

# A multicentre open clinical trial to assess the tolerability and efficacy of Boldocynara<sup>®</sup>, a traditional herbal preparation for functional digestive disorders

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## Conclusion

A newly developed solid form of a traditional herbal multi-extract combination product in twice daily one tablet application demonstrated good clinical value in terms of safety, efficacy and tolerability in the treatment of functional digestive disorders, namely dyspepsia, heartburn, regurgitation, nausea, fat intolerance, upper abdominal pain, epigastric discomfort, abdominal bloating, postprandial fullness, flatulence, abdominal cramps, constipation, diarrhoea and stool irregularities, validated by statistical analysis and the clinically relevant verdict of patients and physicians who rated the efficacy and tolerability good and very good in the majority of cases. All symptoms decreased significantly over the 6 weeks treatment period ( $p < 0.0001$ ), reflected simultaneously by a highly significant improvement of all items assessed via the QoL-SF-12. The high acceptance perceived is reflecting the demand of this patient group for a herbal alternative that is safe, easy to administer and effective in the treatment of functional digestive disorders.

## Introduction

Functional digestive disorders lead the list of visits to gastroenterologists and affect at any one time in life 2 out of 5 people, with only a minority of sufferers seeking medical care for it. Non-ulcer dyspepsia is predominantly a self-managed condition and phytotherapeutics are often used for the relief of symptoms. (1) The same is true for functional constipation, and for irritable bowel syndrome where up to 50 percent of patients turn to complementary alternative medicine due to often unsatisfactory results from conventional medical treatments. (2) Boldocynara<sup>®</sup>, a proprietary herbal combination product consisting of cholagogic and hepatoprotective herbs, namely extracts of artichoke leaves, milk thistle fruits, dandelion herb and root, and boldo leaves, has been traditionally used as a popular and well tolerated natural remedy to treat indigestion.

Based on the long standing positive response to this multi-compound preparation we developed a solid galenic form thereof and investigated the safety and efficacy of its twice daily application, consistent with the traditional defined daily dosage, in an open clinical trial with patients suffering from functional digestive disorders.

## Literature

- 1) Thompson Coon J, Ernst E. Systematic review: herbal medicinal products for non-ulcer dyspepsia. *Aliment Pharmacol Ther.* 2002 Oct;16(10):1689-99.
- 2) Shen, YH.; Nahas, R. (Feb 2009). «Complementary and alternative medicine for treatment of irritable bowel syndrome». *Can Fam Physician* 55 (2): 143-8.
- 3) Fraser A, Delaney BC, Ford AC, Qume M, Moayyedi P. The Short-Form Leeds Dyspepsia Questionnaire validation study. *Aliment Pharmacol Ther.* 2007 Feb 15;25(4):477-86.)

## Results

### Demographic data

We included 75 patients aged 18 to 71 years, suffering from at least three functional digestive symptoms at least twice weekly since at least 2 months.

### Efficacy

- Statistically significant decrease of sum score and single scores of frequency and interference with normal activities of all symptoms of the SF-LDQ (dyspepsia, heartburn, regurgitation and nausea) after 6 weeks
  - o Reduction of the SF-LDQ sum score for frequency of dyspeptic symptoms from  $6.3 \pm 2.9$  to  $1.4 \pm 2.0$  ( $p < 0.0001$ )
  - o Reduction of the SF-LDQ sum score for interference of dyspeptic symptoms with normal activities from  $3.6 \pm 3.8$  to  $0.7 \pm 1.7$  ( $p < 0.0001$ )
- Statistically significant decrease of sum score and single scores of frequency and interference with daily activities of all other assessed gastrointestinal symptoms (fat intolerance, upper abdominal pain, epigastric discomfort, abdominal bloating, postprandial fullness, flatulence, abdominal cramps, constipation, diarrhoea and stool irregularities) after 6 weeks
  - o Reduction of the sum score for frequency from  $17.9 \pm 6.4$  to  $4.9 \pm 5.9$  ( $p < 0.0001$ )
  - o Reduction of the sum score for interference with normal activities from  $9.6 \pm 9.7$  to  $1.2 \pm 2.9$  ( $p < 0.0001$ )
- Statistically significant decrease of all 12 items assessed via the QoL-SF-12

