

Ozanimod in Patients with Ulcerative Colitis - Prospective Real-World Evidence from the Dutch ICC Registry.

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Abstract

Background

Ozanimod, a sphingosine-1-phosphate receptor modulator, was approved for ulcerative colitis [UC] in 2021 but has not been widely adopted in routine clinical practice. As real-world evidence on ozanimod remains scarce, this study evaluated real-world ozanimod use in the Netherlands.

Methods

Data were retrieved from the Dutch ICC Registry, a multicenter, nationwide cohort prospectively collecting data of patients initiating advanced therapies for inflammatory bowel diseases [IBD]. Patients aged ≥ 16 years with UC or IBD-unclassified who initiated ozanimod in routine care were included. The primary outcome was clinical remission (Simple Clinical Colitis Activity Index ≤ 2) at week 24 among patients with clinically active disease at baseline. Effectiveness was assessed through week 104 using modified non-responder imputation (mNRI) and observed-case analyses. Treatment persistence and safety were assessed in all patients.

Results

Forty-two patients were followed for a median duration of 133.0 weeks (Q1, Q3: 80.2, 180.0). Among patients with clinically active disease at baseline, 28.6% (6/21, 95%CI [9.2, 47.9]) achieved clinical remission at week 24 using mNRI, compared with 54.5% (6/11, 95%CI [25.1, 84.0]) using observed-case analysis. The same rates were observed for clinical response. Twenty-seven patients discontinued ozanimod after a median treatment duration of 25.0 weeks (Q1, Q3: 7.5, 51.0). No serious adverse events were reported.

Conclusions

These findings suggest that ozanimod can induce and maintain remission in selected patients with UC, including those with difficult-to-treat IBD, and support its favorable safety profile.

Introduction

The therapeutic landscape for ulcerative colitis [UC] has expanded considerably over the past three decades. Ozanimod, an oral small-molecule that selectively modulates sphingosine-1-phosphate receptors, is among the more recently introduced treatments for UC. Although ozanimod was approved for the treatment of UC in 2021 [(1)], its use in routine clinical care remains limited, possibly owing to its positioning within treatment algorithms, the costs and logistics of the required baseline evaluation, and the lack of real-world evidence.

The efficacy and safety of ozanimod in patients with UC has been demonstrated in the phase II TOUCHSTONE trial and its open-label extension [(2, 3)] and in the phase III True North trial [(4)]. However, patients enrolled in clinical trials are selected according to strict eligibility criteria and only partly represent the heterogeneous patient population encountered in daily clinical practice [(5)]. Therefore, real-world evidence is imperative to confirm the effectiveness and safety of ozanimod in routine clinical practice. But due to the relatively modest prescription rates of ozanimod in clinical practice, real-world evidence remains very limited.

To date, only one real-world study has evaluated ozanimod in patients with UC. This prospective single-center US study included 45 patients and reported promising clinical response and remission rates, although long-term effectiveness appeared more modest [(6)]. Additional multicenter studies are needed to evaluate treatment persistence, effectiveness, and safety of ozanimod in routine clinical practice.

Using data from the Dutch Initiative on Crohn and Colitis [ICC] Registry, a prospective, multicenter, nationwide observational registry for inflammatory bowel diseases [IBD] therapies, we aimed to evaluate the effectiveness of ozanimod in routine clinical care. Additionally, we assessed its safety and investigated potential characteristics predicting effectiveness outcomes and treatment persistence.

Methods

Study design

Analyses were performed using data from the ICC Registry, a Dutch multicenter prospective cohort evaluating the effectiveness and safety of IBD therapies in routine clinical practice [(7, 8)]. Data were collected using a standardized electronic case report form within the ICC Registry, employing well-defined structured variables and a validated data model. The ICC Registry is currently running in 25 academic and non-academic hospitals across the Netherlands. Patients are prospectively followed up to 15 years after treatment initiation or until treatment discontinuation.

Participants

All patients included in the present study were 16 years or older at treatment initiation and had either UC or IBD-unclassified [IBD-U], confirmed with endoscopy and histology. Patients were included in the study if they started using ozanimod before 1st July 2026 as part of routine clinical care for IBD. Because of the general inclusion criteria of the ICC Registry, patients with IBD who used ozanimod exclusively for another indication (e.g. multiple sclerosis [MS]) or who initiated ozanimod as part of a clinical trial were not eligible for inclusion in this study. Patients with a history of colectomy and/or with an ostomy at inclusion were excluded from the analysis (**Supplementary Fig. 1**). Patients were considered as having difficult-to-treat disease if they failed at least two advanced therapies with different mechanisms of action [(9)].

Variables

At baseline, patient characteristics (age, sex, smoking status, comorbidities), disease-specific characteristics (age at diagnosis, Montreal classification), and prior exposure to advanced therapies (anti-tumor necrosis factor-alpha agents, Janus kinase inhibitors, interleukin-(12/23)-inhibitors, integrin receptor antagonist) were extracted from the ICC Registry.

Outcome parameters and definitions

The primary outcome was clinical remission at week 24 in patients with clinically active disease at treatment initiation. Clinical remission was defined as a Simple Clinical Colitis Activity Index [SCCAI] score ≤ 2 . The secondary outcomes included clinical response, corticosteroid-free clinical remission [CSFCR], biochemical remission and response, endoscopic remission, and treatment persistence. Clinical response was defined as a decrease in SCCAI of ≥ 3 from baseline. CSFCR was defined as SCCAI ≤ 2 without systemic corticosteroid use since the previous visit (e.g. CSFCR at week 24 required SCCAI ≤ 2 and no corticosteroid use between weeks 12 and 24). Biochemical remission was defined as fecal calprotectin [FC] ≤ 250 $\mu\text{g/g}$. As no consensus definition exists for biochemical response, a $\geq 25\%$ reduction in FC from baseline was used as a pragmatic threshold reflecting clinically meaningful improvement in the potential absence of biochemical remission. Endoscopic remission was defined as Mayo endoscopic subscore = 0. Treatment persistence was analyzed using Kaplan-Meier survival analysis, with treatment discontinuation and loss to follow-up considered as events. Patients with follow-up exceeding 104 weeks were censored at that time point.

Effectiveness outcomes were assessed at weeks 12, 24, 52, and 104. To account for the observational design, only measurements within predefined time windows were included (**Supplementary Fig. 2**). Missing data were not imputed. Effectiveness analyses were performed in all patients and in patients with active disease at treatment initiation.

Safety was assessed using patient-reported adverse events and hospitalization records. The treating physician classified adverse events as possibly or probably treatment-related. Treatment-related adverse events resulting in withdrawal of ozanimod were recorded as adverse events leading to treatment discontinuation. Infections were categorized as mild if no antibiotic or antiviral treatment was required, moderate if oral antibiotic or antiviral therapy was required, and severe if they resulted in hospitalization or required intravenous antibiotic or antiviral therapy. Reasons for treatment discontinuation were systematically documented by the treating physician.

Exploratory analysis

In patients with at least 52 weeks of follow-up, baseline characteristics were compared between those who discontinued ozanimod before week 52 and those remaining on treatment at week 52.

Statistical analysis

Continuous variables are presented as median with first and third quartiles (Q1, Q3), irrespective of distribution. Categorical variables are presented as counts and percentages. Treatment persistence was estimated using the Kaplan-Meier estimator. Remission rates were calculated using modified non-responder imputation [mNRI] and observed-case analyses. In the mNRI approach, discontinuations and missing data were classified as non-response. In the observed-case analysis, only patients with available data at each time point were included.

