

Efficacy and Safety of Chinese Medicine JCM-16021 for Diarrhea-predominant Irritable Bowel Syndrome: Study Protocol for a Multi-center, Randomized, Double-blind, Placebo Controlled Clinical Trial

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Research

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Abstract

Background: Irritable bowel syndrome (IBS) is a common gastrointestinal functional disease. Adults with IBS may experience abdominal pain, change of bowel habits, and abnormal stool form without organic disease. IBS can seriously affect their work productivity and quality of life, especially diarrhea-predominant Irritable bowel syndrome (IBS-D). Chinese Herbal Medicine JCM-16021 has been shown to be potentially effective in improving the symptoms of IBS-D based on a small scale clinical trial. Hence, a large scale clinical study is designed to further evaluate the efficacy and safety of JCM-16021 for IBS-D with traditional Chinese medicine (TCM) pattern of Liver Stagnation and Spleen Deficiency (LSSD).

Methods: This study is a multi-center, randomized, double-blind, placebo-controlled clinical trial. 392 eligible participants will be enrolled with two-week run-in, eight-week treatment and eight-week follow-up. After run-in period, participants will be randomized to receive either JCM-16021 or placebo for eight weeks, and will have post-treatment follow up for another 8 weeks. The primary outcome is the improvement rate on the Global Assessment of Improvement (GAI) at week 10. The secondary outcomes consist of changes of IBS-D symptoms, TCM pattern improvement, IBS-Quality of Life (IBS-QoL), IBS-Symptom Severity Score (IBS-SSS), safety, etc.

Results: A standard protocol has been developed for the study. The protocol will provide a detailed procedure to conduct a clinical trial and verify if the Chinese medicine JCM-16021 would significantly improve the overall symptoms of IBS-D with LSSD pattern of TCM by relieving abdominal pain, reducing stool frequency, improving the stool consistency and improving quality of life. The consolidated evidence from the study can shed light on the treatment of IBS-D with Chinese medicine.

Conclusion: The protocol will provide details for investigators about the study following SPIRIT Statement. High-quality evidence on the efficacy and safety of Chinese Medicine JCM-16021 for IBS-D will be provided through strict compliance with the protocol.

Trial registration: ClinicalTrials.gov identifier: NCT03457324. Registered 8 February 2018, <https://clinicaltrials.gov/ct2/show/NCT03457324?term=NCT03457324&draw=2&rank=1>

Background

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder, which is diagnosed on the basis of recurrent abdominal pain related to defecation or in association with a change in stool frequency and form¹. Furthermore, no anatomical causes have been found². According to a meta-analysis, the pooled estimate of international IBS prevalence is about 11.2%³. In Hong Kong, based on Rome II criteria, the prevalence was reported to be 6.6%, of which the proportion of IBS-D was 27%⁴.

The pathogenesis of IBS is currently unclear as none of its anatomical causes could be found. It is caused by multiple factors, which include psychological factors, changes in gastrointestinal motility, neural and endocrine factors, infection, diet, drugs etc^{5,6}. Under the influences of the above factors, the

intestinal function is disturbed and that causes abdominal pain, abdominal bloating, constipation or diarrhea. At present, the more accepted mechanisms of IBS include visceral hypersensitivity, abnormal gut motility, abnormal fecal transmission, and mental factors⁷. Recently, some studies show that IBS with diarrhea (IBS-D) is the most common subtype in IBS based on Rome IV⁸⁻¹⁰.

IBS-D greatly affects the quality of life of people. Individuals suffering from IBS-D always complain that they have to avoid travelling or going out because of concerns about toilet access¹¹. However, there is still no very satisfactory therapy or medicine for IBS-D yet. According to a survey in America, people's satisfaction with both over-the-counter (OTC) and prescription treatments for IBS-D are low, with about 20% or 25% of participants being very satisfied with OTC and prescription treatment, respectively¹². Another study of IBS-D also showed that the overall treatment satisfaction was only approximately 20%¹³. In recent years, more and more people have tried to treat their symptoms with traditional Chinese medicine (TCM), which has been evaluated in many clinical studies¹⁴. A meta-analysis indicated that Chinese Herbal Medicine was associated with the improvements of global symptom, IBS-SSS, and IBS-D symptoms¹⁵.

According to the TCM theory, the Liver Stagnation and Spleen Deficiency (LSSD) is believed to be the major mechanism of IBS-D. The Liver governs Qi movement, and the Spleen Qi can maintain the transportation of water and nutrient throughout the whole body. Liver Qi stagnation affects the proper operation of the Spleen. When the Spleen is offended by Liver Qi Stagnation, diarrhea will occur. Therefore, the treatment should base on soothing the Liver Qi and strengthening the Spleen Qi. The Chinese medicine JCM-16021 is a new Chinese Medicine formula designated to sooth the Liver Qi and strengthen the Spleen Qi and hence treat IBS-D with LSSD pattern.