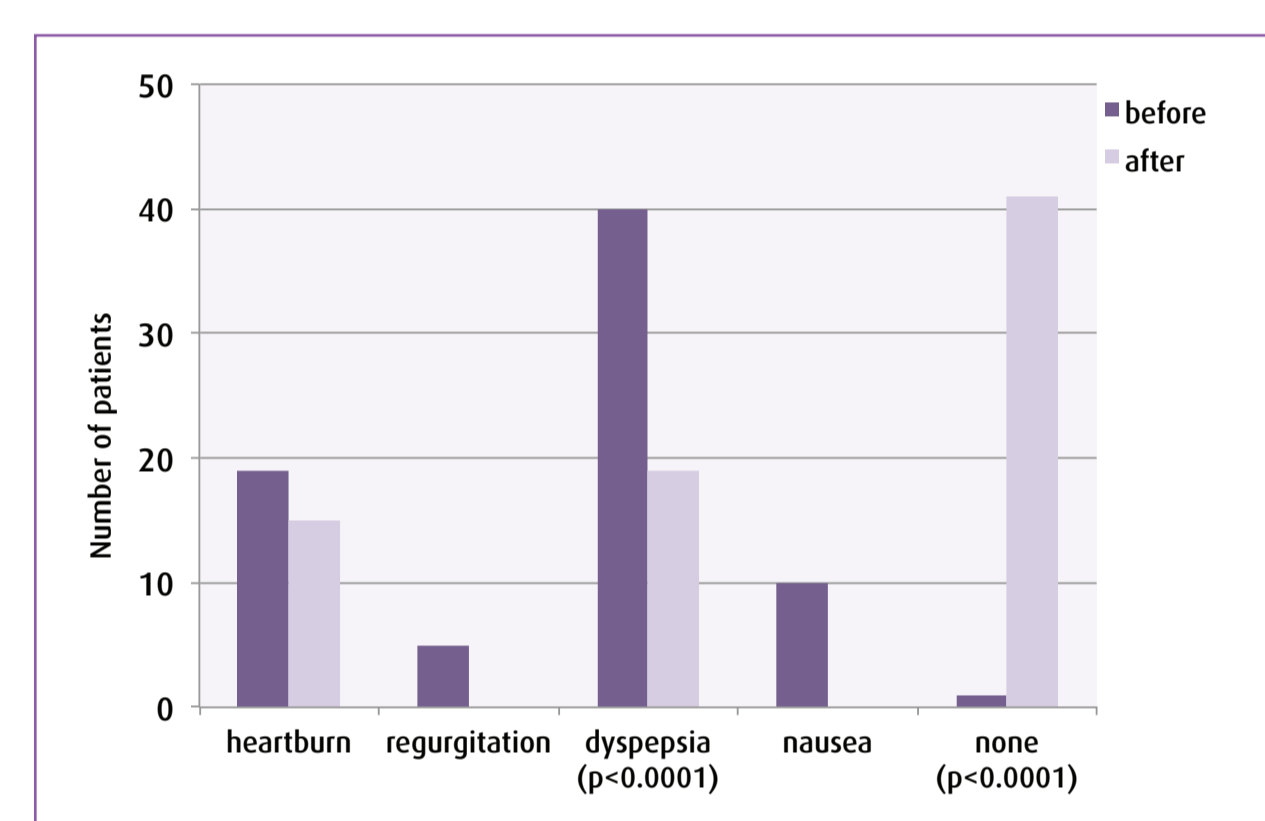


Fig 1 SF-LDQ: Number of patients and their most troublesome dyspeptic symptom before and after treatment (n=75)

