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ORIGINAL RESEARCH ARTICLE

Safety of Apremilast in Patients with Psoriasis and Psoriatic Arthritis: Findings from the UK Clinical Practice Research Datalink

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Abstract

Introduction This real-world safety analysis was requested by the European Medicines Agency following approval of apremilast, an oral treatment for psoriasis or psoriatic arthritis.

Objective We aimed to compare incidence rates of adverse events of special interest identified a priori, in patients receiving apremilast with those receiving other systemic treatments for psoriasis or psoriatic arthritis.

Methods This 5-year cohort study was conducted in Clinical Practice Research Datalink GOLD between January 2015 and June 2020. Incidence rates of adverse events of special interest were estimated for four matched cohorts: apremilast-exposed and three matched non-apremilast cohorts (oral only, injectable only, and oral and injectable psoriasis or psoriatic arthritis treatments).

Results The apremilast-exposed cohort included 341 patients and the three non-apremilast cohorts included 4981 patients. There were no incident cases of vasculitis, hematologic malignancy, non-melanoma skin malignancy, treated depression, treated anxiety, or suicidal behaviors in the apremilast-exposed cohort during the follow-up. Similar incidence rates of all-cause mortality, major adverse cardiac events, tachyarrhythmias, and solid malignancies were recorded in the apremilast and non-apremilast cohorts. The incidence rate (95% confidence interval) per 1000 person-years of opportunistic and serious infections in the apremilast-exposed cohort (64 [40–102])) was similar to incidence rates in the oral (50 [42–60]) and oral and injectable non-apremilast cohorts (57 [47–69]), while the incidence rates were lower in the injectable treatment-only cohort (20 [10–41]). Limitations include small numbers of apremilast-exposed patients and potential exposure misclassification partly owing to missing information on biologic and other specialty treatment use.

Conclusions No new apremilast safety signals were identified in this study. These results provide evidence that the long-term safety of apremilast in psoriasis and psoriatic arthritis in a real-world setting is comparable to that reported in clinical trials.

1 Introduction

Psoriasis (PsO) and psoriatic arthritis (PsA) are chronic inflammatory diseases that can negatively impact a patient's quality of life [1–3]. Apremilast is an oral, non-biologic, small-molecule inhibitor of phosphodiesterase-4, a major enzyme upstream in the inflammatory signaling cascade [4]. Randomized placebo-controlled studies found that apremilast significantly reduced clinical symptoms of patients with

Key Points

Post-marketing safety studies are required for new drugs including apremilast, an oral treatment for psoriasis and psoriatic arthritis.

No new safety signals for apremilast were identified in this 5-year prospective study in a United Kingdom general practice database.

Study limitations include small numbers of apremilast-exposed patients and potential exposure misclassification partly owing to missing information on biologic and other specialty treatment use.

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PsO [5, 6] and PsA [7–9]. Additionally, these studies demonstrated that apremilast has a consistent established safety and tolerability profile.

In 2015, apremilast was approved in Europe [10] for the treatment of moderate-to-severe plaque PsO in adults who do not respond to or who have a contraindication to, or are intolerant of other systemic therapy [11] or for the treatment of active PsA, alone or in combination with disease-modifying antirheumatic drugs (DMARDs), in adults who have had an inadequate response or who have been intolerant to a prior DMARD therapy [12]. Following the European Medicine Agency's approval of apremilast, the European Medicines Agency requested a post-authorization safety study to provide long-term surveillance of adverse events of special interest (AESIs) in patients with PsO and/or PsA exposed to apremilast [13]. In this 5-year, longitudinal, prospective cohort study, we used real-world data from a large UK general practice database to compare incidence rates (IRs) of AESIs in patients with PsO and/or PsA who received oral and/or injectable non-apremilast treatments with rates in patients exposed to apremilast.

