

CLINICAL TRIAL REPORT (PART 1)

Florencia Carbone MSc PhD, Karen Van den Houte MPharm, Linde Besard MSc, Jan Tack MD PhD

UZLEUVEN - KULEUVEN

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A RANDOMIZED CONTROLLED TRIAL TO EVALUATE THE SHORT-TERM EFFICACY AND LONG-TERM HEALTH ECONOMIC IMPACT OF A DIETARY INTERVENTION COMPARED TO PHARMACOTHERAPY WITH A MUSCULOTROPIC SPASMOLYTIC AGENT FOR NEWLY DIAGNOSED OR NEWLY TREATED IRRITABLE BOWEL SYNDROME IN PRIMARY CARE.

The DOMINO trial: Diet Or Medication in Irritable bowel syndrome

- Indication: Irritable bowel syndrome (IBS)
- Sponsor: University Hospital of Leuven
- Principal investigator: Prof Jan Tack, MD, PhD
- Research reference numbers:

EudraCT Number:	2017-003258-18
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- Study initiation date (first patient enrolled): 26/07/2018
- Study completion date (last patient completed): 03/07/2020
- GCP statement: The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in "Directive 2001/20/EC", and any subsequent amendments, GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor's SOPs, and other regulatory requirements as amended.

For and on behalf of the principal investigator of the study	
Signature:	Date:/...../.....
Name:	

- Date of the report: MARCH 2022

Synopsis

Trial Title	A randomized controlled trial to evaluate the short-term efficacy and long-term health economic impact of a dietary intervention compared to pharmacotherapy with a musculotropic spasmolytic agent for newly diagnosed or newly treated irritable bowel syndrome in primary care.	
Short title	The DOMINO trial: Diet Or Medication in Irritable bowel syNdrOme	
Trial Design	Parallel-group randomized trial	
Trial Participants	Newly diagnosed or newly treated irritable bowel syndrome (IBS) patients in primary care	
Planned Sample Size	470	
Treatment duration	8 weeks randomized treatment phase	
Follow up duration	6 months follow-up in total	
Actual Trial Period	Date start recruitment period: 26/07/2018 Date end recruitment period: 16/12/2019 Date of inclusion of first patient: 26/07/2018 Date "last visit last patient": 03/07/2020 Date last close-out visit: 07/10/2020 Date database lock: 20/10/2020	
	Objectives	Results
Primary	Treatment efficacy with diet versus medication after 8 weeks of therapy. A responder is defined as a patient with an improvement of 50 points or more on the IBS-SSS.	Both the diet and medication were beneficial. In line with our hypothesis, the responder rate for the diet was significantly higher compared to the medication (diet: 71.1% vs. medication: 61.3%, $p=0.03$)
Secondary	Quality of life and health economic impact over six months after the start of the initial treatment with diet versus medication	See clinical trial report, part 2.
Exploratory	IBS-SSS responder rate, QoL, Psychologic distress, patient satisfaction, predictors of response.	IBS-SSS, QoL and psychologic distress improved similarly with the diet and the medication, but only the IBS-SSS was significantly lower in the diet arm compared to the medication arm. Patient satisfaction tended to be increased in the diet arm. Prediction analysis showed gender to be a potential predictor of treatment outcome in the diet arm and the level of somatization a predictor of treatment outcome in the medication arm.
Intervention	Simple IBS diet (lowering Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (FODMAPs) intake and partially based on the NICE (National Institute of Health and Care Excellence) diet) versus otilonium bromide 40 mg t.i.d, a frequently used musculotropic spasmolytic	

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List of abbreviations

AE	Adverse events
AR	Adverse reactions
BMI	Body mass index
CSR	Clinical study report
CTC	Clinical trial center
DOMINO	Diet Or Medication in Irritable bowel syNdrOme
EC	Ethical commission
eCRF	Electronic case report form
ePRO	Electronic patient reported outcome
EQ-5D	EuroQol 5 dimensions
FAMHP	Federal Agency for Medicines and Health Products
FODMAPs	Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols
GAD	Generalized Anxiety Disorder questionnaire
GCP	Good clinical practice
GDPR	General Data Protection Regulation
GMP	Good manufacture practice
GPs	General practitioners
HRU	The Health Resource Utilization
IBS	Irritable bowel syndrome
IBS-C	Irritable bowel syndrome – Constipation type
IBS-D	Irritable bowel syndrome – Diarrhea type
IBS-M	Irritable bowel syndrome – Mixed type
IBS-QoL	IBS – Quality of Life
IBS-SSS	IBS – Symptom severity score scale
IMF	Investigator master file
ISF	Investigator site file
ITT	Intention-to-treat
MELR	Mixed effect logistic regression
Mobile app	Mobile application
n	Number
NICE	United Kingdom’s National Institute of Health and Care Excellence
OB	Otilonium bromide
PHQ	Patient health questionnaire
Rx	Randomization
SAE	Serious adverse events
SAE	Serious adverse events
SAR	Serious adverse reactions
SAR	Serious adverse reactions
SD	Standard deviation

SE	Standard error
SOP	Standard operating procedures
WPAI	Work Productivity and Activity Impairment

Ethics

All study procedures were approved by the ethical commission of Leuven University Hospital, Belgium (reference S-number study: S59482; date: 2018) and by the federal agencies (EUdraCT: 2017-003258-18) and was performed in accordance to the 1975 Declaration of Helsinki.

All patients enrolled in this study have been properly informed about the study and have signed an informed consent form approved by the ethical commission of the Leuven University Hospital as by GCP guidelines.

Investigators and study administrative structure

Chief Investigator	Jan Tack, M.D., Ph.D. Department of Gastroenterology and Hepatology, Leuven University Hospitals and TARGID (Translational Research Center for Gastrointestinal Disorders), University of Leuven Herestraat 49, 3000 Leuven, Belgium Email: jan.tack@kuleuven.be
Trial Coordinator	Florencia Carbone, M.Sc., Ph.D. Department of Gastroenterology and Hepatology, Leuven University Hospitals and TARGID (Translational Research Center for Gastrointestinal Disorders) Herestraat 49, 3000 Leuven, Belgium Email: florencia.carbone@uzleuven.be
Sponsor	UZ/KU Leuven
Funder(s)	BELGIAN HEALTH CARE KNOWLEDGE CENTRE (KCE) Administrative Centre Botanique, Doorbuilding, Boulevard du Jardin Botanique 55, B-1000 Brussels, Belgium Trials@kce.fgov.be
Clinical Trials Unit	Clinical Trial Center (CTC) Leuven University Hospitals Herestraat 49, 3000 Leuven, Belgium
Key Protocol Contributors	Prof. Jan Tack, M.D., Ph.D., Head of Clinic at Leuven University Hospitals, Gastroenterology and Hepatology Unit. Principal Investigator, Targid, University of Leuven, Herestraat 49, 3000 Leuven, Belgium. jan.tack@kuleuven.be . Phone +3216344225. Prof. Hubert Piessevaux, M.D., Ph.D., Gastroenterologist at Cliniques Universitaires Saint-Luc and Professor of Medicine (UCL), Dept. of Hepato-gastroenterology. hubert.piessevaux@uclouvain.be . Phone +3227642822; fax +3227648927. Dr. Joris Arts, M.D., Ph.D., Gastroenterologist at St. Lucas Hospital Bruges & University Hospitals Leuven and lector at KULAB Bruges. joris.arts@stlucas.be ; Phone +3250365155; Fax: +3250365159. Dr. Alain Vandenberghe, M.D. Gastroenterologist Chaumont-Gistoux, Director Medical Research Consultant. Email alain@avdbmrc.eu ; Phone +3210688014. Dr. Florencia Carbone, M.Sc., PhD., Postdoc, Targid, University of Leuven. Florencia.carbone@uzleuven.be ; Phone +3216345190. Dr. Jessica Biesiekierski, Ph.D. Postdoc, Targid, University of Leuven. J.Biesiekierski@latrobe.edu.au .

Statistician	Prof. Michael P. Jones, Ph.D. Associate Dean (Research) in the Faculty of Human Sciences and Professor of Psychology at Macquarie University, New South Wales, Australia mike.jones@mq.edu.au; Phone +61298508601; Fax +61298508062.
Data Manager	Florencia Carbone, M.Sc., PhD. Postdoc, Targid, University of Leuven.
Committees	Trial Steering Committee: Prof. Jan Tack, M.D., Ph.D., Head of Clinic at Leuven University Hospitals, Gastroenterology and Hepatology, UZLeuven. Prof. Hubert Piessevaux, M.D., Ph.D., Gastroenterologist at Cliniques Universitaires Saint-Luc and Professor of Medicine (UCL), Dept. of Hepato-gastroenterology. Dr. Joris Arts, M.D., Ph.D., Gastroenterologist at St. Lucas Hospital Bruges & University Hospitals Leuven and lector at KULAB Bruges. Dr. Alain Vandenberghe, M.D. Gastroenterologist Chaumont-Gistoux, Director Medical Research Consultant. Prof. Michael P. Jones, Ph.D. Associate Dean (Research) in the Faculty of Human Sciences and Professor of Psychology at Macquarie University, New South Wales, Australia Dr. Florencia Carbone, M.Sc., PhD. Postdoc, Targid, University of Leuven. Karen Van den Houte, M. Pharm., Targid Linde Besard, M. Sc., UZ Leuven. Prof. Philip Caenepeel, M.D., Ph.D. Ziekenhuis Oost-Limburg. Independent member. Christophe Matthys, PhD. Clinical and Experimental Endocrinology, KULeuven. Steven Ceulemans M.D., general practitioner, expertise on management of irritable bowel syndrome patients in primary care. Ine Vanopdenbosch, member representing the CTC UZ Leuven Nelle Stocquart and Hilde Nevens, member representing the KCE. Member representing the patients.

Introduction

The Irritable Bowel Syndrome (IBS), characterized by abdominal pain related to the stool pattern in the absence of underlying organic disease, is one of the most common conditions in clinical practice (1). In Belgium the prevalence of IBS in the general population, according to Rome III criteria, was found to be up to 14%, and 19% when using a more descriptive definition (2-5). IBS is a condition with major health economic and quality of life impact. A population-based study survey conducted in 2010 showed that 41% IBS patients in the general population, defined by the Rome III criteria, had consulted a physician during the last year, and 20% stayed home from work or school because of the severity of their symptoms (2). Over the preceding year, 44% underwent a radiological examination and 28% a colonoscopy and they used on average 1.6 different medications.

