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Clinical Trial: Evaluating a Single 1600 mg Tablet Regimen of 5-Aminosalicylate for Ulcerative Colitis—The EASI Trial

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ABSTRACT

Background: 5-Aminosalicylate (5-ASA) is recommended for the treatment of mild-to-moderate ulcerative colitis (UC). However, adherence may be low; poor adherence is associated with an increased risk for flares.

Aim: To investigate whether a regimen of a single 1600 mg tablet of 5-ASA improves adherence with preserved remission rates compared to a conventional regimen of three 800 mg tablets.

Methods: We enrolled 178 patients with UC (89 per group) in this open-label randomised controlled phase IV trial. Patients had to have stable remission on 5-ASA for at least 2 months and no concomitant diseases that could affect compliance. We randomised patients (1:1) to either receive Asacol 1600 mg single tablet or Asacol 2400 mg (three tablets of 800 mg once daily) for 12 months. Patients were assessed five times during the 12 months, where medicine was delivered and received, blood and stool samples were collected and symptom scores were determined.

Results: Eighty-two patients taking a single tablet and 78 taking three tablets were adherent ($p = 0.32$). Fewer patients in the 1600 mg group missed doses (24.5 vs. 26.5). There was no difference in the number of relapses or proportions experiencing relapse. Neither adherence nor treatment group was a significant predictor of relapse.

Conclusion: The single-tablet lower dose treatment could be a feasible alternative to the conventional three-tablet regimen.

Trial Registration: The study was registered at Clinicaltrials.gov (ID NCT04133194) and approved by The Danish Medicine Agency and The National Committee on Health Research Ethics (EudraCT 2019-002070-31)

1 | Introduction

Inflammatory bowel diseases (IBD) are chronic, progressive, immune-mediated inflammatory disorders consisting primarily of ulcerative colitis (UC) and Crohn's disease (CD). Affecting approximately 1.3 million people and roughly 0.2% of the population in Europe, IBD is a substantial burden on patients and healthcare systems [1]. UC accounts for a large portion of this population, with an even higher prevalence and incidence of 523 and 14.0 per 100,000 persons in Denmark [2, 3]. Additionally, direct health care costs are high and estimated to be €2000 per UC patient per year [1].

Treatment for UC consists of anti-inflammatory medications including 5-aminosalicylates (5-ASA), immunomodulators, corticosteroids and biologics and surgery with colectomy for refractory UC patients [4–6]. For mild-to-moderate UC, the recommended treatment to induce and maintain remission is oral or topical 5-ASA [4, 5]. Despite its efficacy, adherence to 5-ASA is generally low, with rates ranging from 30% to 60% [7–11]. Adherence is important in maintaining remission, and UC patients with low adherence have a significantly increased risk for flares [7, 11, 12]. Additionally, low adherence can lead to an increased risk of colorectal cancer and hospital costs [9, 10, 13, 14].

Reasons for adherence or nonadherence are multifactorial. Factors like age, perceived need for treatment, use of other medications, regimen complexity and many more have been found to be associated with 5-ASA adherence [11, 15–21]. Typical oral 5-ASA dosages for maintaining remission require taking three to four tablets once or multiple times daily. However, multiple tablet treatments in comparison to single tablet treatments have been shown to decrease adherence in other diseases like HIV, type 2 diabetes and cardiovascular disease [22–24]. Additionally, other studies looking specifically at adherence for UC patients taking 5-ASA suggest that pill burden affects adherence, and patients prefer treatment regimens with a lower pill-burden [7, 8, 21, 25, 26]. To our knowledge, no studies have examined the effect of single tablet treatment on adherence in IBD patients. By treating UC patients with a single tablet, adherence could be improved and thereby decrease the risk for relapse and hospital costs.

A single once-daily 1600 mg Asacol tablet containing mesalamine was approved for maintenance treatment for UC by Danish health authorities in 2018. The 1600 mg Asacol tablet uses OPTICORE technology shown to delay the release of active ingredients [27, 28]. Previous studies have shown that once-daily 5-ASA dosing is as effective as multiple-daily dosing [29, 30]. Additionally, a previous study by D'Haens et al. showed that a single 1600 mg Asacol tablet was effective in maintaining remission in patients with mild-to-moderate UC and noninferior to 3200 mg (two 1600 mg tablets) Asacol [31]. Our aim for this study was to investigate whether a simplified treatment regimen of 5-ASA with a single 1600 mg tablet improves adherence with preserved remission rates compared to conventional therapy with three tablets of 800 mg.

