Sequencing JAK-inhibitors in ulcerative colitis: effectiveness and safety of switching within treatment class

Authors:

Tommaso Innocenti[1,2 a], Jurij Hanžel[3 a], Marie Truyens[4,5], Milan Lukaš[6], Hannah Gordon[7], Anneline Cremer[8], Tamás Molnár[9], Mette Julsgaard[10,11], Sara Onali[12], Alessia Todeschini[13], Olga Maria Nardone[14], Nurulamin M. Noor[15], Flavio Caprioli[16,17], Franco Scaldaferri[18,19], Konstantinos Argyriou[20], Edoardo Vincenzo Savarino[21], Marko Brinar[22], Charlotte R.H. Hedin[23,24], Milagros Vela González[25], Alessandro Armuzzi[26,27], Andreas Blesl[28], Annalisa Aratari[29], Alessandro Quadarella[30], Tommaso Lorenzo Parigi[31], Lorenzo Bertani[32], Concetta Ferracane[33], Mathieu Uzzan[34], George Michalopoulos[35], Alice De Bernardi[36], Konstantinos Katsanos[37], Paola Balestrieri[38], Gisela Piñero[39], Konstantinos Karmiris[40], Ana Gutierrez Casbas[41], Sara Nikolic[42], Carla Felice[43], Daniela Pugliese[19,44], Pastras Ploutarchos[45], Giammarco Mocci[46], Lieven Pouillon[47], Gerassimos J. Mantzaris[48], Laura Ramos[49], María José Casanova[50], Ioannis E. Koutroubakis[51], María José García[52], **The JAKi-SEQ Study Group**, Triana Lobaton[4,5 b], and Gabriele Dragoni[1,2 b] *

[a] shared first authorship

[b] shared senior authorship

*__Correspondence__:

Prof. Gabriele Dragoni, MD, PhD

IBD Referral Centre, Clinical Gastroenterology Unit, Careggi University Hospital, Florence, Italy

Largo G. A. Brambilla 3 – 50134 Florence, Italy

gabriele.dragoni@unifi.it

The JAKi-SEQ Study Group: Livio Bonacci[14], Erica Bonazzi[21], Peter Bossuyt[47], Cristina Bezzio[26,27], Carolina Cardoso de Castro Gonçalves[23,24], María Chaparro[50], Triantos Christos[45], Armando Curto[2], Silvio Danese[31], Bernadett Farkas[9], Agnese Favale[12], Stefano Festa[29], Kalliopi Foteinogiannopoulou[51], Fotios Fousekis[37], Andreas Kapsoritakis[20], Željko Krznarić[22], Lucrezia Laterza[18], Claire Liefferinckx[8], Míriam Mañosa[39], Daniele Noviello[16,17], Laura Parisio[44], Simone Saibeni[36], Mohmmed Tauseef Sharip[15], Enrico Tettoni[30]

Affiliations:

1. IBD Referral Centre, Gastroenterology Unit, Careggi University Hospital, Florence, Italy

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2. Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy
3. Department of Gastroenterology, UMC Ljubljana, Ljubljana, Slovenia
4. Department of Internal Medicine and Pediatrics, Ghent University, Ghent, Belgium
5. Department of Gastroenterology, Ghent University Hospital, Ghent, Belgium
6. Clinical and Research Center for Inflammatory Bowel Diseases, ISCARE Clinical Centre, Prague, Czechia
7. Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford University Healthcare Trust, Oxford, United Kingdom
8. Department of Gastroenterology, Erasme University Hospital, Brussels, Belgium
9. University of Szeged, Center for Gastroenterology, Szeged, Hungary
10. Department of Hepatology & Gastroenterology, Aarhus University Hospital, Aarhus, Denmark
11. Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
12. Department of Medical Science and Public Health, University of Cagliari, Cagliari, Italy
13. IBD Unit, IRCCS "Sacro Cuore - Don Calabria", Negrar di Valpolicella, Italy
14. Department of Public Health, "Federico II" University of Naples, Naples, Italy
15. Department of Gastroenterology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom
16. Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy
17. Gastroenterology and Endoscopy Unit, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico di Milano, Italy
18. IBD Unit, CEMAD, UOC Medicina Interna e Gastroenterologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy
19. Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy
20. IBD Unit, Department of Gastroenterology, University Hospital of Larissa, Larissa, Greece
21. University of Padua, Department Of Surgery, Oncology And Gastroenterology, Division of Gastroenterology, Padua, Italy
22. Department of Gastroenterology and Hepatology, University Hospital Centre Zagreb, Zagreb, Croatia
23. Karolinska University Hospital, Centre for Digestive Health, Department of Gastroenterology, Dermatovenereology and Rheumatology, Stockholm, Sweden
24. Karolinska Institutet, Department of Medicine, Solna, Stockholm, Sweden
25. Hospital Universitario Nuestra Señora de Candelaria, Tenerife, Spain
26. IBD Unit, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy
27. Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy
28. Division of Gastroenterology and Hepatology, Medical University of Graz, Graz, Austria

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29. Department of Gastroenterology, IBD Unit, "San Filippo Neri" Hospital, Asl Roma 1, Rome, Italy
30. Gastroenterology and Digestive Endoscopy Unit, Fondazione Poliambulanza Istituto Ospedaliero, Brescia, Italy
31. Department of Gastroenterology and Endoscopy, IRCCS San Raffaele Hospital, Milan, Italy
32. Department of Internal Medicine - Pontedera Hospital - Tuscany Northwest ASL, Pontedera, Italy
33. Gastroenterology Unit, Policlinico-San Marco, Catania, Italy
34. Hôpital Henri-Mondor, Créteil, France
35. General Hospital of Athens "G. Gennimatas", Gastroenterology Department, Athens, Greece
36. IBD Unit, Gastroenterology Unit, Rho Hospital, ASST Rhodense, Rho (Milan), Italy
37. Division of Gastroenterology, Department of Internal Medicine, University of Ioannina, Ioannina, Greece
38. Gastroenterology Unit, Fondazione Policlinico Campus Bio-Medico, Rome, Italy
39. Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain
40. Department of Gastroenterology, Venizeleio General Hospital, Heraklion, Greece
41. Department of Gastroenterology, Hospital General Universitario Dr Balmis de Alicante, ISABIAL, CIBERehd, Alicante, Spain
42. Department of Gastroenterology, UMC Maribor, Maribor, Slovenia
43. Medicine 1, University Hospital of Treviso, Department of Medicine (DIMED), University of Padova, Padua, Italy
44. UOS Gastroenterologia, Ospedale Isola Tiberina Gemelli Isola, Rome, Italy
45. Division of Gastroenterology, Department of Internal Medicine, University Hospital of Patras, Patras, Greece
46. Division of Gastroenterology, "Brotzu" Hospital, Cagliari, Italy
47. Gastroenterology-Hepatology, Imeldaziekenhuis Bonheiden, Bonheiden, Belgium
48. Department of Gastroenterology, White Cross Hospital, Athens, Greece
49. IBD Unit Complejo Hospitalario Universitario de Canarias, Santa Cruz de Tenerife, Spain
50. Department of Gastroenterology, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Universidad Autónoma de Madrid (UAM) and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain
51. University General Hospital of Heraklion, Heraklion, Greece
52. IBD Unit, Gastroenterology Department, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain

Short title: Sequencing JAK-inhibitors in UC

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Abbreviations: AEs=adverse events, CI=confidence interval, ECCO=European Crohn's and Colitis Organisation, EIMs=extra-intestinal manifestations, FC=faecal calprotectin, FILGO=filgotinib, IBD=inflammatory bowel disease, IMIDs=immune mediated inflammatory disorders, IPTW=inverse probability of treatment weighting; IQR=interquartile range, JAKi=Janus kinases inhibitors, MACE=major adverse cardiac events, MES=Mayo endoscopic subscore, NRI=non-responder imputation, OR=odds ratio, PAMS=Partial Adapted Mayo Score, PP=per protocol, PY=patient-years; RBS=rectal bleeding subscore, REDCap=Research Electronic Data Capture, SFCR=steroid-free clinical remission, SFS=stool frequency subscore, TNF=tumour necrosis factor, TOFA=tofacitinib, UC=ulcerative colitis, UPA=upadacitinib, VTE=venous thrombo-embolic events

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The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions:

T.I.: Study design, data collection, data analysis, writing of the first draft, manuscript review and editing.

J.H.: Study design, data collection, writing of the first draft, manuscript review and editing.

M.T., M.L., H.G., A.C., T.M., M.J., S.O., A.T., O.M.N., N.M.N., F.C., F.S., K.A., E.V.S., M.B., C.R.R.H., M.V.G., A.Arm., A.B., A.Ara., A.Q., T.L.P., L.B., C.F., M.U., G.Mic., A.D.B., K.Kas., P.B., G.P., K.Kar., A.G.C., S.N., C.F., D.P., P.P., G.Moc., L.P., G.J.M., L.R., M.J.C., I.K., M.J.G.: Data collection, manuscript review and editing.

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Abstract

Background and aims: Evidence from rheumatology supports a within-class treatment switch for JAK-inhibitors (JAKi), but data in ulcerative colitis (UC) remain limited. We aimed to assess the effectiveness and safety of initiating a second JAKi in patients with UC previously treated with another JAKi.

Methods: We conducted a multicentre retrospective study, including patients with UC starting a second JAKi after prior JAKi exposure. The primary endpoint was week 12 steroid-free clinical remission (SFCR – rectal bleeding subscore=0, stool frequency subscore≤1, and no steroids).

Results: We included 243 patients [median follow-up: 38 (21-57) weeks]. At weeks 12, 26, and 52, SFCR was achieved in 116/243 (48%), 120/243 (49%), and 69/243 (28%), respectively. Secondary loss of response to the first JAKi was associated with higher SFCR at week 12 compared to primary failure (OR=1.92, 95%CI=1.11-3.30, p=0.02). Higher baseline disease activity (OR=0.68, 95%CI=0.68-0.55, p<0.01) and steroid use (OR=0.23, 95%CI=0.13-0.42, p<0.01) had lower odds of week 12 SFCR. Endoscopic remission occurred in 22/243 (9%) (<week 26) and 27/243 (11%) (26-78 weeks), and endoscopic improvement in 53/243 (22%) and 45/243 (19%), respectively. Sixty-seven (28%) patients discontinued the second JAKi, mostly due to primary (36/67) or secondary failure (22/67). Sixty-six adverse events (mostly acne and infections) occurred in 56 (23%) patients, without major thromboembolic or cardiovascular events.

