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CLINICAL SCIENCE

Incidence rates of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis treated with secukinumab: a retrospective analysis of pooled data from 21 clinical trials

Stefan Schreiber,[1] Jean-Frederic Colombel,[2] Brian G Feagan,[3] Kristian Reich,[4] Atul A Deodhar,[5] Iain B McInnes,[6] Brian Porter,[7] Ayan Das Gupta,[8] Luminita Pricop,[9] Todd Fox[7]

Handling editor Josef S Smolen

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2018-214273).

For numbered affiliations see end of article.

Correspondence to
Professor Stefan Schreiber, University Hospital Schleswig Holstein, Christian-Alrechts-University, Kiel 24105, Germany;
s.schreiber@mucosa.de

Received 13 August 2018
Revised 13 December 2018
Accepted 19 December 2018

ABSTRACT

Objectives Here, we present the reported incidence rates of inflammatory bowel disease (IBD) in patients receiving treatment with secukinumab for psoriasis (PsO), psoriatic arthritis (PsA) or ankylosing spondylitis (AS), in a pooled analysis of 21 clinical trials.

Methods Data from all patients who had received at least one dose of secukinumab were included. Safety analyses were conducted to evaluate cumulative IBD rates as well as per-year rates, by indication. Crohn's disease (CD), ulcerative colitis (UC) and IBD unclassified (IBDU) events were analysed using exposure-adjusted incidence rates (patient incidence rates per 100 patient-years (PY)).

Results A total of 7355 patients with a cumulative exposure of 16 226.9 PY were included in the pooled analysis. Among 5181 patients with PsO, there were 14 cases of UC, 5 cases of CD and 1 case of IBDU, with exposure adjusted incidence rates (EAIRs) of 0.13, 0.05 and 0.01, respectively. Of these 20 cases, 14 were new-onset. In 1380 patients with PsA, there were 3 cases of UC, 3 cases of CD and 2 cases of IBDU (EAIRs 0.08, 0.08 and 0.05); 7 of these represented new-onset cases. Among 794 patients with AS, there were 4 cases of UC, 8 cases of CD and 1 case of IBDU (EAIRs 0.2, 0.4 and 0.1); 9 were new-onset cases. In the per year analysis, the EAIRs for each indication did not increase over time with secukinumab treatment.

Conclusions In this pooled secukinumab safety analysis of 7355 patients across 21 clinical trials, cases of IBD events (including CD, UC and IBDU) were uncommon.

Key messages

What is already known about this subject?

- Secukinumab is a fully human monoclonal antibody that inhibits interleukin (IL)-17A and has shown significant efficacy in the treatment of psoriasis (PsO), psoriatic arthritis (PsA) and ankylosing spondylitis (AS).
- There is evolving evidence regarding the association of inflammatory bowel disease (IBD) (ulcerative colitis and Crohn's disease) and IL-17A inhibition.

What does this study add?

- This manuscript includes data from a large safety analysis (n=7355; cumulative exposure=16 2260.9) across 21 clinical trials, spanning up to 5 years of treatment for PsO and PsA and up to 4 years in AS. Additionally, available postmarketing safety surveillance data are also included.
- IBD events were uncommon with secukinumab treatment and the observed exposure adjusted incidence rates of IBD did not increase over time.

How might this impact on clinical practice or future developments?

- This manuscript adds clinically meaningful evidence regarding the observed incidence rates of IBD in patients with PsO, PsA and AS treated with secukinumab.

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To cite: Schreiber S, Colombel J-F, Feagan BG, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2018-214273

INTRODUCTION

Psoriasis (PsO), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) are chronic immune-mediated inflammatory diseases (IMID) that show significant coheritability with inflammatory bowel disease (IBD). Patients with PsO, PsA and AS have a 1–4-fold increased risk,[1–6] relative to the background population, of developing IBD (see online supplementary table S1). IBD comprises two principle phenotypes, Crohn's disease (CD) and ulcerative colitis (UC). CD and UC are chronic disorders characterised by intermittent phases of remission and relapse of active inflammation[7] and have symptoms including abdominal pain, diarrhoea and rectal bleeding. The risk architecture of PsO, PsA, AS and IBD is polygenic and often overlapping,[8–11] which may explain aggregation of IMID with multiple phenotypes across different generations. Moreover, one half of all patients with spondyloarthritis have documented microscopic intestinal inflammation,[12] and of these, approximately 7% develop IBD that satisfy accepted diagnostic criteria.[13]

Dysregulation of mucosal cytokines, including interleukins (IL)-1 and IL-12, and tumour necrosis factor alpha (TNF),[14] promotes IBD pathogenesis. TNF antagonist therapy is effective and widely used for management of active CD and UC. Recently, IL-23 has been implicated in murine chronic intestinal inflammation; genome-wide association studies of patients with CD suggest a central role for IL-23 gene variants in human disease.[15] Blockade of IL-12/IL-23 or IL-23 alone can improve CD.[16–18] Discrete from IL-12/IL-23 biology, several murine studies implicate IL-17A in gastrointestinal homeostasis and tissue repair, rather than driving pathogenic inflammation as it does in PsO.[19] Thus, contrasting data inform the roles of IL-23 and IL-17A in gastrointestinal health and disease. In theory, inhibition of IL-17A may have dual effects, reducing inflammation, but also potentially impairing residual function of an already damaged epithelial barrier.[20 21]

Secukinumab, a fully human monoclonal antibody that inhibits IL-17A, has shown significant efficacy in the treatment of PsO, PsA and AS demonstrating rapid onset of action.[22–27] Detection of IBD has been reported in patients being treated with IL-17 inhibition.[28–30] Herein, we comprehensively evaluated the observed incidence rates of IBD in patients receiving treatment with secukinumab for a primary indication of PsO, PsA or AS. Specifically, we report the incidence of CD, UC and IBD-unclassified (IBDU) from a pooled database of 21 phase III/IV clinical trials of secukinumab across the three indications and also review the postmarketing data from secukinumab periodic safety reports.

