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Five or ten cycles of granulocyte-monocyte apheresis (GMA) show equivalent efficacy and safety in ulcerative colitis

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**Five or ten cycles of granulocyte-monocyte apheresis (GMA)
show equivalent efficacy and safety in ulcerative colitis**

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view

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3 **Five or ten cycles of granulocyte-monocyte apheresis (GMA) show**
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6 **equivalent efficacy and safety in ulcerative colitis**
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10 Dignass AU¹, Eriksson A², Kilander A³, Pukitis A⁴, Rhodes JM⁵, Vavricka S⁶
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26
27
28 AD was the Principal Investigator in this multinational study, and led the development of both the
29
30 protocol and the manuscript. AE, AK, AP, JMR, SV participated in the study and the
31
32 development of the manuscript, have reviewed the final draft and approve its submission.
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Disclosures:

Prof. Axel Dignass has served on advisory boards and received consultancy and lecturing funding from Essex Pharma, Centocor, Otsuka Germany, Ferring, Falk Foundation, Merckle Recordati, Shire, Abbott GmbH, UCB, Millenium, and PDL. Prof. Jonathan Rhodes has served on advisory boards for Procter and Gamble, Falk, UCB, Genentech; with the University of Liverpool and Provexis UK, he holds a patent for use of a soluble fibre preparation as maintenance therapy for Crohn's disease.

Keywords: apheresis, dosing, ulcerative colitis, GMA, Adacolumn

ABSTRACT

BACKGROUND: Ulcerative colitis is characterized by leukocyte infiltration into the colonic mucosa. Granulocyte-monocyte-apheresis depletes these cells.

Aim: To assess the non-inferiority of 5 to 10 apheresis treatments in patients with steroid-dependent or steroid-refractory ulcerative colitis.

METHODS: 196 adults with moderate-severe ulcerative colitis were randomized 1:1 to 5 (n=96), or 10 (n=90) open label apheresis treatments. The primary endpoint was non-inferiority of clinical activity index (CAI) score after 12 weeks.

RESULTS: The intent-to-treat population comprised 82 and 80 patients for the 5- and 10-treatment groups, respectively. The difference between the two groups in mean CAI was 0.24 with an upper 95% confidence interval of 1.17, which was below a predefined non-inferiority threshold of 1.33. CAI score improved from baseline in both groups (from 8.7 to 5.6 with 5 treatments, and from 8.8 to 5.4 with 10), with no significant difference between the groups ($P=0.200$). Outcomes for the 5- and 10-treatment groups were similar: Clinical remission: 44% and 40%, respectively ($P=0.636$); clinical response: 56% and 59%, respectively ($P=0.753$). Treatment was well tolerated in both groups.

CONCLUSIONS: This first prospective study comparing apheresis regimens in ulcerative colitis demonstrates that 5 treatments were not inferior to 10 treatments in steroid-refractory or -dependent ulcerative colitis.

Clinical trial URL: <http://www.clinicaltrials.gov/ct2/show/NCT00366925?term=dignass&rank=1>

Clinical trial no. NCT00366925

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3 Ulcerative colitis (UC) is a chronic disease characterized by inflammation of the mucosa
4 of the colon and rectum. Symptoms range from mild to severe and include persistent
5 diarrhea, abdominal pain, urgency and rectal bleeding, as well as extra intestinal
6 symptoms such as fever, weight loss, arthralgia and skin or eye irritations.¹
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12 Aminosalicylates (5-ASA) such as mesalamine are the current standard of care for
13 active UC and are given for the initial induction and maintenance of remission. In cases
14 of insufficient efficacy, second-line treatment is usually with immunosuppressants and
15 corticosteroids. Steroids are well known to be associated with a broad range of adverse
16 events and are not suitable for long-term use for the maintenance of remission.²
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Biologics such as infliximab are a more recent addition to UC therapy, however 30%–
40% of patients do not respond to treatment.³

Active UC is associated with extravasation of large numbers of activated
granulocytes and monocytes into the colonic mucosa.⁴ This infiltration is promoted by
potent pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) interleukin-8
(IL-8), leukotriene B4 and platelet-activating factor.⁴ These leukocytes can cause
extensive mucosal tissue injury through the release of degradative proteases, reactive
oxygen derivatives and pro-inflammatory cytokines.⁵ Inhibiting or removing such
activated leukocytes could therefore be attractive therapeutic approaches to treating UC.