For general practitioners (GPs) in primary care, clinical management of IBS patients is challenging. This is attributable to its high prevalence, diagnostic uncertainty in the absence of biochemical or structural markers, the chronic nature of symptoms, fear of underlying serious disease, and the limited efficacy of available therapies. This context leads to repetitive medical consultations, additional technical examinations that are often not very useful and chronic use of sometimes multiple drug therapies, with limited therapeutic gain and often use of alternative or complimentary medicine.

In Belgium, muscletropic spasmolytic agents are the most frequently used (up to 36%) as IBS therapy. However, their efficacy is limited. A recent meta-analysis found a response to spasmolytics in 61% of IBS patients compared to 44% with placebo, but there was considerable heterogeneity amongst studies and a possibility of publication bias (6, 7). A more recent large placebo-controlled study of 15 weeks with otilonium bromide showed only a modest margin over placebo, with uncertain clinical relevance over the first 10 weeks (8, 9). An extensive analysis of an earlier similarly designed study with otilonium bromide demonstrated symptomatic benefit over placebo observed during weeks 5-8 of treatment (10).

Many IBS patients (up to 40%) experience worsening of symptoms in relation to meals (11, 12). GPs often provide general dietary recommendations such as taking regular meals, sufficient fibre, low fat, avoiding caffeine, carbonated beverages and spicy foods. However, there is a lack of evidence that these are efficacious. The view on dietary approaches changed dramatically with the introduction of the low FODMAP diet that targets poorly absorbed short chain carbohydrates and sugar alcohols: Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (FODMAPs). During the low FODMAP diet, foods containing FODMAPs will be eliminated from the daily diet for at least 6

weeks. This restriction period is followed up by a reintroduction period of at least 9 weeks where the FODMAPs are gradually reintroduced in the diet (13-15). Studies in secondary and tertiary care showed a significant favourable effect of the low FODMAP diet for overall IBS symptom evaluation and for individual symptoms of abdominal pain, bloating and flatulence (13-15). However, this diet is not without limitations for its broad implementation in primary care IBS patients, as it is complex, and requires individualized explanation and close follow-up by a skilled and trained dietitian. Furthermore, the low FODMAP diet is associated with reduced calorie intake and changes in faecal microbiota that are potentially unfavourable. Hence, in primary care, dietary instructions should be provided in a format that allows the patient to understand and implement it independently.

Most recently, a randomized study from Sweden, conducted in a tertiary care center, demonstrated that a mixed approach composing of a simpler diet and altering eating patterns, based on guidelines from the United Kingdom's National Institute of Health and Care Excellence (NICE) and the British Dietetic Association, yielded similar symptom benefit as the low FODMAP diet (16, 17). Additionally, this was largely confirmed in a preliminary report from a similar randomized study in a tertiary care setting in the U.S.(18).

Study aim

The primary aim of in this project was to study the efficacy in IBS symptom control benefit between newly managed IBS patients in primary care treated with a muscolotropic spasmolytic agent, otilonium bromide (OB), or a patient-administered dietary intervention. The dietary intervention aimed at reducing large serving sizes of the fermentable oligo-, di- monosaccharides and polyols, and also implemented the NICE dietary guidelines. Additionally, we aimed to evaluate whether symptom control gain with the dietary approach leads to health economic benefits compared to the traditional treatment. Finally, a number of exploratory outcomes were assessed such as biological markers to study pathophysiological mechanisms and predictors of response to the therapy such as microbiota composition and genetic polymorphisms.

Materials and methods

Study design

The setting of this pragmatic study was primary care practice in Belgium. All recruitment and study visits were carried out in the general practice setting. The IBS diagnosis was based on clinical evaluation and judgement by the GP. However, all participating GPs received state-of-the-art information on the current consensus for diagnosing IBS during investigator meetings.

This was an open, randomized, parallel-group study design in which a total of 470 IBS patients (newly diagnosed or new to be treated) were included and randomized with the objective to allocate 235 to each treatment arm. The treatment arms consisted of (1) traditional first-line medical therapy with a spasmolytic agent, OB or (2) a relatively simple diet, a FODMAP lowering diet.

Throughout the study, the GPs followed the required GCP guidelines and all subjects provided informed consent before any study related activity took place. The study included 5 visits at the general practice of the participating GP. One baseline visit, visit 0, and 4 study visits on site.

After the IBS diagnosis was made or confirmed by the GP a baseline assessment was done at Visit 0. During this visit, patients received access to the electronic patient reported outcome (ePRO) questionnaires through the electronic case report form (eCRF) system and according to the GDPR privacy European law. Patients would receive via e-mail a link to the questionnaires that needed to be completed before the next planned visit. The eCRF would send e-mail reminders to the participants as long as the questionnaires were not completed. Additionally, the GP would also remind the patients about the need of the questionnaires before and during the visit if necessary. A flexibility period of 3 days after the study visit was set for the patients to complete the questionnaires. The option to complete the questionnaires on paper was only granted if the patient did not own a PC or had failed to complete it in the electronic system. The ePRO questionnaire included questions on IBS symptom severity, stool pattern, quality of life, work productivity impact and psychosocial co-morbidity status (see questionnaires section here below).

Randomization was done at visit 1, which could be planned up to 14 days after visit 0 (Figure 1). The random treatment was allocated by the eCRF that would automatically generate the instruction of treatment for each patient. Patients in the medication arm were prescribed OB to be obtained from the pharmacy. The diet was self-administered by the patient based on information and instructions provided in an electronic application that was to be downloaded in a smartphone or tablet. For

subjects who did not own the needed electronic devices, the possibility to acquire the diet instructions in a paper format (diet booklet) was also available. During this visit, the GP together with the patient, completed health economic information (HRU) up to 6 months retrospectively. Four weeks in the treatment phase, a “patient alone moment” was planned where the patient was requested to complete the ePRO alone. To plan each consequent study visit (visit 2, 3 and 4) the eCRF system would help the GP to set the best date, but with an available flexible window of +/- 7 days.

Visit 2 was set as the primary endpoint where the improvement of IBS symptoms severity was measured after 8 weeks of therapy (Figure 1). The timing for 8 weeks of treatment was a compromise between IBS medication trials where the endpoint is usually evaluated after 12 weeks, IBS diet trials where the endpoint is usually evaluated after 3 to 4 weeks, and clinical practice by dedicated dieticians where IBS dietary interventions are usually followed up to 6 weeks.

At baseline and after 8 weeks of treatments, the patients had the option to provide blood samples and stool samples for scientific purpose (Figure 1).

Visit 3 and 4 were set as follow up visits. Patients were allowed to change their treatment under the guidance and expert opinion of their GP (Figure 1). The GPs were instructed not to propose the study diet nor the NICE or FODMAP diet or variations of these diets to the patients recruited in the medication arm. This is because the introduction of the study diet or the closely related diets might have impact the data. Nevertheless, it was allowed to introduce other diets normally used in clinical practice, such as a lactose free diet, a diet rich in fibre or others. At visit 2, 3 and 4, the HRU data was acquired prospectively, questioning the prior 8 weeks in the study, thereby generating a total prospective health economic data collection time of 6 months.

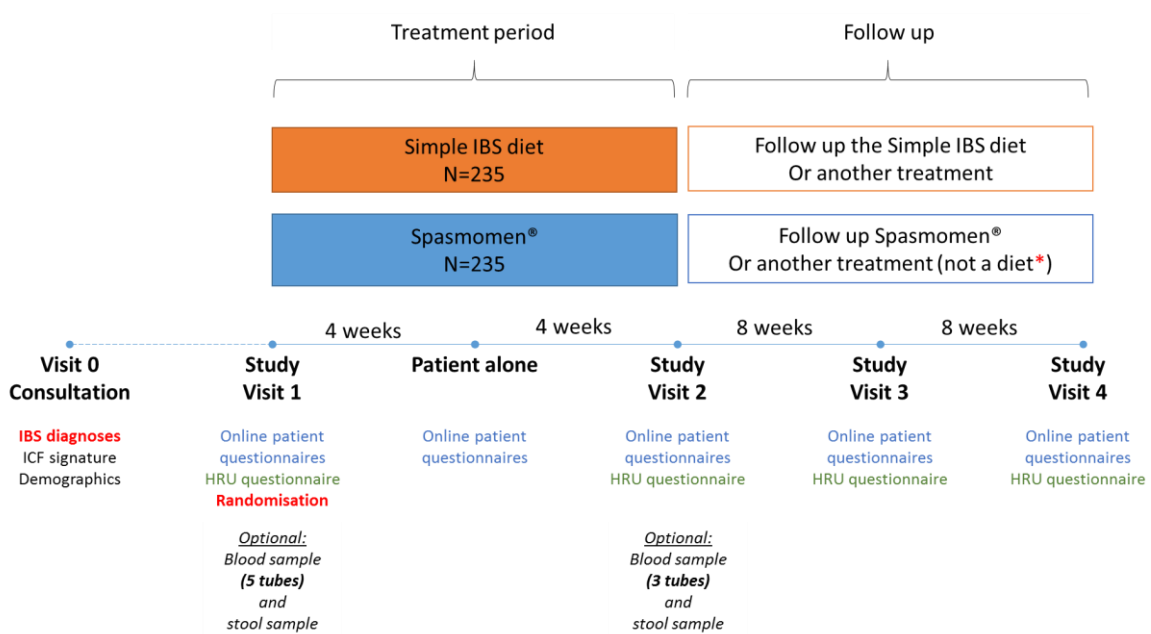


Figure 1. Study design

Objectives

Primary endpoint

The primary endpoint was to assess the treatment efficacy and responder rate with the diet versus medication after 8 weeks of therapy in primary care.

Secondary endpoint

The secondary endpoint included the change in IBS-SSS over time and the impact of the treatment in patient's quality of life, psychologic comorbidities such as depression, anxiety and somatization and in the IBS Rome IV subgroup.

Moreover, different parameters for the prediction of symptom response and patient satisfaction during and after the different treatment modalities were explored.

Additionally, we hypothesize that initial treatment with diet, compared to medication, generates less health economic costs over a 6-months follow-up period. Therefore, the next endpoint of this study was to study the health economic impact over six months after the start of the initial treatment with diet versus medication. Results of these analyses will be discussed separately in an additional study report.

Exploratory endpoint

Finally, the exploratory endpoint included hypothesis free pathophysiologic research of genetic polymorphisms and microbiome in IBS and their prediction to treatment response. Results of these analyses are not discussed in the current rapport.

Interventions

The medication arm in the study used OB (40 mg t.i.d.) which is a well-established and well-tolerated treatment modality. In accordance with the pragmatic design of this trial, patients received the medication prescribed by the GP and were requested to buy it at the pharmacy.