Conclusion: Treatment with a second JAKi is effective and safe in patients with UC already exposed to JAKi. Primary failure to a first JAKi and steroid use at initiation of the second JAKi might reduce the likelihood of success with the second JAKi.

Keywords: ulcerative colitis, JAK-inhibitors, steroid-free clinical remission, treatment cycling, real-word evidence

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Introduction

Despite the expanding therapeutic armamentarium for inflammatory bowel disease (IBD), many patients experience treatment failure or adverse events leading to treatment discontinuation. Within-class switch has proven effective for anti-tumour necrosis factor (TNF) agents in case of secondary loss of response, with lower beneficial effects in case of primary non response.[1] With newer molecules available, there are still insufficient data regarding the optimal first line treatment and sequencing strategies for patients with IBD.[2] Moreover, specific clinical scenarios such as older age, comorbidities, and extra-intestinal manifestations (EIMs) are involved in driving the decision process to select a treatment, and can limit treatment alternatives.

Janus kinases (JAK) are cytoplasmic non-receptor tyrosine kinases involved in intracellular signalling via the signal transducer and activator of transcription pathway; among the four members JAK1, JAK2, JAK3, and TYK2, JAK1 plays a key role in innate and adaptative immune responses.[3, 4] The currently available orally administered JAK-inhibitors (JAKi) include tofacitinib (TOFA), filgotinib (FILGO) and upadacitinib (UPA). These are fast-acting small molecules with demonstrated effectiveness in IBD as well as in other immune mediated inflammatory disorders (IMIDs).[5]

Data on intra-class JAKi switching are lacking in IBD. Theoretically, as immunogenicity has not been described in this drug class, effectiveness should be less impacted by previous exposure to a similar molecule.[5] In rheumatoid arthritis (RA) a switch from one JAKi to another showed higher drug retention rates and effectiveness comparable to switching to other treatments, supporting intra-class cycling of JAKi in this setting.[6-8] Few recent reports[9-13] suggested that JAKi-experienced and JAKi-naïve patients may respond similarly in ulcerative colitis (UC). Therefore, with this study we aimed to assess the real-world effectiveness and safety of switching JAKi in patients with UC.

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Methods

Study design

A retrospective, observational study was conducted in 45 IBD Centres across Europe after a general call sent out with the support of European Crohn's and Colitis Organisation (ECCO). The study was approved by the Ethical Committee of one of the coordinating centres (Careggi University Hospital, Florence, Italy) on September 3rd, 2024 (Reference number: CEAVC-27559). Every participating centre independently uploaded patient data in specific electronic case report forms (eCRF) using REDCap (Research Electronic Data Capture) platform[14] hosted on the server of Careggi University Hospital (Florence, Italy).

Adult patients with UC that have been previously treated with a JAKi and who received a second JAKi (either TOFA, FILGO, or UPA) for active UC between January 2019 and December 2024, regardless of intervening therapies between the first and second JAKi, and with at least 12 weeks of follow-up, were included in the study. Exclusion criteria included diagnosis of IBD-unclassified or Crohn's disease, patients hospitalized for acute severe UC, patients with an ostomy, pouchitis or EIMs/IMIDs as leading indication for the second JAK-inhibitor, and patients receiving a JAKi in combination treatment with biologics or immunosuppressants. Demographic and clinical co-variates that were collected were: gender, age, disease duration, disease extension according to the Montreal classification[15], smoking habits, recombinant Zoster vaccination status, ongoing combined hormonal contraception, concomitant EIMs/IMIDs, comorbidities [including diabetes mellitus, hypertension, dyslipidaemia, peripheral vascular disease, previous history of major adverse cardiac events (MACE) or venous thrombo-embolic events (VTE)], switch sequence [i.e., TOFA first, UPA second = "TOFA to UPA"; and direct switch from the first JAKi (i.e., the patients did not receive any treatment from another drug class in the interim) vs indirect switch from a different mechanism of action], reason for discontinuation of first JAKi (including primary failure, secondary loss of response, adverse events, remission/patient choice), concomitant treatment of any formulations of systemic or topical corticosteroids, whole blood count, blood lipid panel, and inflammatory biomarkers [C-reactive protein and faecal calprotectin (FC)] at treatment start and at each clinical timepoint whenever available, induction regimen and maintenance dosing of each study drug.

Outcomes

The primary outcome was to assess the rates of steroid-free clinical remission (SFCR) at 12 (±4) weeks. We selected this endpoint not only because it represents the most widely adopted time window in clinical trials, but also for its strong clinical relevance in a real-world setting. Indeed, the first follow-up visit typically takes places around week 12 (end of induction period), when treatment

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effectiveness is assessed by evaluating clinical response together with steroid discontinuation. Secondary outcomes included the following:

- to assess the SFCR rates at 26 (±8) and 52 (±8) weeks;
- to assess the clinical response and biochemical remission rates at 12 (±4), 26 (±8), and 52 (±8) weeks;
- to assess the endoscopic improvement and remission rates within 26 weeks ("Early endoscopic evaluation") and between 26 and 78 weeks ("Late endoscopic evaluation");
- to assess the treatment persistence at last follow-up;
- to assess the incidence of major adverse outcomes (colectomy, malignancy, death);
- to assess the incidence of adverse events (AEs), namely infections including Herpes Zoster reactivations, MACE, VTE, acne, and abnormalities of laboratory tests (including whole blood count and blood lipid panel).

Clinical activity was assessed with the Partial Adapted Mayo score [rectal bleeding subscore (RBS) + stool frequency subscore (SFS)] (PAMS).[16] Endoscopic activity was assessed with the Mayo endoscopic subscore (MES).[17] SFCR was defined as RBS=0 and SFS≤1, and no steroid therapy (including both systemic and topical formulations). For week 12 (±4), this refers to the time of assessment; for subsequent assessments, it refers to the previous 90 days. Clinical response was defined as a decrease in PAMS of ≥1 point and ≥30% from baseline, and a decrease in RBS of ≥1 point or an absolute RBS of ≤1. Clinical response was defined as steroid-free according to the same parameters described above. Endoscopic remission was defined as a MES=0, while endoscopic improvement was defined as a MES≤1. Biochemical remission was defined as a FC<250 µg/g.

Statistical analysis

Continuous variables were expressed as medians and interquartile ranges (IQR), while categorical variables were presented as percentages; AE rates were also expressed per 100 patient-years (PY) and stratified by age (<65/≥65 years), sex, comorbidity status, smoking, and JAKi used. Univariate and multivariate binary logistic regression were used to determine primary outcome (SFCR at week 12) predictors among the relevant co-variates. Odds ratios (OR) were expressed with a 95% confidence interval (CI). Overall and steroid-free clinical response and remission rates at the three timepoints were compared based on the reason for discontinuation of the 1st JAKi and on the different switch sequences, and group comparisons were performed using the Chi-squared test. Patients who discontinued the first JAKi due to remission and switching sequences different from "TOFA to UPA", "TOFA to FILGO", and "FILGO to UPA", were not included in the Chi-squared analyses due to the paucity of events. Other sequences included "FILGO to TOFA", "UPA to TOFA", and "UPA to FILGO". Patients discontinuing the first JAKi due to remission were also not included due to the

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paucity of events. Kaplan–Meier curves weighted by inverse probability of treatment weighting (IPTW) were used to describe treatment persistence. Comparisons across exposure groups (reason for discontinuation of the first JAKi, and treatment sequence) were assessed using Cox proportional hazards models with IPTW. Propensity scores for IPTW were estimated from baseline covariates including centre, country, disease extension, first JAKi, reason for discontinuation of the first JAKi (except when used as the exposure of interest), calendar year of index treatment, clinical activity (PAMS), standard/prolonged induction, and steroid use at baseline. Results are reported as hazard ratios (HR) with 95% confidence intervals. Effectiveness and safety data were analysed at the three time points using non-responder imputation (NRI) for missing data. However, per protocol (PP) analyses were also presented for the main outcomes. A two-sided p-value <0.05 was considered significant. All statistical analyses were performed using R version 4.4.2.

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Results

Study population

Between January 2019 (initiation of the first patient on TOFA) and December 2024 (last initiation of TOFA or UPA), we included 243 patients with UC who started a second JAK inhibitor: 212 received UPA, 24 FILGO, and 7 TOFA. **Figure 1** reports switch sequence information for the three drugs, while baseline and demographic information of patients are detailed in **Table 1**. Induction and maintenance schemes, where available, are reported in **Supplementary Table S1**. **Supplementary Figure S1** presents a flowchart illustrating, at each time point, the number of patients who either discontinued treatment or did not reach the time point.

Effectiveness at week 12

At week 12, 221 (91%) patients had their treatment ongoing. All patients had data available for this follow-up, as per inclusion criteria. Twenty patients (8%) discontinued their treatment due to failure, while 2 (1%) due to AEs. SFCR was reported in 116 (48%) patients (**Figure 2A**). Steroid-free clinical response and biochemical remission were reported in 138 (57%) and 89 (37%) patients, respectively (**Figure 2B-C**).

Univariate analysis showed higher chances of achieving SFCR at week 12 in patients who discontinued the first JAKi due to secondary loss of response compared to those with primary failure (OR 1.92, 95%CI 1.11-3.30, p=0.02), although this was not confirmed at multivariate analysis. A higher clinical disease activity and concomitant steroid (either systemic or topical) use at baseline were associated with reduced chance of week 12 SFCR at both univariate (OR 0.62, 95%CI 0.52-0.74, p<0.01 and OR 0.17, 95%CI 0.10-0.30, p<0.01, respectively) and multivariate analyses (OR 0.68, 95%CI 0.55-0.83, p<0.01 and OR 0.23, 95%CI 0.13-0.42, p<0.01, respectively, **Table 2**). No significant association was found between different switching sequences and the main outcomes including SFCR, clinical remission, steroid-free clinical response, and clinical response (**Figure 3A**). The same results were found comparing reasons for discontinuation of the first JAKi (**Figure 3B**).

Effectiveness at week 26

At week 26, 216 (89%) patients had data available, while 176 (72%) had their treatment ongoing. Twenty-two (10% of the 221 patients with ongoing treatment at week 12) discontinued their treatment between week 12 and week 26, due to treatment failure (n=18, 8%), AEs (n=3, 1%), and pregnancy (n=1, 1%). SFCR was reported in 120 (49% and 56% with NRI and PP analyses, respectively) patients (**Figure 2A**). Steroid-free clinical response was reported in 138 (57% at NRI and 64% at PP

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analyses) patients (**Figure 2B**). When compared to "TOFA to FILGO" sequence, "TOFA to UPA" sequence had a significantly greater proportion of patients who were in SFCR (54% vs 26%, p=0.02), clinical response (69% vs 44%, p=0.03), and steroid-free clinical response (63% vs 35%, p=0.02) (**Supplementary Figure S2A**). The reason of discontinuation of the first JAKi did not impact the effectiveness outcomes (**Supplementary Figure S2B**).

