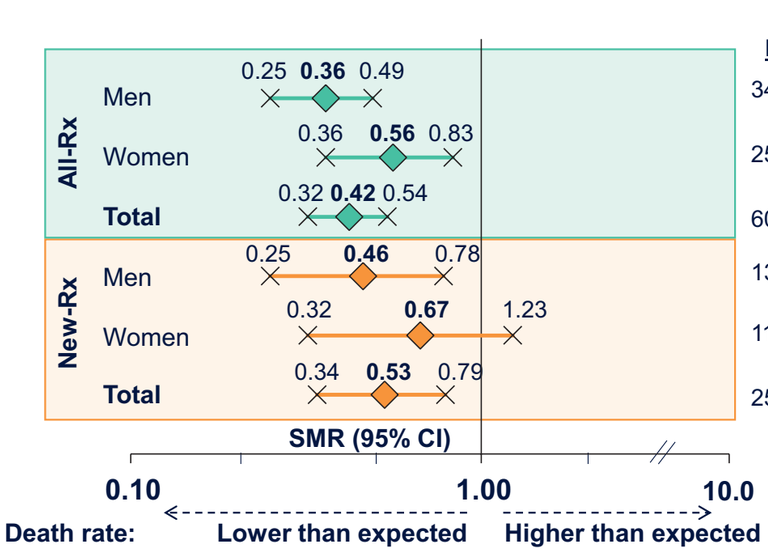
- SMR (All-Rx) was 0.42 (95% CI, 0.32, 0.54), indicating that the observed number of deaths was below expected (ie, <1.0) in an age-, sex- and country-matched population **(Figure 3)**

Figure 2. Overall Incidence Rates (IR) are Within Range of Published IRs[5–11]



CV, cardiovascular; CHF, congestive heart failure; MI, myocardial infarction; CVA, cerebrovascular accident.

Figure 3. Standardized Mortality Ratios (SMRs), Overall and by Gender



	N	PY	Expected Deaths, n	Observed Deaths, n
All-Rx Men	3463	14,203.3	100.9	36
All-Rx Women	2551	8370.6	43.2	24
All-Rx Total	6014	22,573.9	**144.1**	**60**
New-Rx Men	1370	4839.4	30.3	14
New-Rx Women	1174	2986.2	14.9	10
New-Rx Total	2544	7825.5	**45.2**	**24**

All-Rx, all-treated population; New-Rx, new prescription population; PY, patient year..

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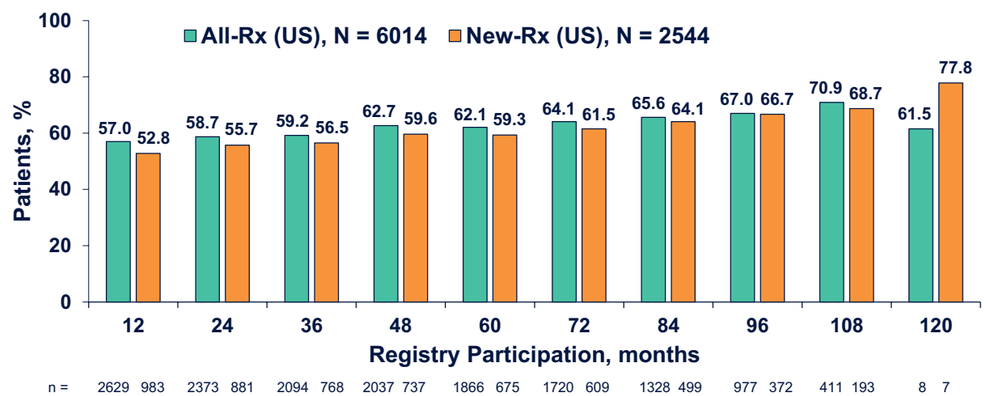
RESULTS (CONTINUED)

EFFECTIVENESS

- 57.0% to 66.6% of All-Rx and 52.8% to 65.8% of New-Rx patients achieved a PGA of 0 or 1 through the first 10 years of registry participation that are included in this analysis **(Figure 4)**

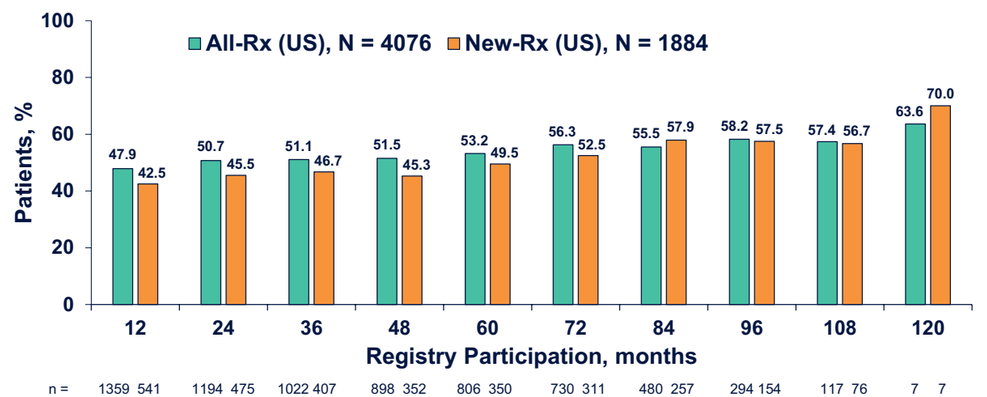
Figure 4. Achievement of PGA 0/1 Over Years 1–10 (as observed)



*The total number of patients at month 120 (N = 13) is based on available data at the time of this interim analysis. PGA, Physician Global Assessment; 0, clear disease; 1, minimal disease; All-Rx, all-treated population; New-Rx, new prescription population.

- Achievement of DLQI 0 or 1 from baseline was generally maintained through the first 10 years of registry participation that are included in this interim analysis **(Figure 5)**

Figure 5. Achievement of DLQI 0/1 (as observed)



*The total number of patients at month 120 (N = 11) is based on available data at the time of this interim analysis. DLQI, Dermatology Life Quality Index; 0, no effect on disease; 1, little effect on disease; All-Rx, all-treated population; New-Rx, new prescription population.

CONCLUSIONS

- During this 10-year interim analysis, safety was consistent with the known safety profile of ADA and no new safety signals were observed
- IRs of serious infections, CV events, and malignancy remained stable with more than 9 years of overall ADA exposure
- The number of treatment-emergent deaths in the registry was below the expected rate compared with the general population
- As-observed ADA effectiveness and DLQI 0 or 1 achievement were maintained through 120 months

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