One option for removing the activated cells, and possibly also reducing the
associated circulating cytokines implicated in the pathogenesis of UC, is therapeutic
granulocyte-monocyte adsorptive (GMA) apheresis using an Adacolumn[®] GMA
apheresis device. In this procedure, patient cells such as activated leukocytes, or
proteins such as IgG immune complexes, are removed by selective adsorption to

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3 cellulose beads. Complement fragments such as C3b in the UC patient's blood are
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5 believed bind to the column and render it adsorptive for leukocytes, in particular for
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7 activated cells with a high density of Fc receptors, by a process similar to bacterial
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9 opsonization. Blood is then recirculated back to the patient. The removal of the activated
10
11 cells is followed by a decrease in proinflammatory cytokines.^{6,7} Unlike pharmaceutical
12
13 interventions, selective removal of blood cells or plasma components without the use of
14
15 replacement fluids is associated with minimal side effects^{8,6}. Several studies have
16
17 indicated that GMA apheresis is effective in inducing remission in patients with IBD even
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19 after failure of conventional treatments.⁹⁻¹¹
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25 Conventional apheresis treatment for **inflammatory bowel diseases (IBD)** in the
26
27 European Union uses 5 consecutive weekly treatments as standard.¹² However, in other
28
29 countries, 10 or more GMA apheresis treatments are often used in patients with active
30
31 UC.¹³⁻¹⁵ Obviously, if efficacy and tolerability between the two regimes are comparable,
32
33 the shorter treatment regimen may be of advantage for both patients and prescribers, as
34
35 it would be more convenient, less interventional, and less costly. This prospective
36
37 randomized investigation assessed the non-inferiority of 5-treatment cycles to 10-
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39 treatment cycles with GMA apheresis in moderate-to-severe, active, steroid-dependent
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41 or steroid-refractory UC.
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46 47 **Methods**

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50 This study was approved by the Institutional Review Boards for each study center.
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52 Written informed consent was obtained from all patients before inclusion. The study was
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54 conducted in accordance with the institutional guidelines, Good Clinical Practice
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3 (CPMP/ICH/135/95), the principles outlined in the Declaration of Helsinki, and with
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5 ISO14155, 1 and 2.
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8 **Clinical trial URL:** <http://www.clinicaltrials.gov/ct2/show/NCT00366925?term=dignass&rank=1;>
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10 **Clinical trial no.** NCT00366925
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12 13 14 15 **Objectives** 16

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18 The primary objective of the investigation was to demonstrate the non-inferiority
19
20 of 5-treatment cycles versus 10-treatment cycles with the Adacolumn[®] apheresis device.
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22 The secondary objectives were to assess induction of remission, time to remission,
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24 response and differences between baseline and week 12 levels in: Endoscopic Activity
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26 Index (EAI), fecal calprotectin and C-reactive protein (CRP).
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30 31 **Patients** 32

33 **Inclusion criteria.** At entry, patients were required to be 18–75 years old and to
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35 have a clinical diagnosis of moderate to severe active steroid-dependent or steroid-
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37 refractory UC (diagnosis based on clinical and endoscopic findings, and histology). The
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39 severity of UC was classified using the Clinical Activity Index (CAI; according to
40
41 Rachmilewitz)¹⁶ and patients were required to have a CAI \geq 6 with a stool frequency
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43 score of 2 or 3. Patients were required to have UC for at least 3 months, with colonic
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45 involvement 15 cm beyond the anal verge, for which they were receiving one or more of
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47 the following therapies: a) sulfasalazine, mesalamine or other 5-ASA agents for \geq 4
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49 weeks with a stable dose for the last 2 weeks; b) a maximum of 20 mg/day of
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51 prednisone with a stable dose for the last 2 weeks; or c) 6-mercaptopurine or
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60 azathioprine for \geq 12 weeks with a stable dose for the last 4 weeks. Patients could be

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3 included if they were not receiving the above therapies because of intolerance or
4
5 demonstrated non-response to 5-ASA agents or prednisone after ≥ 2 weeks, or 6-
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7 mercaptopurine or azathioprine after ≥ 4 weeks. Demonstrably adequate peripheral
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9 venous access to allow for completion of the apheresis treatments was also a
10
11 requirement.
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15 **Exclusion criteria.** Patients were excluded from the study if they had evidence of
16
17 toxic megacolon, if surgery within 12 weeks was foreseen, or if they had any known
18
19 obstructive diseases of the gastrointestinal system. Patients were also excluded if they
20
21 had: prior colectomy, total colectomy, ileostomy, stoma or ileal pouch-anal
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23 anastomosis; history of allergic reaction to heparin or heparin-induced
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25 thrombocytopenia; history or hypersensitivity reactions associated with an apheresis
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27 procedure; hypotension ($< 90/65$ mmHg) or uncontrolled hypertension ($> 180/120$ mmHg
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29 despite medical therapy); history of myocardial infarction, unstable angina, coronary
30
31 artery bypass surgery or angioplasty within the last 6 months; liver disease, history of
32
33 cirrhosis or renal insufficiency (serum creatinine $> 150\%$ of upper reference level);
34
35 insulin dependent type I or II diabetes; known bleeding or hypercoagulability disorders;
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37 received infliximab within the last 8 weeks, budesonide within the last 2 weeks, topical
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39 therapy for UC within the last 2 weeks, or previous Adacolumn[®] treatment.
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46 47 ***Study design***