The dietary arm in the study is the FODMAP lowering diet, also partially based on the dietary recommendations from the NICE and the British Dietetic Association. The diet was provided to the patients as a mobile phone application. The app included, among other tools, instructions to follow the diet, indications on what foods to avoid, to decrease ingestion or to use as alternatives. The possibility to acquire the diet on paper format was possible if the patient did not own a smart phone or tablet or if he had fail to download it.

Questionnaires

To be completed by the patient alone: Patients complete the ePRO questionnaires at baseline and before each visit online alone. The possibility to complete the questionnaires on paper was only possible if the patient did not own the needed electronic devices or had fail to complete it in the electronic system.

- **Rome IV questionnaire:** To assess the frequency and severity of IBS symptoms as defined by the Rome criteria. This questionnaire includes the Bristol stool scale to assess the subtype of IBS based on the stool type.
- **IBS – symptom severity score scale (IBS-SSS) questionnaire:** To assess the severity of IBS (19). The maximum achievable score is 500. Mild, moderate and severe cases were indicated by scores of 75 to 175, 175 to 300 and >300 respectively. Controls scored below 75 and patients scoring in this range can be considered to be in remission.
- **IBS – Quality of Life questionnaire:** To assess the IBS generic functional status and well-being, perceived quality of life specific to IBS, and work disability (20). This questionnaire includes a 5-point Likert response scale was used to assess how much the statement described the feelings of the respondent: 1=not at all, 2=slightly, 3=moderately, 4=quite a bit, and

5=extremely or a great deal. All items were sum-scored to calculate total scores. Hence, higher scores indicate a lower quality of life.

- **Patient health questionnaire (PHQ)** is a number of questionnaires used to assess the level of psychologic distress in IBS patients. For this study we assessed depression based on the PHQ-9 questionnaire (scores represent 0-5 mild, 6-10 moderate, 11-15 moderately severe, 16-20 severe depression), anxiety based on the GAD-7 questionnaire (scores represent 0-5 mild, 6-10 moderate, 11-15 moderately severe anxiety and 15-21 severe anxiety) and somatization based on the PHQ-15 questionnaire (scores of 5, 10, and 15 represent cut points for low, medium, and high somatic symptom severity, respectively) (21).
- **Treatment satisfaction questionnaire** to understand treatment acceptability for patients and evaluate the value of the treatment from the patient perspective. Subjects completes this questionnaire 8 weeks after randomization and before every subsequent visit. A responder is defined as a patient that scores “quite satisfied” and “very satisfied” to the satisfaction question.
- **Treatment adherence questionnaires** to study the risk of poor adherence and persistence to the allocated treatment. Subjects complete a treatment adherence questionnaire 8 weeks after randomization and before every subsequent visit.
- **EQ-5D questionnaire:** EuroQoL instrument to assess quality of life and health state of patients by focusing on 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
- **Work Productivity and Activity Impairment (WPAI):** quantifying the effect of IBS symptoms on absenteeism, presenteeism, work productivity loss, and activity impairment.

Questionnaires to be completed during the study visit

- **The Health Resource Utilization (HRU) questionnaire** related to IBS was collected in a retrospective (6 months recall) manner at baseline and during the study prospective (6 months) to address direct and indirect medical costs.
- **Treatment adherence questionnaires:** The GP will ask at every study visit if the patient was able to follow the treatment in the period prior the visit and if he/she would like to continue with the treatment.

Recruitment of GPs

Recruitment sources

Different sources to recruit GPs for the DOMINO study were used.

GPs from a private dataset that have previously participated in academic lectures regarding the topic of functional gastrointestinal disorders and have shown interest in our research, were contacted and invited to participate in the study.

Awareness to the study and its aims was introduced by using the general media: small articles and spots in the “Artsenkrant” and “Medipres”. Support was requested from Domus Medica and the Association des Médecins Généralistes Wallonne. Additional recruitment was done by organizing educative meetings for GPs (Bruges, Gent, Genk, Leuven, Antwerp, La Hulpe-Rixensart). At the end of the seminar, the DOMINO study design and aims were introduced.

From all these sources, GPs who were motivated to participate in the study were included to a list for “interest of participation”. These physicians were later contacted for the study initiation investigator meeting. Based on the location of most GPs, the sites for the meetings were set in Bruges, Genk, Antwerp, Leuven and Antwerp.

Investigator initiation visit

During the investigator initiation meetings the study design was explained in detail, and this was combined with a GCP course. The eCRF, investigator site file (ISF), use of the diet smartphone application and all relevant aspects related to the organization of the DOMINO study were highlighted. At the end of the meeting, those GPs that still keen on participating in the trial, would be requested to sign the participation agreement with UZLeuven. Additionally, they would receive a GCP certificate signed by Prof Tack, acquire the ISF with all needed documents to use in the study, kits with study material needed for the acquisition of biological samples and additional tools such as posters and flyers to support recruitment.

Recruitment of patients and criteria for participation

IBS patients were recruited by GPs in primary care. Patients were eligible if they were newly diagnosed with IBS or newly to be treated for IBS. The diagnostic gold standard, in line with clinical practice, was the clinician’s diagnostic judgment. Also, patients who did not receive treatment with OB over the

preceding 3 months, and who did not receive long-term treatment (>3 consecutive weeks) with OB in the past were eligible for the trial.

Patients who did not fit the IBS diagnosis by suffering from a concurrent organic gastrointestinal disease (e.g. inflammatory bowel disease), having a history of major bowel surgery or with major uncontrolled diabetes, major psychiatric disease, uncontrolled thyroid disease, active malignant disease (not including patients with cancer free diagnosis for more than 5 years), symptomatic uncontrolled endometriosis, were not eligible for the study. Patients not capable to understand or be compliant with the study, or patients who are pregnant, lactating or with active pregnancy plans in the coming 6 months were not eligible for the trial.

In terms of prohibited medication, patients who received treatment with OB in the past for more than 3 weeks consecutively or who received OB recently for any duration in the last 3 months or who have used a FODMAP or NICE diet before, were not eligible for the study. However, patients who recently (last 3 weeks) used other medication for IBS, including pharmacologically prepared probiotic formulations, or who changed their diet for IBS or for any other reason over the last 3 months, were allowed to participate in the study after stopping these treatments according to the advice of their GP.

To help the GPs, the definition and diagnosis of IBS was highlighted during the investigators meetings and supportive material was provided. Additionally, the DOMINO study team contact information was made available for any question or concern the GPs might have regarding the eligibility of a patient. The eCRF included as well a checklist of the inclusion and exclusion criteria for the GP to revise during the inclusion visit of the patient.

Monitoring and quality assurance

Monitoring of GPs

GPs were monitored throughout the study remotely and on-site. On a daily basis, the DOMINO study team followed data entry in the eCRF. Additionally, all trial sites that included patients were monitored on-site during the trial by the DOMINO study team to ensure the quality of the trial. During the visits, the DOMINO study team monitor reviewed the source documents and the ISF and ensured that all essential documents have been completed and filed accordingly. Queries or inconsistencies were noted, clarified and corrected according to the GCP guidelines. **For more details on monitoring and quality assurance, consult the study coordination and monitoring plan.**

Quality assurance

To ensure the quality of the study, a number of strategies were set up by the DOMINO team. These include: a risk assessment plan based on a pragmatic study approach, a study coordination and monitoring plan, a data management and statistical plan and SOPs for handling of biological samples and safety procedures. The DOMINO team also provided guidelines for the use of the investigator trial file and the eCRF for GPs and the mobile application for patients.

The clinical trial center (CTC) set up time specific checkpoints to review the quality of the site monitoring and completeness of the trial master file. Additionally, an experienced member of our department but independent from the DOMINO study, also reviewed the quality of the monitoring reports.

Steering committee meetings (every 3 months) and KCE meetings (every 2 weeks and every month) were also planned to update the progress of the study and address possible issues.

Collection, storage and analysis of biological samples

Stool samples were collected at home by the patient before the planned visits. The DOMINO team provided specific kits with instructions for the collection of the samples. Blood samples were collected during the visit by the GP. Blood samples analysis included one sample for genetic research and samples for a general routine parameters check of which a report was also provided to the respective GPs. Samples collection was organized at the GPs site by CRI laboratories where all samples were stored in -80°C freezer. **For more information, see SOP biological samples.**

Safety reporting

The DOMINO trial was considered a low risk trial. For this reason, information regarding adverse events (AE) and serious adverse events (SAE) for the study treatments was indicated to GPs but collection of these data specific for this trial was not requested. It was the GP's responsibility to determine all AEs and SAEs and manage them in the patient's medical record in accordance with standard clinical practice guidelines, and this for up to 30 days after the end of the trial.

Only serious adverse reactions (SAR) clearly related to OB were to be registered in the eCRF by the GP. In addition, the GP was responsible for ensuring that all events concerning the safety of their patient(s) were reported to the DOMINO study team in accordance with the instructions provided during the investigators meetings. SARs were to be reported up to the end of the trial in the eCRF and up to 90

days after the end of the trial to the sponsor. All SARs were monitored until resolved or until a final result was achieved.

Yearly, a safety study report was provided to the ethics committee of UZLeuven.

Development of eCRF

The company Lambda Plus developed the eCRF. The development of this tool was done in accordance to the necessary GMP, safety and privacy regulations. Development was done in three steps, a first prototype, a beta 1 version, a Pre-Production version that after approval was retitled the live or production version. Though each step, a data validation plan was set to check the validity and functionality of the eCRF tool. The eCRF was extensively tested by the DOMINO study team.

Specifications of the eCRF development are described in the data management plan.

Development of Mobile app

The company EverywhereIm managed the development of the dietary mobile application. For the development of the mobile app, different functional designs were discussed and tested. The mobile app was extensively tested by our study team and volunteers with and without IBS symptoms. The app is available to patients in Dutch, French and English. Specifications of the app include: introduction and explanation regarding the clinical trial, instructions to follow the study diet, overview of alternatives to foods, additional explanation on what to eat and what to avoid or decrease consumption, recipes that includes a tool to set up a week menu, favourites and adapt proportions, tips to eat out and to improve the lifestyle. **Specifications of the mobile app development are described in the data management plan.**

Statistical methods

The primary outcome variable of the trial was treatment responder rate after 8 weeks. A responsive patient was defined as a patient with at least 50-point drop from baseline on the IBS IBS-SSS (19).

The secondary endpoints were the improvement of the IBS-SSS score from baseline after 8 weeks of treatment (short-term treatment outcome), and at follow-up (4 and 6 months, long-term treatment outcome). Furthermore, the continuous outcome of the mean IBS-SSS scores were analysed to indicate magnitude of symptom improvement, taking into account the treatment modalities (diet vs. medication) after 8 weeks.

