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Randomised clinical trials: Early assessment after two weeks of high-dose mesalazine for moderately active ulcerative colitis – new light on a familiar question

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Early assessment after 2 weeks of high dose 5-ASA for moderately active UC: new light on a familiar question

Response to comments

Editor

Can you assure me that you can provide written permission from the Authors of the two studies that provided the data, and that this is the only post-hoc analysis of these data that is being published?

The two original ASCEND studies and the current analysis were all sponsored by Procter & Gamble Pharmaceuticals/Warner Chilcott. As such, we are pleased to confirm that permission has been granted for the current analysis to be conducted and submitted for publication.

We are also pleased to confirm that the current analysis is the only post-hoc analysis of the patient diary data and the time to symptom improvement that has been performed. We acknowledge that other analyses of the ASCEND data have been presented (including a recent analysis of mucosal healing, Lichtenstein *et al.*, *Aliment Pharmacol Ther* 2011), but the current study is the only analysis of the symptom data. As such, this manuscript presents a new and unique insight into symptom resolution with high-dose 5-ASA therapy, and evaluates practical recommendations on the timescales for treatment review.

AP&T has a specific style for some Titles, for example “Randomised clinical trial: ...”, hence this Title should be, “Randomised clinical trials: early assessment after two weeks of high-dose mesalazine for moderately active ulcerative colitis”.

The title of the manuscript has been amended accordingly:
“Randomised clinical trials: Early assessment after two weeks of high-dose mesalazine for moderately active ulcerative colitis – new light on a familiar question”

AP&T has a specific style for the Summary: Background, Aim, Methods, Results, Conclusions - all in <250 words. The Clinical trial number should be at the end of the Summary, and not within the word limit.

As requested, the clinical trial numbers for the ASCEND I and II studies has been added to the end of the Summary. Additional amends have been made to the Summary in line with the requested word limit.

“(Clinicaltrials.gov: NCT00577473, NCT00073021)”

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Reviewer: 1

Orchard et al present an analysis of data combined from ASCEND I and II. In these studies, patients with moderately active ulcerative colitis were randomised to 2.4g/ day or 4.8g/ day of asacol. They show a more rapid improvement and resolution of rectal bleeding and the combined endpoint of rectal bleeding and stool frequency but no more rapid an improvement in stool frequency with 4.8g.

There are a number of problems with this paper.

1. It has all of the inherent weaknesses of industry sponsored studies particularly with relation to post-hoc analyses.

Some elements of this study are indeed based on *post hoc* analyses, although we note that the time to symptom resolution was a prespecified secondary endpoint of the ASCEND studies. We acknowledge that such *post hoc* analyses display certain limitations with regard to their interpretation. We have amended the Summary section to clearly state upfront that *post hoc* analyses were employed.

Summary, pg 3:

"A combination of pre-specified and post hoc analyses were used."

It is stated in the Materials and Methods section that the analysis of time to symptom resolution was prespecified, whereas the remainder of the analyses were *post hoc*.

Materials and Methods, pg 8–9:

"Time to symptom resolution was a prespecified secondary endpoint of ASCEND I and II..."

"The time to symptom improvement and the proportion of patients achieving improvement or resolution of rectal bleeding and/or stool frequency at the clinically relevant time point of day 14 were evaluated in post hoc analyses."

The limitations of *post hoc* analysis are also briefly highlighted in the Discussion section.

Discussion, pg 17:

"There are some limitations in the current analyses, as with all post hoc analyses."

2. What role did the authors have in conception and design of the study? None of them are listed in the author list of the Marion et al abstract.

The authors confirm that they were involved in the conception and design of the analyses presented in this manuscript, although they were not involved in the conduct of the ASCEND I and II studies. Stefan van der Geest is an employee of Warner Chilcott Pharmaceuticals, and was involved in the conception and design of all analyses. Tim

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3 Orchard and Simon Travis played lead roles in proposing and designing the *post hoc*
4 analyses of symptom scores at day 14. All three authors contributed to the interpretation
5 of the data and were involved in preparation of the manuscript.
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10 **3. The oft quoted (in this paper) ECCO statement about assessing response of rectal**
11 **bleeding at 10-14 days is not evidence based and appears to have been derived from**
12 **the results of ASCEND II which leads to a circular logic – ASCEND II shows a**
13 **median response with 4.8g of asacol of 9 days compared to 16 days with 2.4g/ day**
14 **and a post hoc analysis of ASCEND I and II unsurprisingly supports this opinion.**
15
16

17 The advice from ECCO that treatment response may be assessed after 10–14 days is
18 based on a consensus of several leading experts in the field of IBD. This is indeed partly
19 influenced by initial findings from ASCEND II, but detailed evaluations of symptom
20 resolution at day 14 were not available at that time. One of the aims of the present study
21 was to evaluate this recommendation, by examining in detail the percentage of patients
22 experiencing symptom improvement at a corresponding time point, based on a large
23 patient population from both ASCEND I and II. This is not circular logic, but rather a
24 more detailed and comprehensive analysis of the evidence. The findings of this analysis
25 expand on the previous top-line analyses, and thereby provide evidence to support the
26 practical clinical recommendation from ECCO.
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32 **4. Patients were excluded from ASCEND I and II if taking 5-ASAs. This should be**
33 **explicitly stated in this paper as one cannot necessarily generalise these results to**
34 **those already on maintenance 5-ASAs.**
35
36

37 As the reviewer notes, the exclusion criteria of the ASCEND I and II studies (published
38 previously^{1,2}) included use of oral 5-aminosalicylate-containing products at a dose
39 >1.6 g/day or topical rectal therapies within the last 7 days. However, we note that lower
40 doses were permitted. We acknowledge that this means the findings may not be directly
41 applicable to those patients receiving maintenance 5-ASA therapy at a dosage above
42 1.6 g/day. A sentence has been added to the Discussion section accordingly.
43
44

45 Discussion, pg 17:

46 *“For example, exclusion of patients receiving 5-ASA >1.6 g/day from the original studies*
47 *means that it is unclear how applicable the current findings are to patients receiving*
48 *higher maintenance doses of 5-ASA before treatment of the active disease.”*
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50

