**Title:** A real-world comparison of drug discontinuation, effectiveness and safety between clinical trial eligible and ineligible patients in BADBIR

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**Key Points**

**Question:** What proportion of psoriasis patients on a biologic registered to BADBIR would have been eligible for the pivotal licensing trials of biologics for psoriasis?

**Findings:** Patients identified as “ineligible” for clinical trials had lower effectiveness and higher rates of serious adverse events on biologic therapy in the first 12 months compared with patients identified as “eligible”.

**Meaning:** Clinical trial findings of biologic therapies for psoriasis are not representative of real-world patients who would have been excluded from such trials.

**Abstract**

**Importance:** Patients with psoriasis enrolled in clinical trials of biologics may not be representative of the real-world population. There is evidence that patients ineligible for such trials have a greater risk of serious adverse events (SAEs), but the effect on drug discontinuation and effectiveness are unknown.

**Objective:** To determine whether: (i) drug discontinuation; (ii) effectiveness; and (iii) rates of SAEs differ in patients categorised as “eligible” or “ineligible” for clinical trials.

**Design:** Multi-centre, prospective pharmacovigilance register.

**Setting:** 153 dermatology centres in the United Kingdom and Republic of Ireland.

**Participants:** Psoriasis patients registered to the British Association of Dermatologists Biologic Interventions Register (BADBIR) on etanercept (Enbrel only; n=1509), adalimumab (n=4000) and ustekinumab (n=1627) with at least one follow-up visit.

**Exposures:** Eligibility criteria were extracted from phase III licensing trials for etanercept, adalimumab and ustekinumab for the treatment of moderate to severe psoriasis. Patients in BADBIR with a missing baseline Psoriasis Area and Severity Index (PASI) or baseline PASI value <10 (etanercept) or <12 (adalimumab; ustekinumab) but would otherwise be eligible were investigated separately. Eligibility categories applied to BADBIR included: Eligible; Ineligible; insufficient baseline PASI only; and missing baseline PASI only.

**Main Outcomes and Measures:** (i) drug discontinuation: cumulative incidence at 12 months by stop reason per eligibility category and drug; (ii) effectiveness: linear regression of absolute change in PASI from baseline to 6 and 12 months; and (iii) SAEs: incidence rate ratio (IRR) at 12 months between eligibility categories per drug.

**Results:** 56% etanercept, 56% adalimumab and 46% ustekinumab registrations were categorised as Eligible. The most common reasons for ineligibility were Diabetes (etanercept 9%; ustekinumab 12%) and non-chronic plaque psoriasis (adalimumab 4%). Patients categorised as Ineligible (etanercept 24%; adalimumab 7%; ustekinumab 24%) achieved a smaller absolute change in PASI after 6 and 12 months (adalimumab; ustekinumab), and had significantly higher rates of SAEs when compared with the Eligible category (etanercept IRR 1.9, 95% CI 1.4-2.6; adalimumab IRR 2.0, 95% CI 1.5-2.6; ustekinumab IRR 2.8, 95% CI 2.1-3.8). No significant differences in drug discontinuation were observed between categories.

**Conclusions and relevance:** Clinical trial effectiveness and safety outcomes are not representative of real-world patients in BADBIR categorised as Ineligible for such trials.

**Introduction**

Biologic therapies have revolutionised the treatment of moderate-to-severe psoriasis. However, stringent eligibility criteria applied in clinical trials of biologic therapies for psoriasis can result in selection bias and uncertainty of the external validity to real-world psoriasis populations. This is important as estimating the gap between efficacy and effectiveness is fundamental to evidence-based, cost-effective prescribing.

There is limited data quantifying the differences between clinical trial findings and clinical practice for biologic therapies in the treatment of psoriasis. One approach to investigating relevance of trial data is to examine the impact of eligibility criteria applied to a real-world population of psoriasis patients; 29.8% patients registered to the Spanish Registry of Adverse Events Associated With Biologic Drugs in Dermatology (BIOBADADERM) would be ineligible for clinical trials using common eligibility criteria identified from a meta-analysis of randomised control trials investigating systemic and biologic treatments for psoriasis[1](#_ENREF_1),[2](#_ENREF_2). An increased risk of serious adverse events (SAEs) was detected for ineligible patients in the first 12 months of treatment (incidence rate ratio [IRR] 2.6; 95% confidence interval [CI] 1.5, 4.5) indicating the safety of real-world patients is not adequately represented in clinical trials[1](#_ENREF_1). Differences in drug discontinuation between eligible and ineligible patients are yet to be determined, while the gap between efficacy and effectiveness is also unknown[3](#_ENREF_3).