Quality of life, assessed with the IBS-QoL and EQ-5D questionnaire, was investigated after 8 weeks of treatment and compared to baseline and between treatment arms. Furthermore, the changes on quality of life over time were also analysed. In addition, the psychosocial status assessed with the PHQ (PHQ-9 for depression, PHQ-15 for somatisation, GAD for depression), and changes herein, were also addressed. Some exploratory outcomes were also be assessed to evaluate patient satisfaction for the treatment modalities, IBS subtypes, and predictors to response to treatment.

Direct and indirect health costs (HRU questionnaire), including self-costs to patients, and productivity losses and activity impairment (WPAI questionnaire), were compared at the different time points in the study and were compared to the retrospective cost assessment at baseline. The total direct costs of the utilization of healthcare resources associated with IBS was calculated. **These analyses are not included in this report but will be presented in part 2 of the CSR.**

Additionally, genetic and microbiome analysis was assessed to further investigate the pathophysiology of IBS, as well as to generate important information on predictors of treatment response. **These analyses** were performed on the budget of the investigator, not covered by KCE, and **will not be included in this report.**

Sample size

There is a lack of solid data in the literature on IBS-SSS-based treatment outcomes with diet or spasmolytic agents in IBS. The following data, with limitations, are available in the literature:

- Treatment success rate in the OBIS trial for the otilonium bromide arm was 60% for the whole treatment period, but this trial used as responder criterion an improvement of at least 1 point on a 0-4 scale for 2 key symptoms in diaries and had a very high placebo response of 55% (9, 10).
- Treatment success rate in the Swedish tertiary care trial, evaluated similarly to the current trial by an improvement in IBS-SSS of at least 50 points, was 46% with the NICE-based diet and 50% with the low FODMAP diet (16).
- Similarly, treatment success rate with the NICE-based diet in the U.S. tertiary care trial, evaluated by the binary adequate relief endpoint, was 47% and with low FODMAP diet 54% (18).
- Treatment success with low FODMAP diet in secondary care in Belgium, expressed as a decrease of global IBS symptom severity of at least 50%, showed a response rate of 65% (15).

The sample size of the trial is based on the following assumptions: 1) the response to the NICE diet is close to the one observed in the Belgian secondary care with low FODMAP diet, present in 60% of the patients, 2) the response to medical therapy is present in 45% of the patients. In a parallel-group

superiority trial design with equal number of patients in each group and applying the proportions test, the number of subjects per arm to obtain 85% power at the 0.05 significance level (two-sided) for a contrast of 50% success for otilonium bromide and 65% for dietary intervention is 200, which amounts to a total of 400 subjects.

The sample size is increased to 235 per arm (470 patients in total) to allow drop-outs. In the group on medication, the option for the GP, in agreement with the patient, will be to stop after 8 weeks. Treatment can be continued if considered appropriate by the physician. Ongoing medical therapy and its compliance during follow-up will be recorded in the eCRF. In the diet group, diet can be continued as considered clinically useful by the patient. Diet adherence will be assessed by a simple question during follow-up.

Randomization method

Patients were allocated 1:1 to each treatment arm. The allocation sequence was generated by a random sequence generating program in the eCRF developed by lambda plus. The program generated a randomization sequence per GP. To minimise site influences, a block randomisation schedule was used, based on variable block sizes. The allocation sequence was generated by a random sequence generating program developed by lambda plus.

The patient randomization process was defined as follows by Lambda plus:

- Locate the set of blocks related to the patient's centre and sort the sequence number by ascending number
- Take the lowest not yet allocated sequence number in the centre list (Physician's list)
- Allocate this treatment arm to the patient
- If there is no more sequence number available in the centre list, apply the minimization algorithm.

The minimization algorithm includes 2 factors:

- the province
- the physician: For each next patient, determine which arm to assign will lead to a better balance between two groups. The following algorithm applies:
 - $X = \Sigma (\text{number of patients in ARM1 in this stratum of Minimization factor 1}) + (\text{number of patients in ARM1 in this stratum of Minimization factor 2})$
 - $Y = \Sigma (\text{number of patients in ARM2 in this stratum of Minimization factor 1}) + (\text{number of patients in ARM2 in this stratum of Minimization factor 2})$
 - If $X > Y$, patient should be assigned to ARM2
 - If $Y > X$, patient should be assigned to ARM1

- If $X = Y$, assign patient at random to ARM1 or ARM2 (50%-50%)

Run the random element ('roll the dice'):

If ≥ 30 : assign the arm selected by the algorithm

If < 30 : assign patient at random to ARM1 or ARM2 (50%-50%)

As there is no maximal number of patients determined per GP, to avoid one site to include too many patients, after 12 patients, an evaluation of the total number of patients in the study will be done to assess disproportion within the provinces.

Statistical analysis

Statistical programs used

SAS software (University Edition, SAS Institute Inc., Cary, NC, USA) and Stata (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.) have been used to conduct all statistical analyses.

Primary outcome analysis

All analyses were conducted on an intention-to-treat (ITT) basis. For this analysis, the responder status was determined for all patients and the proportion of responders was compared between treatment arms using mixed effect logistic regression (MELR) which is effectively a mixed-model logistic regression in which treatment group is treated as a fixed effect and general practice as a random effect. Overall, if the analysis violated the assumption of normality, formal statistical inference employed the nonparametric bootstrap with 2000 bootstrap replications.

For the analysis all patient's data was included and no reasons for subject's data exclusion was noted. Therefore, there is no per protocol (PP) analysis included in this report.

Secondary outcome analysis

Change in quantitative measures

The change in IBS-SSS was compared between treatment groups in two ways. The first was via change scores from baseline to a given subsequent visit and therefore only individuals who provided data for that visit (termed completers). Statistical significance of the difference was evaluated via the Mann-Whitney test due to non-normal distributions. The second approach used all the responses available at each visit in a mixed model where the interaction between treatment group and time was used to evaluate differences in change from baseline between treatment groups. Formal statistical inference

employed the nonparametric bootstrap (2000 replications) due to non-normal distribution of the outcome measures. A similar approach was used for the exploratory analysis of the subgroup fulfilling the Rome IV criteria (Rome+ subgroup, see below). The same approach was employed for the scores on anxiety, depression, somatization and IBS quality-of-life. Treatment satisfaction and adherence were evaluated in both treatment groups. The difference in distribution of satisfaction and adherence ratings between medication and diet was tested by Pearson Chi-Square test.

Prediction of symptom response

Parameters for prediction of response were analyzed in both treatment groups (logistic regression) with effect sizes reported as odds ratios (OR). This is a three-part exploratory analysis to determine (1) predictors of response to pharmacotherapy, (2) predictors of response to dietary therapy (3) moderators of the difference between pharmacotherapy and dietary therapy. Analyses of (1) and (2) employed backward elimination of multiple baseline predictors with change in IBS-SSS score as the outcome measure. The analysis of (3) adopted the interaction between treatment group and a baseline measure as the parameter of interest but will build up from simpler models to more complex (forward stepwise) due to the potential for over-parameterization of the model that might occur with a backward approach.

Subgroup analyses

Exploratory subgroup analyses comprised the analysis of the subgroup of patients that fulfilled the Rome IV diagnostic criteria at Visit 0 and that are indicated as “Rome IV positive (+)” patients. The Rome IV IBS criteria includes recurrent abdominal pain on average at least 1 day per week in the last 3 months, associated with two or more of the following: (1) related to defecation and/or (2) associated with a change in the frequency of stool and/or (3) associated with a change in the form (appearance) of stool.

Missing data handling

Missing data on an entire measure was handled using maximum likelihood estimation in mixed models. Missing items within a particular measure, such as the IBS-SSS, employed the half-rule where missing items were replaced by the average of non-missing items as long as at least half of all items were answered. Where more than half of all items were not answered the measure was treated as missing.

Results

Participants' study flow

General practitioners (n=69) assessed 817 patients for eligibility on the study. Of these, 472 were included in the trial and 459 randomized to the diet or medication arm. The intended equal distribution across the Belgian provinces did not succeed due to 1) imbalances in willingness to participate for general practitioners (and their organisation) in the north and south and 2) differential willingness to participate from GPs among Flemish provinces too. The number of patients was recruited mainly in Flemish provinces and the average recruited number of participants per GP was 6 (Table 1).

Table 1: overview included patients per provinces

	Active GPs	Patients included	Ratio number of patients/GP
Antwerp	9	60	6.7
Limburg	11	90	8.2
Vlaams-Brabant	28	221	7.9
Oost-Vlaanderen	6	48	8.0
West-Vlaanderen	9	44	4.9
Waals-Brabant	5	17	3.4
Namen	1	3	3
	Total	Total	Average ratio (SD)
	69	483	6.0 (2.2)

During the treatment phase (8 weeks), six subject dropped out of the study and 65 dropped out during the follow up period. The main reasons for drop-out were lack of efficacy or to experience the study as unpractical or difficult to follow. Overview of the participants' flow is shown in Figure 2.

