



HAL
open science

Clinical Trial: The Association Between Rifaximin And Partially Hydrolyzed Guar Gum Is More Effective Than Rifaximin Alone In Eradicating SIBO

Manuele Furnari, Andrea Parodi, Lorenzo Gemignani, Edoardo G Giannini, Simona Marengo, Edoardo Savarino, Lorenzo Assandri, Valentina Fazio, Daria Bonfanti, Simona Inferrera, et al.

► To cite this version:

Manuele Furnari, Andrea Parodi, Lorenzo Gemignani, Edoardo G Giannini, Simona Marengo, et al.. Clinical Trial: The Association Between Rifaximin And Partially Hydrolyzed Guar Gum Is More Effective Than Rifaximin Alone In Eradicating SIBO. *Alimentary Pharmacology and Therapeutics*, 2010, 32 (8), pp.1000. 10.1111/j.1365-2036.2010.04436.x . hal-00567044

HAL Id: hal-00567044

<https://hal.science/hal-00567044>

Submitted on 18 Feb 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Clinical Trial: The Association Between Rifaximin And Partially Hydrolyzed Guar Gum Is More Effective Than Rifaximin Alone In Eradicating SIBO

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0419-2010.R1
Wiley - Manuscript type:	Clinical Trial
Date Submitted by the Author:	20-Jul-2010
Complete List of Authors:	Furnari, Manuele; University of Genoa, Department of Internal Medicine, Gastroenterology Unit Parodi, Andrea; Sanremo Hospital, Gastroenterology Gemignani, Lorenzo; University of Genoa, Department of Internal Medicine, Gastroenterology Unit Giannini, Edoardo; University of Genoa, Department of Internal Medicine, Gastroenterology Unit Marenco, Simona; University of Genoa, Department of Internal Medicine, Gastroenterology Unit Savarino, Edoardo; University of Genoa, Department of Internal Medicine, Gastroenterology Unit Assandri, Lorenzo; University of Genoa, Department of Internal Medicine, Gastroenterology Unit Fazio, Valentina; University of Genoa, Department of Internal Medicine, Gastroenterology Unit Bonfanti, Daria; University of Genoa, Department of Internal Medicine, Gastroenterology Unit Inferrera, Simona; University of Genoa, Department of Internal Medicine, Gastroenterology Unit Savarino, Vincenzo; University of Genoa, Department of Internal Medicine, Gastroenterology Unit
Keywords:	Functional GI diseases < Disease-based, Small intestine < Organ-based, Malabsorption < Topics, Probiotics/prebiotics < Topics

1
2 **Clinical Trial:** The Association Between Rifaximin And Partially
3
4 Hydrolyzed Guar Gum Is More Effective Than Rifaximin Alone In
5
6 Eradicating SIBO
7
8
9

10
11
12
13
14 Manuele Furnari, MD, Andrea Parodi, MD, Lorenzo Gemignani, MD, PhD, Edoardo G. Giannini, MD,
15
16 Simona Marengo, MD, Edoardo Savarino, MD, Lorenzo Assandri, MD, Valentina Fazio, MD, Daria
17
18 Bonfanti, MD, Simona Inferrera, MD, and Vincenzo Savarino, MD.
19

20
21
22
23 Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy.
24
25

26
27
28 Preliminary data were exhibited at UEGW/WCOG Gastro 2009, London.
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract

Background:

Abnormal intestinal clearance is involved in the pathogenesis of small intestinal bacterial overgrowth (SIBO). It is known that partially hydrolyzed Guar gum (PHGG) affects intestinal motility. Eradication therapy of SIBO is based on antibiotic treatment: no data are available about the role of fibers supplementation in eradicating SIBO.

Aims:

To assess whether the association between PHGG plus rifaximin is more effective than rifaximin alone in the treatment of SIBO.

Methods:

50g-glucose breath test (GBT) was given to 500 consecutive patients. Patients with positive GBT and predisposing conditions to SIBO entered into the study, and were randomized to receive rifaximin 1200mg/die or rifaximin 1200mg/die plus PHGG 5g/die for 10 days. Patients completed a symptom questionnaire and GBT both in basal condition and 1 month after withdrawal of therapy.

Results:

Seventy-seven patients had SIBO. SIBO eradication rate was 62.1% in the rifaximin group (both on per-protocol and intention-to-treat analyses), and 87.1% (per-protocol, $p=0.017$) and 85.0% (intention-to-treat, $p=0.036$) in the rifaximin-plus-PHGG group. Clinical improvement was observed in 86.9% and 91.1% of eradicated cases in rifaximin and rifaximin-plus-PHGG groups, respectively ($p=0.677$).

Conclusion:

The association between rifaximin and PHGG seems to be more useful in eradicating SIBO compared to rifaximin alone.

INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is a condition mainly characterized by diarrhoea, bloating, flatulence and abdominal pain due to an abnormal amount of bacteria in the small intestine[1-4]. Gastric acid production, anatomical integrity of intestinal wall and peristaltic motility are main factors in preserving the fine equilibrium between host and bacteria. Therefore, predisposing conditions that alter the above mentioned mechanisms could heighten the number of bacteria in the small intestine and lead to the development of this syndrome. Furthermore, it has been proposed that gut microflora could play a role in the modulation of some inflammatory diseases. This was suggested by the higher incidence of SIBO among patients with Rheumatoid Arthritis[5] and Non Alcoholic Steatohepatitis[6] and by improvement of Rosacea after eradicating SIBO[7]. Although severe forms presenting remarkable malabsorption can be seen occasionally, the majority of clinical manifestations of SIBO are generally mild and make it hardly distinguishable from other conditions such as Irritable Bowel Syndrome (IBS) or Lactose Intolerance. This difficulty is clearly underlined by the heterogeneous results of several studies that reported IBS comorbidity with SIBO ranging widely from 10% to 80% [8-13].

The presence of at least 10^5 cfu/ml in jejunal aspirate culture is considered the gold standard test to diagnose SIBO, especially when colonic-type bacteria are isolated[1-4,14]. However, hydrogen breath tests are commonly used in clinical practice, being more acceptable to patients and giving quicker information to the clinician[15]. Among them, Glucose Breath Test (GBT) has proved to have the highest accuracy in diagnosing SIBO[14,16]. Once the bacterial overgrowth is diagnosed it can be successfully treated by locally active non absorbable antibiotics. Various studies have shown that rifaximin is successful in eradicating SIBO with no

1
2 or minimal side effects when compared to systemic antibiotics[7,15,17-21]. Of the predisposing
3
4 conditions involved in SIBO pathogenesis, hypomotility seems to play a relevant role by
5
6 impairing intestinal clearance and, as a consequence, the intestinal bacteria distribution[21-24].
7
8 Thus, we have hypothesized that adding a prebiotic such as partially hydrolyzed guar gum
9
10 (PHGG) to rifaximin can be of help in the decontamination of small bowel. In fact, it can have a
11
12 beneficial effect on intestinal motility and therefore, a synergic interaction between rifaximin
13
14 and PHGG may lead to a higher eradication rate of SIBO. The **primary end point** of our study
15
16 was to assess whether the association of rifaximin and PHGG was more effective than rifaximin
17
18 alone in eradicating SIBO, **while the secondary end point was to evaluate whether the**
19
20 **combined treatment allowed to obtain a greater symptomatic improvement than rifaximin**
21
22 **alone.**
23
24
25
26
27
28
29
30
31

32 MATERIALS AND METHODS

33 Patients

34
35 From May 2007 to March 2010, 500 consecutive patients were referred to our centre to
36
37 perform GBT because of gastrointestinal symptoms, such as modification in stool frequency,
38
39 abdominal pain, bloating, flatulence, tenesmus, nausea and vomiting. **In these subjects, the**
40
41 **predisposing conditions for SIBO were: impaired intestinal motility due to medications (i.e.**
42
43 **antidepressant drugs) (n=20), hypothyroidism (n=5), diabetes mellitus (n=4), Scleroderma**
44
45 **(n=1), and Crohn's Disease (n=3); acquired anatomical conditions such as resection of the**
46
47 **ileum-cecal valve (n=3) or partial gastrectomy (n=1), adhesions due to major abdominal surgery**
48
49 **(n=2). Also Rosacea (n=5), Non Alcoholic Steatohepatitis (n=4) and Rheumatoid Arthritis (n=1)**
50
51 **were considered as disorders related to SIBO.** Patients that underwent a previous treatment for
52
53 SIBO and patients with basal H₂ sample >10ppm were excluded from the study. Moreover,
54
55
56
57
58
59
60

1
2 patients had to take neither antibiotic or Proton Pump Inhibitors (PPI), nor pre or probiotics for
3
4 at least 10 days before the examination. Among these, we evaluated 390 patients who had
5
6 both performed GBT and answered our questionnaire based on gastrointestinal symptom. In
7
8 this investigation, we included the 77 patients (male/female: 15/62; mean Age 54; range 26-84
9
10 years) who had a positive GBT. These patients were randomized, **by using a computer**
11
12 **generated random list**, to receive rifaximin 1200mg daily for 10 days or rifaximin 1200mg daily
13
14 plus PHGG 5g/die for 10 days. All patients completed the questionnaire both in basal condition
15
16 and 1 month after therapy. **Adverse events were investigated during and 1 month after the end**
17
18 **of treatment**. Eradication of SIBO was assessed 1 month later after the end of treatment by a
19
20 further GBT. **The study was evaluated and approved by our Institutional Review Board.**
21
22
23
24
25
26
27
28
29

30 **Glucose Breath Test**

31
32 The evening before GBT patients followed a diet containing boiled rice, meat and water alone.
33
34 Then they fasted until the end of the test. Glucose was given in a dose of 50 g dissolved in
35
36 250ml of water. Breath hydrogen concentration, in parts per million (ppm), was measured by
37
38 gas-chromatography (Quintron MicroLizer model DP plus, Milwaukee, USA) on samples of end
39
40 expiratory air collected every 15 minutes for 2 hours. A basal sample was taken before glucose
41
42 intake. Patients were asked to avoid cigarette smoking, food intake and physical exercise during
43
44 test. A single peak of hydrogen excretion higher than 12 ppm was the cut-off value for test
45
46 positivity.
47
48
49
50
51
52
53
54