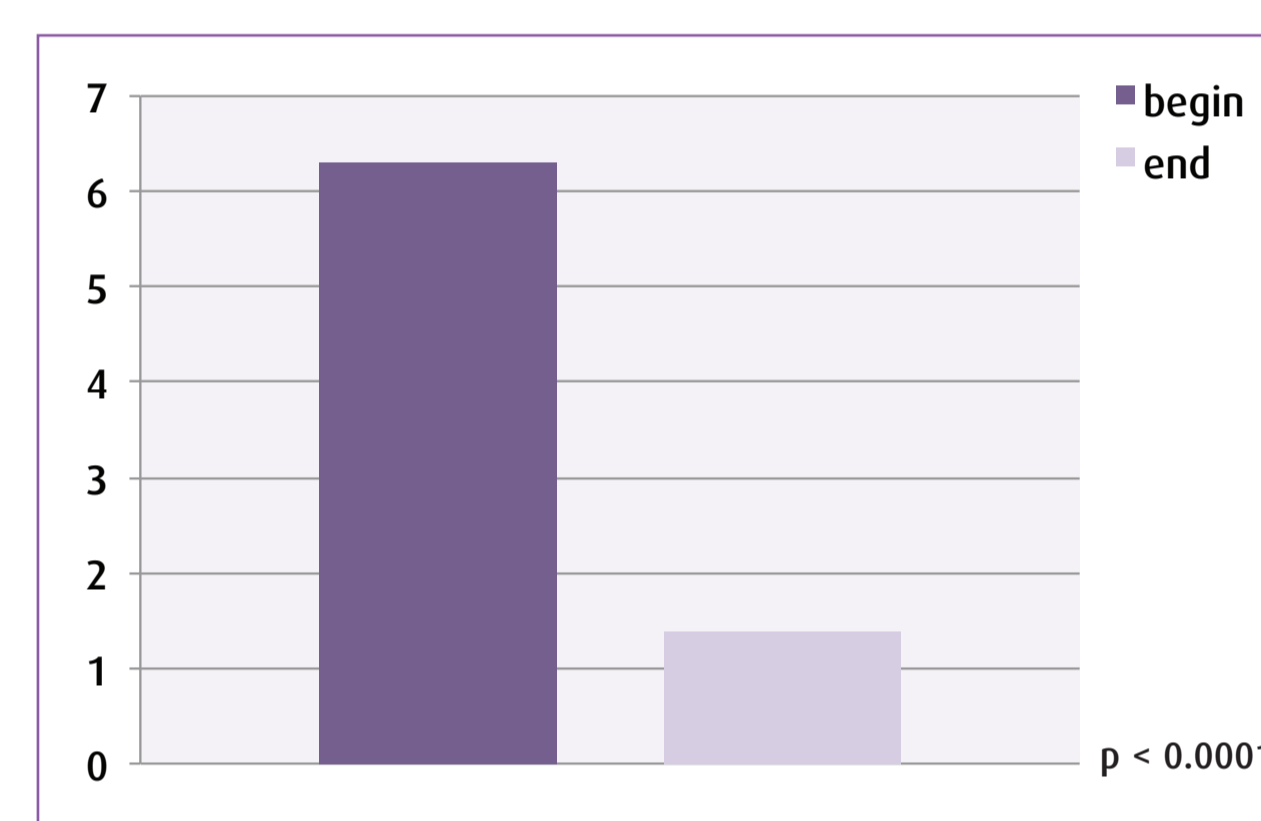


Fig 2 SF-LDQ: Sum Score of frequency of dyspeptic symptoms before and after treatment (n=75) (Scale 0-16) \*

