

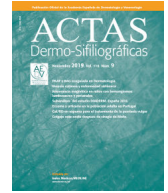


ACADEMIA ESPAÑOLA
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Actas Dermo-Sifiliográficas

journal homepage: www.actasdermo.org



Original Article

Safety Profile of Systemic Therapy for the Management of Psoriasis in Patients With Diabetes Mellitus: Data From the BIOBADADERM Prospective Cohort

J.J. Lluch-Galcerá^{a,b}, J.M. Carrascosa^{c,*}, A. González-Quesada^d, A. Sahuquillo^e, R. Rivera Díaz^f, M. Llamas-Velasco^g, E. Herrera-Acosta^h, I. Belinchónⁱ, F.J. Gómez García^j, O. Baniandrés-Rodríguez^k, D.P. Ruiz-Genao^l, J.L. López-Estebanz^l, L.R. Fernández-Freire^m, P. de la Cueva Dobaoⁿ, M. Ferrán Farrés^o, A. Mateu Puchades^p, R. Ruiz-Villaverde^{q,r}, J. Riera-Monroig^s, M. Ara-Martín^t, M. Roncero Riesco^u, T. Gracia-Cazaña^v, M.T. Abalde Pintos^{w,x}, C. Pujol Marco^e, C. García-Donoso^f, E. del Alcázar^c, C. Santamaría^g, J. Suárez Pérez^h, B. Rodríguez Sánchez^k, K. Díez-Madueñoⁿ, V. Lezcano Biosca^t, A.M. Morales Callaghan^v, L. Salgado-Boquete^{w,x}, A. Montes-Torres^t, B. González-Sixto^{w,x}, M.Á. Descalzo^y, I. García-Doval^{y,z}

^a Department of Dermatology, Hospital General de Granollers, Granollers, Spain

^b Universitat Autònoma de Barcelona, Departament de Medicina, Barcelona, Spain

^c Department of Dermatology, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Departament de Medicina, Badalona, Barcelona, Spain

^d Department of Dermatology, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Islas Canarias, Spain

^e Department of Dermatology, Hospital Universitario y Politécnico La Fe, Valencia, Spain

^f Department of Dermatology, Hospital Universitario 12 de Octubre, Universidad Complutense, Madrid, Spain

^g Department of Dermatology, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria de La Princesa (IIS-LP), Madrid, Spain

^h Department of Dermatology, Hospital Universitario Virgen de la Victoria, Málaga, Spain

ⁱ Department of Dermatology, Hospital General Universitario Dr Balmis-Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Universidad Miguel Hernández, Alicante, Spain

^j Department of Dermatology, Hospital Universitario Reina Sofía, Córdoba, Spain

^k Department of Dermatology, CEIMI, Hospital General Universitario Gregorio Marañón, Madrid, Spain

^l Department of Dermatology, Hospital Universitario Fundación Alcorcón, Alcorcón, Madrid, Spain

^m Department of Dermatology, Hospital Virgen del Rocío, Sevilla, Spain

ⁿ Department of Dermatology, Hospital Universitario Infanta Leonor, Madrid, Spain

^o Department of Dermatology, Hospital del Mar, Parc de Salut Mar, Barcelona, Spain

^p Department of Dermatology, Hospital Universitario Doctor Peset, Valencia, Spain

^q Department of Dermatology, Hospital Universitario San Cecilio, Granada, Spain

^r Instituto Biosanitario de Granada (ibs.GRANADA), Spain

^s Department of Dermatology, Hospital Clínic de Barcelona, Universitat de Barcelona, Barcelona, Spain

^t Department of Dermatology, Hospital Clínic Universitario Lozano Blesa, Zaragoza, Spain

^u Department of Dermatology, Hospital Universitario de Salamanca, Salamanca, Spain

^v Department of Dermatology, Hospital Universitario Miguel Servet, Zaragoza, Spain

^w Department of Dermatology, Complejo Hospitalario Universitario de Pontevedra, Pontevedra, Spain

^x DIPO Research Group, Instituto de Investigación Sanitaria Galicia Sur, Spain

^y Research Unit, Academia Española de Dermatología y Venereología, Madrid, Spain

^z Department of Dermatology, Complejo Hospitalario Universitario de Vigo, Vigo, Pontevedra, Spain

ARTICLE INFO

Keywords:

Psoriasis
Diabetes mellitus
Systemic therapy
Safety
Real-world evidence
BIOBADADERM

ABSTRACT

Background and objective: Patients with psoriasis and concomitant diabetes mellitus (DM) may be vulnerable to diabetes-related adverse events (DM-AEs). This study aimed to evaluate the incidence of DM-AEs associated with systemic treatments used in patients with psoriasis and DM.

Methods: We conducted a prospective cohort study using data from the BIOBADADERM registry. We calculated incidence rates (IRs) of DM-AEs for each systemic treatment class, including biologics (tumor necrosis factor [TNF] inhibitors, interleukin [IL]-12/23 inhibitors, IL-17 inhibitors, and IL-23 inhibitors), conventional systemic

* Corresponding author.

E-mail address: jmcarrascosa@hotmail.com (J.M. Carrascosa).

<https://doi.org/10.1016/j.ad.2026.104688>

Received 31 December 2025; Accepted 1 February 2026

Available online xxx

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Please cite this article as: J.J. Lluch-Galcerá, J.M. Carrascosa, A. González-Quesada et al., Safety Profile of Systemic Therapy for the Management of Psoriasis in Patients With Diabetes Mellitus: Data From the BIOBADADERM Prospective Cohort, ACTAS Dermo-Sifiliográficas, <https://doi.org/10.1016/j.ad.2026.104688>

therapies (methotrexate [MTX], cyclosporine, and acitretin), and apremilast (APR). The primary outcome was the adjusted incidence rate ratio (aIRR) for DM-AEs comparing patients receiving MTX with those receiving other systemic therapies using Poisson regression models adjusted for potential confounders.

Results: The study included 732 patients, 1401 treatment cycles, and 2865 person-years (Pys) of follow-up. APR (aIRR, 0.30; 95% CI, 0.10–0.60) was associated with a significantly lower risk of DM-AEs compared with MTX. Cyclosporine (aIRR, 7.50; 95% CI, 3.30–17.30) and acitretin (aIRR, 2.10; 95% CI, 1.20–3.70) were associated with a higher risk compared with MTX.

Conclusions: Among patients with psoriasis and DM, APR was associated with a lower incidence of DM-AEs, whereas cyclosporine and acitretin were associated with higher incidences compared with MTX.