2 | Materials and Methods

This was an open-label randomised controlled phase IV trial including 190 patients with ulcerative colitis in remission. Patients were recruited from November 2019 to March 2024 through the outpatient clinic at the Gastrounit, Medical Division at Copenhagen University Hospital—Amager and Hvidovre. The trial was conducted according to the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines. The study was registered at Clinicaltrials.gov (ID NCT04133194) and approved by the Danish Medicine Agency and the National Committee on Health Research Ethics (EudraCT 2019-002070-31) by October 2019. Additionally, the trial was GCP (Good Clinical Practice) monitored by an external third party. All patients provided written informed consent.

2.1 | Study Population

Patients had to have an age between 18 and 70 years, inclusive, at the time of inclusion. Additionally, patients had to be in stable remission on 5-ASA (defined as partial Mayo score ≤ 1) for at least 2 months and have endoscopic remission (Mayo Clinic Endoscopic Score ≤ 1) if inclusion endoscopy was performed. Patients were excluded from the study if they used immunomodulators or biological therapies or had previous abdominal surgery related to UC. Other exclusion criteria included evidence of infectious diarrhoea, presence of chronic infections (i.e., HBV, HCV and HIV), severe concomitant diseases that might influence compliance and addiction to alcohol or narcotics.

2.2 | Study Design

Eligible patients were randomised (1:1) to receive either Asacol 1600 mg single tablet or Asacol 2400 mg (three tablets of 800 mg taken once daily) through a list generated by an independent third party. This list was then uploaded to REDCap, which then randomised the individual patient.

Patients were assessed at inclusion and months 3, 6, 9 and 12 (± 1 week when necessary). Medication was dispensed and left-over medication was collected and counted at each visit. For all visits, partial Mayo score (pMayo) was calculated, and blood and stool samples (for calprotectin analysis) were collected. Patients were then sent a link via e-mail to fill out surveys after the visit: simple clinical colitis activity index (SCCAI), Inflammatory Bowel Disease Disability Index (IBD-DI) and Short Inflammatory Bowel Disease Questionnaire (SIBDQ). Patients were not reminded to fill out surveys so as not to affect compliance and scores. Additionally, self-reported medical adherence was assessed at inclusion, 6 months and 12 months using the Medical Adherence Report Scale (MARS-5). Adverse events (AE) or serious adverse events (SAE) and concomitant medication were noted throughout the study.

An optional sigmoidoscopy was performed at inclusion and end of trial. Additional sigmoidoscopies were performed at relapses as needed. A full Mayo score was calculated at these visits.

2.3 | Outcomes

The primary outcome was medical adherence as measured by MARS-5 score and through drug accountability log. The drug accountability log kept track of the total number of dispensed and received tablets between visits. The total number of tablets used during the trial was calculated from the difference in the total number of tablets dispensed and the total number of tablets received. To calculate the total number of tablets that should have been taken during the trial, the trial duration was used and either multiplied by one or three depending on if the patient was randomised to a single tablet or three tablets. If patients took extra medication due to relapses, the number of extra tablets taken was calculated. To calculate the total number of missed tablets or dosages, the difference between the number of tablets that should have been taken and the total tablets used was calculated. If patients had taken more tablets than necessary, they

were considered to be adherent and the difference was set to zero. A patient was considered to be adherent if they had taken at least 80% of the prescribed medication.

Secondary outcomes included the number of relapses and symptom scores. For relapses, patients contacted the research team between visits if they experienced signs of relapse. Optional sigmoidoscopy was performed, and additional data like Mayo scores (partial or full Mayo scores) and symptom surveys including SCCAI, IBD-DI, and SIDBQ scores were obtained. Blood and stool samples were also collected at relapses. Patients that had relapses that could be treated with escalation of the study drug or escalation with local 5-ASA treatment remained in the study. However, patients that had severe activity that needed treatment with oral corticosteroids or other medications were withdrawn after consultation with a research physician. Possible relapses that got spontaneous better without change in treatment were not included as relapses.

2.4 | Statistics

To detect approximately 20% improvement in adherence with 80% power with an alpha of 0.05, a sample size of 171 total patients was needed. To account for potential dropouts, the study initially aimed to include 200 patients. However, due to COVID-19 and a slow inclusion rate, recruitment was terminated in March 2024 with a final sample size of 190 patients.