51 Interestingly, in another prespecified subgroup analysis of the ASCEND data, it has
52 been demonstrated that the effect of 5-ASA therapy is larger in patients who have
53 previously taken 5-ASAs; detailed discussion of these data is beyond the scope of the
54 current manuscript.
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5 **5. There are several mentions of improvement or resolution in stool frequency.**
6 **These improvements are not statistically significant and in some cases not clinically**
7 **significant (1 day more rapid improvement in stool frequency and 2% more patients**
8 **with improvement or resolution). They would be best referred to as being no**
9 **difference between 2.4g and 4.8g.**
10

11
12 We acknowledge that the differences between doses with regard to stool frequency are
13 not statistically significant, and agree that the presentation of the data may be confusing.
14 We have adapted the text to clarify that the differences between the doses were not
15 significant.
16

17
18 Results, pg 11:

19 *"There was no significant difference between treatments in the median time to resolution*
20 *of stool frequency (12 days vs 15 days for 4.8 g/day and 2.4 g/day, respectively;*
21 *p=0.206; Figure 1A)."*
22
23

24 Results, pg 13:

25 *"No statistically significant differences were observed between doses in the number of*
26 *patients experiencing improvement or resolution of stool frequency, with more than 80%*
27 *of patients in both treatment groups experiencing symptom improvement (improvement,*
28 *p=0.375; resolution, p=0.329; Figure 3)."*
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33 **6. The data presented in relation to 14 day findings is a little confusing (Symptom**
34 **outcomes after 6 weeks in relation to day 14 findings and table 3). 64% of patients in**
35 **the 4.8 g group had resolution of bleeding at day 14. However, only 67% of those**
36 **who had experienced an improvement at day 14 had resolution of bleeding at 6**
37 **weeks. Did large numbers of patients deteriorate after day 14? Should the table read**
38 **"No further improvement"?**
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40
41

42 We acknowledge that the information presented in this section is complex. In order to
43 conduct the comparison of outcomes at day 14 and week 6, it was necessary to include
44 only patients for whom full data were available at both timepoints. Therefore, of the
45 143 patients who experienced improvement in rectal bleeding at day 14, 125 were
46 included in the current analysis.
47
48

49 In addition, it should be noted that improvements in symptom score are defined relative
50 to the baseline symptom score. Therefore, patients experiencing improvement at both
51 day 14 and week 6 may have improved further after day 14, or may have remained the
52 same. The definitions of improvement and resolution are such that any patients
53 experiencing resolution of symptoms would also be classified as experiencing
54 improvement, but patients not showing resolution may still be improved compared to
55 baseline.
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3 Thus, out of 125 patients with improvement in rectal bleeding at day 14, 84 patients
4 (67%) experienced resolution at week 6. A total of 108 patients (86%) displayed
5 improvement in rectal bleeding compared to baseline at week 6. The remaining 17
6 patients (14%) deteriorated to their baseline score or worse.
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8

9 To clarify this issue, footnotes have been added to Table 3 and Table 4.
10

11 Table 3, pg 24:

12 *"All improvements in symptom score are defined relative to the patient's baseline score.*
13 *Patients showing improvement at day 14 but no improvement at week 6 experienced*
14 *deterioration of symptoms to their baseline level or worse."*
15
16

17 Table 4, pg 25:

18 *"All improvements in symptom score are defined relative to the patient's baseline score."*
19
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22 **7. What about those patients who had not improved at day 14? To justify this as a**
23 **valid time for assessment of treatment success it is necessary to show that those who**
24 **had not improved failed to develop resolution of symptoms. Otherwise one would**
25 **simply continue with treatment rather than escalating to corticosteroids. Clearly**
26 **more rapid improvement/ resolution is a worthy goal but there would need to be**
27 **justification for escalation to corticosteroids with their attendant side effects.**
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31 We agree that it is important to consider the treatment outcomes for patients who did not
32 show improvements at day 14, and are pleased to provide an additional analysis of
33 these patients. A paragraph has been added to the Results section, and a sentence
34 added to the Discussion section accordingly. Of patients who did not show
35 improvements in rectal bleeding at day 14, only about half went on to show
36 improvements after 6 weeks. This indicates that only a minority of patients who do not
37 improve by day 14 will show later improvements with prolonged treatment, confirming
38 that day 14 is a valid point at which to consider treatment options.
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42 Results, pg 14:

43 *"To further assess the prognostic value of day 14, patients had not responded at day 14*
44 *were also considered (Table 4). Of those patients who did not show symptom*
45 *improvement in rectal bleeding after 14 days, 54% of these patients did not show*
46 *improvement and 54% did not show symptom resolution at week 6 (4.8 g/day group;*
47 *Table 4). Similarly, for stool frequency, of those patients who did not experience*
48 *improvement at day 14, 75% did not show improvement and 85% did not show*
49 *resolution at week 6 (4.8 g/day group; Table 4). Thus, failure to respond at 14 days*
50 *predicted failure to respond at week 6 in the majority of patients."*
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54 Discussion, pg 15:

55 *"Of patients who did not show improvement in rectal bleeding after 2 weeks, only about*
56 *half went on to experience symptom resolution after 6 weeks."*
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Reviewer: 2

This post hoc analysis of previously published studies clearly sets out its aims and methodology

The discussion is well written and is a helpful view of these data in the context of clinical practice and the ECCO consensus guidelines. It serves as a helpful review for practising clinicians in the use and limitations of higher doses of 5 ASA drugs as studied in AScend 1 and II

We gratefully acknowledge the reviewer's comments. No further amendments to the manuscript have been made.

References

- (1) Hanauer SB, Sandborn WJ, Dallaire C, Archambault A, Yacyshyn B, Yeh C, et al. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCEND I trial. *Can J Gastroenterol* 2007;21(12):827-34.
- (2) Hanauer SB, Sandborn WJ, Kornbluth A, Katz S, Safdi M, Woogen S, et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. *Am J Gastroenterol* 2005;100(11):2478-85.