METHODS

Analysis design and integrated data

Data were pooled from 21 randomised controlled clinical trials of secukinumab in PsO (14 phase III trials and 1 phase IV trial), PsA (3 phase III trials) and AS (3 phase III trials) indications (see online supplementary table S2 for details). An analysis of the entire secukinumab treatment period was performed on safety data pooled at the patient level from commencement date up to 25 June 2017 (cut-off date of the latest periodic safety update report (PSUR)). Data from all patients who had received at least one dose of secukinumab (including non-responder placebo patients who, as per study protocol, were re-randomised to secukinumab treatment at the end of the placebo-controlled observation period) were included; this safety dataset is larger than the dataset used for typical efficacy analyses and thus incorporates a larger representative sample size. A separate safety analysis of short-term treatment (12–16 weeks) from the placebo-controlled phase of trials was also conducted. Similar to the entire treatment period analysis, data from all patients who had received at least one dose of secukinumab were included. Additionally, an analysis for risk difference meta-analysis was undertaken on the short-term (up to 12 and up to 16 weeks), placebo-controlled phase data for phase III trials (4 PsO trials (FIXTURE, ERASURE, FEATURE and JUNCTURE), 5 PsA trials (FUTURE1-FUTURE5) and 4 AS trials (MEASURE1-MEASURE4)). Finally, postmarketing data are reported from the periodic safety surveillance for secukinumab across the PSO, PsA and AS indications from December 2014 to June 2017.

Patients

A history of IBD was not an exclusion criterion in the secukinumab PsO, PsA and AS studies. However, patients were excluded from the AS studies if they had active IBD or from the PsO and PsA studies if they had active ongoing inflammatory diseases other than PsO/PsA that might confound the evaluation of therapy. Patients who received placebo, and who did not meet prespecified response criteria, were switched to secukinumab at the end of the placebo-controlled observation period (Weeks 12–24). Physician-reported IBD included cases of CD, UC and IBDU (all IBD related assessments were based on each physician's clinical judgement, and no specific diagnostic procedures or criteria were mandated). Patients were questioned regarding adverse events (AEs) at each study visit, or AEs were volunteered by the patient during or between visits or through physical examination, laboratory tests or other assessments.

Data analysis

Safety analyses were conducted to evaluate cumulative safety by indication as well as per-year safety by indication (Baseline to Year 1, Year 1 to Year 2 and so on). CD, UC and IBDU rates were analysed using exposure-adjusted incidence rates (patient incidence rates per 100 patient-years (PY)) over the entire secukinumab treatment period and for the postmarketing data analysis, while crude rates (n, %) were used in the short-term (placebo-controlled phase) analysis. All licensed and unlicensed (eg, 75 mg) doses of secukinumab were included in the analyses.

The Medical Dictionary for Regulatory Activities (MedDRA) V.20.0 was used to analyse AEs. A search was conducted for the reporting interval in the Novartis Safety Database (Argus). The following search criterion was used to retrieve cases: 'IBD' (narrow Novartis MedDRA query) as the high level term (or level 1 term), which includes 'Crohn's disease' and 'colitis ulcerative' and 'inflammatory bowel disease' as preferred terms (PTs) (or level 2 terms).

Exacerbations were defined as IBD events occurring in patients with a stated history of the disease at baseline. A history of IBD was physician-assessed based on patient history at baseline. New-onset cases of IBD were IBD events occurring in patients with no prior history of IBD at baseline.

In the risk difference meta-analysis, the following specific PTs were considered separately as risks: 'Crohn's disease' for CD and 'colitis ulcerative' or 'colitis' for UC. The Mantel-Haenszel method of Greenland and Robins[31] was used to estimate the absolute rate difference for all studies combined, assuming a fixed effect model. The results of each meta-analysis are presented as a forest plot (see online supplementary figure S1).

RESULTS

The analysis included a total of 7355 patients with a cumulative secukinumab exposure of 16 226.9 PY pooled from 21 clinical trials and included data for up to 5 years for PsO and PsA and up to 4 years in AS. This included 5181 patients with PsO with a cumulative exposure of 10 416.9 PY, 1380 patients with PsA with a cumulative exposure of 3866.9 PY and 794 patients with AS with a cumulative exposure of 1943.1 PY.

Baseline characteristics

Baseline characteristics are shown in table 1; approximately two-third of the PsO/AS cohort and approximately half of the PsA cohort were male with mean age ranging between 42 and 49 years. Each cohort included a sizeable proportion of patients who had previously been exposed to TNF antagonists and who smoked, which are known risk factors for exacerbation and manifestation of CD, respectively.[32–34] A previous exposure to TNF antagonists for primary disease (with inadequate response) was observed in 31.5% of the patients with PsA and 28.6% of the patients with AS, while 15.1% of the patients with PsO had a

Table 1 Selected baseline characteristics of the safety population

Parameter	PsO cohort (n=5181)	PsA cohort (n=1380)	AS cohort (n=794)
Gender			
Female (n, %)	1743 (33.6%)	742 (53.8%)	265 (33.4%)
Male (n, %)	3438 (66.4%)	638 (46.2%)	529 (66.6%)
Age, years, mean (SD)	45.7 (13.3)	48.8 (12.0)	42.4 (12.3)
Prior exposure (with inadequate response) to TNF antagonists, n (%)	NA*	435 (31.5%)	227 (28.6%)
Prior exposure (with inadequate response) to biological therapy, n (%)	784 (15.1%)	NA	NA
Current smoker at BL, n (%)	1585 (30.6%)	262 (19%)	234 (30%)
Prior azathioprine use, n (%)	7 (0.1%)	15 (1.1%)	1 (0.1%)

*Specific data on prior TNF antagonist exposure is not available for the PSO cohort however 784 (15.1%) of these patients had a previous exposure with inadequate response to biologic therapies including TNF antagonists.
AS, ankylosing spondylitis; BL, baseline; CD, Crohn's disease; PsA, psoriatic arthritis; PsO, psoriasis; UC, ulcerative colitis.

previous exposure to biological therapies, including TNF antagonists. In the PsO, PsA and AS groups, respectively, 30.6%, 19% and 30% of patients were current smokers at baseline. Out of the 5181 patients included in the PsO cohort, a history of either CD, UC or IBDU was reported in 15 patients (CD: 5 (0.1%); UC: 10 (0.19%); IBDU: 0). The corresponding numbers in the 1380 PsA and 794 AS patient cohort were 8 patients (CD: 2 (0.14%); UC: 2 (0.14%); IBDU: 4 (0.29%)) and 25 patients (CD: 5 (0.63%); UC: 3 (0.38%); IBDU: 17 (2.14%)), respectively.