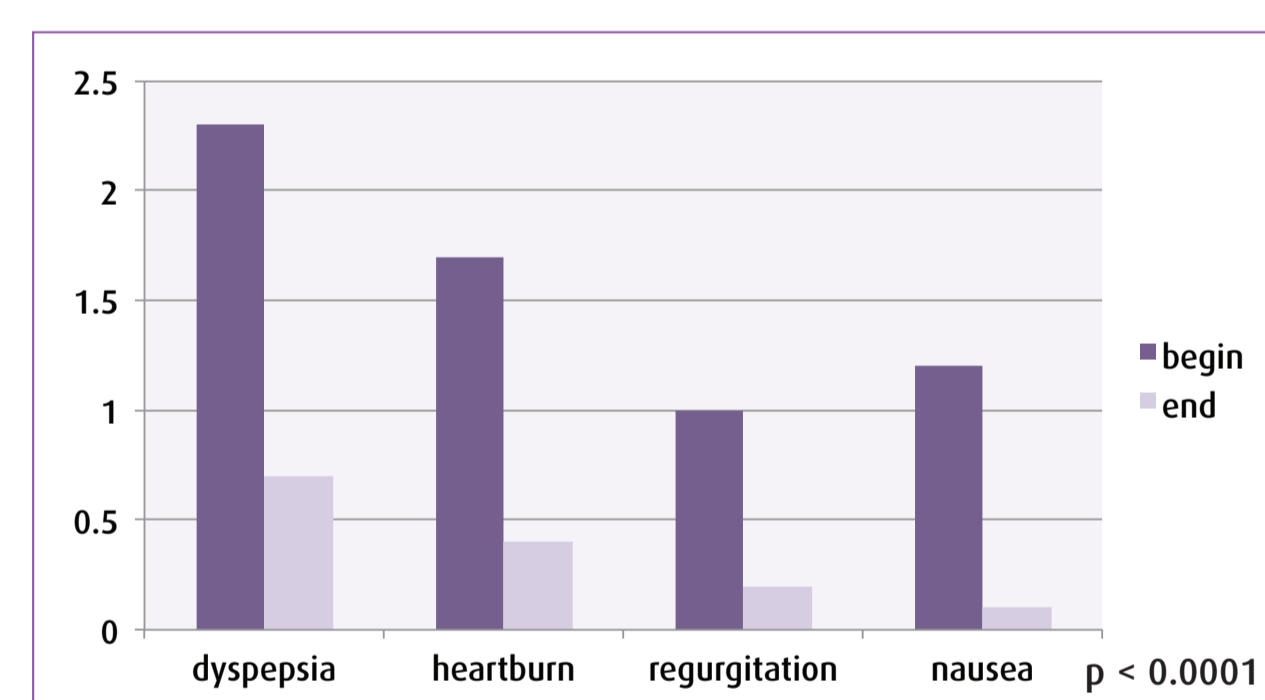


Fig 3 SF-LDQ: Single scores of frequency of dyspeptic symptoms before and after treatment (n=75) (scale 0-4) \*

