Long-term Safety and Effectiveness of Adalimumab for Moderate to Severe Psoriasis: Results from the Eight-Year Interim Analysis of the ESPRIT registry

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INTRODUCTION

- Adalimumab (ADA), a fully human, recombinant, monoclonal antibody directed against tumor necrosis factor-α (TNF-α), is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.[1]
- ESPRIT (NCT00799877) is an ongoing, 10-year international prospective observational registry evaluating the long-term safety and effectiveness of originator ADA prescribed in routine clinical practice according to local product labeling for adult patients with chronic plaque psoriasis.[2]

OBJECTIVE

- To report the interim analysis of long-term safety and effectiveness of ADA treatment over the initial 8 years of the ESPRIT registry (26 September 2008–30 November 2016).

MATERIALS & METHODS

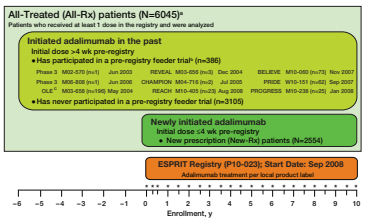
STUDY DESIGN AND PATIENTS

- Enrollment:
  - Patient enrollment was initiated on 26 September 2008 and completed on 8 November 2012.
  - As of 30 November 2016, 6066 patients were enrolled and 6045 patients were analyzed in the ESPRIT registry.
  - Study sites were located in the United States, Canada, Austria, the Czech Republic, Denmark, France, Germany, Greece, Ireland, the Netherlands, Spain, Sweden, and the United Kingdom.
- Treatment: ADA was dosed as recommended in the local product label.
- Main inclusion criteria **(Figure 1)**:
  - Adult patients (≥18 years) with chronic plaque psoriasis who have been prescribed ADA according to local product labeling and meet one of the following criteria:
    - Previously initiated ADA therapy and continued on ADA with no more than 70 consecutive days off drug.
      - The initial ADA dose was received either in a preregistry feeder clinical trial or from an existing prescription outside of a pre-registry feeder trial.
      - Source documentation of serious adverse events (SAEs), AEs of special interest, and dosing information since the initiation of therapy could be provided by the physician.
    - Newly initiated ADA therapy within 4 weeks of registry entry.

STATISTICAL ANALYSES

- Populations **(Figure 1)**:
  - All-treated (All-Rx) patient population: Patients who received at least 1 dose of ADA in the registry and were analyzed.
    - New-prescription (New-Rx) patient population: Patients who newly initiated ADA within 4 weeks prior to registry enrollment.
- Descriptive statistics are presented for baseline patient demographics and disease characteristics.

Figure 1. Study Design and Patient Population of ESPRIT Observational Registry



[a]Start dates are shown for clinical trials. [b]REVEAL and CHAMPION were among the feeder trials for the OLE; the number of patients in these trials was counted separately from the 196 patients in the OLE. [c]Patients were evaluated 3 and 6 months post enrollment, then every 6 months for ≤10 years. Patients are 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 discontinue registry drug are encouraged to remain in the registry.
OLE=open-label extension.

MATERIALS & METHODS (CONTINUED)

ADA EXPOSURE

- **"Overall exposure to ADA"** (outside of and within the registry) was calculated as time from the 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 in the registry.
- **"Registry exposure to ADA"** (within the registry) was calculated as time from first ADA dose in the registry to 14 days after the last ADA dose in registry, excluding the total number of days of treatment interruption in the registry.
- A treatment interruption (TI) is defined as >70 days without any ADA dose; TI starts at day 71 after ADA was stopped.

SAFETY

- All treatment-emergent AEs (All-TEAEs) were events occurring from the date of initial (first ever) ADA dose through 70 days after the date of the last ADA dose in the registry, excluding AEs occurring during TIs. This included AEs collected in the registry, collected retroactively before registry entry, and from feeder studies for patients rolling over from preregistry feeder clinical trials.
- Incidence rates for All-TEAEs are reported as events per 100 patient-years (E/100PY) of overall exposure to ADA.
- Standardized mortality ratio (SMR):
  - SMR was calculated as the ratio of observed to expected treatment-emergent deaths using the 2006 country-specific World Health Organization mortality rates.
  - An SMR <1.0 indicates that the observed number of deaths is lower than the expected rate in an age-, sex-, and country-matched general population.

