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To evaluate the efficacy, safety and tolerability of oral treatment with non-pathogenic bacterial lysate of E. coli and E. faecalis cells (Pro-Symbioflor®) in patients with irritable bowel syndrome

Submission date	**Recruitment status**	[X] Prospectively registered
05/03/2014	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
25/03/2014	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
15/12/2016	Digestive System	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Irritable bowel syndrome (IBS) is characterized by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits. The exact cause of IBS is unknown. Although there is no cure for IBS, there are treatments that attempt to relieve symptoms, including dietary adjustments, medication and psychological interventions. Probiotic therapy has become the first treatment in recent years. Pro-Symbioflor® (made of natural, physiological, non-pathogenic intestinal bacteria) is a type of drug that claims to be effective in the treatment of IBS according to a previous study. IBS was first defined in 1989 but the diagnostic criteria have changed and a new study is needed. The aim of this study is to assess whether Pro-Symbioflor® will reduce the frequency and the severity of IBS symptoms better than taking a dummy treatment (placebo) for people diagnosed with IBS according to the most recent criteria.

Who can participate?
The aim is to recruit about 380 people diagnosed with IBS, male or female, aged ≥ 18 years, in Germany.

What does the study involve?
Participants will be randomly allocated to a treatment group (Pro-Symbioflor®) or a control group (placebo). Participants will be asked to fill in a patient diary daily during the treatment period (26 weeks). There will be a follow-up visit 4 weeks after the end of treatment. Each participant will receive 10 drops (0.71ml) three time a day during the first week, 20 drops (1.42 ml) three time a day in week 2 and 30 drops (2.14 ml) three time a day from week 3 to week 26 (the drug or the placebo depending on the group they belong to).
If participants take selective serotonin reuptake inhibitor (SSRI) drugs, the medication should be constant from 30 days prior to enrolment in the study and throughout the study. If they have to take emergency medications (such as laxatives, anti-spasmodics, anti-diarrhea), the frequency

cannot exceed twice a week and this must be recorded in the patient diary.
Participants will also have to fill in several questionnaires throughout the study. Some questionnaires are included in the patient diary.

What are the possible benefits and risks of participating?
Not provided at time of registration.

Where is the study run from?
The study has been set up by the pharmaceutical company SymbioPharm GmbH in Herborn, Germany in collaboration with the national regulatory authority for medicinal products, BfArM, in Germany. The study will be performed by doctors specialised in the treatment of gastrointestinal disorders. There will be about 25 to 30 recruitment sites. The lead centre is the Department of Internal Medicine Martin-Luther-Hospital, Berlin, Germany.

When is the study starting and how long is it expected to run for?
Recruitment is expected to start in April 2014. Participants will be enrolled in the study for a period of one year.

Who is funding the study?
SymbioPharm GmbH in Herborn, Germany.

Who is the main contact?
Prof. Dr. Hubert Mönnikes
h.moennikes@mlk-berlin.de

Contact information

Type(s)
Scientific

Contact name
Prof Hubert Mönnikes

Contact details
Internal Medicine Martin-Luther-Hospital
Caspar-Theyß-Str. 27-31
Berlin
Germany
14193
+49 (0)30 89 55 3100
h.moennikes@mlk-berlin.de

Additional identifiers

EudraCT/CTIS number
2012-002741-38

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
4039162 SM13031

Study information

Scientific Title
Randomized, double-blind, placebo-controlled, multi-centre study to evaluate the efficacy, safety and tolerability of oral treatment with non-pathogenic bacterial lysate of E. coli and E. faecalis cells (Pro-Symbioflor®) in patients with irritable bowel syndrome

Acronym
SymPro2012

Study objectives
Pro-Symbioflor® is an immunologically active bacterial lysate produced of 1.5-4.5 x 107 bacteria of Escherichia coli DSM 17252 and Enterococcus faecalis DSM 16440. Pro-Symbioflor® is claimed to be effective as an immunomodulatory acting drug in the therapy of irritable bowel syndrome. To prove this, a trial was arranged by the German authorisation authority and the pharmaceutical company to test for the Verum - Placebo superiority in the improvement of the frequency and severity of IBS symptoms in patients with irritable bowel syndrome. In addition the safety and tolerability were to be studied. Additionally, the human gastrointestinal microbiota in IBS patients is part to investigate and also genetic analysis to assess polymorphism of the serotonergic system. According to the current EMA guidance document on IBS, two primary endpoints should be used to assess efficacy. Statistically significant changes must be found in both parameters. An overall responder is defined as a patient, who is classified as responder for both, the IBS Global Assessment of Improvement and the improvement of Abdominal Pain Intensity.
The null hypothesis for the responder analysis is pX=pC, and the alternative is pX≠pC. Where pX and pC are the response rates in the experimental group (Pro-Symbioflor®) and the control group (Placebo), respectively.

