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# Mesalazine in left-sided ulcerative colitis: Efficacy analyses from the PODIUM trial on maintenance of remission and mucosal healing

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## KEYWORDS

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## Abstract

**Background and aim:** Left-sided colitis is the most prevalent subtype of ulcerative colitis, a chronic inflammatory disease of the colon. The standard of care for mild-to-moderate ulcerative colitis is mesalazine. The PODIUM study compared a once daily to a twice daily dosing regimen of a slow-release mesalazine (Pentasa®); here we assess the efficacy, in terms of maintenance of remission and mucosal healing, of both regimens in patients with left-sided disease.

**Patients and methods:** Eligible patients were randomised to once daily (1×2 g) or twice daily (2×1 g) oral treatment with mesalazine, for 12 months. Disease activity was assessed clinically and endoscopically at baseline and at 12 months using the Ulcerative Colitis Disease Activity Index, without endoscopic assessment at months 4 and 8.

**Results:** The study met the primary endpoint of non-inferiority in terms of remission, for once daily versus twice daily dosing, in patients with left-sided ulcerative colitis; an 8% difference was reported in the 12-month clinical and endoscopic remission rates (69% [95% CI: 59.5–76.5] and 61% [95% CI: 51.4–69.6] with once daily and twice daily dosing, respectively;  $p=0.310$ ). Mucosal healing scores after 12 months were 0 or 1 for 84.4% of the once daily and 78.8% of the twice daily population. Slow-release mesalazine was well tolerated in both dosing regimens, with no difference in reported adverse events.

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**Conclusions:** Once daily slow-release mesalazine is similarly effective to the standard twice daily schedule in patients with left-sided ulcerative colitis for the maintenance of remission in mild-to-moderate disease.

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## 1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon that is characterised by periods of remission and relapse,<sup>1</sup> which currently affects 1–2 in every 1000 people in the Western world.<sup>2</sup> UC is classified by location of the disease and includes proctitis, which is confined to the rectum; left-sided colitis, which occurs up to the splenic flexure; and extensive colitis/pancolitis, which occurs up to the hepatic flexure or affects the entire colon.<sup>3</sup> Left-sided colitis is the most prevalent subtype of UC, and as such provides a large and interesting subpopulation to study. Identifying the location of UC is not only relevant for the risk profile but also very important prior to the start of treatment in ensuring that patients receive the most effective therapy for their type of disease.<sup>4,5</sup>

Mesalazine (5-aminosalicylate [5-ASA]) is a long established, well tolerated oral or topical treatment for UC, and is the current standard of care for both the induction and maintenance of remission in patients with mild-to-moderate UC.<sup>3</sup> Many mesalazine preparations are delayed release, and are coated with a pH-sensitive acrylic-based resin (Eudragit®, Evonik Industries, Essen, Germany) that disintegrates at pH 6–7. These preparations do not dissolve in the stomach, but are principally delivered to the small intestine during the interdigestive period, making their value in treating distal UC contentious. Preparations that deliver mesalazine in this pH-dependent manner are most affected by variability in luminal pH.<sup>6–9</sup> In the normal gastrointestinal tract, there is a gradual increase in pH from the duodenum to the terminal ileum, the pH then decreases in the caecum before rising again in the colon and rectum.<sup>10</sup> In some patients with inflammatory bowel disease (IBD), there are data that show abnormal pH measurements with substantial reductions in pH levels in the colon. It is possible that these reduced pH levels may affect the intraluminal availability of some pH-dependent mesalazine preparations.<sup>11,12</sup>

In contrast, Pentasa® (Ferring Pharmaceuticals, St Prex, Switzerland), a slow-release mesalazine, contains microgranules that are covered by a semipermeable ethylcellulose-coated membrane that is not pH dependent. Unlike the other mesalazine formulations, the Pentasa microgranules start to disintegrate in the small bowel. However, the majority of Pentasa is delivered to the colon, providing drug to the whole of the gut, including the left colon.<sup>8,13</sup>

There is a substantial clinical evidence base demonstrating that the different formulations of mesalazine are effective treatment options for the induction and maintenance of remission in UC. The PODIUM (Pentasa Once Daily In Ulcerative colitis for Maintenance of remission) study was a recent European multicentre, randomised controlled trial conducted in eight countries. It compared two dosing regimens of Pentasa granules: 2 g once daily (OD) versus 1 g twice daily (BD) for the maintenance of remission in

patients with mild-to-moderate, quiescent UC.<sup>14</sup> The trial showed that the OD dosing regimen was superior to the established BD dosing, with significantly more patients remaining in remission at 12 months, both clinical and endoscopic (70.9% vs 58.9%,  $p=0.024$ ). The benefit of OD dosing could be due to the higher mucosal concentrations of mesalazine achieved with the Pentasa microgranules OD compared with BD, resulting in better efficacy. In practice, this benefit coupled with increased compliance to the OD dosing regimen may further increase the levels of maintenance of remission.<sup>14,15</sup>

However, while there is a wealth of data showing the efficacy of mesalazine in UC as a whole, there are few studies reporting specifically on oral mesalazine for left-sided UC, so clinical trial data especially on maintaining remission in left-sided UC are rare and rectally administered preparations, or combinations of rectal and oral therapy remain the most recognised treatment options for active disease.<sup>3,16–18</sup> Although combinations of oral and enema treatment have been shown to be more effective in achieving remission, even in pancolitis, compared with oral alone,<sup>19</sup> long-term therapy with enema formulations is accepted by patients reluctantly.<sup>20</sup>

With a lack of data on the maintenance of remission in left-sided UC with OD slow release mesalazine, a further analysis from PODIUM was required, focusing on patients with left-sided UC, in order to address this gap for this patient population. The efficacy of oral Pentasa 2 g OD versus 1 g BD was determined in terms of clinical outcomes (clinical and endoscopic remission) and mucosal healing.

## 2. Methods

PODIUM was designed to compare the efficacy and safety of two dosing intervals (OD vs BD) of oral mesalazine (2 g/day) for the maintenance treatment of UC. The study methods have previously been published in full.<sup>14</sup> To summarise, PODIUM was a phase III, randomised controlled, investigator-blinded trial; the investigator-blinded design was chosen to allow a comparison to be made on the effect of different dosing frequencies on compliance.

The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki; all patients provided written informed consent prior to any study-related procedure ([ClinicalTrials.gov](http://ClinicalTrials.gov) identifier: NCT00209300).

### 2.1. Patients

Patients who were currently in clinical remission, who had relapsed in the previous 12 months, and with UC that extended >15 cm from the anal verge were eligible for inclusion. Patients were also required to be currently receiving oral mesalazine (<2.5 g/day), sulfasalazine

(<2.5 g/day) or olsalazine ( $\leq$ 1.5 g/day), or have received oral aminosalicylates in the last year. Patients were excluded if they had received immunosuppressants in the previous 3 months, oral or rectal corticosteroids in the previous month, oral therapy at a concentration higher than those mentioned above per week in the previous month, or >3 g per week of rectal mesalazine or sulfasalazine in the previous month.

## 2.2. Study treatment

Eligible patients were randomised into two groups to receive oral ethylcellulose-coated mesalazine (Pentasa; 2 g/day). Patients received either once daily treatment with a single sachet of 2 g mesalazine granules, or twice daily treatment with 2 × 1 g sachets, for 12 months.

## 2.3. Efficacy analyses

Disease activity was assessed at baseline and at months 4, 8 and 12 using the Ulcerative Colitis Disease Activity Index (UC-DAI) score, including clinical and endoscopic parameters (abbreviated UC-DAI without endoscopic assessment at months 4 and 8).

The primary endpoint was to demonstrate that 2 g mesalazine OD was non-inferior to 1 g mesalazine BD in terms of remission rate, based on the 95% CI margin of  $-10$  used in the primary analysis. Remission was defined as a UC-DAI score <2. Secondary endpoints included endoscopic evaluation, time to relapse, severity of relapse, rectal bleeding and normal stool frequency, acceptability and compliance.

A planned subgroup analysis was performed to assess non-inferiority of 2 g mesalazine OD to 1 g mesalazine BD in terms of remission rate in patients with left-sided colitis. Mucosal healing was assessed endoscopically. Sigmoidoscopy assessments were undertaken at enrolment and on completion of the study or on withdrawal or discontinuation. Assessment of the mucosa was done according to the UC-DAI dimension 'mucosal appearance' 3-point score (the score could range from 0 to 3 depending on the status of the mucosa: 0 = normal; 1 = erythema, reduced capillary network, mild friability, minimal granularity; 2 = friability, marked erythema, no vascularisation, erosion, pus; 3 = ulceration, spontaneous bleeding, pus).

## 3. Results

### 3.1. Patient disposition/baseline characteristics

A total of 362 patients were included in the study and were randomised to receive either mesalazine 2 g OD (n=175) or mesalazine 1 g BD (n=187). Baseline demographics were well balanced and there were no significant differences between the two treatment groups within the left-sided or overall populations, or between the left-sided and overall population. Of the 362 patients in the study, 71.5% (n=259) had left-sided colitis and 28.5% had extensive disease (pancolitis; n=103). The high number of patients with left-sided colitis who were included in the study makes this a

substantial group to analyse separately. The disease subgroups were evenly distributed across the trial with 74.9% of the OD group and 68.4% of the BD group having left-sided colitis, and 25.1% of the OD group and 31.6% of the BD group having pancolitis (Table 1).

## 3.2. Efficacy outcomes

### 3.2.1. Remission rates

The study met the primary endpoint of non-inferiority for OD versus BD dosing in terms of remission in the subgroup of patients with left-sided UC (Fig. 1) and in the overall population (the data for which have been published previously).<sup>14</sup> The sub-analysis of patients with left-sided UC showed an 8% difference (95% CI:  $-4.8$ – $20.2$ ) in the 12-month clinical and endoscopic remission rates between OD and BD dosing, which indicated non-inferiority between the treatment groups. Clinical and endoscopic remission rates were 69% with OD dosing (95% CI: 59.5–76.5) and 61% with BD dosing (95% CI: 51.4–69.6,  $p=0.310$ ) (Fig. 2). In the overall study population, statistical analysis showed a significant superiority of OD to BD dosing with an 11.9% difference in remission rate (95% CI: 1.4–22.5) in favour of the OD treatment group. Kaplan–Meier analysis demonstrated that 70.9% of the OD treatment group and 58.9% of the BD treatment group remained in clinical and endoscopic remission at 12 months following randomisation ( $p=0.024$ ).<sup>14</sup>

### 3.2.2. Compliance

In this clinical trial setting, compliance measured by the number of sachets used was not significantly different between the two treatment groups. However, compliance as measured by visual analogue scale score was significantly better for OD than BD dosing and this increase in compliance could be the main reason for the better outcomes seen in the OD group compared with the BD group.<sup>14,15</sup> Acceptability of treatment was high in both groups, with 85.6% of patients in the BD group and even more patients, 96.3% in the OD treatment group finding treatment acceptable.

### 3.2.3. Mucosal healing

In the PODIUM subpopulation of patients with left-sided colitis, data on mucosal healing were also analysed. Baseline mucosal scores of 0 or 1 were seen in 99.2% of OD patients and 100% of BD patients. After 12 months, those with scores of 0 or 1 were 84.4% and 78.8%, respectively. The mucosal appearance was normal (score 0) in 49.6% and 61.4% of patients in the OD and BD groups at baseline and in 46.8% and 45.4% after 12 months, respectively (Table 2). The difference between treatment regimens was not significant.

## 3.3. Safety

Safety analyses showed that Pentasa was well tolerated in both dosing regimens, with no statistical difference in the number of adverse events experienced between the treatment groups (42.9% of patients in the OD group and 36.4% in the BD group reported one or more adverse events during the study). Six patients receiving OD treatment and four receiving BD treatment experienced a serious adverse event,

**Table 1** Baseline characteristics and demographics of randomised patients.

		Overall population		Left-sided colitis population	
		2 g Pentasa OD N=175	1 g Pentasa BD N=187	2 g Pentasa OD N=131	1 g Pentasa BD N=128
Gender, n (%)	Male	95 (54.3)	96 (51.3)	74 (56.5)	60 (46.9)
	Female	80 (45.7)	91 (48.7)	57 (43.5)	68 (53.1)
Age, years	Mean (SD)	48.7 (15.0)	47.2 (14.1)	49.1 (14.4)	48.1 (13.7)
	Range	19–80	18–82	19–80	20–82
Smoking status, n (%)	Currently smoking	21 (12.0)	21 (11.2)	13 (9.9)	14 (10.9)
	Smoked in the past	69 (39.4)	87 (46.5)	53 (40.5)	64 (50.0)
	Never smoked	85 (48.6)	79 (42.2)	65 (49.6)	50 (39.1)
Pancolitis, n (%)		44 (25.1)	59 (31.6)		
Left-sided colitis, n (%)		131 (74.9)	128 (68.4)		

Baseline characteristics for the overall population have previously been published in full.<sup>14</sup>  
SD = standard deviation.

all of which were considered to be not related or unlikely related to the study medication. The most frequently reported treatment-emergent adverse events were gastrointestinal disorders (abdominal pain, diarrhoea and flatulence) and infections and infestations (bronchitis, gastroenteritis, nasopharyngitis and sinusitis). The majority of these were mild or moderate and considered by the investigator to be unrelated or unlikely related to the study medication.

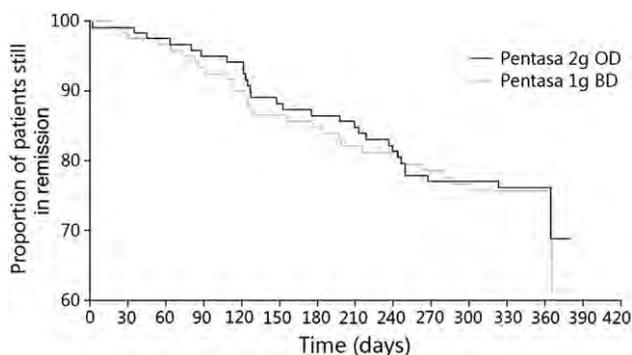
#### 4. Discussion

The clinical efficacy benefit of rectally administered agents for the treatment of left-sided UC is well documented as having good endoscopic and histological outcomes and infrequent side-effects. However, considering the issues associated with topical administration of therapy for left-sided UC, such as patient compliance and disease resistance to topical agents, the need of an alternative, effective oral formulation for this population still remains.<sup>21</sup> The present subgroup analysis compares the efficacy of a OD dosing of slow-release mesalazine granules with the standard BD regimen and reports them as similarly effective in UC patients with left-sided disease. This indicates that sufficient levels of mesalazine are available in the distal colon and that the

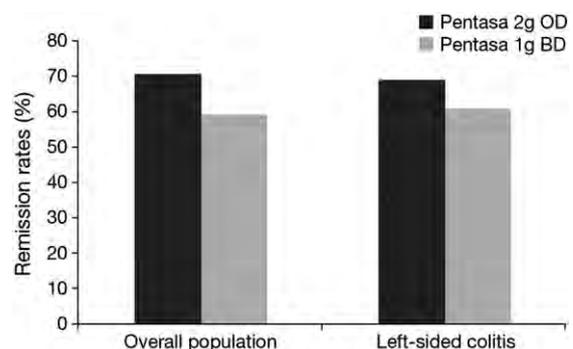
unique release profile of Pentasa enables its use for UC regardless of the specific disease location. In addition, since the release of Pentasa is independent of intestinal pH there will be no negative influence on 5-ASA release due to pH fluctuations, which are often seen in UC patients.<sup>20</sup>

The PODIUM study reported data for clinical and endoscopic remission combined; in contrast many trials report only clinical remission. The difference between the types of remission reported in a trial has a profound effect on the comparability of data, with some types of remission being more subjective and easier to achieve compared with others. Other published long-term studies have compared the effect of OD versus BD mesalazine in the maintenance of remission of UC. A recent study of Salofalk® (Dr. Falk Pharma GmbH, Freiburg, Germany) investigating the efficacy of 3 g OD versus 1.5 g OD versus 0.5 g three times daily showed that 3 g OD was the most effective dose for maintenance of remission in UC.<sup>22</sup> Another study confirmed that OD dosing of mesalazine-MMX was non-inferior to BD dosing, however this was primarily a safety study.<sup>23</sup>

The value of mucosal healing as a trial endpoint is beginning to be more widely accepted in patients with UC. Mucosal healing has been significantly associated with a low risk of future colectomy ( $p=0.02$ ),<sup>24</sup> and has recently become a



**Figure 1** Kaplan–Meier estimated UC-DAI remission rates in patients with left-sided UC, where remission is defined as a UC-DAI total score <2.



**Figure 2** Twelve-month clinical and endoscopic remission rates for patients in the overall population and in the left-sided colitis subgroup.

**Table 2** Mucosal appearance at baseline and after 12 months of treatment. (0 = normal; 1 = erythema, reduced capillary network, mild friability, minimal granularity; 2 = friability, marked erythema, no vascularisation, erosion, pus; 3 = ulceration, spontaneous bleeding, pus) Score could range from 0 to 3 depending on the status of the mucosa.

	Mucosal healing score	Overall population		Left-sided colitis population	
		2 g Pentasa OD N=175	1 g Pentasa BD N=187	2 g Pentasa OD N=131	1 g Pentasa BD N=128
		Patients, %	Patients, %	Patients, %	Patients, %
Baseline	0	54.3	58.6	49.6	61.4
	1	45.1	40.9	49.6	38.6
	0 or 1	99.4	99.5	99.2	100
End of study (12 months)	0	49.3	46.2	46.8	45.4
	1	36.1	35.2	37.6	33.3
	0 or 1	85.4	81.4	84.4	78.8

pivotal therapeutic goal.<sup>25</sup> However, the different terminology and definitions that are used across clinical trials make the comparison of the effect of mesalazine across studies difficult.<sup>26</sup> After 12 months of maintenance therapy in the PODIUM study of Pentasa, 85.4% and 81.4% of patients in the OD and BD groups, respectively, showed a mucosal score of 0 or 1 in the overall population. This is similar to published data for mucosal healing in other studies of mesalazine, including up to 80% of patients achieving mucosal healing (score 0 or 1) with 4.8 g/day mesalazine at week 6 in the ASCEND studies.<sup>27,28</sup> However it should be noted that a mucosal healing score of 1 does include some signs of minor inflammation such as erythema (excluding marked erythema) and mild friability. In another study that used a different definition of mucosal healing (score <1) 77.6% of patients achieved mucosal healing with 4.8 g/day mesalazine at week 12.<sup>29,30</sup> In the left-sided UC population from the present study, the data indicate that mucosal healing was maintained (score 0 or 1) in a high number of patients in both treatment arms (84.4% in the OD group and 78.8% in the BD group). Importantly, almost half of the patients with left-sided UC in our study had a 'normal' mucosal appearance at 12 months (score 0; 46.8% in the OD group and 45.4% in the BD group), the 'ideal outcome' in UC.<sup>25</sup> Although the results based on mucosal appearance (score 0 or 1) were not significantly different between the two study groups, a tendency towards a higher percentage of patients with near-normal appearance of the mucosa was observed in those patients receiving 2 g Pentasa OD. There may also be a trend for potential benefit of the OD group in maintaining a normal mucosa (score 0); 61.4% patients in the Pentasa BD group had a mucosal score of 0 at baseline compared with only 45.4% at 12 months (16.0% fewer), whereas in the Pentasa OD group there was little difference between the two time points (49.6% at baseline versus 46.8% at 12 months; only 2.8% fewer). The smaller difference of the OD group (2.8% versus 16.0%) in maintaining a mucosal healing score of 0 between baseline and 12 months in this study could be a hint at higher mucosal healing rates with OD dosing. However it is difficult to draw conclusions from these data, given the intergroup variability at the beginning of the study.

Endoscopic findings in patients with UC are linked to the clinical response of the patient. It may be that mucosal healing serves as an important surrogate endpoint with

prognostic value.<sup>31,32</sup> This study showed that more than 80% of patients in both treatment groups in the overall population, and more than 75% in both treatment groups in the left-sided UC population, maintained mucosal healing. A Norwegian study has shown that patients who achieved mucosal healing were at a lower risk of needing surgery than those without mucosal healing within the following 12 months. Patients who achieved mucosal healing had a 78% reduced risk of having to undergo colectomy compared with patients without healing after 12 months and also had a reduced risk of severe recurrence for the following 5 years.<sup>33</sup> In addition, the St. Mark's surveillance database showed that the risk of developing colorectal cancer was 5 times higher in patients with histological inflammation, and 2.5 times higher in patients with endoscopic inflammation.<sup>34</sup> Patients with left-sided colitis have a greater risk of developing CRC than patients with proctitis due to the extent of the disease.<sup>35</sup> Treatments such as Pentasa that provide availability of drug throughout the colon and lead to increased mucosal healing may be related to long-term improved outcome. Current ECCO guidelines recommend continued use of mesalazine as long-term maintenance therapy since this may reduce the risk of colon cancer.<sup>3</sup>

In conclusion, the additional results presented here from the phase III PODIUM study indicate similar efficacy with mesalazine in patients with left-sided colitis compared with the overall trial population for the maintenance of remission in mild-to-moderate quiescent UC. This supports the hypothesis that slow-release oral mesalazine granules (Pentasa) provide sufficient availability of the active drug in the distal colon, independent of intestinal pH, confirming its effectiveness in distal disease. The availability of OD preparations of mesalazine that can be taken orally and still provide sufficient concentrations to treat distal disease allows physicians greater flexibility in prescribing. An added benefit of tailoring therapy according to the patient's preferences for treatment and lifestyle is that it may also increase adherence to therapy in patients with left-sided disease.

## Conflict of interest

B Bokemeyer: lectures supported by the following companies; Ferring, Falk, Abbott, MSD, UCB, and Shire. Study

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I Gill: no conflict of interest declared.

P Broberg: is an employee of Ferring Pharmaceuticals.

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