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The evolving demographics of patients recruited to phase III randomised controlled trials of biologic drugs, JAK inhibitors and Apremilast in peripheral Psoriatic Arthritis:

A Systematic Review

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BACKGROUND

Psoriatic arthritis (PsA) is a typically seronegative inflammatory arthritis which is prevalent in up to 30% of individuals with psoriasis [1]. Men and women are affected in similar proportions, and the prevalence in the United States (US) is estimated to be 0.25% [2].

Our understanding of the geoepidemiology of PsA is limited, due to the small number of epidemiological studies utilising validated classification criteria, heterogeneity in methodology, and variability in healthcare access. Broadly speaking, the prevalence of PsA appears to be higher in patients of Northern European descent and particularly low amongst Japanese, but significant knowledge gaps remain [3,4].

The availability of and access to biologic, targeted synthetic, and other novel disease-modifying anti-rheumatic drugs (DMARDs) has advanced significantly over the past two decades. Randomised controlled trials (RCTs) of these agents provide a unique opportunity to assess differences in genetic profiles of participants of different sexes, countries and racial groups, and the impact these have on treatment responses. In this systematic review, we describe the evolution in the demographics of participants recruited to RCTs of bDMARDs, tsDMARDs and Apremilast between 2000-2022.

METHODS

Search methods

We searched the electronic databases MEDLINE and EMBASE using the search terms “psoriatic arthritis” AND “randomized controlled trials” between 1 January 2000 and 1 June 2022. The filter for publication type “article” was applied in EMBASE.

Eligibility criteria

Studies identified through this search criteria were reviewed by two independent authors (WZ and AA) to determine their eligibility for inclusion. We included all full-text English language placebo-controlled phase III RCTs with the primary objective of assessing the efficacy of b/tsDMARDs and Apremilast in peripheral joint PsA. Studies with the primary objective of assessing the efficacy of treatment strategies or efficacy on axial disease, dactylitis and imaging outcomes were not included. Studies were excluded if they did not have a published initiation date on ClinicalTrials.gov. Duplicates, subgroup analyses and post-hoc analyses were excluded so that each study population was only represented once.

Data collection and analysis

Data was independently extracted by two authors (WZ and AA) from the studies, including: inclusion criteria, age, sex, race, disease duration, swollen joint count (SJC), tender joint count (TJC), C-reactive protein (CRP), and Health Assessment Questionnaire – Disability Index (HAQ-DI). Data were extracted from the active treatment arm of each study for consistency. Where there were two active treatment arms for the study drug of interest, the treatment arm with the lowest approved treatment dose was selected.

The date of study initiation and countries in which the study was conducted was extracted from ClinicalTrials.gov. Where available, information regarding recruitment within individual countries/regions and amongst different races were also extracted.

The collected data were grouped according to year of study initiation (2000-2004, 2005-2009, 2010-2014, and 2015-2020) and analysed using descriptive statistics. The distribution of missing data was included in the results.

RESULTS

We identified 34 eligible RCTs from 33 reports (Figure 1). The included studies (n=34) assessed the efficacy of IL-17 inhibitors (10), TNF inhibitors (7), IL-23 inhibitors (5), Apremilast (5), JAK inhibitors (4), IL-12/23 inhibitors (2), and Abatacept (1) (supplementary material 1).

All studies were initiated between 2000 and 2019; 4 studies were initiated between 2000-2004, 2 studies between 2005-2009 , 18 studies between 2010-2014 and 10 studies between 2015-2019 (Table 1). Twelve RCTs were exclusively in b/tsDMARD-naïve cohorts, with proportion of these decreasing over time. Disease duration among patients at baseline evolved slightly; the lowest mean disease duration decreased from 7.5 years (2000-2004) to 3.6 (2015-2019) while the highest mean disease duration remained unchanged.

Age and Gender

The central tendency of study participant age did not appear to evolve over time (Table 1). The range of mean ages across studies was stable between 2000-2004 (45.6-50.4 years) and 2015-2019 (44.0-53.0).

