The association of age at psoriasis onset and HLA-C*06:02 with biologic survival in patients with moderate-to-severe psoriasis: a cohort study from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR)

Running head: Predictors associated with effectiveness and safety profile of patients with moderate-to-severe psoriasis

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Ethics statement: BADBIR received approval from the Northwest Research Ethics Committee in March 2007 and BSTOP received approval from the Southeast London REC 2 Ethics Committee (11/H0802/7).

What is already known about this topic?

- Most studies evaluating clinical or genetic determinants of treatment response in psoriasis use change in disease severity from baseline as the primary outcome. This approach might restrict analyses to only those with complete records at baseline and periodic time points, a common issue in longitudinal studies, leading to small sample size which might affect the robustness and generalisability of the findings.

What does this study add?

- We used biologic survival as a proxy marker of drug effectiveness, safety, and real-world utility to test whether response to biologics is affected by age at psoriasis onset and HLA-C*06:02 status.
- We found that age at psoriasis onset has no significant effect on adalimumab, etanercept, secukinumab or ustekinumab survival in patients with moderate-to-severe psoriasis.

- We showed that HLA-C*06:02 is a predictive biomarker of drug survival associated with ineffectiveness for ustekinumab but neither for adalimumab, etanercept nor secukinumab in patients with moderate-to-severe psoriasis.
- We showed that neither age at psoriasis onset nor HLA-C*06:02 affect biologic survival associated with the occurrence of adverse events.

Abstract

Background

Few studies have used real-world data to investigate the association between biologic therapy survival and age at psoriasis onset or HLA-C*06:02 status in patients with moderate-to-severe psoriasis. The robustness of these studies is limited by small sample size, short follow-up and diverse safety and effectiveness measures.

Objectives

To describe biologic survival and explore whether the response to biologics is modified by age at psoriasis onset or HLA-C*06:02 status in patients with moderate-to-severe psoriasis.

Methods

Data from patients in the UK and the Republic of Ireland registering to the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) from 2007-2022 on first course of adalimumab, etanercept, secukinumab or ustekinumab with at least 6 months' follow-up and a subset of BADBIR patients with available HLA-C*06:02 information registered to Biomarkers and Stratification To Optimise outcomes in Psoriasis (BSTOP) were analysed. Patients aged ≥50 years at treatment initiation were classified into early onset psoriasis (EOP; presenting ≤40 years of age) and late onset (LOP; presenting > 40 years of age); BADBIR patients with available information in BSTOP were categorised into HLA-C*06:02-ve and HLA-C*06:02+ve. Biologic survival was defined as treatment discontinuation associated with ineffectiveness or occurrence of adverse events (AEs). Adjusted survival function and hazard ratio (aHR) with 95% confidence interval (CI) were estimated using a flexible parametric model to compare discontinuing therapy between age at psoriasis onset and HLA-C*06:02 groups. Each model included exposure (biologics), effect modifier (age at onset or HLA-C*06:02 status), interaction terms and several baseline demographic, clinical and disease severity covariates.

Results

Final analytical cohorts included 4250 patients (2929 [69%] EOP vs. 1321 [31%] LOP) and 3094 patients (1603 [52%] HLA-C*06:02+ve vs. 1491 [48%] HLA-C*06:02-ve). There was no significant difference between EOP and LOP in drug survival associated with ineffectiveness or AEs for any biologics. However, HLA-C*06:02+ve compared with HLA-C*06:02-ve patients were less likely to discontinue ustekinumab associated with ineffectiveness 0.56 [0.42, 0.75].

Conclusions

HLA-C*06:02 but not age at psoriasis onset is a predictive biomarker for biologic survival in psoriasis patients. Findings from this large cohort provide further, important information to aid clinicians using biologic therapies to manage psoriasis patients.

Introduction

Plaque psoriasis is a chronic, inflammatory skin disease affecting at least 60 million people worldwide and associated with significant comorbidities and poor quality of life.[1] Several different biologic therapies with distinct mechanisms of action have each proven highly effective for some individuals with psoriasis.[2] National Institute for Health and Care Excellence (NICE) guidelines for psoriasis management recommend considering a person's age, disease phenotype, pattern of activity and previous treatment history, disease severity and impact, the presence of psoriatic arthritis, conception plans, comorbidities and the person's views when prescribing systemic therapy for psoriasis.[3] However, there is no clear recommendation on selection between the biologic treatments, with dermatologists reliant on a potentially lengthy and expensive trial-and-error approach to effective control a patient's psoriasis.[4] In 1985, Henseler and Christophers categorised two subtypes of chronic plaque psoriasis: early onset (EOP) starting at or before 40 years of age and late onset (LOP) starting after 40 years of age,[5,6] in Western Europe. EOP is more prevalent and is more strongly associated with the human leucocyte antigen (HLA)-C*06:02 allele than LOP.[7,8] Using the Psoriasis Area and Severity Index (PASI) as a measure of achieving effectiveness, pooled data from four clinical trials showed a better response to etanercept in EOP compared with LOP patients.[9] However, there are few clinical trials and even fewer real-world data which included LOP or older psoriasis patients to investigate response to biologics. Findings from clinical trials and real-world data revealed that HLA-C*06:02 positive patients responded better to ustekinumab compared with HLA-C*06:02 negative patients.[10-12] Dand and colleagues found that HLA-C*06:02 negative psoriasis patients respond better to adalimumab than ustekinumab while HLA-C*06:02 positive patients respond similarly to the two drugs when using an interaction effect model of drug type and HLA-C*06:02. Nevertheless, findings from separate regression models showed that HLA-C*06:02 is associated with a better response to ustekinumab but poorer response to adalimumab.[13] Identifying those psoriasis patients who respond best to particular biologics is a step towards personalised management of the disease. Yet, most studies, examining the association between potential predictors and response to biologics, have been limited to short follow-up and relatively small numbers of young patients who are in the controlled environment of a clinical trial. Real-world data, however, provide information on long-term drug safety and effectiveness. Using data from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) and the aligned bioresource, Biomarkers and Stratification To Optimise outcomes in Psoriasis (BSTOP), we investigated whether drug survival of adalimumab, etanercept, secukinumab or ustekinumab could be influenced by age at psoriasis onset and/or HLA-C*06:02 status in a large psoriasis population in the UK and the Republic of Ireland (RoI).

Methods

Data source

BADBIR is a prospective, multicentre, pharmacovigilance register designed to assess the long-term safety and effectiveness of biologic therapies in patients with moderate-to-severe psoriasis. BADBIR was established in 2007 and currently includes more than 20,000 patients recruited from 167 dermatological centres across the UK and the RoI. Detailed information on BADBIR design and follow-up visits has been published previously.[14]

Ethical approval

BADBIR received approval from the Northwest Research Ethics Committee in March 2007 and BSTOP received approval from the Southeast London REC 2 Ethics Committee (11/H0802/7).

External data source

HLA-C*06:02 status was obtained for patients who met the study inclusion criteria in BADBIR and were also registered to the linked registry BSTOP which is a prospective phenotyped bioresource to facilitate translational research into determinants of psoriasis treatment outcomes. BSTOP data include biological samples collected from more than 70 dermatological centres in the UK. Details of BSTOP inclusion criteria and clinical information have been described previously. [15] HLA-C*06:02 status was derived by imputation from genotyping array data; full details of included participants, genotyping, quality control and imputation have been described previously. [13,16] Protocols and other documentation for BADBIR and BSTOP are available at http://www.badbir.org/ and https://www.kcl.ac.uk/lsm/research/divisions/gmm/departments/dermatology/research/stru/groups/bstop/documents, respectively.