Incidence rates of IBD over the entire treatment period

The exposure adjusted incidence rates (EAIRs, per 100 PY) of IBD (CD, UC or IBDU) reported during treatment with any secukinumab dose are presented in table 2; the EAIRs of IBD events varied across indications from <0.1 to 0.4. There was no evidence of a dose-response relationship between secukinumab dose (150 mg vs 300 mg) and rates of reported IBD (see online supplementary table S3). EAIRs are presented on a by-year basis in table 3. The EAIRs for each PT and each indication did not increase over time.

Crude incidence rates (n) of IBD during study treatment are presented in table 4; here, data are presented as exacerbations of IBD (for patients with a previous history of IBD) or new-onset IBD (for patients without a prior history of IBD).

Over the entire safety period and across indications, there were 41 cases of IBD out of 7355 patients (0.56%) exposed across the three reported indications. In the PsO cohort, there were 14 cases of UC, 5 cases of CD and 1 case of IBDU, with EAIRs of 0.13, 0.05 and 0.01, respectively. Of these 20 cases, 14 were new-onset. In the PsA cohort, there were three cases of UC, three cases of CD and two cases of IBDU (EAIRs 0.08, 0.08, and 0.05); seven of these represented new-onset cases. In the AS cohort, there were four cases of UC, eight cases of CD and one case of IBDU (EAIRs 0.2, 0.4 and 0.1); of these, nine were new-onset.

The mean age (±SD) of the 41 patients who experienced an IBD event with secukinumab treatment was 46.1±14.9 years which is generally comparable to the mean age of the PsO (45.7±13.3), PsA (48.8±12.0) and AS (42.4±12.3) safety populations examined in this study (table 1). In addition, approximately two thirds of patients who experienced an IBD event were male (63.4%), which is in line with the greater proportion of male patients in the overall safety population (~60%; table 1). Of the total 41 IBD cases observed in the analysis across the 3 indications, most (30, 0.41% of the total study population of 7355 patients) were new cases of which one patient relapsed during the study period. The other 11 (0.15% of the total study population) patients had a previous history of either IBD, CD or UC at baseline and experienced an exacerbation/relapse during the study. Among the patients with a history of, or new-onset IBD, 14 were discontinued from treatment; 11 of these were patients with new-onset IBD.

Reported cases of IBD during the placebo-controlled treatment period (up to 16 weeks)

The reported rates of CD and UC during the placebo-controlled treatment period (from baseline up to 12–16 weeks) are presented in table 5. During this short-term period, there was 1 case of UC and 1 case of CD among 2877 secukinumab-treated PsO patients (median exposure 84 days), no cases of UC or CD among 703 secukinumab-treated PsA patients (median exposure

Table 2 EAIRs (95% CI) of IBD over the entire treatment period for patients taking any dose of secukinumab

	PsO Studies N=5181	PsA Studies N=1380	AS Studies N=794
Median exposure (min–max), days	505.0 (1–1825)	1067.5 (8–1827)	981.5 (1–1530)
Total exposure, PY	10 416.9	3866.9	1943.1
Incidence, identified by standard definition (preferred term)			
CD, EAIR per 100 PY (95% CI)	0.05 (0.02 to 0.11)	0.08 (0.02 to 0.23)	0.4 (0.2 to 0.8)
UC, EAIR per 100 PY (95% CI)	0.13 (0.07 to 0.23)	0.08 (0.02 to 0.23)	0.2 (0.1 to 0.5)
IBDU, EAIR per 100 PY (95% CI)	0.01 (0.00 to 0.05)	0.05 (0.01 to 0.19)	0.1 (0.0 to 0.3)

EAIR data are displayed to two decimals where N>1000; if N<1000, then data are displayed to one decimal.
AS, ankylosing spondylitis; CD, Crohn's disease; EAIR, exposure-adjusted incidence rate; IBD, inflammatory bowel disease; IBDU, IBD-unclassified; PY, patient-years; PsA, psoriatic arthritis; PsO, psoriasis; UC, ulcerative colitis.

Table 3 EAIRs (95% CI) of IBD by year for patients taking any dose of secukinumab

PsO				PsA				AS			
	CD	UC	IBDU		CD	UC	IBDU		CD	UC	IBDU
Year 1 N=5181	0.12 (0.04 to 0.28)	0.17 (0.07 to 0.34)	0.00 (0.00 to 0.09)	Year 1 N=1380	0.08 (0.00 to 0.43)	0.08 (0.00 to 0.43)	0.08 (0.00 to 0.43)	Year 1 N=794	0.7 (0.2 to 1.6)	0.4 (0.1 to 1.2)	0.1 (0.0 to 0.7)
Year 2 N=3268	0.00 (0.00 to 0.14)	0.20 (0.06 to 0.46)	0.00 (0.00 to 0.14)	Year 2 N=1183	0.00 (0.00 to 0.34)	0.09 (0.00 to 0.52)	0.00 (0.00 to 0.34)	Year 2 N=700	0.5 (0.1 to 1.3)	0.0 (0.0 to 0.6)	0.0 (0.0 to 0.6)
Year 3 N=2246	0.00 (0.00 to 0.20)	0.05 (0.00 to 0.30)	0.00 (0.00 to 0.20)	Year 3 N=948	0.3 (0.0 to 1.0)	0.1 (0.0 to 0.8)	0.1 (0.0 to 0.8)	Year 3 N=557	0.2 (0.0 to 1.3)	0.2 (0.0 to 1.3)	0.0 (0.0 to 0.9)
Year 4 N=1627	0.00 (0.00 to 0.25)	0.07 (0.00 to 0.38)	0.07 (0.00 to 0.38)	Year 4 N=587	0.0 (0.0 to 0.9)	0.0 (0.0 to 0.9)	0.0 (0.0 to 0.9)	Year 4 N=332	0.0 (0.0 to 3.1)	0.0 (0.0 to 3.1)	0.0 (0.0 to 3.1)
Year 5 N=1210	0.00 (0.00 to 1.22)	0.00 (0.00 to 1.22)	0.00 (0.00 to 1.22)	Year 5 N=290	0.0 (0.0 to 3.1)	0.0 (0.0 to 3.1)	0.0 (0.0 to 3.1)	NA			

Year 1: Week 0–52; Year 2: Week 52–104; Year 3: Week 104–156; Year 4: Week 156–208; Year 5: Week 208–260.
Data are displayed to two decimals where N>1000; if N<1000, then data are displayed to one decimal.
AS, ankylosing spondylitis; CD, Crohn's disease; EAIR, exposure adjusted incidence rate; IBD, inflammatory bowel disease; IBDU, IBD-unclassified; NA, not available; PsA, psoriatic arthritis; PsO, psoriasis; UC, ulcerative colitis.