In 2000-2004, males represented the majority of participants in all RCTs (range 56.3-71.0%). Over time however, the representation of female participants increased. Males represented 51.7-61.0% of study participants recruited to studies initiated between 2004-2009 and 41.2-54.0% of study participants recruited to studies initiated between 2010-2014 (Table 1).

Race and Number of Countries

The number of countries included as study sites in RCTs increased over time from 1-8 countries in 2000-2004, to 2-46 countries in 2015-2019 (supplementary material 2). Ten studies reported recruitment of patients in categories of: North America, Europe and 'the rest of the world'. In these studies (n=4865), 17.6%, 31.3% and 41.1% of participants were recruited from North America,

Europe and the 'Rest of the World' respectively. Six of these studies specifically reported the numbers of patients recruited from individual countries: GO-VIBRANT, AM-VISION 1 and 2, DISCOVER 1 and 2, and SPIRIT-P2. In these studies (n=2925), a majority of patients were recruited from Russia (21.1%), Poland (20.4%), US (15.6%) and Ukraine (15%). In these studies, 28.5% (n=599) of patients in Europe were recruited in Poland and 87.8% (n=1055) of patients from 'the rest of the world' were recruited from Ukraine or Russia.

Representation of white patients was reported in 28 of 34 studies. In these 28 studies (n=13,847), 7.3% of participants (n=1,013) were not white. In 22 studies reporting the percentage of Black/African American or Asian participants (n=12,121), 0.5% of participants (n=61) were Black or African American and 5.2% (n=634) were Asian. In 8 studies reporting the percentage of Hispanic or Latino participants, 13.3% of participants (n=830/6231) were Hispanic or Latino.

The proportion of non-white participants only increased marginally over time, despite the significant diversification of site participation (Figure 2). The proportion of white participants in the RCTs was 90.0-98.0% between 2000-2009 and 80.9-97.3% between 2015-2019. Non-white participants represented >10% of patients recruited in only 3 RCTs: FUTURE 1 (19.8% of participants; initiated in 2011) [5], FUTURE 5 (19.1%; 2015) [6] and SELECT-PsA 2 (12.3%; 2017) [7].

Baseline joint count, CRP, and physical function

The range of means for SJC and TJC evolved over time, with 22 studies using the 66/68 joint count and 12 studies using the 76/78 joint count (Table 1). A majority of studies (n=27) across all time periods mandated a minimum of 3 active joints for inclusion, while 7 mandated a minimum of 5 active joints. In studies utilising the 66/68 joint count, the swollen joint count decreased from 13.9 (2000-2004) to 7.0-13.0 (2015-2019) and the tender joint count decreased from 24.6 (2000-2004) to

12.9-24.9 (2015-2019). A similar pattern was observed in studies utilising the 76/68 joint count (Table 1).

Baseline CRP and HAQ-DI were reported in a majority of studies (n=32 and 22 respectively) and their central tendencies remained stable over time (Table 1). An abnormal CRP at baseline was mandated in 10 studies.

DISCUSSION

In this systematic literature review of patients enrolled into RCTs assessing the efficacy of bDMARDs, tsDMARDs and Apremilast in peripheral PsA, the key finding was of minimal evolution in non-white patient representation which was discordant with the diversification in study sites. There was however optimisation in the representation of female PsA patients. We also found a slight decrease in the disease activity of participants over time as assessed by swollen and tender joint counts, despite of the relative stability of inclusion criteria.

Understanding the role of genetics and epigenetics in the natural history of PsA and in predicting therapeutic responses is vital. RCTs represent an important platform to achieve this, given the collection of biological samples for genomic analysis with accompanying comprehensive clinical datasets. The lack of racial diversity in patients recruited to RCTs therefore represents a missed opportunity in the advancing of care of patients with psoriatic disease.

Health inequalities in psoriatic disease research is well-recognised [8]. Of the ten most populous countries worldwide, sound epidemiological data regarding PsA are only available for China and the United States [4]. While some have suggested that the prevalence of PsA may be higher in whites than non-whites, others have demonstrated that the prevalence in China for example, is comparable to white-predominant countries [3,9,10]. The extent to which epidemiological differences

can be explained by under-diagnosis among patients with darker skin tones and in populations where there is inequity in access to healthcare is poorly understood. Limited studies into disease phenotype have suggested that non-white patients may have a more severe phenotype, which may well be multifactorial [9,11].