Patients discontinuing ozanimod due to non-response, adverse events, or personal preference without achieving remission were classified as non-responders at subsequent time points and defined as discontinuers. Discontinuations due to pregnancy were censored. Patients with insufficient follow-up for a given time point were censored for that visit. Missing data in patients remaining on treatment were not imputed.

Given the absence of a universally accepted FC threshold for biochemical remission, an alternative and stricter cut-off of ≤ 50 $\mu\text{g/g}$ was evaluated in a sensitivity analysis. Paired binary outcomes were compared using McNemar's exact test.

Analyses were performed using R version 4.5.0. A two-sided p-value ≤ 0.05 was considered statistically significant unless otherwise specified.

Ethics

The ICC Registry was approved by the Committee on Research Involving Human Subjects at the Radboudumc (4076). All participants provided written informed consent.

Results

Baseline characteristics

Forty-two adult patients (female N = 25; 59.5%) with UC (N = 39, 92.9%) or IBD-U (N = 3, 7.1%) and initiating treatment with ozanimod were included (**Supplementary Fig. 1**). Median age at treatment initiation was 49 years (Q1, Q3: 26.0, 65.0) and median disease duration was 5.7 years (Q1, Q3: 3.4, 13.1). Most patients (N = 35, 83.3%) met the definition for difficult-to-treat IBD. Thirteen patients (30.9%) underwent endoscopic examination within 90 days before treatment initiation; out of which seven patients (53.8%) had a Mayo endoscopic subscore of 3. Fifteen patients (35.7%) presented at least one comorbidity; among them, six patients were previously diagnosed with a malignant neoplasm and one patient had MS (Table 1). Median follow-up duration was 133.0 weeks (Q1, Q3: 80.2, 180.0).

Table 1
Baseline characteristics in the whole cohort and based on disease phenotype.

Characteristic	Overall N = 42	UC N = 39	IBD-U N = 3	p
Sex				0.556
Male	17 (40.5%)	15 (38.5%)	2 (66.7%)	
Female	25 (59.5%)	24 (61.5%)	1 (33.3%)	
Age at diagnosis (years)	36.0 (21.0, 48.0) 15.0, 75.0	31.0 (20.0, 48.0) 15.0, 75.0	48.0 (34.0, 75.0) 34.0, 75.0	0.156
Age at inclusion (years)	49.0 (26.0, 65.0) 20.0, 79.0	49.0 (26.0, 65.0) 20.0, 79.0	53.0 (38.0, 78.0) 38.0, 78.0	0.328
Disease location at inclusion [†]				0.162
E1 - proctitis	3 (8.3%)	2 (5.9%)	1 (50.0%)	
E2 - left-sided	16 (44.4%)	16 (47.1%)	0 (0.0%)	
E3 - pancolitis	17 (47.2%)	16 (47.1%)	1 (50.0%)	
Unknown	6	5	1	
Disease duration at inclusion (years)	5.7 (3.4, 13.1) 0.4, 44.2	6.7 (3.2, 13.4) 0.4, 44.2	4.6 (3.9, 5.0) 3.9, 5.0	0.371
Total advanced therapies				0.757
0	3 (7.1%)	3 (7.7%)	0 (0.0%)	
1	4 (9.5%)	3 (7.7%)	1 (33.3%)	
2	5 (11.9%)	5 (12.8%)	0 (0.0%)	
3	13 (31.0%)	12 (30.8%)	1 (33.3%)	
4	10 (23.8%)	9 (23.1%)	1 (33.3%)	
5	6 (14.3%)	6 (15.4%)	0 (0.0%)	
7	1 (2.4%)	1 (2.6%)	0 (0.0%)	
Anti-TNF agent	38 (90.5%)	35 (89.7%)	3 (100.0%)	> 0.999
Interleukin(12/23) inhibitor	27 (64.3%)	25 (64.1%)	2 (66.7%)	> 0.999
JAK inhibitor	27 (64.3%)	26 (66.7%)	1 (33.3%)	0.287

Characteristic	Overall N = 42	UC N = 39	IBD-U N = 3	p
Vedolizumab	25 (59.5%)	23 (59.0%)	2 (66.7%)	> 0.999
Difficult-to-treat IBD [‡]	35 (83.3%)	33 (84.6%)	2 (66.7%)	0.430
Smoking behavior				0.590
Current smoker	1 (2.8%)	1 (3.0%)	0 (0.0%)	
Ex-smoker	8 (22.2%)	7 (21.2%)	1 (33.3%)	
Never smoked	27 (75.0%)	25 (75.8%)	2 (66.7%)	
Unknown	6	6	0	
History of cancer	6 (14.3%)	4 (10.3%)	2 (66.7%)	0.049
MS diagnosis	1 (2.4%)	1 (2.6%)	0 (0.0%)	> 0.999
SCCAI	5.0 (2.0, 7.0) 0.0, 10.0	4.5 (2.0, 7.0) 0.0, 10.0	5.0 (4.0, 10.0) 4.0, 10.0	0.340
SCCAI ≤ 2	12 (30.8%)	12 (33.3%)	0 (0.0%)	0.539
Unknown	3	3	0	
FC (µg/g)	1,046.0 (244.5, 2,452.5) 16.0, 5,479.0	1,052.0 (241.0, 2,828.0) 16.0, 5,479.0	677.0 (677.0, 677.0) 677.0, 677.0	0.800
FC ≤ 250 µg/g	6 (30.0%)	6 (31.6%)	0 (0.0%)	> 0.999
Unknown	22	20	2	
Endoscopic activity				> 0.999
Mayo 1	2 (15.4%)	2 (15.4%)	0 (NA%)	
Mayo 2	3 (23.1%)	3 (23.1%)	0 (NA%)	
Mayo 3	7 (53.8%)	7 (53.8%)	0 (NA%)	
Unknown but active disease	1 (7.7%)	1 (7.7%)	0 (NA%)	
Unknown	29	26	3	
Concomitant medication				
Yes	26 (61.9%)	25 (64.1%)	1 (33.3%)	0.547
Systemic corticosteroids	16 (38.1%)	16 (41.0%)	0 (0.0%)	0.275

Characteristic	Overall N = 42	UC N = 39	IBD-U N = 3	p
Aminosalicylate	10 (23.8%)	9 (23.1%)	1 (33.3%)	> 0.999
† according to Montreal classification ‡ difficult-to-treat IBD defined as the previous exposure to at least two advanced therapies with different mechanisms of action Notes - results presented as absolute value (percentage) or median (Q1, Q3) with minimum, maximum; P-value computed using Fisher's exact test, Wilcoxon rank sum test or Wilcoxon rank sum exact test, wherever applicable Abbreviations - FC, fecal calprotectin; MS, multiple sclerosis; SCCAI, Simple Clinical Colitis Activity Index				

Disease activity at baseline

Signs of disease activity were observed in 32/33 patients (97.0%), either clinically (27/39, 69.2%), biochemically (14/20, 70.0%) or endoscopically (13/13, 100%), at treatment initiation. Disease activity data at baseline were unknown for 9/42 patients (21.4%) (**Supplementary Table 1**).

Twelve patients were in clinical remission at treatment initiation. Of these, three (25.0%) had endoscopic activity at treatment initiation, and two other patients (16.7%) had elevated FC levels. Six patients (50.0%) in clinical remission at treatment initiation used systemic corticosteroids.