EFFECTIVENESS

- The proportion of patients achieving Physician Global Assessment (PGA) score of "clear" or "minimal" were analyzed as observed during registry participation (patients were not necessarily receiving ADA at the time of assessment).

RESULTS

- This 8-year interim analysis used data collected from 6045 patients (2554 New-Rx patients, 42.2%) who were enrolled and dosed between 26 September 2008 and 30 November 2016 **(Table 1)**.
- The majority of patients in ESPRIT were from sites in the United States (69.5%) and Canada (13.9%).

Table 1. Patient Demographics and Disease Characteristics at Registry Entry (All-Rx and New-Rx Patient Populations)

Demographic or Characteristic	All-Rx N=6045	New-Rx N=2554
Sex		
Male, n (%)	3485 (57.7)	1376 (53.9)
Female, n (%)	2560 (42.3)	1178 (46.1)
Race[a], n (%)*		
White	5268 (87.3)	2221 (87.0)
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	251 (4.2)	116 (4.5)
Multi-race	22 (0.4)	12 (0.5)
Age, y, median (range)	47 (18–94)	46 (18–91)
Weight, kg, median (range)*	87.0 (41.0–252.0)[b]	86.0 (41.0–218.0)[c]
BMI, kg/m^2, median (range)	29.4 (16.0–76.8)[d]	29.4 (16.0–69.9)[e]
Psoriatic arthritis, n (%)*	Not analyzed[f]	868 (34.1)[g]
Family history of psoriasis, n (%)*	Not analyzed[f]	1067 (41.9)[h]
Duration of psoriasis[i], y, median (range)	Not analyzed[f]	13.4 (0–68.0)[h]
PGA[i], n (%)*		
Clear	733 (12.2)	53 (2.1)
Minimal	1176 (19.5)	140 (5.5)
Mild	1150 (19.2)	312 (12.3)
Moderate	1778 (29.5)	1117 (43.9)
Severe	973 (16.1)	748 (29.4)
Very severe	213 (3.5)	172 (6.8)

*Percentages calculated on non-missing values. [a]Missing data: All-Rx, n=11; New-Rx, n=2. [b]n=5931; [c]n=2497; [d]n=5912; [e]n=2492. [f]Not analyzed because not all data were captured in the registry database. [g]n=2549; [h]n=2547. [i]Calculated at registry entry. [j]Many patients had received ADA before entering the registry, demonstrated by the number of patients entering the registry with a PGA score of "clear" or "minimal." Missing data: All-Rx, n=22; New-Rx, n=12.
ADA=adalimumab; All-Rx=all-treated patient population; BMI=body mass index; New-Rx=new prescription patient population; PGA=Physician Global Assessment.

RESULTS (CONTINUED)

- 3662 (60.6%) All-Rx and 1372 (53.7%) New-Rx patients are continuing in the registry as of 30 November 2016.
  - Of those, 2494 (41.3%) All-Rx and 791 (31.0%) New-Rx patients have not permanently discontinued ADA.
  - Of those, 1688 (27.9%) All-Rx and 497 (19.5%) New-Rx patients have never interrupted ADA treatment for >70 days or permanently discontinued ADA.
- 2383 (39.4%) All-Rx and 1182 (46.3%) New-Rx patients discontinued from the registry; the most frequent reason for discontinuation was being lost to follow-up (18.2%, All-Rx and 23.9%, New-Rx; **Table 2**).