The British Association of Dermatologists Biologics Intervention Register (BADBIR) is a prospective pharmacovigilance register of psoriasis patients recruited from 157 dermatology centres in the UK and ROI[4](#_ENREF_4). BADBIR is a representative cohort of biologic prescribing in clinical practice enabling the investigation of the gap between clinical trial and real-world outcomes. Our hypothesis is that patients identified as ineligible for clinical trials have lower effectiveness, and greater rates of drug discontinuation and SAEs compared with eligible patients. The objectives of the study were to:

1. identify the eligibility criteria applied in phase III clinical trials of biologics in psoriasis;
2. determine the proportion of patients registered to BADBIR who would have been eligible for those trials;
3. determine whether drug discontinuation, effectiveness and the incidence of SAEs in the first 12 months of biologic exposure differ by eligibility criteria.

**Methods**

*Study design and setting*

Patients registering to BADBIR on etanercept (Enbrel only), adalimumab or ustekinumab who completed at least one follow-up up to 1st December, 2016 were included in the analysis.

*Baseline Assessments*

Patients are recruited and consented during routine appointments at dermatology centres within 6 months of initiating or switching to a biologic or conventional systemic therapy. All data are recorded onto a web-based database including Psoriasis Area and Severity Index [PASI] and clinical history (comorbidities with year of onset; previous anti-psoriatic therapies; concomitant therapies). A PASI value of 10 or more is not required for patients registering on a biologic therapy in BADBIR[4](#_ENREF_4).

*Follow-up Assessments*

Assessments are undertaken by the dermatology team at 6-monthly intervals for the first three years, then annually. These include PASI values and changes in therapy for psoriasis (temporary cessation; discontinuation including the stop reason; dose changes; initiation or switching). Medical records are reviewed for any adverse events since the previous visit. Serious adverse events (SAEs) are untoward medical occurrences that are considered to represent a significant hazard to the patient, including: death; overnight hospitalisation; immediately life-threatening; intravenous antimicrobial administration; significant loss of function or disability; congenital malformation/birth defect; medically important event. Examples of medically important events include malignancies and pregnancies. All SAEs are subsequently coded to the Medical Dictionary for Regulatory Activities (MedDRA).

*Clinical Trial Eligibility Criteria*

Eligibility criteria were extracted from phase III licensing trials for etanercept[5-7](#_ENREF_5), adalimumab[8](#_ENREF_8),[9](#_ENREF_9) and ustekinumab[10](#_ENREF_10),[11](#_ENREF_11) (Supplementary Materials, Table S1); further resources including [www.clinicaltrials.gov](http://www.clinicaltrials.gov), [www.amgentrials.com](http://www.amgentrials.com), clinical study reports (AbbVie) and related manuscripts[12](#_ENREF_12),[13](#_ENREF_13) were searched for additional eligibility criteria. Clinical trial study protocols were requested from AbbVie, Janssen and Pfizer, but were not made available. Licensing trials rarely exceeded 12 months in duration and the most common primary outcomes were number of adverse events and achievement of PASI 75 at specific time points (Supplementary Materials, Table S1).

The eligibility criteria used in the present study are listed in Table 1. It is possible for patients registering to BADBIR to enter a baseline PASI value <10, or have a missing date for a PASI value. Patients in BADBIR would otherwise be categorised as eligible who had a baseline PASI value insufficient for entry into a clinical trial, a missing baseline PASI date, or baseline PASI recorded after the initiation of therapy (also categorised as missing) were investigated separately. The prevalence of >2 comorbidities in patients initiating biologic therapy in BADBIR is 54%[14](#_ENREF_14). In order to identify an approximation for “uncontrolled” comorbidities (Supplementary Materials, Table S1), patients with a diagnosis year matching or preceding the year of consent were designated Ineligible. There was difficulty in mapping eligibility criteria from the trials to BABDIR. Criteria that were not applied to BADBIR included: washout periods (eligible subjects would be washed out if commencing a clinical trial); pregnant or breastfeeding females (data not collected); “immunocompromised” (adalimumab only).

In total, 4 eligibility categories were identified: missing baseline PASI only (m-PASI); insufficient baseline PASI only (i-PASI); Ineligible due to satisfying at least one of the exclusion criteria in Table 1; and Eligible. The criteria applied to patients initiating etanercept, adalimumab or ustekinumab are summarised in Table 1.