2 Methods

2.1 Data Sources

This study was conducted using the UK Clinical Practice Research Datalink (CPRD), which is the largest research database in the UK with longitudinal, representative primary care data linked to data from other healthcare settings (Fig. 1). The CPRD supports international pharmacovigilance by providing a large, anonymized, representative general population database and is the basis of over 2900 published research studies. The UK CPRD encompasses two large population-based electronic medical databases: CPRD GOLD and CPRD Aurum. CPRD Aurum, which is newly available to researchers and continues to undergo validation assessments, was found to have an incomplete capture of apremilast prescriptions. See the Electronic Supplementary Material (ESM) for a summary of CPRD Aurum methods and findings. Methods and results for the CPRD GOLD study are described here. The CPRD GOLD contains electronic patient records of over 3 million currently registered patients from 397 general practices [14] and includes demographics, diagnoses, prescriptions, and lifestyle factors recorded by general practitioners (GPs) as well as clinical information sent to GPs from hospitalizations and specialist encounters [15]. Validation studies have repeatedly demonstrated the high quality and completeness of CPRD GOLD data [16–18]. The study protocol was approved by the Independent Scientific Advisory Committee for MHRA Database Research. The study was conducted in accordance with the principles of the Declaration of Helsinki of 1975, and its later amendments.

2.2 Cohort Definitions

The study population was selected from all adults with research quality data and a prescription for a systemic PsO or PsA treatment (see ESM) recorded between January 2015 and June 2020. There were four exposure groups: apremilast-exposed (with or without other concomitant non-apremilast treatments) and three non-apremilast groups (oral treatment only exposed, injectable treatment only exposed, and oral and injectable treatment [concomitant or sequential] exposed). Non-apremilast treatments included those prescribed for PsO or PsA at the time of the initial protocol approval in 2015 as well as new treatments approved thereafter. These drugs included tumor necrosis factor inhibitor biologics, non-tumor necrosis factor inhibitor biologics, DMARDs, oral or injectable steroids, and azathioprine. Each patient in the apremilast-exposed cohort was matched, with replacement, to up to ten patients in each non-apremilast cohort for age (±3 years), sex, year of record start (±3 years or a longer history for the matches than the apremilast-exposed patient), and calendar time (the non-apremilast patient was required to be present in the database on the date of the first apremilast prescription of the matched apremilast-exposed patient). Matched patients were required to have a diagnosis code for PsO and/or PsA recorded at any time and at least one prescription for a non-apremilast comparison treatment within 6 months or any time after the apremilast-exposed patient's first apremilast prescription.

For patients in the apremilast-exposed cohort, the cohort entry date was the first apremilast prescription. For patients in the non-apremilast cohorts, the cohort entry date was the matched date (date of apremilast user's first apremilast

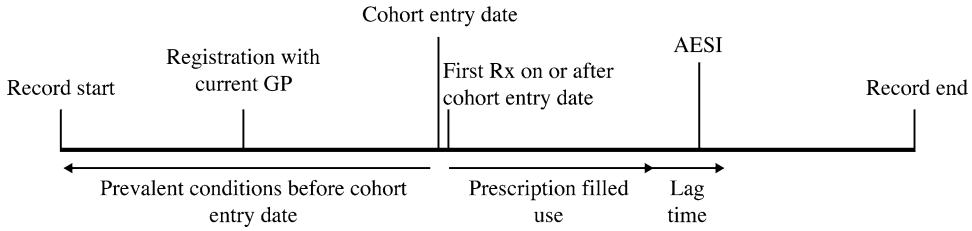

Fig. 1 Study design. *AESI* adverse events of special interest, *GP* general practitioner, *Rx* prescription

Table 1 Description of patients at cohort entry in the apremilast and matched non-apremilast treatment cohorts: CPRD GOLD (2015–20)