The issue of underrepresentation of non-white participants in clinical trials is not unique to either PsA or RCTs. A systematic review of RCTs in RA found similar trends in the stagnancy of non-white participants over time and an under-representation of non-white patients relative to the epidemiology of the disease [12]. In systemic lupus erythematosus (SLE), Falasinnu et al. found that white participants represented 47-56% of patients in RCTs despite only making up 33% of SLE patients in the United States [13]. Furthermore, it was recently reported that 94.2% of PsA patients in the North American CORRONA registry are white [14]. Concerningly, a systematic review of all dermatology RCTs between 2015-2020 found that race and ethnicity was only reported in 75.3% of studies [15].

The hypothesized reasons the under-representation of non-white patients in RCTs in the literature include language barriers, difficulties accessing healthcare due to costs or lack of transportation, mistrust of the healthcare system, and systems-related issues such as health insurance [16-18]. The extent to which other factors contribute, such as the mandating of the imaging assessment of damage as a secondary outcome, is not known.

The US Food and Drug Administration (FDA) have published guidance on practices to enhance the diversity of industry clinical trial populations [14]. As an example, language barriers could be overcome with the provision of patient information and consent forms in multiple languages, validated non-English versions of questionnaires and adequate budgets for interpreter access. The US FDA have also recommended that study recruitment locations include “locations with a higher

concentration of racial and ethnic minority patients and indigenous populations" [19]. While this review noted a demonstrable and significant effort to diversify study site locations over time, this has not clearly translated into optimising patient diversity.

In order to elucidate the key reasons for why non-white patients represented >10% of patients in the active treatment arm in only 3 PsA RCTs, it is important to know where patients were recruited from. In the six RCTs in which this data were available, we found that a high proportion of patients were recruited from white-predominant countries such as Poland, Russia, and Ukraine. The lack of corresponding data in other RCTs does however raise the possibility of publication bias. Furthermore, there is little transparency into the recruitment targets in individual countries. Ultimately, we note that while there is some diversity among white patients recruited to PsA RCTs, there is a glaring absence in the diversity within other racial groups.

Moving forward, we would advocate for the publication of country-specific recruitment targets and actual recruitment numbers in all RCTs in order to ensure transparency. A brief discussion on the key factors contributing to missed recruitment targets in individual countries within the supplementary material would be highly informative. Within individual countries, well-designed epidemiological studies are needed to better understand how this contributes to disparities in RCT recruitment. And finally, we re-iterate an important strategy proposed at the 2021 GRAPPA meeting, which was to improve inclusivity in the selection of patient research partners [8].

The prevalence of PsA among male and female patients is comparable. Our study reports the novel finding of improving gender representation for female patients in PsA RCTs, with 41.2-54.0% of participants being male. This ensures that there is adequate data regarding treatment responses for specific drugs in both male and female patients. No studies reported patient identification of gender.

Finally, we observed a gradual decline in the baseline swollen and tender joint counts of RCT patients over time, which did not appear to be clearly related to any differences in the outcome instrument used, the mandated minimum active joint count at baseline or the duration of disease. This is particularly notable given the increase of studies recruiting bDMARD-experienced patients over time and may reflect advances in early diagnosis and optimal treatment escalation.

There are a number of limitations in this systematic review. We did extract data on baseline radiographic damage scores and severity of psoriasis, however there was significant variability in the instruments used and the measures of central tendency used, which made it difficult to meaningfully synthesise the data. Secondly, we were only able to report the of ranges of the central tendencies for most variables. Therefore, our findings lack supporting data from measures of distribution such as standard deviations and interquartile ranges, which are difficult to synthesise. We did not include RCTs assessing conventional disease-modifying drugs or treatment escalation strategies and RCTs that did not include a placebo arm; these factors may limit the generalisability of our study. Finally, we lacked patient research partner involvement in this systematic review and have not therefore adequately represented their perspective.