55 **Questionnaire**

56
57 All patients completed an interview questionnaire, according to previous studies performed by our
58
59 group[7,9,21] and by other Authors[25-27], based on 10 variables (diarrhea, upper and lower
60

1
2 abdominal pain/discomfort, bloating, flatulence, abdominal tenderness, weight loss, nausea,
3
4 constipation, and tenesmus) scored from 0 (no symptoms) to 3 (severe), providing a global
5
6 symptomatic score (GSS), calculated as the sum of all symptom scores, with a range from 0 to
7
8 30. A decrease of 50% in global symptomatic score after the end of therapy was arbitrarily
9
10 considered as a significant improvement of symptoms, in agreement with other studies carried
11
12 out by our group on this topic[7,9,21].
13
14
15
16
17
18
19

20 Statistical analysis

21
22 Data are shown as mean values, ranges and rates. Data were assessed on both per-protocol
23
24 (PP) and intention-to-treat (ITT) analyses. Fisher's exact test was used to evaluate if the
25
26 difference between the two groups was statistically significant in terms of both SIBO
27
28 eradication rates and symptomatic relief. A p value <0.05 in a two-tailed test was considered
29
30 significant. Statistical analysis was performed with GraphPad Software, QuickCalcs [San Diego,
31
32 CA, USA], and with GNU Software, PSPP [Boston, MA, USA].
33
34
35
36
37
38
39

40 RESULTS

41
42 Table 1 shows the main demographic and clinical characteristics of the study population
43
44 subdivided according to treatment received. There were no statistically differences between
45
46 the two groups. Overall, eradication of SIBO was achieved in 57/77 patients (74.0%). In
47
48 particular, SIBO eradication was obtained in 23/37 patients (62.1%; both PP and ITT analysis)
49
50 treated with rifaximin alone, and in 34/39 (87.1%; PP) and 34/40 (85.0%; ITT) patients treated
51
52 with rifaximin plus PHGG. SIBO eradication rates were significantly different between the two
53
54 treatment arms on both PP (p=0.017; OR=0.241; 0.075, 0.781) and ITT (p=0.036; OR 0.289;
55
56 0.095, 0.884) analyses.
57
58
59
60

1
2 Figure 1 shows the flow of patients within the study, SIBO eradication rates and symptoms
3
4 improvement. Among patients who obtained eradication, clinical improvement was observed in
5
6 86.9% and 91.1% of patients treated with rifaximin alone and rifaximin plus PHGG, respectively
7
8 (p=0.677). On the other hand, among patients who did not obtain eradication, clinical
9
10 improvement was observed in 7.1% (1/14) and 16.6% (1/6), respectively (p=0.521). The overall
11
12 symptomatic improvement in the two treatment arms was 56.7% and 80% in patients treated
13
14 with rifaximin alone and rifaximin plus PHGG, respectively (p=0.1526).

15
16
17 Pre-treatment mean symptomatic scores were: 4.21 in the study population (77/77), 4.19
18
19 among patients included in the rifaximin arm (37/77), and 4.22 among patients included in the
20
21 rifaximin plus PHGG arm (40/77). Post-treatment mean symptomatic scores of the group that
22
23 received rifaximin decreased from 4.10 to 1.85 among eradicated patients with symptomatic
24
25 improvement (20/37), from 4.60 to 4.00 among eradicated patients without symptomatic
26
27 improvement (3/37), and from 4.43 to 4.14 among patients who did not eradicated SIBO
28
29 (13/37). Post-treatment mean symptomatic scores in the group that received rifaximin plus
30
31 PHGG decreased from 4.23 to 1.81 among eradicated patients with symptomatic improvement
32
33 (31/40), from 4.33 to 4.00 among eradicated patients without symptomatic improvement
34
35 (3/40), and from 4.17 to 3.50 among patients without SIBO eradication (6/40).

36
37
38 No serious adverse events were reported during treatment.
39
40
41
42
43
44

45 46 47 48 49 **DISCUSSION**

50
51
52 In patients diagnosed with SIBO, a broad-spectrum antibiotic therapy is recommended in order
53
54 to obtain eradication of intestinal bacterial overgrowth. Rifaximin is a locally active non
55
56 absorbable antibiotic whose efficacy in eradicating SIBO has been demonstrated by several
57
58 studies[7,15,17-21]. Its use is often preferred to other antibiotics such as levofloxacin and
59
60

1
2 metronidazole because of its topical action and absence of adverse events[28]. In this study, we
3
4 aimed at evaluating whether adding PHGG to rifaximin was able to increase SIBO eradication
5
6 rate. Our hypothesis was based on the fact that antibiotics act only on intestinal bacteria, but
7
8 do not solve the conditions predisposing to SIBO. On the other hand, impaired intestinal
9
10 motility, by decreasing intestinal clearance, might promote the development of unfavourable
11
12 habitat for physiologic gut microflora and the invasion of small bowel lumen by colonic
13
14 bacteria.
15
16
17
18

19
20 Our results show that the association of PHGG and rifaximin was significantly more effective
21
22 than rifaximin alone in the eradication of SIBO. Thus, this association reached an eradication
23
24 rate of 87.1%, resulting significantly higher than rifaximin alone (62.1%). This finding suggests
25
26 that fiber supplementation positively interacts with rifaximin in SIBO treatment.
27
28

29
30 Several studies have shown a beneficial effect on intestinal motility by use of alimentary
31
32 fibers[29]. In fact, alimentary fibers increase fecal mass and transit time, easing defecation.
33
34 They could be generally distinguished into two categories. Insoluble fiber is minimally modified
35
36 in the intestinal lumen and mechanically increases fecal mass by retaining water, thus
37
38 decreasing transit time and improving defecation. Otherwise, soluble fiber is metabolized in the
39
40 large bowel, thus producing short chain fatty acids and leading to selective stimulation of
41
42 microbial growth which influences secondarily bowel functions[30]. This is an important
43
44 distinction because several studies conducted on IBS populations have shown that the global
45
46 amelioration of IBS symptoms is mainly associated with the use of soluble fibers rather than
47
48 with the insoluble ones. It was also found that insoluble fiber was no better than placebo at
49
50 improving IBS and, rather surprisingly, that a large amount of insoluble fiber may worsen IBS-
51
52 related symptoms [31,32].
53
54
55
56
57
58
59
60

1
2 In this study we used PHGG, a vegetable, water-soluble, dietary fiber that is derived from guar
3
4 gum with a lower molecular weight than the original guar gum, whose safety has been largely
5
6 proved[33-35]. Noteworthy, PHGG increases fecal acetate content and the colonic
7
8 concentration of Lactobacilli and Bifidobacteria thus providing an important prebiotic
9
10 action[36-41]. As PHGG is not used by these bacteria in vitro, it has been proposed that PHGG is
11
12 degraded in human colon providing substrates that favour the selective growth of
13
14 Bifidobacteria and Lactobacilli[41]. This is an important mechanism because it is proved that
15
16 loss of anaerobes is associated with a depletion in short chain fatty acids and an increase in
17
18 stool pH, allowing overgrowth of other bacteria which may contribute to altering intestinal
19
20 function[42]. Moreover, acetate is one of the most important energy resources for colonocytes
21
22 and is necessary to sustain colonic epithelial cell proliferation[43]. These factors are useful to
23
24 preserve the mucosal integrity and to support its repairing process and, when altered, could
25
26 lead to develop SIBO.
27
28
29
30
31
32
33

34
35 GBT and Lactulose Breath Test (LBT) are the most commonly utilized tests for SIBO. Although
36
37 there is no universal agreement about which test should be performed to diagnose SIBO, in our
38
39 study we used GBT because it is easier to interpret and more accurate in diagnosing SIBO than
40
41 LBT[14]. This has been recently confirmed by the 1st Rome Consensus Conference that reported
42
43 higher diagnostic accuracy for GBT with respect to LBT (71% vs 55%)[16]. In fact, glucose is
44
45 highly absorbed in the proximal small bowel and rarely reaches the colon, showing a single
46
47 “early” H₂ peak in case of SIBO. On the other hand, lactulose passes unabsorbed through the
48
49 small bowel and reaches the large bowel where it is metabolized by colonic bacteria. Thus,
50
51 lactulose investigates bacterial fermentation through the whole gut and can also be used as a
52
53 measure of oro-caecal transit. Nevertheless, being a non-absorbable carbohydrate, lactulose
54
55 itself can accelerate small bowel transit that is a condition in which the “early” peak can merge
56
57
58
59
60

1
2 with the late “colonic” peak, thus making impossible to distinguish SIBO from colonic
3
4 fermentation. Moreover, different portions of the given substrate might reach the colon at
5
6 different times, thus causing two or more peaks in H₂ excretion that simulate SIBO[44]. GBT is
7
8 associated with a lower incidence of false positive results when compared with LBT, and in
9
10 healthy volunteers GBT shows an optimal intra-individual reproducibility[45].
11
12

13
14 Recently, studies on SIBO diagnosed by GBT and treated with rifaximin reported that the
15
16 progressive increase in rifaximin dosage (from 600mg/day up to 1600mg/day for 7 days) may
17
18 lead to an important gain in terms of SIBO eradication without enhancing the occurrence of
19
20 side-effects[18,19]. Similar results were also achieved by Lombardo et al.[46] by prolonging
21
22 high dose (1200 mg daily) rifaximin treatment to 14 days. These Authors studied two specific
23
24 groups and achieved an eradication rate as high as 87% in PPI users and 91% in IBS patients.
25
26 Although the setting of our study was slightly different (i.e, we included patients with all the
27
28 predisposing conditions to SIBO, given the frequent coexistence of different GI disorders in
29
30 them), nevertheless we obtained similar SIBO eradication rates by combining a shorter course
31
32 of antibiotic treatment (1200 mg/day rifaximin for 10 days) with the supplementation of a
33
34 soluble fiber such as PHGG.
35
36

37
38 Lastly, we observed that, although symptom improvement was higher among patients who
39
40 obtained SIBO eradication with the combined therapy, this tendency failed to achieve statistical
41
42 significance. This could be due to the fact that both groups underwent an active treatment,
43
44 rifaximin, whose efficacy has been already proved, and therefore, clinical amelioration was very
45
46 high in both groups.
47
48

49
50 In conclusion, the combined use of rifaximin with PHGG allows us to obtain a higher eradication
51
52 of SIBO as compared with the use of rifaximin alone. Therefore, the prebiotic effect of PHGG is
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

likely to provide a synergistic action with rifaximin inside the bowel lumen, by improving intestinal clearance and favoring the microflora balance.