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3 **Randomised clinical trials: Early assessment after two weeks of**
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5 **high-dose mesalazine for moderately active ulcerative colitis –**
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7 **new light on a familiar question**

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17 ³ Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford, UK

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21 ***For submission to Aliment Pharmacol Ther***

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24
25 **Short title:** Time to symptom resolution with high-dose 5-ASA

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Key words

- 5-aminosalicylic acid (5-ASA)
- Mesalazine
- High-dose
- Ulcerative colitis
- Inflammatory bowel disease (IBD)
- Symptom resolution

Previous presentation of data*Median time to symptom resolution*

Marion JF, Safdi M, Schwartz DA et al. Comparison of time to symptom resolution with oral mesalamine 4.8 g/day (800 mg tablet) versus 2.4 g/day (400 mg tablet): analysis of data from two randomized, double-blind, clinical trials in patients with moderately active ulcerative colitis. *Am J Gastroenterol* 2006;100(s9):s290, Abstract 783.

Symptom resolution and improvement at day 14

Orchard TR, Ramsey D, Geest SAPvd, Travis S. Reducing the time to symptom improvement and resolution for moderately active UC. *J Crohn's Colitis* 2009;3:S48, Abstract P095.

SUMMARY

Background

Rapid resolution of rectal bleeding (RB) and stool frequency (SF) is an important goal for ulcerative colitis (UC) therapy and may help guide therapeutic decisions.

Aim

To explore patient diary data from ASCEND I and II for their relevance to clinical decision making.

Methods

Data from two randomized, double-blind, Phase III studies were combined.

Deleted: (ASCEND I and II)

Patients received mesalazine 4.8g/day (Asacol[®] 800mg MR) or 2.4g/day

(Asacol[®] 400mg MR). Time to improvement or resolution of RB and SF was

assessed and the proportion of patients experiencing symptom improvement or

resolution at day 14 evaluated using survival analysis. Symptoms after 14 days

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were compared to week 6. A combination of pre-specified and post-hoc analyses

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were used.

Results

Median time to resolution and improvement of both RB and SF was shorter with

4.8g/day than 2.4g/day (resolution, 19 vs 29 days, $p=0.020$; improvement, 7 vs

9 days, $p=0.024$). 73% of patients experienced improvement in both RB and SF

by day 14 with 4.8g/day, compared to 61% with 2.4g/day. More patients achieved

symptom resolution by day 14 with 4.8g/day than 2.4g/day (43% vs 30%;

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2 p=0.035). Symptom relief after 14 days was associated with a high rate of
3
4 symptom relief after 6 weeks.
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8 *Conclusions*
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10 High-dose mesalazine 4.8g/day provides rapid relief of the cardinal symptoms of
11 moderately active UC. Symptom relief within 14 days was associated with
12 symptom relief at 6 weeks in the majority of patients. Day 14 is a practical
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14 timepoint at which response to treatment may be assessed and decisions
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16 regarding therapy escalation made.
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21 [\(Clinicaltrials.gov: NCT00577473, NCT00073021\)](#)
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INTRODUCTION

The speed of response to treatment of active ulcerative colitis (UC) matters to patients.¹ The cardinal symptoms of active UC are rectal bleeding, stool frequency, urgency and abdominal pain,²⁻⁴ and these symptoms have substantial detrimental effects on the quality of life of sufferers.^{3,5} Moreover, patients typically experience such symptoms for a considerable number of days per year: nearly 40% of patients experience symptoms for more than 180 days per year and two-thirds of patients experience relapses every few months.^{3,6}

In clinical trials, emphasis is usually placed on treatment response after a fixed period, as assessed using a variety of rating scales for disease activity, such as the UC disease activity index (UC-DAI).^{7,8} Although such scales are useful for providing detailed comparisons and the statistical power necessary for clinical trials,⁸ improvement in symptoms is very important from the point of view of both patients and physicians. Indeed, in a survey conducted by the European Federation of Crohn's and Colitis Associations (EFCCA), both gastroenterologists and UC patients identified fast symptom relief as one of six key treatment goals for UC therapy.¹

Treatment guidelines from the British Society of Gastroenterology (BSG) and the American College of Gastroenterology (ACG), and an evidence-based consensus from the European Crohn's and Colitis Organisation (ECCO) all recommend 5-aminosalicylates (5-ASAs), such as mesalazine, as effective first-line therapies for mildly and moderately active UC.⁹⁻¹¹ When selecting therapy,

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2 physicians should consider a number of factors, including the severity, extent and
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4 natural history of the disease,^{2,11} but the speed of symptom relief should also
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6 form an important part of therapeutic decisions.
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10 Treatment recommendations from ECCO advise that in patients who do not
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12 respond within 10–14 days, escalation of therapy should be considered.¹¹
13
14 However, to date, treatment response after 14 days has rarely been reported in
15
16 clinical trials.
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20 To test this recommendation, symptom relief (improvement and resolution) was
21
22 evaluated by analyzing a series of large clinical trials of mesalazine for the
23
24 treatment of active UC, based on data collected from patients' daily diaries. In the
25
26 ASCEND I and II studies (**A**ssessing the **S**afety and **C**linical **E**fficacy of a **N**ew
27
28 **D**ose of 5-ASA [4.8 g/day, 800 mg tablet]), a high dose of mesalazine, 4.8 g/day
29
30 (Asacol[®] 800 mg MR tablet [UK and Canada], Asacol[®] HD [US], Warner Chilcott
31
32 Ltd, Larnie, UK), was compared to mesalazine 2.4 g/day (Asacol[®] 400 mg
33
34 delayed release tablet [US], Warner Chilcott Ltd, Larnie, UK), over 6 weeks of
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36 treatment. The third study in this series, ASCEND III, differed in methodology
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38 from the previous studies because it did not include patient diaries in its protocol;
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40 therefore only data from ASCEND I and II are included in the current analysis.
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45 In this paper, we report results relating to the prespecified analyses of time to
46
47 improvement and resolution of the hallmark symptoms of UC (rectal bleeding and
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49 increased stool frequency) with high-dose mesalazine (4.8 g/day) compared to
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2 mesalazine 2.4 g/day. We also report a *post hoc* evaluation of the proportion of
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4 patients who experienced symptom improvement or resolution by the clinically
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6 meaningful time point of day 14. Finally, we report an assessment of the clinical
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8 symptoms after 6 weeks of treatment in comparison to the corresponding
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10 symptoms after 14 days, and discuss the relevance of these results for clinical
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12 practice and therapeutic decision-making in UC.
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For Peer Review