Clinical remission and response rates in patients with clinically active disease at baseline

In patients with SCCAI > 2 at treatment initiation (N = 27), the median SCCAI was 6.0 (Q1, Q3: 4.5, 8.5). Seven patients (25.9%) with clinically active disease at baseline discontinued ozanimod before week 12, and SCCAI was measured in 15 patients. Of these, 8 patients (53.3%) were in clinical remission at week 12. Using the mNRI approach, the percentage of patients in clinical remission decreased to 36.4% (8/22, 95%CI [16.3, 56.5]). At week 24, SCCAI was measured in 11 patients, and 10 patients were classified as discontinuers. The percentage of patients in clinical remission at week 24 was 28.6% (6/21, 95%CI [9.2, 47.9]) using the mNRI approach, and 54.5% (6/11, 95%CI [25.1, 84.0]) using the observed-case approach. At all timepoints, clinical remission rates were numerically higher in the whole cohort compared to the subgroup of patients with SCCAI > 2 at baseline (Fig. 1, **Supplementary Table 2–3**).

At week 12, clinical response rate among patients with a baseline SCCAI > 2 was 60.0% (9/15, 95%CI [35.2, 84.8]) using the observed-case approach, and 40.9% (9/22, [20.4, 61.5]) using the mNRI approach. At week 24, clinical response rate was 54.5% (6/11, 95%CI [25.1, 84.0]) using the observed-case approach, and 28.6% (6/21, [9.2, 47.9]) using the mNRI approach. At all timepoints, clinical response rates were numerically higher in the subgroup of patients with SCCAI > 2 at baseline compared to the whole cohort (Fig. 2, **Supplementary Table 4–5**).

Patients using systemic corticosteroids at baseline

At baseline, 16/42 patients (38.1%) were using systemic corticosteroids. All these patients met the definition of difficult-to-treat IBD. Moreover, patients using systemic corticosteroids at baseline showed a lower median age at diagnosis (21.5 years; Q1, Q3: 19.0, 43.5) and at treatment initiation (29.0 years; Q1, Q3: 23.5, 56.5) than those not using systemic corticosteroids at baseline ($p = 0.018$ and $p = 0.043$, respectively) (**Supplementary Table 6**). At week 12, 2/11 patients (18.2%) were in CSFCR, including one patient also in endoscopic remission. Five patients (45.4%) were in clinical remission but were still using systemic corticosteroids. Two patients (18.2%) were in biochemical remission without the use of corticosteroids. At week 52, 3/4 patients (75.0%) were in CSFCR, the fourth patient being in clinical remission without using systemic corticosteroids on the assessment day (**Supplementary Table 7**).

Biochemical remission and response rates in patients with biochemically active disease at baseline

In patients with FC > 250 µg/g at treatment initiation (N = 14), the median FC concentration was 1535 µg/g (Q1, Q3: 1043, 3484; minimum, maximum: 592, 5479). Three patients (21.4%) with biochemically active disease at baseline discontinued ozanimod before week 12, and FC was measured in 8 patients. Of these, 4 patients (50.0%) were in clinical remission at week 12. Using the mNRI approach, the percentage of patients in biochemical remission decreased to 36.4% (4/11, 95%CI [7.9, 64.8]). At week 24, FC was measured in 5 patients, and 5 patients were classified as discontinuers. The percentage of patients in biochemical remission at week 52 was 11.1% (1/9, 95%CI [-9.4, 31.6]) using the mNRI approach, and 100% (1/1, 95%CI [100.0, 100.0]) using the observed-case approach. At week 24 onwards and following the mNRI approach, biochemical remission rates were numerically higher in the whole cohort compared to the subgroup of patients with FC > 250 µg/g at baseline (Fig. 3, **Supplementary Table 8–9**).

At week 12, biochemical response rate among patients with a baseline FC > 250 µg/g was 87.5% (7/8, 95%CI [64.6, 110.4]) using the observed-case approach, and 63.6% (7/11, [35.2, 92.1]) using the mNRI approach. At all timepoints, biochemical response rates were numerically higher in the subgroup of patients with FC > 250 µg/g at baseline compared to the whole cohort (Fig. 4, **Supplementary Table 10–11**).

When lowering the biochemical remission threshold to FC ≤ 50 µg/g, the percentage of patients in biochemical remission was numerically lower than in the primary analysis, except at week 104. The point percentage difference varied between 14.3% (week 12) and 25.0% (week 24) (**Supplementary Table 12**).

Patients with endoscopic disease activity at baseline

All patients (N = 13) with endoscopic data at baseline showed active disease (Mayo endoscopic subscore > 0). Of those, 9 patients (69.2%) discontinued ozanimod after a median treatment duration of 29.0 weeks (Q1, Q3: 25.0, 57.0).

At week 12, 6/7 patients (85.7%) were in clinical remission, 3/7 patients (42.9%) were in biochemical remission, and 1/2 patients (50.0%) were in endoscopic remission, although the second patient was in clinical remission. At week 24, 3/5 patients (60.0%) were in biochemical remission, although the other two patients were in biochemical remission (**Supplementary Table 13**).

Treatment persistence

Kaplan-Meier analysis was performed to estimate treatment persistence in the whole cohort. Over the observation period, 27 patients (64.3%) discontinued treatment, yielding a median time to discontinuation of 50 weeks (95%CI [26, 125]; the restricted mean survival time was 82.5 weeks (standard error: 13.5)). Estimated persistence rates were 68.8% (95%CI [56.1, 84.4]) at week 24, 46.8% (95%CI [33.4, 65.8]) at week 52, and 34.4% (95%CI [21.8, 54.2]) at week 104, with 28, 16, and 9 patients remaining at risk at these respective timepoints (Fig. 5).

Twenty-seven patients (64.3%) discontinued ozanimod after a median treatment duration of 25.0 weeks (Q1, Q3: 7.5, 51.0). The shortest treatment duration was 2 weeks; this patient was prescribed ozanimod as last-resort treatment before undergoing a planned colectomy. The longest treatment duration before discontinuation was 125 weeks of treatment, following loss-of-response.

The three most common reasons for discontinuation were loss-of-response (8/27, 29.6%), primary non-response (6/27, 22.2%), and adverse events (4/27, 14.1%) including headache, musculoskeletal complaints, and lymphopenia. Four patients (14.8%) who were prescribed ozanimod as a last-resort treatment to avoid surgery underwent colectomy after all. Two patients (7.4%) decided to stop using ozanimod: one patient suffered from skin complaints, while the underlying reason for discontinuation was unknown for the other patient. In two other patients (7.4%), diagnosis was changed to Crohn's disease following inflammation extending to the ileum, leading to treatment discontinuation.

Exploratory analysis

Thirty-six patients had a follow-up of at least 52 weeks: 20/36 patients (55.6%) discontinued ozanimod before week 52, after a median of 13.0 weeks (Q1, Q3: 6.0, 25.2). Exploratory analyses revealed that patients who discontinued ozanimod before week 52 had a lower median age at treatment initiation (29.0 years; Q1, Q3: 25.0, 50.0) than their counterparts (62.5 years; Q1, Q3: 43.5, 67.5) ($p = 0.020$). Seven patients (43.7%) who were using ozanimod at week 52 discontinued their treatment afterwards, after a median treatment duration of 58 weeks (Q1, Q3: 55.5, 98; minimum, maximum: 52.5, 125) (**Supplementary Table 14**).

Safety outcomes

Patients used ozanimod for a total of 45.6 person-years. Fourteen infections were reported, including five mild infections (11.0 per 100-person years [100PY]) and eight moderate infections (17.5/100PY). The severity of one infection was unknown. Five cases of respiratory infections (11.0/100PY) were reported (Fig. 6a).