Demographic data was presented as numbers, medians and interquartile ranges (IQRs), as appropriate. Mean with standard deviation (SD) for MARS-5, pMayo, total SCCAI, total IBD-DI and total SIBDQ scores were plotted for each visit. Additionally, mean with SD levels of haemoglobin, albumin, C-reactive protein (CRP) and faecal calprotectin were also plotted for each visit.

To determine significant differences between laboratory data and adherence data between treatment groups, Welch's *t* test and Student's *t* test were calculated as needed.

Multivariable logistic regression analysis predicting 80% adherence was performed using demographic data, drug randomisation and if the patient had relapses during the trial (yes/no). Another multivariable logistic regression analysis predicting relapses was performed using baseline and adherent data including drug randomisation. Predictive mean matching was used for imputation to help with missing data. Stepwise Akaike information criterion (AIC) was used to find the best set of predictor variables for relapses. Odds ratios (OR) and confidence intervals (CI) were reported. Multicollinearity was checked using variance inflation factor (VIF).

Multivariable Cox proportional regression analysis for relapses adjusted for sex, smoking, comorbidities, age at inclusion, disease duration, time since last flare, adherence and drug randomisation was calculated. Hazard ratios (HR) and 95% confidence intervals (CI) were determined. Proportional hazards assumption was assessed using Schoenfeld residuals test, and multicollinearity between covariates was determined through VIF. Kaplan–Meier plots from inclusion to time to first relapse between the two patient groups were performed.

Statistical analyses were performed using Python (Version 3.10.5) via Visual Studio Code and RStudio Team (2022) (RStudio: Integrated Development for R. RStudio Inc., Boston, MA, USA).

3 | Results

3.1 | Demographics

A total of 190 patients were initially included in the study from November 2019 to March 2024. Nine patients were excluded due to disease activity, and three patients were excluded due to other reasons. That left 178 patients with 89 patients in each patient group.

Median age at inclusion was 44 years (Table 1). In the 1600 mg treatment group, 53% of patients were male, 17% were current smokers, 36% had other comorbidities, and patients had a median of 12 months since last flare. In the 2400 mg treatment group, 40% of patients were male, 10% were current smokers, 28% had other comorbidities, and patients had a median of 18 months since last flare.

3.2 | Adherence

Patients taking a 1600 mg single tablet Asacol in comparison to patients taking three 800 mg tablets Asacol had slightly higher self-reported MARS-5 scores (Figure 1) during the study. Additionally, slightly more patients taking a single tablet were adherent (92% vs. 88%, $p = 0.32$), and patients had a lower mean number of missed dosages (24.5 vs. 26.5) (Table 2). However, these differences were not found to be significant ($p = 0.79$).

A multivariable logistic regression predicting 80% adherence using drug randomisation, relapse during trial (yes/no) and demographic data found no significant predictors (Table 3). Drug randomisation had an odds ratio of 1.00 and therefore had no effect on adherence.

3.3 | Relapses

Fifty-four relapses were reported in patients taking 1600 mg versus fifty-three relapses in patients taking 2400 mg (Table 4). 45% and 44% of patients in the 1600 mg and 2400 mg treatment groups experienced at least one relapse requiring escalation of treatment during the trial period. The most common consequence of relapse was escalation of the study drug with the addition of local 5-ASA treatment or escalation alone with topical 5-ASA. Five patients had relapses with initial escalation of the study drug but later needed the addition of either local or systemic steroids. Two patients were treated solely with systemic corticosteroids.

A multivariable Cox regression analysis for relapses adjusted for sex, smoking, presence of comorbidities, age at inclusion, disease duration, time since last flare, adherence and drug randomisation was calculated (Table 5). The presence of one or more comorbidities significantly increased the risk for a relapse, while

TABLE 1 | Population demographics.

Medication dose	All $N = 178$	1600 mg $N = 89$	2400 mg = 89
Age at inclusion, median (IQR)	43 (32, 55)	45 (32, 54)	42 (32, 55)
Age at diagnosis, median (IQR)	30 (22, 41)	30 (22, 43)	30 (22, 38)
Disease duration in years, median (IQR)	10 (4, 17)	10 (4, 18)	10 (5, 17)
Sex: male	83 (47%)	47 (53%)	36 (40%)
Smoking			
Never	87 (50%)	38 (43%)	49 (56%)
Former	64 (37%)	35 (40%)	29 (33%)
Current	24 (14%)	15 (17%)	9 (10%)
Family history of IBD (1st degree relatives)	28 (16%)	16 (18%)	12 (13%)
Max. disease extent			
Proctitis	46 (27%)	26 (30%)	20 (23%)
Left-sided	70 (40%)	32 (37%)	38 (44%)
Extensive	57 (33%)	26 (33%)	28 (33%)
Time since last flare in months, median (IQR)	15 (7, 31)	12 (6, 24)	18 (7, 36)
Extraintestinal manifestation	47 (27%)	26 (30%)	21 (24%)
Appendectomy	11 (6.2%)	8 (9%)	3 (3.4%)
Presence of other comorbidities	57 (32%)	32 (36%)	25 (28%)