112 days) and 1 case of UC and 2 cases of CD among 394 secukinumab-treated AS patients (median exposure 112 days). During this time, 323 patients were treated with etanercept as an active comparator (median exposure 84 days). Among these patients, there was 1 case of UC. The relative risks of developing CD or UC in short-term secukinumab studies are presented in online supplementary figure S1. Across the various forest plots, the risk for CD and UC did not increase when compared with placebo.

Reporting rates of IBD from postmarketing surveillance

The rate of reported IBD was also assessed as part of periodic safety surveillance for secukinumab and is provided in table 6. The cumulative, postauthorisation, non-clinical trial exposure to secukinumab exceeds 96 000 patient-treatment years covering the last five PSUR from December 2014 to June 2017, with the same data cut-off date of 25 June 2017. The cumulative rate of reported events per 100 PY remained stable at approximately 0.20, varying between 0.16 to 0.22 per 100 PY over multiple PSUR cycles.

DISCUSSION

In this large secukinumab safety analysis (n=7355; cumulative exposure=16 2260.9 PY) across 21 clinical trials, and spanning up to 5 years of treatment for PsO and PsA and up to 4 years in AS, cases of IBD were uncommon (<1%). There were 41 (0.56%) observed cases of active IBD reported and of these, 30 (0.41%) were new-onset cases. Furthermore, of the 48 (0.65%) patients with a history of IBD at baseline, 11 (0.15%) patients had an exacerbation during study treatment. The EAIR per 100 PY exposures for CD, UC or IBDU ranged between 0.01 and 0.13 in PsO, between 0.05 and 0.08 in PsA and between 0.1 and 0.4 in the AS cohort. In the postmarketing safety surveillance analysis (cumulative exposure of >96 000 PY), the cumulative reporting rate of IBD remained stable at approximately 0.20 reported events per 100 PY.

The incidence and prevalence of IBD are greater in patients with PsO, PsA and AS compared with the general population (see online supplementary table S1).[1–6] Environmental risk factors associated with bowel inflammation, or relapse of existing IBD,

Table 4 Incidences of exacerbations/new-onset cases of IBD in patients with/without a history of IBD at baseline, respectively

	PsO cohort (n=5181)	PsA cohort (n=1380)	AS cohort (n=794)
History of IBD at baseline*			
History of CD, n (%)†	5 (0.1%)	2 (0.14%)	5 (0.63%)
Exacerbation of CD during study treatment, n	2	0	3
History of UC, n (%)†	10 (0.19%)	2 (0.14%)	3 (0.38%)
Exacerbation of UC during study treatment, n	4	1	1
History of IBDU, n (%)†	0	4 (0.29%)	17 (2.14%)
Exacerbation of IBDU during study treatment, n	0	0	0
New onset cases of IBD‡			
Total number of new-onset cases of CD, n (%)§	3 (0.06%)	3 (0.22%)	5 (0.63%)
Relapses, n	1	0	0
Total number of new-onset cases of UC, n (%)§	10 (0.19%)	2 (0.14%)	3 (0.38%)
Relapses, n	0	0	0
Total number of new-onset cases of IBDU, n (%)§	1 (0.02%)	2 (0.14%)	1 (0.13%)
Relapses, n	0	0	0

*A history of IBD was physician-assessed based on patient history at baseline.
†Medical history percentages are based on n.
‡New-onset cases of IBD were IBD events occuring in patients with no prior history of IBD at baseline.
§New-onset of AE percentages are based on n.
AS, ankylosing spondylitis; CD, Crohn's disease; IBD, inflammatory bowel disease; IBDU, IBD-unclassified; PsA, psoriatic arthritis; PsO, psoriasis; UC, ulcerative colitis.

Table 5 Incidence of CD and UC in the short-term placebo-controlled treatment period

	PsO studies (Week 12)		PsA studies (Week 16)		AS studies (Week 16)	
	Any secukinumab (n=2877)	Placebo (n=793)	Any secukinumab (n=703)	Placebo (n=300)	Any secukinumab (n=394)	Placebo (n=196)
Median exposure (min–max), days	84 (1–223)	84 (1–127)	112 (8–226)	112 (28–156)	112 (8–195)	112 (1–176)
CD, n (%)	1 (0.03)	0	0	1 (0.3)	2 (0.5)	0
UC, n (%)	1 (0.03)	0	0	1 (0.3)	1 (0.3)	0

AS, ankylosing spondylitis; CD, Crohn's disease; PsA, psoriatic arthritis; PsO, psoriasis; UC, ulcerative colitis.

include smoking, infections and high doses of NSAIDs used in AS therapy.[34–37] Additionally, while TNF antagonist therapy is effective in treating CD and UC,[38] previous failure of a TNF antagonist in PsO, PsA and AS populations has also been associated with exacerbations and less disease control.[32 33] Approximately one-third of patients with IBD experience an exacerbation of disease within 12 months of withdrawal of TNF antagonist therapy.[39] Active IBD may develop during TNF antagonist therapy for inflammatory rheumatic disease, mostly in patients with spondyloarthritis receiving etanercept, at a frequency of approximately 0.15%.[40] In a study of the Food and Drug Administration Adverse Event Reporting System (FAERS), 443 cases of de novo IBD and 43 cases of flares of existing IBD were reported in association with etanercept therapy,[41] suggesting that IBD should be suspected by the treating physician in patients receiving etanercept who develop GI symptoms, particularly CD. This has also been observed in a clinical trial where etanercept was found to be an ineffective therapy for active CD.[42]

In the present study, almost one-third of all patients with PsA and AS were previously exposed (with inadequate response) to TNF antagonist treatments; previous biological exposure was also apparent in the PsO cohort, but rates were lower (15.1%). Each cohort also included a sizeable patient population of current smokers (~30% in the PsO and AS cohorts and 19% in the PsA group). The roles played by current smoking and prior TNF antagonist therapies in contributing to IBD in secukinumab-treated patients, however, are unclear at this time.