MATERIALS AND METHODS

Study design and participants

Data from two multi-centre, Phase III, randomized, double-blind, double-dummy, active-controlled studies of 6 weeks duration (the ASCEND I and II trials^{12,13}) were combined and analysed. Study design and methodology of both ASCEND I and II trials have been reported in detail.^{12,13}

Eligible patients were randomized in a 1:1 ratio to receive oral mesalazine 2.4 g/day (400 mg tablet) or oral mesalazine 4.8 g/day (800 mg tablet). All patients also received one of two placebo treatments, to maintain a double-dummy design. Both patients and investigators were blinded to treatment assignment. Although not prespecified in the protocols, the trials were designed so that data from the individual trials could be combined into one data set following completion of both studies.

Efficacy assessments and post hoc analyses

Evaluations of efficacy were performed in the intent-to-treat (ITT) population, defined as all randomized patients who received at least one dose of study medication and had a known treatment outcome at week 6. Time to symptom resolution was a prespecified secondary endpoint of ASCEND I and II, and comprised two elements: a) normalization of stool frequency and b) resolution of rectal bleeding. Patients recorded data regarding rectal bleeding and stool frequency symptoms using daily diaries. Patient diary data were collected

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2 through daily telephone calls to an interactive voice response system (IVRS),
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4 from which the time to symptom resolution was calculated.
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9 Analyses of the time to symptom resolution were based on the number of days
10 between the first day of study medication and the first day of symptom resolution,
11 determined from patient diary data. Symptoms were scored using a four-point
12 scale (Table 1). Resolution of rectal bleeding was defined as a rectal bleeding
13 symptom score of 0 (no visible blood in stool). Similarly, resolution of stool
14 frequency was defined as a symptom score of 0 (normal stool frequency). The
15 median time to symptom resolution was calculated as the time at which 50% of
16 patients achieved symptom resolution. Improvement in rectal bleeding and stool
17 frequency were defined as a decrease of at least one point from baseline in the
18 respective symptom score.
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31 The time to symptom improvement and the proportion of patients achieving
32 improvement or resolution of rectal bleeding and/or stool frequency at the
33 clinically relevant time point of day 14 were evaluated in post-hoc analyses.
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36 Additional analyses investigated the appropriateness of day 14 for assessing the
37 response to 5-ASA therapy, by evaluating patients' symptom improvement or
38 resolution after 6 weeks in comparison to their corresponding symptom scores at
39 day 14.
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1
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3 *Statistical analysis*

4 Statistical analyses and sample size calculations in the ASCEND I and II studies
5 have been reported previously.^{12,13} In the current analyses, times to symptom
6 improvement and resolution were evaluated using survival analysis methods and
7 Kaplan–Meier estimates. Kaplan–Meier estimates are provided for each
8 treatment group. Log-rank tests were used to evaluate differences between the
9 2.4 g/day and 4.8 g/day doses. Patients with a known treatment outcome at
10 week 6 who withdrew from the study prior to completion were censored at the
11 time of withdrawal. Patients who did not achieve symptom improvement or
12 resolution at the end of the 6-week study period were also censored.
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RESULTS

Patient characteristics

A total of 687 patients with mild to moderately active UC were randomized to treatment in the two studies. Of these patients, 448 had moderately active disease. In total, 423 patients with moderately active UC were included in the overall efficacy ITT population, comprising 200 patients in the 4.8 g/day group and 223 patients in the 2.4 g/day group. Symptom score data were available for the majority of patients in the ITT population. Baseline demographic and disease characteristics were similar between treatment groups (Table 2).

Median time to symptom resolution and improvement

Median times to resolution and improvement of rectal bleeding and stool frequency symptoms are shown in Figure 1. Resolution of rectal bleeding was achieved in a shorter median time with mesalazine 4.8 g/day, compared to mesalazine 2.4 g/day (9 days vs 16 days, respectively; $p=0.007$; Figure 1A).

There was no significant difference between treatments in the median time to resolution of stool frequency (12 days vs 15 days for 4.8 g/day and 2.4 g/day, respectively; $p=0.206$; Figure 1A). When rectal bleeding and stool frequency were evaluated together (i.e. both resolution of rectal bleeding and normalization of stool frequency), the median time to symptom resolution was significantly shorter with the 4.8 g/day dose, compared to the 2.4 g/day dose (19 days and 29 days, respectively; $p=0.020$; Figure 1A).

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2 Similar results were observed for symptom improvement. The median time to
3 improvement in both rectal bleeding and stool frequency combined was shorter
4 with 4.8 g/day than 2.4 g/day (7 days vs 9 days, respectively; $p=0.024$; Figure
5
6
7 1B). The individual symptoms of rectal bleeding and stool frequency both
8 improved in median times of 4 and 5 days with mesalazine 4.8 g/day and
9 2.4 g/day, respectively ($p=0.027$ and $p=0.348$ for rectal bleeding and stool
10 frequency, respectively; Figure 1B).
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18 *Symptom improvement and resolution over time*

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20 Survival analyses for improvement or resolution of both rectal bleeding and stool
21 frequency combined are shown in Figure 2. Treatment with mesalazine 4.8 g/day
22 was associated with consistently higher rates of both symptom improvement and
23 complete resolution of symptoms, compared to mesalazine 2.4 g/day. Visual
24 separation of the curves was observed within 1 week of treatment initiation, and
25 was maintained throughout the study (Figure 2).
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35 *Symptom improvement and resolution at day 14*