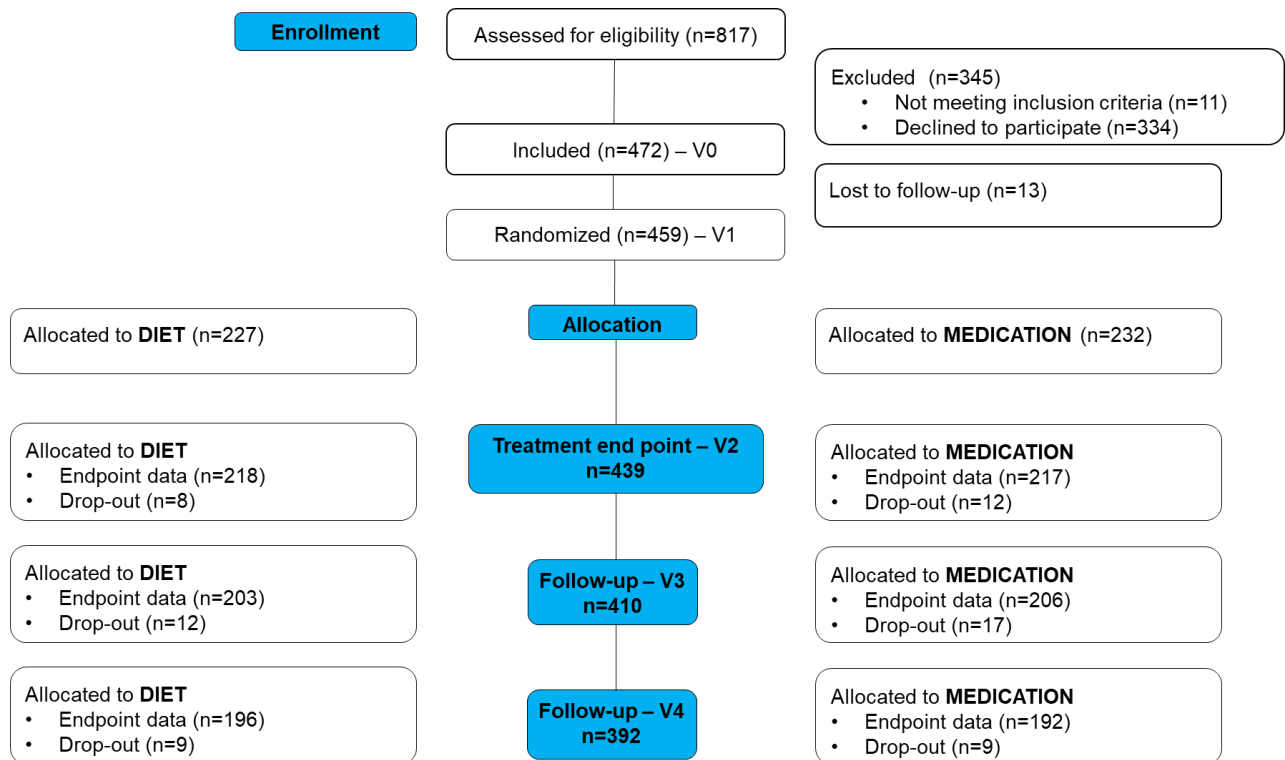


Figure 2: Participants' flow Table: Patients lost to follow-up.

Table 2: Overview reason for drop-out

At visit 1 (Not randomized)	Concurrent disease= 2 Trial being too difficult/impractical= 7 Withdrawn by investigator= 2 Withdrew consent (deceased family member)= 1 Withdrew consent (patient not motivated)= 1 TOTAL= 13	
	Diet arm	Medication arm
At Visit 2	Concurrent disease= 1 Treatment inefficacy= 2 Trial being too difficult/impractical= 4 Withdrew consent (acute disease of partner)= 1 TOTAL= 8	Concurrent disease= 3 Treatment inefficacy = 1 Trial being too difficult/impractical= 5 Withdrawn by investigator= 1 Withdrew consent= 2 TOTAL= 12
At visit 3	Lost to follow up= 2 Treatment inefficacy= 2 Trial being too difficult/impractical= 6 Withdrew consent= 2 TOTAL= 12	Lost to follow up= 2 Treatment inefficacy= 5 Trial being too difficult/impractical= 5 Withdrawn by investigator= 1 Withdrew consent= 4 TOTAL= 17
At visit 4	Treatment inefficacy= 5 Trial being too difficult/impractical= 3 Withdrew consent= 1 TOTAL= 9	Concurrent disease= 1 Treatment inefficacy= 5 Trial being too difficult/impractical= 2 Withdrew consent= 1

		TOTAL= 9
Total	29	38

**Includes the number of patients and the reason for lost in follow-up. Even though, some of the patients withdraw the study at the visit with the GP, many patients completed the study questionnaires before the visit, therefore the number of missing data are minimal. For example: between at visit 2, 8 patients wanted to stop with the study, but only 3 patients has not completed the IBS-SSS questionnaire which is necessary for the assessment of the primary endpoint.*

Demographic and characteristics of patients

Throughout the study, there were no demographic differences between subjects at each study visit as well as between study arms (Table 3). Baseline questionnaire assessment showed high to moderate IBS symptom severity scores. At baseline, patients showed moderate levels of anxiety, depression and somatization. Symptom scores did not differ between treatment subgroups at baseline.

Table 3. Overview of demographics at baseline and per study arm

	Baseline (n=453)		
Average age, years (SD)	40.9 (14.7)		
Gender (Female) n, (%)	343 (75.7%)		
Weight, Kg (SD)	70.5 (14.1)		
BMI, m/kg ² (SD)	24.6 (4.5)		
Stool type IBS, n (%)			
IBS-D:	125 (28%)		
IBS-C:	92 (20%)		
IBS-M:	182 (40%)		
Not abnormal:	54 (12%)		
IBS-SSS, mean (SD)	267.0 (97.7)		
IBS-QoL, mean (SD)	31.9 (17.0)		
IBS-SSS severity grading, n (%)			
Mild:	82 (18%)		
Moderate:	208 (46%)		
Severe:	163 (36%)		
IBS Rome IV positive	321 (71%)		
Anxiety levels, mean (SD)	6.0 (3.6)		
Depression levels, mean (SD)	6.9 (5.0)		
Somatization levels, mean (SD)	9.9 (4.0)		
Per study arm	Diet (n=227)	Medication (n=232)	P-value
Average age (SD)	40.6 (14.5)	41.2 (14.9)	0.61

Gender (Female)	168 (75.7%)	175 (75.8%)	0.98
Weight	69.7 (13.8)	71.1 (14.3)	0.30
Average BMI (kg/m ²) (SD)	24.3 (4.4)	24.9 (4.6)	0.16
Stool type IBS, n (%)			
IBS-D:	28 (62%)	27 (63%)	0.60
IBS-C:	20 (44%)	21 (48%)	
IBS-M:	38 (85%)	42 (97%)	
Not abnormal:	14 (31%)	10 (23%)	
IBS-SSS severity grading, n (%)			
Mild:	44 (20%)	38 (16%)	0.5
Moderate:	97 (44%)	111 (48%)	
Severe:	81 (36%)	82 (36%)	
IBS-SSS mean (SD)	267.1 (95.9)	266.9 (99.5)	0.87
IBS-QoL	31.6 (16.3)	32.1 (17.7)	0.99
IBS Rome IV Positive	155 (69.8%)	166 (71.9%)	0.5
Anxiety levels, mean (SD)	6.1 (3.6)	5.9 (3.7)	0.47
Depression levels, mean (SD)	7.0 (5.0)	6.8 (4.9)	0.62
Somatization levels, mean (SD)	9.8 (4.1)	10.0 (3.9)	0.47
IBS-QoL mean (SD)	31.6 (16.3)	32.1 (17.7)	0.99

Primary endpoint outcome: Treatment response in IBS symptom severity score

In the diet group 71% (95% CI: 65-77) of patients were responders at 8 weeks, which was significantly higher than the 61% (95% CI: 54-68) responder rate in the medication arm ($p=0.03$, Figure 3.a). A significant responder rate was already present after 4 weeks of treatment (diet 62% (95%CI: 55-68) vs. OB 51% (95%CI: 44-57), $p=0.02$).

In a completers analysis, IBS-SSS improved significantly after 4 and 8 weeks compared to baseline in the diet group (respectively change of -88 ± 7.3 ($p<0.001$) and -97 ± 7.4 ($p<0.001$)) and medication group (respectively a change of -60 ± 7.5 ($p<0.001$) and -77 ± 17.4 ($p<0.001$)) (Figure 3.b, Table 4).

In a mixed model analysis, the difference between treatment groups in change from baseline was statistically significant after 4 weeks ($p=0.007$) and after 8 weeks ($p=0.049$).

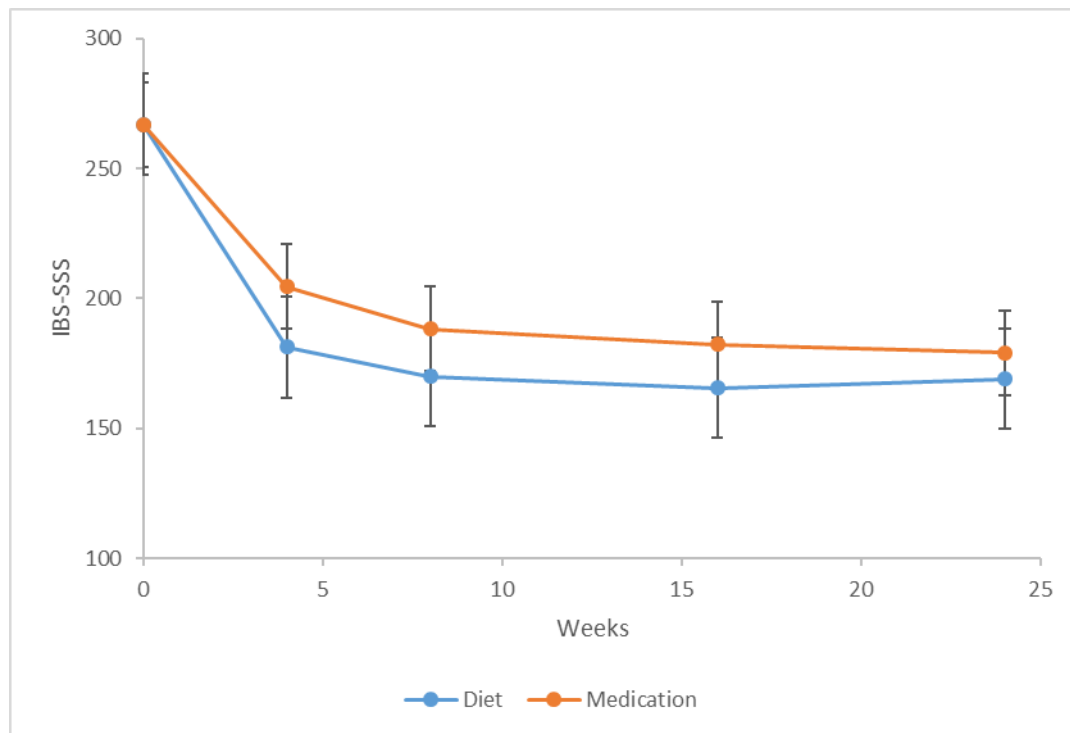


Figure 3: Change in IBS-SSS from baseline for the diet and medication arm.

Table 4. Primary endpoint: number of patients who responded to treatment after 8 weeks of intervention (who had a change of at least 50 points in the IBS-SS scale) (ITT population)

	Diet (n=218)	Medication (n=217)	^A p-value	^B p-value	^d Estimation of treatment effect
Change in IBS-SSS ^c at 4 weeks (SE)	-88.2 (7.3)	-60.6 (7.5)	<0.001	0.007	27.6 (7.4, 47.7) ^d
Change in IBS-SSS at 8 weeks (SE)	-97.4 (7.4)	-76.9 (7.4)	<0.001	0.049	20.5 (0.1, 40.9) ^d
Responder rate at 8 weeks (SE)	155 (71%)	133 (61%)		0.03	1.55 (1.04, 2.32) ^e

^ACompared to baseline

^BBased on all available data and mixed models

^CA change of -50 points or higher is considered clinically significant

^dDifference between medication and diet arms with respect to change from baseline in IBS-SSS, comparing diet and medication arms.