For Peer Review

References

1. Husebye E. The pathogenesis of gastrointestinal bacterial overgrowth. *Chemotherapy* 2005; 51: 1-22.
2. Gregg CR. Enteric bacterial flora and bacterial overgrowth syndrome. *Semin Gastrointest Dis* 2002; 13: 200-9.
3. Sherman P, Lichtman S. Small bowel bacterial overgrowth syndrome. *Dig Dis* 1987; 5: 157 - 71.
4. Bouhnik Y, Alain S, Attar A, et al. Bacterial populations contaminating the upper gut in patients with small intestinal bacterial overgrowth syndrome. *Am J Gastroenterol* 1999; 94: 1327-31.
5. Henriksson AE, Blomquist L, Nord CE, et al. Small intestinal bacterial overgrowth in patients with rheumatoid arthritis. *Ann Rheum Dis* 1993; 52: 503-510.
6. Drenick EJ, Johnson D. Hepatic steatosis after intestinal bypass-prevention and reversal metronidazole, irrespective of protein-calorie malnutrition. *Gastroenterology* 1982; 82: 535-548.
7. Parodi A, Paolino S, Greco A, et al. Small intestinal bacterial overgrowth in rosacea: clinical effectiveness of its eradication. *Clin Gastroenterol Hepatol*. 2008; 6:759-64
8. Lin HC. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. *JAMA* 2004; 292: 852-8.
9. Parodi A, Dulbecco P, Savarino E, et al. Positive glucose breath testing is more prevalent in patients with IBS-like symptoms compared with controls of similar age and gender distribution. *J Clin Gastroenterol*. 2009; 43:962-6.

- 1
2 10. Pimentel M, Park S, Mirocha J, et al. The effect of nonabsorbed oral antibiotic (rifaximin)
3
4 on the symptoms of the irritable bowel syndrome: a randomized trial. *Ann Intern Med*
5
6 2006; 145: 557-63.
7
8
9
10 11. Posserud I, Stotzer PO, Björnsson ES, et al. Small intestinal bacterial overgrowth in
11
12 patients with irritable bowel syndrome. *Gut* 2007; 56: 802-8.
13
14
15 12. Ford AC, Spiegel BM, Talley NJ, Moayyedi P. Small intestinal bacterial overgrowth in
16
17 irritable bowel syndrome: systemic review and meta-analysis. *Clin Gastroenterol*
18
19 *Hepatol* 2009; 7: 1279-86.
20
21
22 13. Grover M, Kanazawa M, Palsson OS, et al. Small intestinal bacterial overgrowth in
23
24 irritable bowel syndrome: association with colon motility, bowel symptoms, and
25
26 psychological distress. *Neurogastroenterol Motil* 2008; 20: 998-1008.
27
28
29
30 14. Corazza GR, Menozzi MG, Strocchi a, et al. The diagnosis of small bowel bacterial
31
32 overgrowth. Reliability of jejunal culture and inadequacy of breath hydrogen testing.
33
34 *Gastroenterology* 1990; 98: 302-9.
35
36
37 15. Peralta S, Cottone C, Doveri T, et al. Small intestine bacterial overgrowth and irritable
38
39 bowel syndrome-related symptoms: experience with rifaximin. *World J Gastroenterol*
40
41 2009; 15: 2628-31.
42
43
44 16. Parodi A, Capurso G, Perri F, et al. H₂-breath testing for small-intestinal bacterial
45
46 overgrowth. *Aliment Pharmacol Ther* 2009; 29 (Suppl. 1): 18-26.
47
48
49
50 17. Majewski M, McCallum RW, Sostarich S, et al. Efficacy of rifaximin, a nonabsorbed oral
51
52 antibiotic, in the treatment of small intestinal bacterial overgrowth. *Am J Med Sci*
53
54 2007; 333: 266-70.
55
56
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
18. Lauritano EC, Gabrielli M, Lupascu A, et al. Rifaximin dose finding study for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther.* 2005; 22: 31-5.
19. Scarpellini E, Gabrielli M, Lauritano CE, et al. High dosage rifaximin for the treatment of small intestinal bacterial overgrowth. *Aliment Pharmacol Ther.* 2007 Apr 1; 25: 781-6.
20. Pimentel M. Review of rifaximin as treatment for SIBO and IBS. *Expert Opin Investig Drugs.* 2009 Mar; 18: 349-58.
21. Parodi A, Sessarego M, Greco A, et al. Small intestinal bacterial overgrowth in patients suffering from scleroderma: clinical effectiveness of its eradication. *Am J Gastroenterol* 2008; 103: 1257-62.
22. Ellen L. Bacterial overgrowth. In: Yamada T, Owyang C, et al (eds). *Textbook of gastroenterology.* 4th ed. JB Lippincott, Philadelphia. Vol 2: 1617-25.
23. Resmini E, Parodi A, Savarino V, et al. Evidence of prolonged orocecal transit time and small intestinal bacterial overgrowth in acromegalic patients. *J Clin Endocrinol Metab* 2007; 92: 2119-24.
24. Lauritano EC, Bilotta AL, Gabrielli M, et al. Association between hypothyroidism and small intestinal bacterial overgrowth. *J Clin Endocrinol Metab* 2007; 92: 4180-4.
25. Latella G, Pimpo MT, Sottili S et al. Rifaximin improve symptoms of acquired uncomplicated diverticular disease of the colon. *Int J Colorectal Dis* 2003; 18: 55-62.
26. Papi C, Ciaco A, Koch M, et al. Efficacy of rifaximin in the treatment of symptomatic diverticular disease of the colon. A multicentre double-blind placebo controlled trial. *Aliment Pharmacol Ther.* 1995; 3: 33-9.
27. Di Mario F, Aragona G, Leandro G, et al. Efficacy of mesalaxine in the treatment of symptomatic diverticular disease. *Dig Dis Sci.* 2005.; 50 (3): 581-6.

- 1
2 28. Lauritano EC, Gabrielli M, Scarpellini E, et al. Antibiotic therapy in small intestinal
3
4 bacterial overgrowth: rifaximin versus metronidazole. *Eur Rev Med Pharmacol Sci* 2009;
5
6 13: 111-6.
7
8
9
10 29. Muller-Lissner SA. Effect of wheat bran on weight of stool and gastrointestinal transit
11
12 time: a meta-analysis. *Br Med J* 1988; 296: 615-7.
13
14
15 30. Stephen AM, Cummings JH. Mechanism of action of dietary fibre in the human colon.
16
17 *Nature* 1980; 284: 283-4.
18
19
20 31. Bijkerk CJ, Muris JW, Knottnerus JA, et al. Systematic review: the role of different types
21
22 of fibre in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2004; 19:
23
24 245-51.
25
26
27 32. Francis CY, Whorwell PJ. Bran and irritable bowel syndrome: time for a reappraisal.
28
29 *Lancet* 1994; 344: 39-40.
30
31
32 33. Lina BAR. Sub-chronic (13 week) oral toxicity study with Sunfiber and Sunfiber ST in rats.
33
34 TNO report V97.080. Amsterdam: TNO Nutrition and Food Research Institute; 1997.
35
36
37 34. Takahashi H, Yamamoto T. Effect of partially hydrolyzed guar gum on fecal output in
38
39 human volunteers. *Nut Res* 1993; 13: 649-57.
40
41
42 35. Giaccari S, Montefusco A, et al. Gomma guar parzialmente idrolizzata: una fibra come
43
44 coadiuvante nella sindrome del colon irritabile. *Clin Ter* 2001; 152: 21-5.
45
46
47 36. Giannini EG, Mansi C, Dulbecco P, et al. Role of partially hydrolyzed guar gum in the
48
49 treatment of irritable bowel syndrome. *Nutrition* 2006; 22: 334-42.
50
51
52 37. Takahashi H, Yamamoto T. Influence of partially hydrolyzed guar gum on constipation in
53
54 women. *J Nutr Sci Vitaminol* 1994; 40: 251-7.
55
56
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
38. Tuohy KM, Gibson GR. The prebiotic effects of biscuits containing partially hydrolyzed guar gum and fructo-oligosaccharides-a human volunteer study. *Br J Nutr* 2001; 86: 341-8.
39. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microflora-introducing the concept of prebiotics. *J Nutr* 1995; 125: 1401-12.
40. Weaver GA, Tangel C, Krause JA, et al. Dietary guar gum alters colonic microbial fermentation in azoxymethane-treated rats. *J Nutr* 1996; 126: 1979-81.
41. Okubo T, Ishihara T, Takahashi H, et al. Effects of partially hydrolyzed guar gum intake on human intestinal microflora and its metabolism. *Biosci Biotechnol Biochem* 1994; 58: 1364-9.
42. Lupp C, Robertson ML, Wickham ME, et al. Host-mediated inflammation disrupts the intestinal microbiota and promotes the overgrowth of Enterobacteriaceae. *Cell Host Microbe* 2007; 2: 204.
43. Philips SF. Physiology and pathophysiology of the colon: relationship to constipation. In: Barbara L, Stanghellini V, editors. *Chronic constipation*. London: WB Saunders; 1996, p. 19-37.
44. Riordan SM, McIver CJ, Walker BM, et al. The lactulose breath hydrogen test and small intestinal bacterial overgrowth. *Am J Gastroenterol* 1996; 91: 1795-803.
45. A. Rocco, G. De Martino, G. De Nucci, et al. Intra-individual reproducibility of the glucose hydrogen breath test in a cohort of healthy subjects. *Dig Liver Dis* 2010; 42 (Suppl. 2): 118.
46. Lombardo L, Foti M, Ruggia O, et al. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. *Clin Gastroenterol Hepatol* 2010 Jun; 8 (6): 504-8. Epub 2010 Jan 6.