45 Background

46 **Q3** Psoriasis is a chronic inflammatory skin disease associated with me-
47 tabolic and cardiovascular comorbidities.^{1,2} Diabetes mellitus (DM) is
48 more prevalent among individuals with psoriasis and correlates with
49 disease severity.^{3,4}

50 In patients with psoriasis and established DM, a clinically relevant
51 question is whether systemic psoriasis therapies modify the inciden-
52 ce of diabetes-related adverse events (DM-AEs), such as major adverse
53 cardiovascular events (MACE), diabetic nephropathy, and metabolic
54 disturbances, reflecting the combined effects of diabetes, psoriatic in-
55 flammation, and drug mechanisms rather than attributing risk to either
56 condition alone.^{1–3} Because therapeutic classes have distinct mecha-
57 nisms and cardiometabolic profiles, they may differentially influence
58 these outcomes. Moreover, when psoriasis and DM coexist, baseline car-
59 diovascular risk is already elevated, making MACE a central concern.^{2,4}

60 Although increasing evidence exists regarding cardiovascular risk as-
61 sociated with psoriasis and its systemic treatments,^{4–8} data specifically
62 addressing DM-AEs in patients with DM receiving therapy for psoriasis
63 remain limited.

64 This study aimed to evaluate the safety of different systemic the-
65 rapies for psoriasis in patients with DM. Given the limited real-world
66 evidence on how these treatments influence the incidence of DM-AEs
67 and serious adverse events (DM-SAEs), we examined this association
68 using data from the nationwide BIOBADADERM registry.

69 Methods

70 BIOBADADERM is a nationwide, prospective, multicenter cohort
71 registry of individuals with psoriasis receiving systemic treatment in
72 routine clinical practice. A comprehensive description of BIOBADA-
73 DERM has been published previously.^{9,10}

74 All patients with moderate-to-severe psoriasis who initiated systemic
75 therapy for the first time between January 2008 and November 2024 at
76 21 participating hospitals were included in the registry. Additionally,
77 a cohort of patients with psoriasis receiving classic nonbiologic syste-
78 mic treatment for the first time was included. Standardized definitions
79 of DM-AEs were collected during follow-up using the Medical Dictio-
80 nary for Regulatory Activities (MedDRA). BIOBADADERM undergoes
81 continuous online monitoring, and data are validated annually through
82 on-site audits. The registry was approved by the *Hospital Universitario 12*
83 *de Octubre* Ethics Committee (216/07), and its operation adheres to the
84 principles of the Declaration of Helsinki. All patients provided written
85 informed consent before participation.

86 Study groups and outcomes

87 Only individuals with psoriasis and DM were included in this analy-
88 sis.

89 Patients were considered exposed to study drugs from treatment
90 initiation until the last administered dose, November 2024, or the cen-
91 soring date for patients lost to follow-up. For these individuals, the

92 censoring date corresponded to their last dermatology visit. Pharmaco-
93 logic groups included classic systemic therapies, such as acitretin (ACT),
94 methotrexate (MTX), and cyclosporine (CYA); phosphodiesterase-4
95 (PDE4) inhibitors, such as apremilast (APR); tumor necrosis factor
96 alpha (TNF- α) inhibitors, including adalimumab, certolizumab, etaner-
97 cept, infliximab, and corresponding biosimilars; interleukin (IL)-12/23
98 inhibitors, such as ustekinumab and biosimilars; IL-23 inhibitors,
99 including guselkumab, risankizumab, and tildrakizumab; and IL-
100 17 inhibitors, including brodalumab, ixekizumab, bimekizumab, and
101 secukinumab.

102 Patients could contribute more than 1 treatment cycle during follow-
103 up and, therefore, could be included in more than 1 treatment group
104 over time. Treatment groups were defined at the treatment-cycle level,
105 independently of outcome occurrence. DM-AEs were attributed to a gi-
106 ven treatment cycle if they occurred between treatment initiation and
107 the last dose or within 90 days after the last dose.¹¹ Patients receiving
108 combination therapy were excluded from this analysis.

109 Based on previous literature, we defined DM-AEs as events invol-
110 ving the development or progression of clinically recognized diabetic
111 complications, including macrovascular outcomes (e.g., MACE4), mi-
112 crovascular complications (e.g., diabetic nephropathy, retinopathy,
113 neuropathy, and diabetic foot disorders, including ulcers and os-
114 teomyelitis), and acute metabolic disturbances, such as hypoglycemia,
115 hyperosmolar hyperglycemic state, and diabetic ketoacidosis.^{2,12,13}
116 We also prespecified new-onset or clinically meaningful worsening of
117 hyperglycemia and hypertriglyceridemia as DM-AEs because these drug-
118 modifiable metabolic abnormalities are diabetes related, prompt clinical
119 intervention, and are established intermediates associated with acute
120 metabolic decompensation and downstream micro- and macrovascular
121 complications.

122 To ensure clinical relevance, DM-AEs were restricted to specific
123 complications with established associations with diabetes. Nonspec-
124 ific conditions, such as frequent infections (e.g., candidiasis), which
125 are more common in patients with DM but are also associated with immu-
126 nosuppressive treatments and lack specific coding and causality, were
127 excluded. Inclusion of these conditions could introduce heterogeneity
128 and dilute results, particularly in the context of real-world evidence.

129 The classification of an AE as DM related was predefined exclusively
130 through review of MedDRA codes in the database before any statistical
131 analysis was performed.

132 The primary outcome measure was the adjusted incidence rate ra-
133 tio (aIRR) for DM-AEs and DM-SAEs among patients receiving MTX
134 compared with those receiving other systemic therapies.

135 Statistical analysis

136 Categorical variables are presented as No. (%), and continuous va-
137 riables as mean (SD) or median (IQR), as appropriate. Descriptive data
138 were compared between groups using the Student *t* test or Mann-
139 Whitney *U* test and the Pearson's chi-square test (or Fisher exact test
140 when appropriate), depending on variable distribution.

Missing data were assumed to be missing at random and were handled using multiple imputation by chained equations (20 datasets), with estimates pooled according to Rubin rules after convergence.

Incidence rates (IRs) were calculated as the number of new DM-related complications per 1000 person-years (PYs) of exposure.

We estimated adjusted incidence rate ratios (aIRRs) and 95% CIs for DM-AEs and DM-SAEs by comparing IRs in the MTX group with those of each treatment group using robust Poisson regression models. MTX was selected as the comparator for patients with DM despite not being recommended in some clinical guidelines for this population. This decision was based on its widespread use in routine clinical practice, where MTX remains one of the most frequently prescribed conventional systemic therapies for psoriasis and is often used as first-line systemic treatment, including in patients with metabolic comorbidities. Its use is further driven by structural and organizational factors, including low cost, broad accessibility, and frequent requirement by hospital pharmacy protocols before initiation of biologic therapies. Therefore, using MTX as the reference treatment reflects routine clinical decision-making in public healthcare settings rather than guideline-based recommendations alone.¹⁴

To mitigate confounding bias resulting from nonrandomized treatment assignment, we calculated a propensity score (PS) for the indication of each drug relative to MTX. The PS was calculated using variables associated with both exposure and outcome¹⁵: sex, age, smoking status, alcohol consumption, disease duration, presence of psoriatic arthritis, body mass index (BMI), number of previous cardiovascular comorbidities, Psoriasis Area and Severity Index (PASI), and prior classic systemic treatments. These variables were selected based on clinical expertise and previously identified significant confounders.¹⁶ All confounders were assessed at baseline. Propensity scores were incorporated into the Poisson regression models as inverse probability of treatment weights (IPTW).