CONCLUSION

The racial diversity of participants in placebo-controlled phase III RCTs of b/tsDMARDs and Apremilast in PsA have evolved minimally over two decades, despite significant expansion of international study sites. Consistent reporting of patient recruitment within individual countries or regions and within the non-white population could allow for synthesis of these data in a more meaningful way. This has the potential to improve our understanding of the contributing factors and facilitate the development of effective solutions.

Figure 1. PRISMA flow diagram of selection of studies

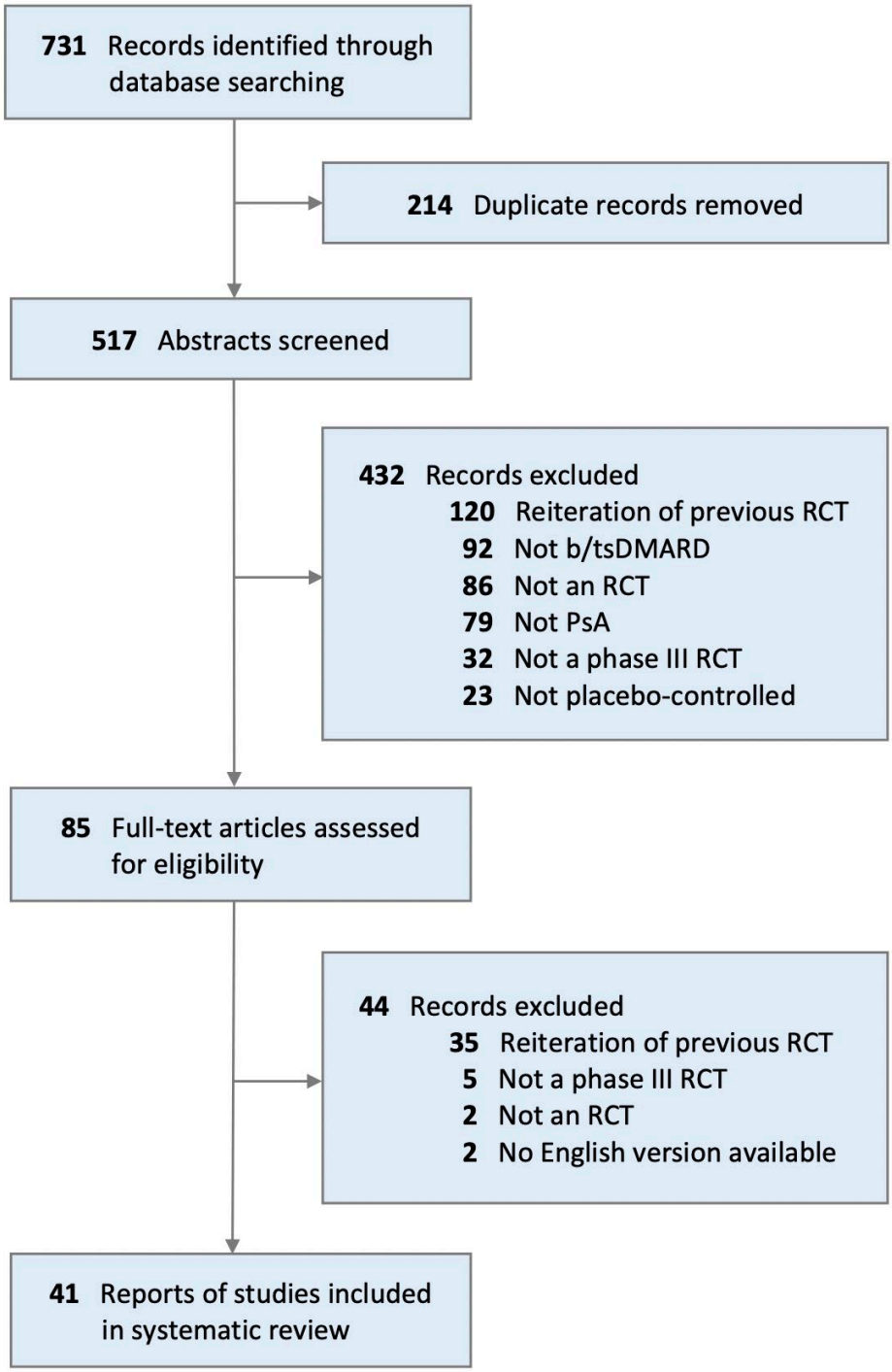
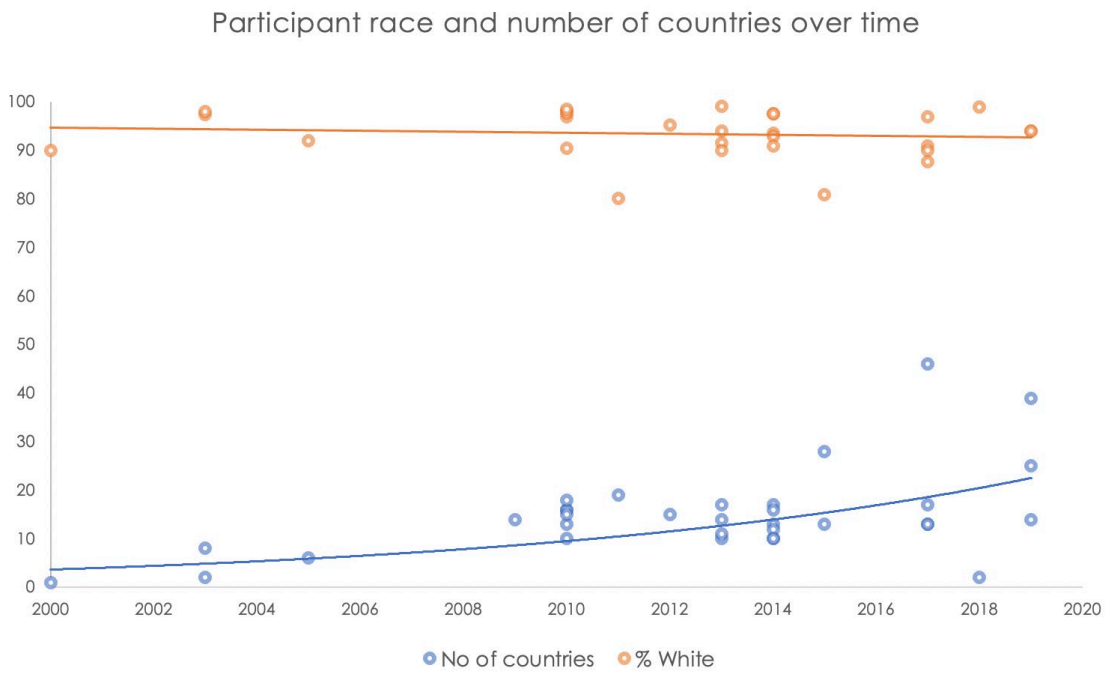