Eighteen non-infectious adverse events deemed at least possibly related to the use of ozanimod were reported: 13 adverse events (28.5/100PY) were categorized as possibly related and five adverse events (11.0/100PY) as probably related to ozanimod. Most reported non-infectious adverse events were skin complaints (6/18, 33.3%, 13.2/100 PY), headache and dizziness (4/18, 22.2%, 8.8/100PY), and musculoskeletal complaints (2/18, 11.1%, 4.4/100PY) (Fig. 6b). No treatment-related hospitalizations or deaths were reported.

Discussion

This is the first nationwide, multicenter, prospective real-world cohort study of patients with UC and IBD-U initiating ozanimod. Among patients with clinically active disease at baseline, 28.6% achieved clinical remission at week 24 using mNRI, compared with 54.5% using observed-case analysis. Moreover, biochemical response was also observed, often leading to biochemical remission. Notably, this cohort predominantly represented a difficult-to-treat population, with most patients previously exposed to three or more advanced therapies. These findings support the effectiveness of ozanimod in inducing and maintaining clinical remission, even among patients with multiple previous advanced therapy failures. In addition, no new safety signals were identified, and the findings are consistent with the relatively favorable safety profile previously reported in patients with UC or with MS.

The efficacy of ozanimod for patients with UC has been demonstrated in the phase III True North Trial, in which 645 patients were randomized to receive either a placebo or a daily dose of 0.92 mg of ozanimod during a 10-week induction phase [(4)]. At week 10, the percentage of patients in clinical remission, based on complete Mayo score, was significantly higher in the ozanimod group than in the placebo group (18.4% versus 6.0%, $p < 0.001$). During the maintenance phase, in which patients with clinical response at week 10 ($N = 457$) were further randomized, results showed again a significantly higher percentage of clinical remission in the ozanimod group than in the placebo group (37.0% versus 18.5%, $p < 0.001$). When focusing on the results of the observed-cases analysis, clinical remission rates at week 52 were numerically lower in the True North Trial than in the current study (54.1% versus 66.7%). However, the differences in approaches to assess clinical remission, the clinical setting and the sample size do not allow direct comparison.

Although ozanimod has been approved by the Food and Drug Administration and European Medicines Agency for the treatment of moderate to severe UC since 2021, its use in daily practice is relatively limited. While the reasons for this observation have not been studied here, its positioning within treatment algorithms, the costs and logistics of the required baseline evaluation, and the lack of real-world evidence may play a role. To our knowledge, only one monocenter study assessed the effectiveness ($N = 45$) and safety ($N = 48$) of ozanimod in patients with UC [(6)]. In this study, clinical remission rate at week 10 was 58% in patients with UC. In patients with SCCAI > 2 at baseline, clinical remission rates at week 24 and week 52 were 37.0% (10/27) and 31.8% (7/22), respectively. In our study, similar rates were observed with the mNRI approach at week 24 (6/21, 28.6%), but were lower at week

52 (2/17, 11.8%). This discrepancy could be attributed to the higher percentage of advanced therapy-naïve patients in the American monocenter study (8/45, 17.8%).

Our results suggest that ozanimod has a favorable safety profile for patients with UC. While no infections were observed in the earlier real-world UC study with ozanimod by Cohen *et al.* [(6)], we reported in total 14 non-serious infections, which is more in line with data from clinical trials. Nevertheless, treatment-related hospitalizations or deaths were not reported in either the study by Cohen *et al.* or in the present study. Furthermore, a recent integrated analysis of the long-term safety of ozanimod, with up to 10 years of follow-up in patients with UC and relapsing MS, further supported its favorable safety profile [(10)]. Among patients with UC enrolled in clinical trials of ozanimod (N = 1,158), the incidence rate of herpes zoster was reported as 1.0/100PY. In the present study, the corresponding incidence rate was 2.2/100PY. Although this difference may appear notable, it should be interpreted with caution given the substantially smaller sample size of the current cohort, which may have resulted in less precise incidence estimates.

The main limitation of our study is its sample size. On the other hand, the number of patients included in this study reflects the relatively low prescription rates for ozanimod for UC in the Netherlands, which might also be the case for other countries. Limited evidence from routine clinical practice may lead to uncertainty and hesitancy among IBD-specialists regarding the prescription of novel therapy. Therefore, even relatively small studies, such as the present one, contribute valuable evidence for clinical decision-making. Another limitation is the paucity of endoscopic assessment at baseline and during follow-up. Although endoscopy remains the gold standard in IBD care, it is invasive, burdensome for patients, and costly for healthcare systems. Consequently, it is used selectively in routine clinical practice.

This study has several strengths. The most important is the inclusion of patients who would not have been eligible for participation in randomized controlled trials (RCTs), such as those with comorbidities (e.g. a history of malignancy) or those receiving concomitant corticosteroids at treatment initiation. Evaluating treatment persistence, effectiveness and safety in a population representative of routine clinical practice enhances the generalizability of the findings. Although the primary outcome was treatment effectiveness at week 24, the cohort also included patients who had received ozanimod for more than three years, providing additional insight into longer-term treatment use. This shows that ozanimod is effective to maintain disease remission in certain patients, even in those with difficult-to-treat IBD. Another strength of this study is its data analysis. There is currently no consensus on how to analyze real-world data when patients discontinue a treatment or when variables are missing, which is common in real-world studies. To optimize the interpretation, methods and results are presented as transparent as possible. Therefore, effectiveness was assessed using two approaches: a more liberal approach, in which only patients who remained on ozanimod and had available follow-up data were included (observed-cases analysis), and a more conservative approach, in which patients who discontinued ozanimod were classified as non-responders in the effectiveness analysis (mNRI analysis), which provides the most complete representation of real world practice and outcomes of treatment with ozanimod in patients with UC.

In conclusion, results from this prospective nationwide real-world study show that ozanimod may benefit some patients with UC, also in the context of difficult-to-treat disease. Moreover, no new safety signals were observed. Prospective studies enrolling more patients with longer follow-up are warranted to confirm these real-world findings.

Abbreviations

95%CI, 95% confidence interval

CSFCR, corticosteroid-free clinical remission

100PY, 100 person-years

FC, fecal calprotectin

IBD, inflammatory bowel disease

IBD-U, IBD-unclassified

mNRI, modified non-responder imputation

MS, multiple sclerosis

SCCAI, Simple Clinical Colitis Activity Index

UC, ulcerative colitis

Declarations

Ethics approval and consent to participate

The ICC Registry was approved by the Committee on Research Involving Human Subjects at the Radboudumc (4076). Written, informed consent was obtained from each patient included in the study. The study was conducted in accordance with the Declaration of Helsinki and relevant institutional guidelines.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are derived from the Dutch Initiative on Crohn and Colitis (ICC) Registry. The data are not publicly available due to privacy and ethical restrictions concerning participant data. Data may be made available upon reasonable request to the corresponding author, subject to approval by the Dutch ICC and applicable institutional and ethical requirements.