^eOdds ratio comparing diet and medication arms with respect to odds of being a responderodds ratio with responder as outcome, comparing diet and medication arms.

Secondary endpoint outcome

Impact of treatment to quality of life and psychologic distress after 8 weeks of treatment

Both treatments showed a significant improvement in quality of life, anxiety, depression and somatization. However, no significant differences between treatments were observed (Table 5).

Table 5. Quality of life and psychologic distress compared between treatments after 8 weeks of treatment

	Diet (n=218)	Medication (n=217)	^A P-value	^B P-value
IBS-QoL (SE)	-8.1 (0.8)	-7.4 (0.9)	<0.001	0.45
Anxiety (SE)	-1.2 (0.2)	-0.96 (0.2)	<0.001	0.32
Depression (SE)	-1.4 (0.3)	-1.1 (0.3)	<0.001	0.39
Somatization (SE)	-1.8 (0.2)	-1.3 (0.2)	<0.001	0.09

^Acompared to baseline

^Bbased on all available data and mixed models

Rome IV Subgroup analysis

Seventy percent (n=321) of all patients fulfilled the Rome IV criteria (Rome+) of which 155 were randomized to diet and 166 to medication, with similar IBS symptom severity (p=0.7). In this subgroup, after 8 weeks of treatment, the responder rate diet was 77% (n=118) for diet and 62% (n=98) for medication. The responder rate for diet was significantly higher than for medication (OR (95% CI): 2.06 (1.26, 3.39); p= 0.004) (Figure 3). The change in IBS-SSS from baseline to week 4 and week 8 was statistically significantly higher in the diet group than the medication group (week 4: -107.1±8.3 vs. -71.4±8.5, p=0.002; week 8: -116±8.6 vs. -82±8.1, p=0.003).

Overall, both treatments improved quality of life and psychologic distress, yet, only somatization showed a difference between treatment arms (Table 6).

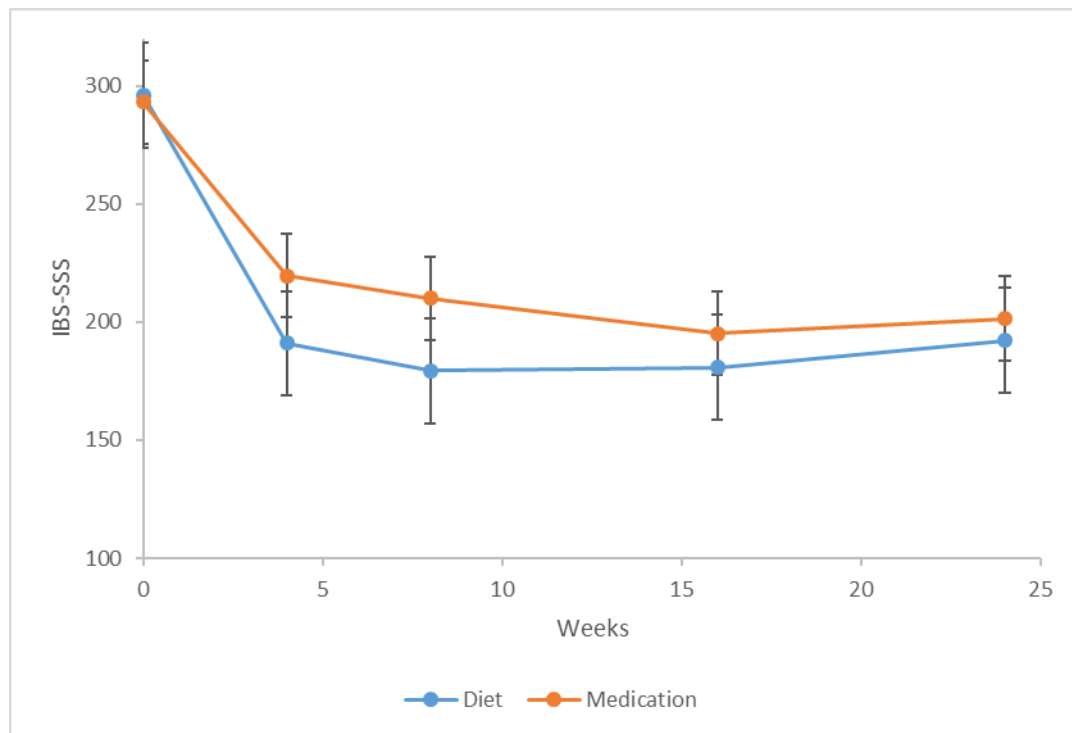


Figure 4. Change in IBS-SSS from baseline for the diet and medication arm for Rome IV positive patients.

Table 6. Overview quality of life and psychologic distress in Rome IV positive IBS patients at week 8.

	Medication (n=166)	Diet (n=155)	^A P-value	^B P-value
IBS-QoL (SE)	-8.3 (1.3)	-9.0 (1.2)	<0.001	0.57
Anxiety (SE)	-1.1 (0.2)	-1.2 (0.2)	<0.001	0.62
Depression (SE)	-1.1 (0.3)	-1.3 (0.3)	<0.001	0.69
Somatization (SE)	-1.4 (0.3)	-2.3 (0.3)	<0.001	0.03

^Acompared to baseline

^Bbased on all available data and mixed models

Table 7. Demographics IBS Rome IV positive patients

Rome IV	Baseline (n=321)		
Average age, years (SD)	38.4 (13.8)		
Gender (Female)	257 (80.06%)		
Weight, Kg (SD)	69.31 (13.94)		
BMI, m/kg ² (SD)	24.38 (4.46)		
Stool type IBS, n (%)			
IBS-D:	96 (29.91%)		
IBS-C:	63 (19.63%)		
IBS-M:	142 (44.24%)		
Not abnormal:	20 (6.23%)		
IBS-SSS, mean (SD)	294.55 (82.25)		
IBS-SSS severity grading, n (%)			
Mild:	29 (9.03%)		
Moderate:	148 (46.11%)		
Severe:	144 (44.86%)		
IBS-QoL, mean (SD)	35.3 (16.8)		
Anxiety levels, mean (SD)	6.5 (3.6)		
Depression levels, mean (SD)	7.4 (5.1)		
Somatization levels, mean (SD)	10.8 (3.9)		
Per study arm	Diet (n=155)	Medication (n=166)	P-value
Average age (SD)	37.79 (13.10)	38.96 (14.50)	0.45
Gender (Females, %)	122 (78.7%)	135 (81.3%)	0.5
Weight (kg) (SD)	68.93 (13.96)	69.66 (13.96)	0.64
Average BMI (SD)	24.15 (4.38)	24.60 (4.54)	0.37
Stool type IBS, n (%)			
IBS-D:	47 (30.32%)	49 (29.52%)	0.49
IBS-C:	33 (21.29%)	30 (18.07%)	
IBS-M:	63 (40.65%)	79 (47.59%)	
Not abnormal:	12 (7.74%)	8 (4.82%)	
IBS-SSS mean (SD)	296.13 (82.67)	293.07 (82.08)	0.74
IBS-SSS severity grading, n (%)			
Mild:	15 (9.68%)	14 (8.43%)	0.73
Moderate:	68 (43.87%)	80 (48.19%)	
Severe:	72 (46.45%)	72 (43.37%)	
IBS-QoL	34.2 (15.9)	36.4 (17.5)	0.26
Anxiety levels, mean (SD)	6.3 (3.6)	6.6 (3.7)	0.51
Depression levels, mean (SD)	7.2 (5.1)	7.6 (5.0)	0.43
Somatization levels, mean (SD)	10.7 (4.0)	10.9 (3.8)	0.69

Predictors of treatment response

Prediction analysis showed gender to be a potential predictor of treatment outcome in the diet arm (Table 8.A). The table shows that 59.6% of males and 74.7% of the females responded to the trial (χ^2 , $p=0.036$) and this was 62.3% of males and 61.0% of females in the medication arm (χ^2 , $p=0.86$). In the medication arm, the level of somatization seemed to be a good predictor of treatment outcome ($p=0.02$) (Table 8. B).

Table 8. Predictors of response at Week 8 in the diet and medication arm.

A. Diet arm	Non-responder (n=63)	Responder (n=155)	p-value
Age (years), mean (SD)	43.8 (16.6)	39.4 (13.5)	0.10
Gender - Male, n (%)	21 (33.3%)	31 (20.0%)	0.036
- Female, n (%)	42 (66.7%)	124 (80.0%)	
BMI (m/kg ²), mean (SD)	24.7 (4.4)	24.1 (4.4)	0.22
Primary stool type n (%)			0.49
- Constipation	9 (14.3%)	34 (21.9%)	
- Diarrhoea	18 (28.6%)	43 (27.7%)	
- Mixed	28 (44.4%)	55 (35.48%)	
- Normal	8 (12.7%)	23 (14.84%)	
Anxiety, mean (SD)	6.0 (3.8)	6.1 (3.5)	0.59
Depression, mean (SD)	7.0 (5.3)	7.0 (4.9)	0.92
Somatization, mean (SD)	9.4 (4.5)	9.9 (3.9)	0.29
Quality of life, mean (SD)	31.7 (16.8)	31.7 (16.0)	0.86
B. Medication arm	Non-responder (n=84)	Responder (n=133)	p-value
Age (years), mean (SD)	42.8 (15.7)	40.7 (14.3)	0.10
Gender - Male, n (%)	20 (37.7%)	33 (62.3%)	0.87
- Female, n (%)	64 (39%)	100 (60.9%)	
BMI (m/kg ²), mean (SD)	24.26 (3.4)	25.22 (5.1)	0.40
Primary stool type n (%)			0.57
- Constipation	21 (25.0%)	23 (17.3%)	
- Diarrhoea	22 (26.2%)	40 (30.1%)	
- Mixed	33 (39.3%)	58 (43.6%)	
- Normal	8 (9.5%)	12 (9.0%)	
Anxiety, mean (SD)	5.8 (3.7)	6.0 (3.6)	0.44
Depression, mean (SD)	6.6 (5.1)	6.7 (4.7)	0.58
Somatization, mean (SD)	9.2 (3.8)	10.5 (3.8)	0.02
Quality of life, mean (SD)	31.5 (17.5)	32.6 (17.2)	0.70

Treatment response during the follow up period

Treatment responses at the end of the follow-up period showed persisting benefit for both treatment groups for the IBS symptom severity score at visit 3 (week 16; diet: -104.9(7.6), $p<0.001$; medication - 78.5(8.04), $p<0.001$; $p=0.017$) and visit 4 (week 24; diet: -97.1(8.1), $p<0.001$; medication:-86.6(7.8), $p<0.001$; $p=0.4$) and the percentage of responders at visit 3 (diet: 74% (n=149) vs. medication: 57% (n=118), OR (95% CI): 2.10 (1.38, 3.18), $p=0.001$) remained significantly higher in the diet arm compared to medication ($p<0.001$). At visit 4, a good treatment response was still observed in both study arms, but this was not significantly different between treatments (diet: 69% (n=134) vs. medication: 70% (134), OR (95% CI): 0.95 (0.62, 1.46), $p=0.8$). At the end of the follow up period, IBS-QoL and psychologic distress continue to be improved compared to baseline, but without significant difference between treatment arms (Table 8). Similar results were observed for Rome IV positive patients.