All analyses were performed using Stata Statistical Software, release 17 (StataCorp LLC). A two-sided $P < .05$ was considered statistically significant.

Results

A total of 732 patients with psoriasis and comorbid DM were included in the analysis, contributing 2865 PYs of follow-up and 1401 treatment cycles. Treatment groups included TNF- α inhibitors (36.6%), IL-12/23 inhibitors (14.6%), IL-17 inhibitors (21.6%), IL-23 inhibitors (23.6%), APR (15.7%), ACT (18.7%), CYA (4.8%), and MTX (16.8%). Median treatment duration was 2.8 years (IQR, 1.2–5.3).

Patient characteristics

Patient characteristics are summarized by treatment group in Table 1.

The mean age was 67.5 years (SD, 13.2); 41% of patients were women, and plaque psoriasis was the most common clinical subtype (84%). Mean baseline PASI was 11.3 (SD, 7.8). Mean BMI was 31 kg/m² (SD, 5.6).

Cardiovascular comorbidities other than DM, such as hypertension (69%) and hypercholesterolemia (70%), were the most prevalent comorbidities. Only 17% of patients had no previous cardiovascular comorbidities other than DM. Noncardiovascular comorbidities were less frequent, and 63% of patients had none. Fifty-six percent of patients were current or former smokers.

Incidence rates of DM-related complications by treatment group

A total of 298 DM-AEs and 83 DM-SAEs were reported during 2865 PYs of exposure.

The most frequent DM-AEs included hypertriglyceridemia ($n = 31$), hyperglycemia ($n = 24$), hypertension ($n = 15$), increased creatinine levels ($n = 11$), and heart failure ($n = 10$).

The overall IR of DM-AEs ranged from 51.9 (95% CI, 28.7–93.7) per 1000 PYs in patients treated with APR to 457.9 (95% CI, 260.0–806.2) per 1000 PYs among those receiving CYA. Regarding DM-SAEs, the lowest IR was also observed in the APR group at 9.4 (95% CI, 2.4–37.7), whereas the highest DM-SAE rate occurred in the CYA-treated group, with 76.3 (95% CI, 19.1–305.1) per 1000 PYs. The IR of DM-AEs in the MTX group was 110.7 (95% CI, 77.9–157.5), with a DM-SAE rate of 32.1 (95% CI, 16.7–61.8). Detailed IRs for each treatment group are presented in Table 2.

Comparison of incidence rate ratios of DM-related complications by treatment group M (Tables 3 and 4; Fig. 1)

Compared with MTX, CYA showed the highest crude IRR for all adverse events (IRR, 4.1; 95% CI, 2.1–8.1; $P < .001$), followed by ACT (IRR, 1.7; 95% CI, 1.1–2.6; $P = .020$). Conversely, APR demonstrated a significantly lower crude risk (IRR, 0.5; 95% CI, 0.2–0.9; $P = .031$).

After adjustment for confounders, CYA remained associated with the highest aIRR (aIRR, 7.5; 95% CI, 3.3–17.3; $P < .001$), and ACT also continued to show a significantly increased adjusted risk (aIRR, 2.1; 95% CI, 1.2–3.7; $P = .014$). APR remained significantly associated with a reduced adjusted risk of DM-AEs compared with MTX (aIRR, 0.3; 95% CI, 0.1–0.6; $P = .003$).

In subgroup analyses by sex, female patients treated with IL-12/23 inhibitors showed a significantly lower crude risk of DM-related adverse events compared with MTX (IRR, 0.3; 95% CI, 0.1–0.8; $P = .019$); however, this association was not retained after adjustment (aIRR, 0.4; 95% CI, 0.1–1.0; $P = .054$).

The remaining systemic treatments did not show statistically significant increases or reductions in the risk of DM-AEs compared with MTX.

Regarding DM-SAEs, no statistically significant differences were observed between treatment groups and MTX in either crude or adjusted analyses (all $P > .05$), although APR (aIRR, 0.1; 95% CI, 0.0–1.4; $P = .092$) and CYA (aIRR, 5.6; 95% CI, 0.8–37.7; $P = .075$) remained close to statistical significance.

Discussion

Within our cohort, treatment with CYA and ACT was associated with a significantly increased risk of DM-AEs compared with MTX after adjustment. In contrast, APR was associated with a significantly lower adjusted risk (aIRR, 0.3; 95% CI, 0.1–0.6). No statistically significant differences in adjusted risk were observed for biologic therapies. Additionally, no treatment group was associated with a significant increase in the risk of serious DM-SAEs. These findings suggest clinically relevant differences in the risk of DM-related complications among systemic psoriasis therapies and may help clinicians select optimal treatments for patients with DM.

Traditional systemic treatments

MTX was selected as the reference treatment in our study because of its widespread use and role as first-line systemic therapy in psoriasis management. However, MTX has been associated with a significantly increased risk of hepatic fibrosis in patients with DM (adjusted HR, 2.40; 95% CI, 1.05–5.51).¹⁷ This elevated risk has been linked to reduced renal clearance in patients with diabetic nephropathy, potentially increasing hepatotoxicity.³ Although short-term studies have not demonstrated direct hyperglycemic effects of MTX,¹⁸ current clinical guidelines recommend lower starting doses, appropriate dose adjustments, and rigorous monitoring in patients with DM to minimize potential safety risks.¹⁹

Table 1
Patient characteristics by treatment.