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37 A *post hoc* analysis of symptom improvement and resolution at day 14 was
38 conducted, based on the survival analysis. At this time point, more patients had
39 experienced improvement or resolution of symptoms with 4.8 g/day, compared to
40 2.4 g/day (Figure 3). In total, 73% of patients in the 4.8 g/day group
41 demonstrated improvement in both rectal bleeding and stool frequency by day
42 14, compared to 61% in the 2.4 g/day group ($p=0.046$; Figure 3). Resolution of
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2 both rectal bleeding and stool frequency occurred in 43% of patients receiving
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4 4.8 g/day, and 30% of patients receiving 2.4 g/day (p=0.035; Figure 3).
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8 Overall, 89% of patients experienced improvement in rectal bleeding by day 14
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10 with 4.8 g/day, of whom 64% observed a complete absence of blood in their stool
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12 at this time point (Figure 3). Significantly more patients in the 4.8 g/day group
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14 experienced improvement or resolution of rectal bleeding, compared to the
15
16 2.4 g/day group (improvement, p=0.040; resolution, p=0.011; Figure 3). No
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18 statistically significant differences were observed between doses in the number
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20 of patients experiencing improvement or resolution of stool frequency, with more
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22 than 80% of patients in both treatment groups experiencing symptom
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24 improvement (improvement, p=0.375; resolution, p=0.329; Figure 3).
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Deleted: More patients receiving 4.8 g/day experienced improvement or resolution of stool frequency, compared to 2.4 g/day; however, no statistically significant difference was observed

27 28 *Symptom outcomes after 6 weeks in relation to the 14 day findings*

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30 Of the patients in the 4.8 g/day group who experienced symptom resolution at
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32 week 6, 85% displayed symptom improvement and 65% displayed symptom
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34 resolution at day 14 (rectal bleeding and stool frequency combined). Similar
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36 results were observed when each symptom was examined separately; of
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38 particular note, 95% of the patients who experienced resolution of rectal bleeding
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40 at week 6 (4.8 g/day group) had experienced improvements by day 14. In
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42 addition, similar findings were observed in the 2.4 g/day group.
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47 In order to assess the prognostic value of assessments at day 14, patients who
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49 experienced symptom improvements at day 14 were examined at the conclusion
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2 of the study (where data were available). Of the patients in the 4.8 g/day group
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4 who displayed improvement in rectal bleeding after 2 weeks, 86% also showed
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6 improvement in rectal bleeding at week 6, and 67% experienced resolution of
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8 bleeding (Table 3). Correspondingly, of patients experiencing stool frequency
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10 improvement at 2 weeks (4.8 g/day group), 74% experienced improvements at
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12 week 6, and 52% showed resolution of this symptom at week 6 (Table 3). Similar
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14 findings were observed in the 2.4 g/day group (Table 3). These findings suggest
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16 that the majority of patients who have a clinical improvement at day 14 maintain
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18 this improvement at 6 weeks.
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22 To further assess the prognostic value of day 14, patients who had not
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24 responded at day 14 were also considered (Table 4). Of those patients who did
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26 not show symptom improvement in rectal bleeding after 14 days, 54% did not
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28 show improvement and 54% did not show symptom resolution at week 6 (4.8
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30 g/day group; Table 4). Similarly, for stool frequency, of those patients who did not
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32 experience improvement at day 14, 75% did not show improvement and 85% did
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34 not show resolution at week 6 (4.8 g/day group; Table 4). Thus, failure to respond
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36 at 14 days predicted failure to respond at week 6 in the majority of patients.
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DISCUSSION

Evaluation of treatment efficacy based on symptom resolution and improvement provides a practical measure of treatment success from the patient's point of view. Symptom resolution is, naturally enough, one of the key goals for UC therapy.^{1,14} However, clinicians are also concerned about under-treatment of active UC and need objective criteria upon which to base decisions to augment therapy, usually with the introduction of steroids. The activity indices that are used in clinical trials, which include endoscopy in addition to symptom scores, may provide a more comprehensive assessment of disease activity; however, it is the assessment of resolution or improvement in symptoms that is of paramount importance to patients. Hence, in daily clinical practice, simple symptom assessments form an integral part of therapeutic decision-making.

The ECCO consensus recommends that if rectal bleeding persists beyond 10–14 days, then response to 5-ASA treatment can be considered slow, and treatment may be augmented if necessary. This often involves the use of oral corticosteroids.¹¹ Nearly two-thirds of patients receiving mesalazine 4.8 g/day achieved resolution of rectal bleeding by day 14, and almost 90% demonstrated improvement. This suggests that initial treatment with mesalazine 4.8 g/day alone is a valid treatment option for patients experiencing moderately active UC, since it provides effective relief of symptoms within 2 weeks. Moreover, 67% of patients who showed improvement of rectal bleeding after 2 weeks went on to display resolution of rectal bleeding after 6 weeks. Of patients who did not show improvement in rectal bleeding after 2 weeks, only about half went on to

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2
3 experience symptom resolution after 6 weeks (irrespective of 5-ASA dose).

4 These analyses, combined with the high rate of treatment response at day 14,
5
6 confirm that 2 weeks is a clinically relevant period for assessing the response to
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8 5-ASA therapy for patients with moderately active UC, in line with the interval
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10 recommended in the ECCO consensus on UC management.¹¹ In addition, a
11
12 recent analysis of the PINCE study has demonstrated that when combining rectal
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14 and oral formulations of slow-release mesalazine (Pentasa, Ferring
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16 Pharmaceuticals Ltd, Langley, UK), symptom relief can be achieved within 2
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18 weeks for the majority of patients.¹⁵
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22 This confirmation of the value of the 2-week time point is helpful as it allows
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24 clinicians to give patients clear advice about the timescale over which
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26 improvement may be expected: it can be explained to patients that improvement
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28 of symptoms can be expected within 2 weeks, and if that does not occur then
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30 appropriate adjustment of therapy can be made. For example, those patients who
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32 still have rectal bleeding after 2 weeks could be asked to telephone to request an
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34 early follow-up appointment, or an advice line or telephone follow-up could be
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36 offered at 2 weeks to assess progress. This is a more sophisticated approach
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38 than making routine follow-up appointments in outpatient clinics. Furthermore,
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40 knowledge of the likely timescale of symptoms may help some patients to cope
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42 with their symptoms and reduce the impact on their daily lives.
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47 It is generally accepted that corticosteroids, although effective, exert negative
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49 side effects and that their use should be avoided if possible. The question is how
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2 to do this safely, without exposing the patient to a prolonged period of miserable
3 symptoms through under-treatment. The data at day 14 show resolution of rectal
4 bleeding in 64% of patients, normalization of stool frequency in 58% of patients,
5 and resolution of both symptoms in 43% of patients (4.8 g/day group), with
6 improvement of symptoms occurring in even higher percentages. These numbers
7 justify the use of high-dose 5-ASA as first-line treatment in moderately active UC,
8 reserving steroids for those who do not respond.
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18 The data in Figure 3 also allow a comparison between the two mesalazine doses,
19 with regard to the potential need for therapy escalation. If response to treatment
20 were assessed after 14 days, steroids may potentially be used in those patients
21 with persistent rectal bleeding. Thus, in the 2.4 g/day group, 51% of patients
22 would receive steroids, compared to 36% of patients in the 4.8 g/day group – a
23 potential reduction in steroid use of 29%.
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33 There are some limitations in the current analyses, as with all *post hoc* analyses.

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35 For example, exclusion of patients receiving 5-ASA >1.6 g/day from the original
36 studies means that it is unclear how applicable the current findings are to patients
37 receiving higher maintenance doses of 5-ASA before treatment of the active
38 disease. Furthermore, it is not known how well symptom relief correlates with
39 overall clinical remission, or endoscopic mucosal healing. Symptom scores in
40 these analyses were based on patient self-assessments, so are relatively
41 subjective, although it can be argued that the perception of their own symptoms
42 is what matters most to the patient. There is considerable variability in what
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2 patients consider a 'normal' stool frequency to be, and the definition of normality
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4 may change over time for individual patients.⁵ Since the definition of remission in
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6 any individual clinical trial may have a considerable effect on the study
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8 outcome,¹⁶ variations in patients' definitions of normality would almost certainly
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10 affect apparent treatment efficacy. However, it is difficult to see how more
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12 objective methods of measuring symptoms might be achieved, and patient-
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14 assessed symptom relief provides a valuable insight into their perspective of
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16 treatment success.
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20 The data presented here suggest that assessment of the response to treatment
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22 can be judged at 14 days, since the large majority of those who will respond to
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24 mesalazine will have experienced cessation of rectal bleeding or noticeable
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26 improvement in their symptoms within this period. By starting mesalazine
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28 treatment with a high dose of 4.8 g/day, symptoms can be relieved rapidly,
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30 allowing patients to cope better with the relapse and resume normal daily
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32 activities. The comparison of results seen after 2 weeks with the results after
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34 6 weeks provides useful information (albeit limited), which supports making
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36 assessment after 2 weeks of treatment a nodal point for therapeutic decision
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38 making.
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STATEMENT OF INTERESTS

Authors' declaration of personal interests

1. Dr Timothy Orchard has served as a speaker, a consultant and an advisory board member for Procter & Gamble Pharmaceuticals (now Warner Chilcott), Ferring Pharmaceuticals and Shire, as well as companies making treatment for ulcerative colitis other than

1
2 aminosalicylate derivatives. He has received research funding from
3 Procter and Gamble Pharmaceuticals and Johnson and Johnson.
4

- 5
6 2. Dr Simon Travis has served as a speaker, a consultant or an advisory
7 board member for Procter & Gamble Pharmaceuticals (now Warner
8 Chilcott), Ferring Pharmaceuticals, Giuliani SpA, UCB Pharma, Shire and
9 Tillotts, as well as companies making treatment for ulcerative colitis other
10 than aminosalicylate derivatives. He has received research funding from
11 Procter & Gamble Pharmaceuticals (now Warner Chilcott), Ferring
12 Pharmaceuticals, Cosmo Pharmaceuticals and UCB Pharma.
13
14 3. Stefan van der Geest is an employee of Warner Chilcott UK Ltd, and was
15 involved in the design of the *post hoc* analyses.
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28 **Declaration of funding interests**

29 The research and writing of this paper were funded in full by Warner Chilcott UK
30 Ltd.
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TABLES**Table 1.** Symptom scoring scales for rectal bleeding and stool frequency (based on the ulcerative colitis disease activity index, UC-DAI)

Stool frequency

0	Normal stool frequency
1	1–2 stools per day greater than normal frequency
2	3–4 stools per day greater than normal frequency
3	5 or more stools per day greater than normal frequency

Rectal bleeding

0	No visible blood in stool
1	Streaks of blood with stool less than half of the time
2	Obvious blood with stool most of the time
3	Blood alone passed

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Table 2. Baseline demographics and disease characteristics for all randomized patients with moderately active ulcerative colitis

	2.4 g/day (N=235)	4.8 g/day (N=213)
	n (%)	n (%)
Number of patients with symptom score data		
Rectal bleeding	174	161
Stool frequency	186	160
Rectal bleeding and stool frequency combined	158	133
Age (years)		
Mean	42.6	43.4
Disease extent		
Proctitis	35 (14.9)	32 (15.0)
Left-sided colitis	147 (62.6)	134 (62.9)
Pancolitis	53 (22.6)	47 (22.1)
Prior treatment		
Corticosteroids (oral or intravenous)	80 (34.0)	68 (31.9)
Immunomodulators	10 (4.3)	9 (4.2)
Sulfasalazine	89 (37.9)	65 (30.5)
Sulfa-free oral 5-ASA	93 (39.6)	96 (45.1)
Any oral 5-ASA	142 (60.4)	127 (59.6)
Rectal therapy	94 (40.0)	86 (40.4)
Baseline stool frequency score		
0 (normal)	17 (7.2)	18 (8.5)
1 (1–2 greater than normal)	86 (36.6)	60 (28.2)
2 (3–4 greater than normal)	80 (34.0)	96 (45.1)
3 (≥ 5 greater than normal)	52 (22.1)	39 (18.3)
Baseline rectal bleeding score		
0 (none)	30 (12.8)	14 (6.6)
1 (streaks, < 50% of time)	58 (24.7)	62 (29.1)
2 (obvious, most of time)	126 (53.6)	123 (57.7)
3 (blood alone)	21 (8.9)	14 (6.6)

Table 3. Response after 6 weeks for patients with symptom improvement at day 14, for patients with moderately active ulcerative colitis

	2.4 g/day	4.8 g/day
	n (%)	n (%)
Improvement in stool frequency at day 14	131 (100)	121 (100)
Improvement in stool frequency at Week 6	99 (76)	89 (74)
No Improvement in stool frequency at Week 6	32 (24)	32 (26)
Improvement in stool frequency at day 14	131 (100)	121 (100)
Resolution of stool frequency at Week 6	69 (53)	63 (52)
No Resolution of stool frequency at Week 6	62 (47)	58 (48)
Improvement in rectal bleeding at day 14	112 (100)	125 (100)
Improvement in rectal bleeding at Week 6	94 (84)	108 (86)
No Improvement in rectal bleeding at Week 6	18 (16)	17 (14)
Improvement in rectal bleeding at day 14	112 (100)	125 (100)
Resolution of rectal bleeding at Week 6	69 (62)	84 (67)
No Resolution of rectal bleeding at Week 6	43 (38)	41 (33)

All improvements in symptom score are defined relative to the patient's baseline score. Patients showing improvement at day 14 but no improvement at week 6 experienced deterioration of symptoms to their baseline level or worse.

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Table 4. Response after 6 weeks for patients not showing symptom improvement at day 14, for patients with moderately active ulcerative colitis

	<u>2.4 g/day</u>	<u>4.8 g/day</u>
	<u>n (%)</u>	<u>n (%)</u>
<u>No improvement in stool frequency at day 14</u>	<u>18 (100)</u>	<u>20 (100)</u>
<u>Improvement in stool frequency at Week 6</u>	<u>7 (39)</u>	<u>5 (25)</u>
<u>No Improvement in stool frequency at Week 6</u>	<u>11 (61)</u>	<u>15 (75)</u>
<u>No improvement in stool frequency at day 14</u>	<u>18 (100)</u>	<u>20 (100)</u>
<u>Resolution of stool frequency at Week 6</u>	<u>1 (6)</u>	<u>3 (15)</u>
<u>No Resolution of stool frequency at Week 6</u>	<u>17 (94)</u>	<u>17 (85)</u>
<u>No improvement in rectal bleeding at day 14</u>	<u>24 (100)</u>	<u>13 (100)</u>
<u>Improvement in rectal bleeding at Week 6</u>	<u>12 (50)</u>	<u>6 (46)</u>
<u>No Improvement in rectal bleeding at Week 6</u>	<u>12 (50)</u>	<u>7 (54)</u>
<u>No improvement in rectal bleeding at day 14</u>	<u>24 (100)</u>	<u>13 (100)</u>
<u>Resolution of rectal bleeding at Week 6</u>	<u>10 (42)</u>	<u>6 (46)</u>
<u>No Resolution of rectal bleeding at Week 6</u>	<u>14 (58)</u>	<u>7 (54)</u>

All improvements in symptom score are defined relative to the patient's baseline score.

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FIGURE LEGENDS

Figure 1. Median time to improvement or resolution of rectal bleeding, stool frequency and both symptoms combined, in patients with moderately active ulcerative colitis. **(A)** Median time to symptom resolution (symptom score = 0); **(B)** Median time to symptom improvement (symptom score decreased by ≥ 1).

Figure 2. Symptom improvement and resolution over time (rectal bleeding and stool frequency symptoms combined) in patients with moderately active ulcerative colitis.

Figure 3. Percentage of patients with moderately active ulcerative colitis who experienced symptom improvement (symptom score decreased by ≥ 1) or resolution (symptom score = 0) at day 14.

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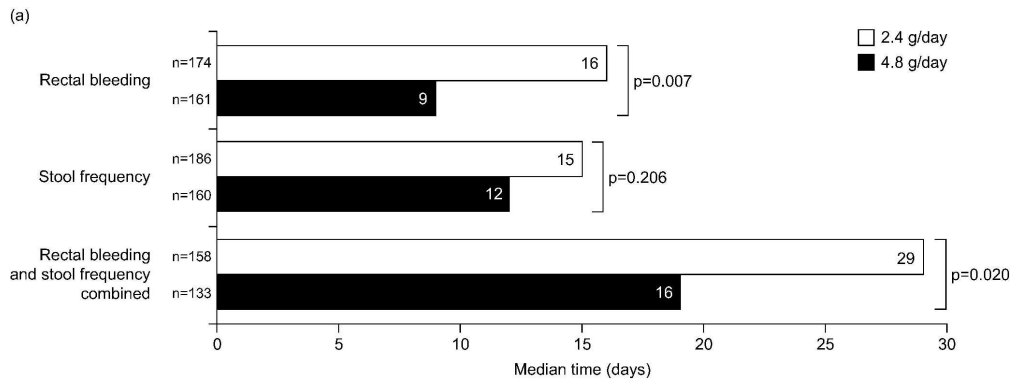


Figure 1A
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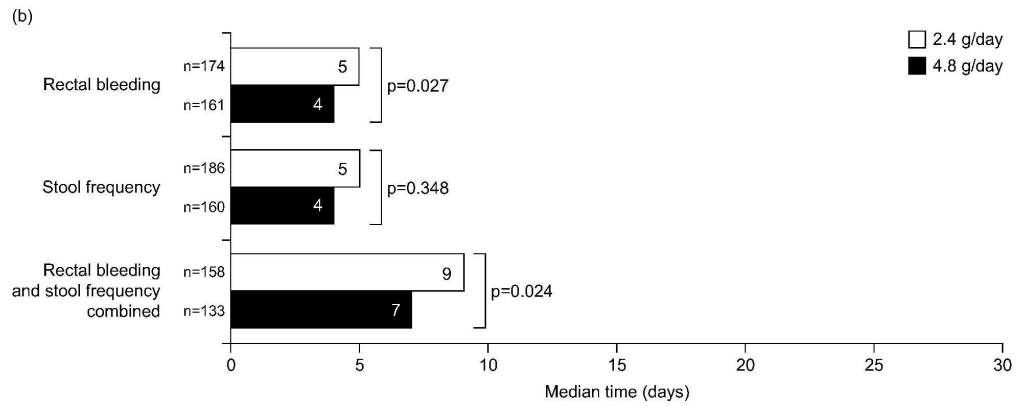


