**Dose escalation of adalimumab, golimumab or ustekinumab in inflammatory bowel diseases: characterization and implications in real-life clinical practice**

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**Short title:** Dose escalation of biologicals in IBD

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**Non-standard abbreviations:** 5-ASA, 5-aminosalicylic acid; CD, Crohn's disease; CS, corticosteroid; IBD, inflammatory bowel disease; IS, immunosuppressant; SC, subcutaneous; SPC, summary of product characteristics; UC, ulcerative colitis

**Abstract**

***Objectives:***

Dose escalation is a common practice to optimize treatment with subcutaneously administered biologicals in Crohn's Disease (CD) and Ulcerative Colitis (UC). However, limited data is available on the extent of dose-escalation in real-life. Here, we analyzed treatment persistence, dose-escalation, concomitant corticosteroid use, and costs of adalimumab, golimumab, and ustekinumab in inflammatory bowel diseases (IBD).

***Methods:***

This was a nationwide, retrospective, non-interventional registry study. All adult patients who were diagnosed with CD or UC and had purchased adalimumab, golimumab, or ustekinumab from Finnish pharmacies between 2008 and 2018 were included in the study and followed up for 24 months after treatment initiation.

***Results:***

A total of 2,884 patients were included in the analyses. For adalimumab, treatment persistence was higher for CD patients compared to UC patients both at months 12 (46.2% vs. 37.1%; $p<0.0001$) and 24 (26.1% vs. 19.7%; $p<0.0001$). For golimumab (UC), treatment persistence was 48.3% at month 12 and 28.1% at month 24. The 12-month treatment persistence rate for patients on ustekinumab (CD) was 47.1%. Cumulative doses exceeding the regular dosing according to the summary of product characteristics (SPC), was observed for adalimumab in CD during the first 6 months of treatment (62.9% of the treatment periods), golimumab in the later stages of the UC treatment (52–54% of treatment periods at months 7–24), and ustekinumab during the first 6 months (70.7%).

***Conclusions:***

Based on this study, dose-escalation of subcutaneously administered biologicals is a common clinical practice in IBD. This has implications for treatment costs, use of concomitant medications, and treatment outcomes.

**Keywords:** Subcutaneous IBD therapy, adalimumab, golimumab, ustekinumab, treatment persistence, treatment cost, dosing, corticosteroid

## Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory bowel diseases (IBD) which are characterized by alternating episodes of disease remission and relapse. Inflammatory bowel diseases are estimated to be a consequence of an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host [1]. However, the exact cause of IBD is still unknown. Despite some shared characteristics, CD and UC can be distinguished by differences in genetic predisposition, risk factors, and clinical, endoscopic, and histological features [2]. Both CD and UC are lifelong, potentially disabling, diseases that may significantly impact a patient's quality of life.

Biological medication is the standard of care in the treatment of moderate-to-severe CD and UC for patients with inadequate response or intolerance to conventional therapy [3, 4]. In clinical practice, biological medication is often used concomitantly with corticosteroids (CS), immunosuppressants, or both. Tumor necrosis factor-alpha is a pro-inflammatory cytokine that has an important role in the pathogenesis of inflammatory bowel disease [5, 6]. Tumor necrosis factor (TNF) antagonists (infliximab, adalimumab, golimumab) are the most widely used biological medicines for treatment of IBD. Ustekinumab and vedolizumab differ greatly from TNF-alpha blockers in that they target different specific components of the immune system. Ustekinumab is a human monoclonal IgG1κ antibody that binds to the p40 subunit of interleukin 12 and 23, whereas vedolizumab is a humanized immunoglobulin G1 monoclonal antibody which acts against α4β7 integrin heterodimer and blocks its interaction with MAdCAM-1 [7, 8]. Clinical efficacy and safety of all these biologicals has been demonstrated in clinical trials and all have been granted EMA marketing authorization for the treatment of both moderate-to-severe CD and UC, with the exception of golimumab which has an indication for UC only.

There is limited data available on the dose escalation of biologicals in the treatment of CD and UC. The aim of this study was to both increase understanding of the use of biologicals in clinical practice and to derive insights through utilization of versatile outcome measures. We focused on use of subcutaneously administered biologicals in IBD, adalimumab, golimumab, and ustekinumab, in an out-patient setting by using real-world, nationwide registry data. The study objective was to characterize patients diagnosed with CD or UC using self-injectable biologicals, and to assess treatment persistence and used cumulative drug dosing. In addition, the relationship of cumulative dosing of biologicals with cumulative corticosteroid use and treatment persistence was evaluated.

Drug costs related to the use of biologicals were calculated in order to explore the cost differences in real-life.

## Patients and Methods

### *Study population and data collection*

This was a nationwide, retrospective, non-interventional registry study designed to analyze dose escalation of subcutaneously (SC) administered adalimumab, golimumab, and ustekinumab in IBD. Data was collected from the Registry for Reimbursed Drugs of Social Insurance Institution of Finland. All adult (≥18 years of age) IBD patients who had purchased IBD-related reimbursed medications from Finnish pharmacies between 2008 and 2018 were included in the study. The study cohort was formed on the basis of recorded ICD-10 and ICD-9 codes (K50* or 555* for CD; K51* or 556* for UC) and pharmacy purchases with ATC-codes for adalimumab, golimumab, and/or ustekinumab. The patients were retrospectively followed up for 24 months after treatment initiation. For adalimumab and golimumab, treatment initiation was defined as the first pharmacy purchase. According to Finnish treatment practices, ustekinumab treatment is started by an intravenous dose administered at a hospital. Therefore, the first pharmacy purchase was defined to be the patient's second dose at week eight of the treatment, according to the ustekinumab summary of product characteristics (SPC).

The following baseline variables were collected: age, gender, diagnosis, disease onset (age at first IBD-related drug reimbursement), disease duration (time from the first IBD-related drug reimbursement to the start of the first SC biological), and conventional medication use for 12 months before the initiation of the first biological treatment. Data were analyzed only for on-label indications during the study period: CD and UC for adalimumab, UC for golimumab, and CD for ustekinumab. Outcome variables included the date of purchase, number of claimed packages, package size, and strength/concentration of the product (mg, mg/ml).

In addition to Registry for Reimbursed Drugs, more detailed clinical data were obtained for a subgroup of patients from the hospital databases of Hospital District of Southwest Finland (www.auria.fi). The subgroup of patients included all patients who were treated with adalimumab, golimumab, or ustekinumab in the Hospital District of Southwest Finland during 2014 and 2018. This subgroup was used to analyze treatment lines of biologicals after adalimumab, golimumab, or ustekinumab treatment. The data source is described in detail elsewhere [9].

***Outcome measures***

The primary outcome measure was to assess 24-month treatment persistence. Treatment discontinuation was defined as the end of treatment effect for each product (the point in time when the next dosage should have been purchased according to SPC) with an added grace period to ascertain that a patient had had a significant break before a potential re-initiation of treatment. The time after which the treatment was considered discontinued was 2 weeks from the previous purchase +12 weeks for adalimumab, 4 weeks from previous purchase +12 weeks for golimumab, and 8 weeks from previous purchase +24 weeks for ustekinumab. Each patient could have several treatment periods for the same or different products.