*Statistical methods*

Drug discontinuation was determined using the cumulative incidence of patients discontinuing therapy in the first 12 months by drug, eligibility category and stop reason (adverse events; ineffectiveness; other; missing).

For effectiveness, baseline PASI values were identified if reported within 6 months of the drug start date (-183 to 0 days). PASI values recorded between 4-8 months and 10-14 months after initiating therapy were used to determine response to treatment at 6 months and 12 months, respectively. Patients with a baseline, 6 month and 12 month PASI were included in the analysis. A two-sample T-test was used to determine differences between the Ineligible and i-PASI categories with Eligible patients for the median PASI values at all time points and absolute change at 6 and 12 months. Linear regression was used to identify predictors of absolute change in PASI at 6 and 12 months, with the Eligible category as the reference group. The predictors included: Ineligible and i-PASI categories; aged >70; body mass index; >3 comorbidities; prevalent psoriatic arthritis; male sex; ever smoked (current or past). Selection bias between patients with complete PASI values and those with missing values at 6 and/or 12 months was investigated by determining whether the proportion of females, median age and baseline PASI values differed (Supplementary Materials, Table S4).

An incidence rate (IR) per 1000 person years was calculated by drug and eligibility category for SAEs reported in the first twelve months following treatment initiation; IRR were calculated using Poisson regression between the eligibility categories with the Eligible category as the reference group.

All analyses were performed using Stata version 13.1 (StataCorp, College Station, TX).

*Ethical Approval*

BADBIR received approval from the North West Research Ethics Committee (07/MRE08/9) in March 2007. All patients provided written informed consent in accordance with the Declaration of Helsinki.

**Results**

*Patient Characteristics*

A total of 8,533 patients were registered to the biologic cohort. Of those, 7408 (87%) completed at least one follow-up; 1509 (18%) patients registered on etanercept, 4000 (47%) registered on adalimumab and 1627 (19%) registered to ustekinumab (Supplementary Materials, Figure S1). The eligibility criteria extracted from phase III licensing trials were applied to patients registering to each biologic. Common criteria included: chronic plaque psoriasis; patients aged 18 or over; a PASI value of >10 (etanercept) or >12 (adalimumab; ustekinumab); and exclusions for comorbidities, recent infections and previous cancer (Table 2).

In total, 839 (56%) etanercept, 2219 (56%) adalimumab and 754 (46%) ustekinumab patients were categorised as Eligible (Table 1). Fewer patients were identified as Ineligible for adalimumab (282, 7%; etanercept 367, 24%; ustekinumab 394, 24%). Similar proportions of patients had missing baseline PASI values (etanercept 145, 10%; adalimumab 333, 8%; ustekinumab 109, 7%). A greater proportion of adalimumab (1166, 29%) and ustekinumab (370, 23%) patients had an insufficient baseline PASI value compared with etanercept patients (158, 10%) due to the lower PASI threshold identified for the etanercept trials[5-7](#_ENREF_5).

Patient characteristics differed between drugs. A lower proportion of ustekinumab patients were biologic-naïve at registration (64%; etanercept 92%; adalimumab 84%) and a higher proportion of patients reporting having ever smoked (62%; etanercept 51%; adalimumab 57%; Table 2). A higher proportion of etanercept patients were receiving concomitant therapy at registration (19%; adalimumab 16%; ustekinumab 12%; Table 2).

*Drug Discontinuation*

The cumulative incidence of drug discontinuation was similar between eligibility categories per drug (Table 3). The most common reason for discontinuation in the first twelve months of treatment was ineffectiveness for each eligibility category per drug (etanercept, 11%-15%; adalimumab 6%-8%; ustekinumab 3%-5%; Table 3) with similar proportions stopping for adverse events (etanercept, 2%-4%; adalimumab 3%-5%; ustekinumab 2%-3%).

*Effectiveness*

In the adjusted analysis, significantly smaller changes in PASI values were reported at 6 and 12 months for i-PASI patients for all three biologics, with significantly smaller changes in PASI values also reported for Ineligible adalimumab patients (Table 4). Increased BMI (adalimumab only) and >3 comorbidities (ustekinumab only) predicted a smaller absolute change in PASI at 6 or 12 months, whereas male sex predicted a significantly greater absolute change in PASI (etanercept at 6 months; adalimumab at 6 and 12 months; Table 4).