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49 This was an open-label, randomized, multicenter, controlled investigation. We
50
51 aimed to recruit a total of 186 patients to be randomized in a 1:1 ratio to receive either 5
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53 GMA apheresis treatments, once a week over 5 consecutive weeks, or 10-treatments,
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55 twice weekly for the first 2 weeks followed by treatments once a week for the following 6
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3 consecutive weeks. Randomization was performed through a computer generated list.
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5 Patients were allocated to groups by the investigator opening the randomization
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7 envelopes in sequence, and treating the patient according to the dictated treatment
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9 scheme. The randomization scheme utilized blocks, with the aim of ensuring that the
10
11 proportion of patients allocated to the 5- or 10-treatment group was approximately 50%
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13 within a site, within a given country, and in total.
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18 The permitted baseline medication (sulfasalazine, mesalamine or other 5-ASA agents,
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20 6-mercaptopurine or azathioprine, prednisone or glucocorticoids) was continued
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22 throughout the study at constant doses. No newly started treatment was allowed during
23
24 the study period.
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28 Patients attended assessments every week for the full 12 week study period, during
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30 which CAI, hematology values, vital signs, concomitant medication and adverse events
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32 were recorded. Flexible endoscopy (colonoscopy or sigmoidoscopy) for determination of
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34 EAI was performed at screening and at week 12.
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37 38 ***Apheresis treatment***

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40 All patients underwent apheresis treatment using the Adacolumn[®] GMA
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42 apheresis device (JIMRO, Japan; in Europe Otsuka Pharmaceutical Europe Ltd.), which
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44 is an adsorptive, single-use, column filled with cellulose acetate beads of 2 mm in
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46 diameter. These adsorb leukocytes, mainly activated granulocytes and monocytes /
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48 macrophages from blood. Venous blood from one antecubital vein was passed through
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50 the column at a flow rate of 30 ml/min, and returned to the contralateral antecubital vein.
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52 One apheresis treatment lasts 60 minutes, thus a total of 1.8L blood was exposed to the
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54 carriers during one session.¹²
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Response assessment

Disease activity was classified using the Clinical activity Index (CAI) according to Rachmilewitz (Table 1) which comprises assessments for stool frequency, blood in stool, presence of abdominal pain / cramps, investigator's global assessment of symptomatic state, temperature due to colitis, extraintestinal manifestations and laboratory findings.¹⁶ Treatment outcome was classified at week 12 as remission (CAI \leq 4), response (CAI decrease of \geq 3 points), or non-response (all other outcomes). In addition, changes from baseline values to week 12 were compared between groups in macroscopic findings by Endoscopic Activity Index (EAI) according to Rachmilewitz (Table 1), blood C-reactive protein levels, fecal calprotectin levels, and quality of life by European Quality of Life (EuroQoL) and Inflammatory Bowel Diseases Questionnaire (IBDQ) questionnaires.

Statistical analysis

Based on previous post-treatment CAI values (mean \pm standard deviation) of 5.3 \pm 3.5, and defining a non-inferiority limit of 25% by t-test with one-sided $\alpha = 0.05$, our power analysis indicated that 87 patients would be needed in each arm to confirm non-inferiority with 80% power. We therefore aimed to randomize at least 174 patients, at a 1:1 ratio to the 5- or 10-treatment group.

Datasets analyzed in this investigation were the safety, intent-to-treat (ITT), and per-protocol (PP) datasets. The safety dataset included all randomized patients, in whom at least one treatment was initiated. The primary efficacy endpoint was based on the ITT population, which was defined as all randomized patients who received at least one treatment and for whom there was at least one valid post-baseline CAI measurement. The PP analysis set was defined as the subset of the ITT population who

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3 received the full course of assigned treatment and for whom there were valid efficacy
4 values at week 12. All results are presented for the ITT population unless otherwise
5 stated (respective ITT populations were used for secondary endpoints).
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11 The primary efficacy analysis tested the hypothesis that the mean difference in
12 CAI scores between the 5-treatment group minus the 10-treatment group was greater
13 than 1.33. If the upper limit of the 95% confidence interval of this difference was 1.33 or
14 lower, the 5-treatment regimen was considered non-inferior to the 10-treatment. Clinical
15 parameters are expressed as mean \pm standard deviation (SD). Statistical comparisons
16 between treatment groups were performed using appropriate parametric and
17 nonparametric methods, including Fisher's Exact Test for categorical variables and t-test
18 for continuous variables; all statistical analyses were performed using SAS[®] Version 9.1
19 (or higher) under Windows[®] 2000 Terminal. Tests were two-sided and differences were
20 considered significant at $P < 0.05$.
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35 Results