Effectiveness at week 52

Week 52 evaluation was assessed after a median of 52 (50-56) weeks, with 136 (56%) patients having data available; 108 (44%) had their treatment ongoing. Twenty-eight (16% of the 176 patients with ongoing treatment at week 26) discontinued their treatment between week 26 and week 52, due to treatment failure (n=23, 13%), AEs (n=4, 2%), and remission (n=1, 1%). SFCR was reported in 69 (28% and 51% with NRI and PP analyses, respectively) patients (**Figure 2A**). Steroid-free clinical response was reported in 87 (36% at NRI and 64% at PP analyses) patients (**Figure 2B**). No significant associations were found comparing patients based on the reason of discontinuation of the first JAKi nor the switch sequences (**Supplementary Figure S3A-B**).

Endoscopic outcomes

Ninety-two (38%) patients with ongoing treatment underwent an early endoscopic evaluation after a median of 13 (9-20) weeks, with early endoscopic improvement in 53 (22% and 58% with NRI and PP analysis, respectively) patients, and early endoscopic remission in 22 (9% and 24%) patients. A late endoscopic evaluation was performed in 79 (33%) patients with ongoing treatment after a median of 49 (36-58) weeks, with endoscopic improvement in 45 (19% and 57%) and endoscopic remission in 27 (11 and 34%) (**Figure 2D**).

Treatment persistence

One hundred seventy-six (72%) patients had their treatment ongoing at their last follow-up visit, with a median follow-up time of 38 (21-57) weeks. Sixty-seven (28%) patients discontinued the treatment during the follow-up, mainly due to primary failure (n=36, 54%), with other reasons being secondary loss of response (n=23, 34%), AEs (n=7, 10%), and pregnancy (n=1, 2%). **Figure 4A** reports the overall Kaplan-Meier curve for treatment persistence. After IPTW adjustment, the "TOFA to FILGO" sequence was associated with a higher risk of treatment discontinuation during follow-up compared to "TOFA to UPA" (HR 2.86, 95%CI 1.37-5.98, p<0.01), whereas no significantly higher risk was observed for the "FILGO to UPA" sequence (HR 1.47, 95%CI 0.85-2.54, p=0.17) (**Figure 4B**). Patients who had discontinued the first JAKi due to secondary loss of response showed a trend towards a lower risk of treatment withdrawal compared with those who discontinued the first JAKi

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due to primary failure (HR 0.55, 95%CI 0.27-1.14, p=0.11), although this difference did not reach statistical significance (**Figure 4C**).

Safety

We recorded a total of 66 AEs in 56 (23%) patients (**Supplementary Table S2**). AE per 100 PY and stratification by risk factors are reported in **Supplementary Table S3**. At week 12, 14 (6%) patients had acne and 18 (7%) had an infection, mainly upper respiratory tract infections (n=8) and urinary tract infections (n=3); 2 patients had a Herpes Zoster reactivation at week 12, of whom one had already received the recombinant vaccination. Between week 12 and week 26, 8 (3%) patients had acne and 15 (6%) had an infection, mainly upper respiratory tract infections (n=5) and urinary tract infections (n=5). Between week 26 and week 52, 3 (1%) patients had acne and 8 (3%) had an infection, mainly upper respiratory tract infections (n=3). Only 7 patients had to discontinue the treatment with the second JAKi due to infections. Of these, only one had already discontinued the first JAKi due to an AE.

Among the major adverse outcomes, 21 (9%) patients underwent a colectomy, due to primary failure (n=14), secondary loss of response (n=6) and AE with no more available treatments (n=1). One patient, a man with multiple comorbidities receiving UPA 15 mg, died due to urinary sepsis. We also recorded one malignancy in a patient with UC refractory to multiple prior agents who developed metastatic prostate cancer requiring anti-androgen treatment while on UPA; the treatment with UPA was continued at 15 mg daily based on the increased flare risk and the history of multiple treatment failures.

Laboratory results

Laboratory tests including whole blood count, C-reactive protein, FC, and blood lipid panel were available in a decreasing proportion of patients from treatment start to week 52 (**Supplementary Table S4**). We found a significant increase of haemoglobin (p=0.02), and a significant decrease of white blood cells (p<0.01), C-reactive protein (p<0.01) and FC (p<0.01) across the timepoints (**Supplementary Table S5**). Interestingly, no significant changes were found in the blood lipid panel (including triglycerides, and total, HDL and LDL cholesterol).

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Discussion

The therapeutic landscape for UC has rapidly evolved over the past decade, yet primary failure, loss of response, and AEs remain frequent, often necessitating treatment switches. While switching within class has been explored for anti-TNF treatments – with different rates of effectiveness depending on the reason for discontinuation[1] – data regarding the feasibility of intra-class switches with JAKi in UC are limited. After being demonstrated in RA,[6-8] this raised the important question regarding the applicability of sequential JAKi therapy to UC. To the best of our knowledge, this is the largest cohort of patients specifically recruited to evaluate effectiveness and safety of a second JAKi in JAKi-experienced patients with UC.

Our primary outcome, SFCR at week 12, was achieved by 48% of patients. This result is consistent with the first-reported findings by Danso *et al.* in an abstract presented at the 19th Congress of ECCO (Stockholm, February 2024), including a retrospective UK cohort of 99 patients who had switched between JAKi, with a SFCR of 49% among patients with available data.[10] Similarly, in the recently published J2J multicentre study from the French group GETAID, 81/169 (47.9%) patients achieved SFCR at week 8–14, perfectly reflecting our primary outcome results.[9] While the GETAID cohort found higher odds of post-induction SFCR in patients treated with UPA compared to FILGO (OR 2.47, 95%CI 1.26-4.97, p=0.03 at univariate analysis),[9] our week 12 SFCR was not significantly impacted by the choice of second JAKi – despite our population being heavily unbalanced in favour of UPA – nor treatment sequence or history of intervening therapies between the two JAKi. On the other hand, we found that patients with secondary loss of response to the first JAKi had higher odds of achieving week 12 SFCR than those with primary failure – consistent with anti-TNF literature[1] – although this was not confirmed at multivariate analysis. Among the other predictors, higher baseline clinical disease activity and steroid use at the start of the second JAKi (irrespective of the formulation) were inversely associated to week 12 SFCR. These findings are similar to those of the GETAID cohort, particularly baseline steroids (OR 0.28, 95%CI 0.12-0.58, p<0.01).[9] Importantly, all steroid formulations were considered to maintain consistency with our steroid-free definitions. Sensitivity analyses, considering systemic steroids only, led to the same results at both univariate and multivariate regressions (data not shown).

Beyond week 12 SFCR, we also assessed objective markers of disease activity, including biochemical and endoscopic endpoints. While the UK study reported a higher PP proportion of biochemical remission (22/25 patients, 88%), changes of FC from baseline to the first timepoint appear similar, with FC reducing from 783 (279-1864) µg/g to 154 (51-490) µg/g in our cohort and from 650 (331-1500) µg/g to 62 (31-173) µg/g in the UK cohort.[10] On the other hand, the French study showed stable median values over time – from 721 (390–1800) to 748 (92–1767) µg/g. Importantly, the number of patients with available FC data was substantially lower in both studies –

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approximately one third of those included in our analysis – highlighting one of the key strengths of our study in terms of depth and completeness of biochemical data collection. In addition to biochemical markers, we reported mucosal outcomes, which were available in about one third of patients both at “Early evaluation” and “Late evaluation”. NRI rates of endoscopic remission were generally lower than those coming from the registration trials of UPA (9% vs 14-18% after induction and 11% vs 24-26% after one year)[16] and FILGO (9% vs 2.1-3.4% after induction in biologic-experienced patients, and 11% vs 13.4-15.6% after one year)[18], with higher proportions at PP analysis. However, our results are difficult to compare to the real word evidence due to the heterogeneity of data collection across studies: the J2J study did not report any endoscopic outcome,[9] while in the UK cohort endoscopy at week 8 was available in only 14 patients – interestingly, their endoscopic remission definition matched with our endoscopic improvement definition, with similar PP proportions (64% vs 58%).[10] This supports the strength of our work in providing endoscopic endpoints that are often missing in real-world studies. Unfortunately, only a minor proportion of patients had an endoscopic assessment, thus potentially underpowering our finding of a suboptimal endoscopic response. However, proportions of our main outcomes among patients who underwent the endoscopic assessment were in line with those of the whole cohort (data not shown).

We then explored effectiveness at subsequent timepoints, as well as treatment persistence, which may serve as a pragmatic indicator of long-term performance and tolerability of a second JAKi. Kaplan-Meier analyses showed a significant superior drug retention in patients with a “TOFA to UPA” sequence, and a non-significant trend towards a lower risk of treatment discontinuation in patients with secondary loss of response to the first JAKi. These findings mirror the trends seen in clinical effectiveness, as patients with primary failure to the first JAKi being also less likely to achieve SFCR at week 12. As the comparison of patients based on the reason for discontinuation of the first JAKi was balanced, the interpretation of the result based on the switching sequence requires caution, given the limited number of patients in some subgroups and the consequent reduced statistical power. Nevertheless, all analyses were performed with IPTW adjustment, in order to mitigate the risk of bias related to group imbalance. In line with persistence results, while we found a great percentage of patients with SFCR at week 12, this proportion gradually decreased at week 26 and 52. However, as eligibility for inclusion required only week 12 data, some patients had not yet reached week 26 or 52 by the time of data analysis, irrespective of treatment effectiveness or drug persistence status. Therefore, PP analyses were also conducted, restricting the population to those with adequate follow-up duration to reach each respective timepoint. While looking at PP analysis, SFCR data remained substantially unvaried across the 3 timepoints, and the same applied to steroid-free clinical response and biochemical remission. Differences between sequences (“TOFA to UPA” vs “TOFA to FILGO”) were statistically significant at week 26 but underpowered due to small numbers, thus limiting interpretability (SFCR achieved in 6/23 patients in the “TOFA to FILGO” vs

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89/165 in the “TOFA to UPA” group). Due to the intrinsic retrospective nature of this study and the timeline of JAKi approvals in UC, a proper head-to-head comparison between different treatment sequences could not be performed, as most included patients started with TOFA (available in Europe since 2018) rather than the JAK1-selective FILGO or UPA (available since 2021 and 2022, respectively). However, we found a higher risk of discontinuing the treatment in the “TOFA to FILGO” sequence compared to “TOFA to UPA”. On the other hand, the “FILGO to UPA” sequence showed a similar treatment persistence compared to “TOFA to UPA”, suggesting a better performance of UPA as a second-line JAKi compared to FILGO. Despite the undeniable interest of these findings, they should be interpreted with caution for several reasons. Most importantly, the limited number of patients in the “TOFA to FILGO” group, and the inability to stratify patients by induction or maintenance dosing. These limitations prevented us from drawing firm conclusions regarding a potentially superior benefit of switching to UPA over FILGO in UC patients previously exposed to TOFA. Moreover, it is not possible to provide a mechanistic explanation for this finding without being purely speculative. Only a few numerical differences in cytokine suppression among the various JAKi have been reported, primarily in the context of RA, and therefore not necessarily applicable to UC[19]. Further basic and translational studies are warranted to clarify this aspect.