*Serious Adverse Events*

The incidence of SAEs in the first twelve months of treatment was highest in the Ineligible categories for each biologic (etanercept IR 386 per 1000 person years [95% CI 279, 536]; adalimumab IR 514 [95% CI 367, 719]; ustekinumab IR 630 [95% CI 490, 809]; Table 5). Ineligible patients were significantly more likely to have an SAE in the first twelve months when compared to the Eligible categories for each biologic (etanercept IRR 1.91 [95% CI 1.40, 2.60]; adalimumab IRR 2.00 [95% CI 1.55, 2.59]; ustekinumab IRR 2.81 [95% CI 2.12, 3.72]; Table 5).

*Other Analyses*

Clinical trials of biologics in psoriasis most commonly report PASI 75 (the proportion of patients achieving a 75% reduction in PASI values from baseline) as the primary outcome (Supplementary Materials, Table S1). Differences in PASI 75 values at 6 months, 12 months, and both 6 and 12 months by eligibility category were determined using Chi2 test (Supplementary Materials, Table S2). Significantly lower proportions of Ineligible patients achieved PASI 75 at 6 months, 12 months, or both 6 and 12 months when compared with Eligible patients. The proportion of Eligible patients achieving PASI 75 at 6 months (etanercept 42%; adalimumab 51%; ustekinumab 56%) was lower than the proportion of patients achieving PASI 75 at 24 weeks (etanercept 59% and 54%, respectively[5](#_ENREF_5),[6](#_ENREF_6); adalimumab 64%[8](#_ENREF_8)) or 28 weeks (ustekinumab 71% and 79%, respectively[10](#_ENREF_10),[11](#_ENREF_11)) in the licensing trials (Supplementary Materials, Table S1).

Missing 6 and/or 12 month PASI values were common in the effectiveness analysis (58%-63% with at least one missing value; Supplementary Materials, Table S3). Selection bias in baseline PASI, age and sex was explored; baseline PASI values for ustekinumab were significantly different between complete and missing PASI values for each time point (Supplementary Materials, Table S3). No other significant differences were observed for age, sex or baseline PASI.

The number of events and incidence rates per MedDRA SOC for each biologic and eligibility status are provided in Supplementary Materials, Table S4; the most common events were infections, neoplasms and surgeries.

**Discussion**

Patients with psoriasis receiving biologic therapies who were identified as Ineligible for clinical trials were twice as likely to experience an SAE and had significantly smaller absolute changes in PASI (adalimumab and ustekinumab) when compared with Eligible patients in the first 12 months of treatment. However, eligibility status was not associated with the overall discontinuation rate as there were no differences between eligible and ineligible categories for any of the biologics investigated.

*Key Findings*

The eligibility criteria applied to clinical trials of biologics in psoriasis patients creates a restricted sample in which the efficacy and safety of new therapies are investigated prior to licensing. In the present study, 24% etanercept, 7% adalimumab and 24% ustekinumab patients were identified as Ineligible for their respective biologic clinical trials. It is likely that patients categorised as m-PASI or i-PASI would be eligible for clinical trials as the drug discontinuation and SAE rates were comparable to patients categorised as Eligible.

The cumulative incidence of discontinuing therapy in the first 12 months was similar for each stop reason and eligibility criteria per biologic (Table 3). Patients who discontinued etanercept were more likely to do so for ineffectiveness, with fewer patients discontinuing adalimumab and ustekinumab in the first 12 months. The similarities in discontinuation rates by eligibility category per drug suggest survival analyses may not be good proxy measures for either effectiveness or safety outcomes[15](#_ENREF_15).

Eligible patients were significantly more likely to achieve a greater improvement in PASI values at 6 and 12 months when compared to i-PASI patients for all three biologics and Ineligible adalimumab patients (Table 4). However, the proportion of Eligible patients achieving PASI 75 at 6 months (etanercept 42%; adalimumab 51%; ustekinumab 56%) was lower than the proportions reported in the licensing trials (etanercept 54% and 59%; adalimumab 64%; ustekinumab 71% and 79%; Supplementary Materials, Table S1). There are a number of potential reasons for the efficacy-effectiveness gap present in this study: the level of clinical care received in a clinical trial setting differs to that of standard clinical care[16](#_ENREF_16); adherence to therapies in clinical trials of biologics for psoriasis may exceed adherence in clinical practice, although this is yet to be robustly quantified[17](#_ENREF_17); and washout periods are uncommon. The use of concomitant systemic therapies in clinical practice with biologic therapies is more common (12%-19%; Table 2) making it harder to generate a large change on PASI. There were also methodological reasons contributing to the efficacy-effectiveness gap in this study: baseline PASI in BADBIR can be reported up to 6 months prior to the biologic start date, therefore the baseline PASI may not capture true disease severity and will also influence the absolute change in PASI; and patients enrolled in the licensing trials extracted all received the highest permitted doses compared with of 65% etanercept and 53% ustekinumab patients in BADBIR (Table 2). The findings of the present study emphasises the difference between reports of efficacy and effectiveness[18](#_ENREF_18); expectations of response levels should therefore be tempered in clinical practice.

Patients categorised as Ineligible were significantly more likely than Eligible patients to experience an SAE in the first 12 months after initiating biologic therapy. Only one previous study has demonstrated the IRR of SAEs to be elevated by 2.6-fold (95% CI 1.5, 4.5) in 29.8% BIOBADADERM patients categorised as Ineligible[1](#_ENREF_1), which is comparable to the IRR in the present study (Table 5). However, a lower proportion of patients in BADBIR were categorised as Ineligible (24% etanercept; 7% adalimumab; 24% ustekinumab) compared to BIOBADADERM due to the application of criteria extracted from the phase III licensing trials for each biologic[1](#_ENREF_1); Ineligible patients in the present study had a greater number of comorbidities (Table 1), similar to the previous study.

*Study Limitations*

Despite extracting criteria from manuscripts of the licensing trials and additional sources where possible, only 7% of patients were classified as Ineligible for adalimumab resulting from fewer comorbidity exclusions extracted compared with etanercept and ustekinumab (Table 1; Supplementary Materials, Table S1). This is likely to have introduced selection bias resulting in lower effectiveness and a higher SAE rate in the Eligible adalimumab patients, and therefore an underestimation of the gap between the two populations in our results for adalimumab. However, reporting standards of clinical trials having evolved during the past decade with the establishment of the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network guidelines in 2008[19](#_ENREF_19),[20](#_ENREF_20). Eligibility criteria were identified as under-reported in manuscripts prior to 2009 when compared with the criteria extracted from clinical trial protocols of systemic psoriasis therapies obtained from the relevant pharmaceutical companies[21](#_ENREF_21); however, the rationale for the additional criteria is unclear. If any of the exclusion criteria are identified as unnecessary, newer biologic therapies could be tested in a more representative sample of psoriasis patients in order to bridge the efficacy-effectiveness and safety gaps.

There were limitations in applying the extracted eligibility criteria to patients in BADBIR; comorbidities in BADBIR are reported with the year of onset and it was not possible to identify cases of “uncontrolled” comorbid conditions (e.g. diabetes; psychiatric disorders) within the definitions reported. Exclusion of females of child-bearing potential who do not use contraceptives was also not possible to implement as only hormonal contraceptives are captured as a concomitant therapy with low levels of reporting (n=327 females; 6%). There was also a high proportion of missing data for 6 and/or 12 month PASI values (17%-23%; Supplementary Materials, Table S3). Selection bias was explored between patients with missing and non-missing PASI values for the effectiveness analysis with no significant differences in age or sex observed, but significant differences in baseline PASI values for ustekinumab only (Supplementary Materials, Table S3); therefore, patients included in the effectiveness analysis are considered to be representative of those with missing PASI values at either follow-up.

*Conclusion*

Patients identified as Ineligible in BADBIR did not have the same levels of effectiveness and were at between 2-3 times increased risk of developing SAEs in the first 12 months following initiation of biologic treatment compared with Eligible patients, similar to previous findings[1](#_ENREF_1). Psoriasis patients enrolled in clinical trials of biologics are not representative of real-world patients, particularly those categorised as Ineligible in the present study (higher BMI, more patients aged >70, and a greater number of comorbidities). Clinicians should be mindful of these differences when counselling patients on biologic treatment initiation based on evidence from clinical trials. All trials should publish their full protocol and justify the eligibility criteria selected; this would provide clinicians with a better understanding of the impact the trial results will likely have on their patients.

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Study concept and design:* Mason, Barker, Smith, Hampton, Lunt, McElhone, Warren, Griffiths and Burden. *Acquisition; analysis; and interpretation of data:* Mason, Barker, Smith, Hampton, Lunt, McElhone, Warren, Griffiths and Burden. *Drafting of the manuscript:* Mason, Barker, Smith, Hampton, Lunt, McElhone, Warren, Griffiths and Burden. *Critical revision of the manuscript for important intellectual content:* Mason, Barker, Smith, Hampton, Lunt, McElhone, Warren, Griffiths and Burden. *Statistical analysis:* Mason and Lunt.   
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*Conflicts of Interest*

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**Table 1 Eligibility Status**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Criteria; N (%) \*** | |  | **Etanercept; n=1509** | **Adalimumab; n=4000** | **Ustekinumab; n=1627** |
| Eligible | | | 839 (56%) | 2219 (56%) | 754 (46%) |
| Insufficient baseline PASI only (†<10; ‡<12) | | | 158 (10%)† | 1166 (29%)‡ | 370 (23%)‡ |
| Missing baseline PASI only | | | 145 (10%) | 333 (8%) | 109 (7%) |
| Ineligible | | | 367 (24%) | 282 (7%) | 394 (24%) |
| Age <18 years | | | 6 (<1%) | 19 (<1%) | 5 (<1%) |
| Non-chronic plaque psoriasis | | | 86 (6%) | 157 (4%) | 75 (5%) |
| Comorbidities \*\* | Psychiatric | | 43 (3%) | **N/A** | 51 (3%) |
| Myocardial Infarction | | 2 (<1%) | **N/A** | 10 (<1%) |
| Angina | | 47 (3%) | **N/A** | 62 (4%) |
| Diabetes / Endocrine | | 143 (9%) | **N/A** | 201 (12%) |
| Hypertension | | 89 (6%) | **N/A** | **N/A** |
| Renal | | **N/A** | 9 (<1%) | 4 (<1%) |
| Gastrointestinal | | **N/A** | 22 (<1%) | 13 (1%) |
| Blood / Lab Values | | **N/A** | 6 (<1%) | **N/A** |
| Infections | Recent | | 7 (<1%) | **N/A** | 6 (<1%) |
| HIV / HBV / HCV | | 2 (<1%) | 6 (<1%) | 1 (<1%) |
| Latent TB | | **N/A** | 39 (1%) | 23 (1%) |
| Cancers | | | 8 (<1%) | 28 (1%) | 2 (<1%) |
| Two or more ineligibility criteria; n (%) | | | 60 (4%) | 7 (<1%) | 58 (4%) |

\* No exclusions based on prior exposure to therapies targeting tumour necrosis factor-α (etanercept; adalimumab) or interleukin 12/23 (ustekinumab); \*\* No reports of multiple sclerosis, congestive heart failure, hepatic, or pulmonary disorders as comorbidities.  
HIV = human immunodeficiency virus; HBV = hepatitis B virus; HCV = hepatitis C virus; TB = tuberculosis; N/A = not applicable.

**Table 2 Baseline Characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Etanercept | Adalimumab | Ustekinumab |
| Total; n (%) | 1509 | 4000 | 1627 |
| Age; years† | 45 (36, 54) | 45 (36, 54) | 46 (37, 55) |
| Females\* | 635 (42%) | 1645 (41%) | 644 (40%) |
| Disease duration; years† | 21 (13, 30) | 21 (13, 30) | 21 (12, 31) |
| *Missing (n; %)* | *12 (1%)* | *50 (1%)* | *13 (1%)* |
| BMI; kg/m2† | 29 (26, 34) | 30 (26, 34) | 31 (27, 36) |
| *Missing (n; %)* | *120 (8%)* | *278 (7%)* | *134 (8%)* |
| Baseline PASI† | 14 (11, 19) | 14 (11, 19) | 15 (11, 20) |
| 6 month PASI† | 4 (2, 8) | 2 (0, 5) | 2 (0, 6) |
| *Missing (n; %)* | *558 (37%)* | *1571 (39%)* | *649 (40%)* |
| 12 month PASI† | 4 (2, 7) | 2 (0, 5) | 2 (0, 4) |
| *Missing (n; %)* | *533 (35%)* | *1482 (37%)* | *649 (40%)* |
| Age; >70 years\* | 60 (4%) | 109 (3%) | 68 (4%) |
| Disease duration; >10 years\* | 1272 (84%) | 3392 (85%) | 1375 (85%) |
| Concomitant therapy\* | 280 (19%) | 645 (16%) | 197 (12%) |
| Registration dose \*‡ | 977 (65%) | 3329 (83%) | 859 (53%) |
| *Missing (n; %)* | *263 (17%)* | *687 (17%)* | *239 (15%)* |
| Biologic-naïve\* | 1386 (92%) | 3372 (84%) | 1037 (64%) |
| Baseline PsA\* | 349 (23%) | 963 (24%) | 329 (20%) |
| >3 comorbidities\* | 107 (7%) | 247 (6%) | 148 (9%) |
| Ever smoked\* | 772 (51%) | 2280 (57%) | 1016 (62%) |

i-PASI = insufficient baseline Psoriasis Area and Severity Index; m-PASI = missing baseline PASI; p = p-value ; † median (interquartile range); **\*** number (percent); ‡ doses reported are etanercept 50mg weekly, adalimumab 40mg fortnightly and ustekinumab 90mg 12 weekly after loading schedules were complete; BMI = body mass index; PsA = psoriatic arthritis.

**Table 3 Cumulative Incidence of Drug Discontinuation in the first 12 months of therapy by Eligibility and Stop Reason**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Stop Reason; | Etanercept | | | Adalimumab | | | Ustekinumab | | |
| Mean (95% CI) | Eligible | Ineligible | i-PASI | Eligible | Ineligible | i-PASI | Eligible | Ineligible | i-PASI |
| Adverse Events | 3% (2%-4%) | 4% (3%-6%) | 2% (1%-5%) | 3% (3%-4%) | 5% (3%-7%) | 3% (2%-4%) | 3% (2%-4%) | 2% (1%-3%) | 2% (1%-4%) |
| Ineffectiveness | 11% (9%-13%) | 15% (12%-19%) | 15% (11%-20%) | 8% (7%-9%) | 6% (4%-9%) | 7% (5%-9%) | 3% (2%-4%) | 5% (3%-7%) | 3% (2%-5%) |
| Other | 4% (3%-5%) | 2% (1%-3%) | 4% (2%-8%) | 2% (2%-3%) | 5% (3%-7%) | 3% (2%-4%) | 2% (1%-3%) | 2% (1%-3%) | 2% (1%-4%) |
| Missing | 4% (3%-5%) | 6% (4%-8%) | 8% (5%-13%) | 3% (2%-4%) | 2% (1%-3%) | 2% (1%-3%) | 1% (0%-1%) | 2% (1%-4%) | 2% (1%-3%) |

CI = confidence interval; i-PASI = insufficient baseline Psoriasis Area and Severity Index.  
The table presents the cumulative incidence of drug discontinuation by stop reason (adverse events; ineffectiveness; other; missing) per eligibility category (Eligible; Ineligible; i-PASI), per drug (etanercept; adalimumab; ustekinumab). The proportion of patients discontinuing therapy for each eligibility category is similar.

**Table 4 Absolute change from baseline PASI at 6 and 12 months**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Etanercept | | Adalimumab | | Ustekinumab | |
| 6 months | 12 months | 6 months | 12 months | 6 months | 12 months |
| **Absolute change in PASI from baseline; median (interquartile range) \*** | | | | | | |
| Eligible | -10.4 (-13.7, -6.9) | -10.8 (-14.3, -7.3) | -14.6 (-19.5, -11.2) | -14.6 (-19.5, -11.1) | -14.5 (-18, -11.3) | -14.4 (-18.3, -11) |
| Ineligible | -9.4 (-13.2, -5.5) | -10.5 (-15.7, -7.2) | **-10.6 (-16.9, -6.6)** | **-9.9 (-15.5, -8.5)** | **-11.2 (-18.3, -6.4)** | **-11.1 (-17.9, -7.7)** |
| i-PASI | **-2.4 (-5.5, 0)** | **-2.8 (-4.5, -1)** | **-7.4 (-9.8, -3.6)** | **-7.3 (-9.6, -3.6)** | **-7.6 (-9.6, -2.6)** | **-7.8 (-9.8, -4.6)** |
| **Unadjusted linear regression of absolute change in PASI; β-coefficient (95% confidence interval) \*\*** | | | | | | |
| Ineligible | 0.7 (-0.8, 2.2) | -0.3 (-1.8, 1.1) | **3.3 (1.0, 5.5)** | **2.7 (0.5, 4.9)** | **2.0 (0.3, 3.8)** | **1.8 (0.1, 3.5)** |
| i-PASI | **8.8 (6.8, 10.8)** | **8.3 (6.4, 10.2)** | **9.5 (8.6, 10.4)** | **9.1 (8.3, 10.0)** | **8.6 (7.0, 10.2)** | **8.5 (6.9, 10.1)** |
| **Adjusted linear regression of absolute change in PASI; β-coefficient (95% confidence interval)\*\*** | | | | | | |
| Ineligible | 0.6 (-1.2, 2.5) | 0.1 (-1.7, 1.8) | **3.1 (0.8, 5.5)** | **2.9 (0.6, 5.1)** | 0.5 (-1.4, 2.5) | 0.5 (-1.5, 2.4) |
| i-PASI | **8.8 (6.8, 10.9)** | **8.3 (6.3, 10.3)** | **9.4 (8.5, 10.3)** | **9.1 (8.3, 10.0)** | **8.7 (7.0, 10.4)** | **8.5 (6.9, 10.2)** |
| Age >70 years | -0.1 (-3.7, 3.5) | 0.5 (-3.0, 3.9) | 2.3 (-0.5, 5.2) | 0.5 (-2.3, 3.3) | 1.0 (-2.5, 4.5) | 0.9 (-2.5, 4.4) |
| BMI; kg/m2 | 0.1 (0.0, 0.2) | 0.0 (-0.1, 0.1) | **0.1 (0.0, 0.1)** | **0.1 (0.0, 0.2)** | 0.1 (-0.0, 0.2) | 0.1 (-0.0, 0.2) |
| >3 comorbidities | 0.0 (-2.7, 2.7) | -0.3 (-2.9, 2.3) | 0.3 (-1.5, 2.1) | 0.1 (-1.7, 1.8) | **3.2 (0.5, 5.9)** | **3.2 (0.6, 5.9)** |
| Prevalent PsA | 0.7 (-0.8, 2.2) | 0.5 (-1.0, 1.9) | -0.5 (-1.5, 0.5) | 0.1 (-0.9, 1.0) | 0.6 (-1.1, 2.3) | 0.4 (-1.3, 2.1) |
| Male sex | -0.9 (-2.2, 0.4) | **-1.3 (-2.5, -0.0)** | **-1.0 (-1.9, -0.2)** | **-0.9 (-1.8, -0.1)** | -0.8 (-2.2, 0.7) | 0.1 (-1.3, 1.5) |
| Ever smoked | 0.2 (-1.1, 1.5) | -0.3 (-1.5, 0.9) | -0.3 (-1.1, 0.6) | -0.1 (-0.9, 0.8) | 0.0 (-1.4, 1.5) | -0.2 (-1.6, 1.3) |

\* Two-sample T-test - Eligible group vs Ineligible or i-PASI group; \*\* Eligible group as reference category; p<0.05 if bold; i-PASI = insufficient baseline Psoriasis Area and Severity Index; BMI = body mass index; PsA = psoriatic arthritis.

**Table 5 Incidence rates and incidence rate ratios of serious adverse events in the first 12 months by registration therapy and eligibility criteria**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Eligible** | **Ineligible** | **i-PASI** | **m-PASI** |
| **Etanercept** | SAEs (n) | 42 | 36 | 9 | 2 |
| IR per 1000 | 226 (167, 305) | 386 (279, 536) | 249 (130, 479) | 73 (18, 293) |
| IRR (95% CI) | (Reference) | **1.91 (1.40, 2.60)** | 0.98 (0.58, 1.64) | 1.28 (0.80, 2.03) |
| **Adalimumab** | SAEs (n) | 131 | 34 | 65 | 18 |
| IR per 1000 | 269 (227, 319) | 514 (367, 719) | 271 (213, 346) | 258 (163, 410) |
| IRR (95% CI) | (Reference) | **2.00 (1.55, 2.59)** | 0.91 (0.74, 1.11) | 0.96 (0.71, 1.30) |
| **Ustekinumab** | SAEs (n) | 40 | 61 | 18 | 11 |
| IR per 1000 | 282 (207, 384) | 630 (490, 809) | 237 (149, 375) | 382 (211, 689) |
| IRR (95% CI) | (Reference) | **2.81 (2.12, 3.72)** | 0.94 (0.65, 1.37) | **1.69 (1.04, 2.74)** |

n = number; IR per 1000 = incidence rate per 100 person years; IRR = incidence rate ratio; CI = confidence interval; i-PASI = insufficient baseline Psoriasis Area and Severity Index; m-PASI = missing baseline PASI.