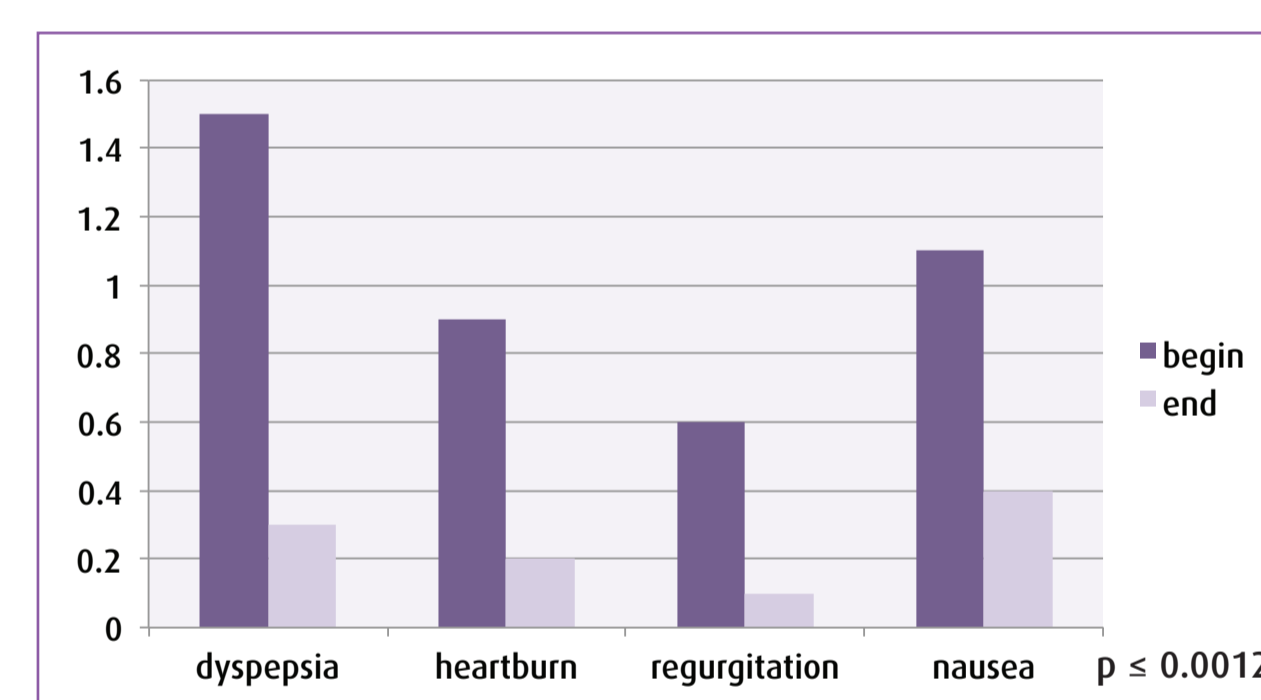


Fig 4 SF-LDQ: Single scores of interference of dyspeptic symptoms with normal activities before and after treatment (n=75) (scale 0-4) \*

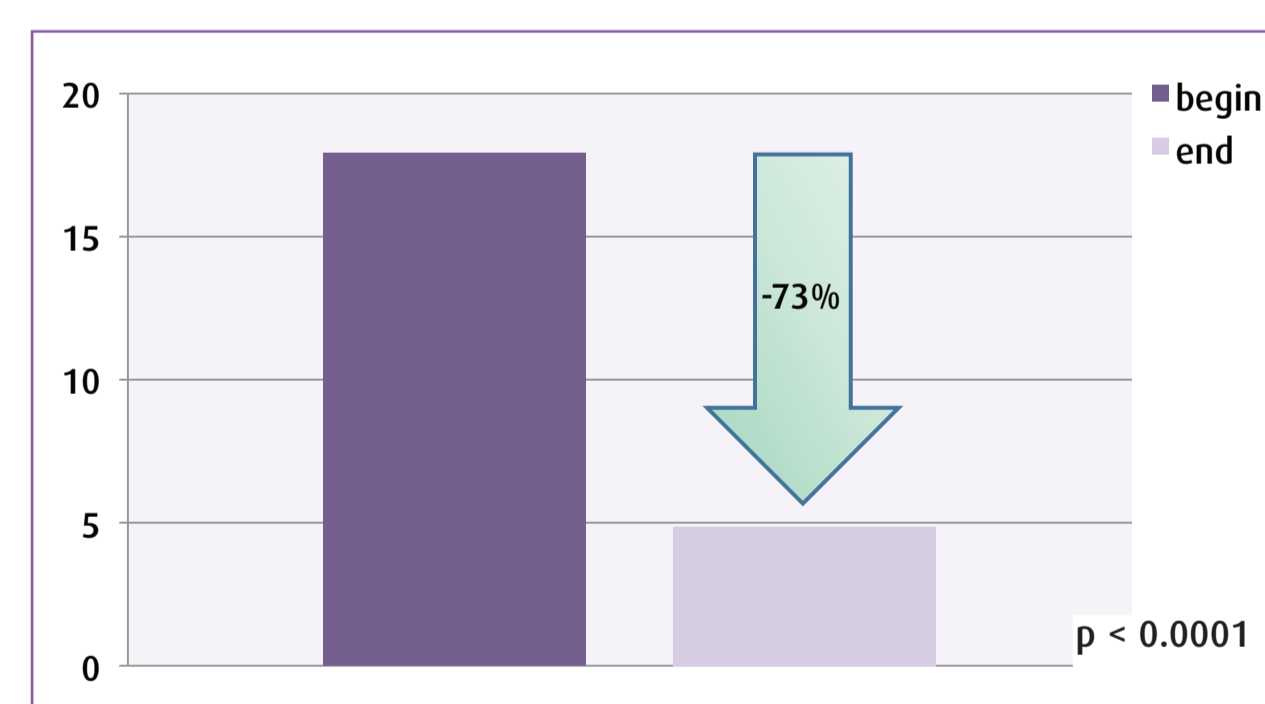


Fig 5 Sum score of the frequency of other gastrointestinal symptoms before and after treatment (n=75) (scale 0-40) \*

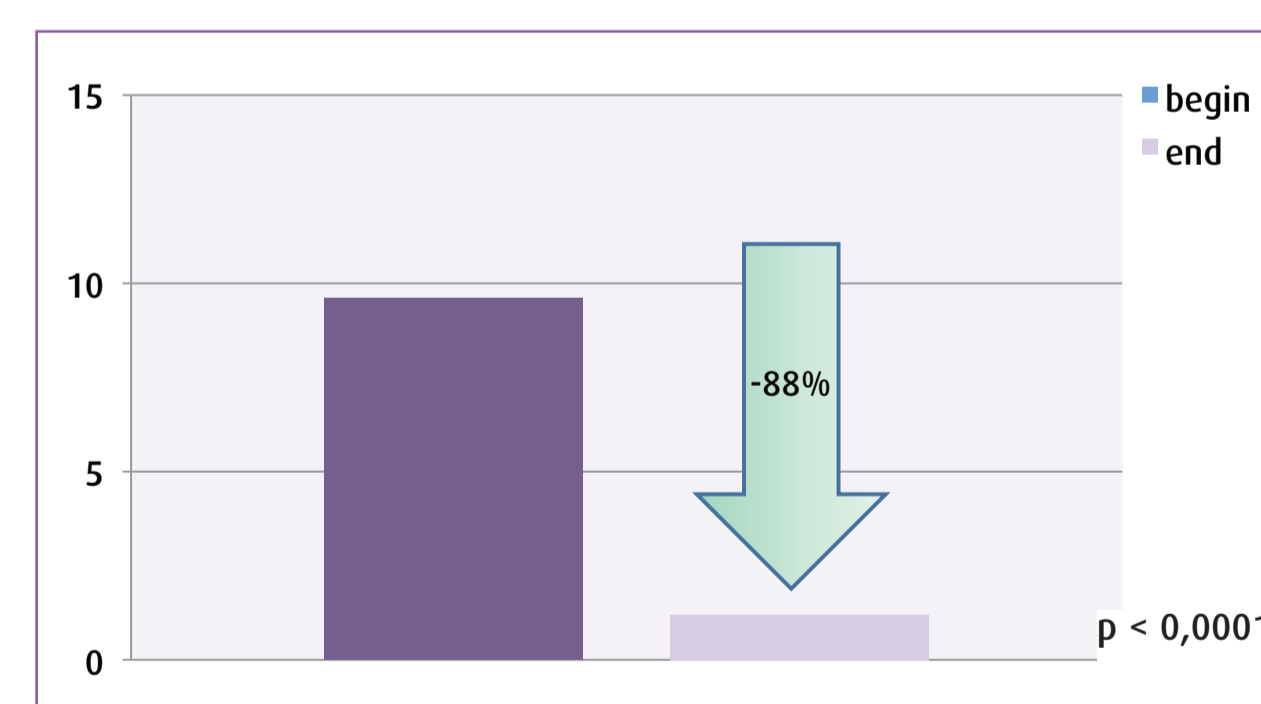


Fig 6 Sum score of the interference with normal activities of other gastrointestinal symptoms before and after treatment (n=75) (scale 0-40) \*

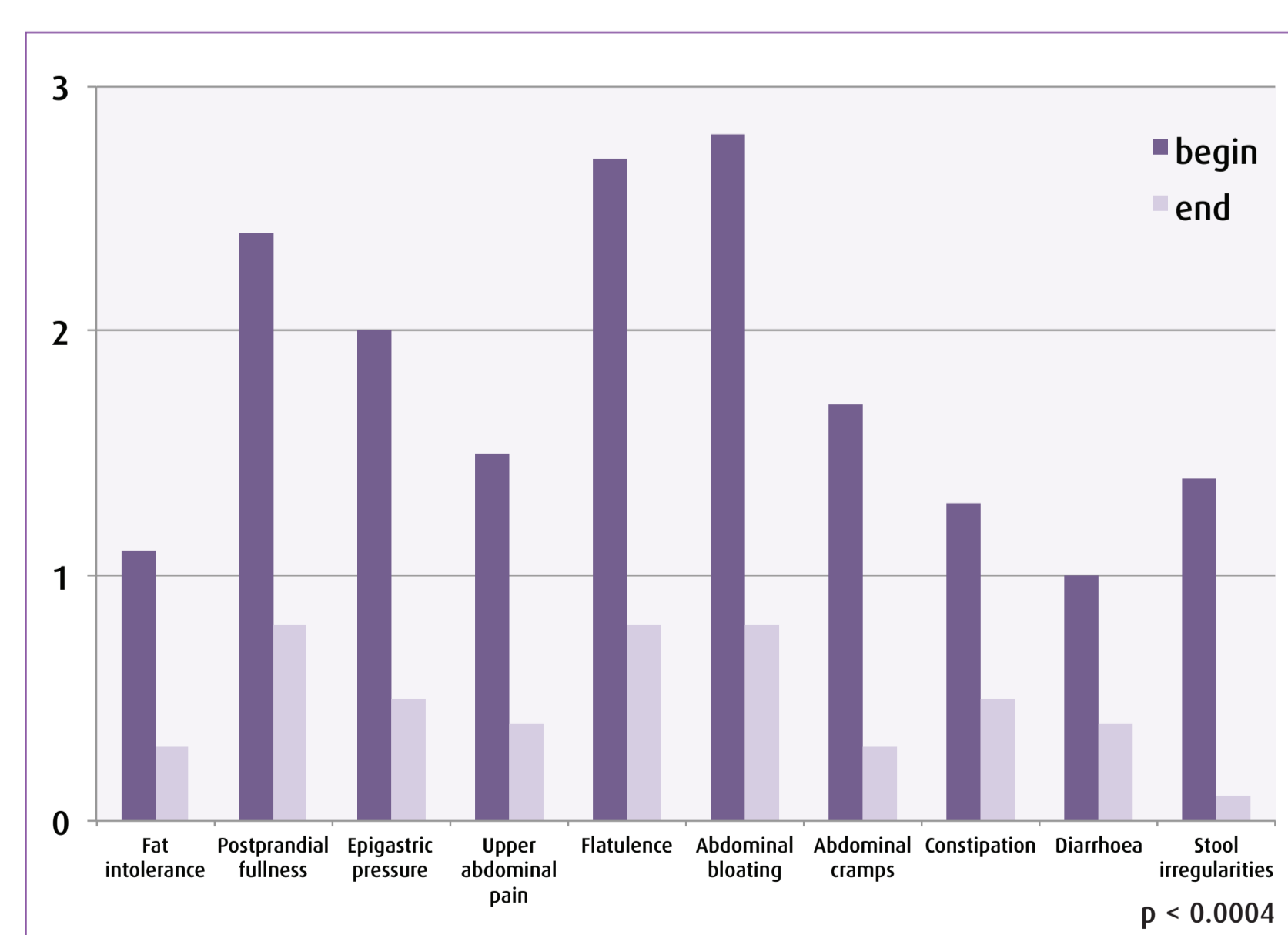


Fig 7 Single scores of the frequency of other gastrointestinal symptoms before and after treatment (n=75) (scale 0-4) \*