As secondary outcome measures, we compared (i) the actual real-life dosing with the theoretical standard dosing as stated in the respective SPC, (ii) analyzed monthly medication costs, and characterized the effect of cumulative dosing on (iii) treatment persistence, and (iv) concomitant CS use for each product.

The real-life cumulative dosing was calculated for 6-month intervals (0–6, 7–12, 13–18, and 19–24 months) based on drug purchases. Theoretical cumulative doses were calculated for each 6-month interval based on the SPC dosing information. Three dosage groups were formed. The "SPC regular" group included patients whose cumulative dosing (mg) was equal to or lower than the standard dosing regimen for patients with adequate response according to SPC. The "SPC high" group included patients whose dosing was above the SPC regular dosing regimen, but not higher than the increased dosing regimen for patients with inadequate response according to the SPC. Finally, the "SPC over" group included patients whose dosing regimen exceeded the highest dosing regimen according to the SPC. For ustekinumab, the first hospital-administered infusion was not included in the dosing analyses. The dose ranges for each product in different treatment periods are shown in Annex Table 1.

The real-life treatment costs were calculated based on the Finnish wholesale prices on January 1$^{st}$, 2020, and compared with the theoretical costs for "SPC regular" and "SPC high" dosing regimen. As the pricing for different sizes of pre-filled syringes was the same (50 mg and 100 mg doses of golimumab, €857.60; 45 mg and 90 mg doses of ustekinumab, €2,608.00) was the same, the actual ratios at which the syringes were purchased at the pharmacy was considered in the cost calculations (0.54:0.46 ratio for 50 mg:100mg doses of golimumab; 0.12:0.88 ratio for 45 mg:90 mg doses in

ustekinumab). The cost of the hospital-administered first ustekinumab dose (€2,223.23 in October 2019) was included in ustekinumab cost calculations.

Secondary outcome measures also included the characterization of the effect of cumulative dosing on treatment persistence and concomitant CS use. The patients were assigned to two groups ("SPC regular" or "SPC high+over") based on the cumulative dose of the biological during the first 6 months of treatment. Treatment persistence was followed-up at months 7–24 after the treatment initiation. CS use was only analyzed for treatment persistent treatment periods in each 6-month window (0–6, 6–12, 13–18, and 19–24 months). The cumulative CS amounts (mg) were converted into prednisone equivalents (https://www.mdcalc.com/steroid-conversion-calculator).

***Statistical analyses***

The Kaplan-Meier method was used to present treatment persistence (%) estimates, discontinuation of adalimumab, golimumab, or ustekinumab treatment being the failure event. The log-rank test was used to analyze differences between groups and $p<0.05$ was considered statistically significant. Statistical analyses were conducted using R version 3.1.3 (https://www.r-project.org/)

***Ethical considerations***

The study was approved by Social Insurance Institution (Kela; 18/522/2019) and Hospital District of Southwest Finland (T260/2017). No ethics approval or informed consent from the cohort was required by Finnish legislation, as the persons were not contacted, the study did not affect the treatment of the patients, and only pseudonymized data were used.

## Results

### *Patient Characteristics*

A total of 53,250 patients had claimed IBD-related purchases at the Finnish pharmacies between 2008 and 2018. Overall, 8,534 patients did not have any diagnosis recorded and were therefore removed from further analyses. Of the remaining patients (n=44,716), 11,970 (27%) had a diagnosis of CD (ICD-10 K50* or ICD-9 555*) and 32,746 (73%) had a diagnosis of UC (ICD-10 K51* or ICD-9 556*). A total of 2,884 patients had purchased adalimumab, golimumab, and/or ustekinumab between 2008 and 2018 and were included in the further analyses.

The majority of the patients included in the analyses were male (53–59%) and the mean age for disease onset was 32–34 years (Table 1). The mean disease duration at the time of initiation of adalimumab, golimumab, or ustekinumab ranged from 64.2 months in CD patients treated with adalimumab to 122.0 months for patients starting ustekinumab. Most patients had prior use of CS at the baseline and the use of immunosuppressants and 5-aminosalicylic acid was also common. Patients treated with adalimumab were likely to have more than one adalimumab treatment period during the 10-year study period. CD patients had on average 1.7 treatment periods and UC patients 1.5 treatment periods with adalimumab, whereas golimumab and ustekinumab users had typically only one treatment period with the product.

### *Treatment persistence*

Treatment persistence during the 24-month follow-up was assessed for all adalimumab, golimumab, and ustekinumab treatment periods independent of the treatment line. For adalimumab, the persistence was higher for CD patients compared to UC patients, both at months 12 (46.2% vs. 37.1%; $p<0.0001$) and 24 (26.1% vs. 19.7%; $p<0.0001$) (Figure 1A). For UC patients treated with golimumab, the treatment persistence was 48.3% at month 12 and 28.1% at month 24 (Figure 1B). Treatment persistence was higher with ustekinumab than with the other medications during the first six months. However, there was a more rapid decline after that and the persistence was only 2.9% at the end of the 24-month follow-up (Figure 1C). It should also be noted, that because the first ustekinumab dose was administered at a hospital, treatment discontinuations at the very beginning of treatment (the first 8 weeks) could not be determined in this dataset.

The mean treatment length was 84 (±95.7) weeks for CD and 64 (±75.3) weeks for UC patients on adalimumab treatment, 80 (±79.1) weeks for UC patients on golimumab, and 42 (±35.8) weeks for CD patients treated with ustekinumab.

Treatment lines for the biologicals were available for a subgroup of patients originating from the Hospital District of Southwest Finland (adalimumab CD, n=64; adalimumab UC, n=28; golimumab UC, n=33; ustekinumab CD, n=9). The switches between biologicals are illustrated in Annex Figure 1. Adalimumab was more commonly used as the first line biological in CD than in UC. Golimumab (UC) and ustekinumab (CD) were mainly used as second or third-line biologicals.

***Dosing analysis***

In patients with CD, real-life dosing of adalimumab exceeded the regular SPC dose in the majority (62.9%) of the treatment periods during the first 6 months of the treatment (Figure 2A). By contrast, the regular dose was exceeded in only 27.4% of the UC treatment periods at the start of the treatment (Figure 2B). In the later stages (months 7–24) of adalimumab treatment, real-life dosing was mostly consistent with the regular SPC dose in both CD (67–69%) and UC (66–74%) patients.

In UC patients treated with golimumab, 40.4% of the treatment periods exceeded the SPC regular dosing during the first 6 months. The proportion of dose escalations increased in the later stages of the treatment: 52–54% of treatment periods exceeded the SPC regular dosing at months 7–24. In CD patients treated with ustekinumab, dosing exceeded the regular SPC dosing in as many as 70.7% of treatment periods during the first 6 months. In the later stages of treatment, this ratio reduced dramatically: at months 7–12 the percentage of treatment periods with increased dosing was 43.2% and at months 13–18, all the treatment periods had regular dosing. It is to be noted, however, that the number of patients who persisted on ustekinumab was very low after 12 months.