Table 9. Follow up IBS-SSS, IBS-QoL, anxiety, depression and somatization in the entire cohort.

Changes after 16 weeks of treatment				
	Medication (n=206)	Diet (n=203)	^A P-value	^B P-value
Responder rate	57%	74%		0.001
IBS-SSS (SE)	-78.5 (8.0)	-104.9 (7.7)	<0.001	0.017
IBS-QoL (SE)	-8.7 (0.9)	-9.2 (0.8)	<0.001	0.5
Anxiety (SE)	-1.0 (0.2)	-1.3 (0.2)	<0.001	0.3
Depression (SD)	-1.2 (0.3)	-1.6 (0.3)	<0.001	0.2
Somatization (SE)	-1.9 (0.2)	-1.9 (0.3)	<0.001	0.3
Changes after 24 weeks of treatment				
	Medication (n=196)	Diet (n=192)	^A P-value	^B P-value
Responder rate	70%	69%		0.8
IBS-SSS (SE)	-86.6 (7.8)	-97.1 (8.2)	<0.001	0.4
IBS-QoL (SE)	-9.6 (0.9)	-10.0 (0.9)	<0.001	0.6
Anxiety (SE)	-1.2 (0.2)	-1.3 (0.2)	<0.001	0.5
Depression (SE)	-1.1 (0.3)	-1.5 (0.3)	<0.001	0.4
Somatization (SE)	-1.9 (0.2)	-1.8 (0.3)	<0.001	0.9

^A compared to baseline

^B based on all available data and mixed models

Table 10. Follow up IBS-SSS, IBS-QoL, anxiety, depression and somatization in Rome IV positive IBS patients.

Rome IV patients: Changes after 16 weeks of treatment				
	Medication (n=137)	Diet (n=133)	^AP-value	^BP-value
Responder rate	63%	79%		0.003
IBS-SSS(SE)	-90.4 (9.2)	-119.2 (9.1)	<0.001	0.02
IBS-QoL (SE)	-9.8 (1.2)	-9.9 (1.1)	<0.001	0.9
Anxiety (SE)	-1.2 (0.3)	-1.3 (0.2)	<0.001	0.9
Depression (SE)	-1.4 (0.4)	-1.5 (0.3)	<0.001	0.8
Somatization (SE)	-1.7 (0.3)	-2.2 (0.3)	<0.001	0.2
Rome IV patients: Changes after 24 weeks of treatment				
	Medication (n=115)	Diet (n=118)	^AP-value	^BP-value
Responder ate	74%	72%		0.8
IBS-SSS (SE)	-95.9 (9.1)	-112. 9 (9.3)	<0.001	0.2
IBS-QoL (SE)	-10.8 (1.2)	-10.2 (1.1)	<0.001	0.8
Anxiety (SE)	-1.4 (0.3)	-1.2 (0.3)	<0.001	0.7
Depression (SE)	-1.3 (0.4)	-1.4 (0.3)	<0.001	0.8
Somatization (SE)	-2.2 (0.3)	-2.1 (0.3)	<0.001	0.9

^Acompared to baseline

^Bbased on all available data and mixed models

Exploratory endpoint outcome

Patient treatment satisfaction

During the study, before every study visit, subjects were asked to rate their overall treatment response with the current treatment over the previous week. After 8 weeks of treatment, more than 50% of the subjects in both study arms reported symptom improvement, without significant difference between groups (Table 11). This decreased to 42% in the diet arm and 32% in the medication, yet, without reaching significance. Compared to the period before starting the study treatment, 69% of the patients in the diet arm reported to feel slightly better, compared to 58% of the patients in the medication arm ($p=0.2$) (Table 12). At the end of the study, 67% of the patients in the diet arm reported to feel slightly better, compared to 51% of the medication arm ($p=0.02$).

Table 11. Reported treatment satisfaction in the last week before the scheduled visit

Improvement in IBS symptoms in the last week?		Diet (n=218)	Medication (n=217)	P-value
Week 4	No	67 (35%)	87 (45%)	0.05
	Yes	125 (65%)	108 (55%)	
Week 8	No	91 (43%)	97 (48%)	0.30
	Yes	123 (58%)	107 (53%)	
Week 16	No	85 (48%)	104 (58%)	0.06
	Yes	94 (52%)	77 (43%)	
Week 24	No	92 (58%)	100 (68%)	0.08
	Yes	67 (42%)	48 (32%)	

Table 12. Reported treatment satisfaction compared to the period before the study treatment

Improvement in IBS symptoms compared to the period before the study treatment		Diet (n=218)	Medication (n=217)	P-value
Week 8	Extremely better	4 (2%)	2 (1%)	0.2
	A lot better	44 (21%)	28 (14%)	
	Moderately better	44 (21%)	42 (21%)	
	Slightly better	54 (25%)	45 (22%)	
	Quite the same	49 (23%)	53 (26%)	
	Slightly worse	9 (4%)	15 (7%)	
	Moderately worse	8 (4%)	17 (8%)	
	A lot worse	2 (1%)	2 (1%)	
Week 16	Extremely better	4(2%)	6 (3%)	0.08

	A lot better	40 (22%)	28 (19%)	
	Moderately better	48 (27%)	35 (19%)	
	Slightly better	33 (18%)	27 (15%)	
	Quite the same	39 (22%)	65 (36%)	
	Slightly worse	6 (3%)	7 (4%)	
	Moderately worse	7 (4%)	11 (6%)	
	A lot worse	2 (1%)	2 (1%)	
Week 24	Extremely better	5 (3%)	6 (4%)	0.02
	A lot better	34 (21%)	28 (19%)	
	Moderately better	36 (23%)	24 (16%)	
	Slightly better	32 (20%)	18 (12%)	
	Quite the same	31 (20%)	58 (39%)	
	Slightly worse	4 (3%)	1 (1%)	
	Moderately worse	15 (9%)	11 (7%)	
	A lot worse	2 (1%)	2 (1%)	

Treatment adherence

Treatment was followed up for a total of an additional 16 weeks after the end of the initial randomized treatment period. Subjects were allowed to change treatment, guided by the opinion of the general practitioner. After each visit, the subject was asked if he/she has followed the allocated treatment up to the visit and if he/she would like to change the treatment (Table 13). Additionally, subjects were asked prior each study visit, how often they forgot to follow the allocated treatment (Table 14). Overall, 24 subjects (5.3%) changed treatment at some point during the follow up period. Subjects in the diet treatment showed a significantly higher adhesion their allocated treatment arm compared to the medication arm. Furthermore, subjects in the diet arm tended to adhere more consistently to the diet compared to patients allocated to the medication arm. At week 8, 52% of the patients in the medication arm forgot to follow the study treatment more times per week compared to 34% in the diet arm ($p < 0.001$). At week 24, this was 48% for the medication arm and 37% for the diet arm ($p = 0.2$).

Table 13. Intention to remain in the allocated treatment per study visit

		Diet n (%)	Medication n (%)	P-value
Week 8	Has stayed in the same allocated treatment?	207 (98.10%)	192 (90.57%)	<0.001
	Will stay in the same?	179 (84.83%)	121 (57.08%)	<0.001
Week 16	Has stayed in the same allocated treatment?	199 (98.51%)	187 (91.67%)	0.001
	Will stay in the same?	174 (86.14%)	118 (57.84%)	<0.001
Week 24	Has stayed in the same allocated treatment?	192 (98.46%)	175 (92.11%)	0.003

Table 14. Average treatment adherence reported by the patients

Week 8 How often have you forgot to follow the treatment?	Diet (n=212)	Medication (n=202)
Never	19 (9%)	27 (13%)
<3 times /months	62 (29%)	43 (21%)
1 time /week	58 (27%)	26 (13%)
2-3 times /week	60 (28%)	52 (26%)
4-7 times /week	9 (4%)	30 (15%)
>7 times /week	3 (1%)	11 (6%)
Mostly	1 (0.5%)	13 (6%)

Week 16 How often have you forgot to follow the treatment?	Diet (n=139)	Medication (n=82)
Never	8 (6%)	12 (15%)
<3 times /months	34 (25%)	19 (23%)
1 time /week	39 (28%)	9 (11%)
2-3 times /week	48 (35%)	22 (27%)
4-7 times /week	7 (5%)	10 (12%)
>7 times /week	2 (1%)	4 (5%)
Mostly	1 (1%)	6 (7%)

Week 24 How often have you forgot to follow the treatment?	Diet (n=120)	Medication (n=52)
Never	6 (5%)	9 (17%)
<3 times /months	28 (23%)	11 (21%)
1 time /week	42 (35%)	7 (14%)
2-3 times /week	34 (28%)	13 (25%)
4-7 times /week	8 (7%)	6 (12%)
>7 times /week	2 (2%)	4 (8%)
Mostly	0 (0%)	2 (4%)

Monitoring and quality assessment

Overview of on-site monitoring visits

Throughout the study, 75 monitoring visits at GP sites took place. At the end of the study, 103 close-out visits were organized. All included subjects were closed by the monitor on the eCRF and 468 subjects were electronically signed by the participating GPs. Close-out visits and end of trial signatures (4 patients) are missing from 2 GPs. The reason for this was illness of a GP and inaccessibility of a GP.

Queries and main protocol deviations

During the study, the eCRF produced queries: 492 of which only were two not solved. These were related to the two missing GPs referred here above. Additionally, 517 protocol deviations were reported. None of these deviations were considered high risk and could not affect the integrity of the collected study data and the safety of the patients. An overview report of all queries and protocol deviations was annually provided to the ethical commission of UZLeuven.