Acknowledgement

Declaration of personal interests:

Dr. Manuele Furnari was responsible for writing the manuscript, contributed data acquisition and participated in the statistical analysis; Dr Andrea Parodi designed the study and participated in the statistical analysis; Dr Vincenzo Savarino and Dr Edoardo Giannini participated in the writing of the manuscript and participated in the statistical analysis; Dr Lorenzo Gemignani participated in the writing of the manuscript and contributed to data acquisition; Dr Simona Marengo, Dr Edoardo Savarino, Dr Lorenzo Assandri, Dr Valentina Fazio, Dr Simona Inferrera, and Dr Daria Bonfanti participated in patient management and data collection. All authors have seen and approved the final version of the manuscript. All authors declare that they have no conflicts of interest and that the work is original.

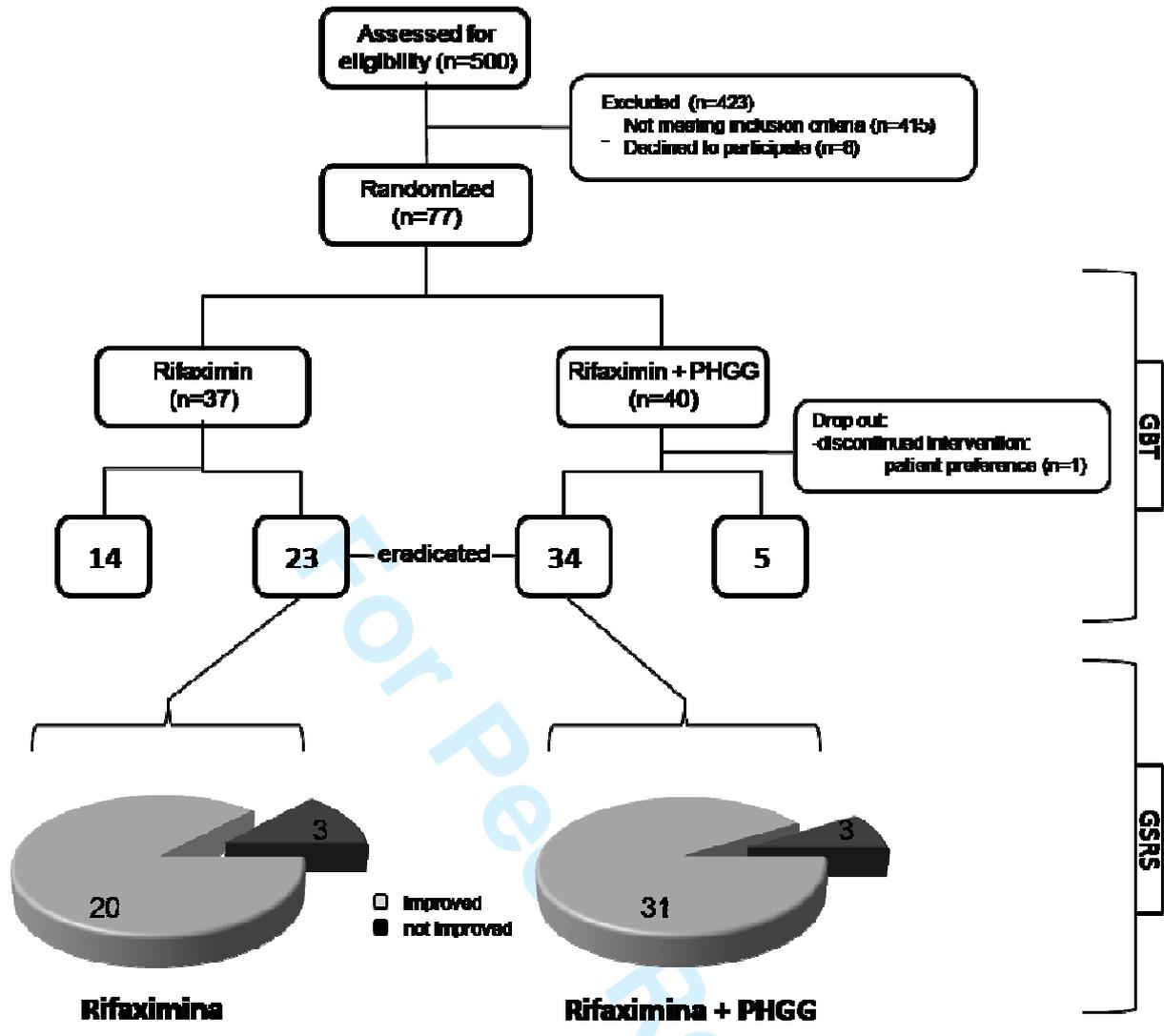
Table 1. Main demographic and clinical characteristics of the study population subdivided according to treatment receive.