Finally, we evaluated the safety profile of a second JAKi in a real-world setting. The overall incidence of AEs in our study was consistent with the established safety profiles of JAKi, as described in clinical trials in UC.[16, 18, 20] Importantly, no MACE or VTE were observed, with this finding likely reflecting the low prevalence of high-risk comorbidities at baseline, as well as the relatively young median age of our population. These factors may also indicate a more cautious patient selection process in a real-world setting. While increases in lipid levels and cytopenia have been reported in literature,[21, 22] laboratory monitoring over time revealed no significant alterations in lipid profiles or blood counts in our cohort. Notably, acne was one of the most frequently reported AEs, in line with emerging evidence linking JAK1-selective inhibition to acneiform eruptions [6.2% in a recent meta-analysis, with an OR of 4.79 (95% CI 3.61-6.37) for UPA compared to placebo], although the underlying mechanism is yet to be characterised.[23]

While our study provides relevant data, several limitations must be acknowledged. First, its retrospective design inherently carries a risk of missing data, especially at later follow-up timepoint. As only week 12 data were required for inclusion, not all patients had evaluable data at week 26 and 52. To mitigate potential bias, we reported both PP and NRI analyses to ensure transparency. Second, selection bias may have influenced our findings, particularly due to differential accessibility of JAKi across the study period. In this context, data on different sequences should be interpreted with particular caution, as we collected data coming from several European countries, where differences in regulatory approvals and national reimbursement policies might strongly influence treatment decisions. Third, for the same reasons, the sample sizes were unbalanced across treatment sequences, precluding definitive head-to-head comparisons – although the study was not

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designed specifically for this aim. Fourth, endoscopic assessments were unavailable for a substantial proportion of patients, limiting conclusions regarding mucosal healing. Fifth, detailed and standardized information on maintenance dosing was not consistently available. This precluded us from stratifying patients according to the initial treatment dose and evaluating potential dose-related differences in longer-term outcomes. Moreover, due to the retrospective nature of the study, we could not retrieve the clinical rationale behind the choice of a prolonged induction in some patients. Nonetheless, by selecting a time window for the primary outcome, we were able to consistently assess treatment effectiveness at the end of induction, even for patients undergoing extended induction regimens (i.e., 16 weeks for UPA), thus minimizing potential bias related to different induction durations. Finally, under-reporting or misclassification bias may have led to an underestimation of the proportion of patients using combined hormonal contraception or vaccinated against Herpes Zoster. Despite these limitations, our study is strengthened by its large sample size with multiple JAKi-experienced patients, and the breadth of clinical, biochemical, and endoscopic endpoints assessed across multiple timepoints, with a follow-up of more than one year for the majority of patients.

In conclusion, our study demonstrates that switching to a second JAKi remains a viable and generally safe therapeutic option also in JAKi-experienced patients, with encouraging rates of SFCR and treatment persistence. While clinical effectiveness did not significantly differ based on the reason for discontinuation of the first JAKi, primary failure was associated with reduced treatment persistence, suggesting a poor drug class responsiveness and serving as a negative predictor of sustained benefit from a second JAKi. Similarly, in this cohort, the “TOFA to UPA” sequence showed the best drug persistence during follow-up. However, due to the limited number of patients receiving FILGO as a second-line agent after TOFA, further data are required to draw definitive conclusions regarding optimal sequencing strategies. As the therapeutic landscape in inflammatory bowel disease is continuously expanding, with the introduction of different new molecules targeting distinct immune pathways, studies like ours are essential to inform on the optimal positioning of each available agent. Prospective studies and controlled trials comparing different sequencing strategies are warranted to validate our observations and support tailored, evidence-based guidance on the use of JAKi in daily clinical practice.

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Conflict of interest

Tommaso Innocenti reports speaker's fees from Ferring, and travel grants from Abbvie, Alfasigma, Celltrion, Eli Lilly, Ferring, Malesci, Pfizer. **Jurij Hanžel** reports speaker's fees from Abbvie, Eli Lilly, and Takeda, and consulting fees from Alimentiv Inc and Janssen. **Milan Lukaš** reports speaker´s fee from: Abbvie, Celltrion, Pfizer, Johnson et Johnson and Takeda. **Hannah Gordon** reports consulting fees from AbbVie, Galapagos, Takeda, J&J, and speaker fees from AbbVie, Ferring, IBDscope, J&J and Takeda. **Anneline Cremer** reports speaker and/or consultancy fees from Pfizer, Abbvie, Celltrion, Johnson & Johnson, Takeda, Eli Lilly and Alfasigma. **Tamás Molnár** has received speaker's honoraria from MSD, AbbVie, Egis, Goodwill Pharma, Takeda, Pfizer, Janssen, Sandoz, MundiPharma, Phytotec, Roche, Fresenius and Teva. **Mette Julsgaard:** has received research grants for other investigator-driven studies from Takeda, and the NOVO Nordisk Foundation (grant no. NNF23OC0081717), has been on the advisory board of Eli Lilly, Abbvie, PharmaCosmos and Tillotts Pharma, has received consultation fees from Eli Lilly, Ferring and Takeda, and has received speaker's fees from Tillotts Pharma, MSD, Ferring, and Takeda. **Sara Onali** served as Advisory board member and/or consultant for Abbvie, Galapagos, Johnson & Johnson, Takeda, Alfasigma, Pfizer. **Alessia Todeschini** served as a speaker and/or advisory board member for Abbvie, Janssen, Ferring, Celltrion, Lion Health. **Paola Balestrieri** served as advisory board member or speaker for Abbvie, Johnson & Johnson, Takeda, Eli Lilly. **Olga Maria Nardone** served as advisory board member for Nestle and J&J, and as a speaker for AbbVie, J&J, Ferring, Eli Lilly, Pfizer, Alfa Sigma, Noòs. **Nurulamin M. Noor** reports educational/travel grants Celltrion, J&J, Pharmacosmos and speaker fees from AbbVie, BMS, Celltrion, Dr Falk Pharma, Ferring, J&J, Lilly, Pfizer, Pharmacosmos, Takeda and Tillotts Pharma. **Flavio Caprioli** served as consultant to Abbvie, MSD, Takeda, Janssen, Roche, Celgene, Bristol-Meyers Squibb, Galapagos, Gilead, Pfizer, Mundipharma, Biogen, Ferring, Eli-Lilly, Nestlè, Lionhealth, AlfaSigma, Dr Falk, Celltrion, received lecture fees from Abbvie, Ferring, Takeda, Allergy Therapeutics, Janssen, Pfizer, Biogen, Sandoz, Tillotts Pharma, Vifor Pharma, AlfaSigma, Celltrion, and unrestricted research grants from Giuliani, Sofar, MSD, Takeda, Abbvie, Celltrion, Pfizer, Actial. **Franco Scaldaferri** reports funding from Janssen, Abbvie, Takeda, Lilly, Pfizer, Ferring, Sandoz, Celltrion, Sanofi, MSD, Alfasigma, Abivax. **Edoardo Vincenzo Savarino** has served as speaker and/or consultant for Abbvie, Aboca, Abivax, Agave, AGPharma, Alfasigma, Apoteca, Apogee, AstraZeneca, Biogen, Biosline, Bristol-Myers Squibb, CaDiGroup, Celltrion, Dr Falk, EG Stada Group, Eli Lilly, Fenix Pharma, Ferring, Galapagos, Giuliani, Grunenthal, Johnson&Johnson, JB Pharmaceuticals, Innovamedica/Adacyte, Lionhealth, Malesci, Mayoly Biohealth, Merck & Co, Montefarco, Nestlè, Novartis, Omega Pharma, Pfizer, PRO.MED.CS Praha a.s., Rafa, Reckitt Benckiser, Sandoz, Sanofi/Regeneron, SILA, Takeda, Tillots, Unifarco. **Charlotte R.H. Hedin** served as a speaker and/or advisory board member for AstraZeneca, Abbvie, Dr Falk Pharma and the Falk Foundation, Galapagos, Janssen, Pfizer, Ferring, Takeda, Tillotts Pharma, and received grant support from Tillotts and Takeda. **Alessandro Armuzzi** served as a speaker and/or Advisory board member for AbbVie, Abivax, AG Pharma, Alfa Sigma, Astra Zeneca, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celltrion, Eli-Lilly, Enthera, Ferring, Galapagos, Gilead, Giuliani, Janssen, Lionhealth, Merck, Nestlé, Pfizer, Protagonist Therapeutics, Roche, Sanofi, Samsung Bioepis, Sandoz, Takeda, Teva Pharmaceuticals, Tillots, and received grant support from Biogen, Merck, Pfizer, Takeda. **Andreas Blesl** has served as speaker and consultant for Abbvie, Aengus, Boston Scientific, Bristol-Myers Squibb, Dr. Falk Pharma, Genericon, Gilead, Janssen, Lilly, MSD, Olympus, Pfizer, PSI, Sandoz, Takeda, Vifor. **Annalisa Aratari** served as advisory board member for