	TNF- α inhibitors	IL-12/23 inhibitors	IL-17 inhibitors	IL-23 inhibitors	Apremilast	Acitretin	Cyclosporine	Methotrexate	Total	Missing, n (%)
<i>Demographic data</i>										
Number of patients, n (% of total)	268 (36.6)	107 (14.6)	158 (21.6)	173 (23.6)	115 (15.7)	137 (18.7)	35 (4.8)	123 (16.8)	732 (100)	
Patients-years, total	792	451	428	382	212	295	26	280	2865	
Number of cycles, total	380	135	210	196	123	167	40	150	1401	
Time exposed, years, mean (SD)	3 (3.2)*	4.2 (3.8)*	2.7 (2.1)	2.2 (1.5)	1.8 (1.9)	2.2 (2.9)	0.7 (1)*	2.3 (2.8)	3.9 (3.7)	
Time exposed, years, median (p25–p75)	1.9 (0.8–3.7)	3.4 (1.2–5.8)	2 (1.1–3.9)	2 (0.9–3.3)	1.3 (0.4–2.6)	1 (0.5–2.5)	0.4 (0.1–1.2)	1.1 (0.5–3)	2.8 (1.2–5.3)	
Women, n (%)	123 (46)	42 (39)	65 (41)	68 (39)	57 (50)	63 (46)	12 (34)	51 (41)	299 (41)	
Age, years, mean (SD)	65.6 (12.4)*	70.5 (13.8)	64.2 (12)*	66.1 (11.4)*	65.9 (13.1)*	73.9 (11.6)*	71.8 (12.3)	69.5 (13.6)	67.5 (13.2)	
Age at start of treatment, years, mean (SD)	58.2 (11.7)	61 (14.4)	60.3 (12)	63.6 (11.6)*	62.2 (12.4)	64.7 (10.5)*	59.7 (11.4)	60.6 (12.1)	60.3 (12.4)	
Duration of disease at start of treatment, years, mean (SD)	19.1 (14.5)*	20.6 (15)*	18.7 (14.8)*	20.7 (16.2)*	14.7 (15.1)	16.5 (15.5)	18.8 (15.7)	15 (14.7)	16.7 (15.2)	24 (3)
Psoriasis Area Severity Index (PASI), mean (SD)	12.2 (9)*	12.8 (6.5)*	9.7 (7.7)	10.3 (6.3)*	7.7 (4.3)	8.5 (6.1)	12.6 (8.1)*	8.9 (5.2)	11.3 (7.8)	138 (19)
Body mass index (BMI), mean (SD)	31.3 (5.9)	30.4 (5.4)	31.8 (5.7)	31.6 (5.9)	32.4 (5.7)*	30.4 (5.6)	30.2 (5)	30.7 (5.2)	31 (5.6)	132 (18)
<i>Diagnosis at entry in the cohort, n (% of total)</i>										
Plaque psoriasis	230 (86)	101 (94)*	134 (85)	151 (87)	93 (81)	100 (73)*	31 (89)	106 (86)	616 (84)	
Guttate psoriasis	7 (3)	3 (3)	5 (3)*	5 (3)	2 (2)	2 (1)	1 (3)	0 (0)	15 (2)	
Erythrodermic psoriasis	5 (2)	1 (1)	3 (2)	2 (1)	0 (0)	6 (4)	3 (9)*	2 (2)	13 (2)	
Generalized pustular psoriasis	2 (1)	0 (0)	3 (2)	2 (1)	1 (1)	6 (4)	0 (0)	1 (1)	12 (2)	
Palmoplantar pustulosis	13 (5)	2 (2)	12 (8)	9 (5)	16 (14)*	23 (17)*	1 (3)	7 (6)	56 (8)	
Psoriatic arthritis	59 (22)*	19 (18)*	37 (23)*	29 (17)*	13 (11)	9 (7)	5 (14)	8 (7)	112 (15)	
<i>Comorbidities, n (% of total)</i>										
Diabetes	268 (100)	107 (100)	158 (100)	173 (100)	115 (100)	137 (100)	35 (100)	123 (100)	732 (100)	
Ischemic heart disease	21 (10)	10 (10)	14 (11)	22 (16)	11 (12)	14 (12)	5 (16)	11 (10)	79 (13)	144 (20)
Heart failure	6 (3)	8 (8)	2 (2)	8 (6)	3 (3)	6 (5)	1 (3)	5 (5)	24 (4)	157 (21)
Arterial hypertension	161 (65)	65 (63)	96 (66)	115 (72)	65 (65)	92 (71)	17 (52)	79 (67)	466 (69)	54 (7)
Hypercholesterolemia	170 (71)	59 (58)	101 (71)	113 (75)*	66 (66)	92 (72)	22 (67)	73 (63)	463 (70)	68 (9)
COPD	13 (7)	11 (12)*	11 (9)	15 (11)*	13 (15)*	11 (9)	3 (10)	4 (4)	54 (9)	151 (21)
Chronic liver disease	50 (25)*	18 (19)*	41 (32)*	38 (28)*	33 (36)*	13 (11)	7 (23)*	6 (6)	129 (22)	147 (20)
Renal insufficiency	10 (5)	6 (6)	10 (8)*	12 (9)*	2 (2)	4 (3)	0 (0)	2 (2)	33 (6)	151 (21)
Prior cancer	10 (5)	10 (11)	19 (15)*	18 (13)	23 (24)*	22 (19)*	3 (10)	7 (7)	72 (12)	140 (19)
Cancer in the last 5 years, excluding non-melanoma skin cancer	0 (0)	1 (1)	2 (2)	2 (1)	3 (3)	0 (0)	0 (0)	0 (0)	7 (1)	140 (19)

Table 1 (Continued)