***Treatment cost***

The mean cumulative costs of adalimumab treatment in CD were €9,923 and €18,763 at months 12 and 24, respectively (Figure 1A). The corresponding cumulative treatment costs in UC were €9,828 at month 12 and €18,242 at month 24 (Figure 1B). At month 24, the cumulative mean cost exceeded the cost of SPC regular dosing by €2,290 in CD and €810 in UC.

The real-life cost of golimumab treatment exceeded the cost of adalimumab in UC. The mean cumulative cost of golimumab was €12,038 at month 12 (€2,210 higher than adalimumab) and

€22,848 at month 24 (€4,606 higher than adalimumab) (Figure 3C). The cumulative cost was €3,698 higher than the cost of the regular dosing of golimumab according to the SPC.

Ustekinumab was the most expensive treatment analyzed. At month 12, the mean cumulative cost was €18,695, which was €8,772€ higher than the real-life cost of adalimumab in CD and €6,550 higher than the cost of regular dosing according to the SPC (Figure 3D).

***Relationship of dosing with CS use and treatment persistence***

Patients with higher dosing of a biological also had also increased cumulative use of CS (Table 2). The only exceptions were patients on golimumab at months 13–18 (mean CS exposure 3,163.8 mg in high+over category vs. 4,787.7 mg in regular category) and UC patients on adalimumab at months 18–24 months (2,229.7mg vs. 2,363.3mg). The highest cumulative CS doses were observed among CD patients treated with ustekinumab.

There was higher treatment persistence among CD patients who were treated with high doses of adalimumab compared with patients on the regular dose. Altogether, 45% of patients in the high+over dosing group persisted on adalimumab at month 24 compared to 25% in the regular dose group ($p<0.001$). A similar effect was not observed among UC patients treated with adalimumab or among patients treated with golimumab or ustekinumab (data not shown).

## Discussion

In this nationwide, retrospective, non-interventional Finnish registry study, dose-escalation of biologicals was found to be common clinical practice in an out-patient setting. We also evaluated treatment persistence, concomitant corticosteroid use, and real-life treatment costs of adalimumab, golimumab, and ustekinumab.

Adalimumab dose escalation has been shown to be an effective approach to manage secondary loss of response in the treatment of CD and, therefore, high rates of dose escalation were expected in this cohort [10, 11]. In a subgroup open-label cohort analysis of the CHARM clinical trial, 59.2% (71/120) of the patients required adalimumab dose escalation and 63% of these patients were able to regain response [12]. In our study, dose-escalation was found to be more common in the treatment of CD than UC during the first 6 months (62.9% vs. 27.4%), which supports the earlier findings. During later stages of treatment (months 7–24), real-life dosing was mostly consistent with the regular SPC dose in both CD (67–69%) and UC (66–74%) patients. These results contrast partly with the findings of Olivares *et al*., who reported that UC patients require adalimumab dose escalation more frequently than CD patients [13]. In their observational cohort study, 56% of CD and 65% of UC patients required dose escalation.

In our cohort, golimumab dose escalation was very common in the treatment of UC and increased in later stages of the treatment compared to the first 6 months (40.4% vs. 52–54%). The amount of dose escalation was found to be higher or at a similar level to previously published results. Iborra and colleagues reported that dose escalation was required by 43.2% of the UC patients treated with golimumab [14]. By contrast, Bressler and colleagues reported that only 7.4% of UC patients needed dose adjustment during maintenance therapy [15]. These differences may partly be explained by differences in treatment practices and study populations.

Dose escalation was very common in the treatment of CD patients with ustekinumab, and it was found to be more common in earlier treatment periods (months 0–6 70.0%) than during later periods (months 7–12 43.2%). After 12 months, the patient numbers were too small to draw any conclusions. Similar to adalimumab, it has been shown that ustekinumab dose escalation may be beneficial for selected CD patients who fail to achieve remission on standard Q8 week dosing [16]. In a large registry-based study from the U.S., ustekinumab dose escalation (defined as dose being outside 20% dose variation from the label) was experienced by 17.9% of CD patients [17].

Treatment practices may have significant differences between Finland and the U.S., which may partly explain the difference. Also, the study period was limited for ustekinumab in our study, because it has had marketing authorization for the treatment of CD in the EU only since 2016.

In the real-world setting, treatment persistence may be viewed as a surrogate measure of drug efficacy and safety. Here, the treatment persistence of adalimumab was higher for CD compared to UC patients both at months 12 (46.2% vs. 37.1%) and 24 (26.1% vs. 19.7%). Earlier, higher treatment persistence rates than observed here have been reported for adalimumab. Hoque and colleagues reported a 12-month treatment persistence rate of 64.6% in UC, whereas Gonczi and colleagues reported the need for dose intensification in 29.5% of patients and loss of response in 25.9% of patients [18, 19]. To compare across therapy areas, the discontinuation probability of adalimumab at 12 months was 25% in a Finnish rheumatoid arthritis cohort, which is significantly lower than reported here for CD or UC [20].

For UC patients treated with golimumab, treatment persistence was 48.3% at month 12 and 28.1% at month 24, which is comparable to adalimumab. In the PURSUIT (Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment) trials, the response was maintained through week 54 in approximately 50.0% of patients in an anti-TNF naïve population [21]. It is a common understanding that response to biologicals is highest in a naïve population, which may explain the difference in addition to the differences in study types. In our study, the golimumab treatment persistence was somewhat lower than reported in other real-world cohorts. For example, Hoque and colleagues reported treatment persistence of 64.4% for golimumab at 12 months in the treatment of UC in the UK [18]. In a 4-year real-life study by Iborra et al., treatment persistence was 63%, 46%, 39%, and 27% at years 1, 2, 3, and 4, respectively [14].

Ustekinumab showed higher persistence in comparison to adalimumab and golimumab during the first six months. However, persistence declined rapidly after that being only 3% at the end of the 24-month follow-up. This may be explained by the small number of patients and ustekinumab being a newcomer to the clinical practice at the time of the study. It is also important to note that ustekinumab treatment discontinuations during the first 8 weeks of the treatment could not be identified in this dataset, which inflates the persistence rate in early treatment.

Due to the lack of available clinical data in a register study such as this one, the reasons for treatment discontinuation cannot be directly addressed. A major reason for discontinuation is likely to be lack of response, as typically 20-40% of patients do not show an adequate response to anti-

TNF therapy in clinical trials [22]. In accordance with this, Lehtola and colleagues reported the main reason for anti-TNF treatment discontinuation during a 2-year follow-up to be lack of response (51%), while other significant reasons were side effects (33%) and remission (17.5%) [23]. Remission towards the end of the follow-up is another plausible explanation for treatment discontinuation, as another study reported 43% of patients discontinuing anti-TNF treatment because of remission (a median of 23-month follow-up) [24]. The rate of IBD-related surgeries has been reported to be low in patients on anti-TNFs. Therefore, the effect of surgeries on treatment continuation probably is not a major contributor [9, 25].