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Takeda, Galapagos, Pfizer, Abbvie. **Tommaso Lorenzo Parigi** has received speaker fees from Abbvie, Takeda, Tillots, Fresenius Kabi, Ferring, and Janssen; Travel grants from Abbvie, Alfasigma, Janssen, CADI group, Pfizer, Takeda. **Lorenzo Bertani** has received lecture fees, consultancy fees, or advisory board honoraria from Abbvie, Aliveda, Bromatech, Celltrion, Eli-Lilly, Johnson&Johnson, Ferring, Italfarmaco, Noos, Pharmanutra, Pfizer and Takeda. **George Michalopoulos** has served as speaker and/or advisory board member for Abbvie, Amgen, Bristol Myers Squibb, Ferring, Genesis, Janssen, MSD, Pfizer, Takeda. **Alice De Bernardi** has served as a speaker/advisory board member for Johnson & Johnson and Malesci. **Gisela Piñero** has served as a speaker or has received education funding or advisory fees from Adacyte Therapeutics, AbbVie, Kern Pharma, Ferring, Alfasigma. **Konstantinos Karmiris** has served as speaker, consultant and/or advisory board member for Abbvie, Amgen, Bristol Myers Squibb, Ferring, Galenica, Genesis, Janssen, MSD, Pfizer, Roche, Takeda and Vianex. **Ana Gutierrez Casbas** has served as speaker, consultant and/or advisory board member for Abbvie, Ferring, FAES, J&J, MSD, Pfizer, Fresenius, Takeda, Celltrion, Kern Pharma, Adacyte, Falk, Lilly and Sandoz. **Carla Felice** served in advisory board for AbbVie and Johnson & Johnson. **Daniela Pugliese** served as Advisory board member and/or consultant for Abbvie, Galapagos, Johnson & Johnson, Takeda, Alfasigma, Pfizer. **Giammarco Mocci** reports funding from Janssen, Abbvie, Takeda, Lilly, Pfizer, Ferring, Sandoz, Celltrion, Alfasigma, Omegapharma, Abivax. **Lieven Pouillon** received advisory board fees from AbbVie, Alphasigma, Celltrion, Galápagos, Janssen-Cilag, Sandoz and Takeda; consultancy fees from Ipsos NV and Ismar Healthcare funded by Viatris; presentation fees from AbbVie, Alphasigma, Celltrion, Eli Lilly, Ferring, Galápagos and Pfizer; and personal fees (congress support) from AbbVie, Ferring, Galápagos, Janssen-Cilag, Norgine and Takeda. **Gerassimos J. Mantzaris** reports speaker fees or consultancy fees from Aenorasis, AbbVie, BMS, Celtrion, CUBE, Falk Pharma, Ferring, Genesis, Janssen, MSD, Pfizer, Sandoz, Takeda, και Vianex, and research grants from AbbVie, Ferring, MSD, and Vianex. **María José Casanova** has received education or research funding from Pfizer, Takeda, Janssen, MSD, Dr. Falk, Shire, Ferring, Galápagos, Lilly and Abbvie. **Ioannis E. Koutroubakis** reports funding from Aenorasis, AbbVie, BMS, Faran, Ferring, Genesis, Janssen, MSD, Pfizer, Sandoz, Takeda, Uni-Pharma, Viatris, και Vianex. **María José García** has received financial support for travelling and educational activities from Janssen, Pfizer, AbbVie, Takeda, Kern Pharma, Lilly, Faes Farma and Ferring. **Triana Lobaton** reports financial support for research from Abbvie, Ferring, Viatris, MSD, EG, Mundipharma, Biogen, Janssen, Pfizer, Takeda and Galapagos, speaker fees from MSD, Abbvie, Janssen, Amgen, Fresenius Kabi, Galapagos, Viatris, Ferring and Takeda, consultancy fees from Janssen, Galapagos, Amgen, Bristol Myers Squibb Fresenius Kabi, Takeda and Abbvie. **Gabriele Dragoni** reports speaker fees from Alfasigma, Ferring, Johnson & Johnson, LionHealth, Novartis, Pfizer, and Takeda, and has served in advisory board for AbbVie, Celltrion Healthcare, Eli Lilly, Johnson & Johnson and Pfizer. **The other authors** have no conflicts of interest to declare.

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Tables

Table 1. Baseline and demographic characteristics of patients

		Total (n = 243)	Upadacitinib (n = 212)	Filgotinib (n = 24)	Tofacitinib (n = 7)
Sex, n (%)	Female	105 (43%)	89 (42%)	13 (54%)	3 (43%)
	Male	138 (57%)	123 (58%)	11 (46%)	4 (57%)
Median age (IQR)		36 (25-49)	36 (25-49)	38 (25-50)	39 (37-61)
Median disease duration (IQR)		7 (3-12)	7 (3-12)	7 (3-12)	8 (6-9)
Disease extension, n (%)	E1	11 (5%)	7 (3%)	3 (13%)	1 (14%)
	E2	87 (36%)	78 (37%)	8 (33%)	1 (14%)
	E3	145 (60%)	127 (60%)	13 (54%)	5 (71%)
History of EIMs, n (%)		65 (27%)	54 (26%)	8 (33%)	3 (43%)
History of concomitant IMIDs, n (%)		14 (6%)	12 (6%)	2 (8%)	0 (0%)
Recombinant Zoster vaccination status, n (%)	No doses	143 (59%)	122 (58%)	15 (63%)	6 (86%)
	One dose	9 (4%)	7 (3%)	2 (8%)	0 (0%)
	Two doses	66 (27%)	63 (30%)	2 (8%)	1 (14%)
	Unknown	25 (10%)	20 (9%)	5 (21%)	0 (0%)
Combined hormonal contraception		7 (3%)	6 (3%)	1 (4%)	0 (0%)
Comorbidities, n (%)		36 (15%)	32 (15%)	2 (8%)	2 (29%)
	Diabetes mellitus	6 (2%)	5 (2%)	1 (4%)	0 (0%)
	Hypertension	20 (8%)	18 (9%)	1 (4%)	1 (14%)
	Dyslipidaemia	7 (3%)	7 (3%)	0 (0%)	0 (0%)
	Peripheral vascular disease	1 (1%)	1 (1%)	0 (0%)	0 (0%)
	Previous history of MACE or VTE	1 (1%)	0 (0%)	0 (0%)	1 (14%)
Experienced to biologics/small molecules (JAKi excluded), n (%)		237 (98%)	208 (98%)	22 (92%)	7 (100%)
	Previous 1 Anti-TNF	164 (67%)	145 (68%)	16 (67%)	3 (43%)
	Previous 2+ anti-TNF	63 (26%)	52 (25%)	7 (29%)	4 (57%)
	Previous Vedolizumab	158 (65%)	135 (64%)	18 (75%)	5 (71%)
	Previous Ustekinumab	104 (43%)	90 (43%)	12 (50%)	2 (29%)
	Previous anti-IL23p19	9 (4%)	9 (4%)	0 (0%)	0 (0%)
	Previous S1PR modulators	4 (2%)	3 (1%)	1 (4%)	0 (0%)
	Previous Trial	10 (4%)	9 (4%)	1 (4%)	0 (0%)
Reason for discontinuation of first JAKi, n (%)	Primary failure	97 (40%)	85 (40%)	11 (46%)	1 (14%)
	Secondary loss-of-response	120 (49%)	115 (54%)	4 (17%)	1 (14%)
	Adverse event	19 (8%)	8 (4%)	8 (33%)	3 (43%)
	Remission	7 (3%)	4 (2%)	1 (4%)	2 (29%)
Direct switch from the first JAKi, n (%)		58 (24%)	51 (24%)	5 (21%)	2 (29%)
MES (n = 196), n (%)	MES 2	76 (39%)	69 (38%)	6 (46%)	1 (50%)
	MES 3	120 (61%)	112 (62%)	7 (54%)	1 (50%)
Adapted Partial Mayo score (0-6) (IQR)		3 (2-5)	4 (2-5)	3 (2-5)	1 (0-3)
Systemic steroids at the start of second JAKi, n (%)		84 (35%)	76 (36%)	7 (29%)	1 (14%)
Topical steroids at the start of second JAKi, n (%)		18 (7%)	14 (7%)	2 (8%)	2 (29%)
Induction	Standard regimen	159 (65%)	136 (64%)	17 (71%)	6 (86%)
	Prolonged induction	84 (35%)	76 (36%)	7 (29%)	1 (14%)

EIMs=extra-intestinal manifestations; IL=interleukin; IQR=interquartile range; IMIDs=immune-mediated inflammatory disorders; IQR=interquartile range; JAKi=JAK-inhibitor; MACE=major adverse cardiac events (MACE); MES=Mayo endoscopic subscore; S1PR=sphingosine 1-phosphate receptor; TNF=tumour necrosis factor; VTE=venous thrombo-embolic events

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Table 2. Univariate and multivariate analysis for the primary outcome (steroid-free clinical remission at week 12)

Week 12 SFCR	Univariate				Multivariate			
Variable	**OR**	**95%CI**		**p-value**	**OR**	**95%CI**		**p-value**
Males	1.32	0.79	2.20	0.29				
Active smoking	1.80	0.67	4.80	0.24				
Disease extension: E1	reference							
Disease extension: E2	1.12	0.32	3.95	0.86				
Disease extension: E3	1.09	0.32	9.73	0.89				
EIMs/IMIDs history	0.87	0.50	1.50	0.61				
Comorbidities	1.17	0.57	2.38	0.67				
Bio-experienced	1.85	0.33	10.32	0.48				
First JAKi: FILGO-UPA vs TOFA	0.89	0.49	1.62	0.70				
Discontinuation of first JAKi: primary failure	reference				reference			
Discontinuation of first JAKi: secondary LOR	**1.92**	**1.11**	**3.30**	**0.02**	1.49	0.81	2.74	0.21
Discontinuation of first JAKi: AE	1.179	0.43	3.20	0.75	0.68	0.21	2.24	0.53
Discontinuation of first JAKi: remission	**9.73**	**1.13**	**84.06**	**0.04**	1.36	0.14	13.17	0.79
Second JAKi: TOFA	reference							
Second JAKi: FILGO	0.64	0.12	3.47	0.60				
Second JAKi: UPA	0.68	0.15	3.12	0.62				
Sequence: TOFA to UPA	reference							
Sequence: TOFA to FILGO	0.67	0.28	1.62	0.38				
Sequence: FILGO to UPA	1.32	0.66	2.62	0.43				
Sequence: other sequences	1.03	0.24	4.46	0.97				
Switch from different MOA vs. direct switch	0.89	0.49	1.60	0.69				
Age at second JAKi start	1.00	0.98	1.02	0.76				
Disease duration at second JAKi start	1.02	0.99	1.05	0.26				
Adapted PMS at start of second JAKi start	**0.62**	**0.52**	**0.74**	**< 0.01**	**0.68**	**0.55**	**0.83**	**< 0.01**
MES 3 vs MES 2	0.75	0.42	1.34	0.33				
Steroids at start*	**0.17**	**0.10**	**0.30**	**< 0.01**	**0.23**	**0.13**	**0.42**	**< 0.01**

CI=confidence interval; EIMs=extra-intestinal manifestations; FILGO=filgotinib; IMIDs=immune-mediated inflammatory disorders; JAKi=JAK-inhibitor; LOR=loss of response; MES=Mayo endoscopic subscore; MOA=mechanism of action; OR=odds ratio; SFCR=steroid-free clinical remission; TOFA=tofacitinib; UPA=upadacitinib

*Including both systemic and topical steroids.

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Figure legend

Figure 1. Switching directions. Each arrow represents the number of patients switching in each direction. Tofacitinib (TOFA) first, Upadacitinib (UPA) second: 165 patients; TOFA first, Filgotinib (FILGO) second: 23 patients; FILGO first, TOFA second: 4 patients; FILGO first, UPA second: 47 patients; UPA first, TOFA second: 3 patients; UPA first, FILGO second: 1 patient.

Figure 2. Main outcomes. Each panel shows non responder imputation and per protocol analysis across the three timepoints, for steroid-free clinical remission (A), steroid-free clinical response (B), biochemical remission (C), and endoscopic improvement and remission (D).

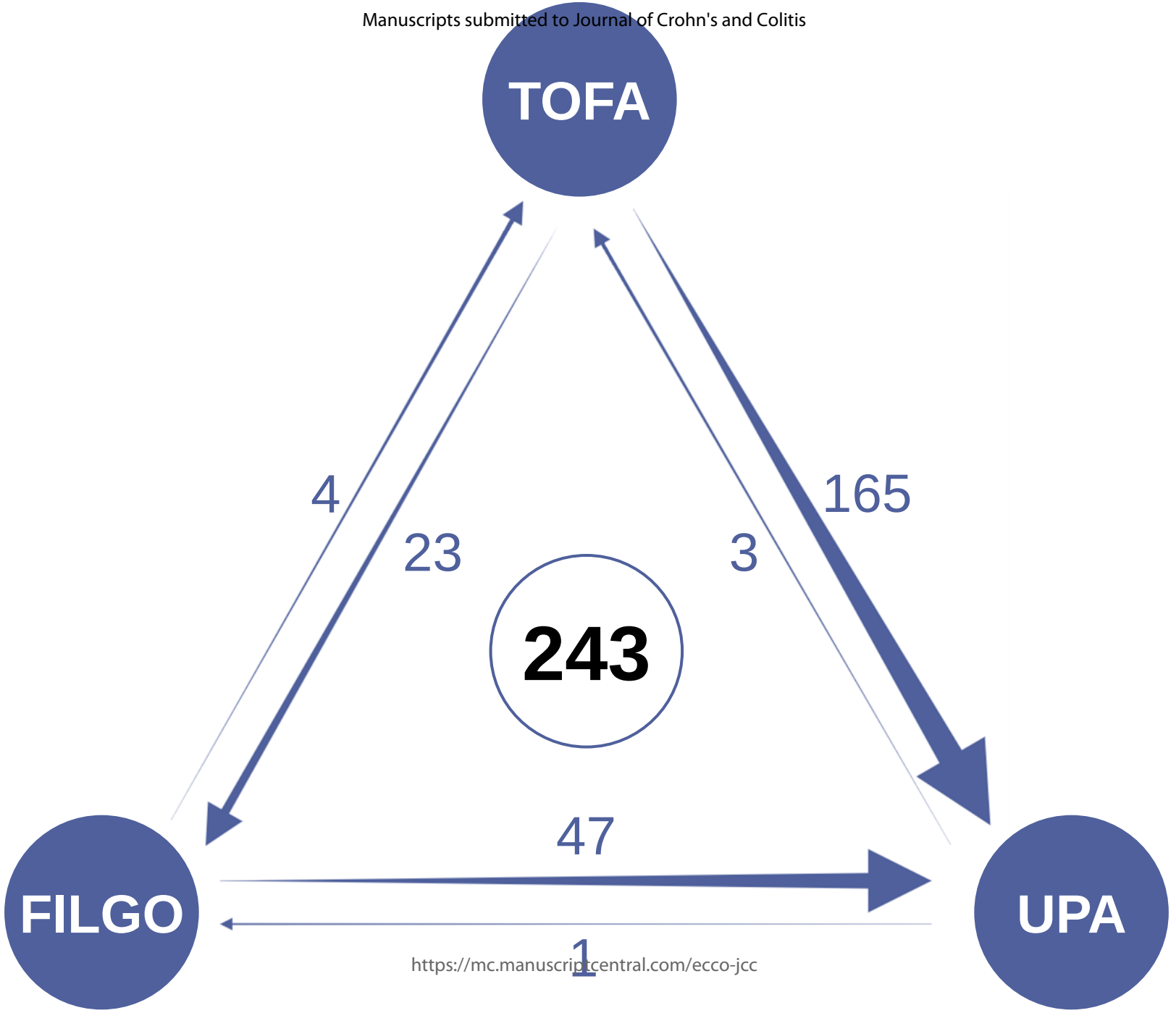
Figure 3. Comparison of different switching sequences and reasons for discontinuation of first JAK-inhibitor for the main outcomes at week 12. Steroid-free clinical remission, clinical remission, steroid-free clinical response, and clinical response are compared based on the switching sequences (A) and the reasons for discontinuation of the first JAK-inhibitor (B). In panel A, 8 patients with “Other sequences” were not included in the chi-squared test analysis. The same applies to patients who discontinued the first JAK-inhibitor due to remission in panel B.

Footnote: ns=non-significant (p>0.05); FILGO=filgotinib; JAKi=JAK-inhibitor; TOFA=tofacitinib; UPA=upadacitinib

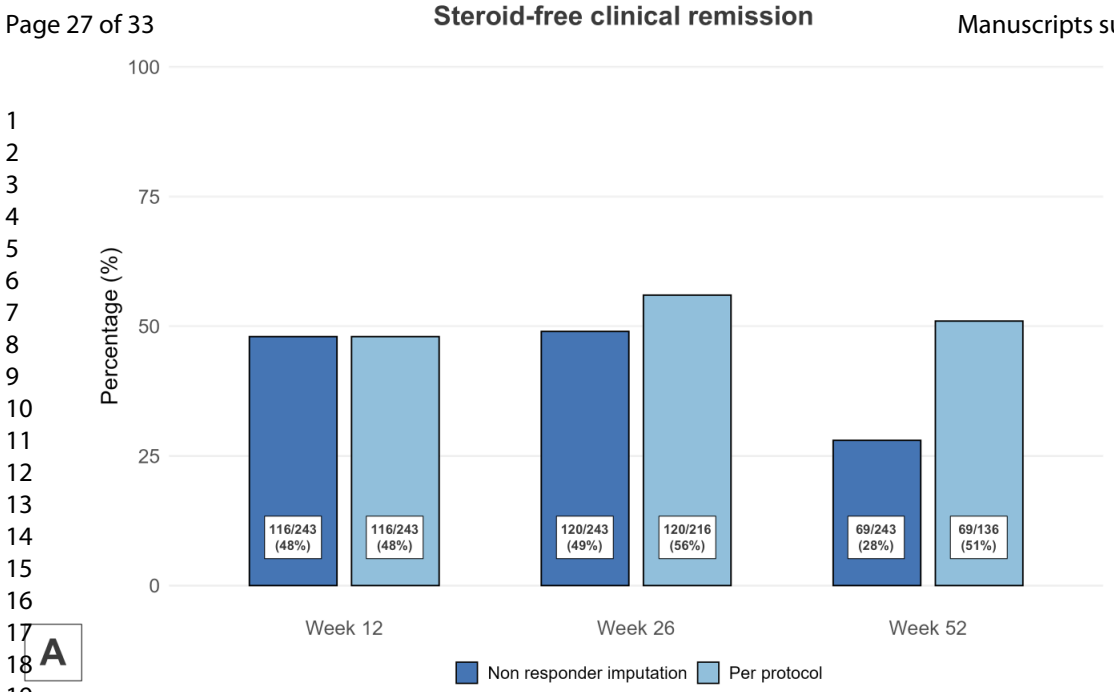
Figure 4. Kaplan–Meier analysis of treatment persistence with the second JAK inhibitor using inverse probability of treatment weighting (IPTW). Treatment persistence is shown with 95% confidence intervals for the overall study population (A), as well as stratified by treatment sequence (B) and by the reason for discontinuation of the first JAK inhibitor (C). Comparisons in Panels B and C were performed after IPTW adjustment to account for baseline differences between groups.

Footnote: FILGO=filgotinib; JAKi=JAK-inhibitor; TOFA=tofacitinib; UPA=upadacitinib

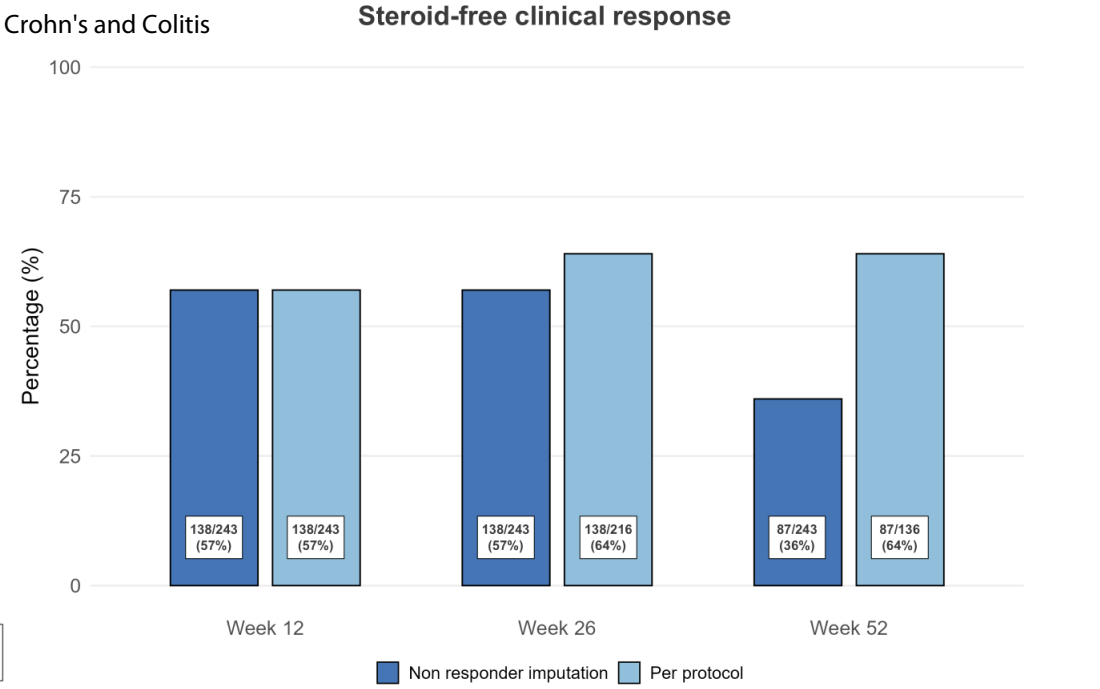
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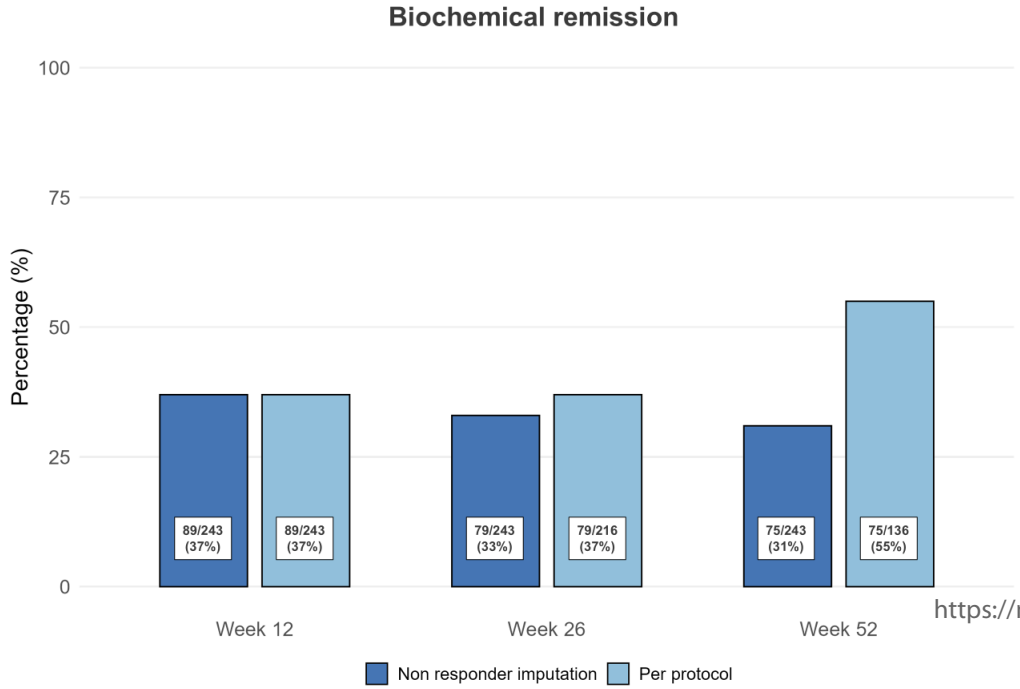
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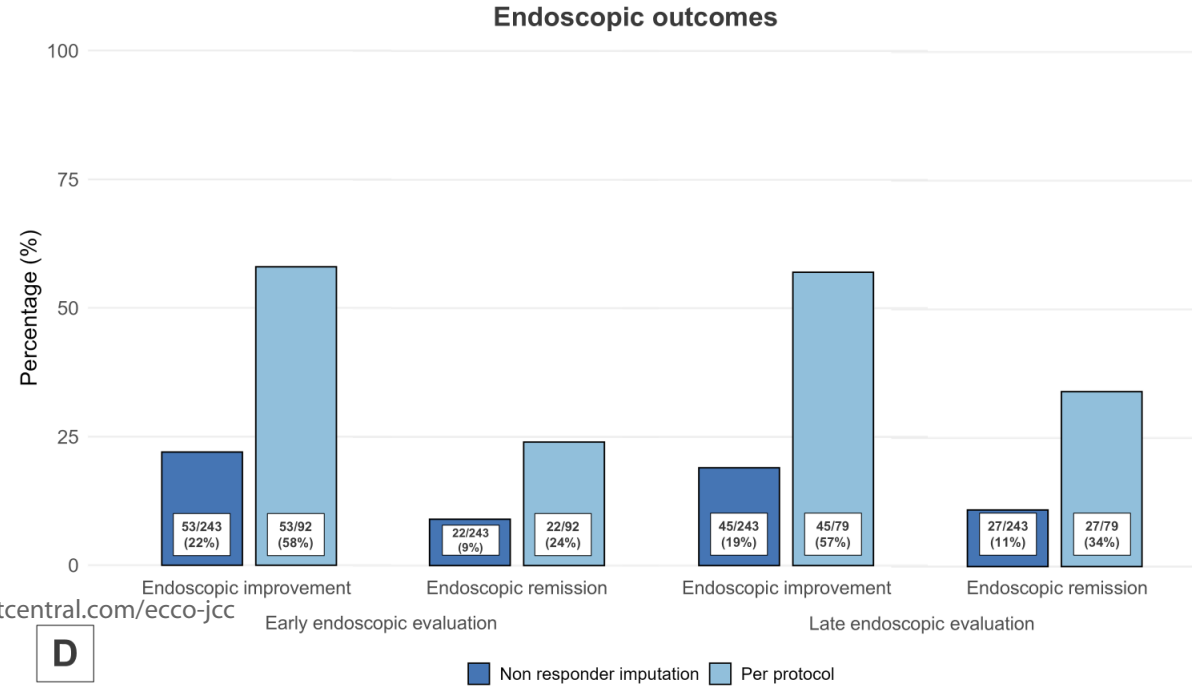
A



B



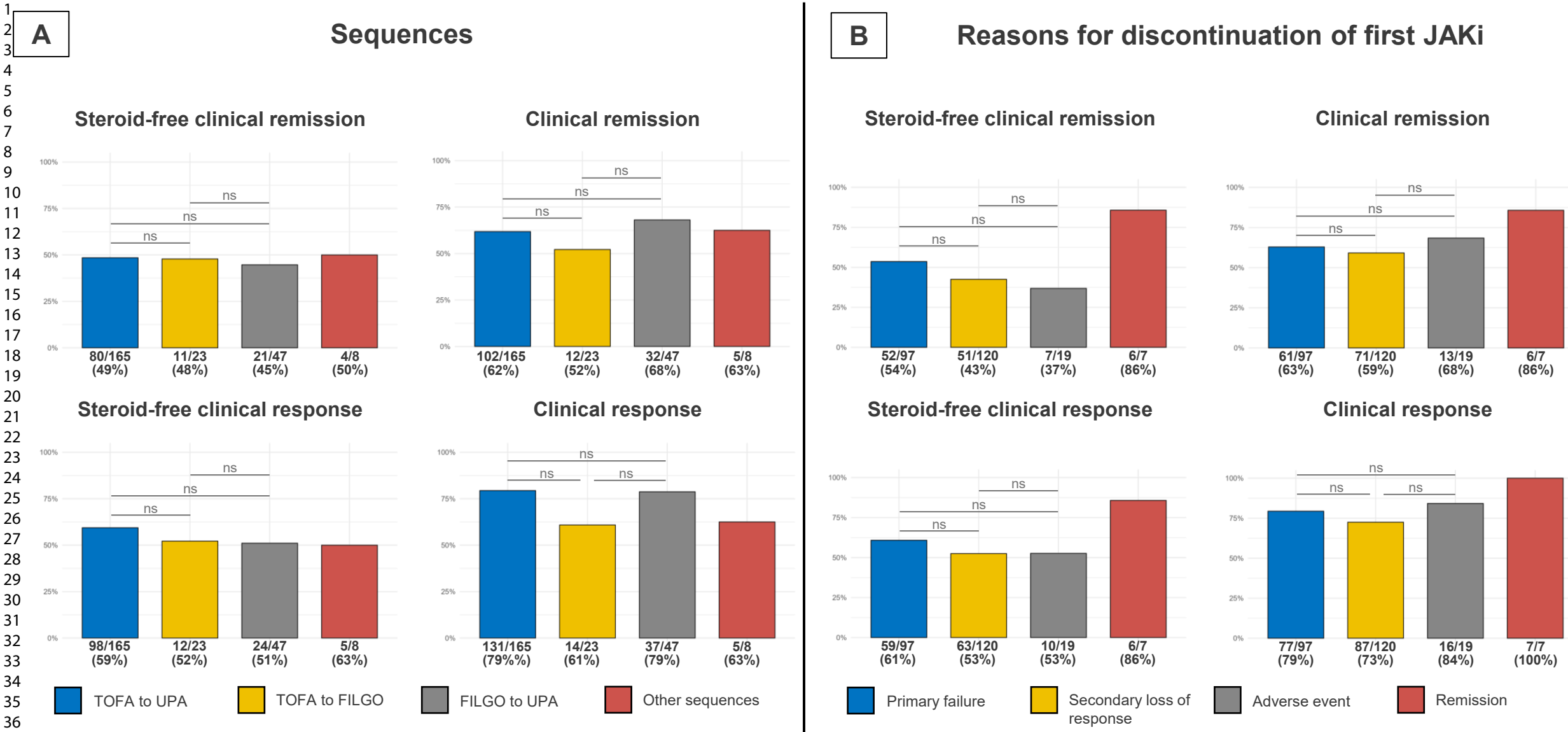
C



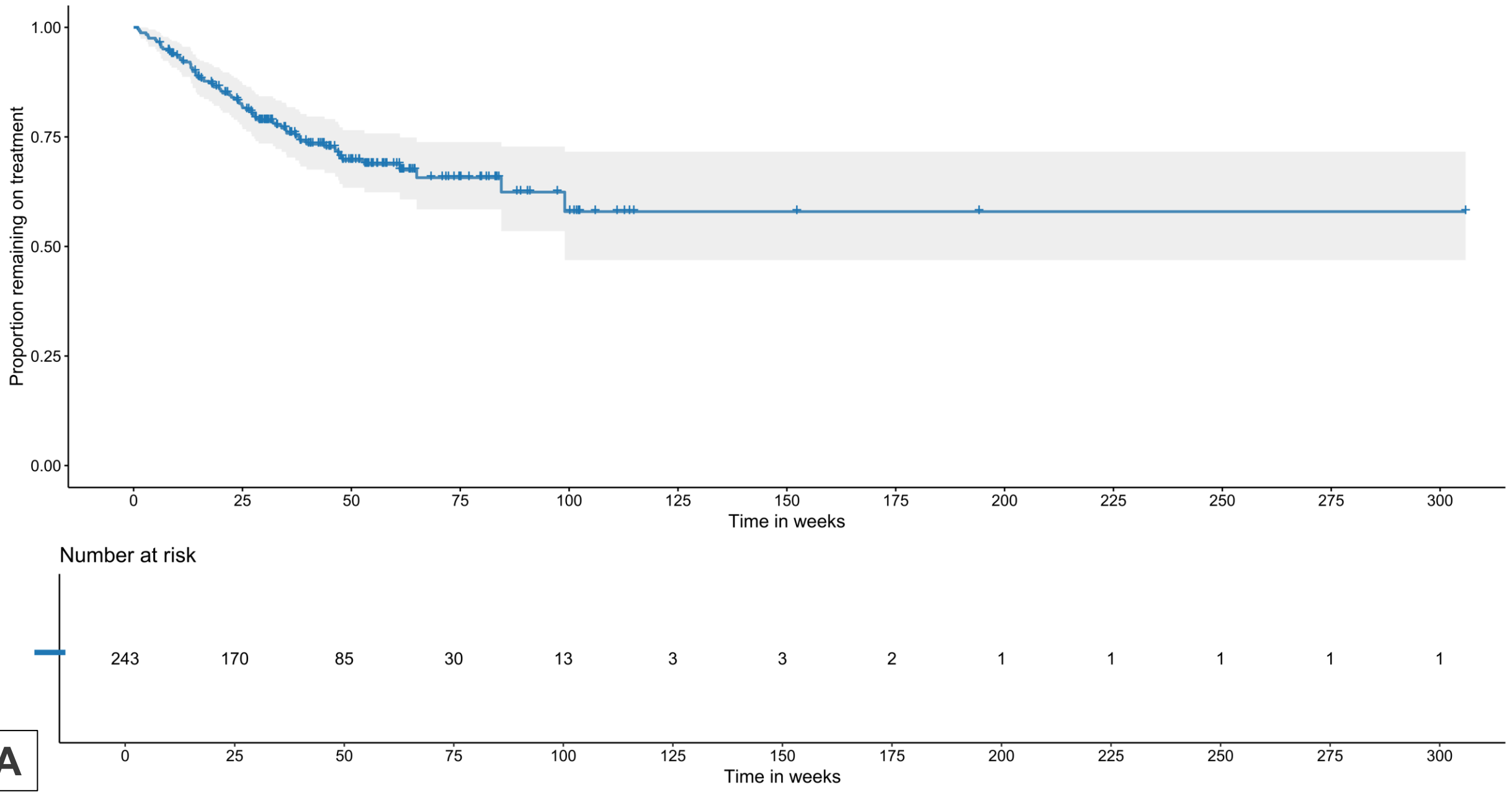
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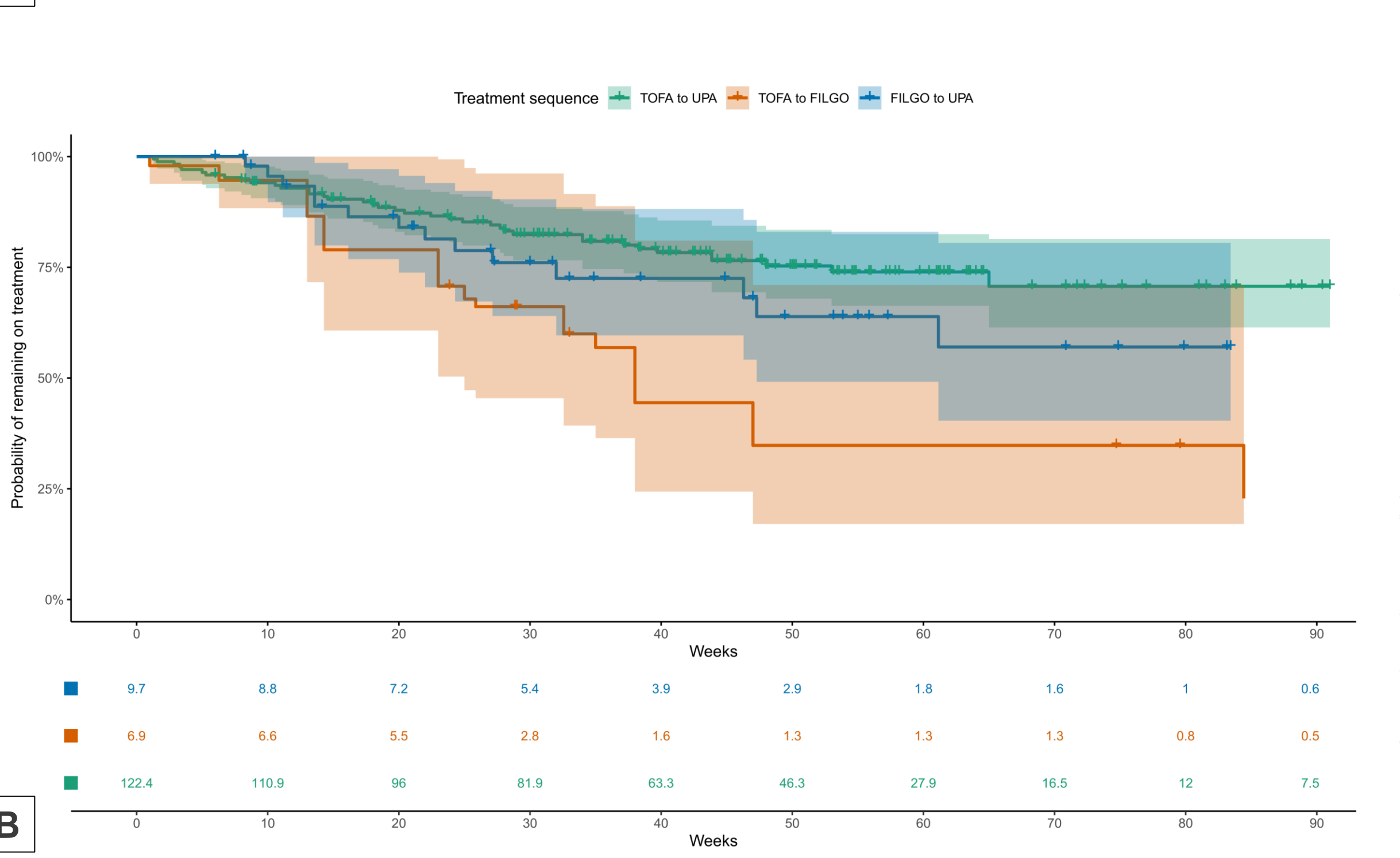
WEEK 12



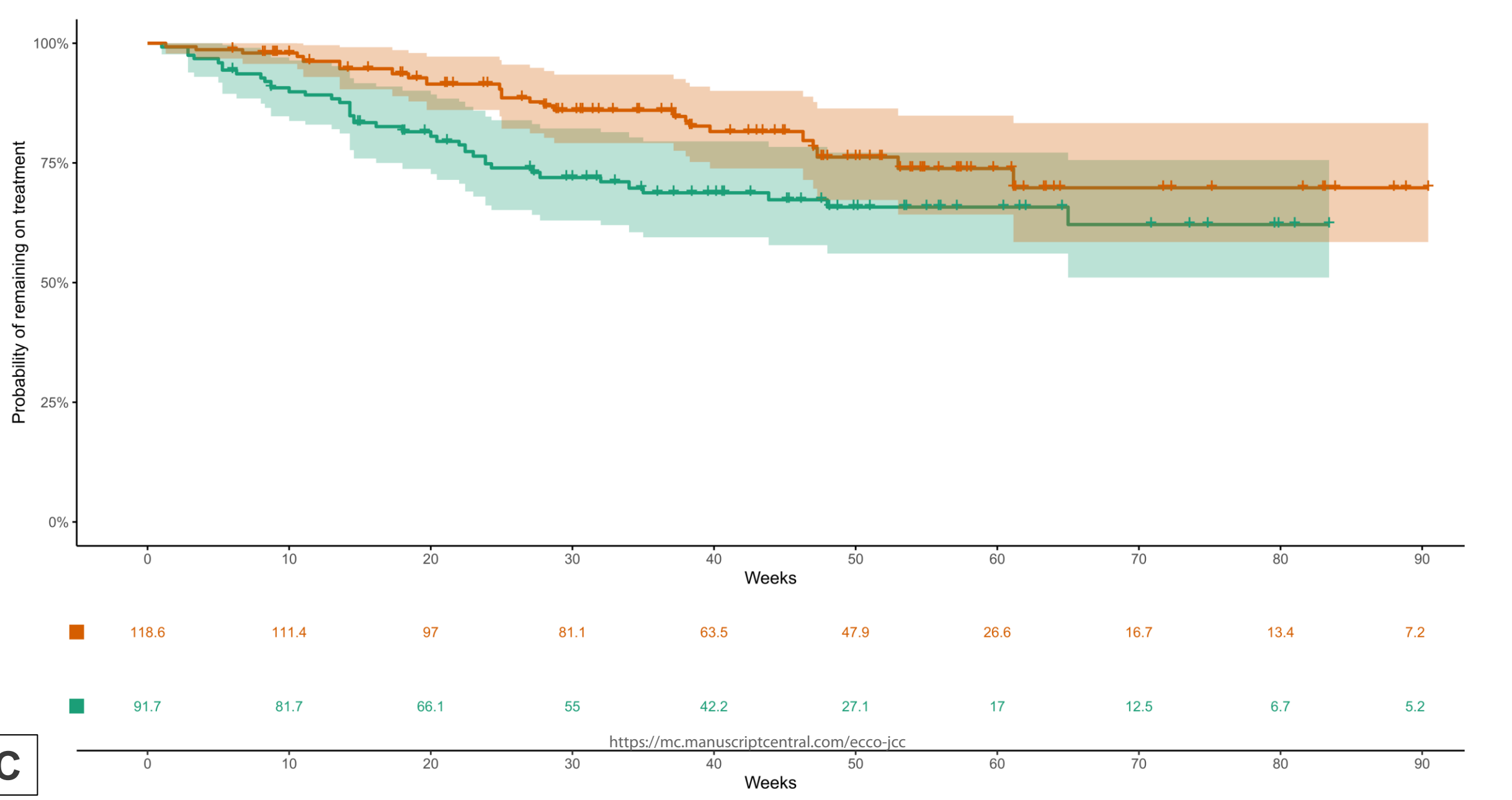
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A



B



C

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