	TNF- α inhibitors	IL-12/23 inhibitors	IL-17 inhibitors	IL-23 inhibitors	Apremilast	Acitretin	Cyclosporine	Methotrexate	Total	Missing, n (%)
Lymphoma	1 (1)	0 (0)	1 (1)	3 (2)	2 (2)	3 (3)	0 (0)	0 (0)	8 (1)	163 (22)
Hepatitis B	17 (7)	10 (11)	8 (6)	9 (6)	10 (10)	10 (11)	1 (3)	5 (5)	46 (7)	112 (15)
Hepatitis C	8 (3)	3 (3)	3 (2)	5 (3)	2 (2)	1 (1)	1 (3)	2 (2)	14 (2)	114 (16)
HIV	1 (0)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	3 (1)	141 (19)
<i>Number of comorbidities NO CV, n (%)</i>										
No comorbidities	180 (67)*	67 (63)*	88 (56)*	95 (55)*	55 (48)*	88 (64)*	25 (71)	104 (85)	462 (63)	
1 comorbidities	71 (26)*	27 (25)*	54 (34)*	60 (35)*	38 (33)*	39 (28)*	8 (23)	16 (13)	201 (27)	
2 comorbidities	13 (5)*	8 (7)*	9 (6)*	13 (8)*	18 (16)*	7 (5)*	1 (3)	1 (1)	52 (7)	
3 or more comorbidities	4 (1)*	5 (5)*	7 (4)*	5 (3)*	4 (3)*	3 (2)*	1 (3)	2 (2)	17 (2)	
<i>Number of comorbidities CV, n (%)</i>										
No comorbidities	51 (19)	24 (22)	27 (17)	26 (15)	25 (22)	18 (13)	5 (14)	18 (15)	122 (17)	
1 comorbidities	96 (36)	34 (32)	60 (38)	54 (31)	45 (39)	48 (35)	16 (46)	51 (41)	257 (35)	
2 comorbidities	102 (38)	41 (38)	60 (38)	76 (44)	35 (30)	57 (42)	13 (37)	46 (37)	287 (39)	
3 or more comorbidities	19 (7)	8 (7)	11 (7)	17 (10)	10 (9)	14 (10)	1 (3)	8 (7)	66 (9)	
<i>Alcohol consumption, n (%)</i>										
Current	53 (27)	25 (30)	33 (27)	40 (30)	16 (21)	27 (25)	9 (36)	23 (24)	140 (26)	199 (27)
Previous	2 (1)	3 (4)	2 (2)	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	6 (1)	
Smoker, n (%)										
Current	75 (34)	31 (34)	50 (36)	55 (37)*	29 (33)	45 (38)	8 (28)	27 (26)	193 (32)	
Previous	46 (21)	16 (17)	27 (20)	45 (30)*	25 (28)	23 (19)	7 (24)	21 (20)	147 (24)	
<i>Previous treatments, n (%)</i>										
Systemic treatments	195 (73)*	84 (79)*	114 (72)*	124 (72)*	70 (61)*	54 (39)	25 (71)*	38 (31)	366 (50)	
Phototherapy	97 (36)*	62 (58)*	60 (38)*	68 (39)*	43 (37)*	34 (25)	11 (31)	23 (19)	238 (33)	
<i>Number of previous biological treatments</i>										
0	161 (60)*	33 (31)*	34 (22)*	34 (20)*	84 (73)*	110 (80)*	25 (71)*	121 (98)	554 (76)	
1	69 (26)*	43 (40)*	46 (29)*	51 (29)*	19 (17)*	12 (9)*	2 (6)*	1 (1)	120 (16)	
2	19 (7)*	11 (10)*	36 (23)*	44 (25)*	9 (8)*	8 (6)*	3 (9)*	0 (0)	31 (4)	
3	12 (4)*	13 (12)*	17 (11)*	18 (10)*	0 (0)*	3 (2)*	2 (6)*	1 (1)	16 (2)	
4 or more	7 (3)*	7 (7)*	25 (16)*	26 (15)*	3 (3)*	4 (3)*	3 (9)*	0 (0)	11 (2)	

TNF- α (adalimumab, certolizumab, etanercept, infliximab); IL-12/23, ustekinumab; IL-17 (brodalumab, risankizumab, tildrakizumab, tiltrakizumab); IL-23 (guselkumab, risankizumab, tildrakizumab, tiltrakizumab); IL-17 (brodalumab, secukinumab, ixekizumab); PASI, Psoriasis Area Severity Index; BMI, body mass index; SD, standard deviation; CV, cardiovascular.

‡ The total number of patients reported for each group does not equal the total number of patients in the study because some patients belong to more than one treatment group.

* $P < 0.05$.

Table 2
Adverse events incidence rates.

Systemic therapy for psoriasis	Number of person years of exposure	All adverse events		Serious adverse events		Fatal adverse events	
		Number of events	Incidence (95% CI)	Number of events	Incidence (95% CI)	Number of events	Incidence (95% CI)
<i>TNF-α</i>	792	77	97.3 (77.8; 121.6)	21	26.5 (17.3; 40.7)	0	NA
Male	466	52	111.6 (85.1; 146.5)	13	27.9 (16.2; 48.1)	0	NA
Female	326	25	76.7 (51.8; 113.6)	8	24.6 (12.3; 49.1)	0	NA
<i>IL-12/23i</i>	451	40	88.7 (65; 120.9)	12	26.6 (15.1; 46.8)	0	NA
Male	274	33	120.4 (85.6; 169.4)	8	29.2 (14.6; 58.4)	0	NA
Female	177	7	39.5 (18.8; 82.9)	4	22.6 (8.5; 60.2)	0	NA
<i>IL-17i</i>	428	35	81.8 (58.7; 113.9)	8	18.7 (9.3; 37.4)	0	NA
Male	246	19	77.3 (49.3; 121.2)	4	16.3 (6.1; 43.4)	0	NA
Female	182	16	87.8 (53.8; 143.4)	4	22 (8.2; 58.5)	0	NA
<i>IL-23i</i>	382	37	97 (70.3; 133.9)	13	34.1 (19.8; 58.7)	0	NA
Male	240	21	87.4 (57; 134)	7	29.1 (13.9; 61.1)	0	NA
Female	141	16	113.3 (69.4; 184.9)	6	42.5 (19.1; 94.6)	0	NA
<i>Apremilast</i>	212	11	51.9 (28.7; 93.7)	2	9.4 (2.4; 37.7)	0	NA
Male	108	7	64.9 (30.9; 136.1)	2	18.5 (4.6; 74.1)	0	NA
Female	104	4	38.4 (14.4; 102.4)	0	0 (0; 0)	0	NA
<i>ACT</i>	295	55	186.7 (143.3; 243.1)	16	54.3 (33.3; 88.6)	2	6.8 (1.7; 27.1)
Male	160	31	193.7 (136.2; 275.4)	12	75 (42.6; 132)	2	12.5 (3.1; 50)
Female	135	24	178.3 (119.5; 266.1)	4	29.7 (11.2; 79.2)	0	0 (0; 0)
<i>CYA</i>	26	12	457.9 (260; 806.2)	2	76.3 (19.1; 305.1)	0	NA
Male	20	6	301.2 (135.3; 670.4)	1	50.2 (7.1; 356.4)	0	NA
Female	6	6	954.1 (428.6; 2123.6)	1	159 (22.4; 1128.8)	0	NA
<i>MTX</i>	280	31	110.7 (77.9; 157.5)	9	32.1 (16.7; 61.8)	0	NA
Male	170	18	105.6 (66.5; 167.6)	6	35.2 (15.8; 78.4)	0	NA
Female	110	13	118.7 (68.9; 204.4)	3	27.4 (8.8; 84.9)	0	NA

Incidence rates (per 1000 person-years). CI, confidence interval; *TNF- α* (adalimumab, certolizumab, etanercept, infliximab); *IL-12/23i*, ustekinumab; *IL-23i* (guselkumab, risankizumab, tildrakizumab); *IL-17i* (brodalumab, secukinumab, ixekizumab); *ACT*, acitretin; *CYA*, cyclosporine; *APR*, apremilast; *MTX*, methotrexate; NA, not available.