Competing interests

LMMV - none

DE - none

ZM - reports grants from ZonMw, Niels Stensen Fellowship, MDL Fonds, Academische Alliantie Fonds (AAF), Top consortium for Knowledge and Innovation (TKI), and Galapagos; advisory board fees from Johnson & Johnson, Eli Lilly, and Pfizer (paid to host institution); and speaker's fees from Friso-Friesland Campina, Galapagos/Alfasigma, Dr Falk, Celltrion, Eli Lilly, Takeda and Coloplast (paid to host institution)

MRN - none

DGB - reports speaker's fees from Takeda and Galapagos

TEHR - none

LFW - none

RLG - reports speaker's fees from Janssen-Cilag, Pfizer, Celltrion, and Alfasigma

PBFM - none

FDMvS - reports consultancy fees from Takeda, Galapagos and Alfa Sigma; speaker's honoraria from Galapagos, Lilly, AbbVie, and Janssen-Cilag B.V.; hospitality fees from Ferring; and an unrestricted research grant from Takeda

Bas Oldenburg - reports grants from AbbVie, Alfasigma, and Takeda; served as advisory board for Johnson & Johnson, AbbVie, Takeda, Pfizer, and Galapagos

MCV - reports consultancy/lecture fees from AbbVie, Alfasigma, Janssen-Cilag, and Takeda; these fees are invoiced by the speakerfee desk of the university

AAvB - reports grant from TEVA; consultancy fees from Ferring, Johnson & Johnson /Janssen; and lecture fees from E-wise, Celltrion, and Galapagos

AGLB - reports speaker's fees from Johnson & Johnson; and served as advisory board for Sanofi and Eli Lilly

ML - reports consultancy/lecture fees from AbbVie, Eli Lilly, Galapagos, Janssen-Cilag, Johnson & Johnson, Pfizer, Takeda, and Tillotts; and grants from Alfasigma, NFU, ZonMW, and TK; these fees are invoiced by the speakerfee desk of the university

WAvD - none

MD - reports speaker's fees from Bristol Meyers Squibb, Takeda, Galapagos, Janssen, Eli Lilly, and Dr. Falk; advisory board fees from AbbVie, Bristol Meyers Squibb, Celltrion, Galapagos/Alfasigma, Janssen, and Takeda; and grant/research support from Pfizer, Bristol Meyers Squibb, Galapagos Alfasigma, and Janssen - none related to this work and paid to host institution

MJP - reports research grants from Takeda, AbbVie, Alfasigma, and TKI-Health Holland; speaker or advisory board fees from Bristol Meyers Squibb, AbbVie, Pfizer, Takeda, Galapagos, and Janssen-Cilag all paid to institution; and non-financial support from Immunodiagnostics, Janssen-Cilag, Bristol Meyers Squibb, and Galapagos all outside the submitted work

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Author's contribution statements

LMMV set the study design, collected the data, analyzed the data, interpreted the results, and completed the article. DE helped with data collection, helped with data analysis, and helped with draft manuscript preparation. ZM, MD and MJP set the study design, helped with data collection, revised the final draft, and oversaw supervision. MRN, DGB, TEHR, LFW, RLG, PBFM, FDMvS, BO, MCV, AAvB, AGLB, ML and WAvD helped with data collection and revised the final draft. All authors contributed to the article, provided critical review of the manuscript, and approved the submitted version

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Stack Overflow was consulted for technical questions related to RStudio. Freddie's Academic Style Checker (developed by Mark Sinnott) was used for language refinement and manuscript editing.

Collaborators

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Figures

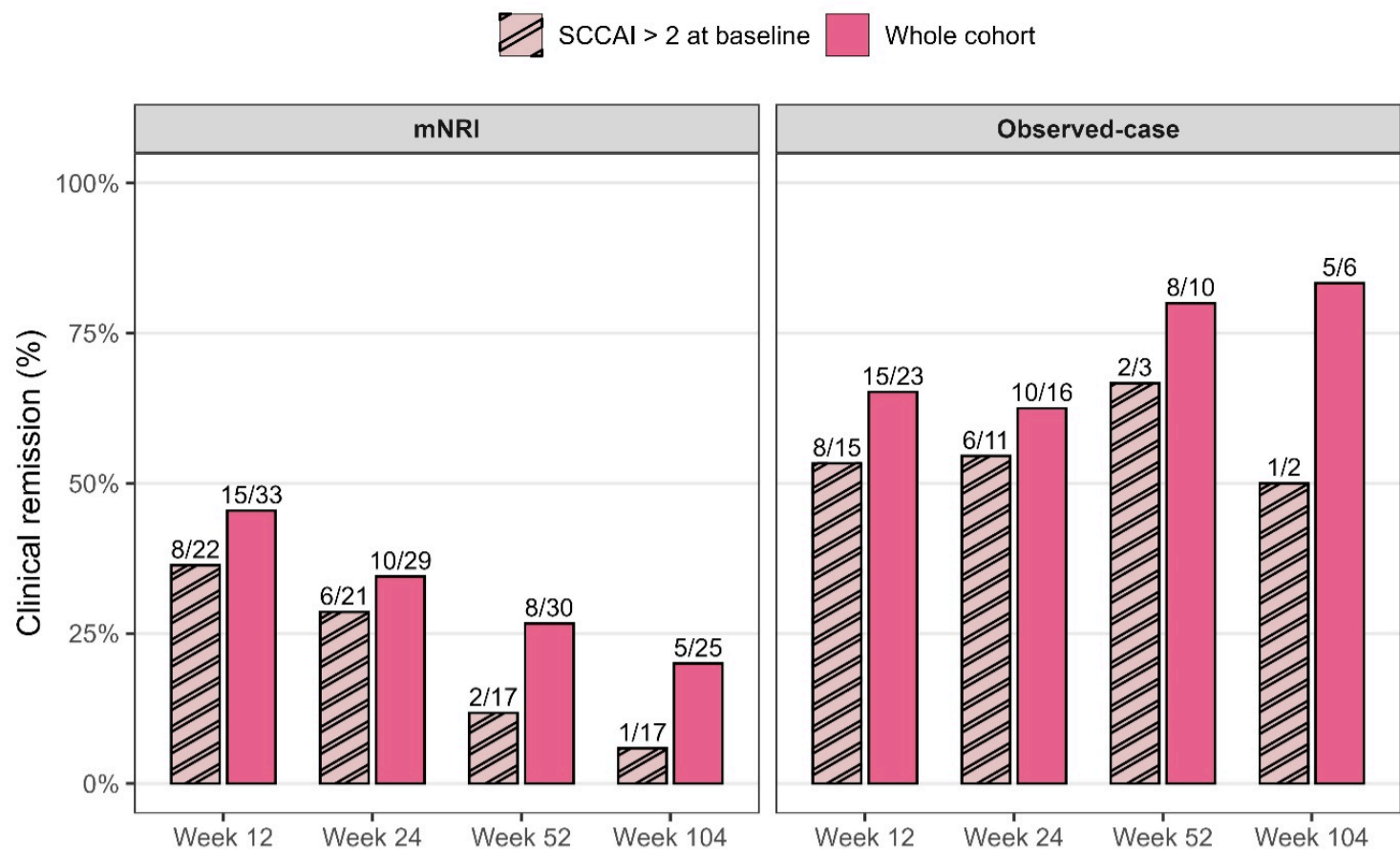


Figure 1

Clinical remission ($SCCAI \leq 2$) rates during follow-up in patients with $SCCAI > 2$ at treatment initiation and in the whole cohort; **left:** remission rates using the mNRI approach show a decrease over time, in both the subgroup of patients with $SCCAI > 2$ at baseline and in the whole cohort; **right:** remission rates using the observed-case analysis show an increase over time in the whole cohort.

Abbreviations - mNRI, modified non-responder imputation; SCCAI, Simple Clinical Colitis Activity Index

Alt text - Barplots on clinical remission over time in patients with $SCCAI > 2$ at baseline (dashed) and in the whole cohort (plain), as analyzed with the mNRI approach (left panel) and the observed-case approach (right panel).