As only subcutaneously administered biologicals are covered by the Finnish drug reimbursement system, data on hospital-administered products cannot be tracked from the Register for Reimbursed Drugs. Therefore, we analyzed regional hospital data from Southwest Finland to describe treatment lines of the biologicals in IBD in 2014-2018. Infliximab was clearly the most commonly used first-line biological in both CD and UC. Adalimumab was also quite commonly used as the first-line biological in CD. In line with the earlier data, golimumab and ustekinumab were typically used as second- or third-line treatments [26–28]. Since 2018, reimbursed subcutaneous formulations for infliximab and vedolizumab as well as tofacitinib have become available, which will be included in a future study focusing on drug switches.

Corticosteroids are key components in the treatment of IBD. Commonly, the use of corticosteroids continues after the induction phase of biological treatment despite the known side-effects [29]. Corticosteroid load has been reported to decrease during biological therapies, which has been shown, for example, with vedolizumab [30, 31]. In this study, patients with higher dosing of a biological had generally also increased cumulative use of CSs. This is understandable considering the fluctuating nature of these diseases and the occurrence of relapses. Also, secondary loss of response could be managed with dose escalation and concomitant use of CS. Interestingly, treatment persistence was higher in patients using high doses of adalimumab in CD. However, a similar effect was not observed among UC patients.

Besides clinical efficacy and safety, the cost of biologicals has become an increasingly important component of treatment decisions. Therefore, it was important to analyze the real-life costs of adalimumab, golimumab, and ustekinumab treatments as part of this study. In Finland, at least a 30% lower wholesaler price compared to originator product is required for a biosimilar to get national reimbursement in an out-patient setting. Several adalimumab biosimilars have entered the

Finnish market lowering the costs of adalimumab treatment. The decreased price level of adalimumab has affected the prices of patent-protected biologicals as well. Taking the real-life dose escalation into account, in both CD and UC the treatment costs were the lowest with adalimumab. The price difference between adalimumab use in CD and UC was very small. Real-life costs of golimumab exceeded the costs of adalimumab in UC. Ustekinumab costs were highest with an annual cost difference of more than 8,000€ per patient in comparison to adalimumab. However, it should be noted that the patient numbers in this study were the lowest for ustekinumab and the results for different biologicals cannot be directly compared.

To our knowledge, this is the first study that aims to characterize real-world dose escalation of biologicals in the treatment of CD and UC in the Finnish population. The main strength of this study is the real-world setting and complete nationwide coverage of patients using subcutaneous biologicals for CD or UC in Finland. Basically, all subcutaneously administered biologicals are purchased from the pharmacies and recorded in the Registry for Reimbursed Drugs. On the other hand, we did not capture data of hospital-administered products, such as infliximab, vedolizumab, or the first dose of ustekinumab from the Registry for Reimbursed Drugs. Therefore, we included regional hospital data to describe treatment lines of all biologicals in a subgroup of patients. Also, we did capture data on CS purchases, but not on the actual use of CS (how many tablets were taken) or indication for CS prescriptions. This may have led to a slight overestimation of CS used by IBD patients in this study. An additional limitation is that there is variation in healthcare systems and treatment practices in different countries, and therefore the results from this study cannot necessarily be generalized to other countries.

To conclude, dose escalation of biologicals in the treatment of CD and UC is common in real-life clinical practice. Dose escalation may increase treatment costs, but at the same time improve treatment persistence. More research is needed on the factors influencing treatment persistence in real-life as loss of efficacy and adverse events alone do not give a conclusive explanation to the phenomena. Additional data on the real-life use of biologicals will take us closer to having the right treatment for the right patient and, thereby, improving the quality of life of IBD patients.

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**Declaration of interest**

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**Table 1.** Baseline characteristics.

| | Adalimumab | | Golimumab | Ustekinumab |
|---|---|---|---|---|
| | CD | UC | UC | CD |
| | n=1813 | n=716 | n=385 | n=173 |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Male | 992 (54.7%) | 376 (52.5%) | 226 (58.7%) | 93 (53.8%) |
| Female | 821 (45.3%) | 340 (47.5%) | 159 (41.3%) | 80 (46.2%) |
| | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** |
| Age at disease onset (years) | 31.9 (15.9) | 33.0 (15.1) | 34.3 (14.1) | 31.8 (16.6) |
| Disease duration at treatment initiation (months)[1] | 64.2 (67.1) | 76.5 (68.0) | 80.8 (67.7) | 122.0 (82.2) |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Corticosteroids (CS) | 1214 (67.0%) | 559 (78.1%) | 293 (76.1%) | 104 (60.1%) |
| Immunosuppressants (IS) | 1226 (67.6%) | 399 (55.7%) | 228 (59.2%) | 70 (40.5%) |
| 5-aminosalicylic acid (5-ASA) | 923 (50.9%) | 569 (79.5%) | 301 (78.2%) | 35 (20.2%) |
| | **n** | **n** | **n** | **n** |
| Treatment periods | 3103 | 1060 | 424 | 174 |

[1]Defined as the time between the first reimbursement status for IBD and the start of the first treatment period.
Abbreviations: CD, Crohn's disease; UC, ulcerative colitis.

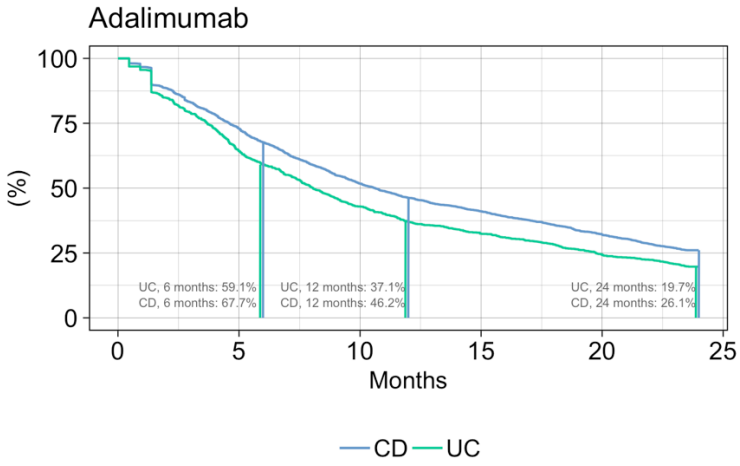
**Table 2.** Cumulative CS use (mg in prednisone equivalents) in different dosing groups during the 24-month follow-up. Assignment to SPC regular and SPC high+over groups was made based on dosing during the first 6 months of treatment. Only treatment persistent patients at each time point are included.