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38 From April 2006 until January 2008, 228 patients with moderate-to-severe, active,
39 steroid-dependent or steroid-refractory UC were screened for inclusion at 42 centers. A
40 total of 186 patients satisfied the eligibility criteria and were randomized to receive
41 treatment; similar proportions of patients completed the study in the two groups (Figure
42 1). The ITT population comprised 82 and 80 patients for the 5- and 10-treatment groups,
43 respectively; the PP population comprised 35 and 39 patients, respectively. Most of the
44 patients lost from the ITT population had to be excluded due to intake of medication not
45 permitted by the protocol or for missing one or more dates for a study treatment.
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3 Patients were well balanced between the two groups at baseline (Table 2). Mean age in
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5 both groups was around 40 years, and nearly all patients were Caucasian. A quarter of
6
7 the patients had severe rather than moderate UC. Mean baseline CAI was 8.7–8.8 in the
8
9 two groups. Mean compliance rates for the 5- and 10-treatment groups were 68.8% and
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11 88.5% respectively.
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14 15 16 **Primary Endpoint**

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18 CAI score improved with time with both treatment regimens (Figure 2). The
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20 patients in the 10-treatment group showed slightly greater improvements, but this was
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22 not statistically significant ($P = 0.200$).
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26 Mean CAI for the 5-treatment group was 5.59 versus 5.35 for the 10-treatment
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28 group. The mean difference was 0.24 with an upper 95% confidence limit of 1.17, as this
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30 was below the predefined non-inferiority threshold of 1.33, it indicated that the non-
31
32 inferiority endpoint was achieved. Patients in the PP analysis set showed similar results
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34 and conclusions: 5.31 and 5.46 for the 5- and 10-treatment groups, respectively; the
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36 mean difference -0.15 with an upper 95% confidence limit of 0.90, again confirming the
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38 non-inferiority of the 5-treatment regimen.
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43 44 **Remission**

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46 The clinical remission rates for the 5- and 10-treatment groups were similar: 44%
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48 and 40%, respectively ($P = 0.636$). Similar data were seen from the PP analysis (46% vs
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50 36%, 5- and 10-treatment groups, respectively: $P = 0.479$).
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54 Mean time to remission was slightly shorter with the more intense treatment: 46.8 days
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56 in the 5-treatment group and 39.9 days in the 10-treatment group. However, Kaplan-
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3 Meier analysis of time to remission for both treatment groups, showed that the survival
4 probability for remission over time was similar between the two groups, which was
5 confirmed by the non-significant log-rank test ($P = 0.445$) and hazard ratio 0.732 ($P =$
6 0.298) between groups. Similar values and conclusions were obtained for the PP
7 analysis set.
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10 11 12 13 14 15 **Response**

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18 Clinical response rates were similar at week 12 (56.1% for the 5-treatment group
19 versus 58.8% for the 10-treatment group, $P = 0.753$), with no significant difference
20 between the treatment groups. Similar outcomes were seen by PP analysis (52.8 vs
21 44.5 days 5- and 10-treatment respectively, $P = 0.644$).
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28 29 30 **Other endpoints**

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32 Flexible endoscopy showed that each of the EAI components of granulation,
33 vascular pattern, vulnerability of mucosa and mucosal damage were similar between the
34 2 treatment groups at all time points measured. The overall EAI score improved in both
35 groups with no significant difference ($P = 0.740$; Table 3). Similarly, blood and fecal
36 samples showed no significant difference in CRP or calprotectin levels between groups
37 from baseline to week 12 (Table 3; [$P = 0.179$ and $P = 0.185$ respectively]). There was
38 no clear trend over time in either CRP or calprotectin levels, especially in the latter,
39 which showed considerable inter-sample variability. Descriptive analysis of the quality of
40 life questionnaires gave similar results for both treatment groups. Results were similar
41 for all measures in the PP populations.
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54 55 56 57 58 59 60 **Adverse events**