The EAIR of IBD reported during treatment with any secukinumab dose over the entire treatment period varied across indication from <0.1 to 0.4/100 PY. In the per year analysis, EAIRs of IBD ranged from 0.0 to 0.7/100 PY. These IBD rates appear to be within the range of expected background IRs (per 100 PY) of CD and UC among patients with PsO, PsA and AS, which are approximately 0.1 in patients with PsA, 0.3 in PsO and 0.7 in AS.[5 43 44] In an analysis of 72 phase II–IV adalimumab clinical trials, including 23 735 patients representing 36 404.6 PY of exposure, rates of IBD events ranged from <0.1 to 0.8/100 PY across therapeutic indications.[45] It should be noted that there are limitations to any direct comparison of IBD rates in adalimumab clinical trials with those of therapies not indicated to treat IBD. It should also be noted that IBD events were not adjudicated in the current secukinumab analysis.

In line with the reported background incidence of IBD, the observed EAIR of CD was slightly higher among patients with AS (0.4) compared with patients with PsO (0.1) and PsA (0.1) in the present study (table 2). Rates of UC were generally comparable across indications and ranged from 0.1 to 0.2. Genetic/genomic data to further elucidate these findings are not available.

Studies using IL-17 inhibitors for the treatment of PSO, PsA and AS have previously reported both exacerbations and new-onset cases of IBD.[28 46] A small (n=59) phase II proof-of-concept study found that secukinumab was ineffective in treating patients with moderate to severe CD. Disease activity worsened in 6/39 (15.4%) patients assigned to active treatment and there were more serious infections in the treatment group compared with those receiving placebo.[28] Conclusions from this study are limited by its study design, statistical methods, imbalance in baseline characteristics and small sample size. Study patients randomised to secukinumab had numerically greater disease duration (12.2 years vs 10.3 years), previous bowel surgery (48.7% vs 15.0%), previous TNF antagonist therapy exposure (17.9% vs 0.0%) and prior antibiotic use (17.9% vs 5.0%) compared with placebo-treated patients. Also, patients received a higher dose of secukinumab (10 mg/kg) than that approved for PsO and PsA (300 mg).[28] Nevertheless, further clinical development in the general population of patients with CD has not been pursued. IBD has also been reported in patients with PsO receiving ixekizumab, another IL-17A blocker, in which CD and UC cases were uncommon (<1%).[30] In another study using brodalumab, an IL-17 receptor blocker, a disproportionate number of cases of worsening CD was noted in patients with active CD and no evidence of clinically meaningful efficacy was reported.[29] It should be, however, noted that brodalumab acts by blocking the IL-17 receptor and, hence, may have a broader effect on bowel inflammation when compared with secukinumab and ixekizumab, which only target IL-17A. Caution is recommended when prescribing IL-17 inhibitors to patients with active IBD in the special warnings section of the summary of product characteristics for secukinumab and these patients should be followed closely.

Table 6 Reporting rates for IBD in postmarketing experience from the secukinumab periodic safety update report

	PSUR date					
	26 December 2014–25 June 2015	26 June 2015–25 December 2015	25 December 2015–25 June 2016	25 June 2016–25 December 2016	25 December 2016–25 June 2017	Cumulative rate
Cases (n)	4	12	37	46	93	195
Exposure (PY)	1838	7450	16 871	28 549	41 346	96 054
Reporting rate (per 100 PY)	0.22	0.16	0.22	0.16	0.22	0.20

IBD, inflammatory bowel disease; PSUR, periodic safety update reports; PY, patient-years.

In the current study, the EAIRs for CD, UC and IBDU did not appear to increase over time through 5 years of secukinumab treatment in patients with PSO and PsA or through 4 years of secukinumab treatment in patients with AS. This is consistent with previously reported long-term secukinumab data, which demonstrated that the safety profile of secukinumab remains favourable through 5 years of PsO treatment with no increases in yearly AE rates.[47] Similarly, postmarketing surveillance data from the secukinumab PSUR indicates that the overall reporting rates for IBD, including CD and UC, were stable over five PSUR cycles (Dec 2014–June 2017) and occurred infrequently. Also, in the separate short-term placebo-controlled treatment period (12–16 weeks), CD and UC occurred infrequently with secukinumab.

Studies from the three licensed indications of secukinumab (PsO, PsA and AS) only were included in the present analysis. However, additional secukinumab phase III trials have been undertaken in patients with rheumatoid arthritis (RA) and phase II trials in uveitis.[48–51] In three RA studies (n=1430) and in three uveitis studies (n=274), there were no reported cases of IBD among secukinumab-treated patients. The absence of IBD cases in RA clinical trials is particularly important to note as, unlike in patients with PsO, PsA and AS, patients with RA are typically not considered at the same increased risk of IBD.[52] Likewise, a considerable overlap has been described between genetic risk architectures of AS, PsO and CD,[53 54] but not between RA and CD.

An interesting point of discussion is whether the aetiology of IBD coinciding with PsO, PsA or AS, respectively, is the same as in general IBD. IBD is an extremely polygenic disease with a diverse range of pathophysiologies that are probably related to the individual genetic distortions in the patient.[55] Genetic risk architecture in IBD, however, relates to the specific intestinal phenotype.[56] While a surprisingly large overlap has been seen in genetic risk factors between populations of patients with an isolated diagnosis of IBD (CD in particular) and those with PsO or AS,[53 54] very little is known about individuals who develop both diseases, who most likely represent a specific aetiology and pathophysiology common to both diseases. This could explain why IL-17 blockade may not be effective in patients with active CD, but does not appear to be a risk factor in individuals developing CD as a comorbidity in PsA, PsO and AS. This area will represent an important area for future research with respect to both specific (genetic) aetiopathology and therapeutic behaviour.

Of the 7355 patients with PsO, PsA and AS included in the current study, 48 (0.65%) had a previous history of IBDU/CD/UC. This baseline rate of IBD incidence does appear to be generally lower than rates of IBD previously reported among patients with PsO (0.2%–1.6%),[57 58] PsA (3.8%),[59] and AS (6.6%–8.5%).[59 60] This may be explained by the exclusion of patients with active ongoing IBD in the AS studies or patients with active ongoing inflammatory diseases other than PsO/PsA that might confound the evaluation of therapy in the PsO and PsA studies, respectively. The strength of this report is the fact that the analysis is undertaken in a large patient population pooled from 21 clinical trials across multiple indications and is complemented with substantial postmarketing surveillance data. The use of exposure-adjusted incidence rates also enhances the robustness of the results by adjusting for disease duration. Long-term comparative registry data are needed to further examine the role of IL-17 inhibition on the incidence of IBD.