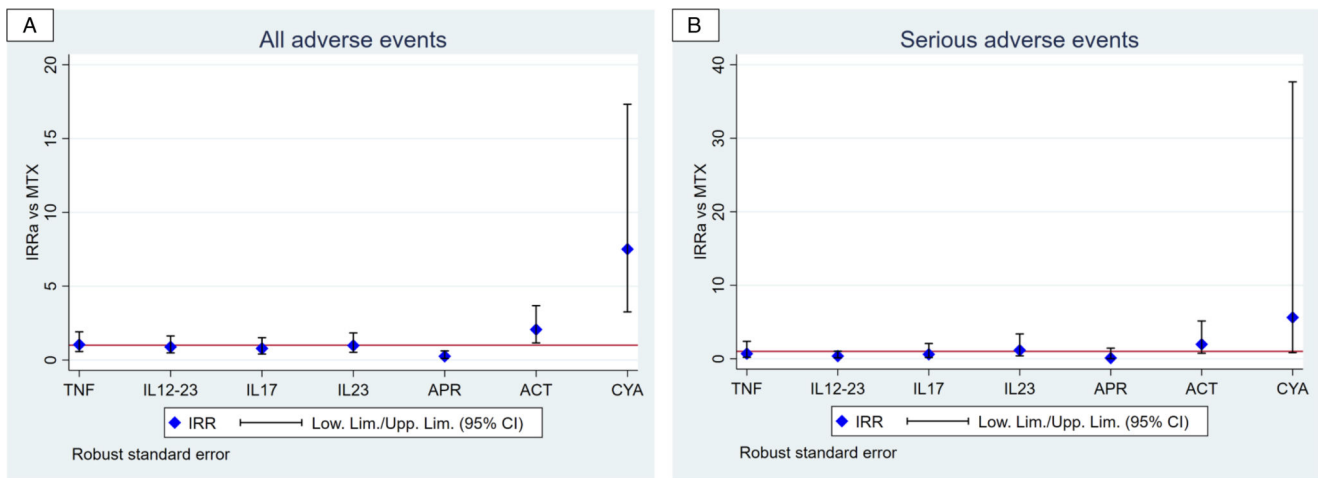


Fig. 1. Adjusted incidence rate ratios (aIRR) for diabetes-related adverse events by treatment group, referenced to methotrexate. (A) All diabetes-related adverse events and (B) serious diabetes-related adverse events. Points indicate adjusted aIRR and horizontal bars the 95% confidence intervals; the red line marks IRR = 1 (MTX reference). Estimates come from IPTW-weighted models with robust standard errors, adjusted for age, sex, body mass index, psoriatic arthritis, PASI, number of cardiovascular comorbidities, and center. Treatment groups: TNFi (anti-TNF), IL12/23i, IL17i, IL23i, APR (apremilast), ACT (acitretin), CYA (cyclosporine).

259 *CYA* has been associated with hyperlipidemia, hypertension, nephro-
 260 toxicity, and an increased risk of MACE in patients with psoriasis.^{4,20,21}
 261 Additionally, *CYA* exhibits diabetogenic effects through inhibition of
 262 insulin secretion from pancreatic islet cells.^{3,22} These findings are con-
 263 sistent with the elevated risk of DM-related complications observed in

our cohort. Given these data, *CYA* is generally not recommended for the
 264 treatment of psoriasis in patients with DM.³

265
 266 *ACT* therapy may induce hyperlipidemia, representing an additive
 267 cardiovascular risk factor in patients with DM.²² Its effects on glyce-
 268 mic control in patients with DM remain insufficiently established.^{23,24}
 269

Table 3
Crude incidence rate ratios compared to methotrexate.

Systemic therapy for psoriasis	All adverse events		Serious adverse events	
	IRR crude (95% CI)	P-value	IRR crude (95% CI)	P-value
<i>TNF-α</i>	0.9 (0.6; 1.3)	0.5421	0.8 (0.4; 1.8)	0.6295
Male	1.1 (0.6; 1.8)	0.8394	0.8 (0.3; 2.1)	0.6379
Female	0.6 (0.3; 1.3)	0.2019	0.9 (0.2; 3.4)	0.8716
<i>IL-12/23i</i>	0.8 (0.5; 1.3)	0.3527	0.8 (0.3; 2)	0.6672
Male	1.1 (0.6; 2)	0.6543	0.8 (0.3; 2.4)	0.7288
Female	0.3 (0.1; 0.8)	0.0190	0.8 (0.2; 3.7)	0.8002
<i>IL-17i</i>	0.7 (0.5; 1.2)	0.2192	0.6 (0.2; 1.5)	0.2645
Male	0.7 (0.4; 1.4)	0.3429	0.5 (0.1; 1.6)	0.2320
Female	0.7 (0.4; 1.5)	0.4198	0.8 (0.2; 3.6)	0.7721
<i>IL-23i</i>	0.9 (0.5; 1.4)	0.5861	1.1 (0.5; 2.5)	0.8932
Male	0.8 (0.4; 1.6)	0.5557	0.8 (0.3; 2.5)	0.7337
Female	1 (0.5; 2)	0.9005	1.6 (0.4; 6.2)	0.5349
<i>Apremilast</i>	0.5 (0.2; 0.9)	0.0308	0.3 (0.1; 1.4)	0.1168
Male	0.6 (0.3; 1.5)	0.2744	0.5 (0.1; 2.6)	0.4324
Female	0.3 (0.1; 1)	0.0485	NA	NA
<i>ACT</i>	1.7 (1.1; 2.6)	0.0201	1.7 (0.7; 3.8)	0.2083
Male	1.8 (1; 3.3)	0.0407	2.1 (0.8; 5.7)	0.1305
Female	1.5 (0.8; 3)	0.2372	1.1 (0.2; 4.8)	0.9149
<i>CYA</i>	4.1 (2.1; 8.1)	0.0000	2.4 (0.5; 11)	0.2688
Male	2.9 (1.1; 7.2)	0.0262	1.4 (0.2; 11.8)	0.7425
Female	8 (3.1; 21.1)	0.0000	5.8 (0.6; 55.8)	0.1277

P value ($P < 0.05$).

IRR, incidence rate ratio; CI, confidence interval; *TNF- α* (adalimumab, certolizumab, etanercept, infliximab); *IL-12/23i*, ustekinumab; *IL-23i* (guselkumab, risankizumab, tildrakizumab); *IL-17i* (brodalumab, secukinumab, ixekizumab); *ACT*, acitretin; *CYA*, cyclosporine; *APR*, apremilast; NA, not available.

Table 4
Adjusted incidence rate ratios compared to methotrexate.

Systemic therapy for psoriasis	All adverse events		Serious adverse events	
	aIRR (95% CI)	P-value	aIRR (95% CI)	P-value
<i>TNF-α</i>	1 (0.6; 1.9)	0.9001	0.7 (0.2; 2.4)	0.5623
<i>IL-12/23i</i>	0.9 (0.5; 1.6)	0.6890	0.4 (0.1; 1)	0.0542
<i>IL-17i</i>	0.8 (0.4; 1.5)	0.4643	0.6 (0.2; 2.1)	0.4289
<i>IL-23i</i>	1 (0.5; 1.8)	0.9435	1.2 (0.4; 3.4)	0.7788
<i>Apremilast</i>	0.3 (0.1; 0.6)	0.0025	0.1 (0; 1.4)	0.0922
<i>ACT</i>	2.1 (1.2; 3.7)	0.0144	2 (0.8; 5.1)	0.1685
<i>CYA</i>	7.5 (3.3; 17.3)	0.0000	5.6 (0.8; 37.7)	0.0753

IPTW adjusted for age, sex, body mass index (BMI), psoriatic arthritis, Psoriasis Area and Severity Index (PASI), number of cardiovascular comorbidities, and centre (site).