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3 Adverse events were reported by 63% of patients in the investigation. In the 5-
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5 treatment group 65% of the patients reported adverse events (233 adverse events in 62
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7 patients) and 60% of the patients in the 10-treatment group (208 adverse events in 53
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9 patients). The most frequently reported adverse events by body system and preferred
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11 term, occurring in > 5% of patients, irrespective of treatment relationship were,
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13 headache (18% vs 27%), nasopharyngitis (12 vs 6%), nausea (5% vs 9%) and fatigue
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15 (7% vs 6%), in 5- and 10-treatment groups, respectively.
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20 All but 16 of the events (3.6%) were of mild or moderate severity; 9% and 6% of
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22 patients in the 5- and 10-treatment groups, respectively, experienced a severe adverse
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24 event.
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28 Overall, 11% of all adverse events were considered probably or definitely related
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30 to study treatment (20 in the 5-treatment group; 30 in the 10-treatment group). These
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32 occurred in 9 patients (9%) in the 5-treatment group, and 8 patients (9%) in the 10-
33
34 treatment group. Only 2 of the 441 events overall were considered probably or definitely
35
36 related to treatment and graded severe. There was one serious adverse event in the 5-
37
38 treatment group that was considered to be probably treatment-related (abdominal pain
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40 with stool frequency of more than 15 times daily).
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45 Abnormal laboratory tests, due to underlying UC and concomitant medication,
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47 were only considered clinically relevant or as adverse events if indicated by the
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49 investigator.
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53 Discussion

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3 The use of GMA apheresis has recently increased for the treatment of UC. To
4 date, there is considerable variation in the number of apheresis sessions used, whether
5 in clinical practice or in investigational studies, ranging from five treatments as
6 recommended in Europe,¹⁷ to 10 or more courses – particularly in severe UC – in the
7 US and Japan.^{18–20} If fewer cycles can be shown to have similar efficacy and safety as
8 more cycles, convenience to the patient and physician may be improved, possibly
9 improving patient compliance, and also providing a more efficient use of healthcare
10 resource. We therefore conducted this investigation to confirm the non-inferiority of 5
11 versus 10 apheresis treatments, given over 5 or 8 consecutive weeks, respectively, in
12 patients with moderate to severe active steroid-dependent or steroid-refractory UC.
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28 Assessment of disease activity by CAI showed that both treatment regimens were
29 effective, with notable decreases in scores, and a number of remissions, in both groups
30 after around 4 weeks of treatment (Figures 2 and 3). The difference between groups in
31 CAI improvement at week 12, our primary endpoint, was within prespecified limits for
32 non-inferiority, and therefore showed that a 5-treatment regimen is at least as effective
33 as 10 treatments.
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Of the secondary efficacy endpoints (remission rate, time to remission, response rate, change from baseline in CRP and calprotectin levels), none revealed any significant difference between treatment groups, further supporting the conclusion that 5 apheresis treatments are not inferior to 10. Both treatment regimens were effective in achieving remission in at least 40% of patients, with mean time to remission of 40–50 days. Good response rates were achieved at similar levels in both groups, with more than 56% of patients responding to GMA. Analysis by a number of measures did not find

1
2
3 any significant difference in response rate or time to remission between groups. Fecal
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5 calprotectin has previously been used to determine active or inactive inflammatory bowel
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7 disease, possibly indicating patients at risk of relapse²¹ but did not prove a useful
8
9 biomarker in our study because of very high inter-patient variability.
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14 Treatment with either regimen was generally well tolerated, with no notable differences
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16 between the groups. This is consistent with earlier studies of the apheresis process
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18 where studies have shown tolerability and efficacy for 5-¹⁷ or 10-treatment regimens of
19
20 Adacolumn apheresis.¹⁸⁻²⁰ Granulocyte-monocyte apheresis has shown efficacy in
21
22 severe, steroid-refractory UC,²² moderately severe, steroid-dependent UC,²³ and
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24 steroid-naïve patients.²² One study was not able to demonstrate a benefit of apheresis
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26 over sham treatment in cases of active moderate to severe UC. This may be related to
27
28 the differences in the activity measure used (Mayo score, rather than CAI), or in the
29
30 baseline characteristics – including previous or concurrent medications – of the patient
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32 population studied. Indeed, a post-hoc analysis in patients with more severe disease
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34 (modified Riley scores of 7) did demonstrate a significant benefit for apheresis.²⁴
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41 A recent meta-analysis of such apheresis trials demonstrated superiority of the
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43 method over steroid therapy in active UC, as indicated by a significantly greater
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45 remission rate at 12 weeks (relative risk 1.41; 95% confidence interval 1.08–1.83).²⁵
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47 Furthermore, the incidence of side-effects was approximately 80% lower with apheresis
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49 than steroids. Others have also shown that dosages of concomitant steroid can
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51 subsequently be tapered or discontinued following apheresis.²⁶ This is clearly a benefit,
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53 since lifelong therapy with steroids has many well-established adverse effects. Because
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55 steroid-naïve UC patients respond very effectively to granulocyte-monocyte apheresis,
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3 studies suggest that progression to steroid therapy could be delayed or obviated
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5 altogether.^{22,7} Similarly, health economic analysis suggests that the greater remission
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7 rate and the reduced need for surgery associated with apheresis make the process a
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9 cost-effective treatment option.²⁷
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13 As our study populations had substantial proportions of patients with both
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15 moderate and severe active UC, and with both left-sided colitis and pancolitis, we
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17 believe our results are applicable to patients with a wide range of UC severity and type.
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19 It may therefore be suitable not only as an option for rescue treatment in patients with
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21 severe UC, but also as a safe treatment in patients with moderate disease with limited
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23 extension, e.g. left-sided colitis. The involvement of 42 centers, participating from 10
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25 countries, also supports the general applicability of our non-superiority findings. Recent
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27 multicenter postmarketing data from Japan confirm that granulocyte-monocyte apheresis
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29 was effective in the real-life setting as well as in clinical trials, achieving an overall
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31 response of 77% in a UC population, 74% of whom were on prednisone.²⁸
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38 Our study is the first to our knowledge with the predefined aim of systematically
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40 investigating the relative efficacy of 5 versus 10 apheresis treatments, and has
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42 demonstrated that a 5-treatment regimen is non-inferior to 10 treatments in a broad
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44 range of patients with moderate or severe UC. Over 40% of patients achieved remission
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46 during the course of treatment, which was well tolerated.
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3 **FIGURE LEGENDS**
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8 **Figure 1** Patient disposition
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12 **Figure 2** Disease severity by CAI score in the 5-treatment (n = 82) and 10-treatment (n
13 = 80) groups over time by visit (ITT population; mean \pm standard deviation)
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19 **Figure 3** Time to remission in days in the 5-treatment (n = 82) and 10-treatment (n = 80)
20 (ITT population)
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3 **TABLES**
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5 **Table 1 Scoring Systems for Clinical Symptoms and Endoscopic Activity**
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7 **Clinical Activity Index (CAI)**