Our previous small scale study indicated that JCM-16021 has a potential therapeutic effect on the relief of IBS-D symptoms compared to holopon and placebo¹⁶. Further, JCM-16021 can dose-dependently attenuate visceral hyperalgesia in neonatal maternal separation (NMS) rats by changing the synthesis and metabolism of 5-HT in the colons¹⁷. Another study also has indicated that JCM-16021 can reduce the EC cell hyperplasia and 5-HT availability and upregulate the decreased levels of certain mucosal cytokines, especially the Th1-related cytokines in post-inflammation-IBS rats¹⁸. Based on these studies, we hypothesize that Chinese medicine JCM-16021 will be an effective remedy for IBS-D. Therefore, a larger scale and rigid clinical trial is designed to further investigate the efficacy and safety of JCM-16021 for IBS-D with LSSD pattern of TCM. The protocol will provide details for investigators about the study following SPIRIT Statement and CONSORT Statement for Chinese Herbal Medicine Formulas¹⁹⁻²¹.

Objective

The major objectives of this study are as follows: 1) investigate the efficacy of JCM-16021 for IBS-D participants with LSSD pattern of TCM; 2) assess the safety of JCM-16021.

Methods/design

The study is a multi-center, randomized, double-blind, placebo controlled clinical trial. Totally, all participants will have 5 visits at week 0, 2, 6, 10, and week 18, respectively. At week 0, the first screening will be conducted to include potential participants. Week 0 to week 2 belongs to run-in period. At week 2, the second visit will be conducted to assess the baseline of participants. Then, those eligible participants will be randomized in 1:1 ratio to receive either JCM-16021 or placebo. At week 6, the third visit will be conducted to assess the situation after treatment of four weeks. At week 10, the fourth visit will be conducted to assess the situation after treatment of eight weeks. Then these participants will be followed up with another eight-week and the fifth visit will be conducted at week 18. In total, the whole study will last for 18 weeks, including two weeks of the run-in period, eight weeks of the treatment period, and eight weeks of the follow-up period. All visits will be conducted at the designated clinics face to face. The flowchart and schedule of the trial are shown in Figure 1 & Figure 2, including schedule of enrolment, interventions and assessments. The trial protocol is written in accordance with Standard Protocol Items for Clinical Trials with Traditional Chinese Medicine 2018: Recommendations, Explanation and Elaboration (SPIRIT-TCM Extension 2018) checklist¹⁴ (Supplementary 1). And the structured study summary is described in Table 1 according to the World Health Organization Trial Registration Data Set.

Setting of the study

The study will be conducted in three centers simultaneously as follows: 1) Hong Kong Baptist University Mr. & Mrs. Chan Hon Yin Chinese Medicine Specialty Clinic and Good Clinical Practice Centre, 2) Hong Kong Baptist University HK Island Wei Ke Qiang Chinese Medicine Specialty Clinic, 3) Center for Integrative Medicine, Hong Kong Institute of Integrative Medicine, The Chinese University of Hong Kong.

Randomization

The randomization sequence for the intervention of the 392 participants will be generated using block randomization with a fixed block size by our statistician with SPSS statistical analysis software. The sequence will be kept in opaque sealed envelopes with consecutive numbers. These envelopes will be prepared by pharmaceutical company. The envelopes numbered 001-100 and 201-392 will be kept at the site of Hong Kong Baptist University. The envelopes numbered 101-200 will be kept at the site of the Chinese University of Hong Kong. These envelopes will be blinded to Chinese Medicine Practitioners who will be responsible for the recruitment and evaluation. Each center will have a research assistant responsible for allocating drugs to participants. The research assistant will open the same numbered envelope based on the randomization enrolment number when an eligible participant can be included in the trial. Then, the research assistant will assign the drugs to the participant according to the sequence. 392 eligible participants will be randomized and assigned to the JCM-16021 group or the placebo group in 1:1 ratio (196 cases/group).

Blinding

The trial is a double-blinded design, in which all the Chinese Medicine Practitioners, research assistants and participants are ignorant of the treatment assignments. The physical appearance of placebo is

consistent with JCM-16021, including the packaging, appearance, color and taste. pharmaceutical company will be responsible for labelling JCM-16021 and placebo according to the blinding codes. '16021A' and '16021B' will be used to label the interventions. The blinding code will be kept strictly confidential by the principal investigators until completion of the final statistical analysis and report of the trial. If there is a serious adverse event (SAE) relevant to the research medication, the assignment code will be broken. The date and reason for breaking the blinding code should be recorded in the Case Report Form (CRF). Relevant institutions, including the Research Ethics Committee and Department of Health of HKSAR should be informed accordingly within 24 hours.

Recruitment

The recruitment of the study is via the press conference, announcement on university website, advertisement on local newspaper or Facebook, promotion posters and leaflets, and specialist's referral. People who are interested in the trial can contact the researchers by telephone and e-mail. Researchers will conduct preliminary screening on the phone and invite these potential candidates to come to the clinics to have a further screening face to face. Chinese Medicine practitioners will be responsible for conducting the screening and explain the details of the study, such as content, arrangement, and possible risks etc. The eligible participants will be invited join the study after signing the informed consent form.