Baseline and Follow up assessments

Patients were recruited during routine appointments at secondary-care dermatology centres across the UK and the RoI within 6 months of initiating or switching to a biologic therapy. Patient-level data concerning demographics, comorbidities, psoriasis risk factors and treatment details were extracted from BADBIR. Baseline PASI and Dermatology Life Quality Index (DLQI) were identified if reported within 6 months prior to drug start date (−183 to 0 days). In the case of multiple baseline PASI and DLQI records per individual, the one closest to the treatment start date was selected.

Details of treatments included start and stop dates, reasons for drug discontinuation and gaps in treatment. Drug discontinuation was defined as any cessation of treatment, including gaps between two courses of treatment with the same drug of more than 90 days. Treatment courses continued throughout the study period until December 2022, or those lost to follow-up were considered censored. Reasons for discontinuation were classified as ineffectiveness or adverse events (AEs).

Study population

Eligible patients for this study were aged 16 years and above, receiving a first course of adalimumab, etanercept, secukinumab or ustekinumab, had completed a minimum of 6 months' follow-up, and were registered to BADBIR between September 2007 and December 2022. For the age at psoriasis onset sub-analysis, the eligibility criteria were restricted to patients aged ≥50 years at registration. [9, 17] The exclusion criteria and final analytical cohorts for each sub-analysis are presented in Figure 1.

Outcome

Drug survival was defined as the duration from drug initiation to discontinuation or censoring at the latest follow-up or data-cut (December 2022) dates. Reasons for discontinuation were ineffectiveness or occurrence of AEs.

Exposure(s)

Treatment choice defined as receiving first course of adalimumab, etanercept, secukinumab or ustekinumab at registration.

Effect modifier(s)

Patients were stratified according to the following effect modifiers:

1. *Age at psoriasis onset*: patients aged 50 years and above at enrolment were categorised into EOP defined as those who first developed psoriasis at or before age 40 years and LOP those who first developed psoriasis after 40 years of age. [5]
2. *HLA-C*06:02*: HLA-C*06:02 -ve refers to no HLA-C*06:02 allele and HLA-C*06:02 +ve refers to the presence of 1 or 2 copies of the HLA-C*06:02 allele. [13, 17]

Statistical Analysis

Baseline characteristics

Percentages to describe categorical variables and means with standard deviation (SD) or median with inter-quartile range (p25, p75 IQR) for continuous variables were used.

*Effect of age at psoriasis onset and HLA-C*06:02 on biologic survival*

To describe the effect of the exposure (treatment choice) for each level of the modifier (age at psoriasis onset and HLA-C*06:02), hazard ratio (HR) with 95% confidence interval (CI) was estimated separately for ineffectiveness and AEs using a flexible parametric model. [18]

Each model included treatment choice as exposure, EOP/LOP or HLA-C*06:02 groups as effect modifier, interaction terms between exposure and effect modifier and adjusted for baseline covariates

including continuous variables such as age at treatment initiation, PASI, DLQI, body mass index (BMI) and binary variables such as sex, biologic naïvety at registration, smoking status, alcohol consumption of any unit, presence of comorbidities (please see Supplement 1) and clinical type of psoriasis. The model with HLA-C*06:02 also included age at psoriasis onset as a covariate which was used instead of disease duration as these two variables contain the same information and are therefore highly correlated (Pearson correlation = 0.9). Covariates were selected on the basis of prior knowledge and model fit diagnosis tests (Bayesian Information Criterion, likelihood ratio and Wald tests). Interaction terms between treatment choice and covariates were added. The proportional excess hazards assumption was assessed by including treatment choice as a time-dependent effect by comparing two models with and without time-dependent effects.

Adjusted standardised survival function with 95% CI and survival curves stratified by reasons of discontinuation across age at psoriasis onset and HLA-C*06:02 groups were obtained at years 1, 2 and 3. Estimating standardised survival curves to a common distribution of confounders allows correction for the different distribution of baseline covariates between the groups. [19] This is important to ensure that the group comparisons are similar therefore the comparison is fair.

Sensitivity analyses

A series of sensitivity analyses were performed to obtain adjusted HR by fitting the same models performed in main analyses when: (i) using complete case analysis (non-imputed covariate data); (ii) conducting stratified models by assessing drug survival separately within each treatment cohort using imputed covariate data; and (iii) testing whether the response to treatments across EOP and LOP will be different within HLA-C*06:02 subset. By including an HLA-C*06:02 covariate and interaction terms in the primary EOP/LOP model (only available for a subset of n=3,094 patients), the latter sensitivity analysis examined whether restricting to only those aged ≥50 years at registration in the age at psoriasis onset model would yield similar estimates. To obtain the response to each biologic across age at psoriasis onset and HLA-C*06:02 groups, separate adjusted standardised survival curves with 95% CI stratified by reasons of discontinuation and treatment choice were plotted at years 1, 2 and 3.

Multiple imputation by chained equations was used to impute 20 datasets to account for missing data using Rubin's rules method. All diagnostic tests were applied on a complete case analysis. All tests were two-tailed, the level of statistical significance pre-specified at 5% ($p < 0.05$) and estimates derived with 95% confidence intervals (CIs). All statistical analyses were performed using Stata version 17.0 (StataCorp), multiple imputation implemented in R version 4.0.4.

Results

Baseline characteristics

1. Age at psoriasis onset

In total there were 4250 patients of whom 2929 [69%] were classified as EOP and 1321 [31%] as LOP. EOP, compared with LOP, patients were younger (median [IQR] years, 56 [52, 61] vs. 61 [56, 67]), with longer disease duration (median [IQR], 34 years [25, 43] vs. 10 years [7, 16]), more likely to have nail disease (1684 [58] vs. 621 [47]) and psoriatic arthritis (945 [32] vs. 363 [26]). However, there was no significant difference between the groups in baseline BMI, smoking, PASI and the proportion receiving biologics at registration (Table 1).

*2. HLA-C*06:02 status*

A total of 3094 patients were included, 1491 [48%] were HLA-C*06:02-ve and 1603 [52%] HLA-C*06:02+ve. HLA-C*06:02+ve patients compared with HLA-C*06:02-ve patients were younger at treatment initiation (median [IQR] years, 43 [34, 52] vs. 47 [37, 55]), more likely classified as EOP (N [%] 1499 [94] vs. 1257 [84]), with longer disease duration (23 years [15, 33] vs 20 years [11, 28]), less likely to have psoriatic arthritis (379 [24] vs. 464 [31]) and other comorbidities (1019 [64] vs. 1030 [69]). However, there was no significant difference between the groups in either baseline PASI or the proportion receiving biologics at registration (Table 2).

*Effect of age at psoriasis onset and HLA-C*06:02 on biologic survival*

1. Age at psoriasis onset

Survival function with 95% CI for EOP and LOP at years 1, 2 and 3 corresponding to ineffectiveness and AEs are presented in Table 3. There was no difference between EOP and LOP in response to adalimumab, etanercept, secukinumab and ustekinumab for ineffectiveness (aHR [95% CI] 1.14 [0.94, 1.39], 1.13 [0.85, 1.51], 1.20 [0.79, 1.80], and 0.96 [0.73, 1.26], respectively) or AEs (0.81 [0.65, 1.02], 0.76 [0.48, 1.20], 1.14 [0.68, 1.90], and 1.24 [0.92, 1.67], respectively). (Table 4 and Figures 2&3).

*2. HLA-C*06:02 status*

Survival function with 95% CI for HLA-C*06:02 groups at years 1, 2 and 3 corresponding to ineffectiveness and AEs are presented in Table 3. Subjects who were HLA-C*06:02+ve were less likely to discontinue ustekinumab associated with ineffectiveness (aHR 0.56 [0.42, 0.75]) compared with those who were HLA-C*06:02-ve. However, HLA-C*06:02 groups responded similarly to adalimumab, etanercept and secukinumab (0.85 [0.70, 1.02], 0.98 [0.77, 1.24], and 1.00 [0.54, 1.85], respectively). There was no difference between HLA-C*06:02 groups in drug survival associated with AEs (Table 4 and Figures 4&5).

Sensitivity analyses

The main results were supported by findings from sensitivity analyses 1-3 when using: i) non-imputed covariate data (Table S1, supplement 1); ii) imputed covariate data stratified by treatment cohort (Table S2, supplement 1); and iii) when comparing survival between EOP and LOP within the HLA-C*06:02 model (Table S3, supplement 1). The overlap in confidence intervals was evident between age at psoriasis onset or HLA-C*06:02 groups in drug survival associated with adverse events (Figures S1, S2 and S4, supplement 1). However, the better response to ustekinumab in HLA-C*06:02+ve compared with HLA-C*06:02-ve subjects was shown in survival associated with ineffectiveness (Figure S3, supplement 1).

Discussion

In this study, we showed no difference between EOP and LOP in drug survival associated with either ineffectiveness or the occurrence of AEs when restricting analysis to only those aged ≥50 years at registration or without age restriction. We found that patients who were HLA-C*06:02+ve had a better response to ustekinumab compared with those who were HLA-C*06:02-ve.

*Effect of age at psoriasis onset and HLA-C*06:02 on biologic survival*

Age at psoriasis onset

We found no significant association between age at psoriasis onset (early or late) and drug survival in response to adalimumab, etanercept, secukinumab or ustekinumab. This is supported by findings from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) assessing treatment response of adalimumab, etanercept, or ustekinumab using percent body surface area (BSA) of <3 % or <1% in 7511 patients with psoriasis. However, when using the Physician Global Assessment (PGA), the same study showed that LOP patients were more likely to have achieved a PGA 0/1 (clear/almost clear) response compared with EOP. [20] Pooled data from four clinical trials showed a greater likelihood of achieving a 75% reduction in PASI (PASI 75), with high-dose, 50 mg etanercept twice weekly in EOP compared with LOP but this response attenuated when using low-dose, 25 mg etanercept twice weekly. [7] Nevertheless, our findings were consistent with a small cohort from Japan, measuring effectiveness using drug survival (drug discontinuation), showing no difference between EOP and LOP in response to adalimumab. [21] However, larger sample size is needed to confirm the current findings.

*HLA-C*06:02 status*

We found that HLA-C*06:02+ve patients were less likely to discontinue ustekinumab associated with ineffectiveness compared with those who were HLA-C*06:02-ve. However, there was no difference between the HLA-C*06:02 groups in drug survival associated with the occurrence of AEs. To date, there are no previous studies investigating the association between HLA-C*06:02 and biologic survival in patients with psoriasis. HLA-C*06:02 status as a biomarker for treatment response was investigated in a randomised clinical trial measuring treatment efficacy in patients with moderate-to-severe psoriasis using PASI 50, PASI 75, PASI 90 and PASI 100 at weeks 2 to 28 after treatment initiation. [10] Consistent with our results, in this trial patients who were HLA-C*06:02+ve had a better, yet modest, response to ustekinumab compared with HLA-C*06:02-ve patients. Likewise, an observational study from Taiwan showed that HLA-C*06:02+ve psoriasis patients were more likely to achieve PASI 75 and PASI 90 compared with HLA-C*06:02-ve patients in response to ustekinumab. [22] The better response with ustekinumab in HLA-C*06:02+ve compared with HLA-C*06:02-ve psoriasis patients was also reported in a multicentre cohort study in the Netherlands using PASI 50 measured at week 4 and PASI 75 at week 12 after treatment initiation [11] Likewise, a recent systematic review and meta-analysis revealed that HLA-C*06:02+ve patients respond better to ustekinumab using PASI 75 outcome at 3 and 6 months compared with HLA-C*06:02-ve patients. [23] Using BADBIR and BSTOP data, Dand and colleagues showed that HLA-C*06:02-ve patients were more likely to achieve a PASI 90 or PASI 100 response to adalimumab than HLA-C*06:02+ve patients after 6 months of treatment, while they were less likely to achieve a PASI 90 or PASI 100 response to ustekinumab. [13] Findings for PASI 75 response and at other time-points varied in terms of statistical significance. The ustekinumab results are broadly consistent with the current findings; however, for adalimumab we report here contrasting (albeit non-significant) effects for HLA-C*06:02 on treatment discontinuation associated with ineffectiveness (aHR 0.85 [0.70, 1.02]) or adverse events (1.13 [0.87, 1.46]). There are several reasons why a direct comparison with the results reported by Dand et al. is challenging, including the use of different sources of information to define response to treatment. In the current analysis, treatment discontinuation associated with ineffectiveness was used to define treatment response while Dand et al., used the change in PASI from baseline up to selected periodic time points. Hence, only complete cases, including available baseline PASI, were included in the final model which eventuated in analysis of less than half the original sample. Further investigation, with larger sample sizes, is therefore warranted to conclusively determine the relationship between HLA-C*06:02 and adalimumab response.

We found evidence that HLA-C*06:02 is associated with ustekinumab survival but no evidence that age at psoriasis onset is. This does not necessarily contradict the well-established relationship between HLA-C*06:02 and age at psoriasis onset. While we did find early-onset disease to be more prevalent among HLA-C*06:02-positive patients, it was still recorded for 84% of HLA-C*06:02-negative patients (Table 2). Our study therefore supports a distinct association for HLA-C*06:02, independent

of age at psoriasis onset, an intriguing finding that will require verification with further large datasets to tease apart the predictive ability of these correlated variables. Our sensitivity analysis of the joint age of psoriasis onset and HLA-C*06:02 model is consistent with the main findings confirming the association of HLA-C*06:02 in response to ustekinumab with no evidence of an association between any of the four biologics with the age of psoriasis onset.

Clinical implications

Due to the high cost of biologics compared with non-biologic systemic therapy, it is important to identify those psoriasis patients who are likely to respond best to a targeted biologic. We have examined characteristics (age of disease onset and HLA-C status) that can be ascertained prior to treatment selection and as such may have predictive utility, and, in drug survival, an outcome that is both a direct measure of clinical efficiency and is more inclusive than an outcome measure requiring valid baseline and post-treatment PASI scores. Our results therefore constitute a further step towards the personalised management of psoriasis which will not only result in reduced treatment cost but most importantly better outcomes.

Limitations

Drug survival could be influenced by i) the recruiting centres; in such the larger dermatology tertiary referral centres, usually academic, would probably see more severe, recalcitrant forms of psoriasis than secondary care district general hospital departments of dermatology; ii) the behaviour of clinicians and patients; while some dermatologists or their patients would stop a drug in case of associated adverse events some others are willing to accept the side effects and continue the drug. [24] Finally, A larger sample size is needed to validate the current findings especially in relation to HLA-C*06:02.

Conclusion

We find no evidence that age at psoriasis onset (early or late) is associated with response to adalimumab, etanercept, secukinumab or ustekinumab survival in patients with moderate-to-severe psoriasis. HLA-C*06:02 is a predictive biomarker of drug survival for ustekinumab but not for adalimumab, etanercept or secukinumab. However, caution is needed in interpreting the current results as it is not clear whether the associations between the outcomes can be fully attributed to the effect modifiers.

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Figure legends

Figure 1 STROBE diagram of exclusion of cases from BADBIR to derive the analytical cohort.

Figure 2 Adjusted standardized drug survival probability associated with ineffectiveness, stratified by EOP and LOP.

Figure 3 Adjusted standardized drug survival probability associated with adverse events, stratified by EOP and LOP.

Figure 4 Adjusted standardized drug survival probability associated with ineffectiveness, stratified by HLA-C*06:02 status.

Figure 5 Adjusted standardized drug survival probability associated with adverse events, stratified by HLA-C*06:02 status.

Table 1 Baseline demographic and disease characteristics stratified by age at psoriasis onset

		N=4,250		
		EOP	LOP	*Difference
Total, n (%)		2,929 (69)	1,321 (31)	-
Age at treatment initiation (year), median (IQR)		56 (52, 61)	61 (56, 67)	**<0.001**
Age at psoriasis onset (years), median (IQR)		23 (16, 32)	49 (45, 55)	**<0.001**
Disease duration (years), median (IQR)		34 (25, 43)	10 (7, 16)	**<0.001**
Follow up time in study (years), median (IQR)		6 (4, 9)	6 (4, 8)	**<0.001**
Male, n (%)		1,729 (59)	776 (59)	0.860
BMI (kg/m2), median (IQR)		31 (27, 35)	31 (27, 36)	0.664
Missing, n (%)		*201 (7)*	*111 (8)*	
Smoking status, n (%)	Never smoked	943 (32)	434 (33)	0.927
	Previous smoker	1,169 (40)	517 (39)	
	Current smoker	594 (20)	274 (21)	
	Missing, n (%)	*223 (8)*	*96 (7)*	
Alcohol consumption, n (%)		1,901 (65)	759 (58)	**<0.001**
Missing, n (%)		*217 (7)*	*100 (8)*	
Baseline PASI score (IQR)		13 (10, 18)	13 (10, 19)	0.445
Missing, n (%)		*253 (9)*	*154 (12)*	
Baseline DLQI Score, median (IQR)		15 (7, 21)	16 (10, 22)	**0.047**
Missing, n (%)		*989 (34)*	*562 (43)*	
Comorbidity		2,369 (81)	1,107 (84)	**0.022**
Psoriatic phenotype, n (%)				
	Nail	1,684 (58)	621 (47)	**<0.001**
	Palmoplantar	567 (19)	286 (22)	0.084
	Scalp	1,924 (66)	827 (63)	0.051
	Flexural	1,038 (35)	447 (34)	0.311
	Unstable	314 (11)	139 (11)	0.846
Psoriatic arthritis, n (%)		945 (32)	363 (26)	**0.002**
Biologic naivety, n (%)		2,307 (79)	1,100 (83)	**0.001**
Registration biologics, n (%)				
	adalimumab	1,352 (46)	582 (44)	0.203
	etanercept	379 (13)	164 (12)	0.635
	secukinumab	358 (12)	177 (13)	0.285
	ustekinumab	840 (29)	398 (30)	0.336
Previous biologics, n (%)				
	adalimumab	275 (9)	90 (7)	**0.006**
	etanercept	382 (13)	115 (9)	**<0.001**
	secukinumab	13 (1)	3 (0)	0.286
	ustekinumab	62 (2)	22 (2)	0.328

Abbreviation: IQR: Inter-quartile range; BMI: Body Mass Index; PASI: the Psoriasis Area and Severity Index; DLQI: Dermatology life quality index; *Differences were assessed using T-test for normally distributed or quantile regression model for non-normally distributed continuous variables, $\chi 2$ for binary variables and Kruskal-Wallis for categorical variables.

1 Table 2 Baseline demographic and disease characteristics stratified by HLA-C*06:02 status

		N=3,094		
		HLA-C*06:02-ve	HLA-C*06:02+ve	* Difference
Total, n (%)		1,491 (48)	1,603 (52)	-
Age at treatment initiation (year), median (IQR)		47 (37, 55)	43 (34, 52)	**<0.001**
Age at psoriasis onset (years), median (IQR)		24 (17, 34)	17 (11, 24)	**<0.001**
Early onset, n (%)		1,257 (84)	1,499 (94)	**<0.001**
Missing, n (%)		*10 (1)*	*13 (1)*	
Disease duration (years), median (IQR)		20 (11, 28)	23 (15, 33)	**<0.001**
Missing, n (%)		*10 (1)*	*13 (1)*	
Follow up time in study (years), median (IQR)		8 (6, 10)	8 (6, 10)	**0.046**
Male, n (%)		974 (65)	824 (51)	**<0.001**
BMI (kg/m2), median (IQR)		30 (27, 35)	30 (26, 35)	**0.031**
Missing, n (%)		*71 (5)*	*104 (7)*	
Smoking status, n (%)	Never smoked	571 (38)	463 (29)	**0.001**
	Previous smoker	468 (31)	544 (34)	
	Current smoker	312 (21)	450 (28)	
	Missing, n (%)	*140 (9)*	*146 (9)*	
Alcohol consumption, n (%)		975 (65)	1,088 (68)	0.252
Missing, n (%)		*137 (9)*	*148 (9)*	
Baseline PASI score (IQR)		14 (11, 19)	13 (10, 18)	0.073
Missing, n (%)		*106 (7)*	*109 (7)*	
Baseline DLQI Score, median (IQR)		16 (9, 22)	15 (8, 22)	**0.019**
Missing, n (%)		*427 (29)*	*424 (27)*	
Comorbidity		1,030 (69)	1,019 (64)	**0.001**
Psoriatic phenotype, n (%)				
	Nail	857 (58)	866 (54)	0.053
	Palmoplantar	271 (18)	252 (16)	0.069
	Scalp	1,050 (70)	1,146 (72)	0.513
	Flexural	557 (37)	591 (37)	0.778
	Unstable	141 (10)	157 (10)	0.751
Psoriatic arthritis		464 (31)	379 (24)	**<0.001**
Biologic naïvety		1,215 (82)	1,369 (85)	**0.003**
Registration biologics, n (%)				
	adalimumab	776 (52)	821 (51)	0.645
	etanercept	259 (17)	297 (19)	0.402
	secukinumab	82 (6)	75 (5)	0.291
	ustekinumab	374 (25)	410 (26)	0.753
Previous biologics, n (%)				
	adalimumab	116 (8)	92 (6)	**0.024**
	etanercept	173 (12)	155 (10)	0.081
	secukinumab	5 (0)	1 (0)	0.085
	ustekinumab	22 (2)	12 (1)	0.053

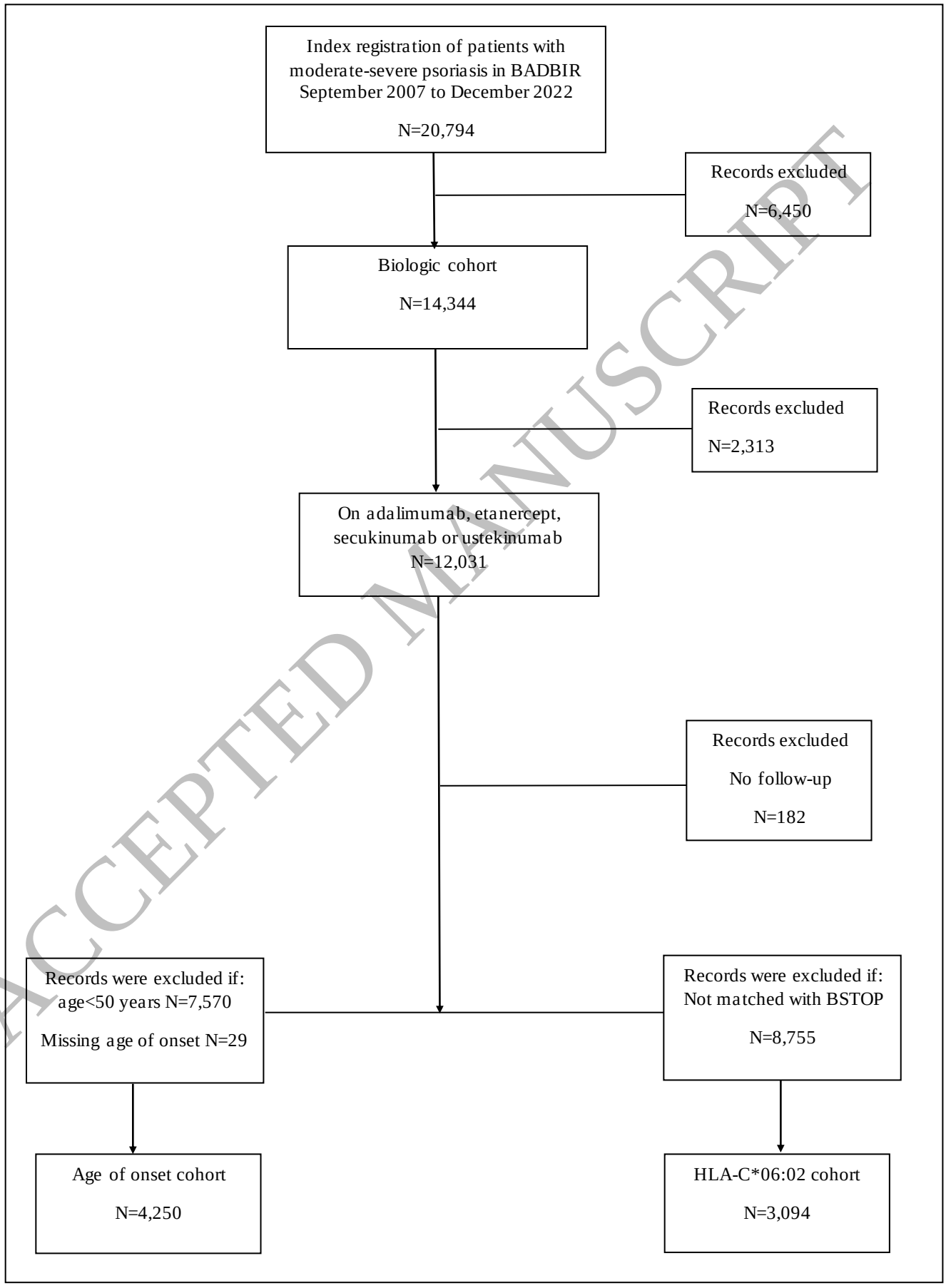
Abbreviation: IQR: Inter-quartile range; BMI: Body Mass Index; PASI: the Psoriasis Area and Severity Index; DLQI: Dermatology life quality index; * Differences were assessed using T-test for normally distributed or quantile regression model for non-normally distributed continuous variables, $\chi 2$ for binary variables and Kruskal-Wallis for categorical variables.

Table 4 Adjusted hazard ratio with 95% CI associated with ineffectiveness and AEs

	Ineffectiveness		AEs	
	aHR (95% CI)	**p value**	**aHR (95% CI)**	**p value**
Age at psoriasis onset				
EOP (reference)				
adalimumab	1.14 (0.94, 1.39)	0.180	0.81 (0.65, 1.02)	0.077
etanercept	1.13 (0.85, 1.51)	0.410	0.76 (0.48, 1.20)	0.241
secukinumab	1.20 (0.79, 1.80)	0.394	1.14 (0.68, 1.90)	0.619
ustekinumab	0.96 (0.73, 1.26)	0.754	1.24 (0.92, 1.67)	0.163
HLA-C*06:02				
HLA-C*06:02-ve (reference)				
adalimumab	0.85 (0.70, 1.02)	0.083	1.13 (0.87, 1.46)	0.356
etanercept	0.98 (0.77, 1.24)	0.864	1.62 (0.99, 2.67)	0.057
secukinumab	1.00 (0.54, 1.85)	1.000	1.71 (0.62, 4.72)	0.297
ustekinumab	**0.56 (0.42, 0.75)**	**<0.001**	0.81 (0.55, 1.19)	0.279

Abbreviation: AEs: adverse events; aHR: adjusted hazard ratio; CIs: confidence intervals.

Figure 1 STROBE diagram of exclusion of cases from BADBIR to derive the analytical cohorts.



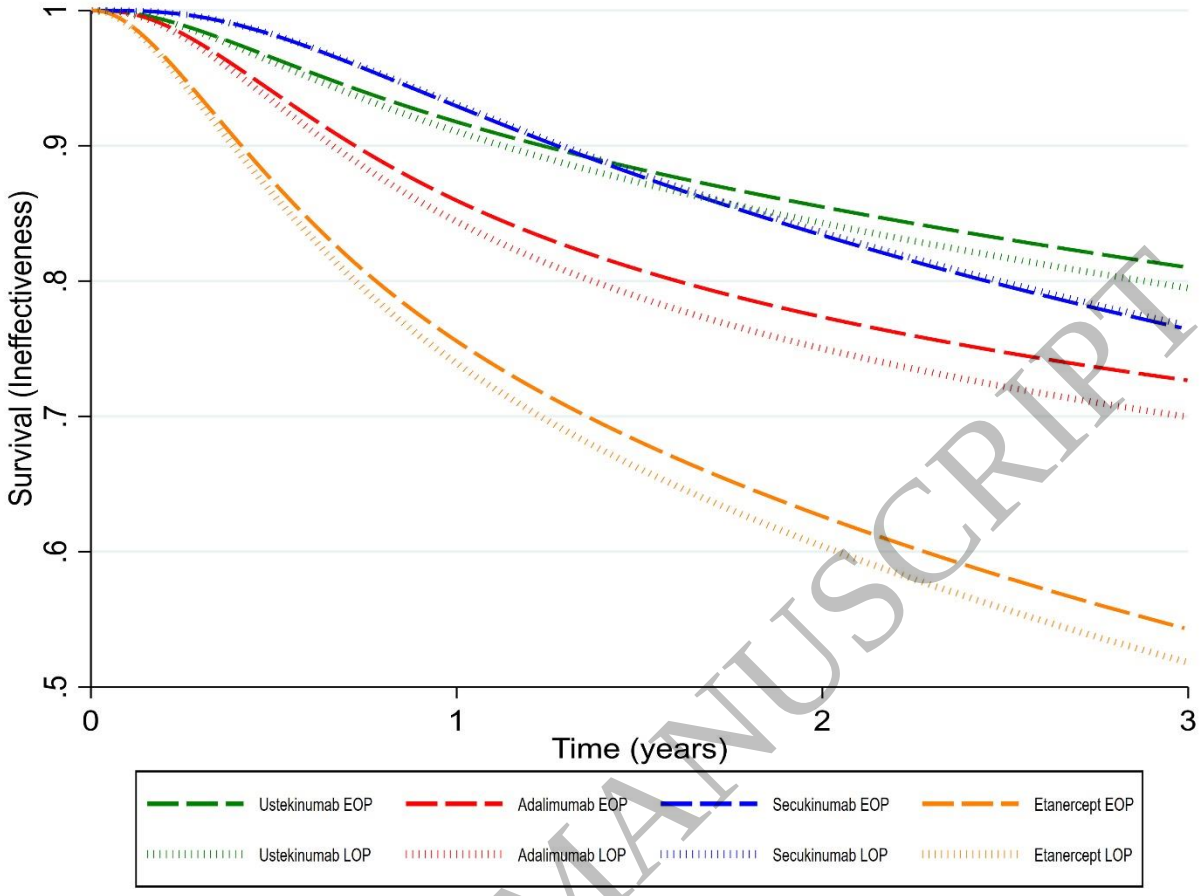


Figure 2
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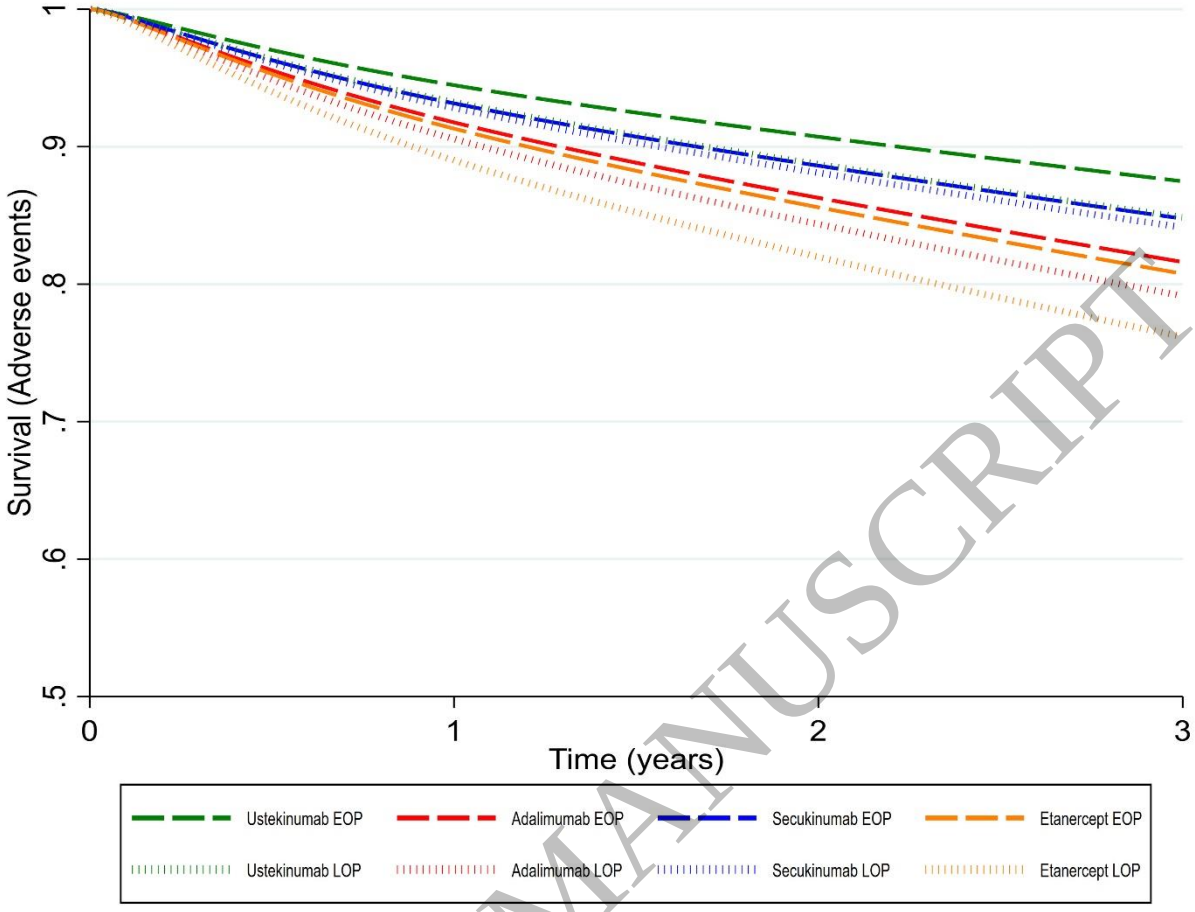

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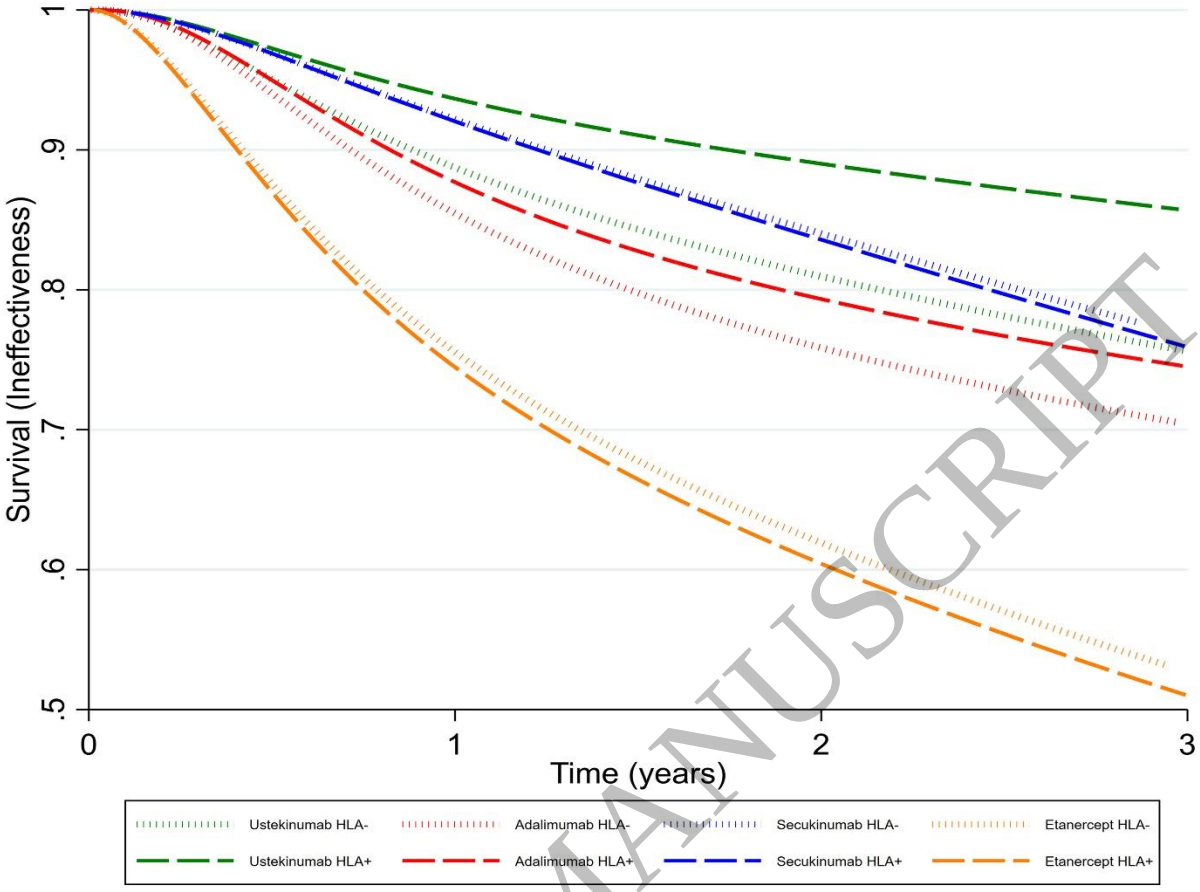

Figure 4
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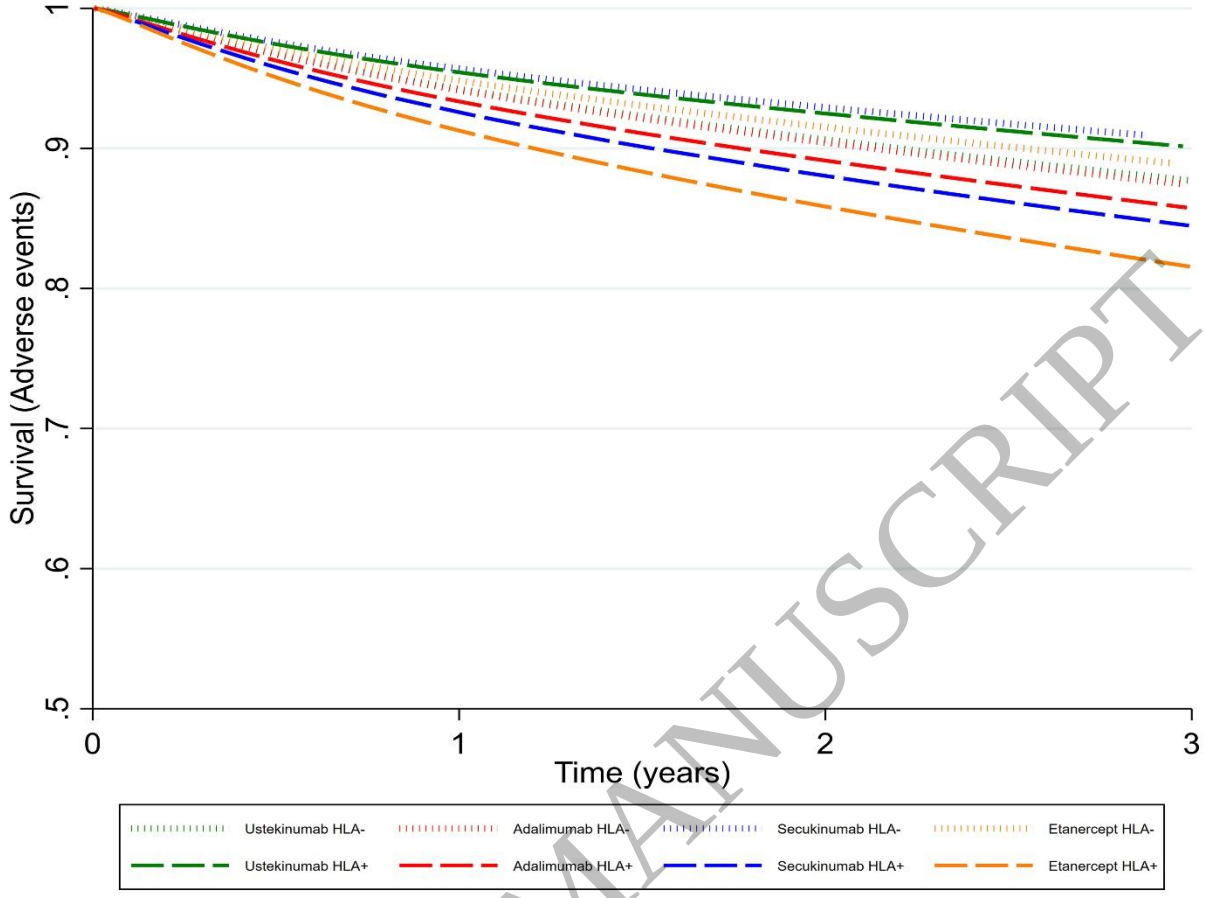
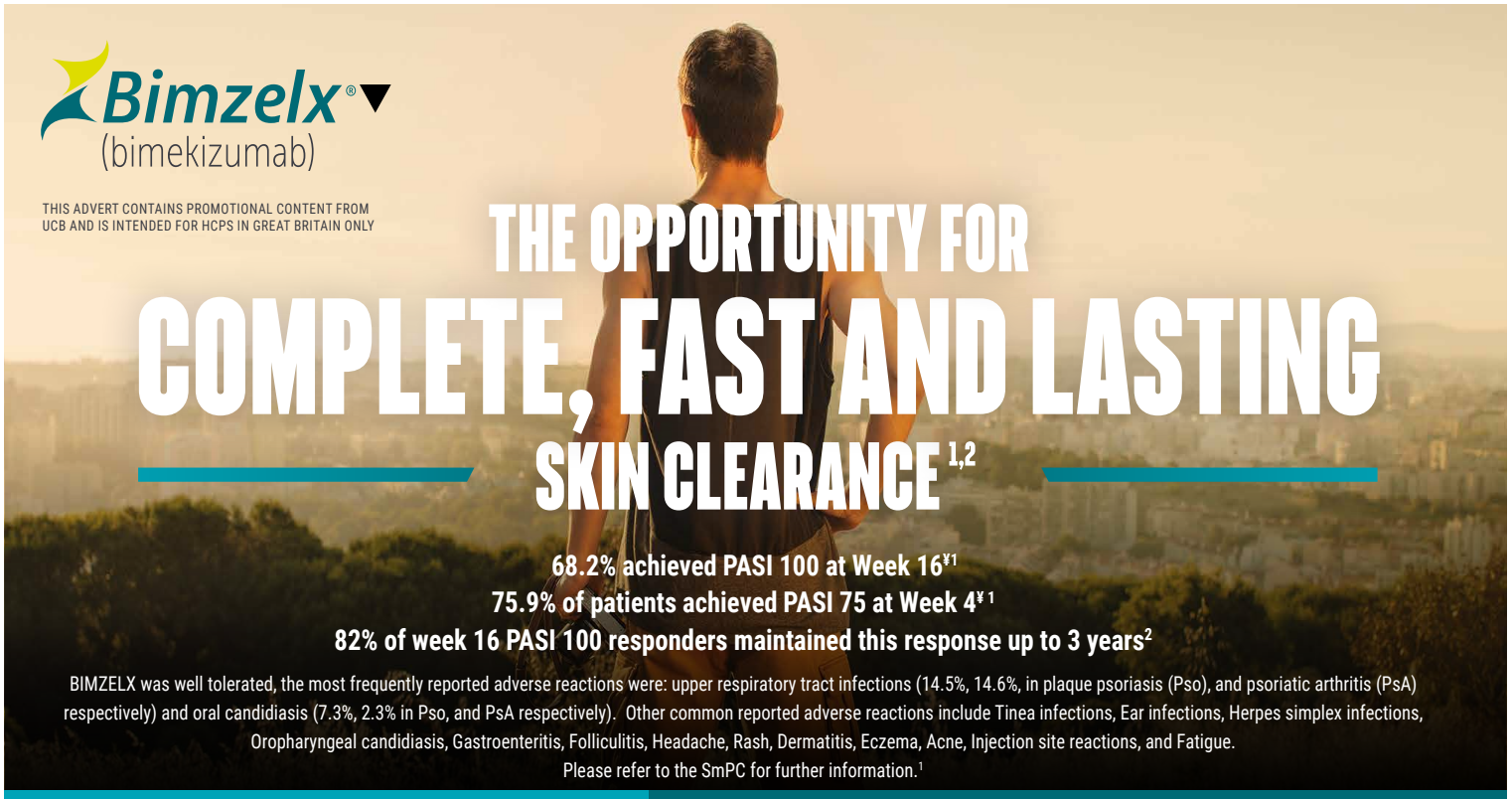


Figure 5
159x119 mm (x DPI)

Bimzelx® ▼
(bimekizumab)

THIS ADVERT CONTAINS PROMOTIONAL CONTENT FROM UCB AND IS INTENDED FOR HCPS IN GREAT BRITAIN ONLY



THE OPPORTUNITY FOR COMPLETE, FAST AND LASTING SKIN CLEARANCE[1,2]

68.2% achieved PASI 100 at Week 16[¥1]
75.9% of patients achieved PASI 75 at Week 4[¥1]
82% of week 16 PASI 100 responders maintained this response up to 3 years[2]

BIMZELX was well tolerated, the most frequently reported adverse reactions were: upper respiratory tract infections (14.5%, 14.6%, in plaque psoriasis (Pso), and psoriatic arthritis (PsA) respectively) and oral candidiasis (7.3%, 2.3% in Pso, and PsA respectively). Other common reported adverse reactions include Tinea infections, Ear infections, Herpes simplex infections, Oropharyngeal candidiasis, Gastroenteritis, Folliculitis, Headache, Rash, Dermatitis, Eczema, Acne, Injection site reactions, and Fatigue.
Please refer to the SmPC for further information.[1]

Challenge expectations in plaque psoriasis[1,2]

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Footnotes: ¥co-primary endpoints PASI 90 and IGA 0/1 at Week 16

Pso - Plaque Psoriais; PsA - Psoriatic Athritis

BIMZELX® (Bimekizumab) is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Bimzelx, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Please refer to the SmPC for further information.[1]

PRESCRIBING INFORMATION FOR HCP'S IN GREAT BRITAIN

BIMZELX® ▼ (Bimekizumab) is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy; and for active psoriasis arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs), alone or in combination with methotrexate.[1] (Please consult the Summary of Product Characteristics (SmPC) before prescribing).

Active Ingredient: Bimekizumab – solution for injection in pre-filled syringe or pre-filled pen: *160 mg of bimekizumab in 1 mL of solution (160mg/mL).* **Indications:** Moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Alone or in combination with methotrexate, for active psoriatic arthritis in adults who have had an inadequate response or intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs). Adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy. **Dosage and Administration:** Should be initiated and supervised by a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated. **Recommended dose:** Plaque Psoriasis: 320 mg (given as two subcutaneous injections of 160 mg each) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter. Psoriatic arthritis: 160 mg (given as 1 subcutaneous injection of 160 mg) every 4 weeks. For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, the recommended dose is the same as for plaque psoriasis. After 16 weeks, regular assessment of efficacy is recommended and if a sufficient clinical response in joints cannot be maintained, a switch to 160 mg every 4 weeks can be considered. Axial spondyloarthritis (nr-axSpA and AS): 160 mg (given as 1 subcutaneous injection) every 4 weeks. For patients with plaque psoriasis (including psoriatic arthritis with coexistent moderate to severe psoriasis) and a body weight ≥ 120 kg who did not achieve complete skin clearance at week 16, 320 mg every 4 weeks after week 16 may further improve treatment response. Consider discontinuing if no improvement by 16 weeks of treatment. Renal or hepatic impairment: No dose adjustment needed. Elderly: No dose adjustment needed. Administer by subcutaneous injection to thigh, abdomen or upper arm. Rotate injection sites and do not inject into psoriatic plaques or skin that is tender, bruised, erythematous or indurated. Do not shake pre-filled syringe or pre-filled pen. Patients may be trained to self-inject. **Contraindications:** Hypersensitivity to bimekizumab or any excipient; Clinically important active infections (e.g. active tuberculosis). **Warnings and Precautions:** Record name and batch number of administered product. *Infection:* Bimekizumab may increase the risk of infections e.g. upper respiratory tract infections, oral candidiasis. Caution when considering use in patients with a chronic infection or a history of recurrent infection. Must not be initiated if any clinically important active infection until infection resolves or is adequately treated. Advise patients to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops an infection, the patient should be carefully monitored. If the infection becomes serious or is not responding to standard therapy do not administer bimekizumab until infection resolves. *TB:* Evaluate for TB infection prior to initiating bimekizumab – do not give if active TB. While on bimekizumab, monitor for signs and symptoms of active TB. Consider anti-TB therapy prior to bimekizumab initiation if past history of latent or active TB in whom adequate treatment course cannot be confirmed. *Inflammatory bowel disease:* Bimekizumab is not recommended in patients with inflammatory bowel disease. Cases of new or exacerbations of inflammatory bowel disease have been reported. If inflammatory bowel disease signs/symptoms develop or patient experiences exacerbation of pre-existing inflammatory bowel disease, discontinue bimekizumab and initiate medical management. *Hypersensitivity:* Serious hypersensitivity reactions including anaphylactic reactions have been observed with IL-17 inhibitors. If a serious hypersensitivity reaction occurs, discontinue immediately and treat. *Vaccinations:* Complete all age appropriate immunisations prior to bimekizumab initiation. Do not give live vaccines to bimekizumab patients. Patients may receive inactivated or non-live vaccinations. **Interactions:** A clinically relevant effect on CYP450 substrates with a narrow therapeutic index in which the dose is individually adjusted e.g. warfarin, cannot be excluded. Therapeutic monitoring should be considered. **Fertility, pregnancy and lactation:** Women of child-bearing potential should use an effective method of contraception during treatment and for at least 17 weeks after treatment. Avoid use of bimekizumab during pregnancy. It is unknown whether bimekizumab is excreted in human milk, hence a risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Bimzelx therapy. No data available on human fertility. **Driving and use of machines:** No or negligible influence on ability to drive and use machines. **Adverse Effects:** Refer to SmPC for full information. Very Common *(≥ 1/10):* upper respiratory tract infection; Common *(≥ 1/100 to < 1/10):* oral candidiasis, tinea infections, ear infections, herpes simplex infections, oropharyngeal candidiasis, gastroenteritis, folliculitis; headache, rash, dermatitis and eczema, acne, injection site reactions, fatigue; Uncommon *(≥ 1/1,000 to < 1/100):* mucosal and cutaneous candidiasis (including oesophageal candidiasis), conjunctivitis, neutropenia, inflammatory bowel disease. Storage precautions: Store in a refrigerator (2ºC – 8ºC), do not freeze. Keep in outer carton to protect from light. Bimzelx can be kept at up to 25ºC for a single period of maximum 25 days with protection from light. Product should be discarded after this period or by the expiry date, whichever occurs first.

Legal Category: POM

Marketing Authorisation Numbers: PLGB 00039/0802 (Pre-filled Syringe), PLGB 00039/0803 (Pre-filled Pen).

UK NHS Costs: £2,443 per pack of 2 pre-filled syringes or pens of 160 mg each.

Marketing Authorisation Holder: UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE, United Kingdom.

Further information is available from: UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 0800 2793177 Email: ucbcares.uk@ucb.com

Date of Revision: August 2023 (GB-P-BK-AS-2300047)

Bimzelx is a registered trademark.

Adverse events should be reported. Reporting forms and information can be found at http://www.mhra.gov.uk/yellowcard. Adverse events should also be reported to UCB Pharma Ltd at ucbcares.uk@ucb.com or 0800 2793177.

References: 1. BIMZELX (bimekizumab) SmPC. Available at: https://www.medicines.org.uk/emc/product/12834/smpc. Accessed September 2023 **2.** Strober et al. [BE BRIGHT open label extension] Br J Dermatol. 2023. 188(6): 749-759.

GB-BK-2300081 Date of preparation: September 2023.

Inspired by patients. Driven by science.

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