| Months from treatment start | | Adalimumab, CD | | Adalimumab, UC | | Golimumab, UC | | Ustekinumab, CD | |
|---|---|---|---|---|---|---|---|---|---|
| | | SPC regular | SPC high+over | SPC regular | SPC high+over | SPC regular | SPC high+over | SPC regular | SPC high+over |
| 0–6 | n | 219 | 566 | 198 | 128 | 72 | 83 | 8 | 8 |
| | Mean | 3,565.9 | 4,675.1 | 2,769.9 | 3,303.7 | 3,040.0 | 3,846.1 | 5,901.9 | 6,208.4 |
| | (SD) | (4,148.1) | (5,692.5) | (5,355.3) | (3,439.8) | (2,778.9) | (3,796.5) | (8,208.0) | (7,459.3) |
| | Median | 2,000 | 2,400 | 1,450 | 2,200 | 2,000 | 2,400 | 3,750 | 4,701.3 |
| | [min-max] | [105-22,480.5] | [100-46,753.2] | [150-52,153.2] | [150-24,428.6] | [105-11,688.3] | [150-21,039] | [500-25,126.6] | [500-23,376.6] |
| 7–12 | n | 62 | 326 | 63 | 72 | 30 | 40 | 2 | 5 |
| | Mean | 3,070.1 | 4,749.8 | 2,844.2 | 3,596.1 | 2,771.3 | 3,479.3 | 4,571.1 | 6,715.6 |
| | (SD) | (3,948.5) | (5,817.9) | (3,957.2) | (4,500.7) | (2,601.5) | (3,805.5) | (5,616) | (6,562.2) |
| | Median | 1,750 | 2,300 | 1,700 | 2,300 | 2,000 | 2,000 | 4,571.1 | 3,896.1 |
| | [min-max] | [150-23,376.6] | [105-54,545.5] | [150-27,272.7] | [181.8-33,361] | [105-11,019.5] | [350-21,039] | [600-8,542.2] | [909.1-15,584.4] |
| 13–18 | n | 33 | 234 | 46 | 38 | 12 | 20 | | |
| | Mean | 2,631.6 | 4,889.9 | 2,402.8 | 2,883.1 | 4,787.7 | 3,163.8 | | |
| | (SD) | (2,512.6) | (5,246.5) | (2,979.9) | (2,911.6) | (5,591.1) | (2,203.7) | | |
| | Median | 2,000 | 3,300 | 1,200 | 2,000 | 4,150 | 2,750 | | |
| | [min-max] | [150-7,792.2] | [105-26,584.4] | [150-16,311.7] | [300-12,000] | [500-21,039] | [350-8,213] | | |
| 18–24 | n | 19 | 150 | 31 | 27 | 14 | 17 | | |
| | Mean | 3,758.8 | 4,847.8 | 2,363.3 | 2,229.7 | 3,762.2 | 4,100.6 | | |
| | (SD) | (3,319.6) | (5,729.9) | (3,036.3) | (3,183.9) | (4,745.7) | (5,327.6) | | |
| | Median | 2,850 | 2,190.9 | 1,000 | 1,000 | 1,200 | 2,750 | | |
| | [min-max] | [350-11,688.3] | [150-31,168.8] | [500-12,019.5] | [150-15,584.4] | [150-14,919.5] | [150-19,100] | | |

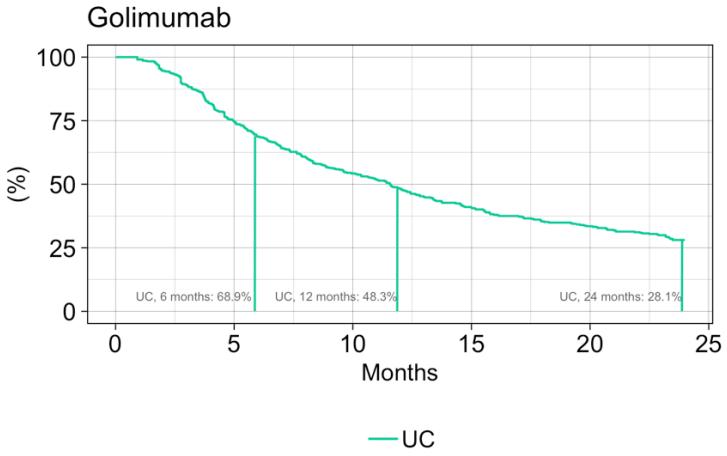
Abbreviations: CD, Crohn's disease; CS, corticosteroid; SD, standard deviation; SPC, summary of product characteristics; UC, ulcerative colitis.

**Figure 1.** Adalimumab, golimumab, and ustekinumab treatment persistence during the 24-month follow-up.

A.




B.




C.