Ethics approval required
Old ethics approval format

Ethics approval(s)
The Independent Ethics Committee (IEC) at Charité, Berlin, Germany, 13/12/2013

Study design
Randomized double-blind placebo-controlled multi-centre parallel group design

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)

Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Irritable bowel syndrome (IBS) with recurrent abdominal pain or discomfort according to S3 Guideline and Rome III criteria

Interventions
Patients are randomised to two groups:
1. Pro-Symbioflor®: 1 mL (14 drops orally) of a bacterial lysate containing 1.5-4.5 x 107 bacterial cells of Escherichia coli DSM 17252 and Enterococcus faecalis DSM 16440.
Dosage:
10 drops (0.71 mL) three times daily (TID) during week 1
20 drops (1.43 mL) TID in week 2
30 drops (2.14 mL) TID from week 3 to week 26
2. Placebo: Pro-Symbioflor® Placebo - Culture medium without bacteria cells or bacterial lysate given orally
Dosage:
10 drops (0.71 mL) three times daily (TID) during week 1
20 drops (1.43 mL) TID in week 2
30 drops (2.14 mL) TID from week 3 to week 24

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
1. Response rate measured by the IBS Global Assessment of Improvement Scale (IBS-GAI). IBS-GAI response is defined as at least 50% moderate or substantial improvement on the 7-point rating scale during the 24 weeks of treatment
2. Response rate measured by the 11-point numeric rating scale (NRS). Abdominal Pain Intensity response is defined as a decrease in the weekly average of worst abdominal pain of at least 30% compared to baseline for a minimum of 12 of the 24 measurements (i.e. at least 50% improvement of Abdominal Pain Intensity during the 24 weeks of treatment)

Secondary outcome measures
1. Response rate measured by the 7-point IBS Global Assessment of Improvement Scale (IBS-GAI) during the 24 weeks of treatment. Response is defined as at least 75% moderate or substantial improvement or 50% improvement and no worsening during the last 4 weeks of treatment
2. Response rate measured by the 11-point numeric rating scale during the 24 weeks of treatment. Response is defined as ≥30%improvement in Abdominal Pain Intensity weekly response compared to baseline for a minimum of 18 of the 24 measurements (i.e. 75% improvement of Abdominal Pain Intensity) or 50% improvement and no worsening during the last 4 weeks of treatment
3. Change from baseline of the IBS specific Quality of Life questionnaire (IBS-QOL)
4. Change from baseline of the EQ-5D questionnaire

5. Stool frequency / week
6. Number of days with straining during a bowel movement / week
7. Number of days with imperative urge to defecate / week
8. Number of pain-free days / week
9. Adverse events
10. Vital signs
11. Laboratory values (Biochemistry, Haematology)

Overall study start date
01/04/2014

Completion date
31/12/2018

Eligibility

Key inclusion criteria
1. Male and female outpatients aged ≥ 18 years
2. Diagnosis of irritable bowel syndrome according to Rome III and the current German S3 guideline on IBS 2011 issued by the relevant German medical associations:
2.1. Recurrent abdominal pain (e.g. discomfort, bloating) at least 3 days per month in the last 3 months associated with 2 or more of the following criteria
2.1.1. Improvement with defecation
2.1.2. Onset associated with a change in frequency of stool
2.1.3. Onset associated with a change in form (appearance) of stool
2.2. Significant reduction in the quality of life as per patients estimation
2.3. Symptom related exclusion of relevant differential diagnoses
2.4. Patient seeks medical help because of gastrointestinal symptoms
3. IBS symptom onset ≥ 6 months
4. Negative colonoscopy (≤ 3 years)
5. Female patients of childbearing potential must be either surgically sterilized or use highly effective contraception at least 3 months prior to enrolment with a negative pregnancy test at screening, baseline/day 0
6. No changes in the dose of selective serotonin reuptake inhibitors (SSRI), if applicable, 30 days prior to screening
7. Willingness to refrain from significant changes in diet, fibre intake, fluid intake, or physical activity during trial participation
8. Willingness to refrain from the use of other medications for IBS treatment, including probiotic medication
9. Ability to comply with treatment
10. Sufficient knowledge of German language to understand trial instructions and rating scales
11. Written informed consent prior to enrolment

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
380 (190 per treatment arm)

Key exclusion criteria
1. History of abdominal surgery within the 6 months prior to screening
2. Presence or suspected presence of unstable coronary artery disease, organic gastrointestinal disease, metabollic diseases, or collagen vascular disease within the 6 months prior to screening
3. Lactose intolerance (in doubtful cases, a diagnostic test has to be performed)
4. Abnormal endoscopy/ abdominal ultrasound requiring further investigation
5. Any alarm symptoms including uninvestigated anaemia, rectal bleeding, weight loss, or unresolved fever within the 6 months prior to screening
6. Participation in another clinical trial or use of any investigational drug within 30 days before dosing
7. Evidence of current or recent alcohol or drug abuse within 6 months prior to screening
8. History or evidence of current laxative abuse
9. Continuous abdominal pain for more than 4 hours before bowel movements
10. Pregnancy or breast feeding
11. Any illness or condition that might impact the safety of study drug administration or evaluability of drug effect based on Investigators discretion
12. No consent to recording and processing of pseudonymised data according to legal requirements

Date of first enrolment
01/04/2014

Date of final enrolment
31/12/2015

Locations

Countries of recruitment
Germany

Study participating centre
Internal Medicine Martin-Luther-Hospital
Berlin
Germany
14193

Sponsor information

Organisation

SymbioPharm GmbH (Germany)

Sponsor details
Auf den Lüppen 8
Herborn
Germany
35745
+49 2772 981 112
kurt.zimmerman@symbio.de

Sponsor type
Industry

ROR
https://ror.org/03d8m2k26

Funder(s)

Funder type
Industry

Funder Name
SymbioPharm GmbH (Germany)

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
31/12/2019

Individual participant data (IPD) sharing plan
The current data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date