Table 2. Reasons for Discontinuation from Registry and Registry Drug (All-Rx and New-Rx Patient Populations)

Reason for Discontinuation (in >1% Patients)	All-Rx N=6045 n (%)	New-Rx N=2554 n (%)
From registry[a], any reason	2383 (39.4)	1182 (46.3)
Lost to follow-up	1100 (18.2)	611 (23.9)
Withdrew consent	521 (8.6)	219 (8.6)
Lack of efficacy	98 (1.6)	63 (2.5)
Death	95 (1.6)	36 (1.4)
Patient moved	98 (1.6)	39 (1.5)
Noncompliant	98 (1.6)	64 (2.5)
Other	472 (7.8)	189 (7.4)
From registry drug[b], any reason	3551 (58.7)	1763 (69.0)
Lack of efficacy	1286 (21.3)	692 (27.1)
Lost to follow-up	757 (12.5)	407 (15.9)
Withdrew consent	376 (6.2)	152 (6.0)
AE	188 (3.1)	95 (3.7)
SAE or SAE of interest	114 (1.9)	47 (1.8)
Other	778 (12.9)	333 (13.0)

[a]Reasons for registry discontinuations in ≤1% of patients were AE, intolerance, SAE or SAE of interest, satisfactory improvement, pregnancy, or unknown. [b]Reasons for registry drug discontinuations in ≤1% of patients were intolerance, patient moved, satisfactory improvement, patient death, noncompliance, pregnancy, required additional therapy, or unknown.
AE=adverse event; All-Rx=all-treated patient population; New-Rx=new prescription patient population; SAE=serious AE.

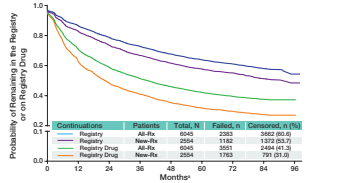
- Median (range) duration of overall exposure to ADA was 1430 (14–5161) and 657.5 (14–2947) days for All-Rx and New-Rx patient populations, respectively.
- Median (range) duration of registry exposure to ADA was 1077 (14–2947) and 656 (14–2947) days for All-Rx and New-Rx patient populations, respectively.
- The number of patients according to duration of overall exposure to ADA and registry exposure to ADA are shown in **Figure 2**.

Figure 2. Number of Patients Based on Duration of ADA Exposure (All-Rx and New-Rx Patient Populations)

ADA=adalimumab; All-Rx=all-treated patient population; New-Rx=new prescription patient population.

- Time to discontinuation from the registry and from registry drug in All-Rx and New-Rx patients is shown in **Figure 3**.

Figure 3. Time to Discontinuation From the Registry and From Registry Drug (ADA, All-Rx, and New-Rx Patient Populations)



[a]Time 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.

SAFETY

- The incidence rates (E/100PY) of All-TEAEs of interest in All-Rx patients by periods of overall exposure to ADA at the time of AE onset remained stable over time **(Table 3)**.

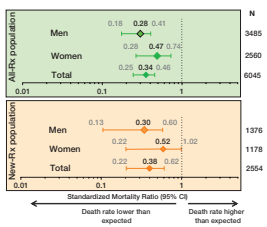
Table 3. Incidence Rates of All-TEAEs of Interest by Periods of Overall Exposure to ADA (All-Rx Patient Population)