CONCLUSION

In this large safety analysis of 7355 patients across 21 clinical trials, events of CD, UC and IBDU were uncommon with secukinumab treatment. The observed EAIRs for these three disease designations did not increase over time with secukinumab treatment.

Author affiliations
[1]University Hospital Schleswig Holstein, Christian-Alrechts-University, Kiel, Germany
[2]Icahn School of Medicine at Mount Sinai, New York City, New York, USA
[3]Robarts Clinical Trials, Western University, London, Ontario, Canada
[4]Dermatologikum Berlin and SCIderm Research Institute, Hamburg, Germany
[5]Oregon Health & Science University, Portland, Oregon, USA
[6]University of Glasgow, Glasgow, UK
[7]Novartis Pharma AG, Basel, Switzerland
[8]Novartis Healthcare Pvt. Ltd, Hyderabad, Telangana, India
[9]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

Acknowledgements The authors thank Brendan Marshall, PhD and Tina Patrick, PhD of Novartis Ireland Ltd. for providing medical writing support which was funded by Novartis Pharma AG, Switzerland in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). The authors also thank Abhijit Shete and Adriana Guana of Novartis Pharma AG, Switzerland for their support in the development of the manuscript.

Contributors All authors provided a substantial contribution to the conception, design and interpretation of the work. Drafted the work or revised it critically for important intellectual content. Provided final approval of the submission version of the manuscript. ADG undertook the statistical data analysis.

Funding Funding for the clinical trials was provided by Novartis Pharma AG, Switzerland.

Competing interests SS has served as a consultant for Abbvie, AstraZeneca/Medimmune, Boehringer, Celltrion, Ferring, Jansen, Novartis, MSD, Pfizer, Sanofi, Takeda, UCB and as a paid speaker for Abbvie, Celltrion, Ferring, MSD and Takeda. J-FC has served as a consultant or advisory board member for Abbvie, Amgen, Boehringer-Ingelheim, Celgene Corporation, Celltrion, Enterome, Ferring, Genentech, Janssen and Janssen, Eli Lilly and Company, Medimmune, Merck & Co, Pfizer, Protagonist, Second Genome, Seres, Shire, Takeda and Theradiag; has been a speaker for Abbvie and Ferring; has been a member of the speaker's bureau for Amgen. BGF has received grant/research support from Millennium Pharmaceuticals, Merck, Tillotts Pharma AG, AbbVie, Novartis Pharmaceuticals, Centocor Inc, Elan/Biogen, UCB Pharma, Bristol-Myers Squibb, Genentech, ActoGenix and Wyeth Pharmaceuticals Inc.; consulting fees from Millennium Pharmaceuticals, Merck, Centocor Inc, Elan/Biogen, Janssen-Ortho, Teva Pharmaceuticals, Bristol-Myers Squibb, Celgene, UCB Pharma, AbbVie, Astra Zeneca, Serono, Genentech, Tillotts Pharma AG, Unity Pharmaceuticals, Albireo Pharma, Given Imaging Inc, Salix Pharmaceuticals, Novonordisk, GSK, Actogenix, Prometheus Therapeutics and Diagnostics, Athersys, Axcan, Gilead, Pfizer, Shire, Wyeth, Zealand Pharma, Zyngenia, GiCare Pharma Inc, and Sigmoid Pharma and speakers fees from UCB, AbbVie and J&J/Janssen. KR has served as a consultant and/or paid speaker for, and/or participated in clinical trials sponsored by, companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Amgen, Biogen-Idec, Celgene, Centocor, Covagen, Eli Lilly, Forward Pharma, GSK, Janssen-Cilag, Leo Pharma, Medac, MSD, Novartis, Pfizer, Vertex, Takeda and Xenoport. AAD has served as a consultant for AbbVie, Amgen, Boehringer Ingelheim, Janssen, Novartis, Pfizer, UCB and has received grant/research support from AbbVie, Amgen, Eli Lilly, GSK, Janssen, Novartis, Pfizer, UCB. IBM has received research grants, consultation fees or speaker honoraria from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Lilly, Novartis, Pfizer and UCB. BP and TF are employees of Novartis Pharma AG (Switzerland). ADG is an employee of Novartis Healthcare Pvt. Ltd (India). LP is an employee of Novartis Pharmaceuticals Corporation (USA).

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data relevant to the study are included in the article or uploaded as supplementary information.

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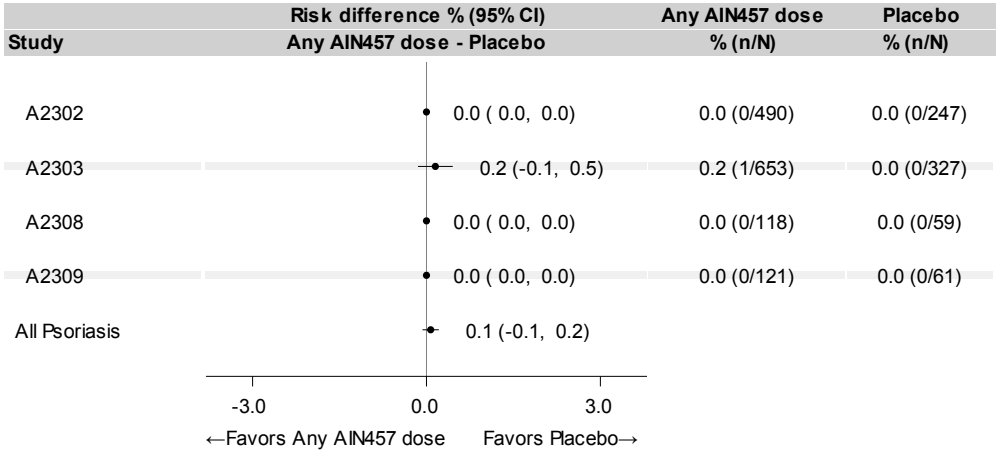
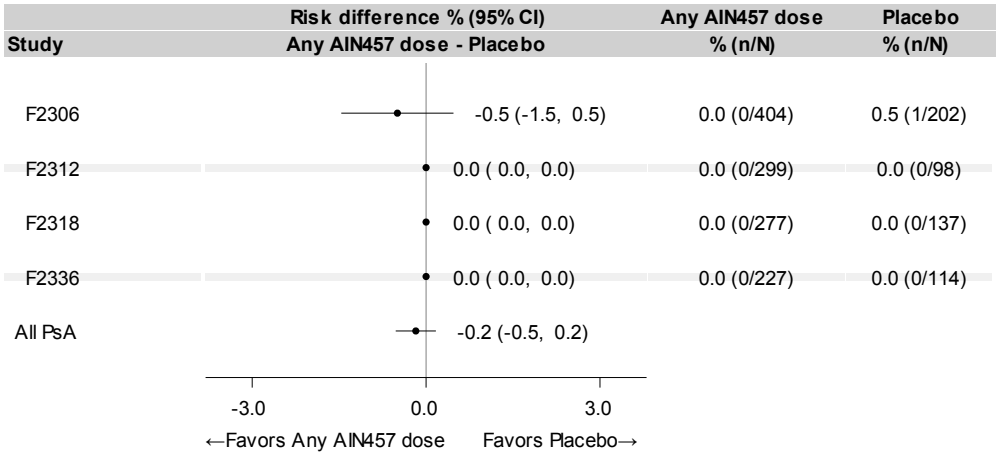
Supplementary Figure 1. Relative risks of developing CD or UC in short term secukinumab studies