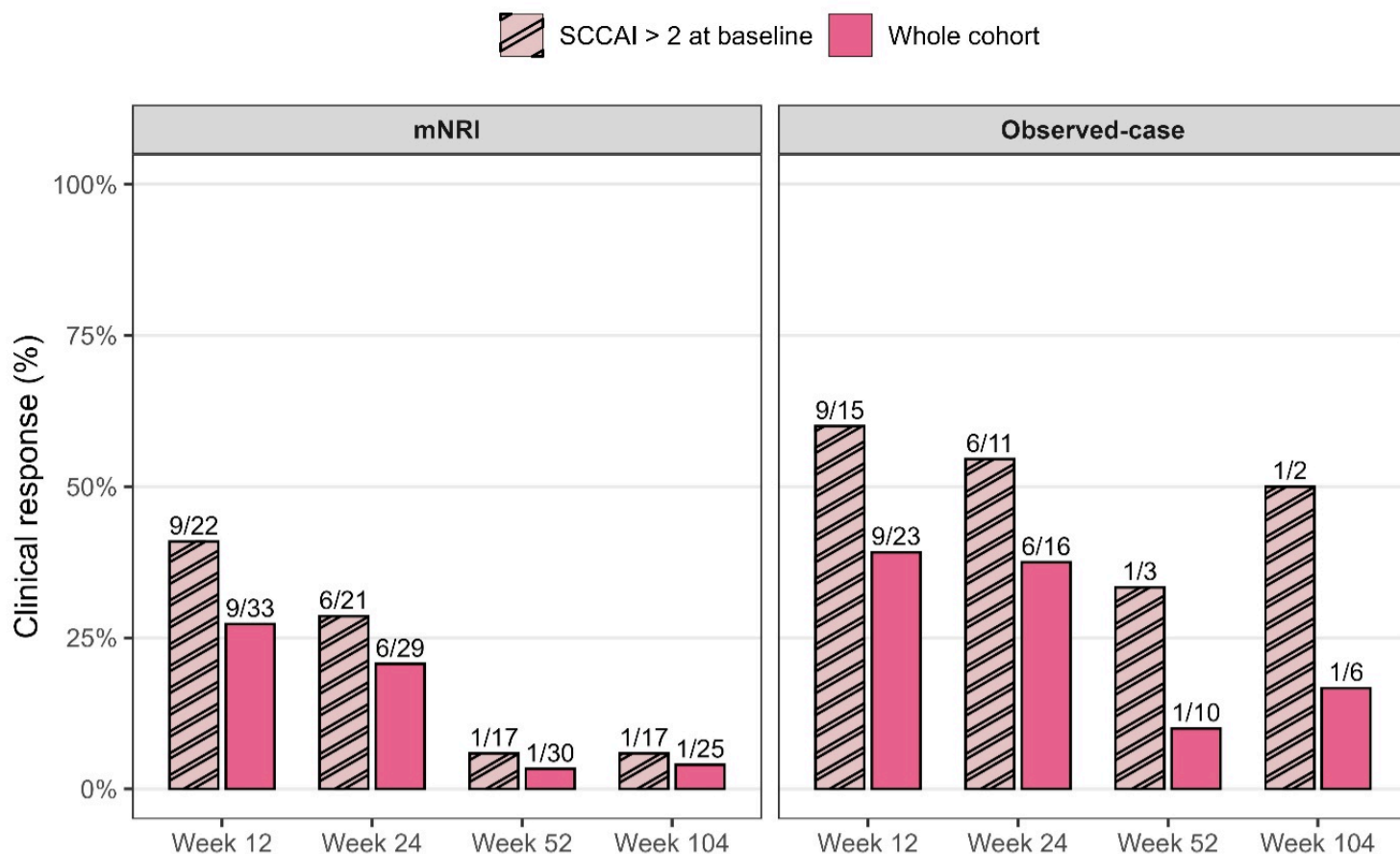


Figure 2

Clinical response (≥ 3 decrease SCCAI compared to baseline SCCAI) rates during follow-up in patients with SCCAI > 2 at treatment initiation and in the whole cohort; **left:** response rates using the mNRI approach show a decrease over time; **right:** response rates using the observed-case analysis tend to remain stable.

Abbreviations - mNRI, modified non-responder imputation; SCCAI, Simple Clinical Colitis Activity Index

Alt text - Barplots on clinical response over time in patients with SCCAI > 2 at baseline (dashed) and in the whole cohort (plain), as analyzed with the mNRI approach (left panel) and the observed-case approach (right panel).