Diagnostic criteria

According to Rome IV Criteria, IBS is diagnosed based on: recurrent abdominal pain, on average, at least one day per week in the last three months and associated with any two or more of followings: i) related to defecation, ii) change in frequency of stool, or iii) change in form (appearance) of stool. Meanwhile, diarrhea predominant is classified by loose (mushy) or watery stools > 25% and hard or lumpy stool <25% of bowel movements²².

The diagnostic criteria of LSSD pattern of TCM is in reference to the "Guiding Principles for Clinical Study of New Chinese Medicines"²³. LSSD is diagnosed when all the main symptoms and signs and associating with two or more secondary symptoms and signs are fulfilled. The main symptoms and signs include: i) abdominal pain and diarrhea (inducing or aggravating by emotional upset or stress), and ii) changes with defecation. Secondary symptoms and signs include: i) borborygmus and passing gas frequently, ii) distention and fullness in chest and hypochondrium, and frequent sighing, 3) emotional depression or irritability, 4) anorexia and abdominal bloating, and 5) pale red tongue with white thin fur and string like pulse.

Inclusion criteria

Participants will be included if they fulfill all of the following: 1) the diagnosis criteria of IBS-D based on Rome IV criteria; 2) the diagnosis of LSSD pattern of TCM based on "Guiding Principles for Clinical Study of New Chinese Medicines"; 3) Age of 18 to 65 years; 4) with written informed consent.

Exclusion criteria

Participants will be excluded if they have one or more of the following: 1) Constipation predominant, mixed or unsubtyped IBS; 2) Abnormal colonoscopy within five years (except for benign polypectomy or hemorrhoids); 3) With severe diseases on the system of heart, lung, liver, and kidney which are diagnosed by TCM theory; 4) Concomitant diabetes, Glucose-6-Phosphate Dehydrogenase deficiency, unstable hypertension, malignant tumor or have undergone thyroid surgery or medication within a year; 5) With diseases on the Spleen-Stomach system or other diseases that affect the movement of qi on the Spleen-Stomach system, which are diagnosed by TCM theory; 6) Current concomitant medication with effects on gastrointestinal function (e.g. anticholinergic drugs, calcium channel blockers, 5-HT₃ receptor antagonists, antidiarrheal agents, antacids, prokinetic agents, antidepressants, anxiolytics and intestinal flora regulating drugs); 7) Medical history of gastrointestinal surgery (except for appendicitis surgery); 8) The serum levels of alanine transaminase (ALT), aspartate transaminase (AST), and creatinine (Cr) exceed 1.5 times of the reference limit; 9) History of allergy in Chinese medicine; 10) Women in pregnancy or breast-feeding; 11) Medical history of neurological diseases or psychiatric disorders; 12) Currently participating in another clinical trial; 13) Taking IBS treatment drugs within 1 week.

Drop out criteria

During the study, participants may opt to withdraw at any time. Those who are lost to follow up or withdraw from the study after randomization will be treated as drop-out cases.

Experimental group

Participants assigned to the experimental group will take JCM-16021 granules (8g/sachet) orally, one sachet each time, three times daily for 8 weeks. According to the original ratio of the JCM-16021 formula, JCM-16021 Granules are processed from seven raw Chinese medicine herbs by a modern technique by the Purapharm (Nanning) Pharmaceutical Co.Ltd. The original JCM-16021 formula is composed of seven herbs as follows: *Rhizoma Atractylodis Macrocephalae* (Baizhu) 20g, *Radix Paeoniae Lactiflorae* (Baishao) 15g, *Cortex Magnoliae Officinalis* (Houpo) 10g, *Semen coicis Lachryma-jobi* (Yiyiren) 20g, *Polygonaceae* (Huotanmu) 20g, *Fructus Terminaliae Chebulae* (Hezi) 10g, *Rhizoma Corydalis Yanhusuo* (Yanhusuo) 15g. The produced JCM-16021 granules will be packaged in a sachet of 8 grams with Aluminum foil composite film. And then the packaged JCM-16021 granules will be packed in a bigger transparent bag with a label. Every bag contains 21 sachets of JCM-16021 granules. For better guaranteeing the safety and quality of the JCM-16021 granules, accelerated stability tests, heavy metal and toxic elements, pesticides residues, and microbial limit will be conducted.

Control group

Participants assigned to the control group will take placebo granules (8g/sachet) orally, one sachet each time, three times daily for eight weeks. The placebo is made from Caramel (0.55%), Sunset Yellow (0.01%), Tartrazine (0.06%), Gardenia Yellow (0.06%), Aspartame (0.8%), Sucrose Octaacetate (0.02%),

Starch (49.25%), and Dextrin (49.25%). The form, color, package, usage, and dosage of placebo is consistent with JCM-16021 granules, as is shown in Supplementary 2.

Quality of Investigational Medicinal product

All investigational medicinal product (IMP) including the JCM-16021 granules and placebo are produced by the Purapharm (Nanning) Pharmaceutical Co. Ltd. The entire manufacturing process will be in strict compliance with the standards of Good Manufacturing Practice (GMP). The production process of the JCM-16021 granules and placebo granules will be compliant with the quality specification standards, respectively. According to the Chinese Pharmacopoeia (2015), all qualified IMP will be delivered to the site of clinical study and stored within a range of $25^{\circ}\text{C}\pm 2^{\circ}\text{C}$ and relative humidity range of $60\%\pm 10\%$ ²⁴. The investigators are responsible for ensuring adequate accountability of all used and unused IMP.