Tab. 1		rifaximin	rifaximin + PHGG
patients (n)		37	40
gender (male/female)		8/29	7/33
mean age (years)		55 [26-79]	52.5 [36-84]
BMI (kg/m ²)		24.3 [18-29]	24.5 [18-31]
symptoms n (%):			
- diarrhoea (d)		13 (35%)	12 (30%)
- constipation (c)		6 (16%)	7 (17.5%)
- alternating d/c		4 (11%)	5 (12.5%)
- abdominal pain		21 (57%)	24 (60%)
- bloating		25 (68.5%)	28 (70%)
- flatulence		14 (38%)	17 (42.5%)
- nausea		6 (16.2%)	5 (12.5%)
- tenesmus		4 (11%)	3 (7.5%)

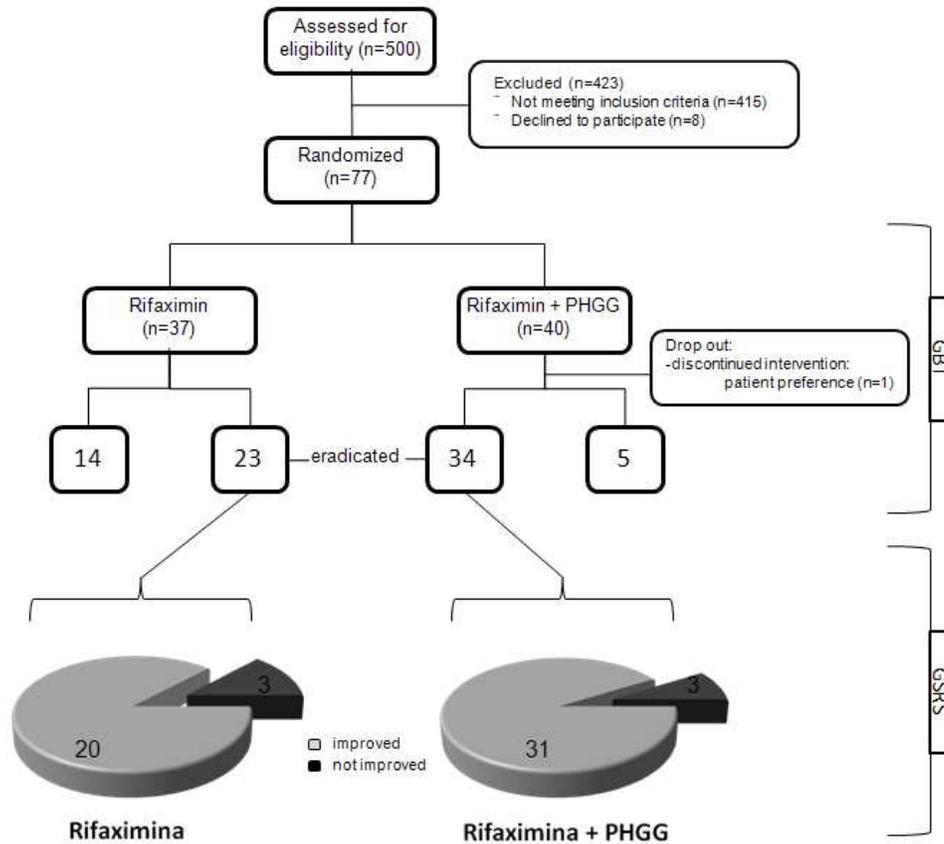
n: number of patients; BMI: body mass index; M: male; F: female.

Figure 1 Flow diagram of the progress through the phases of a randomised trial of two groups (patients within the study, SIBO eradication rates, symptom improvement).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



GBT: glucose breath test; GSRS: gastrointestinal symptom rating scale.



36 Figure 1 Flow diagram of the progress through the phases of a randomised trial of two groups
37 (patients within the study, SIBO eradication rates, symptom improvement).

38 GBT: glucose breath test; GSRS: gastrointestinal symptom rating scale.

39 184x159mm (96 x 96 DPI)

40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3,4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	4
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4,5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	N/A

1		7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
2	Randomisation:			
3				
4	Sequence	8a	Method used to generate the random allocation sequence	5
5				
6	generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	N/A
7				
8	Allocation	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers),	N/A
9				
10	concealment		describing any steps taken to conceal the sequence until interventions were assigned	
11				
12	mechanism			
13				
14	Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to	5
15			interventions	
16				
17	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A
18			assessing outcomes) and how	
19				
20		11b	If relevant, description of the similarity of interventions	N/A
21				
22	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6
23				
24		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
25				
26				
27	Results			
28	Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and	18
29	diagram is strongly		were analysed for the primary outcome	
30				
31	recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	18
32				
33	Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
34				
35				
36				
37				
38				
39				
40				
41				
42				

1		14b	Why the trial ended or was stopped	N/A
2				
3	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	17 (table 1)
4				
5	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was	6
6			by original assigned groups	
7				
8				
9	Outcomes and	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its	6,7
10	estimation		precision (such as 95% confidence interval)	
11				
12		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	6,7
13				
14	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	N/A
15			pre-specified from exploratory	
16				
17				
18	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	7
19				
20				
21				
22	Discussion			
23	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	N/A
24				
25	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	8-10
26				
27	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	8-10
28				
29				
30	Other information			
31	Registration	23	Registration number and name of trial registry	N/A
32				
33	Protocol	24	Where the full trial protocol can be accessed, if available	N/A
34				
35	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	N/A
36				
37				
38				
39				
40				
41				
42				
43				
44				
45				
46				
47				