	Score
(1) Number of stools weekly:	
<18	0
18-35	1
36-60	2
>60	3
(2) Blood in stools (based on weekly average)	
None	0
Little	2
A lot	4
(3) Investigator's global assessment of symptomatic state	
Good	0
Average	1
Poor	2
Very poor	3
(4) Abdominal pain /cramps	
None	0
Mild	1
Moderate	2
Severe	3
(5) Temperature due to colitis (°C)	
37-38	0
>38	3
(6) Extraintestinal manifestations	
Iritis	3
Erythema nodosum	3
Arthritis	3
(7) Laboratory findings	
Sedimentation rate >50 mm in 1 st h	1
Sedimentation rate >100 mm in 1 st h	2
Hemoglobin <100g/l	4

46 **Endoscopic Activity Index (EAI)**

(1) Granulation scattering reflected light:	
No	0
Yes	2
(2) Vascular pattern:	
Normal	0
Faded/ disturbed	1
Completely absent	2
(3) Vulnerability of mucosa:	
None	0

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3	Slightly increased (contact bleeding)	2
4	Greatly increased (spontaneous bleeding)	4
5	(4) Mucosal damage (mucus, fibrin, exudate, erosions, ulcer)	
6	None	0
7	Slight	2
8	Pronounced	4
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Table 2. Patient characteristics and clinical history at baseline (ITT population)

	5-treatment group (n = 82)	10-treatment group (n = 80)	<i>P</i> -value
Male, n (%)	55 (67)	49 (61)	0.513
Age (years; mean ± SD)	39.8 ± 12.3	43.3 ± 13.6	0.089
Race, n (%)			
Caucasian	81 (99)	79 (99)	1.000
Asian	1 (1)	1 (1)	
UC duration (months)	97.7 ± 83.0	80.1 ± 62.8	NT
Smoking history, n (%)			
Never smoked	43 (52)	39 (49)	0.784
Smoker	5 (6)	7 (9)	
Ex-smoker	34 (42)	34 (42)	
CAI score at entry	8.7 ± 2.4	8.8 ± 2.1	0.738
UC severity, n (%)			
Moderate	61 (74)	59 (74)	1.000
Severe	21 (26)	21 (26)	
Localization, n (%)			
Left-sided colitis	45 (55)	39 (49)	NT
Pancolitis	31 (38)	29 (36)	
Other	6 (7)	12 (15)	
Previous medication, n (%)			NT

Aminosalicylate	72 (88)	68 (85)
Metronidazole	4 (5)	6 (8)
Ciprofloxacin	2 (2)	6 (8)
Immunosuppressant	48 (59)	45 (56)
Anti-TNF	18 (22)	11 (14)
Steroids	64 (78)	65 (81)

UC, ulcerative colitis; SD, standard deviation; CAI, Clinical Activity Index; TNF, tumor necrosis factor; NT, not tested.