increasing age at inclusion significantly decreased the risk. Drug randomisation to 2400 mg did not significantly increase or decrease the risk for relapse. Additionally, no difference in relapses between treatment groups can be seen in the Kaplan–Meier plot found in Figure 2.

A multivariable logistic regression analysis using demographic and adherent data showed similar results to the Cox regression: the presence of comorbidities had significantly higher odds of relapse, while higher age at inclusion in trial had significantly lower odds of relapse (Table 6). MARS-5 score, adherence and drug randomisation were not found to be significant predictors.

Predictor selection was performed through stepwise AIC to find the best multivariable logistic regression model out of all inclusion data (Table 7). Left-sided max disease extent (vs proctitis), the presence of comorbidities and higher SCCAI scores had significantly higher odds for relapse. However, older age at inclusion and higher IBD-DI scores had significantly lower odds for relapse. After stepwise AIC selection, the treatment group or adherence were not included in the model.

3.4 | Symptom Scores and Laboratory Data

Symptom scores and laboratory data were gathered for all study visits (Figure 1). No differences between treatment groups were found for pMayo, SCCAI, IBD-DI and SIBDQ scores throughout the study. Additionally, no differences were found for mean haemoglobin, albumin and CRP levels between treatment groups. Mean faecal calprotectin levels were higher for patients who received 1600 mg Asacol in comparison to patients who received 2400 mg Asacol. However, these differences were found to be insignificant.

3.5 | End of Trial

Seventy-nine patients in both treatment groups completed all five visits of the trial (Table 8). Twenty patients withdrew before trial completion primarily due to flares requiring treatment with either corticosteroids or other drugs. Others withdrew due to reasons such as lack of time to participate and side effects of medication like nausea.

4 | Discussion

This phase IV open-label randomised controlled trial compared a single 1600 mg Asacol tablet versus three 800 mg Asacol tablets for maintenance of remission in patients with ulcerative colitis. While patients taking a single tablet exhibited slightly higher adherence in comparison to patients taking multiple tablets, this difference was not significant. Additionally, no significant difference between treatment groups was observed in terms of the risk of relapse during the study. Using a single 1600 mg Asacol tablet instead of three 800 mg Asacol tablets therefore appears to be a feasible alternative.

Our study reported 92% and 88% adherent population for the 1600 mg treatment group and the 2400 mg treatment group, respectively. These rates align with previous clinical trials