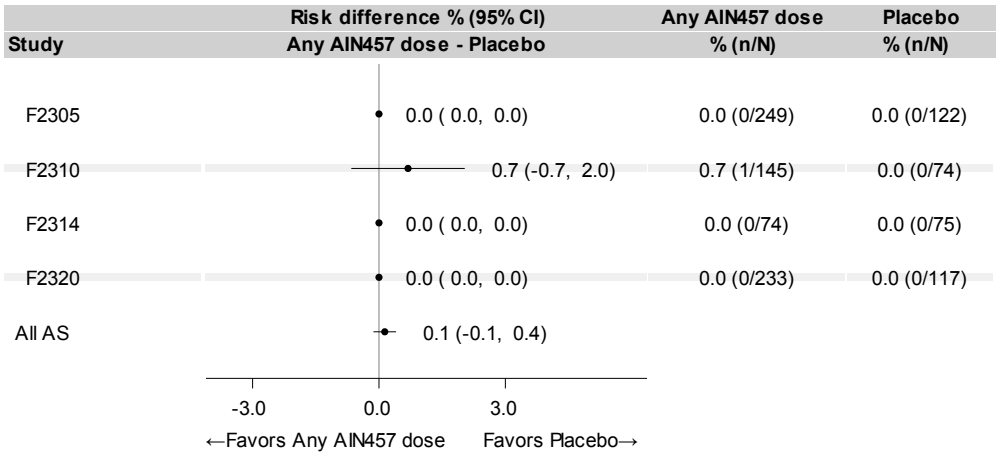
a) Risk of Crohn's Disease in PsO Phase III studies



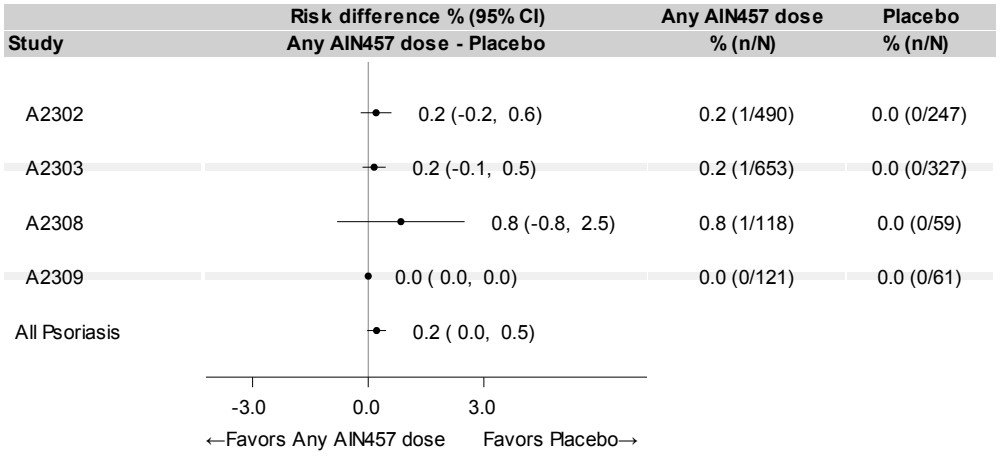
b) Risk of Crohn's Disease in PsA Phase III studies



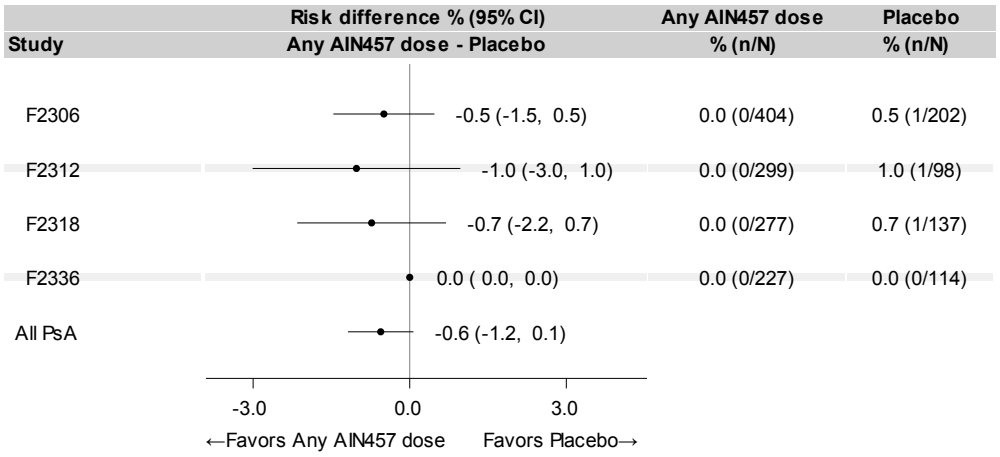
c) Risk of Crohn's Disease in AS Phase III studies