Table 3. Response to Adacolumn® apheresis treatment

	5-treatment group (n = 82)	10-treatment group (n = 80)	<i>P</i> -value
CAI score; mean ± SD (n)	5.6 ± 3.6 (82)	5.4 ± 3.7 (80)	
Remission rate; % (n)	43.9% (82)	40.0% (80)	0.636
Time to remission (days); mean ± SD (n)	46.8 ± 25.2 (76)	39.9 ± 30.2 (69)	
Response rate; mean ± SD (n)	56.1% (46)	58.8% (47)	0.753
Change in EAI (wk12 – baseline); mean ± SD (n)	2.52 ± 2.9 (60)	2.70 ± 3.1 (60)	0.740
Change in CRP (wk12 – baseline); mean ± SD (n)	3.5 ± 18.5 (79)	-0.2 ± 16.3 (78)	0.179
Change in calprotectin (wk12 – baseline); mean ± SD (n)	194 ± 1677 (66)	1291 ± 6470 (65)	0.185

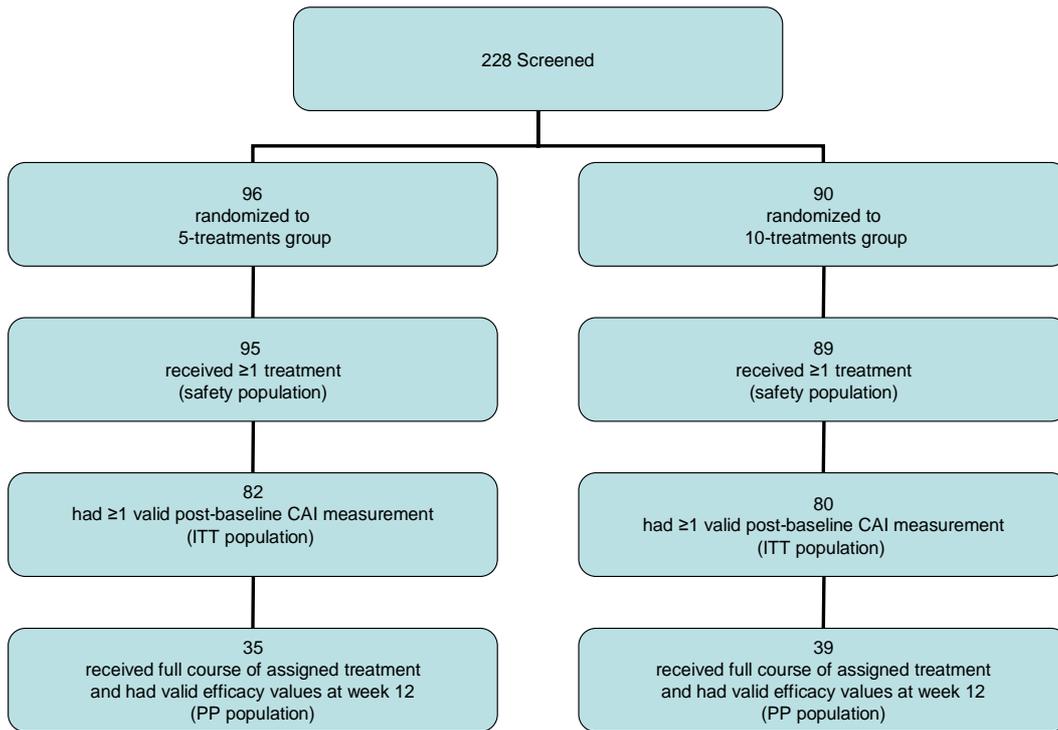


Alimentary Pharmacology & Therapeutic
CONSORT Statement 2001 Checklist
Items to include when reporting a randomized trial

<i>PAPER SECTION And topic</i>	Item	Descriptor	Reported on Page #
<i>TITLE & ABSTRACT</i>	1	<u>How participants were allocated to interventions</u> (e.g., "random allocation", "randomized", or "randomly assigned").	1 & 3
<i>INTRODUCTION</i> Background	2	<u>Scientific background and explanation of rationale.</u>	4
<i>METHODS</i> Participants	3	<u>Eligibility criteria for participants</u> and the <u>settings and locations where the data were collected.</u>	6
Interventions	4	<u>Precise details of the interventions intended for each group and how and when they were actually administered.</u>	7
Objectives	5	<u>Specific objectives and hypotheses.</u>	6
Outcomes	6	<u>Clearly defined primary and secondary outcome measures</u> and, when applicable, any <u>methods used to enhance the quality of measurements</u> (e.g., multiple observations, training of assessors).	6
Sample size	7	<u>How sample size was determined</u> and, when applicable, <u>explanation of any interim analyses and stopping rules.</u>	9
Randomization -- Sequence generation	8	<u>Method used to generate the random allocation sequence, including details of any restrictions</u> (e.g., blocking, stratification)	7
Randomization -- Allocation concealment	9	<u>Method used to implement the random allocation sequence</u> (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	7
Randomization -- Implementation	10	<u>Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.</u>	7
Blinding (masking)	11	<u>Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment.</u> If done, <u>how the success of blinding was evaluated.</u>	7
Statistical methods	12	<u>Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses</u> , such as subgroup analyses and adjusted analyses.	5
<i>RESULTS</i> Participant flow	13	<u>Flow of participants through each stage</u> (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. <u>Describe protocol deviations from study as planned, together with reasons.</u>	6 & Fig1
Recruitment	14	<u>Dates defining the periods of recruitment and follow-up.</u>	10
Baseline data	15	<u>Baseline demographic and clinical characteristics of each group.</u>	Tab1 (p26)
Numbers analyzed	16	<u>Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat".</u> State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	9 & 10
Outcomes and estimation	17	<u>For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision</u> (e.g., 95% confidence interval).	11 ff
Ancillary analyses	18	<u>Address multiplicity by reporting any other analyses performed</u> , including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	-
Adverse events	19	<u>All important adverse events or side effects in each intervention group.</u>	12
<i>DISCUSSION</i> Interpretation	20	<u>Interpretation of the results</u> , taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	13
Generalizability	21	<u>Generalizability (external validity) of the trial findings.</u>	16
Overall evidence	22	<u>General interpretation of the results in the context of current evidence.</u>	13 ff