Figure 1B
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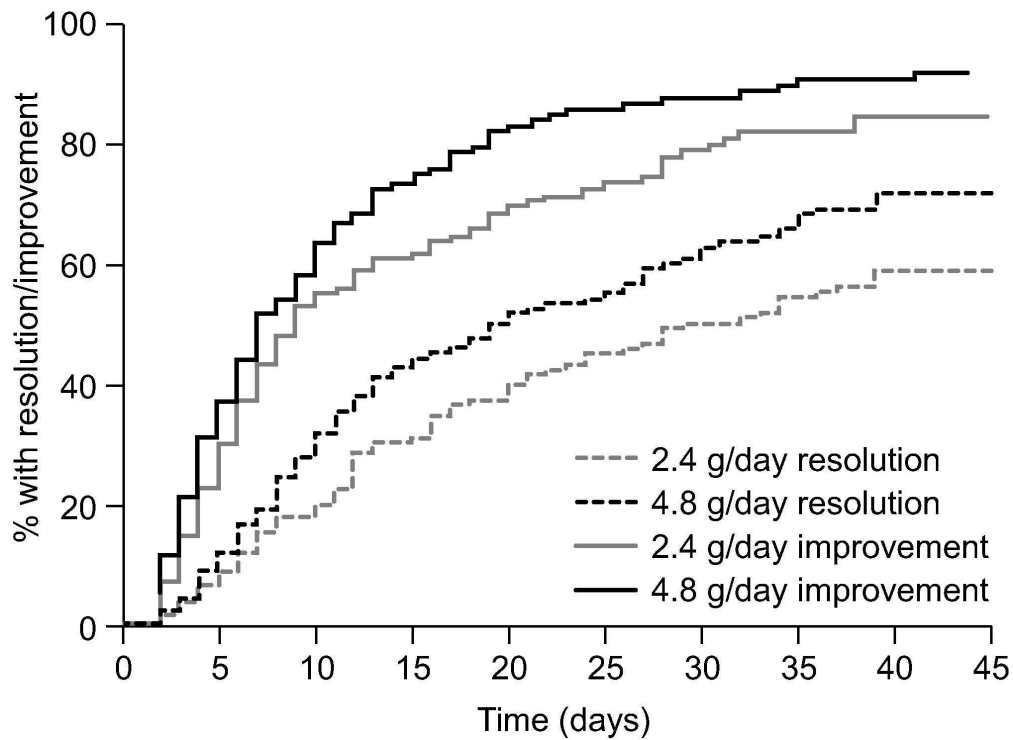


Figure 2
85x62mm (600 x 600 DPI)

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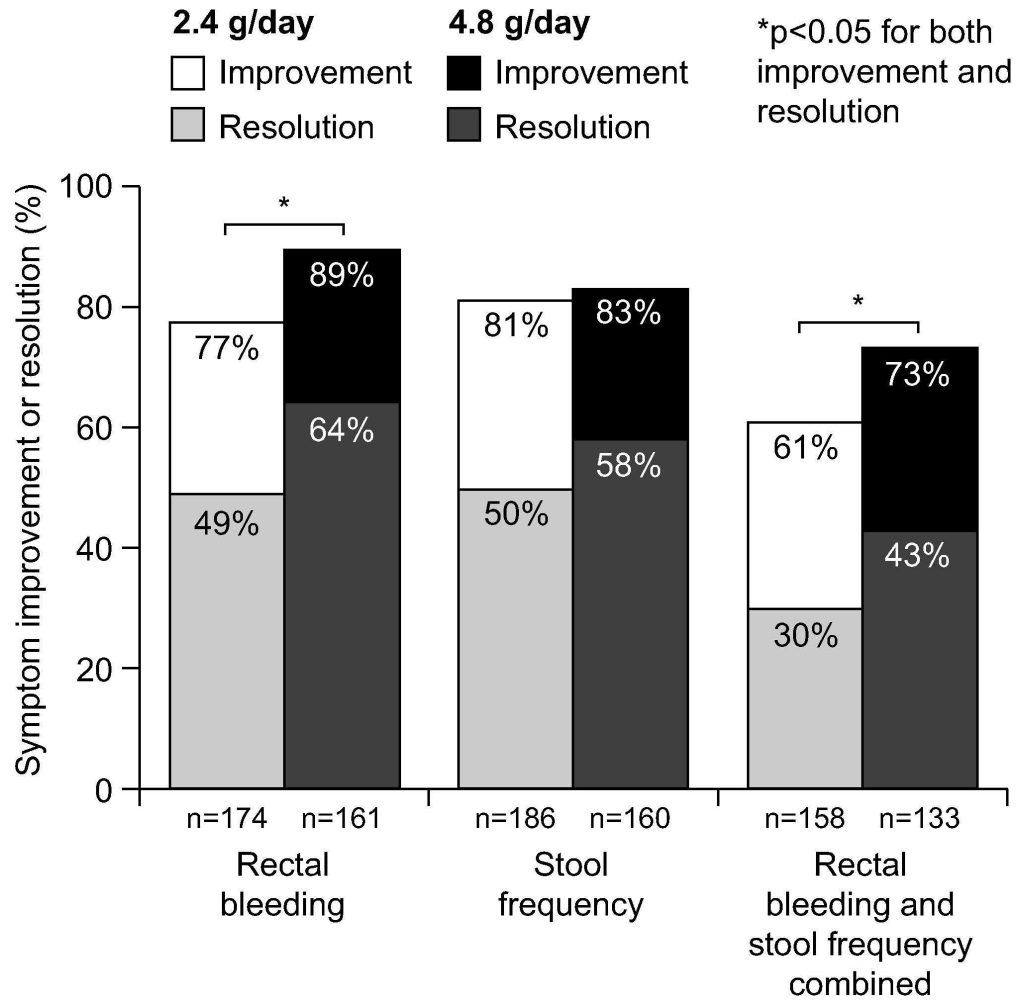


Figure 3
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