		Overall exposure to ADA at the onset of AE (years)										
AE of Interest	N=	0 – <1[a]	1 – <2	2 – <3	3 – <4	4 – <5	5 – <6	6 – <7	7– <8	8 –<9	≥9[b]	Overall
E (E/100PY)	PY=	6045 5363.0	4779 4347.6	3995 3716.8	3470 3221.1	2983 2738.3	2461 2192.2	1943 1660.8	1347 1020.3	671 485.6	324 522.1	6045 25268.1
AE		1724 (32.1)	923 (21.2)	877 (23.6)	753 (23.4)	459 (16.8)	299 (13.6)	222 (13.4)	130 (12.7)	68 (14.0)	93 (17.8)	5548 (22.0)
AE leading to d/c of ADA		164 (3.1)	72 (1.7)	61 (1.6)	47 (1.5)	40 (1.5)	15 (0.7)	19 (1.1)	7 (0.7)	3 (0.6)	8 (1.5)	436 (1.7)
Serious AE		249 (4.6)	186 (4.3)	189 (5.1)	152 (4.7)	130 (4.7)	80 (3.6)	65 (3.9)	40 (3.9)	20 (4.1)	31 (5.9)	1142 (4.5)
Serious infection		64 (1.2)	41 (0.9)	41 (1.1)	28 (0.9)	32 (1.2)	20 (0.9)	12 (0.7)	6 (0.6)	4 (0.8)	8 (1.5)	256 (1.0)
Oral Candidiasis		7 (0.1)	1 (<0.1)	1 (<0.1)	0	0	0	0	0	0	0	9 (<0.1)
Active tuberculosis		3 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	0	0	0	0	0	5 (<0.1)
Opportunistic infection, other[c]		1 (<0.1)	0	0	0	1 (<0.1)	0	2 (0.1)	0	0	0	4 (<0.1)
Malignancy		54 (1.0)	46 (1.1)	41 (1.1)	37 (1.1)	35 (1.3)	20 (0.9)	22 (1.3)	14 (1.4)	6 (1.2)	7 (1.3)	282 (1.1)
Congestive heart failure		3 (<0.1)	1 (<0.1)	2 (<0.1)	3 (<0.1)	2 (<0.1)	0	1 (<0.1)	0	0	0	12 (<0.1)
Lupus-like reactions and systemic lupus[d]		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)
AE leading to death		8 (0.1)	12 (0.3)	6 (0.2)	5 (0.2)	2 (<0.1)	2 (<0.1)	4 (0.2)	2 (0.2)	3 (0.6)	0	44 (0.2)

[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 retroactive collection of AEs for patients who initiated adalimumab therapy outside of an AbbVie clinical trial before the registry. [b]Patients with ≥9 years of overall exposure to adalimumab are a selected subgroup from the overall population who had 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 the 7 patients with 10 events of lupus-like reactions and systemic lupus during the registry.
All-TEAE=All treatment-emergent adverse event; All-Rx=all-treated patient population; AE=adverse event; ADA=adalimumab; d/c=discontinuation.

- SMR was 0.34 (95% CI, 0.25–0.46) for All-Rx and 0.38 (95% CI, 0.22–0.62) for New-Rx, indicating that the observed number of deaths was below expected for age-, sex-, and country-matched population **(Figure 4)**.

Figure 4. Standardized Mortality Ratios (SMRs), Overall and by Gender (All-Rx and New-Rx Patient Populations)

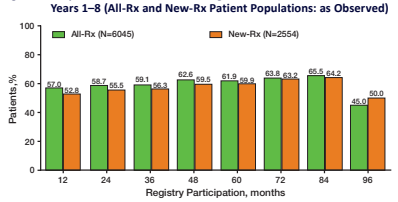


All-Rx=all-treated patient population; New-Rx=new prescription population; PY=patient-years.

EFFECTIVENESS

- 45.0%–65.5% of All-Rx and 50.0%–64.2% of New-Rx patients achieved a PGA score of "clear" or "minimal" during years 1–8 of registry participation **(Figure 5)**.

Figure 5. Proportion of Patients Achieving PGA "Clear" or "Minimal" Over Years 1–8 (All-Rx and New-Rx Patient Populations: as Observed)



N*=number of patients with non-missing PGA data at the respective visit; All-Rx=all-treated patient population; New-Rx=new prescription population; PGA=Physician Global Assessment.

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CONCLUSIONS

- No new safety signals were observed with ADA treatment during this 8-year interim analysis, and safety was consistent with the known safety profile of ADA.
- Incidence rates of serious infections and malignancies remained stable with up to >8 years of overall exposure to ADA.
- The number of treatment-emergent deaths in the registry was below the expected rate compared with the general population.
- As-observed effectiveness of ADA remained stable through 96 months.

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