Table 1: Baseline characteristics of participants in included studies

	2000-2004	2005-2009	2010-2014	2015-2019
Studies (n)	4	2	18	10
Drug	Adalimumab Etanercept Infliximab	Golimumab Ustekinumab	Abatacept Apremilast Brodalumab Certolizumab Golimumab Ixekizumab Secukinumab Tofacitinib Ustekinumab	Guselkumab Risankizumab Secukinumab Upadacitinib Netakimab
No. Countries Not reported	1-8 1 study	6-14 N/A	10-19 N/A	2-46 N/A
Patients in study (n)	100-313	405-615	219-606	97-1704
Inclusion Criteria Joint count bDMARD/tsDMARD Naive Abnormal CRP (and/or Erosion)	 3 (3 studies) 5 (1 study) 4/4 studies 0 studies	 3 (1 study) 5 (1 study) 2/2 studies 1/2 studies	 3 (16 studies) 5 (2 studies) 4/18 studies 6/18 studies	 3 (7 studies) 5 (3 studies) 2/10 studies 4/10 studies
Data from active treatment arm				
Age (years) **Mean** **Median**	 45.7-50.4 (4 studies) N/A	 45.7 (1 study) 48.0 (1 study)	 45.7-52.6 (17 studies) 49 (1 study)	 44.0-53.0 (8 studies) 52 -53 (2 studies)
Sex (% Male)	56.3-71.0	51.7-61.0	41.4 - 52.6	41.2 - 54.0
Race (% White) Not reported	90-98 (3 studies) 1 study	97 (1 study) 1 study	80.2 - 99.1 (16 studies) 2 studies	80.9 – 99.0 (8 studies) 2 studies
Disease Duration **Mean** **Median** Not reported	 7.5 - 9.8 (4 studies) N/A	 7.5 - 9.8 (4 studies) 5.0 (1 study) N/A	 3.6 - 11.0 (15 studies) 5.3 (1 study) 2 studies	 5.1 - 9.6 (10 studies) N/A N/A
66/68 SJC/TJC **Mean** **Median** Not reported	 S: 13.9, T: 24.6 (1 study) N/A 1 study	 S: 14.1, T: 24.0 (1 study) S: 10, T: 18 (1 study) N/A	 S:10.5-14.0, T: 19.6-25.1 (9 studies) S: 12, T: 22 (1 study) N/A	 S: 7.0-13.0, T: 12.9-24.9 (7 studies) S: 10, T: 21 (1 study) N/A
76/78 SJC/TJC **Mean** **Median** Not reported	 S: 13.4 - 18.2, T: 22.2 - 25.3 (3 studies) N/A N/A	 N/A	 S: 9.0 - 12.8 T: 17.2 - 24.1 (8 studies) N/A N/A	 S: 9.6 - 12.1 T: 20.1 - 21.2 (2 studies) N/A N/A