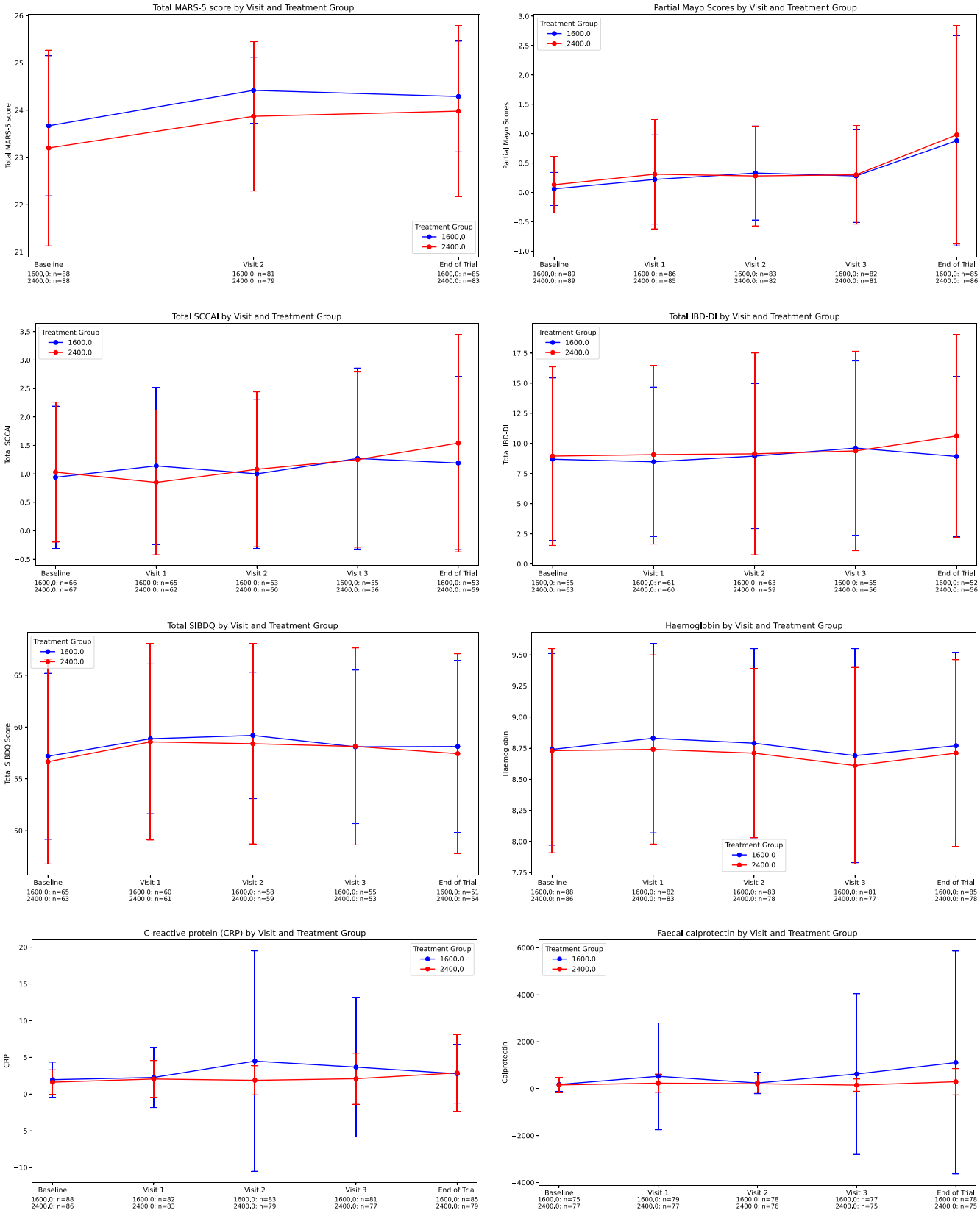

FIGURE 1 | Adherence score, symptom scores and laboratory data for each visit grouped by randomisation.

where patients are closely monitored, which have reported mesalamine adherence between 85% and 98% [31–35]. However, real-world settings have reported much lower adherence rates, ranging from 30% to 60% [7–10]. Therefore, the high adherence rates in our RCT are expected, due to the nature and structure of the trial with close monitoring. Notably, when calculating adherence, many patients had taken more tablets than prescribed. The median disease duration at inclusion was 10 years

TABLE 2 | Adherence of medication between treatment groups.

Medication dose	1600 mg	2400 mg	*T*-test
Medication Adherence Report Scale, mean (SD)			
Baseline	23.7 (1.48)	23.2 (2.07)	0.09
Visit 2	24.4 (0.70)	23.9 (1.58)	< 0.01
End of Trial	24.3 (1.17)	24.0 (1.81)	0.18
Number (%) of population adherent, ≥ 80%			
At end of trial	82 (92%)	78 (88%)	0.32
Differences in treatment			
Differences in treatment (should take—treatment taken) *per tablet*			< 0.01
Median (IQR)	5.0 (0, 18)	19.0 (0, 116)	
Mean (SD)	24.5 (56.4)	79.5 (122)	
Differences in treatment (should take—treatment taken) *per dose*			0.79
Median (IQR)	5.0 (0, 18)	6.0 (0, 39)	
Mean (SD)	24.5 (56.4)	26.5 (40.8)	

TABLE 3 | Multivariable logistic regression predicting adherence.

	Odds ratio (CI)	P-value
2400 mg Asacol	1.00 (1.00–1.00)	0.09
Relapse during trial (vs. no)	0.45 (0.13–1.43)	0.18
Sex (male)	1.96 (0.63–6.87)	0.26
Smoking: former (vs. current)	0.71 (0.09–3.64)	0.70
Smoking: never (vs. current)	1.58 (0.21–8.43)	0.61
Max Montreal classification: left-sided (vs. proctitis)	1.29 (0.36–4.48)	0.69
Max Montreal classification: extensive (vs. proctitis)	2.45 (0.55–13.40)	0.26
Time since last flare in months	1.01 (1.00–1.05)	0.41
Comorbidity (yes vs. no)	0.90 (0.28–3.10)	0.86
Disease duration	0.95 (0.90–1.02)	0.13
Age at inclusion	1.02 (0.97–1.07)	0.52

TABLE 4 | Relapses between treatment groups.

Medication dose	1600 mg	2400 mg
Nr of relapses	54	53
% of original population that experienced relapses	40 (45%)	39 (44%)
Relapse consequence		
Relapse with escalation of study drug	9 (17%)	8 (15%)
Relapse with escalation to another drug	21 (39%)	25 (47%)
Local 5-ASA	18	23
Corticosteroids	—	2
Other	3	—
Relapse with escalation of study drug and another drug	24 (44%)	20 (38%)
Local 5-ASA	22	16
Corticosteroids	2	3
Other	—	1

for both groups. Therefore, we found that patients knew their disease and recognised early signs of flares and did not hesitate to adjust treatment as necessary despite specific instructions to contact the research team with signs of relapse. Nonetheless, we would still expect lower adherence rates in non-trial settings, particularly in patients in remission.

Previous studies have suggested multiple factors associated with adherence for 5-ASA such as marital status, dosing frequency, gender, smoking and age [11, 15–20]. In our trial, no significant predictors of ≥ 80% adherence were found. Factors like drug randomisation, relapse during the trial, sex, age, smoking and presence of comorbidities were not significant. Given the variability in reported factors across studies, it is unsurprising that our findings differ from prior research.

While examining adherence between treatment groups, patients taking a single tablet had fewer missed dosages and slightly higher self-reported adherence (MARS-5). However, these differences were not significant. For other chronic diseases like type 2 diabetes and cardiovascular disease, patients on single-tablet regimens have been associated with approximately 10% higher adherence compared to multiple-tablet regimens [23, 24]. Also, other studies

examining adherence for UC patients have shown that patients prefer treatment regimens with lower pill burden [7, 25, 26]. Additionally, a retrospective study by Lachaine et al. suggests that a lower pill burden positively influences adherence [21]. The exact reason for the lack of significant difference remains unclear. One possibility is recruitment bias, where the patients who chose to participate in our trial were more aware of the importance of adherence or more motivated to take their medication. As a result, adherence rates were high, making the difference negligible. A larger sample size or an observational study design, where adherence rates tend to be lower, might have enhanced any differences.

Neither medical adherence (self-reported and calculated) nor the treatment group significantly predicted relapse in our logistic regression analysis. Previous studies have shown an increased relapse risk among nonadherent patients [11, 15]. However, a study from our research group did not find a significant difference in relapse between adherent and nonadherent patients [36]. Our results with a lack of association could be due to the relatively small number of non-adherents in our patient group and large number of relapses.

Over the 12-month trial period, 45% of patients in both treatment groups experienced symptomatic relapse. Other studies showed similar results: between 30% and 70% of ulcerative colitis patients

TABLE 5 | Cox regression analysis for relapses adjusted for covariates.

	Hazard ratios (CI)	*p*
Sex (male)	1.19 (0.75–1.91)	0.46
Smoking: former (vs. current)	1.66 (0.80–3.43)	0.17
Smoking: never (vs. current)	1.19 (0.55–2.56)	0.65
Comorbidities (yes)	2.03 (1.25–3.30)	< 0.01
Age at inclusion	0.96 (0.94–0.98)	< 0.01
Disease duration	0.98 (0.95–1.01)	0.26
Time since last flare in months	1.00 (1.00–1.00)	0.06
Adherent (yes vs. no)	0.69 (0.34–1.41)	0.31
2400 mg Asacol	0.86 (0.54–1.38)	0.54

TABLE 6 | Multivariable logistic regression predicting relapse using demographic and adherent data.

	Odds ratio (CI)	*p*
2400 mg Asacol	0.99 (0.48–2.04)	0.99
Adherent (yes vs. no)	0.45 (0.12–1.56)	0.21
Total MARS-5 score at baseline	1.01 (0.82–1.24)	0.94
Sex (male)	1.16 (0.57–2.40)	0.68
Smoking: former (vs. current)	2.02 (0.69–6.12)	0.20
Smoking: never (vs. current)	0.98 (0.34–2.89)	0.97
Max Montreal classification: left-sided (vs. proctitis)	1.70 (0.72–4.11)	0.23
Max Montreal classification: extensive (vs. proctitis)	0.97 (0.39–2.44)	0.96
Time since last flare in months	1.00 (1.00–1.00)	0.28
Comorbidities (yes)	3.47 (1.61–7.83)	< 0.01
Disease duration	0.98 (0.94–1.02)	0.37
Age at inclusion	0.94 (0.91–0.97)	< 0.01

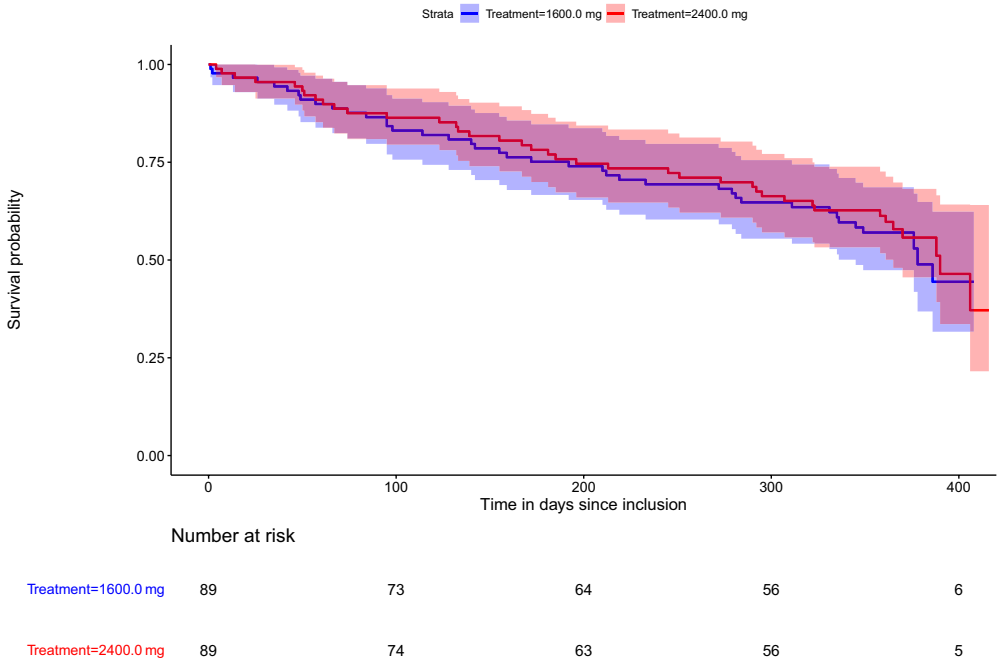

FIGURE 2 | Kaplan–Meier plot from inclusion to time to first relapse grouped by randomisation.

TABLE 7 | Multivariable logistic regression predicting relapse after stepwise AIC and imputation through predictive mean matching.

	Odds ratio (CI)	*p*
Max Montreal classification: left-sided (vs. proctitis)	2.54 (1.06–6.30)	0.04
Max Montreal classification: extensive (vs. proctitis)	1.10 (0.44–2.75)	0.85
Comorbidity (yes)	4.51 (2.02–11.0)	< 0.01
Age at inclusion	0.93 (0.90–0.96)	< 0.01
Sum IBD-DI score at inclusion	0.89 (0.81–0.97)	0.01
Sum SCCAI score at inclusion	1.48 (1.10–2.04)	0.01
Sum SIBDQ score at inclusion	0.96 (0.89–1.03)	0.22
Calprotectin > 250 (vs. ≤ 250)	1.69 (0.64–4.56)	0.29
Calprotectin > 500 (vs. ≤ 250)	2.80 (0.66–14.80)	0.18

TABLE 8 | End of trial data.

Medication dose	1600 mg	2400 mg
Completion of trial	79 (89%)	79 (89%)
Days to withdrawal/end of trial after inclusion, median (IQR)	366 (357, 378)	368 (354, 384)
Withdrawal to trial	10 (11%)	10 (11%)
Reason for withdrawal		
Flare	5	5
Withdrawn consent	—	3
Side effects	2	—
Other	3	2

treated with oral 5-ASA medications experienced symptomatic or endoscopic relapses within 12 months [32, 33, 37–39]. For relapses, we included all noted increased numbers of stools that required a change of treatment with either escalation of study drug or addition of topical 5-ASA medications or steroids. In most cases, patients contacted the research team, and treatment would be adjusted as needed after consultation with a physician. However, in 22% of relapses (11% in 1600 mg group and 34% in 2400 mg group), patients self-adjusted their medication. Additionally, 38 (35%) relapses were confirmed with endoscopy. Therefore, rates could differ depending on definition. Lastly, it is important to note that the study was not specifically powered to detect differences in relapse rates, and therefore the results should be interpreted as exploratory.

Our findings indicate no significant differences in adherence or relapse rates between the standard three-tablet 800 mg Asacol regimen and the single 1600 mg Asacol tablet regimen. Our strengths include a relatively long follow-up. Patients had five visits with 3 months between visits over a 12-month span. Additionally, patients had open communication between visits to the research team as needed. Therefore, through close monitoring and close contact with our patients, we could detect early signs of relapse and adjust treatment as necessary.

The main limitations to our study involve patient deviation from the study protocol. Patients occasionally forgot to return leftover medication and packaging, and others had relapses that required drug escalation either prescribed by a physician or self-adjusted. For these cases, the estimated number of tablets was adjusted, but we still found patients taking more medication than required. Another limitation is our lower patient number. Due to COVID-19 and a slow inclusion rate, we were able to include 178 patients and not the 200 patients planned. However, we were still able to reach our minimum goal of 171 patients needed to detect a 20% improvement with 80% power. As with all clinical trials, missing data is a limitation. Response rates for symptom scores ranged from 60% to 75%, and completed laboratory results ranged from 85% to 98%. However, because rates were relatively high, we only needed data imputation for our multivariable logistic regression model using all inclusion data. Lastly, the structured clinical trial setting, which includes close patient monitoring, may contribute to higher adherence and remission rates compared to less controlled, real-world observational studies.

5 | Conclusions

In conclusion, our phase IV open-label randomised controlled trial showed no significant difference in adherence or relapse with ulcerative colitis treatment of either a single 1600 mg Asacol tablet or three 800 mg Asacol tablets. Therefore, the simplified single 1600 mg tablet treatment could be a feasible alternative to typical multiple tablet treatments of 2400 mg.

Author Contributions

Rie Louise Møller Nordestgaard: conceptualization, methodology, data curation, investigation, validation, formal analysis, writing – original draft, writing – review and editing, project administration. **Bobby Lo:** conceptualization, methodology, data curation, investigation, validation, funding acquisition, project administration, writing – review and editing. **Rosalina Bergstrøm:** data curation, writing – original draft, project administration. **Izabella Adzioski:** data curation, project administration, writing – review and editing. **Helene Skotte:** data curation, project administration, writing – review and editing. **Ida Marie Hawwa:** data curation, project administration, writing – review and editing. **Signe Krogsgaard Holme:** data curation, project administration, writing – review and editing. **Bermal Tiftikci:** data curation, project administration, writing – review and editing. **Katarzyna Majchrzak:** data curation, writing – review and editing, project administration. **Ida Vind:** conceptualization, writing – review and editing, supervision. **Flemming Bendtsen:** conceptualization, writing – review and editing, supervision. **Johan Burisch:** conceptualization, formal analysis, supervision, writing – review and editing.

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OpenAI's ChatGPT was used to assist in coding in R and Python. No code was directly copied, and all code was verified for accuracy.

Ethics Statement

The study was registered at Clinicaltrials.gov (ID NCT04133194) and approved by the Danish Medicine Agency and the National Committee on Health Research Ethics (EudraCT 2019-002070-31).

Consent

The trial was conducted according to the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent.

Conflicts of Interest

R.L.M.N.: Travel and congress fees from Pfizer. BL: Research grant from Janssen Cilag A/S, BETA.HEALTH, The Danish Innovation Fund; consultancy fee from Tillotts Pharma AB, Bristol Myers Squibb; travel support from Tillotts Pharma AB, Pharmacosmos A/S; speaker fee from Tillotts Pharma AB, Johnson and Johnson. R.B., I.A., H.S., I.M.H., S.K.H., B.T., K.M., I.V., F.B.: None. J.B.: Grants from AbbVie, Janssen-Cilag, MSD, Takeda, Tillots Pharma, Bristol Myers Squibb and Novo Nordisk Foundation; personal fees from AbbVie, Janssen-Cilag, Celgene, MSD, Pfizer, Takeda, Tillots Pharma, Bristol Myers Squibb, Samsung Bioepis, Pharmacosmos, Ferring, Galapagos, Eli Lilly, Dr. Falk Pharma, Celltrion and Orion Pharma.

Data Availability Statement

Anonymized and summarised data will be made available to other researchers upon publication after reasonable requests have been made to the corresponding author.

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