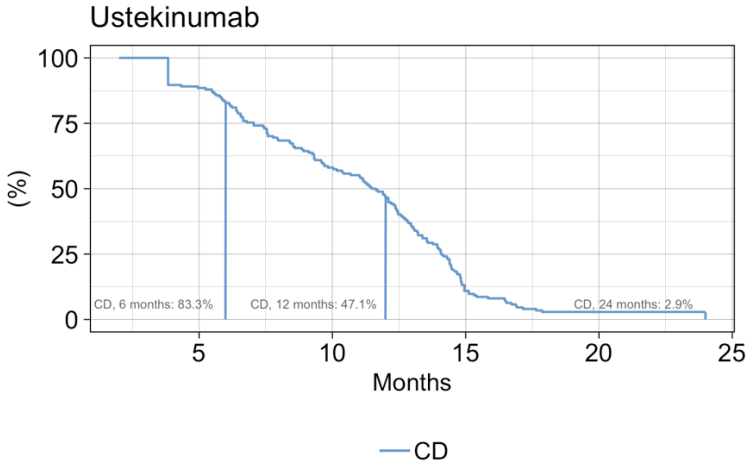
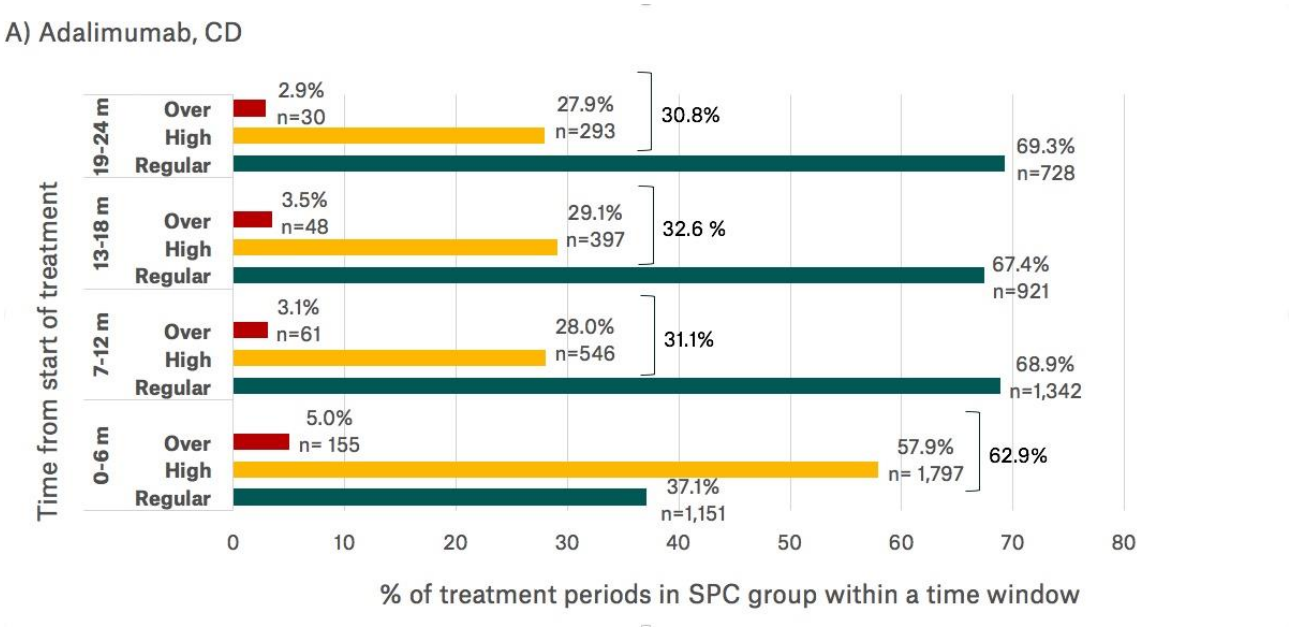
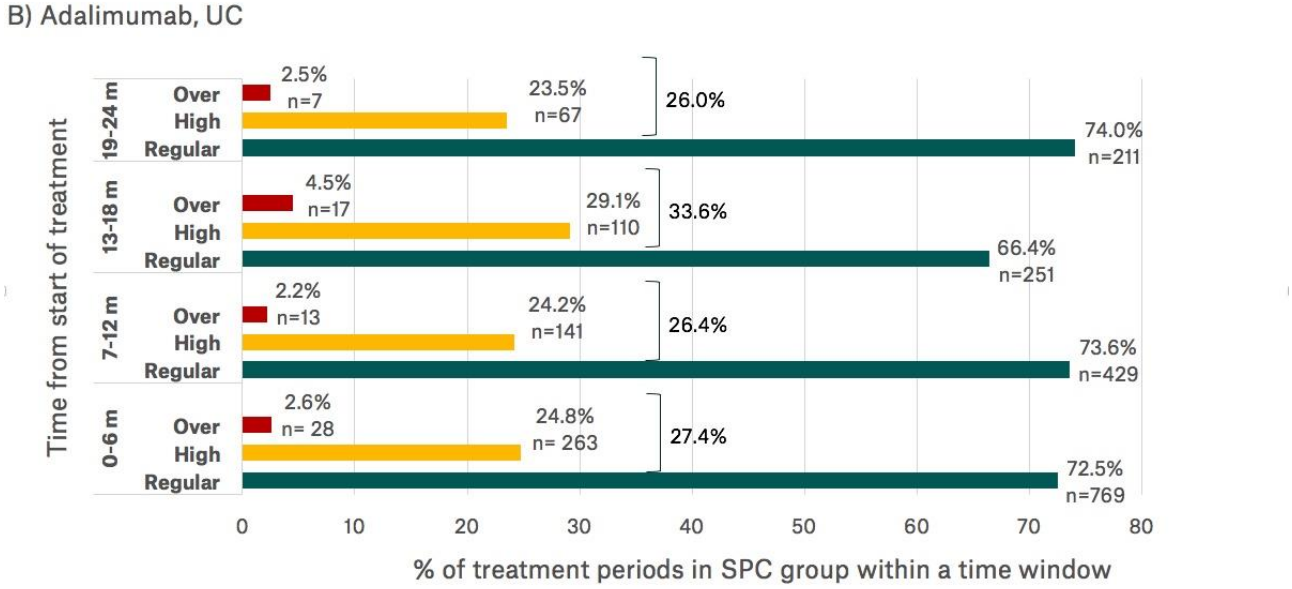
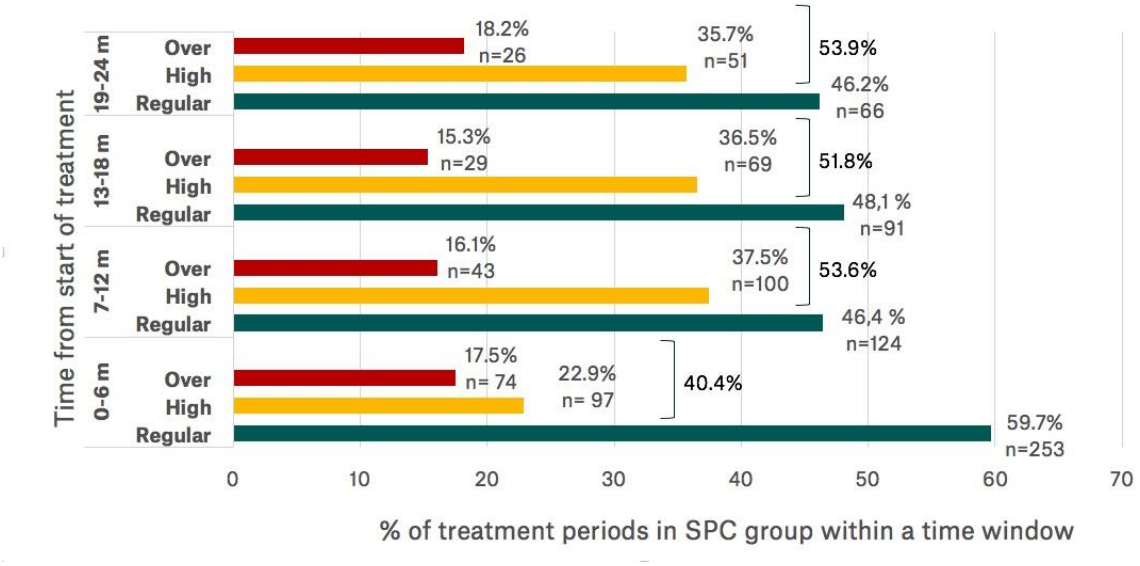


**Figure 2.** Distribution of SPC regular, SPC high and over SPC dose groups during different stages of 24-month follow-up. A) adalimumab (CD), B) adalimumab (UC), C) golimumab (UC), D) Ustekinumab (CD)[1].