P value ($P < 0.05$).

IRR, incidence rate ratio; CI, confidence interval; *TNF- α* (adalimumab, certolizumab, etanercept, infliximab); *IL-12/23i*, ustekinumab; *IL-23i* (guselkumab, risankizumab, tildrakizumab); *IL-17i* (brodalumab, secukinumab, ixekizumab); *ACT*, acitretin; *CYA*, cyclosporine; *APR*, apremilast.

269 Nevertheless, our findings suggest that ACT use in patients with DM
270 should be limited because it was associated with an increased risk of
271 DM-related AEs compared with MTX.

of metformin.^{22,26} These observations are consistent with the findings
of our cohort.

272 PDE4 inhibitors

273 APR has demonstrated favorable effects on metabolic parameters in
274 patients with psoriasis, including those with DM,²⁵ as well as reductions
275 in MACE incidence.⁴ APR has also been reported to modestly reduce
276 body weight in a subset of patients, independently of gastrointestinal
277 adverse effects such as nausea and diarrhea. Additionally, APR may posi-
278 tively influence glucose metabolism and potentially enhance the efficacy

Biologics

In our cohort, biologic therapies were not associated with statisti-
cally significant increases or reductions in the risk of DM-related AEs or
SAEs compared with MTX. Available data regarding DM-related compli-
cations in patients with psoriasis remain limited.

TNF inhibitors may improve insulin sensitivity in patients with
psoriasis by counteracting inflammation-driven insulin resistance. How-
ever, in a retrospective registry study, Kalb et al. reported that the

289 presence of DM was a significant predictor of serious infection in patients
290 treated with adalimumab, etanercept, or ustekinumab (HR, 1.7;
291 95% CI, 1.25–2.23).²⁹

292 IL-17 inhibitors have demonstrated neutral^{30,31} or beneficial³² ef-
293 fects on cardiovascular parameters and have been associated with lower
294 cardiovascular disease risk compared with MTX.⁴ However, these agents
295 may further increase the risk of candidiasis, a well-recognized class AE,
296 particularly in patients with DM.^{32–35}

297 The metabolic profile of IL-23 inhibitors in patients with psoriasis
298 and DM appears favorable. These therapies have been associated with
299 improvements in fasting glucose, insulin levels, triglycerides, and in-
300 flammatory markers.³² IL-23 inhibitors have not been associated with
301 increased risks of metabolic complications, such as hyperglycemia,
302 diabetic ketoacidosis, cardiovascular events, or serious infections, com-
303 pared with the overall psoriasis population.^{33–35}

304 This study has several limitations. As an observational analysis
305 conducted in a high-risk population, residual and unmeasured con-
306 founding factors (e.g., physical activity, diet, baseline diabetes control,
307 and time-varying metabolic control) cannot be excluded despite IPTW
308 adjustment. Therefore, findings should be interpreted as associations
309 rather than causal effects. Diabetes status was recorded only at base-
310 line, and information regarding antidiabetic therapies (e.g., insulin,
311 glucagon-like peptide-1 receptor agonists, sodium-glucose cotranspor-
312 ter 2 inhibitors) and changes in metabolic control during follow-up was
313 unavailable. These concomitant treatments may have modified the ob-
314 served associations.³⁶

315 MTX was selected as a pragmatic reference treatment instead of
316 placebo, topical therapy, or alternative systemic therapies because it
317 remains widely prescribed in routine psoriasis care. Nevertheless, sev-
318 eral clinical guidelines do not recommend MTX in patients with DM.
319 DM-AEs were predefined using MedDRA codes to reduce adjudication
320 bias; however, misclassification remains possible, and many reported
321 signals were laboratory defined (e.g., dyslipidemia and hyperglycemia).
322 Although statistically significant, some findings may have limited clini-
323 cal relevance and should primarily guide monitoring strategies and
324 optimization of cardiovascular risk factors.

325 Certain exposure groups, particularly CYA, were relatively small, re-
326 sulting in wide confidence intervals, and follow-up duration may have
327 been insufficient to fully assess rare or long-latency outcomes. Diffe-
328 rential monitoring across therapies and channeling by indication may
329 have persisted despite propensity weighting, and exclusion of combina-
330 tion therapy limits generalizability to monotherapy regimens. Because
331 patients could contribute multiple treatment cycles, observations were
332 not fully independent. Although robust variance estimation was used to
333 mitigate within-patient correlation, residual correlation and treatment-
334 sequencing effects cannot be excluded.

335 This study also has several strengths. Its prospective design and
336 use of the BIOBADADERM registry, which includes continuous pharmaco-
337 vigilance procedures, provided high-quality, systematically collected
338 real-world evidence that is uncommon in observational studies. The large
339 multicenter sample across Spain improves generalizability. Inclusion
340 of all systemic therapies routinely used in clinical practice enabled com-
341 prehensive treatment comparisons. Major confounders, including age,
342 lifestyle factors (e.g., smoking and alcohol consumption), and cardio-
343 vascular and noncardiovascular comorbidities, were addressed using
344 robust adjustment methods. Classification of DM-related adverse events
345 was performed before analysis and without knowledge of study results,
346 reducing adjudication bias. Finally, consistency between our findings,
347 established mechanistic pathways, and previous evidence supports the
348 validity of the observed associations.

349 Conclusions

350 Cyclosporine and acitretin were associated with an increased risk of
351 DM-related AEs, whereas apremilast was associated with a decreased

risk compared with MTX. Most AEs were laboratory defined and may
352 have limited clinical relevance. Biologic therapies showed results similar
353 to those of MTX, with no significant differences between groups. These
354 findings may help clinicians select systemic therapies for patients with
355 psoriasis and concomitant DM.
356

ORCID ID

Mar Llamas-Velasco: 0000-0002-1187-1341 358

Isabel Belinchón: 0000-0002-6007-7320 359

Marta Ferrán Farrés: 0000-0003-1198-0641 360

Mariano Ara-Martín: 0000-0001-8789-6783 361

Ethical approval

362
363 Observational study approved by the *Hospital Universitario 12 de Oc-*
364 *tubre* Ethics Committee (BIOBADADERM protocol No. 216/07).