Primary outcome

The primary outcome is the improvement rate on the Global Assessment of Improvement (GAI) score at week 10, same as the previous small scale study¹⁶. The participants will be asked to give a global assessment of their IBS symptoms at visit 3, 4 and 5 with the question "In the past 7 days, compared with your IBS symptoms before you started the trial, are you now: substantially worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, or substantially improved?"²⁵ The global symptom improvement will be evaluated by scales (substantially worse=0, moderately worse =1, slightly worse=2, no change=3, slightly improved=4, moderately improved=5, substantially improved=6). The 0-2 score, 3 score and 4-6 score represent worsen, no change and improvement, respectively.

Secondary outcomes

IBS symptoms

IBS symptoms, including abdominal pain (with scores from 0 to 10 representing none to most severe), stool frequency and stool consistency will be recorded by participants in a diary throughout 18 weeks of study. Investigators will grade each symptom by Cardinal symptoms evaluation quantitation scale (None=0, Mild=1, Moderate=2, Severe=3) shown in Table 1 in Supplementary 3. The changes of these IBS symptoms before and after the treatment will be used for efficacy evaluation. The details are as below:

i) Pain Responder Rate In Daily Worst Abdominal Pain Scores: According to the guidance of the U.S. FDA, pain responder is defined as that participant who meets the daily pain response criteria for at least 50% of the days with diary entries during the observational period of interest. Daily pain response is defined as the $\geq 30\%$ decrease in the worst abdominal pain scores in the past 24 hours compared to baseline (average of daily worst abdominal pain the 2-week prior to randomization). Pain score is ranked from 0 to 10 representing none to the most severe²⁶.

ii) Stool consistency Responder Rate In Daily Stool Consistency Scores: Stool consistency responder is defined as that participant who meets daily stool consistency response criterion (ie, score of 1, 2, 3, or 4 or

absence of bowel movement if accompanied by $\geq 30\%$ decrease in worst abdominal pain scores compared to baseline pain) for at least 50% of days with diary entries during the observational period of interest. Bristol stool scale is defined as 7-point Scale in which a score of 1 = separate hard lumps, 2 = sausage shaped but lumpy, 3 = sausage-like with cracks on the surface, 4 = sausage-like but smooth and soft, 5 = soft blobs with clear cut edges, 6 = fluffy pieces with ragged edges, and 7 = watery with no solid pieces²⁶.

iii) Improvement Rate and Efficacy Rate: The standards of efficacy assessment of single symptom are as follows: a) Excellent: symptoms disappearing; b) Effective: symptom score decreased ≥ 2 points; c) Helpful: symptom score decreased 1 point; d) Invalid: no change in symptom score. Improvement rate is defined as the proportion of participants in excellent, effective and helpful. Comprehensive efficacy judgement standard of cardinal symptoms is calculated by “(total scoring of prior treatment – total scoring of post treatment) / total scoring of prior treatment x 100%”. Clinical remission is defined as symptom disappearing, Symptom improvement ($\geq 80\%$), Helpful (between 50% and 80%), Invalid ($< 50\%$). Total effective rate is defined as the proportion of participants with clinical remission and symptom improvement²³.

TCM pattern

Five typical symptoms for LSSD are assessed to evaluate the changes of TCM Pattern, involving i) abdominal distension, ii) borborygmus and flatus, iii) distension and fullness in chest and hypochondrium, iv) frequent sighing, poor appetite, and v) mental depression or irritability. Investigators will grade the TCM pattern scale (None=0, Mild=1, Moderate=2, Severe=3) as shown in Table 2 in Supplementary 3. Efficacy assessment standards of Syndrome of Chinese medicine are as follows: Clinical remission: clinical symptoms and signs disappear or basically disappear, total scoring declining $\geq 95\%$; Excellence: clinical symptoms and signs are significantly improved, total scoring declining $\geq 70\%$; Effective: clinical symptoms and signs are improved, total scoring declining $\geq 30\%$; Invalid: clinical symptoms and signs are without obvious improvement or even with exacerbation, total scoring declining $< 30\%$. The effective rate on TCM pattern will be evaluated with following calculation formula (nimodipine method): [(total score of prior treatment – total score of post treatment) / total score of prior treatment] $\times 100\%$ ²³.

Irritable Bowel Syndrome-Quality of Life

Participants who are enrolled will fill in the Irritable Bowel Syndrome-Quality of Life (IBS-QoL) questionnaire during the study. IBS-QoL includes 34 items and involves 8 aspects: dysphoria (Q1), interference with activity (Q2), body image (Q3), health worry (Q4), food avoidance (Q5), social reaction (Q6), sexual (Q7) and relationship (Q8)²⁷. Each item will be rated on a 5-point Likert scale. Higher score reflects better quality of life. The difference of score before and after the medication will be evaluated.

Irritable Bowel Syndromes-Symptom Severity Score

The Irritable Bowel Syndromes-Symptom Severity (IBS-SSS) Score questionnaire will be completed at visit 2, 3, 4, 5. The IBS-SSS involves five aspects: the severity of abdominal pain, the frequency of abdominal pain, the severity of abdominal discomfort, defecation satisfaction, and interference with daily life. The range of score is 0-500 points scale²⁸. The change of score before and after the medication will be evaluated.

Safety outcome

In this study, adverse events (AEs) or serious adverse events (SAEs) related to Investigational medicinal products (IMP) are used for safety evaluation, including new incurrence symptoms or diseases, abnormal vital signs, clinically significant abnormal laboratory examination. The severity of AEs are graded based on the Common Terminology Criteria for Adverse Events v4.0.

Quality control and assurance

Firstly, all investigators will be required to complete the TRREE on-line training programme on the ethics and regulation of health research involving human participants (<https://elearning.trree.org/>) and get the online certification of Good Clinical Practice (GCP) before the start of the study. Secondly, all investigators will be arranged to study the details of the protocol and investigator's brochure together at the research centre of Hong Kong Baptist University. If there are some modifications, investigator will also study the revision of the protocol and the investigator's brochure in time. Thirdly, a regular monthly meeting will be held to report the study progress (either recruitment, compliance or adverse events etc.) to principal investigators, assess the investigators' activities (either data collection, data entry, or compliance with the protocol and investigator's brochure etc.), discuss and solve the problems (if any). In general, the meeting will be conducted at the office of Hong Kong Baptist University.

In addition, investigators are required to explain details of clinical trial to participants and obtain informed consent. Investigators should also let participants be fully informed of the significance of trial and importance of medication on time. For participants with low compliance, investigators should follow the participant in time and record the reasons in details. Every study site needs to strictly master the standard of quality control individually and implement strict pharmaceutical administration.

Data collection, management and monitoring

All data will be collected through patient diaries, questionnaires, and CRFs. All enrolled participants have to record their abdominal pain, stool frequency, stool consistency in a paper-based patient diary throughout 18 weeks of study. At each visit, participants will be required to return the diaries and complete some questionnaires, including the GAI questionnaire, the IBS-QoL questionnaire, and the IBS-SSS questionnaire. Chinese Medicine Practitioners and study coordinators have to fill in the CRFs to record relevant information, such as the blood pressure, the changes of TCM Pattern, and compliance/noncompliance with research medication and concomitant conventional maintenance therapy etc. These data collected in visit 2 will be the baseline data. All personal information of

participants will be kept confidential. The Research Electronic Data Capture (REDCap)^{29,30} will be used to collect and manage all participants' data by researchers. All centers have corresponding personnel to input the data timely. The researchers with authorized accounts can log in and browse the data. All raw data collected by patient diaries, questionnaires, and CRFs could be shared based on the request and special approval from the team. During the whole study, all AEs (new incurrence symptoms or diseases, abnormal vital signs, clinically significant abnormal laboratory examination) should be recorded in CRF and investigators are also required to fill in the relevant information in the "Adverse Event Report Form", which include start time, duration, severity, and relationship with IMP etc. Once there is an adverse event which results in hypersensitivity towards research medication or significant abnormality on liver or renal function, investigators can require participants to stop IMP and report it to principal investigators in time. If there are any SAEs, investigators should fill in the "Serious Adverse Event Report Form" with signature and report to the Research Ethics Committee within 24 hours. Also, all AEs and SAEs are required to be reported to Department of Health of HKSAR every year. The trial document will be kept for 7 years after the completion of the trial. Research Ethics Committee and Department of Health play a role to monitor the data. The principal investigators need to submit the progress reports to the Research Ethics Committee and the Department of Health every year, and to the funding agency Innovative Technology Commission (ITC) of the government of Hong Kong Special Administrative Region (HKSAR) every 6 months.

Biological specimen collections

During the clinical study, the blood, urine and feces will be collected from all participants with written informed consent on 2nd and 10th week, respectively. All samples will be delivered to the lab of the School of Chinese Medicine, Hong Kong Baptist University and be stored at -80°C for the metabolomics and metagenomics sequencing analysis. Blood, urine and fecal samples will be collected to analyze the metabolites profile of gut microbiota and the host before and after the treatment. Metagenomics sequencing will be used to monitor the gut microbiota composition profile before and after treatment. Both metabolomics and metagenomics sequencing are served as the methods to explore the mechanism of JCM-16021 attenuating the bowel symptoms by modulating gut microbiota.

Sample size calculation

From our previous study, improvement rate on the Global Assessment of Improvement was 52% in JCM-16021 group and 32% in western medicine group, respectively¹⁸. According to the previous clinical trial guidelines for pharmacological treatment of irritable bowel syndrome, a 15% improvement of the global outcome measure over placebo could be considered as a clinically significant therapeutic gain³¹. We assumed that there would be a 15% difference in the proportion of participants who report an improvement in their global symptoms after eight weeks of treatment (either slight, moderate, or substantial) between the placebo group and the JCM-16021 group. Thus, 166 participants are required in each group with 80% power and two-sided 5% alpha. Further assuming a 15% drop-out rate, a total of 392

participants (196 per arm) will be enrolled to ensure that the study is sufficiently powered to answer the research question of interest.

Statistical analysis

Baseline data will be descriptively summarized. Categorical variables will be summarized by frequencies and percentages. Continuous variables will be summarized with mean and standard deviation [Mean±SD].

For the outcome analysis, Comparisons between two groups for continuous variables will be conducted by using an analysis of variance (ANOVA), with other confounding factors like a multicenter character conducting the covariate analysis. Statistical analysis for the data which do not meet above conditions (e.g. non-normal) will be conducted with the use of non-parametric test. Categorical data of different groups will be reported as frequency (proportion). Comparisons between groups for these categorical data will be assessed with the use of chi-square test (CMH test) or non-parametric testing. For the repeatedly measured outcomes, the difference with the baseline data (follow-up minus the baseline) will be analyzed and the baseline data will be included in the model as covariables. Subgroup analyses will be carried out irrespective of whether there is a significant treatment effect on the primary outcome. The participants' drop-out will be descriptively summarized. Both per-protocol analysis (PP) and intention-to treat (ITT) analysis will be used to conduct the efficacy analysis. All treatment groups' comparisons except for the primary outcome will be performed at a two-sided level of 0.05.

The safety analysis will mainly be performed by analysis of the incidence of adverse events between groups and the incidence of abnormal laboratory data before and after treatment between groups. A detailed description of the statistical analysis plan (SAP) is provided in supplementary 3.

Discussion

Irritable Bowel Syndrome (IBS) is a persistent or intermittent episode of functional gastrointestinal disease with abdominal pain, bowel habits and/or stool traits that change clinically³². Many people with IBS are eager for an effective treatment. However, at present, due to the complexity and uncertainty of its etiology, there is no clear biochemical diagnostic index clinically, and the efficacy of many drugs is not very satisfactory. Therefore, it is important to investigate the effective method for IBS. Many RCTs have suggested that TCM formulas have significant efficacy for IBS symptoms and the mechanisms of these TCM formulas has been also explored that is related to the regulation of neurotransmitters and hormones in the enteric nervous system, attenuation of intestinal inflammation and restoration of intestinal flora, etc^{33,34}. JCM-16021 is a new Chinese Medicine formula developed by our team for the treatment of IBS-D based on the Chinese medicine theories and clinical experience. Our research group has conducted a series of studies on JCM-16021 to evaluate its pharmacology, efficacy, safety for more than ten years. In the previous small scale clinical trial, it has shown that participants with JCM-16021 had the highest percentage improvement at the end of 8-week treatment and the end of 16-week follow up¹⁶. But a large

scale trial is needed to further evaluate the efficacy and safety of this formula for IBS-D. Recently, disorder of the gut microbiota has been considered to be one of potential aetiological factors^{32, 35–37}. Our previous basic studies have also shown that JCM-16021 could effectively relieve intestinal hyperalgesia by altering the gut microbiota and improving the co-metabolism of the gut microbiota and its host, and also through regulating host's immune response to gut microbiota as well as enhancing gut barrier. It is likely to be an important mechanism for the effective treatment of IBS-D by JCM-16021³⁸. This study will provide an opportunity to reassess the mechanism in a large scale trial.

Conclusion

In conclusion, the protocol will provide details for investigators about the study following SPIRIT Statement. High-quality evidence on the efficacy and safety of Chinese Medicine JCM-16021 for IBS-D will be provided through strict compliance with the protocol. The results may also help to discover the underlying mechanism of this herbal remedy for the condition.

Abbreviations

IBS: Irritable Bowel Syndrome; TCM: Traditional Chinese Medicine; RCTs: Randomized clinical trials; LSSD: Liver Stagnation and Spleen deficiency; IMP: Investigational medicinal product; CRF: Case report form; ALT: Alanine Transaminase; AST: Aspartate Transaminase; Cr: Creatinine; GAI: Global Assessment of Improvement; IBS-QoL: Irritable Bowel Syndrome-Quality of Life; IBS-SSS: Irritable Bowel Syndromes-Symptom Severity; AEs: Adverse events; SAEs: Serious adverse events; GCP: Good Clinical Practice; CMH: Cochran-Mantel-Haenszel; ANCOVA: Analysis of covariance; PP: Per-protocol analysis; ITT: Intention-to-treat analysis; NMS: Neonatal maternal separation; ITC: Innovative Technology Commission; REDCap: Research Electronic Data Capture; SAP: Statistical Analysis Plan.

Declarations

Trial status

Participants' recruitment started in October 2018. Today, 392 participants have been recruited. The actual date for the start of recruitment was the 8th November 2018. The actual date for the end of recruitment was the 29th October 2020. The last participant completed the follow-up on 17th February 2021.

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Availability of data and material

The datasets will be available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interest.

Consent for publication

All authors have approved to submit the manuscript.

Ethics approval and consent to participate

The study has been approved by the Hong Kong Baptist University Research Ethics Committee (HASC/16-17/C01) and Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (2016.718-T). Clinical Trial Certificate has been awarded by Department of Health, HKSAR China (CTMT-00007). The study is also registered in the ClinicalTrials.gov (NCT03457324). All protocol amendment have been approved by the above ethics committees. Before each participant being enrolled into the study for efficacy and safety assessment and biological specimen (Urine, Blood and feces) collection, written and informed consent to participate will be gotten from all participants after clear explanation about the study (Supplementary 4).

Ancillary and post-trial care

The study is covered by a professional liability insurance policy for each participant. If there are any harm happened, the insurance company will pay the compensation according to the insurance policy. After the completion of this study, there is no other compensation to participants.

Dissemination policy

The results will be reported to the Research Ethics Committee, Department of Health, and the funding agency Innovative Technology Commission, HKSAR. And then, all participants will be also informed of the results by phone or email. Moreover, all results of the study will be published following CONSORT Statement for Chinese Herbal Medicine Formulas.

Authors' contributions

ZXB and JW are the principal investigators of the trial. ZXB and JW manage the progress of the trial. JC, LLDZ, KLC, WCL participate to design the protocol. YZ drafts the manuscript of the protocol. JC also helps to develop the protocol and monitor the study. So JC and YZ contribute equally and could be considered as co-first authors. CWC revises the manuscript of the protocol. YZ, XZ, CWC, PYL, XYW, and MK contribute to enroll the participants in the site of Hong Kong Baptist University clinics. KLC, PKC, CWL, and JC manage and promote the recruitment of participants in the site of the Chinese University of Hong

Kong clinics. YZ drafts the manuscript of the SAP. PHC participates in writing the SAP. The SAP is prepared without knowledge of the data. ZXB finalizes the manuscript of protocol and SAP. All the members of this study participate in critical reviews of the SAP and approve the all final manuscript.

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Table

Table 1 WHO Trial Registration Data Set - Structured Summary

Data category	Information
Primary registry, trial identifying number	ClinicalTrials.gov (NCT03457324) February 8, 2018
Date of registration in primary registry	Innovative Technology Commission of the government of Hong Kong Special Administrative Region ZXB, MD, PHD[bzxiang@hkbu.edu.hk]
Secondary identifying numbers	ZXB, MD, PHD[bzxiang@hkbu.edu.hk]
Sources of monetary support	Efficacy and Safety of Chinese Medicine JCM-16021 for Diarrhea-predominant Irritable Bowel Syndrome Efficacy and Safety of Chinese Medicine JCM-16021 for Diarrhea-predominant Irritable Bowel Syndrome: Study protocol for a Multi-center, Randomized, Double-blind, Placebo Controlled Clinical Trial
Contact for public queries	Hong Kong, China Diarrhea-predominant Irritable Bowel Syndrome
Contact for scientific queries	Experimental group: JCM-16021 granules (8g/sachet for each time, three times daily for 8 weeks)
Public title	Control group: Placebo granules (8g/sachet for each time, three times daily for 8 weeks)
Scientific title	Inclusion criteria 1) the diagnosis criteria of IBS-D; 2) the diagnosis of LSSD; 3) Age of 18 to 65 years; 4) with written informed consent. Exclusion criteria 1) Constipation predominant, mixed or unsubtyped IBS; 2) Abnormal colonoscopy within five years (except for benign polypectomy or hemorrhoids); 3) With severe diseases on the system of heart, lung, liver, and kidney which are diagnosed by TCM theory; 4) Concomitant diabetes, Glucose-6-Phosphate Dehydrogenase deficiency, unstable hypertension, malignant tumor or have undergone thyroid surgery or medication within a year; 5) With diseases on the spleen-stomach system or other diseases that affect the movement of qi on the spleen-stomach system, which are diagnosed by TCM theory; 6) Current concomitant medication with effects on gastrointestinal function (e.g. anticholinergic drugs, calcium channel blockers, 5-HT3 receptor antagonists, antidiarrheal agents, antacids, prokinetic agents, antidepressants, anxiolytics and intestinal flora regulating drugs); 7) Medical history of gastrointestinal surgery (except for appendicitis surgery); 8) The serum levels of alanine transaminase (ALT), aspartate transaminase (AST), and creatinine (Cr) exceed 1.5 times of the reference limit; 9) History of allergy in Chinese medicine; 10) Women in pregnancy or breast-feeding; 11) Medical history of neurological diseases or psychiatric disorders; 12) Currently participating in another clinical trial; 13) Taking IBS treatment drugs within 1 week.
Country of recruitment	
Health problem	
Intervention(s)	
Key inclusion and exclusion criteria	Interventional Allocation: randomized Intervention model: parallel assignment Masking: double blind (participants and Physicians, Chinese Medicine Practitioners)

and research assistants)
Primary purpose: Treatment
Phase III

October 2018

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Completed

The improvement rate on the Global Assessment of Improvement (GAI) at week 10.

Changes of IBS symptoms, TCM pattern improvement, IBS-Quality of Life (IBS-QoL), IBS-Symptom Severity Score (IBS-SSS), safety.

Study type

Date of first
enrollment

Target sample
size

Recruitment
status

Primary
outcome

Figures

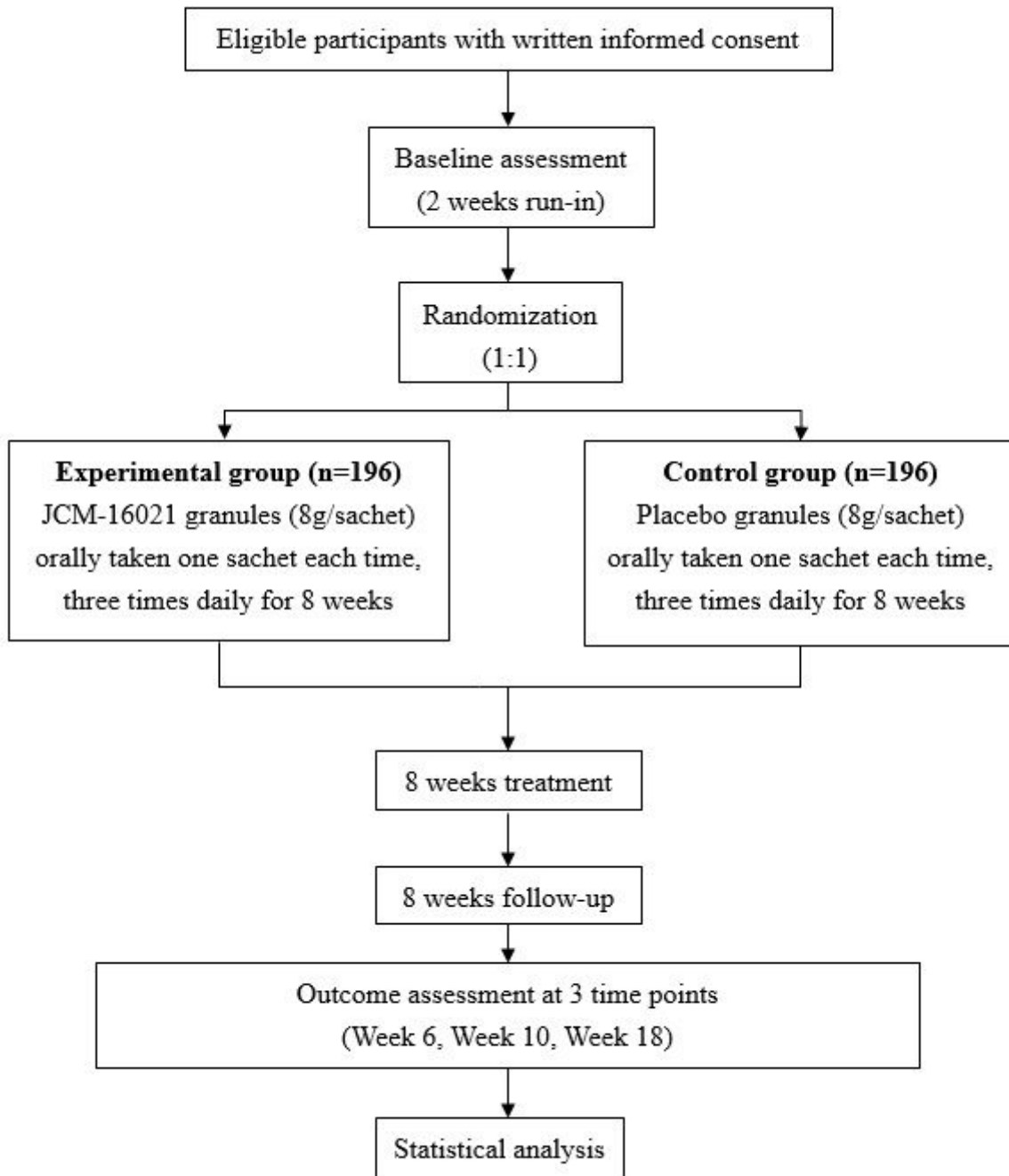


Figure 1

Flow chart

STUDY PERIOD											
	Enrolment	Allocation	Treatment								Follow-up
TIMEPOINT(week)	0	2	3	4	5	6	7	8	9	10	18
ENROLMENT:											
Eligibility screen	X										
Informed consent	X										
Randomization		X									
INTERVENTIONS:											
JCM-16021			◆—————◆								
Placebo			◆—————◆								
ASSESSMENTS:											
GAI*						X				X	X
IBS § symptoms	X	X				X				X	X
TCM† pattern	X	X				X				X	X
IBS-QoL‡		X				X				X	X
IBS-SSS**		X				X				X	X
Adverse events			X	X	X	X	X	X	X	X	X
Laboratory test	X									X	

Figure 2

The schedule of enrolment, interventions, and assessments *GAI: Global Assessment of Improvement; §IBS: Irritable Bowel Syndrome; †TCM: Traditional Chinese Medicine; ‡IBS-QoL: Irritable Bowel Syndrome-Quality of Life; IBS-SSS**: Irritable Bowel Syndromes-Symptom Severity Score

Supplementary Files

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