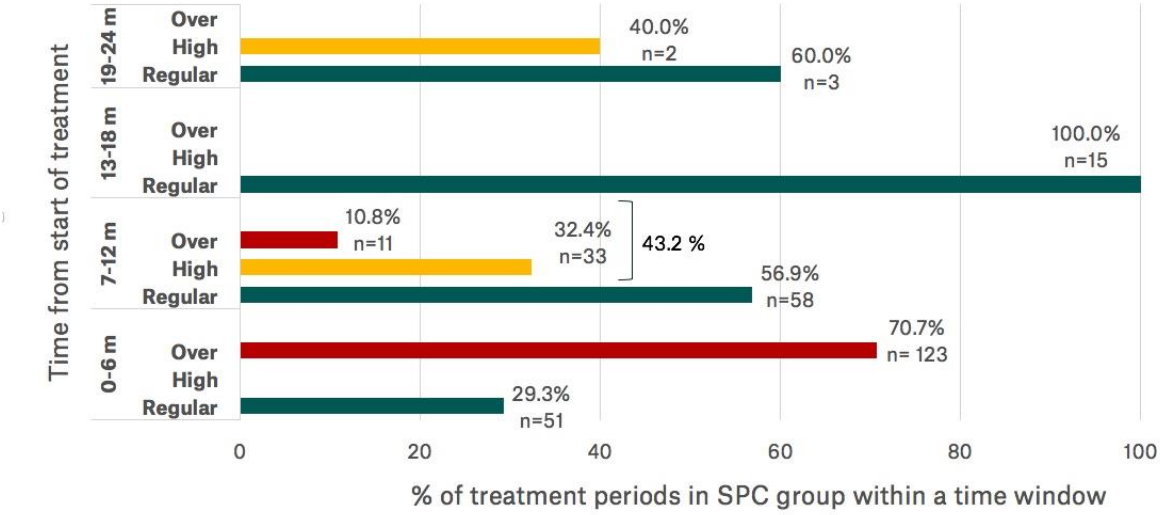


C) Golimumab, UC



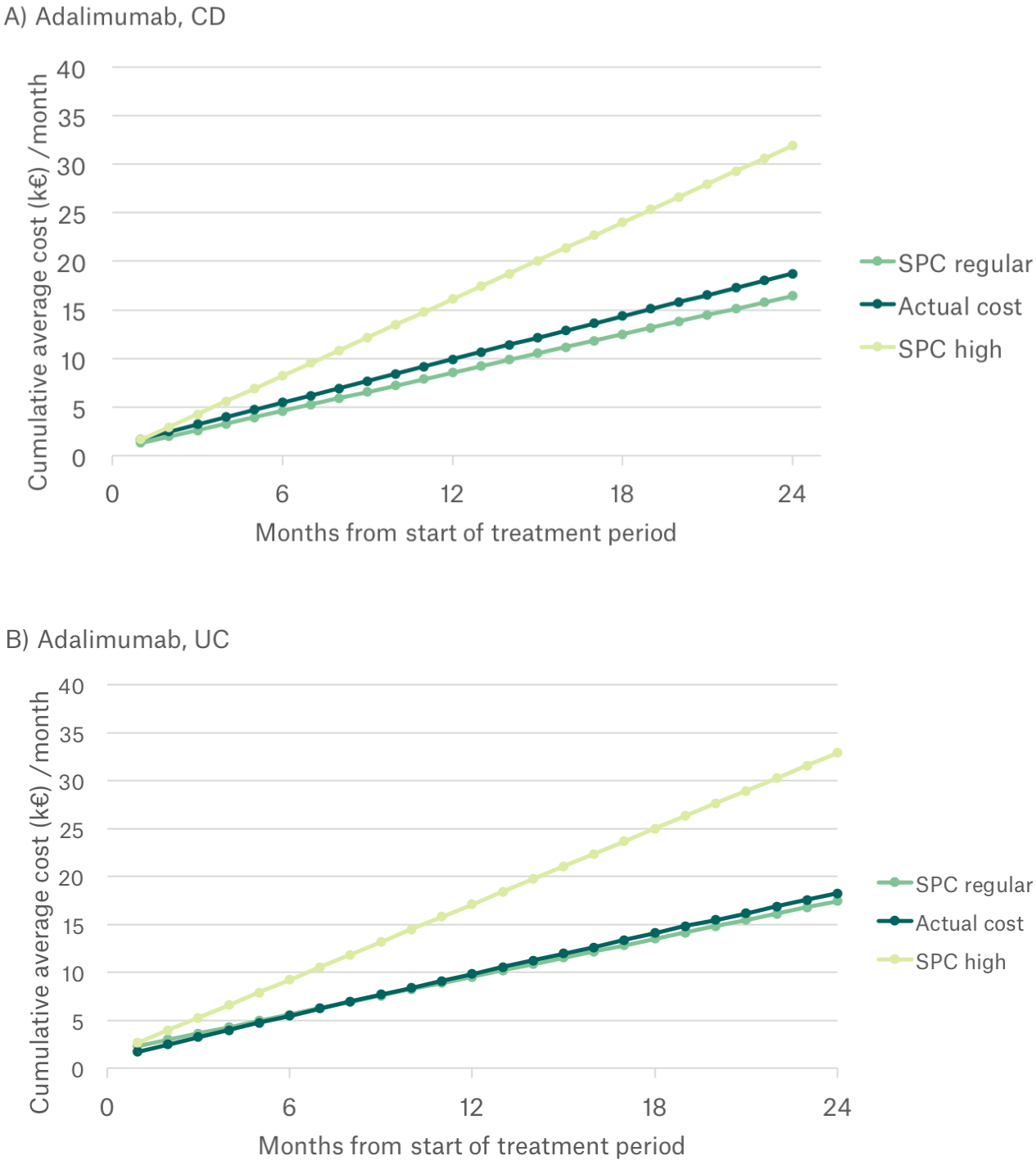

D) Ustekinumab, CD



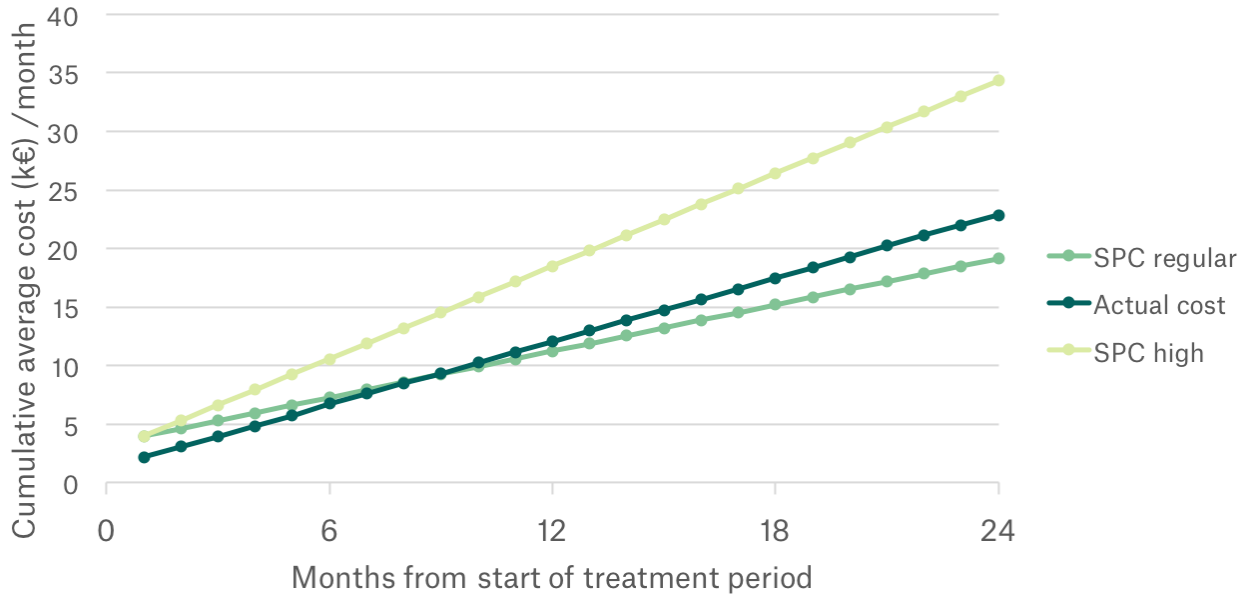

[1]The hospital-administered first ustekinumab dose is not included in the calculations.

Abbreviations: CD, Crohn's disease; SPC, summary of product characteristics; UC, ulcerative colitis.