Baseline CRP **Mean**	1.0 - 19.0 (3 studies)	1.3 (1 study)	0.8-17.0 (10 studies)	1.2-11.9 (4 studies)
Median	N/A	10 (1 study)	13 (1 study)	0.7 - 1.3 (2 studies)
Not reported	1 study	N/A	6 studies	4 studies
HAQ-DI **Mean**	0.9 - 1.1 (3 studies)	N/A	1.1 - 1.3 (17 studies)	1.1 - 1.3 (9 studies)
Median	N/A	1.3 (1 study)	1.4 (1 study)	N/A
Not reported (n)	1 study	1 study	N/A	1 study

Figure 2. Evolution of participant race and number of countries in included studies over time



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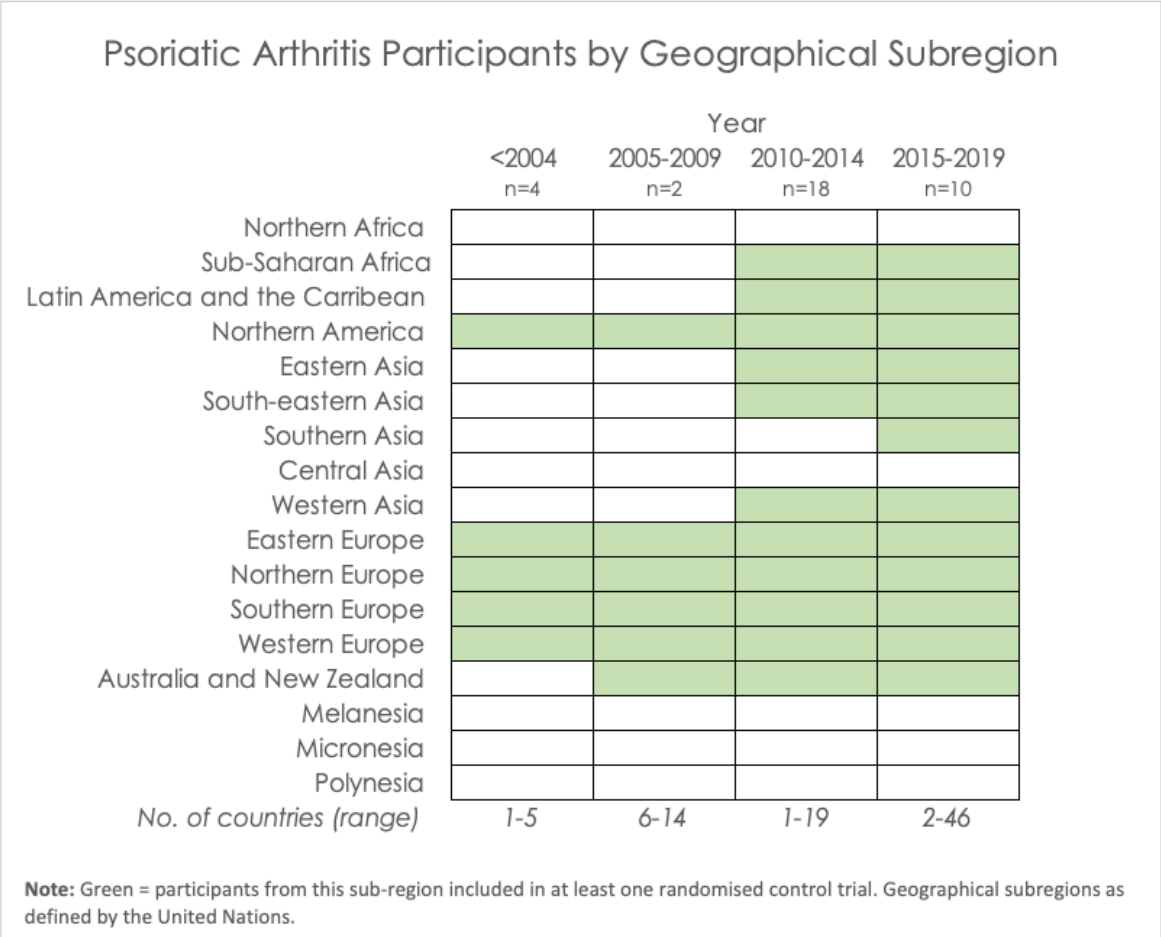
SUPPLEMENTARY MATERIAL