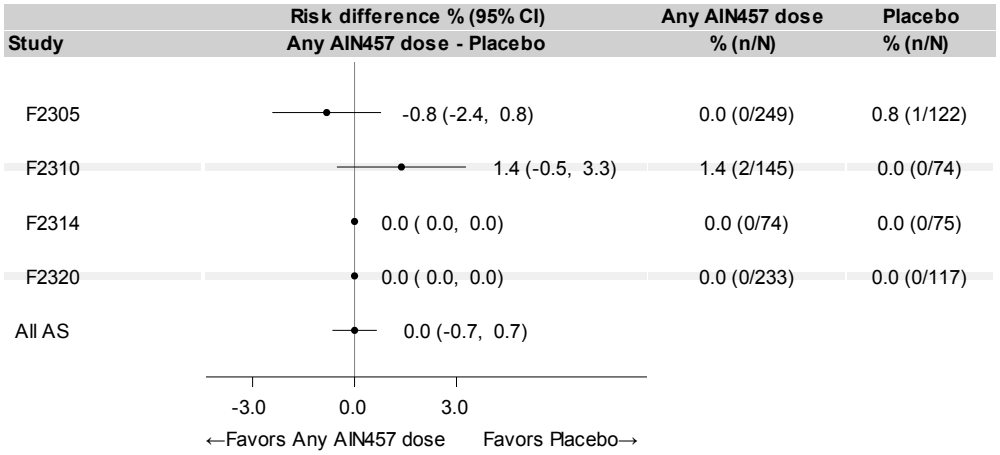
d) Risk of UC in PsO Phase III studies



e) Risk of UC in PsA Phase III studies



f) Risk of UC in AS Phase III studies



Total IBD cases (n, %) among secukinumab treated patients in the included studies: PsO (4, 0.3%), PsA (0, 0.0%), AS (3, 0.4%)
AIN457, secukinumab; AS, ankylosing spondylitis; CD, Crohn's disease; CI, confidence interval; CD, Crohn's disease; PsA, psoriatic arthritis; PsO, psoriasis; UC, ulcerative colitis

Supplementary Table 1. Approximate increased incidence risk of CD and UC in patients with PsO, PsA, and AS compared to the general population

	Approximate increased incidence compared to the general population*	
	Crohn's Disease	**Ulcerative Colitis**
PsO	2–4 fold[1-4]	1–2 fold[2-4]
PsA	2–3 fold[4, 5]	2 fold[4, 5]
AS	3 fold (IBD)[6]	

[a]Cited studies examined disease rates using different methodologies including incidence rates, relative risks, odds ratios and prevalence ratios

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Supplementary Table 2. Summary of studies included in the pooled safety analysis of the entire secukinumab treatment period (from commencement date up to the cut-off date of June 25, 2017)

Study name	Study identifier	Number of patients included	Comparator	Dose of secukinumab
Psoriasis studies				
CLEAR (2317)	NCT02074982	335	Ustekinumab, placebo	300 mg qw/q4w SC
GESTURE (2312)	NCT01806597	199	Placebo	300, 150 mg qw/q4w SC
ERASURE (2302)	NCT01365455	702	Placebo	300, 150 mg qw/q4w SC
JUNCTURE (2309)	NCT01636687	177	Placebo	300, 150 mg qw/q4w SC
FIXTURE (2303)	NCT01358578	936	Etanercept and Placebo	300, 150 mg qw/q4w SC
SCULPTURE (2304)	NCT01406938	966	N/A	300, 150 mg qw/q4w SC, RAN
FEATURE (2308)	NCT01555125	174	Placebo	300, 150 mg qw/q4w SC
TRANSFIGURE (2313)	NCT01807520	190	Placebo	300, 150 mg qw/q4w SC
2PRECISE (3301)	NCT02008890	214	Placebo	300, 150 mg qw/q4w SC
CARIMA (ADE02)	NCT02559622	150	Placebo	300, 150 mg qw/q4w SC
PSORITUS (ADE03)	NCT02362789	130	Placebo	300 mg qw SC
GAIN (ADE04)	NCT02474069	772	N/A	300 mg q4w SC

PRIME (ADE06)	NCT02474082	105	Fumaric acid esters	300 mg qw/q4w SC
JP01	NCT02547714	34	N/a	300 mg q4w SC
SCALP (AUS01)	NCT02267135	97	Placebo	300 mg q4w SC
Psoriatic arthritis studies				
FUTURE 1 (2306)	NCT01392326	587	Placebo	10 mg/kg IV → 150, 75 mg q4w SC
FUTURE 2 (2312)	NCT01752634	387	Placebo	300, 150, 75 mg qw/q4w SC
FUTURE 3 (2318)	NCT01989468	406	Placebo	300, 150 mg qw/q4w SC
Ankylosing spondylitis studies				
MEASURE 1 (2305)	NCT01358175	360	Placebo	10 mg/kg IV → 150, 75 mg q4w SC
MEASURE 2 (2310)	NCT01649375	211	Placebo	150, 75 mg qw/q4w SC
MEASURE 3 (2314)	NCT02008916	223	Placebo	10 mg/kg IV → 300, 150 mg q4w SC

IV, intravenous; Qw, once a week; Q4w, every 4 weeks; SC, subcutaneous; RAN, retreatment as needed

Supplementary Table 3. EAIRs (95% CI) of IBD over the entire treatment period for patients receiving secukinumab 150 mg or secukinumab 300 mg

	PsO Studies		**PsA Studies**		**AS Studies**	
	150 mg	300 mg	150 mg	300 mg	150 mg	300 mg
Total exposure, PY	3815.5	6601.4	1913.1	940.9	961.8	196.0
Incidence, identified by standard definition (Preferred Term)						
	150 mg	300 mg	150 mg	300 mg	150 mg	300 mg
CD, EAIR per 100 PY [95% CI]	0.05 [0.01, 0.19]	0.05 [0.01, 0.13]	0.0 [0.0, 0.2]	0.1 [0.0, 0.6]	0.2 [0.0, 0.8]	0.0 [0.0, 1.9]
UC, EAIR per 100 PY [95% CI]	0.16 [0.06, 0.34]	0.12 [0.05, 0.24]	0.1 [0.0, 0.3]	0.1 [0.0, 0.6]	0.2 [0.0, 0.8]	0.0 [0.0, 1.9]
IBDU, EAIR per 100 PY [95% CI]	0.03 [0.00, 0.15]	0.00 [0.00, 0.06]	0.0 [0.0, 0.2]	0.2 [0.0, 0.8]	0.0 [0.0, 0.4]	0.0 [0.0, 1.9]

AS, ankylosing spondylitis; CI, confidence interval; CD, Crohn's disease ; EAIR, exposure-adjusted incidence rate; IBD, inflammatory bowel disease; IBDU, IBD-unclassified; PsA, psoriatic arthritis; PsO, psoriasis; PY, patient-years; UC, ulcerative colitis