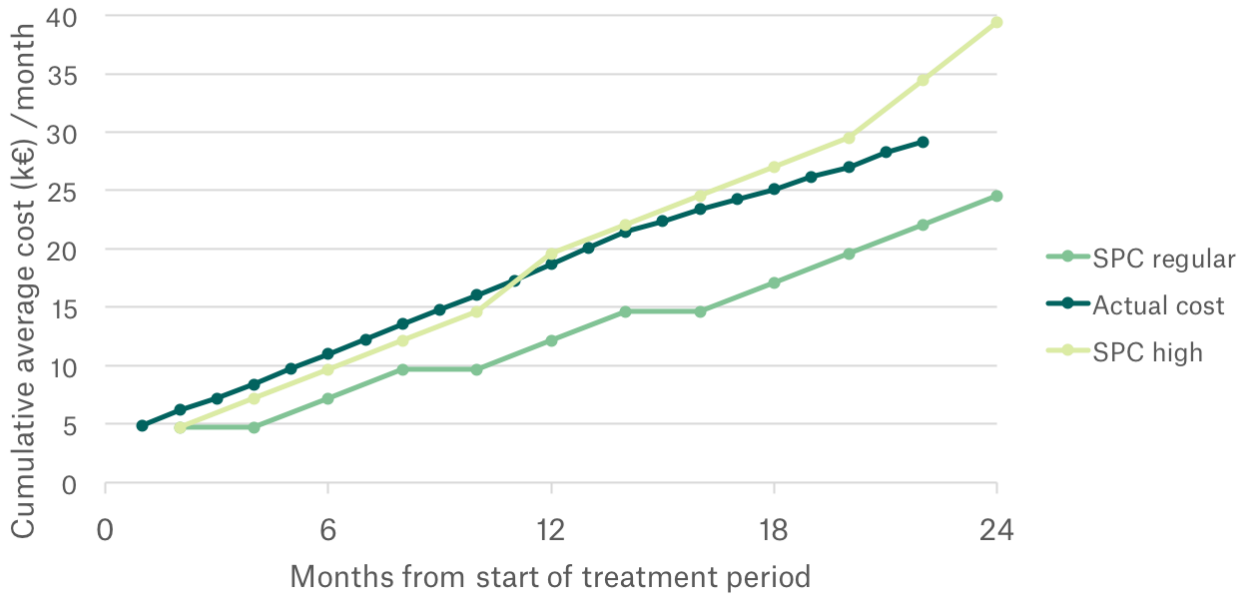
**Figure 3.** Real-life cumulative costs of A) adalimumab in CD, B) adalimumab in UC), C) golimumab[1] (UC), and D) ustekinumab[2] (CD) during the 24-month follow-up and corresponding theoretical costs for SPC regular and SPC high dosing. Retail prices on January 1, 2020 were used for calculations.



C) Golimumab, UC




D) Ustekinumab, CD




[1]Wholesale pricing (January 1, 2020) for both a 50 mg and a 100 mg golimumab injection was €857.60. The two syringe sizes were purchased in 0.54/0.46 ratio, which was considered in SPC cost calculations.

[2]Wholesale pricing (January 1, 2020) for both a 45 mg and a 90 mg ustekinumab injection was €2,608.00. The two syringe sizes were purchased in 0.12/0.88 ratio, which was considered in SPC cost calculations. The cost of the hospital-administered first ustekinumab dose (€2,223.23 in October 2019) is included in the cost calculations.

Abbreviations: CD, Crohn's disease; CS, corticosteroid; SPC, summary of product characteristics; UC, ulcerative colitis.

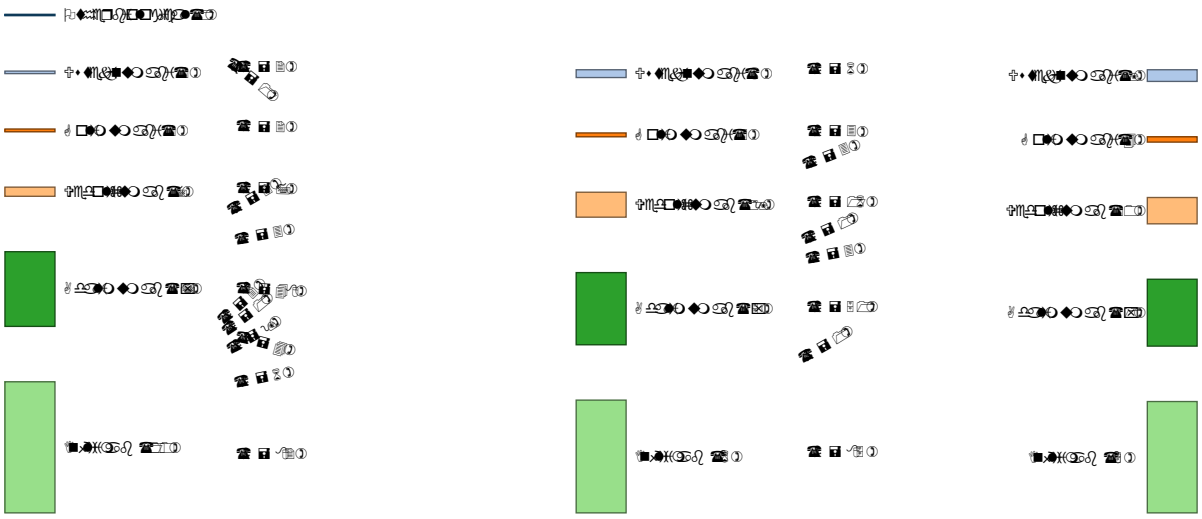
**Annex Table 1.** Characterization of theoretical SPC groups based in different phases of the treatment.

| Time from start of treatment (months) | "SPC regular" mg total | "SPC high" mg total | "SPC over" mg total |
|---|---|---|---|
| **Adalimumab (CD)** | | | |
| 0–6 | ≤520 | 520–920 | >920 |
| 7–12 | ≤480 | 480–960 | >960 |
| 13–18 | ≤480 | 480–960 | >960 |
| 19–24 | ≤480 | 480–960 | >960 |
| **Adalimumab (UC)** | | | |
| 0–6 | ≤640 | 640–1040 | >1040 |
| 7–12 | ≤480 | 480–960 | >960 |
| 13–18 | ≤480 | 480–960 | >960 |
| 19–24 | ≤480 | 480–960 | >960 |
| **Golimumab** | | | |
| 0–6 | ≤550 | 550–800 | >800 |
| 7–12 | ≤300 | 300–600 | >600 |
| 13–18 | ≤300 | 300–600 | >600 |
| 19–24 | ≤300 | 300–600 | >600 |
| **Ustekinumab** | | | |
| 0–6 | ≤180 | - | >180 |
| 7–12 | ≤180 | 180–270 | >270 |
| 13–18 | ≤180 | 180–270 | >270 |
| 19–24 | ≤180 | 180–270 | >270 |

Abbreviations: CD, Crohn's disease; SPC, summary of product characteristics; UC, ulcerative colitis.

**Annex Figure 1.** Treatment lines of biologicals in A) Crohn's disease and B) ulcerativc colitis in the Hospital District of Southwest Finland in 2014-2018.

A) Crohn's disease



B) Ulcerative colitis