Funding

365
366 The BIOBADADERM project is supported by the *Fundación Piel Sana*
367 *de la Academia Española de Dermatología y Venereología*, which receives
368 financial support from the *Agencia Española de Medicamentos y Produc-*
369 *tos Sanitarios* and pharmaceutical companies (Abbott/AbbVie, Ammirall,
370 Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Janssen,
371 and UCB). The following companies have also collaborated: Leo Pharma,
372 Novartis Pharma, Lilly, MSD, and Pfizer.

373 Collaborating pharmaceutical companies were not involved in the
374 design or execution of the study; the collection, management, analysis,
375 or interpretation of the data; the preparation, review, or approval of the
376 manuscript; or the decision to submit the manuscript for publication.

Conflicts of interest

377
378 Dr Lluch-Galcerá has participated as a speaker for Johnson & John-
379 son, Sanofi, and Ammirall.

380 Dr Carrascosa has participated as a speaker, advisor, and PI/SI in cli-
381 nical trials sponsored by Celgene, Janssen, Lilly, Leo Pharma, Novartis,
382 Pfizer, MSD, Biogen, Mylan, Amgen, AbbVie, and Sandoz.

383 Dr González-Quesada has acted as a consultant and/or speaker
384 and/or participated in clinical trials as PI and sub-investigator for Abb-
385 Vie, Ammirall, Amgen, Boehringer Ingelheim, Janssen, Leo Pharma, Lilly,
386 Novartis, MSD, Pfizer-Wyeth, and UCB.

387 Dr Sahuquillo has served as a consultant and/or paid speaker and/or
388 participated in clinical trials sponsored by companies that manufacture
389 drugs used for the treatment of psoriasis, including AbbVie, Celgene,
390 Janssen-Cilag, Leo Pharma, Lilly, Novartis, and Pfizer.

391 Dr Rivera has acted as a consultant and/or speaker and/or parti-
392 cipated in clinical trials as PI for AbbVie, Ammirall, Amgen, Boehringer
393 Ingelheim, Janssen, Leo Pharma, Lilly, Novartis, MSD, Pfizer-Wyeth, and
394 UCB.

395 Dr Llamas-Velasco has acted as a consultant and speaker and partici-
396 pated in clinical trials for Janssen-Cilag, AbbVie, Boehringer Ingelheim,
397 Celgene, Pfizer, Novartis, Lilly, Ammirall, UCB, Kyowa Kirin, and Leo
398 Pharma.

399 Dr Belinchón has acted as a consultant and/or speaker and/or parti-
400 cipated in clinical trials sponsored by companies that manufacture drugs
401 used for the treatment of psoriasis, including Janssen Pharmaceuticals
402 Inc, Ammirall SA, Lilly, AbbVie, Novartis, Celgene, Biogen Amgen, Leo
403 Pharma, UCB, Pfizer-Wyeth, Bristol Myers Squibb, Sandoz, and MSD.

404 Dr Herrera-Acosta has served as a consultant and/or speaker for Leo
405 Pharma, Novartis, Janssen, Lilly, Celgene, and AbbVie.

406 Dr Ruiz-Genao has received reimbursement from Pfizer, Janssen,
407 Celgene, AbbVie, Novartis, and Leo Pharma for advisory services and
408 conferences.

Dr López-Esteban has participated as an advisory board member and received educational grants from Janssen, AbbVie, MSD, Lilly, Novartis, Leo Pharma, and Pfizer.

Dr Baniandrés-Rodríguez has acted as a consultant and/or speaker for Janssen-Cilag, AbbVie, Pfizer, Novartis, Lilly, Celgene, Leo Pharma, Amgen, Boehringer Ingelheim, UCB, and Almirall.

Dr Ferran has participated as a speaker and/or advisor for Janssen, Lilly, Novartis, Pfizer, MSD, AbbVie, Celgene, and Almirall.

Dr de la Cueva has acted as a consultant and/or speaker for Janssen-Cilag, AbbVie, MSD, Pfizer, Novartis, Lilly, Almirall, UCB, Biogen, Celgene, Amgen, Sandoz, Sanofi, and Leo Pharma.

Dr Rodríguez Fernández-Freire has acted as a consultant and speaker for Janssen-Cilag, AbbVie, MSD, Pfizer, Novartis, Lilly, Almirall, Celgene, and Leo Pharma.

Dr Mateu has acted as a consultant and/or speaker for AbbVie, Almirall, Celgene, Janssen, Leo Pharma, Lilly, and Novartis.

Dr Riera-Monroig has acted as a consultant and/or speaker and/or participated in clinical trials sponsored by AbbVie, Almirall, Johnson & Johnson, Leo Pharma, Novartis, UCB, Pfizer, Lilly, Amgen, Boehringer Ingelheim, and Bristol Myers Squibb.

Dr Ruiz-Villaverde has acted as a consultant and speaker and participated in clinical trials for Janssen-Cilag, AbbVie, Boehringer Ingelheim, Celgene, Pfizer, Novartis, Lilly, Almirall, UCB, Sanofi, and Leo Pharma.

Dr Ara-Martín has participated as a speaker, advisor, and PI/SI in clinical trials sponsored by Boehringer Ingelheim, Bristol Myers Squibb, Almirall, Celgene, Janssen, Lilly, Leo Pharma, Novartis, Pfizer, MSD, Amgen, AbbVie, and UCB.

Dr Gracia-Cazaña has acted as a consultant and/or speaker and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including Janssen Pharmaceuticals Inc, Almirall SA, Lilly, AbbVie, Novartis, Celgene, Biogen Amgen, Leo Pharma, UCB, Pfizer-Wyeth, and Boehringer Ingelheim.

Dr Abalde has participated as a speaker, advisor, and PI/SI in clinical trials sponsored by Amgen, Janssen, Lilly, Leo Pharma, Novartis, Pfizer, AbbVie, Almirall, Boehringer Ingelheim, and Sandoz.

Dr Pujol-Marco has acted as a consultant and/or speaker for Janssen-Cilag, AbbVie, MSD, Pfizer, Novartis, Lilly, Almirall, UCB, Celgene, and Leo Pharma.

Dr García-Donoso has participated as an advisory board member for AbbVie and Almirall and as a speaker for Janssen, Lilly, and Celgene.

Dr Del Alcázar has participated as a speaker and/or PI/SI in clinical trials sponsored by Amgen, Almirall, Janssen, Lilly, Leo Pharma, Novartis, UCB, and AbbVie.

Dr Díez-Madueño has received grants/honoraria from and/or served as a speaker for Eli Lilly, Amgen, LEO Pharma, AbbVie, Almirall, UCB, Johnson & Johnson, and Boehringer Ingelheim.

Dr García-Doval has received travel grants for congresses from AbbVie, MSD, Pfizer, and Sanofi.

The remaining authors declare no conflicts of interest.

Data availability

The data supporting the findings of this study are available from the BIOBADADERM Study Group upon reasonable request.

Uncited references

27,28.

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