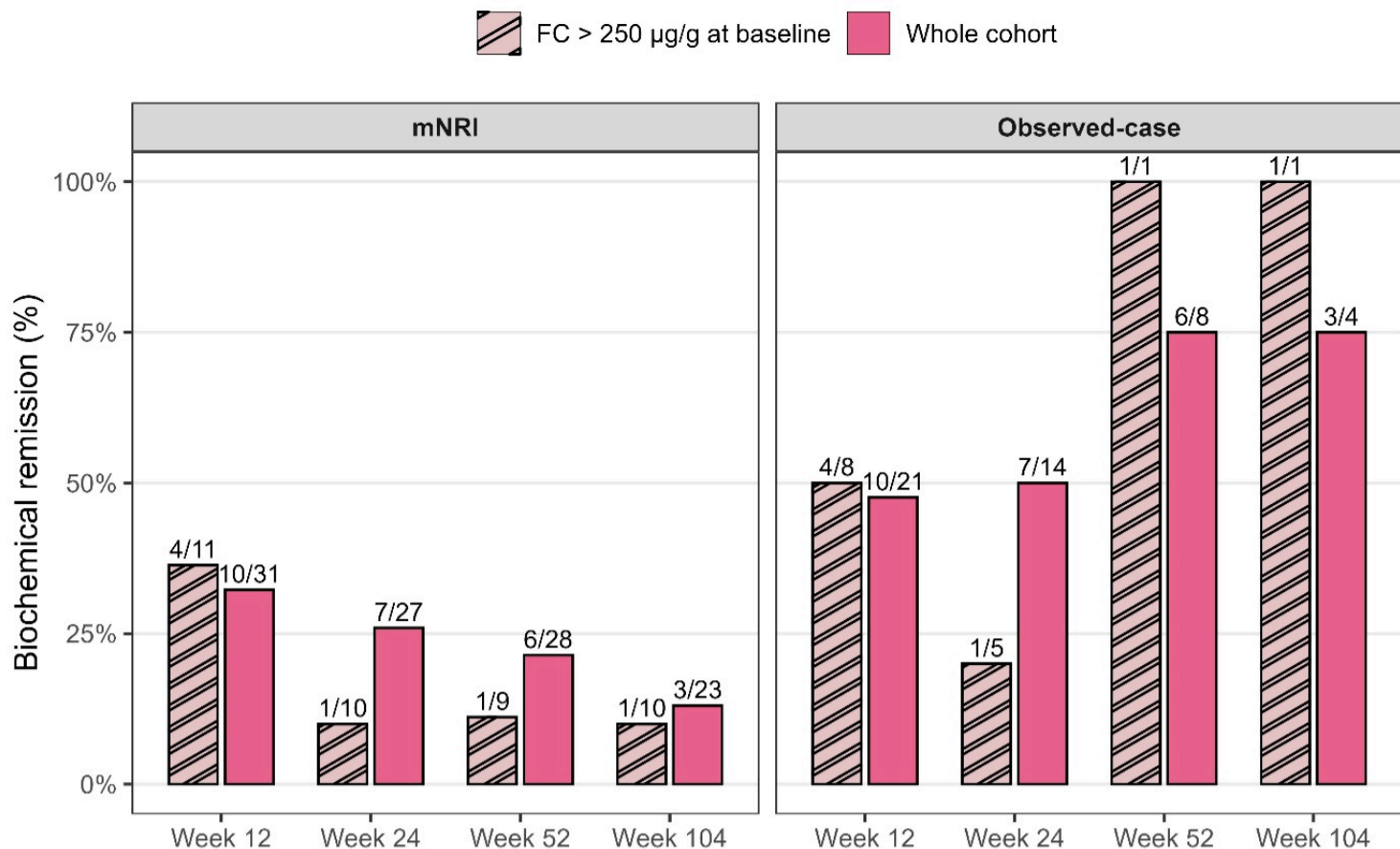


Figure 3

Biochemical remission (FC ≤ 250 µg/g) rates during follow-up in patients with FC > 250 µg/g at treatment initiation and in the whole cohort; **left:** remission rates using the mNRI approach tend to decrease over time in the whole cohort but stay stable from week 24 on in the subgroup of patients with FC > 250 µg/g at treatment initiation; **right:** remission rates using the observed-case analysis stay stable over time in the whole cohort, but show an inverted peak at week 24 in patients with FC > 250 µg/g at treatment initiation.

Abbreviations - FC, fecal calprotectin; mNRI, modified non-responder imputation

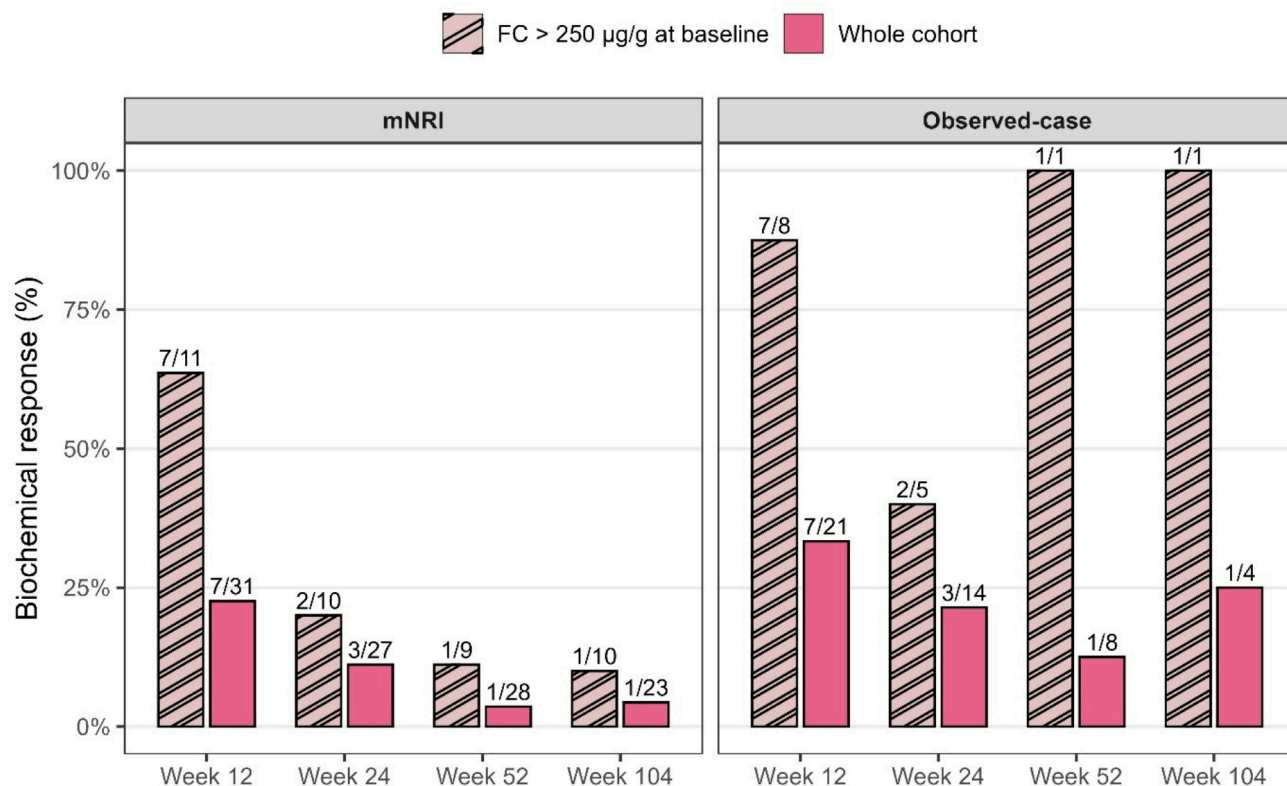


Figure 4

Biochemical response ($\geq 25.0\%$ decrease FC levels compared to baseline FC) rates during follow-up in patients with FC > 250 µg/g at treatment initiation and in the whole cohort; **left:** response rates using the mNRI approach tend to decrease over time, with one patient in biochemical remission at baseline also showing biochemical response at week 24; **right:** remission rates using the observed-case analysis stay stable over time in the whole cohort, but show an inverted peak at week 24 in patients with FC > 250 µg/g at treatment initiation.

Abbreviations - FC, fecal calprotectin; mNRI, modified non-responder imputation

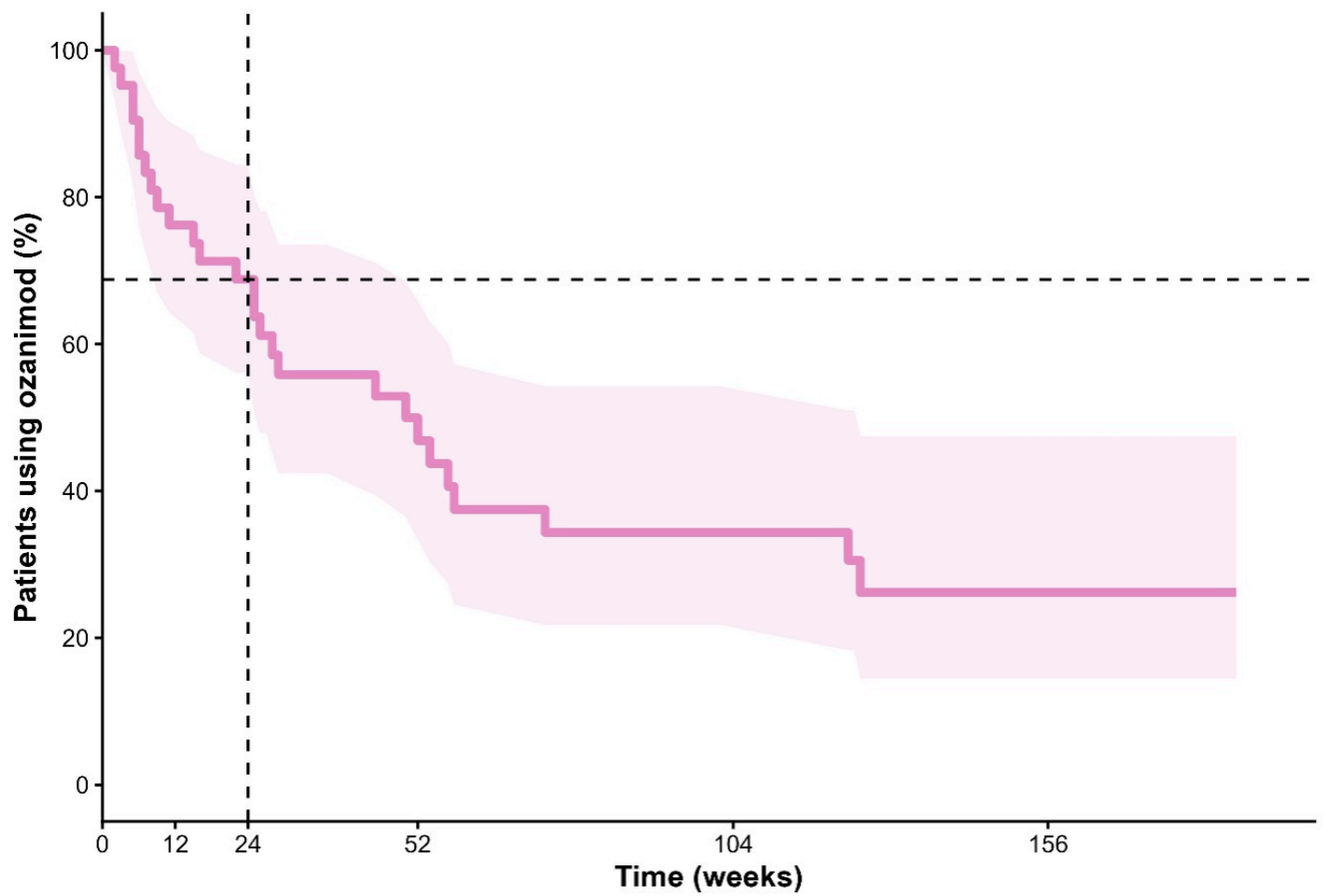
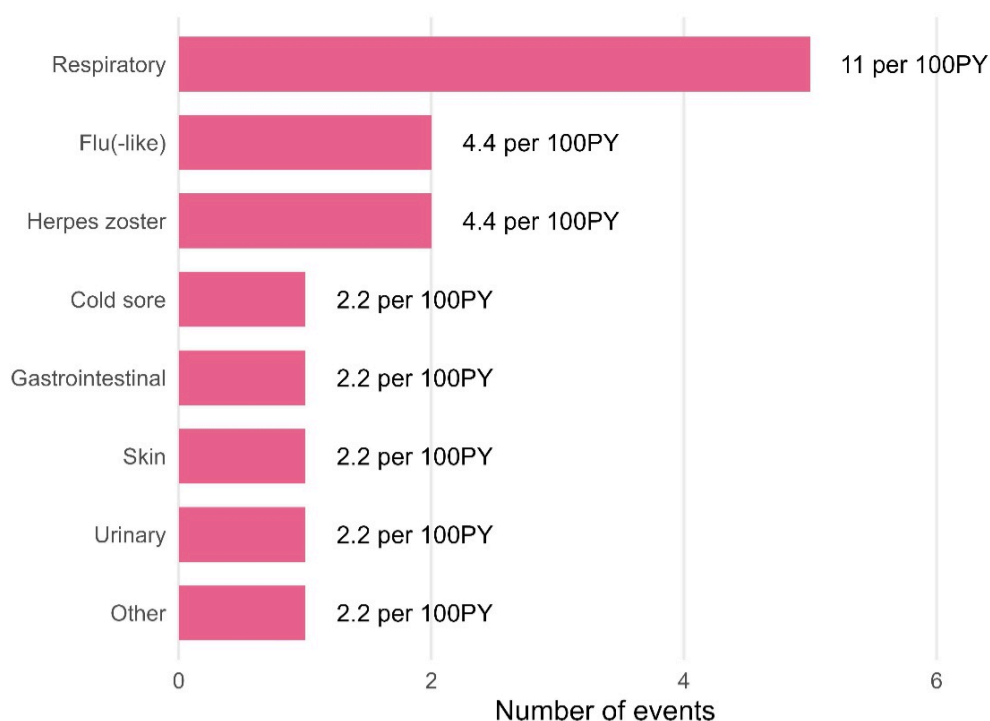


Figure 5

The probability of using ozanimod at week 24 was 68.6% in the whole cohort.

Alt text: Kaplan-Meier estimates of overall treatment persistence in patients with UC or IBD-unclassified who initiated ozanimod as part of routine clinical care.

A



B

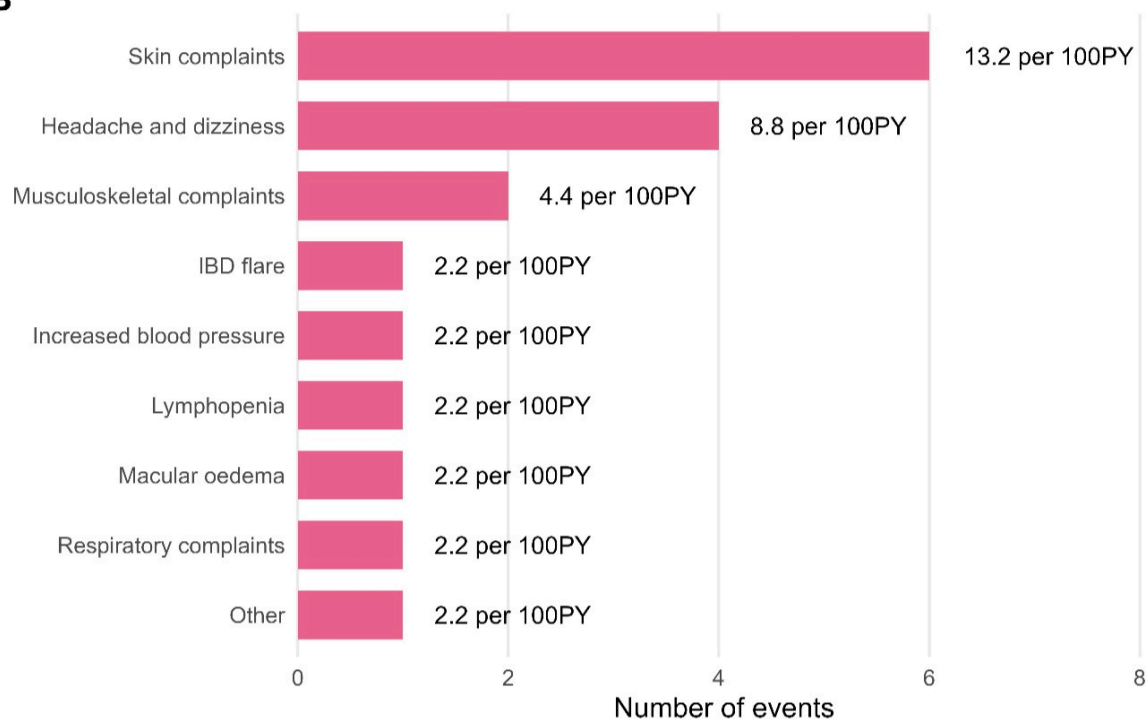


Figure 6

Visual representation of the (non-)infectious adverse events observed in the patients included in this study.

a. Respiratory infections were the most reported infections type possibly or probably related to the use of ozanimod. Reported infections were only mild or moderate, and none required hospitalization.

b. Patients with non-infectious adverse events mainly reported skin complaints and headache.

Abbreviation - 100PY, 100 person-years

Alt text - Horizontal barplots, with infection type (upper panel) and adverse event type (lower panel) on the y-axis and number of events on the x-axis. Number of events per 100 person-years showed at the end of each bar.

100 person-years showed at the end of each bar.

Supplementary Files

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