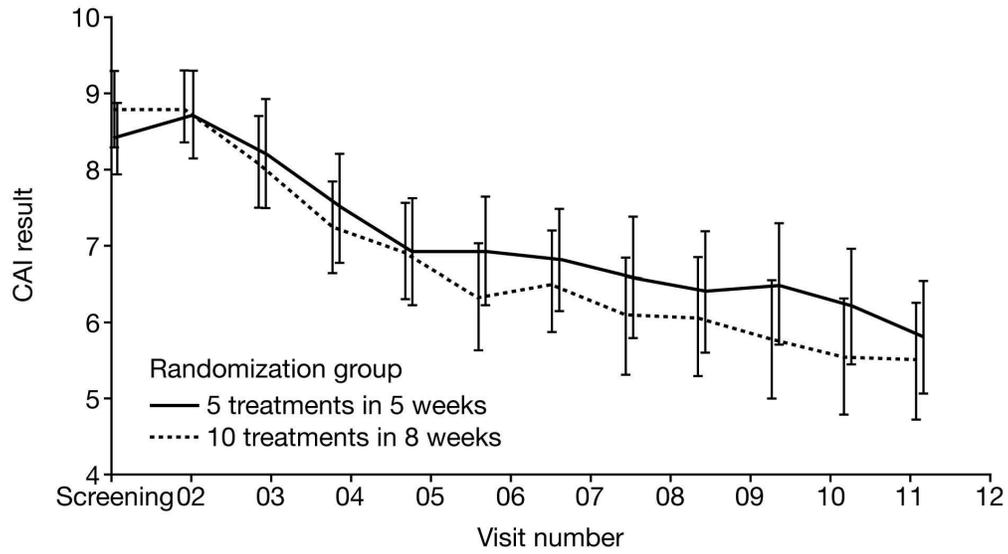
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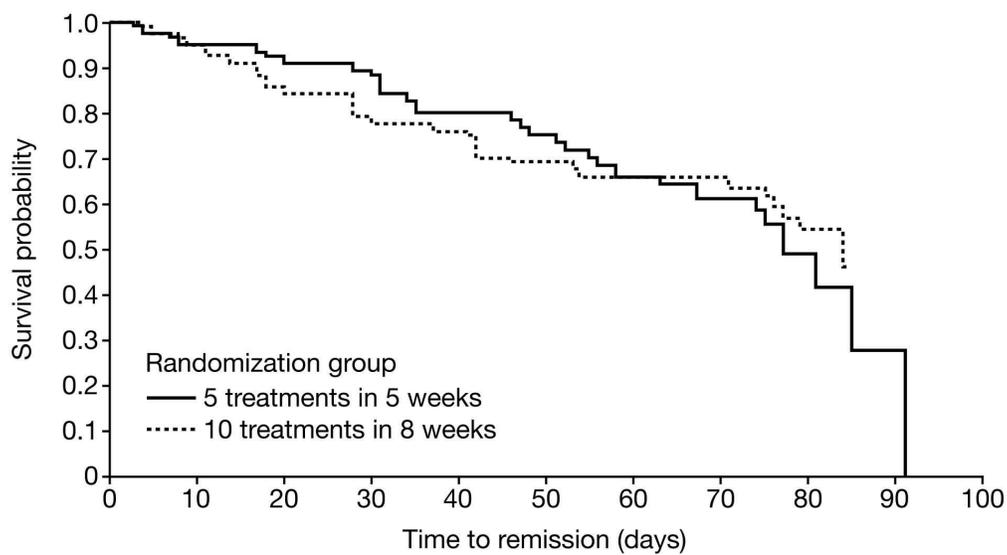


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