Characteristic	Apremilast $N=341$	Non-apremilast		
		Oral only $N=3129$	Injectable only $N=775$	Oral + injectable $N=1077$
Sex				
Female	197 (58)	1818 (58)	426 (55)	647 (60)
Male	144 (42)	1311 (42)	349 (45)	430 (40)
Age (years)				
Mean ± SD	53 ± 14	53 ± 14	58 ± 13	55 ± 15
18–44	95 (28)	837 (27)	115 (15)	258 (24)
45–59	124 (36)	1202 (38)	317 (41)	425 (39)
≥ 60	122 (36)	1090 (35)	343 (44)	394 (37)
Diagnosis				
PsA with or without PsO	149 (44)	1329 (42)	239 (31)	703 (65)
PsO only	172 (50)	1800 (58)	536 (69)	374 (35)
Neither diagnosis code in record[a]	20 (6)[a]	0 (0)	0 (0)	0 (0)
Smoking status				
Current smoker	76 (22)	753 (24)	136 (18)	191 (18)
Former smoker	123 (36)	1234 (39)	351 (45)	492 (46)
Non-smoker	133 (39)	1120 (38)	282 (36)	393 (36)
Unknown smoking status	9 (3)	22 (1)	6 (1)	< 5 (< 1)
BMI (kg/m^2) before cohort entry				
< 18.5	< 5 (1)	54 (2)	5 (1)	13 (1)
18.5 to < 25.0	55 (16)	667 (21)	155 (20)	197 (18)
25.0 to < 30.0	87 (25)	980 (31)	245 (32)	329 (31)
≥ 30.0	168 (49)	1221 (39)	323 (42)	485 (45)
Unknown	27 (8)	207 (7)	47 (6)	53 (5)
Time between registration with GP and cohort entry (years)				
Mean ± SD	16 ± 9	17 ± 8	19 ± 8	18 ± 8
< 1[b]	19 (6)[b]	0 (0)	0 (0)	0 (0)
1–9	78 (23)	800 (26)	123 (16)	207 (19)
≥ 10	244 (72)	2329 (74)	652 (84)	870 (81)
Prevalence of comorbidities				
MACE	15 (4)	140 (4)	30 (4)	43 (4)
Tachyarrhythmias	16 (5)	154 (5)	36 (5)	53 (5)
Vasculitis	< 5 (1)	21 (1)	0 (0)	7 (1)
Malignancy[c]	30 (9)	251 (8)	83 (11)	104 (10)
Solid	26 (8)	162 (5)	53 (7)	72 (7)
Hematologic	< 5 (< 1)	16 (1)	5 (1)	< 5 (< 1)
Non-melanoma skin	6 (2)	87 (3)	33 (4)	36 (3)
Treated depression[d]	68 (20)	715 (23)	176 (23)	249 (23)
Treated anxiety[e]	49 (14)	598 (19)	141 (18)	225 (21)
Suicidal behaviors	31 (9)	291 (9)	57 (7)	97 (9)
Acute comorbidities in the year before cohort entry				
Opportunistic infections[f]	9 (3)	96 (3)	23 (3)	48 (4)
Hypersensitivity reactions	13 (4)	61 (2)	10 (1)	20 (3)

Results are presented as *n* (%), unless specified otherwise. Cell sizes less than 5 were not reportable per license agreement

BMI body mass index, *CPRD* Clinical Practice Research Datalink, *MACE* major adverse cardiac events, *PsA* psoriatic arthritis, *PsO* psoriasis, *SD* standard deviation

[a]PsO and PsA were the only approved indications for apremilast during the study period. Based on specialist referrals, symptoms, and laboratory values and other treatments captured in the electronic record, this group includes 6 patients with PsA, 7 patients with PsO, and 7 patients whose diagnosis cannot be determined from available data

Table 1 (continued)

[b]The study population included patients with at least 1 year of recorded data. Given the small number of apremilast-exposed patients present in the data, we included all apremilast-exposed patients regardless of record length before the first apremilast prescription

[c]Patients may have had more than one malignancy at cohort entry

[d]Record contains at least 1 prescription for an antidepressant recorded within 60 days of a depression diagnosis, with both treatment and diagnosis codes recorded before the cohort entry date

[e]Record contains at least 1 prescription for an anti-anxiety treatment recorded within 60 days of an anxiety diagnosis, with both treatment and diagnosis codes recorded before the cohort entry date

[f]Serious (i.e., hospitalized) infections before cohort entry are not captured here

prescription) unless their last prescription was recorded before the matched date. In these instances (2%), the cohort entry date was the date of the first prescription received in the 6 months before the matched date. While matched non-apremilast patients were required to have at least 1 year of registration before the cohort entry date, 19 (6%) apremilast-exposed patients had < 1 year of registration prior to cohort entry. This was done to capture as many apremilast-exposed patients as possible, given the small number of these patients available in the database (Table 1).

2.3 Outcomes

Adverse events of special interest were identified a priori based on those observed in apremilast clinical trial programs [5–9, 19], the mechanism of action of apremilast, apremilast non-clinical data, possible class effects, known comorbidities in patients with PsO or PsA, and safety issues identified with currently marketed compounds in the proposed indications. These events were identified using Read codes (see ESM) and included cancers, opportunistic and serious infections, major adverse cardiac events (MACE), vasculitis, tachyarrhythmia, hypersensitivity reactions, suicidal behaviors, treated depression, and treated anxiety/nervousness. All-cause mortality was also included to capture important potentially drug-related events resulting in death.

All AESIs were required to be incident (i.e., first recorded after cohort entry) with the exception of episodic AESIs (opportunistic and serious infections and hypersensitivity reactions). That is, analyses for a specific AESI excluded patients with a history of that outcome on or before cohort entry. Treated depression required at least one prescription for an antidepressant recorded within 60 days of a depression diagnosis and analyses excluded patients with the treated condition at any time before cohort entry or who received an antidepressant without a recorded depression diagnosis in the year before cohort entry. Treated anxiety was defined similarly, using records for anti-anxiety treatments and anxiety diagnoses. Major adverse cardiac events included myocardial infarction, non-traumatic stroke, and sudden cardiac death. Tachyarrhythmias included atrial fibrillation and flutter, supraventricular tachyarrhythmia and tachycardia, and ventricular tachycardia, fibrillation, and flutter. Opportunistic and serious infections included pneumocystis pneumonia, cryptosporidiosis, mycobacterial infections (including tuberculosis), bartonellosis, leukoencephalopathy, candidiasis, cryptococcosis, other mycoses, cytomegaloviral disease, herpes simplex, herpes zoster, human papilloma virus, viral hepatitis, Epstein–Barr virus infection, histoplasmosis, and toxoplasmosis, and infections that required hospitalization, were life threatening, or resulted in death. We reviewed the electronic record of each case of MACE, cancer, vasculitis, and tachyarrhythmia to confirm that the records contained additional clinical evidence for the diagnosis and a sample of cases of depression, anxiety, infection, and hypersensitivity reaction to ensure that these conditions were appropriately coded. No cases were excluded as potential rule-outs or miscoded diagnoses.

2.4 Analysis

Person-days were accumulated for each patient from the first study drug prescription on or after cohort entry until the first of the following: (1) study outcome occurred (separately for each outcome), (2) end of study drug filled use and outcome-specific lag time, (3) end of patient record, (4) death, or (5) end of data collection. Lag times were set a priori to reflect the amount of time it could take for the outcome to manifest after exposure; 90 days for all-cause mortality, MACE, and vasculitis; 30 days for infections, suicidal behaviors, depression, and anxiety; and 14 days for tachyarrhythmia and hypersensitivity reactions. Cases of malignancy were assessed starting 1 year after the date of the first study drug after cohort entry through the end of the patient record. The electronic record of each case of an AESI was reviewed to confirm that the patient was exposed to a study drug (including lag times) at the time of the event.

We estimated IRs per 1000 patient-years with 95% confidence intervals (CIs) for each AESI by cohort. For AESIs with more than five events in the apremilast-exposed cohort, we calculated crude incidence rate ratios (IRRs) with 95% CIs using Poisson regression for each non-apremilast cohort versus the apremilast-exposed cohort (i.e., apremilast was used as the common reference for all IRR estimates). For

outcomes with more than five events in the apremilast-exposed cohort, we also provided cumulative incidence functions for each AESI by cohort using the Kaplan–Meier method. Statistical analyses were carried out using Stata 15 (StataCorp LLC, College Station, TX, USA).

3 Results

Overall, 341 apremilast-exposed patients were matched for age, sex, and length of record before cohort entry to 4981 patients exposed to other PsO and PsA treatments. The proportion of patients with PsA was lower in the apremilast-exposed cohort than in the oral and injectable cohort (44% vs 65%), whereas it was higher than that in the oral-only (42%) or injectable-only (31%) cohorts. More apremilast-exposed patients than those exposed to non-apremilast treatments had a body mass index ≥ 30 kg/m^2. The presence of comorbidities was generally similar across all cohorts at cohort entry. However, apremilast-exposed patients had a lower prevalence of anxiety and depression than the respective non-apremilast cohorts (Table 1).

Patients with non-apremilast oral treatments had a similar number of study drug prescriptions during follow-up as apremilast-exposed patients, while patients with injectable treatments had fewer prescriptions, and patients with oral and injectable treatments had twice as many prescriptions, regardless of whether the oral and injectable treatments were concomitant or sequential. A total of 89 (26%) patients used apremilast in combination with one or more other treatments, most commonly methotrexate or prednisolone. These two treatments, along with methylprednisolone and sulfasalazine, were the most common treatments used in

Table 2 Characteristics of patients in the apremilast and matched non-apremilast treatment cohorts during the study follow-up: CPRD GOLD (2015–20)

Characteristic	Apremilast $N=341$	Non-apremilast		
		Oral only $N=3129$	Injectable only $N=775$	Oral + injectable $N=1077$
Length of medical record after cohort entry (months)[a]				
Mean ± SD	21 ± 15	22 ± 15	30 ± 16	31 ± 16
Median (IQR)	16 (9–31)	18 (9–31)	29 (15–45)	30 (17–46)
< 6	52 (15)	452 (14)	47 (6)	49 (5)
6–11	71 (21)	655 (21)	84 (11)	120 (11)
12–23	86 (25)	767 (25)	172 (22)	199 (18)
24–35	72 (21)	662 (21)	187 (24)	293 (27)
36–47	31 (9)	299 (10)	149 (19)	180 (17)
≥ 48	29 (9)	294 (9)	136 (18)	236 (22)
Number of study drug prescriptions on or after cohort entry[b]				
Mean ± SD	8 ± 10	7 ± 10	4 ± 8	19 ± 21
1	98 (29)	1015 (32)	498 (64)	0 (0)
2	31 (9)	412 (13)	86 (11)	92 (9)
3–5	58 (17)	583 (19)	74 (10)	180 (17)
6–9	59 (17)	387 (12)	31 (4)	141 (13)
≥ 10	95 (28)	732 (23)	86 (11)	664 (62)
Study drugs used by ≥ 5% of patients in any cohort during the follow-up				
Apremilast	341 (100)	0 (0)	0 (0)	0 (0)
Leflunomide	< 5 (1)	148 (5)	0 (0)	106 (10)
Methotrexate	40 (12)	959 (31)	164 (21)	723 (67)
Methylprednisolone	< 5 (1)	< 5 (< 1)	348 (45)	307 (29)
Prednisolone	37 (11)	1778 (57)	0 (0)	498 (46)
Sulfasalazine	11 (3)	433 (14)	0 (0)	268 (25)
Triamcinolone	< 5 (1)	0 (0)	238 (31)	165 (15)

Results are presented as *n* (%), unless specified. Cell sizes less than 5 were not reportable per license agreement

CPRD Clinical Practice Research Datalink, *IQR* interquartile range, *SD* standard deviation

[a]Length of available medical record after cohort entry date. Patients may have been censored at an earlier date (see "Methods")

[b]In the apremilast-exposed cohort, only prescriptions for apremilast were assessed for this measure (i.e., concomitant oral or injectable treatments are not included)

Table 3 Incidence rates and IRRs of AESI among patients in the apremilast and matched non-apremilast treatment cohorts: CPRD GOLD (2015–2020)

AESI Treatment cohort	Events	PY	IR per 1000 PY (95% CI)	Crude IRR (95% CI)[a]
Opportunistic and serious infections[b]				
Apremilast	18	282	64 (40–102)	Reference
Oral only	119	2370	50 (42–60)	0.8 (0.5–1.3)
Injectable only	8	394	20 (10–41)	0.3 (0.1–0.7)
Oral + injectable	105	1853	57 (47–69)	0.9 (0.5–1.5)
Hypersensitivity reactions[b]				
Apremilast	11	281	39 (22–71)	Reference
Oral only	169	2324	73 (63–85)	1.9 (1.0–3.4)
Injectable only	19	388	49 (31–77)	1.2 (0.6–2.6)
Oral + injectable	117	1849	63 (53–76)	1.6 (0.9–3.0)
MACE				
Apremilast	< 5	281	7 (2–29)	
Oral only	10	2343	4 (2–8)	
Injectable only	< 5	393	10 (4–27)	
Oral + injectable	6	1911	3 (1–7)	
Tachyarrhythmias				
Apremilast	< 5	273	11 (4–34)	
Oral only	10	2350	4 (2–8)	
Injectable only	< 5	378	5 (1–21)	
Oral + injectable	7	1900	4 (2–8)	
Malignancy, solid				
Apremilast	< 5	267	8 (2–30)	
Oral only	13	2293	6 (3–10)	
Injectable only	< 5	377	11 (4–28)	
Oral + injectable	10	1859	5 (3–10)	
All-cause death				
Apremilast	< 5	292	7 (2–27)	
Oral only	61	2471	25 (19–32)	
Injectable only	6	404	15 (7–33)	
Oral + injectable	42	2005	21 (16–28)	

Cell sizes less than 5 were not reportable per license agreement

AESI adverse events of special interest, *CI* confidence interval, *IR* incidence rate, *IRR* incidence rate ratio, *MACE* major adverse cardiac events, *PY* person-years

[a]IRRs (95% CI) are provided for AESI with 5 or more cases in the apremilast-exposed cohort

[b]First exposed event after cohort entry regardless of history before cohort entry

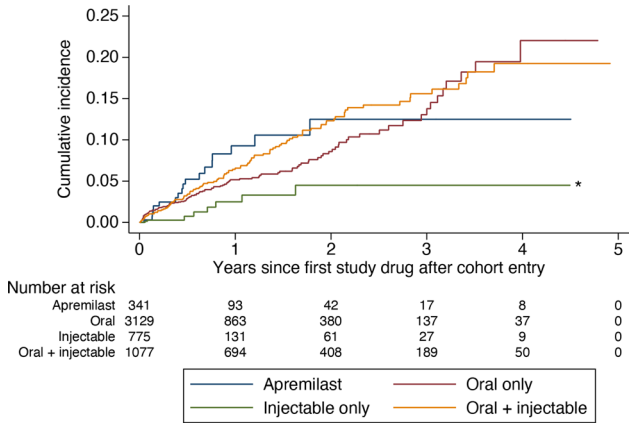

Fig. 2 Cumulative incidence of first opportunistic or serious infection among patients in the apremilast and matched non-apremilast treatment cohorts: Clinical Practice Research Datalink GOLD (2015–20). *$P < 0.05$ for the injectable-only treatment cohort compared with the apremilast-exposed cohort (pair-wise log-rank test)

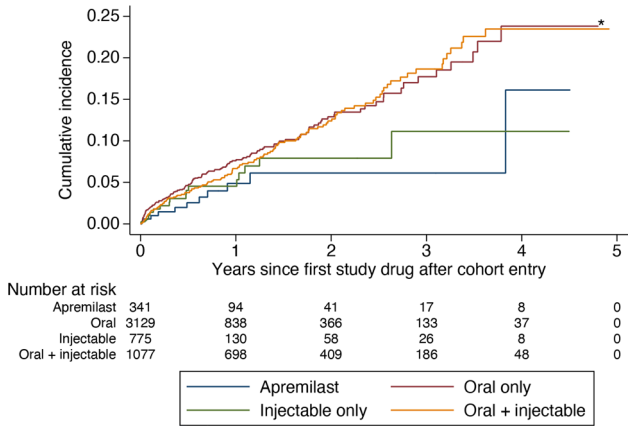

Fig. 3 Cumulative incidence of first hypersensitivity reaction among patients in the apremilast and matched non-apremilast treatment cohorts: Clinical Practice Research Datalink GOLD (2015–2020). *$P < 0.05$ for the oral-only treatment cohort compared with the apremilast-exposed cohort (pair-wise log-rank test)

the non-apremilast cohorts. Newer biologic treatments were rarely recorded in CPRD GOLD (Table 2).

No incident apremilast-exposed cases of vasculitis, hematologic malignancy, non-melanoma skin malignancy, treated depression, treated anxiety, or suicidal behaviors were recorded in the apremilast-exposed cohort during the follow-up (range 0–59 months). Incidence rates for MACE, tachyarrhythmias, and solid malignancies were low and similar across treatment cohorts (Table 3). Opportunistic and serious infections were common across all treatment cohorts. Incidence rates of infections among patients in the oral and oral and injectable cohorts were similar to those in the apremilast-exposed cohort. However, IRs and cumulative incidences of infections were lower in the injectable-only cohort than in the apremilast-exposed cohort (Table 3 and Fig. 2). Of the 18 apremilast-exposed infection cases, 13 were exposed to apremilast monotherapy and five were also exposed to a non-biologic DMARD or a steroid. The infections included hospitalized infections (respiratory, urinary tract, and kidney infections) and outpatient infections (candidiasis, herpes zoster, and other opportunistic infections).

Oral, injectable, and oral and injectable cohorts had higher IRs and cumulative incidences of hypersensitivity reactions than in the apremilast-exposed cohort (Table 3 and Fig. 3). No study outcomes were recorded among the 19 apremilast-exposed patients with less than 1 year of data before cohort entry.

4 Discussion

Patients enrolled in clinical trials are not necessarily representative of real-world patients, especially with regard to comorbidities and prior treatments [20, 21]. In an observational study of patients with PsO receiving biologics in the British Association of Dermatologists Biologic Interventions Register, Mason et al. applied clinical trial eligibility criteria to patients and stratified them as eligible or ineligible [22]. The authors found that patients in the British Association of Dermatologists Biologic Interventions Register deemed ineligible by clinical trial criteria had smaller improvements in the Psoriasis Area and Severity Index and experienced higher rates of serious adverse events compared with those in the eligible criteria group [22]. In this real-world study, we identified 341 patients with apremilast prescriptions in CPRD GOLD in the first 5 years after approval of apremilast in the UK. Among these patients, the number of AESIs was low and the IRs of most AESIs were similar compared with patients with prescriptions for non-apremilast treatments available in the UK at the time of the study and recorded in CPRD data.

In this study, no incident cases of apremilast-exposed vasculitis, hematologic malignancy, skin malignancy, treated depression, treated anxiety, or suicidal behaviors were recorded in CPRD data. Rates of death, MACE, tachyarrhythmias, and solid malignancies were similar between patients exposed to non-apremilast treatments and apremilast-exposed patients. These findings are concordant with an earlier study using a US database that reported lower IRs of myocardial infarction (1.4 vs 2.1 per 1000 person-years) and stroke (1.1 vs 1.3 per 1000 person-years) among patients treated with apremilast compared with patients treated with DMARDs [23].

The unadjusted rate of opportunistic and serious infections was higher in the apremilast-exposed cohort than in the injectable-only cohort. Of the 18 apremilast-exposed infection cases, five patients were also exposed to non-biologic DMARDs or a steroid. However, as the rates of infections were similar between the apremilast, oral-only, and oral and injectable cohorts, this increased risk of infections in the apremilast-exposed cohort compared with the injectable-only cohort should be considered in this greater context. The majority (58%) of patients in the injectable-only cohort were steroid users with only one recorded study drug prescription. Possibly, these patients had less severe disease, or their exposed person-time was overestimated. We applied a 30-day exposure window to each injection prescription, which may have been an overestimate of relevant exposure. Furthermore, when a patient had only one injectable treatment recorded, their person-time doubled with the addition of the 30-day lag time assigned a priori to infection outcomes. If person-time was overestimated in the injectable cohort, this could have resulted in a lower rate if there were a true association that diminished over the 30-day lag time.

In apremilast clinical trials, the rates of infections did not increase over time in the long-term, 5-year, open-label, follow-up phase [24]. However, the results from this study are not directly comparable to those studies. In this real-world study, most injectable treatments were steroids or methotrexate, and the use of biologic therapies was low. Importantly, methotrexate and prednisolone were the most common concomitant treatments used in the apremilast-exposed cohort: 21% of patients in this cohort received one or both of these treatments during the follow-up. Other studies that examined the risk of serious infections in patients initiating apremilast have reported either a decreased risk, [25] or no increased risk compared with patients who received non-apremilast prescriptions [26]. In a study of two large US health insurance claims databases, Dommasch et al. found a decreased risk of serious infections in patients with PsO initiating treatment with apremilast compared with those initiating treatment with methotrexate [25]. Additionally, an analysis of patients with PsO initiating new treatment in a large French database observed that serious infection rates in apremilast users were similar to users of other biologics (etanercept) [26]. Wakkee et al. observed that PsA disease severity correlated with a higher risk of serious infections not attributed to systemic anti-psoriatic treatments and comorbidities [27].

While the CPRD is a large database, it does have limitations that may have affected these results. The capture of PsO and PsA treatments in CPRD data is not complete. Drugs administered via infusions are typically received in outpatient clinics and are not recorded in the GP record. Furthermore, it is possible that injectable biologics and other oral specialty treatments (e.g., tofacitinib) were prescribed by specialists (rheumatologists and dermatologists) and these were not captured in the GP data. Thus, some person-time may have been misclassified as unexposed and some patients may have been included in the wrong non-apremilast cohort (e.g., oral-only cohort rather than the oral and injectable cohort). Some of the treatments (i.e., methotrexate and prednisolone) were prescribed concomitantly to 21% of the patients in the apremilast-exposed cohort. It is also possible that there are patients who received apremilast from a specialist but whose GP did not record any apremilast prescriptions. This would have led to an exposure misclassification. As rates of the study outcomes were generally

similar across all exposure cohorts, it is unlikely that the results of this study would have been materially different even with some exposure misclassification.

It is also possible that some AESIs were not captured. Conditions treated in hospitals or managed by specialists rather than by GPs may not have been coded in the GP record. This is unlikely for AESIs such as MACE and other serious cardiovascular disease, malignancies, and treated psychiatric outcomes requiring ongoing care by a GP. However, certain less serious infections and hypersensitivity reactions may have been managed entirely by a specialist and not reported to or recorded by a GP. Although it is possible that some events were missed (particularly in March–June 2020 because of coronavirus disease 2019), it is unlikely that missing events would be differential by exposure.

To control for confounding by indication, all patients in the non-apremilast comparison cohorts had a diagnosis code for PsO or PsA and received at least one study drug during the follow-up period. However, a large proportion of patients in the non-apremilast cohorts had prescriptions for steroids or methotrexate; there were few patients with prescriptions for biologics. We matched for age, sex, calendar year, and length of record before cohort entry to address confounding by these factors. Because of the small numbers of younger eligible matches with injectable treatments, the age distribution in the apremilast and injectable-only cohorts was not similar. We included 19 apremilast-exposed patients with less than 1 year of registration with the current GP who were matched to patients with registration lengths greater than 1 year. The majority ($n = 11$) of these patients had more than 1 year of historical data that recorded diagnoses, which occurred before registration with their current GPs. None of these 19 patients had any AESI recorded in their records. Nevertheless, the inclusion of these patients may have impacted the results given the small numbers of events. Additionally, access to apremilast in the UK is restricted to patients with higher disease severity and may only be prescribed by specialists for PsO [11, 28].

While the PsA criteria are less stringent, primary care physicians may have more delays in diagnosing and referring PsA early [12, 29]. As a result, apremilast-exposed patients may have entered the study later in the patient disease pathway than non-exposed apremilast patients, which was not controlled for although sicker patients may experience more adverse events. Furthermore, because of the small numbers of events for each AESI among apremilast-exposed patients, we were unable to adjust estimated IRRs by any additional potential confounders including disease severity, comorbidities, or other treatments.

5 Conclusions

In this 5-year prospective study in a large UK primary care database, no new safety signals for apremilast were identified. These results provide evidence that the long-term safety profile of apremilast in PsO and PsA in a real-world setting is comparable to that reported in clinical trials and other real-world publications.

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Declarations

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Conflict of interest Rebecca Persson received research grants to her institution from Amgen Inc. Myriam Cordey and Maria Paris are employees of Amgen Inc. Susan Jick received research grants to her institution and is a consultant for Amgen Inc.

Ethics approval This study is based in part on data from the CPRD obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the National Health Service as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. This study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research (protocol no.: 16_083) and registered in the European Union Post-Authorization Studies register (EUPAS11891). The protocol can be made available to the journal's reviewers upon request. Hospital Episode Statistics Copyright © (2020), re-used with the permission of The Health and Social Care Information Centre. All rights reserved.

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability Per our license agreement with CPRD, we cannot make data available. Requests to access data can be made directly to the CPRD.

Code availability Raw CPRD data were accessed using the custom Delphi code. Datasets were analyzed using Stata version 15.

Author contributions All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. Author contributions were as follows: RP (design, electronic record review, analysis, interpretation, manuscript writing, manuscript revision), MC (interpretation, manuscript writing, manuscript revision), MP (design, interpretation, manuscript writing, manuscript revision), SJ (conception, design, electronic record review, acquisition, interpretation, manuscript writing, manuscript revision).

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