\*Frequency or interference rating of each of the assessed symptoms:  
 • not at all = 0  
 • less than once monthly = 1  
 • between once monthly and once weekly = 2  
 • between once weekly and once daily = 3

### Safety

#### Adverse events

- 4 adverse events occurring in 4 patients were reported, of these only 2 (loss of appetite and abdominal distension), both of mild nature, were seen as related to the study medication.
- Tolerability was rated as very good or good by 89% of physicians and 91% of patients.

#### Laboratory assessments

- The evaluation of the laboratory parameters demonstrated a high degree of safety. No clinically relevant change in the mean of leucocyte counts, erythrocyte counts, hemoglobin, hematocrit, MCV, MCH, MCHC, ESR/erythrocyte sedimentation rates, thrombocyte counts, ALAT (GPT), AAT (GOT), bilirubin, creatinine, glucose and cholesterol was observed.

## Patients and Methods

### Multicentric open clinical safety trial Inclusion criteria

- Patients aged from 18 to 70 years suffering from at least three functional digestive symptoms at least twice weekly for at least 2 months
- No serious illnesses, no other medication, including FS, with an influence on digestive symptoms unless if taken at identical dosage for at least 2 months prior to inclusion

### Investigated parameters

#### Safety (primary objective)

- Safety laboratory parameters at start and end of treatment
- Adverse events during treatment period
- Tolerability assessment by physician and patient at the end of treatment

#### Efficacy (secondary objective)

- Short Form Leeds Dyspepsia Questionnaire (SF-LDQ) for dyspeptic symptoms (indigestion, heartburn, regurgitation, nausea): single symptom score and sum score of frequency and interference of symptoms with normal activities (eating, sleeping, work, leisure)
- Global Questionnaire for ten other gastrointestinal symptoms (fat intolerance, upper abdominal pain, epigastric discomfort, postprandial fullness, abdominal bloating, flatulence, abdominal cramps, constipation, diarrhoea and stool irregularities): single symptom score and sum score of frequency and interference of symptoms with normal activities (eating, sleeping, work, leisure)
- Quality of Life (QoL SF-12)
- Global assessment of efficacy by patient and investigator

#### Treatment regimen

2 x daily 1 tablet containing a four component spissum extract of 485 mg tincture per tablet for 6 weeks

Table 1 The Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ) (3)

Patient ID:	A		B	
	How often have you had this symptom over the last 2 months? *		How often has this symptom interfered with your normal activities (eating, sleeping, work, leisure) over the last 2 months? *	
Doc:	Tick only one box per question			
1. Indigestion Indigestion is a pain or discomfort in the upper abdomen.	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more
2. Heartburn Heartburn is a burning feeling behind the breastbone.	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more
3. Regurgitation Regurgitation is an acid taste coming up into your mouth from your stomach.	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more
4. Nausea Nausea is a feeling of sickness without actually being sick.	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more	<input type="checkbox"/> Not at all <input type="checkbox"/> Less than once a month <input type="checkbox"/> Between once a month and once a week <input type="checkbox"/> Between once a week and once a day <input type="checkbox"/> Once a day or more
5. Which, if any, of these symptoms has been the most troublesome to you in the last 2 months? *	<input type="checkbox"/> Heartburn <input type="checkbox"/> Indigestion <input type="checkbox"/> Nausea <input type="checkbox"/> Regurgitation <input type="checkbox"/> None of these have troubled me			

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