Supplementary material 1. Characteristics of Included Studies

Study	Year of initiation	Drug	n	Target	b/tsDMARD naive?
Enbrel	2000	Etanercept	101	TNFα	Y
IMPACT II	2003	Infliximab	146	TNFα	Y
M02-570	2003	Adalimumab	51	TNFα	N
ADEPT	2003	Adalimumab	151	TNFα	N
GO-REVEAL	2005	Golimumab	131	TNFα	Y
P-SUMMIT 1	2009	Ustekinumab	205	IL-12/23	N
P-SUMMIT 2	2010	Ustekinumab	103	IL-12/23	Y
RAPID-PsA	2010	Certolizumab	135	TNFα	Y
PALACE 1	2010	Apremilast	168	PDE4	Y
PALACE 2	2010	Apremilast	162	PDE4	Y
PALACE 3	2010	Apremilast	167	PDE4	Y
PALACE 4	2010	Apremilast	176	PDE4	N
FUTURE 1	2011	Secukinumab	202	IL-17A	Y
SPIRIT-P1	2012	Ixekizumab	107	IL-17A	N
FUTURE 2	2013	Secukinumab	100	IL-17A	Y
ASTRAEA	2013	Abatacept	213	CD80/86	Y
OPAL-Beyond	2013	Tofacitinib	110	JAK1/3	N
ACTIVE	2013	Apremilast	107	PDE4	Y
OPAL-Broaden	2014	Tofacitinib	159	JAK1/3	N
AM-VISION 1	2014	Brodalumab	163	IL-17RA	N
AM-VISION 2	2014	Brodalumab	240	IL-17RA	N
FUTURE 3	2014	Secukinumab	138	IL-17A	Y
GO-VIBRANT	2014	Golimumab	284	TNFα	Y
SPIRIT-P2	2014	Ixekizumab	122	IL-17A	Y
FUTURE 4	2015	Secukinumab	114	IL-17A	Y
FUTURE 5	2015	Secukinumab	220	IL-17A	Y
SELECT-PsA 1	2017	Upadacitinib	429	JAK1	Y
SELECT-PsA 2	2017	Upadacitinib	211	JAK1	N
DISCOVER 2	2017	Guselkumab	248	IL-23	Y
DISCOVER 1	2017	Guselkumab	127	IL-23	N
PATERA	2018	Netakimab	97	IL-17	N
COSMOS	2019	Guselkumab	189	IL-23	N
KeepSAKE 1	2019	Risankizumab	483	IL-23A	Y
KeepSAKE 2	2019	Risankizumab	224	IL-23A	N

Supplementary material 2. Geographical subregions where participants were recruited