Study safety

As per protocol, in this study the GP was only asked to report SAR in the eCRF. SAE were recorded in the source documents of the GP (patients' file). During this study, no serious adverse reactions were reported during the study. Two SAE were reported, (1) Short hospitalization due to fracture (fall), (2) Pregnancy whereas the patient was included in the trial, but excluded before starting the study therapy. Both SAE were not related to the therapy and have been reported to the EC.

Weight change during the study

Weight was not affected by the diet compared to the medication treatment during the trial (Table 15)

Table 15. Weight of subjects at each study visit for the diet arm, the medication arm and the entire cohort.

	Diet (SD)	Medication (SD)	Total (SD)	p-value
Baseline	69.7 (13.8) (n=222)	71.1 (14.3) (n=231)	70.4 (14.0) (n=453)	
4 weeks	69.7 (13.9) (n=213)	70.7 (14.0) (n=215)	70.2 (13.9) (n=428)	0.22
8 weeks	69.6 (13.9) (n=218)	71.1 (14.1) (n=217)	70.4 (14.0) (n=435)	0.81
16 weeks	69.7 (14.1) (n=203)	70.9 (14.4) (n=206)	70.3 (14.2) (n=409)	0.63
24 weeks	70.0 (14.3) (n=196)	70.6 (14.2) (n=192)	70.3 (14.2) (n=388)	0.12

End of trial notification report to regulatory authorities

After database lock, an end of study rapport that included all final overview of queries and protocol deviations and study safety was provided to the ethical commission of UZLeuven. Additionally, the end of study notification rapport and a safety rapport was provided to the FAMHP. A copy of the present study report will also be provided to the EC and FAMHP.

Discussion and future perspectives

This was a pragmatic multicentre parallel study in 472 primary care IBS patients. The study was designed with the aim to mirror primary care approaches to IBS diagnosis and management. Even though some aspects required for traditional clinical trials were present and these might not reflect the usual clinical routine (e.g. treatment randomization, strict monitoring of GPs, ePROs), we believe this project succeeded in approaching the nearest possible settings to standard clinical care and that therefore, the reported results can be applicable to routine clinical practice.

Subjects were randomly allocated to a medication arm, classical therapeutic approach, where they received a prescription for a spasmolytic agent, otilonium bromide (OB), to buy in their local pharmacy or, they were indicated to a simple FODMAP lowering diet, new treatment approach, that was implemented in a mobile app intended for patients to follow independently.

The primary objective of this study was to evaluate efficacy of the new FODMAP lowering diet provided as a mobile app compared to the classical clinical approach with OB. This objective was met and results show that both treatments can be considered efficacious and, moreover, that the proposed diet approach is significantly more effective at week 8 (71% response rate) than OB (61% response rate). Follow up treatment assessment of 16 weeks, showed a long-term beneficial effect of both treatment arm, but then again this was larger in the diet arm (74% vs. 57%, change in IBS SSS -104.9 vs. -78.5). The beneficial effect of the treatments was still present after 24 weeks of treatment (69% vs. 70%, change in IBS-SSS -97.1 vs. -83.6), but no significant difference was observed between treatment. In the absence of a treatment stop or a placebo arm, it is unclear to which extent the symptomatic benefit at 16 and 24 weeks reflects ongoing therapeutic effects or spontaneous evolution. They do confirm the acceptability of both treatment arms for longer term use, both with patients and physicians (who had the option to change therapy at every visit from week 8 onwards).

In the present study, subjects were selected by their own GPs and inclusion in the trial was mainly based on the GPs' expert opinion. Nevertheless, 70% of the subjects fulfilled the Rome IV strict IBS criteria suggesting a good agreement with IBS definition used in secondary and tertiary care centres as well as in traditional clinical trials. In addition, results in this subset of patients showed an even higher benefit for the FODMAP lowering diet compared to OB (77% vs. 62%).

IBS has shown to have an important impact in patients' quality of life and to lead to a number of co-morbidities such as depression, anxiety and somatization. Secondary analyses showed a clear improvement of quality of life and psychologic distress for both treatment arms. However, even

though a trend was observed for somatization, no significant differences were observed between treatments. Furthermore, prediction of response analysis showed female gender to be a predictor of treatment outcome in the diet arm and a higher baseline level of somatization to be a predictor of treatment response in the medication arm. The predictive value of somatization for response to a spasmolytic agent has not been reported before, but industry-sponsored studies have not taken this variable in consideration.

Overall, patients showed a good adherence to the allocated treatments. At visit 2, twenty subjects dropped out of the study and 47 dropped out during the follow up period. The main reasons for dropout were lack of efficacy and experiencing the study as unpractical or difficult to follow. During follow-up, patients could opt, based on the GPs' recommendations, to change their IBS treatment. Results show that more subjects (> 85%) in the diet arm continued with their initial allocated treatment compared to the medication arm. Additionally, although not significant, patients following the study diet reported a trend to be more satisfied about their treatment compared to subjects in the medication arm.

The low FODMAP diet as initiated in tertiary care is very complex, demanding and it needs close follow up with a specialized dietitian. Consequently, many patients tend to drop out, especially during the reintroduction period of the traditional low FODMAP diet (22). The results in the present study show that the proposed diet in the form of a mobile application is a good and simple alternative for patients that can be followed for a long time in a personalized and independent manner, leading to a higher adherence to the diet and treatment satisfaction. Furthermore, the diet does not exclude the patients from all FODMAPs strictly, but it meets a level of flexibility and shares alternatives foods for subjects to keep variation in their day-to-day nutritional intake. Therefore, there is no need for an extensive and complex reintroduction phase. GPs feedback to the study team during the study showed that, after a period of time, the patients recognize which foods are more likely to lead to symptoms and adapt their diet to them.

The spasmolytic agent OB showed also to be efficacious in a large proportion of patients. It has been understood, based on feasibility interviews to GPs made during the preparation of this trial, that in primary care, OB is generally prescribed for a maximum of 3 weeks. Clinical studies, however, demonstrated that significant symptomatic benefit over placebo is observed after 5-8 weeks of treatment. This approach was considered for the present study and it shows that the indicated treatment term is relevant for a good result. In the future, increased awareness regarding the treatment duration with OB may be needed in general practice.

Another aspect that has to be taken into account when interpreting the results of the study, is the number of study visits planned at the GPs' site compared to standard clinical practice. For this study, subjects were requested to attend four visits with their GP in a period of 6 months, whereas, in common practice, IBS patients are less frequently followed up. This does not imply that IBS patients should be reviewed every 3 months, but it does suggest that predefining a number of follow-up consultations might help to guarantee the longer-term treatment adherence and efficacy.

During the study, there were no notable safety concerns and overall data collection was properly done and well monitored. If not followed correctly, the strict low FODMAP diet may limit the amount of ingested calories and it may lead to important weight lost. Therefore, the patients' weight was closely monitored at every study visit. Results show, however, no significant change in the patients' body weight. This suggest that the simplified FODMAP lowering diet is safe and well tolerated to use in standard clinical practice.

Strengths of this study are the large number of patients recruited from primary care, the follow-up over 24 weeks, and the use of a novel simple standardized dietary intervention tool. This pragmatic study closely followed usual clinical approaches in primary care IBS. The study has a number of limitations, in part due to its pragmatic nature. This includes the absence of daily symptom diaries, of food or diet intake tracking, and the use of open-label treatment without placebo or sham intervention. Not all patients enrolled in this study fulfilled the Rome IV criteria, but this is in line with clinical reality and should not necessarily be considered a major limitation. While the 24-week follow-up is longer than standard IBS efficacy trials of 12 weeks, the effects of this FODMAP lowering diet beyond 6 months would require additional long-term follow-up studies. In tertiary care, with follow-up of close to 2 years, practical issues and social factors lead to a decrease in treatment adherence to the standard low FODMAP diet, which is more complex and more demanding (23).

As a conclusion, the FODMAP lowering diet mobile application is a new and efficacious treatment alternative for IBS that can be used in the usual care setting of primary care. OB has also shown a positive symptomatic outcome if prescribed for at least 8 weeks, but the diet has shown to be more effective with a long-term beneficial impact.

Next steps include the applicability to the FODMAP lowering diet mobile app in a larger setting for standard clinical use in primary care. The app, aimed to be available at a minimal cost, will be updated to include the present study in layman's terms. Additionally, public awareness and instructions for the use of this app will be make. The DOMINO app is available for public use under the name "DOMINO trial" in the app store for Android and iOS. Additionally, the link to the app is available in the website

of DOMUS MEDICA. It is stated in the disclaimer of the app that its use is preferably allocated to patients clearly diagnosed with IBS by a certified physician. It is the physician responsibility to follow up the patient during treatment and re-evaluate the IBS symptoms after a period of at least 4 weeks to assess treatment response.

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Annex A: End of trial notification report

Includes SAEs and list of protocol deviations



END OF TRIAL NOTIFICATION REPORT

S-nummer: S59482

Titel protocol: DOMINO: A randomized controlled trial to evaluate the short-term efficacy and long-term health economic impact of a dietary intervention compared to pharmacotherapy with a musculetropic spasmolytic agent for newly diagnosed or newly treated irritable bowel syndrome in primary care

Hoofdonderzoeker: Prof. dr. Jan Tack

Datum rapport: 27-11-2020

Periode van gegevens in rapport:

- Datum eerste patiënt geïncludeerd: 26-7-2018
- Datum "last visit last patient": 3-7-2020
- Datum laatste close-out visite: 7-10-2020

Gegevens van:

- ☐ UZ Leuven
- ☐ Belgische studiecentra
- ☒ alle deelnemende studiecentra

1. Huidige status:

Datum database lock: 20/10/2020

2. Ontwikkeling van de studie sinds start

	Aantal patiënten in alle studiecentra
voorzien:	470
gescreend (= getekend ICF):	483
	(incl. 13 screening failures)
geïncludeerd:	472
drop outs:	56
overleden:	0

Gelieve duiding te geven indien er grote verschillen zijn tussen het aantal voorziene en geïncludeerde patiënten: Zoals per protocol, werd na inclusie van de 470ste patiënt het einde van de rekruteringsperiode ingeroepen en werd aan de eCRF provider gevraagd om de vergrondeling voor nieuwe inclusies in het eCRF toe te passen. Echter, vóór deze aanvraag toegepast werd werden er nog 2 extra patiënten geïncludeerd in de studie door twee deelnemende artsen. Er werd door de Principal Investigator (prof. dr. Tack) beslist om deze patiënten niet uit de studie te excluseren om de pragmatische opzet van de studie te kunnen behouden.

- De studie werd tijdelijk onderbroken:
 - ☒ Neen
 - ☐ Ja, omwille van: