ClinicalTrials.gov Identifier:
NCT05175131

CLINICAL STUDY PROTOCOL

MESI3001

Study title:	Multicenter, randomized, parallel-group, open-label, comparative clinical study to evaluate efficacy and safety of Mebeverine+Simethicone fixed-dose combination versus Duspatalin® (mebeverine) and versus Espumisan® (simethicone) in patients with functional bowel disorders with abdominal pain and excess gas formation
Study number:	MESI3001
Study phase:	III
Study drug name:	Mebeverine+Simethicone
Planned Indication:	Symptomatic treatment of pain, spasms dysfunction and abdomen discomfort associated with functional bowel diseases. Symptoms may include abdominal pain, cramps, bloating and flatulence, changes in stool frequency (diarrhea, constipation, or alternating diarrhea/constipation) and consistency.
Sponsor:	Abbott Products Operations AG
Contact person:	[redacted]
Protocol date:	Amendment 1.0 dated 07 April 2021

[redacted]

PROTOCOL APPROVAL PAGE

Signature_____ Date_____
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Signature_____
[redacted] Date_____
[redacted]

Signature_____ Date_____
[redacted]

Signature_____
[redacted] Date_____
[redacted]

PRINCIPAL INVESTIGATOR STATEMENT

Name:	
I, the undersigned certify that I have read and understood the Protocol. I give consent to following Protocol MESI3001: Multicenter, randomized, parallel-group, open-label, comparative clinical study to evaluate efficacy and safety of Mebeverine+Simethicone fixed-dose combination versus Duspatalin® (mebeverine) and versus Espumisan® (simethicone) in patients with functional bowel disorders with abdominal pain and excess gas formation. I undertake to conduct this study in accordance with the requirements of International Conference on Harmonization Good Clinical Practice Guideline (ICH GCP(E6)) and Resolution № 79 "Concerning adoption of the Good clinical practice of Eurasian Economic Union (EEU)", principles provided in Helsinki Declaration, as well as in accordance with the applicable legislation and regulations of the Russian Federation.	
Date:	**Signature:**

CONTACT INFORMATION ON CLINICAL STUDY

SPONSOR, PHARMACOVIGILANCE	Abbott Product Operations AG [redacted]
[redacted]	[redacted]
CRO, MEDICAL EXPERTISE, DATA MANAGEMENT, BIOSTATISTICS	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
DEPOT	[redacted]
[redacted]	[redacted]
LABORATORY	[redacted]

[redacted]	[redacted]
CLINICAL SITES	According to list of approved sites

SYNOPSIS

Sponsor: Abbott Product Operations AG	**Study drug:** Mebeverine+Simethicone	**Active substance:** Mebeverine hydrochloride and Simethicone

Study title:

Multicenter, randomized, parallel-group, open-label, comparative clinical study to evaluate efficacy and safety of Mebeverine+Simethicone fixed-dose combination versus Duspatalin® (mebeverine) and versus Espumisan® (simethicone) in patients with functional bowel disorders with abdominal pain and excess gas formation.

Study centers (planned):

[redacted]

Study duration:	**Study phase:**
Approximately 9 months (from the first visit of the first patient until the last visit of the last patient)	III

Study objectives:

Primary objectives:

To assess the efficacy of Mebeverine+Simethicone fixed-dose combination versus Duspatalin® (mebeverin) and Espumisan® (simethicone) based on the change of abdominal pain and bloating/flatulence intensity, assessed with NRS-11 scales after 4 weeks of treatment in patients with functional bowel disorders with abdominal pain and bloating/flatulence.**Secondary objectives:**

To evaluate the following efficacy and safety parameters of Mebeverine+Simethicone fixed-dose combination versus Duspatalin® (mebeverin) and versus Espumisan® (simethicone) in patients with functional bowel disorders with abdominal pain and excess gas formation (bloating/flatulence), including analysis in subgroups (patients with IBS and other functional bowel diseases, patients with constipation, diarrhea, both constipation and diarrhea, neither of them):

- Change from baseline of NRS-11 pain intensity after 4 weeks of treatment
- Proportion of patients with the NRS-11 pain intensity reduction of ≥30% versus baseline during at least 50% of treatment weeks over treatment period
- Proportion of patients with the NRS-11 pain intensity reduction of ≥ 50% versus baseline during at least 50% of treatment weeks over treatment period.
- Proportion of patients with the abdominal pain assessed in the Patient Dairy completely resolved during at least 50% of treatment weeks over treatment period (NRS-11 0 assessment).
- Change from baseline of NRS-11 bloating/flatulence intensity after 4 weeks of treatment
- Proportion of patients with the NRS-11 bloating/flatulence intensity reduction of ≥30% versus baseline during at least 50% of treatment weeks over treatment period.
- Proportion of patients with the NRS-11 bloating/flatulence intensity reduction of ≥ 50% versus baseline during at least 50% of treatment weeks over treatment period.

- Proportion of patients with the bloating/flatulence assessed in the Patient Dairy completely resolved during at least 50% of treatment weeks over treatment period (NRS-11 0 assessment).
- For patients with constipation: proportion of patients with any increase in number of CSBM per week versus baseline during at least 50% of treatment weeks.
- For patients with diarrhea: proportion of patients with any decrease in the number of days per week with at least one stool consistency of Type 6 or Type 7 BSS versus baseline during at least 50% of treatment weeks.
- Change in number of days per week during study treatment period when drotaverine was taken.
- Change in quality of life evaluation using IBSQOL questionnaire versus baseline.
- The incidence and severity of adverse events (AE) and serious adverse events (SAE), physical examination, vital signs and lab results.

Study methodology:

Study design:

An open-label, randomized, comparative Phase III clinical study. The study is performed to evaluate efficacy and safety of Mebeverine+Simethicone fixed-dose combination versus Duspatalin ® (mebeverin) and versus Espumisan ® (simethicone) after 4 weeks of treatment in patients with functional bowel disorders with abdominal pain and excess gas formation.

The study will be conducted at approximately 45 clinical sites in Russia.

A total of 465 patients with functional bowel disorders with abdominal pain and excess gas formation will be randomized in the study at a 1:1:1 ratio (155 patients in each of the three groups).

Taking into account a possible screen-failure rate approximately 30%, up to 665 patients will be screened to include 465 patients in study.

Clinical study will include three periods: Screening and Run-in period (1 week), study treatment period (4 weeks), and follow-up period (1 week).

Screening and run-in period

On the Visit 1 (Week -1, Day -7) after signing the Patient Information Leaflet and the Informed Consent Form, screening procedures will be performed, including collection of demographic data and medical history, physical examination, height and body weight measurements, BMI determination, vital signs assessment, sampling of biological material for hematology and biochemistry blood tests, urinalysis, test for fecal calprotectin. For patients older than 50[1] years old who have not had a colonoscopy performed during the cause of the last 12 months prior to screening which confirms the absence of significant pathological changes, this procedure will be performed as part of the screening examination. Screening period will be prolonged for 2 more weeks (up to 3 weeks) for these patients. Colonoscopy should be performed not later than 10 days before the randomization visit. Assessment of abdominal pain and bloating/flatulence intensities will be performed using an 11-point Numeric Rating Scale (NRS-11). An ECG and urine pregnancy test for women of childbearing potential will be performed.

The drotaverin intake not more than 80 mg 1 – 3 times a day during one day after pain episode will be allowed for intensive abdominal pain during the study; No-spa® will be recommended to the patients for this purpose. Other drugs for abdominal pain and bloating/flatulence treatment

will be prohibited. Any changes in diet and probiotic therapy (including drug and dose regimen changes) will be also prohibited.

Patients will be given Patient Diaries for daily self-assessment of abdominal pain, bloating/flatulence severity with NRS-11 (the most severe episode during last 24 hours), study drug and drotaverin intake, stool frequency and consistency with Bristol Stool Chart (BSC). Women with childbearing potential will register menstrual bleeding days.

At the end of the Screening and Run-in period, patients will be invited to the center to assess the abdominal pain and bloating/flatulence intensities and confirm compliance with the inclusion/exclusion criteria. The baseline abdominal pain and bloating/flatulence intensity for the inclusion/exclusion criteria assessment will be determined as average daily NRS-11 abdominal pain and bloating/flatulence score during last week of screening period (7 days before randomization).

Study treatment period

On Visit 2 (Week 0, Day 1) patients who meets all inclusion/exclusion criteria, will be randomized into one of the three groups at a 1:1:1 ratio. Vital signs and body weight will be evaluated. Patients will assess their quality of life by completing IBSQOL.

Group	Study product	Number of patients
1	Mebeverine+Simethicone, 135 mg+80 mg, three times a day	155
2	Duspatalin® 135 mg three times a day	155
3	Espumisan®, 80 mg (2 capsules 40 mg) three times a day	155

The study will be open, with no treatment blinding.

Throughout the study, patients will keep diaries for daily recordings of the abdominal pain and bloating/flatulence intensities on the NRS scale (the most intensive episode during last 24 hours), study drug and drotaverin intake which will be allowed as rescue medication not more than 80 mg 1 – 3 times a day during one day for intensive pain episode; patients will also evaluate the frequency and consistency of stools, women with childbearing potential will register menstrual bleeding days.

Study treatment period duration will be 4 weeks. On Week 2, Day 15, the telephone contact (TC) for adverse events (AEs) and concomitant medications assessment will be performed.

On Visit 3 (Week 4, Day 29) the abdominal pain and bloating/flatulence intensities registration according to the Patient Diary will be checked by investigator, as well as the frequency and consistency of stool, drotaverin intake, the adverse events and concomitant medications. Physical examination, vital signs, and body weight will be assessed, blood and urine for haematology and biochemistry tests and urinalysis will be sampled. Patients will assess their quality of life by completing IBSQOL. At this visit study treatment will be completed and patients will receive recommendations for further treatment of abdominal functional disorder.

Follow-up period

Follow-up period will last for 1 more week after study treatment completion. At Week 5, Day 36, the TC will be performed to assess the adverse events and concomitant medications.

Main inclusion and exclusion criteria:

Inclusion criteria

1. Signed Informed Consent Form;
2. Males and females aged 18 to 75 years old (inclusive);
3. Abdominal pain and bloating/flatulence due to functional bowel disorder (including IBS, chronic functional constipation, chronic functional diarrhea or functional abdominal bloating);
4. Episodes of abdominal pain for at least 3 months, with a frequency of at least 3 times a month;
5. Abdominal pain intensity of 4 to 9 points (inclusive) when assessed on the NRS-11 scale (i.e. weekly average, with daily recording of the worst pain for the last 24 hours during last week of Screening and Run-in period);
6. Bloating/flatulence intensity of of 4 to 9 points (inclusive) when assessed on the NRS-11 scale (i.e. weekly average, with daily recording of the worst bloating episode for the last 24 hours during last week of Screening and Run-in period);
7. Patients' consent to use adequate contraception methods throughout the study. Adequate contraception methods include:
    a. oral contraceptives or contraceptive patches,
    b. condom or diaphragm (barrier method) with spermicide, or
    c. an intrauterine device

Exclusion criteria:

1. Hypersensitivity to mebeverine, simethicone, drotaverine, excipients of the studied products, or contraindications;
2. Intake of tricyclic antidepressants, eluxadoline, linaclotide, selective serotonin re-uptake inhibitors, rifaximin, lubriprostone within the last week before screening;
3. New prescription or any change in probiotic drug therapy (including change in the drug or dosage regimen) during the last month before screening;
4. History of intestinal obstruction, stricture, toxic megacolon, GI (gastro-intestinal) perforation, fecal impaction, gastric banding, bariatric surgery, adhesions, ischemic colitis, or impaired intestinal circulation (e.g. aorto-iliac disease);
5. History of major gastric, hepatic, pancreatic or intestinal surgery (appendectomy, hemorrhoidectomy, or polypectomy allowed as long as occurred > 3 months prior to trial screening; uncomplicated laparoscopic or open cholecystectomy is allowed if no history of post-operative biliary tract pain and surgery occurred > 3 months prior to screening);
6. Significant and progressive enlargement of the liver, spleen, lymph nodes; ascites; palpable tumor formation in the abdominal cavity / pelvis according to physical examination, hepatic cirrhosis;
7. Significant concomitant acute or chronic disease (cardiovascular, gastrointestinal, endocrine, immunological, metabolic, bronchopulmonary, urinary system) or any

condition that, according to Investigator, is a contraindication for the patient to participate in the study if interference with the study performance;

8. Any inflammatory bowel disease (Crohn's disease, ulcerative colitis, any infection including bacterial, viral, protozoa, helminthosis);
9. Elevated fecal calprotectin level 1 month before or at screening which indicates the presence of inflammatory GIT disease;
10. Unexplained GI bleeding within 3 months prior to screening;
11. Confirmed diagnosis of bile acids malabsorption;
12. History of any malignant disease except basal cell carcinoma of skin and vesical cervix carcinoma in situ which were cured ≥ 5 years ago;
13. Confirmed diagnosis of celiac disease;
14. Confirmed hereditary galactose or fructose intolerance , total lactase deficiency, sucrase-isomaltose insufficiency, glucose-galactose malabsorption syndrome;
15. Diet changes (e.g, switching to fermented foods, a gluten-free diet) within the 1 months prior to screening;
16. Planned elective surgery during the study;
17. Pancreatic exocrine insufficiency or acute pancreatitis;
18. Endometriosis in women;
19. Positive results of tests for HIV, hepatitis B or C, at the moment of screening;
20. Drugs or alcohol abuse at screening or in the past, which, in the Investigator's opinion, makes the patient not eligible for participation in the study;
21. Participation in another clinical study or another study drug administration within 30 days prior to screening;
22. Pregnant or lactating women, or women planning to get pregnant during the clinical study; women of child-bearing potential (including those without history of surgical sterilization and women with <2 years post-menopause) not using adequate contraception methods;
23. Inability to read or right; unwillingness to understand and comply with Protocol procedures; non-compliance with medication dosing regimen or procedures which, in the Investigator's opinion, may affect study results or the patient's safety and prevent the patient's participation in the study; any other concomitant diseases or severe mental disorders, which make the patient ineligible for study participation, limit the legal basis for Informed Consent procedure, or may affect the patient's ability to participate in the study.

Study product, dosage, and route of administration:

Name: Mebeverine+Simethicone

Drug substances: mebeverine hydrochloride and simethicone

Drug formulation: film-coated tablets

Dosage: 135 mg + 80 mg

Route of administration: orally 1 tablet 3 times a day before meal

Storage conditions: In a light-protected place at a temperature not above 25°C.

Manufacturer: [redacted]

Comparator products, dosage, and route of administration:

Duspatalin®

Drug substance: mebeverine hydrochloride

Drug formulation: film coated tablets

Dosage: 135 mg

Route of administration: orally

Dosing regimen: 135 mg three times a day in before meals

Storage conditions: at a temperature below 30˚C

[redacted]

Espumisan®

Active substance: Simethicone

Drug formulation: capsules

Dosage: 40 mg

Route of administration: orally 2 capsules 3 times a day with and without meals

Storage conditions: at a temperature below 30˚C

[redacted]

Treatment duration:

Each patient will be participating in the study for approximately 6 weeks, including 1 week of screening and run-in period, 4 weeks of study treatment, and 1 follow-up week.

Start of patient enrollment is scheduled for November 2020. All patients are planned to complete all study visits until April 2021, and the study is planned to be completed in August 2021.

Assessment criteria:

Efficacy assessment

Primary endpoint:

- Change from baseline of sum of NRS-11 abdominal pain and bloating/flatulence intensity scores after 4 weeks of treatment.

The baseline abdominal pain and bloating/flatulence intensity will be determined as the average of the NRS-11 daily assessment during 7 days before randomization (weekly average of last week of screening and run-in period). The Week 4 assessment is the same (data from last 7 days of the corresponding week).

Secondary end points:

- Change from baseline of NRS-11 pain intensity after 4 weeks of treatment

- Proportion of patients with the NRS-11 pain intensity reduction of ≥30% versus baseline during at least 50% of treatment weeks over treatment period
- Proportion of patients with the NRS-11 pain intensity reduction of ≥ 50% versus baseline during at least 50% of treatment weeks over treatment period.
- Proportion of patients with the abdominal pain assessed in the Patient Dairy completely resolved during at least 50% of treatment weeks over treatment period (NRS-11 0 assessment).
- Change from baseline of NRS-11 bloating/flatulence intensity after 4 weeks of treatment
- Proportion of patients with the NRS-11 bloating/flatulence intensity reduction of ≥30% versus baseline during at least 50% of treatment weeks over treatment period.
- Proportion of patients with the NRS-11 bloating/flatulence intensity reduction of ≥ 50% versus baseline during at least 50% of treatment weeks over treatment period.
- Proportion of patients with the bloating/flatulence assessed in the Patient Dairy completely resolved during at least 50% of treatment weeks over treatment period (NRS-11 0 assessment).
- For patients with constipation: proportion of patients with any increase in number of CSBM per week versus baseline during at least 50% of treatment weeks.
- For patients with diarrhea: proportion of patients with any decrease in the number of days per week with at least one stool consistency of Type 6 or Type 7 BSS versus baseline during at least 50% of treatment weeks.
- Change in number of days per week during study treatment period when drotaverine was taken.
- Change in quality of life evaluation using IBSQOL questionnaire versus baseline.
- The incidence and severity of adverse events (AE) and serious adverse events (SAE), physical examination, vital signs and lab results.

The baseline abdominal pain and bloating/flatulence intensity will be determined as average of the worst daily episodes NRS-11 assessment during 7 days before randomization (last week of screening and run-in period). The data from last week of screening and run-in period will be also used for baseline assessment of stool frequency and consistency and number of days of drotaverin intake. Week 1, Week 2, Week3 and Week 4 assessments are the same (data from the last 7 days of the corresponding week).

Safety assessment

Safety will be assessed per treatment arm, based on the incidence and severity of AE and SAE, physical examination, vital signs and lab results.

Statistical Analysis methods

Statistical analysis will be performed according to the Statistical Analysis Plan created and finalized before the database lock.

The Safety Population will consist of all randomized patients who received at least one dose of the study product.

The Full Analysis Set (FAS) will consist of all randomized patients who received at least one dose of the study product and have at least one post-baseline assessment of the efficacy parameters.

Per Protocol set (PP) will consist of all FAS patients who completed study treatment and had no significant protocol violations.

Also, secondary endpoint analysis will be performed in the following subgroups:

- Patients with IBS
- Patients with other functional bowel diseases
- Patients with constipation
- Patients with diarrhea
- Patients with both constipation and diarrhea

Patients with neither constipation nor diarrhea.

Primary efficacy endpoint analysis

The FAS will be the main sample for efficacy assessment in this study performed to confirm superiority. Additional analysis of the primary efficacy endpoint will be performed in the per protocol (PP) set.

For the difference of changes in sum scores of NRS-11 pain and bloating/flatulence intensities after 4 weeks of treatment versus baseline between the groups Mebeverine+Simethicone versus Duspatalin® and Mebeverine+Simethicone versus Espumisan®, a two-sided 95% confidence interval (CI) will be constructed, which is equivalent to a 97.5% one-sided CI. The confidence interval will be constructed using ANCOVA, which will include treatment and site as fixed effect, and baseline parameter will be included in the model as covariate. To test the hypothesis of superiority of the FDC Mebeverine+Simethicone versus every comparator (Duspatalin® and Espumisan®), the upper confidence limit will be used. The null hypothesis (H_0: no difference in change from baseline of sum of bloating/flatulence and pain scores between the FDC and corresponding comparator, will be rejected in favor of the alternative hypothesis (H_a: larger change from baseline of sum of bloating/flatulence and pain scores in the fixed-dose combination Mebeverine+Simethicone group) only if the upper limit of two-sided 95% CI does not contain the value 0. In addition the study will be considered successful in case the both superiority hypothesizes are proven, i. e. upper limit of two-sided 95% CI does not contain the value 0 for both constructed confidence intervals. In this case, a conclusion will be drawn on the fixed-dose combination of Mebeverine+Simethicone is superior versus Duspatalin® (mebeverin) and Espumisan® (simethicone) for the pooled decrease of pain and bloating/flatulence intensity.

Secondary endpoint analysis

Intergroup comparisons will also be performed for secondary efficacy endpoints using the χ^2/Fisher exact test and 95% confidence intervals for differences in proportions will be given. Additionally, the proportion of patients with reduced severity of pain in the bowel region and bloating/flatulence during each week of the 4-week treatment period charts will be constructed.

ANCOVA model, which will include treatment and site as fixed effect, and baseline value as covariate, will be used for continuous covariates comparison presenting treatment effect estimates and associated 95% CIs.

Safety endpoint analysis

The safety sample will be used for the analysis of the safety and tolerability data.

Treatment Emergent Adverse Events (TEAEs) including AE and SAE will be presented by frequencies (number of patients with AEs and number of events) and are summarized by unique treatment (Mebeverine+Simethicone, Duspatali®, Espumisan®), primary System Organ Class

(SOC) and Preferred terms (PT) and relation to the study drug and severity. Severity and drug-event relationship of the treatment emergent AEs are summarized separately.

Laboratory values and vital signs by visit and their changes from baseline will be summarized in tables of descriptive statistics. Abnormal values (according to the reference ranges) will be presented in frequency tables (low, normal and high values).

Patient distribution, demographic characteristics, and analysis of baseline characteristics

Patient distribution, demographic and baseline characteristics will be summarized using descriptive statistics. The number and proportion (%) of patients receiving concomitant medication will be provided in frequency tables by the 2 and 4 level ATC codes. The number and proportion (%) of patients with prior medical conditions will be provided. Information on dosing, including daily doses, exposure time, and total dose, will be presented descriptively for each group.

Sample size

There are no published data on bloating/flatulence and abdominal pain assessment with NRS-11 for simethicone versus placebo and mebeverin versus placebo. Comparison of Linaclotide treatment versus placebo for bloating decrease in chronic constipation patients was assessed with NRS-11 and found out 1.0 point difference between groups with approximately 2.5 standard deviation.[2] Comparison of B. coagulans Unique IS2 treatment versus placebo for pain decrease in IBS patients was assessed with NRS-11 and found out 3.2 point difference between groups with 2.5 standard deviation.[3]

An assumption was taken that Mebeverin+Simethicone fixed dose combination will decrease the sum of pain and bloating/flatulence scores on average at least 1.0 point more than simethicone or mebeverine as monotherapy.

For primary endpoint to demonstrate the superiority of the FDC versus separately each mono-component assuming an expected 1.0 point difference between the two treatment groups and standard deviation 2.5 with type I error $\alpha = 0.05$ (two-sided) and power 90% for each comparison individually in a group-sequential design with one interim stage at information fraction 40%, about 132 patients should be included in both groups. The overall power to demonstrate superiority for both comparisons (FDC vs mebeverine monotherapy and FDC vs simethicone monotherapy) is about 80%.

Thus, 396 should be included into the analysis.

1. mebeverin	superiority /sum NRS-11 scores for pain and bloating/flatulene intensity	$\alpha = 0.05$ (two-sided) $\beta = 0.1$ Power = 90% Mean diff. = 1.0 SD = 2.5 Alpha spending function: O'Brien-Fleming Beta spending function (non-binding): O'Brien-Fleming Max. num, of stages = 2 Info. proportion at Interim stage = 0.40	n1 = n2 = 132
2. simethicone	superiority /sum NRS-11 scores for pain and bloating/flatulene intensity	$\alpha = 0.05$ (two-sided) $\beta = 0.1$ Power = 90% Mean diff. = 1.0 SD = 2.5 Alpha spending function: O'Brien-Fleming	n1 = n2 = 132

		Beta spending function (non-binding): O'Brien-Fleming Max. num, of stages = 2 Info. proportion at Interim stage = 0.40	

Thus, taking into account a 15% drop-out rate, about 155 patients should be included in each group. A total of 465 patients should be randomized.

Randomization

Patients will be randomized into three equal groups (1:1:1) using the IWRS system.

Protocol version number and date:

Protocol MESI3001 Amendment 1 dated 07 April 2021

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LIST OF ABBREVIATIONS

FAS	Full analysis set
IBSQOL	Irritable bowel syndrome quality of life
MedDRA	Medical Dictionary for Regulatory Activities
NRS-11	11-point Numeric Rating Scale
PP	Population per protocol
TEAE	Treatment emergent adverse events
BSS	Bristol stool score
VAS	Visual Analogue Scale
HIV	Human immunodeficiency virus
WHO	World Health Organization
ED	Early discontinuation
CI	Confident interval
EAEU	Eurasian Economic Union
GIT	Gastrointestinal tract
BMI	Body mass index
IP	Investigational product
eCRF	Electronic Case Report Form(s)
SOC	System organ class
AR	Adverse reaction
IEC	Independent Ethics Committee
AE(s)	Adverse event(s)
ET	End of treatment
PT	Preferred term
SUSAR	Suspected Unexpected Serious Adverse Reaction
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
IBS	Irritable bowel syndrome
TC	Telephone contact
FGID	Functional gastrointestinal disease
FBD	Functional bowel disease
HR	Heart rate
ECG	Electrocardiogram

1. INTRODUCTION

1.1. Frequency and prevalence of chronic abdominal pain and abdominal bloating .

Abdominal pain has been and remains a serious problem of internal diseases and gastroenterology.[4]

According to R. Hunt et al., the frequency of abdominal pain associated with spasm of smooth musculature of the hollow organs of the digestive system is 10-46% regardless of age. However, women are more likely to suffer from such pains[5]

In a fairly large epidemiological study (S.A. Kurilovich and co-authors) conducted in Novosibirsk, in a random sample of 416 men and 473 women between the ages of 45 and 70, the frequency of chronic abdominal pain was 17.3%, disturbing women more often than men (23.5 and 10.5% respectively).[6]

In the general population, the frequency of complaints of bloating and overcrowding was 30%, and in the population of patients with irritable bowel syndrome the frequency of such complaints is close to 100%[7]

1.2. Mechanisms of origin, types and characteristics of abdominal pain

In general, 4 main types of abdominal pain are distinguished by the mechanism of formation: visceral, parietal, radiating and psychogenic [4]

One of the variants of abdominal pain due to organic causes may be parietal pain resulting from the involvement of the peritoneum in the pathological process.

Due to the large number of synapses between neurons, double innervation often occurs, which underlies the irradiation of pain.

Psychogenic pain occurs in the absence of somatic causes and is caused by a deficiency of inhibitory factors and/or amplification of normal incoming afferent signals due to lesions of central control mechanisms and/or reduction in synthesis of biologically active substances. This pain is constant, acutely reducing the quality of life and not associated with dysmotility, eating, intestinal peristalsis, defecation and other physiological processes.

The most frequent mechanism of abdominal pain is visceral pain, which caused by increased pressure, distension, tension, local circulatory disorder, which is usually based on the development of spastic contraction of the smooth muscles of the hollow organ. Spasm that causes pain may also be the result of organic diseases, but most often it is the main manifestation of functional pathology of the GIT organs. Pain is usually dull, spastic, burning and has no clear localisation.

1.3. Abdominal pain and bloating in functional bowel disorders

In functional bowel disorders (FBD) the mechanisms of pain formation are different and may be isolated or combined: visceral genesis is often combined with radiating and/or psychogenic mechanisms. It is characteristic that spastic pain in the FBD disturbs patients while they are awake and rarely occurs during sleep[5,8]

Management of the abdominal pain is a serious separate problem, even if the main cause of its occurrence is correctly and promptly diagnosed. The choice of a drug depends on both, the mechanism of pain and the specific nosological form. In everyday practice, considering the often combined character of pain, it is not unusual to use a combination of different medicines.

Spasmolytic drugs are used to relieve visceral abdominal pain of any genesis - both organic and functional. They not only relieve pain, but also help to recover the blood flow affected by spasm, mucous membrane trophicity, the passage of intestinal contents and the absorption of nutrients and gas, leading to a feeling of overflow and laceration in the

abdomen.[4] The prescription of spasmolytics is not accompanied by direct intervention in the mechanisms of pain sensitivity and does not complicate the recognition of acute surgical pathology, can be very often effective to eliminate the pain and improve the quality of life of patients suffering from recurrent abdominal pain associated with the FBD, which determines their widespread use. [5,9]

Essential to the patient's quality of life is to get rid of pain. Appropriate symptomatic therapy, even if it does not have an etiopathogenetic focus, but relieves pain, is crucial. Another fact that should be taken into consideration is that the prescription of spasmolytics reduces pain during endoscopic examination which allows to conduct various diagnostic procedures.

Muscle spasm it is a universal reaction of smooth muscles to any pathological effects, which inevitably leads to excitation of nociceptors located in the gastrointestinal muscular layer. It is the muscle spasm that is one of the key mechanisms underlying the most commonly occurring variant of abdominal pain - visceral pain. Considering the importance of spasm as a universal link in the development and other symptoms of many gastroenterological diseases, it must be admitted that spasmolytic treatment is pathogenetically justified. [5,10]

1.4. Functional bowel disorders: epidemiology and social significance, evolution of terminology, limitations of the Rome criteria IV edition

According to the latest version (IV) of the Rome criteria for Functional Gastrointestinal Disorders (FGID), approved in 2016,[11] the FBD includes:

- Irritable bowel syndrome (constipation predominant IBS, diarrhea predominant IBS, mixed IBS, unclassified IBS)
- Functional constipation
- Functional diarrhea
- Functional abdominal bloating/distension
- Nonspecific functional intestinal syndrome
- Opioid-induced constipation

Population studies show that the prevalence of IBS is 10% - 20%, the frequency of detection of new cases - 1% - 2% per year[12] Only 10% - 20% of patients with IBS seek medical help.

The prevalence of other FBDs is less studied. In the adult population, the frequency of functional constipation is 14% on average and ranges widely from 1.9% to 40.1%, with the frequency of simple complaints about constipation significantly higher than the frequency of diagnoses according to the Rome criteria.[13]

The prevalence of functional diarrhea ranges from 1.5% to 17%[14,15,16,17,18]

The prevalence of functional bloating has not been examined in major prospective studies, but there is evidence of the prevalence of a symptom such as bloating. According to a telephone survey of 2,510 subjects in the U.S., 15.9% of those surveyed reported episodes of bloating during the last month.[19] Patients with FGID often noted a concomitant symptom of bloating, especially patients with IBS and functional constipation.[20,21,22,23,24,25]

Since the main manifestations of FBD are abdominal pain (the dominant symptom for IBS and may be present in other functional bowel disorders) and lifestyle changes due to a defecation disorder, people with FBD are more likely to lose wages because of absences from work due to the illness.[26] The negative impact of FBD on the quality of life of patients has been clearly demonstrated.[27] Many social activities, such as eating, traveling long distances, participating in festive activities, are significantly complicated by symptoms specific to FBD.

The pathophysiology of the FBD, even the IBS (the most studied disease in this group), is not fully understood. There is evidence of multiple pathogenetic pathways: [28]: visceral hypersensitivity

or autonomous dysfunction, [29,30,31,32] and also influence of psychological factors causing disturbance of the nervous system of intestine and disturbance of interconnection of brain and intestine that in any case leads to disorders of intestinal motility.[33,34]

Prior to the creation of the Rome Foundation for the study of gastrointestinal functional pathology, the FBD group included the so-called "spastic constipation, chronic irritable bowel, mucous colitis, spastic colitis", etc., the symptoms of which could include: abdominal pain, spasms, a feeling of bloating and flatulence, change in stool frequency.

In 1999, the Rome criteria II first presented a new scientific direction in gastroenterology called "neurogastroenterology", which began to study the fundamental and applied aspects of FGID. At the same time, a new concept of gastrointestinal diseases, motor disorders and FGID was proposed, based on three basic positions: 1) organic (structural) disorders (e.g., esophagitis, inflammatory bowel diseases, etc.) are classified within the framework of organic morphology; criteria for their diagnosis are based on macro- and microscopic changes; 2) motility disorders (e.g., gastroparesis, intestinal pseudo-obstruction) are classified within the framework of organ function and specific motility disorders. They are diagnosed on the basis of repeated physiological tests (e.g. measuring time of intestinal transit or gastric emptying); 3) FGID (e.g. functional dyspepsia, irritable bowel syndrome) depend on the patient's interpretation and perception of the disease, i.e. they are classified and diagnosed primarily on the basis of a set of symptoms. In the mid-1990s, the American pharmaceutical agency FDA recommended to use the Rome criteria for irritable bowel syndrome (IBS) in pharmacological studies, after which the Rome Foundation began to support leading pharmaceutical companies around the world. The Rome Criteria III were different from previous versions in that for the first time they were developed using approaches based on evidence-based medicine rather than consensus of experts. Since 2006, the Rome Criteria III have been considered worldwide as the fundamental diagnostic criteria of FGID for both clinicians and investigators. It is mentioned in Rome criteria III that there are certain limitations to their application, in particular: 1) the term FGID itself, although widely referenced in the literature, is not entirely accurate and has a degree of stigmatization; 2) whilst diagnostic criteria have been developed for use in clinical practice, they are not specific to examining the pathogenetic features of this pathology.

The current criteria are the Rome criteria, IV edition.

It is generally accepted that the Rome criteria version IV, based on symptoms, have their limitations in clinical practice, although they are widely used in clinical trials. Specifically, diagnoses established under these criteria may exclude patients who do not fully meet the Rome criteria, although they require the same treatment.

These limitations had a particular impact on IBS. The concept of "discomfort" was excluded from the fourth edition of IBS diagnostic criteria as having different translations in different languages or not even being present in some of them; in the previous edition of the Rome criteria the frequency of abdominal pain was at least 3 times per month, the pain had to be episodically present for 12 weeks, not necessarily sequential; in the new edition the frequency of episodic pain was increased to 4 per month, and the duration of pain had to be at least 6 months. Thus, the acceptance of the new, fourth edition of the Rome criteria significantly reduced the patient population with IBS. Patients who were previously classified as suffering from IBS were no longer consistent with this diagnosis, their disease began to be classified as other functional bowel disorders. For example, patients with abdominal pain and bowel dysfunction for less than 6 months or with a frequency of less than 1 episode per week, or those who have less than 2 of the 3 criteria for association of abdominal pain with stool disorders, or those in whom abdominal pain is not associated with stool disorders, does not meet Rome criteria IV and they are not diagnosed with IBS, they have a diagnosis of functional diarrhea or constipation, and at some time may be included in the group of IBS with diarrhea or constipation in terms of pain frequency.

Thus, efficacy and safety studies of spasmolytics in patients with IBS, conducted prior to the approval of the Rome criteria IV, were carried out on a patient population which corresponds to a wider group of functional bowel disorders as per the IV edition of the Rome criteria, including functional constipation, functional diarrhea, functional bloating

1.5. Spasmolytics, simethicone and their combination in FBD therapy

Spasmolytics are included in the previous (before the acceptance of the Rome criteria IV) and the latest version of the Guidelines of the Russian Gastroenterological Association, Russian Association of Coloproctologists for the diagnosis and treatment of patients with irritable bowel syndrome as first-line therapy.[35,36] According to the Guidelines of the World Organisation of Gastroenterologists for the treatment of IBS in 2015,[1](i.e. also prepared within the framework of the previous version of the Rome criteria), first-line therapy for the treatment of this pathology also include spasmolytics, among which are: mebeverine, otilonium, hyoscine, cimetropium, pinaverium and dicyclomine.

Although currently simethicone is not included in the guidelines for the treatment of patients with IBS due to a lack of clinical research data, it can be assumed that its addition to basic therapy would be effective and would bring relief to a significant number of patients since, according to the published data, virtually all FBD patients suffer from flatulence.[20,21,22,23,24,25,37] Many investigators have emphasised the particularly negative role of flatulence in worsening the wellbeing of FBD patients, since this symptom, by changing its intensity, intensifies during the day, worsens after a meal, usually decreasing by night[18,36,38] It is the simethicone, which has the properties of a defoamer, which reduces flatulence, discomfort and abdominal pain by increasing the gastrointestinal gas excretion.[39,40]

Taking into consideration the important role of spasmolytics in the treatment of FBD, favorable effect of simethicone on one of the key symptoms of FBD, flatulence, it is obviously expedient to try to study the effectiveness of spasmolytics and simethicone co-use in patients with FBD, suffering from stool disorders, bloating and abdominal pain, expressed in different extents and thus having different diagnoses: one or another type of IBS, functional diarrhea, functional constipation. Such generalization can also be made by the idea of a single etiopathogenetic mechanism of the development of these diseases. It is assumed that their development is based on the changes in the gut-brain axis and is realized in the form of intestinal motility disorders,[41] which are eliminated by mebeverine. These motility disorders are probably an important pathogenetic link in the formation of both diarrhea and constipation, as well as bloating [37,42]

Functional abdominal bloating is a common symptom of many forms of functional bowel pathology, with adverse effects on general well-being and quality of life. Symptomatic treatment of bloating according to modern ideas can be aimed not only at microbiota, visceral sensitivity and psychological concomitant pathology, but also at intestinal motility, its muscle tone. [42,43]
The currently available literature reviews on functional abdominal bloating indicate a wide practical use of spasmolytics and simethicone in everyday practice as the main symptomatic therapy for this group of patients. [7] At the same time, modern guidelines, acknowledging the low quality of evidence for the long-term effectiveness of these drugs, recommend their use in FBD.
Two meta-analyses of clinical studies were conducted to assess bloating/distension. The first included 6 clinical studies involving 885 patients and 5 different medicines.[44] According to the meta-analysis data, spasmolytics were more likely to relieve bloating/distension symptoms in patients with IBS (the diagnosis was made according to the Rome criteria before the acceptance of version IV) compared to placebo (chance ratio = 1.46; 95% confidence interval: 1.10-1.94). According to the results of another meta-analysis, which included data from 7 clinical studies in 1419 patients receiving 4 different spasmolytics, administration of drugs was more effective than placebo (chance ratio 1.455; 95% confidence interval 1.17-1.81).[45]

In a prospective randomized placebo-controlled study in 285 patients with IBS (according to the Rome criteria of III edition), it was revealed that the combination of pinaverium bromide and simethicone decreased the severity of bloating and abdominal pain to a greater extent than placebo[46]

Further research is needed to clarify the pathophysiological foundations of bloating formation. Clinical studies in which bloating and distension are endpoints are necessary to justify the use of safe medicines[7] with already proven efficacy against other symptoms (e.g. mebeverine).

Moreover, the inertness, local effect and lack of absorption of simethicone in the gastrointestinal tract suggests the absence of pharmacokinetic interaction between simethicone and other products.

Thus, the addition of simethicone to spasmolytics provides an additional significant advantage in the treatment of patients, improving quality of life and reducing the severity of symptoms characteristic of FBD.

1.6. Fixed-dose combination Mebeverine + Simethicone

[redacted]

Fixed-dose combination was developed by [redacted] in one dosage:

- Mebeverine + Simethicone, film-coated tablets, 135 mg + 80 mg

1.6.1. Indications and dosage

Fixed-dose combination Mebeverine + Simethicone is indicated for the symptomatic treatment of pain, spasms dysfunction and abdomen discomfort associated with functional bowel diseases. Symptoms may include abdominal pain, cramps, bloating and flatulence, changes in stool frequency (diarrhea, constipation, or alternating diarrhea/constipation) and consistency.

Fixed-dose combination will be administered as 1 tablet 3 times per day before meal. The tablet of fixed-dose combination Mebeverine + Simethicone should be taken with water.

1.6.2. Contraindications

It should also be noted that, according to the instruction for use for individual drugs, mebeverine intake in a dose of 135 mg is contraindicated for children under 18 years of age, pregnant and lactating women, patients with hypersensitivity to any component of the drug. Simethicone is contraindicated in the presence of hypersensitivity to any component of the drug, for children under 6 years old, and in the presence of intestinal obstruction. Administration of the combination Mebeverine + Simethicone is contraindicated for children under 18 years of age, for pregnant and lactating women, in the case of hypersensitivity to any of the components of the drug, in the case of intestinal obstruction and in cases of hereditary galactose or fructose intolerance, total lactase deficiency, sucrase-isomaltose insufficiency, glucose-galactose malabsorption syndrome.

1.6.3. Reference safety information

At present the reference safety information for the FDC Mebeverine+Simethicone is based on the instructions for use for Duspatalin® (mebeverine) and Espumisan® (simethicone) which are presented in the Appendix 1, and also is described in the Investigator Brochure for the FDC Mebeverine+Simethicone.

2. STUDY AIMS

2.1. Primary objectives

- To assess the efficacy of Mebeverine+Simethicone fixed-dose combination versus Duspatalin® (mebeverin) and Espumisan® (simethicone) based on the change of

abdominal pain and bloating/flatulence intensity, assessed with NRS-11 scales after 4 weeks of treatment in patients with functional bowel disorders with abdominal pain and bloating/flatulence

2.2. Secondary objectives:

To evaluate the following efficacy and safety parameters of Mebeverine+Simethicone fixed-dose combination versus Duspatalin® (mebeverin) and versus Espumisan® (simethicone) in patients with functional bowel disorders with abdominal pain and excess gas formation (bloating/flatulence), including analysis in subgroups (patients with IBS and other functional bowel diseases, patients with constipation, diarrhea, both constipation and diarrhea, neither of them):

- Change from baseline of NRS-11 pain intensity after 4 weeks of treatment
- Proportion of patients with the NRS-11 pain intensity reduction of ≥30% versus baseline during at least 50% of treatment weeks over treatment period
- Proportion of patients with the NRS-11 pain intensity reduction of ≥ 50% versus baseline during at least 50% of treatment weeks over treatment period.
- Proportion of patients with the abdominal pain assessed in the Patient Dairy completely resolved during at least 50% of treatment weeks over treatment period (NRS-11 0 assessment).
- Change from baseline of NRS-11 bloating/flatulence intensity after 4 weeks of treatment
- Proportion of patients with the NRS-11 bloating/flatulence intensity reduction of ≥30% versus baseline during at least 50% of treatment weeks over treatment period.
- Proportion of patients with the NRS-11 bloating/flatulence intensity reduction of ≥ 50% versus baseline during at least 50% of treatment weeks over treatment period.
- Proportion of patients with the bloating/flatulence assessed in the Patient Dairy completely resolved during at least 50% of treatment weeks over treatment period (NRS-11 0 assessment).
- For patients with constipation: proportion of patients with any increase in number of CSBM per week versus baseline during at least 50% of treatment weeks.
- For patients with diarrhea : proportion of patients with any decrease in the number of days per week with at least one stool consistency of Type 6 or Type 7 BSS versus baseline during at least 50% of treatment weeks.
- Change in number of days per week during study treatment period when drotaverine was taken.
- Change in quality of life evaluation using IBSQOL questionnaire versus baseline.
- The incidence and severity of adverse events (AE) and serious adverse events (SAE), physical examination, vital signs and lab results.

3. STUDY DESIGN

3.1. Overall study design

This study is an open-label randomized comparative clinical phase III study. The purpose of this study is to assess efficacy and safety of Mebeverine+Simethicone fixed-dose combination versus Duspatalin® (mebeverine) and versus Espumisan® (simethicone) after 4 weeks of treatment in patients with functional bowel disorders with abdominal pain and excess gas

formation (bloating/flatulence).

The study will be conducted at approximately 45 sites in Russia.

Clinical study will include three periods: Screening and Run-in period (1 week), study treatment period (4 weeks), and follow-up period (1 week).

3.2. Screening and run-in period

3.2.1. Visit 1 (Week -1, Day -7, for colonoscopy patients Week -3, Day -21)

After signing the Patient Information Leaflet and the Informed Consent Form, screening procedures will be performed, including collection of demographic data and medical history, physical examination, height and body weight measurements, BMI determination, vital signs assessment, sampling of biological material for hematology and biochemistry blood tests, urinalysis, test for fecal calprotectin. For patients older than 50**Error! Bookmark not defined.** years old who have not had a colonoscopy conclusion in the last 12 months prior to screening which confirms the absence of significant pathological changes, this procedure will be performed as part of the screening examination. Screening period will be prolonged for 2 more weeks (up to 3 weeks) for these patients. Colonoscopy should be performed not later than 10 days before the randomization visit. Assessment of abdominal pain and bloating/flatulence intensities will be performed using an 11-point Numeric Rating Scale (NRS-11). An ECG and urine pregnancy test for women of childbearing potential will be performed. The drotaverin intake drotaverin intake not more than 80 mg 1 – 3 times a day during one day after pain episode will be allowed for intensive abdominal pain during the study; No-spa® will be recommended to the patients for this purpose. Other drugs for abdominal pain and bloating/flatulence treatment will be prohibited. Any changes in diet and probiotic therapy (including drug and dose regimen changes) will be also prohibited.

Patients will be given Patient Diaries for daily self-assessment of abdominal pain, bloating/flatulence severity with NRS-11 (the most severe episode during last 24 hours), study drug and drotaverin intake, stool frequency and consistency with Bristol Stool Chart (BSC). Women with childbearing potential will register menstrual bleeding days.

At the end of the Screening and Run-in period, patients will be invited to the center to assess the abdominal pain and bloating/flatulence intensities and confirm compliance with the inclusion/exclusion criteria. The baseline abdominal pain and bloating/flatulence intensity for the inclusion/exclusion criteria assessment will be determined as average daily NRS-11 abdominal pain and bloating/flatulence score during last week of screening period (7 days before randomization).

3.3. Study treatment period

3.3.1. Visit 2, Randomization (Week 0, Day 1)

On Visit 2 (Week 0, Day 1) patients who meets all inclusion/exclusion criteria, will be randomized into one of the three groups at a 1:1:1 ratio. Vital signs, body weight, AEs and concomitant medication will be evaluated. Patients will assess their quality of life by completing IBSQOL.

Group	Study product	Number of patients
1	Mebeverine+Simethicone, 135 mg+80 mg, three times a day	155
2	Duspatalin® 135 mg three times a day	155
3	Espumisan®, 80 mg (2 capsules 40 mg) three times a day	155

The study will be open, with no treatment blinding.

3.3.2. Telephone contact 1 (Week 2, Day 15)

Throughout the study, patients will keep diaries for daily recordings of the abdominal pain and bloating/flatulence intensities on the NRS scale (the most intensive episode during last 24 hours), study drug and drotaverin intake; patients will also evaluate the frequency and consistency of stools, women with childbearing potential will register menstrual bleeding days.

During TC the Investigator will ask patients about possible AEs/SAEs, correctness of Patient Diary completion and study drug intake.

3.3.3. Visit 3, End of study treatment (Week 4, Day 29)

Duration of study treatment is 4 weeks.

On Visit 3 (Week 4, Day 29) the abdominal pain and bloating/flatulence intensities registration according to the Patient Diary will be checked by investigator, as well as the frequency and consistency of stool, drotaverin intake, and the adverse events and concomitant medications. Physical examination, vital signs, and body weight will be assessed, blood and urine for haematology and biochemistry tests and urinalysis will be sampled. Patients will assess their quality of life by completing IBSQOL. At this visit study treatment will be completed and patients will receive recommendations for further treatment of abdominal functional disorder.

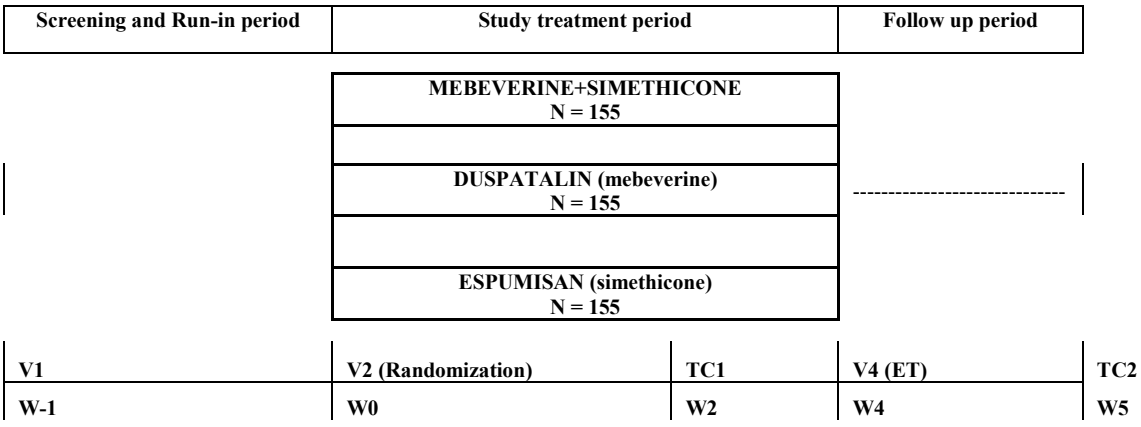
3.4. Follow up period

3.4.1. Telephone contact 2 (Week 5, Day 36)

At Week 5, Day 36 the TC will be performed to assess the adverse events and concomitant medication.

Clinical study design is presented on Figure 1

Figure 1. Clinical study MESI3001design



Abbreviations: ET – end of treatment, V – Visit, TC – telephone contact, W – Week

Table 1 MESI3001 study chart

Periods	**Screening and run-in period**	**Treatment period**			**Follow up**	**ED**
Visits (V)	**V1**	**V2**	**TC1**	**V3 (ET)**	**TC2**	
Week	***W-1[1]***	***W0***	***W2***	***W4***	***W5***	
Day	***Day -7***	***Day 1***	***Day 15***	***Day 29***	***Day 36***	
Visit window	***-21…-7 days***		***±1 day***	***±1 day***	***+1 day***	
Informed Consent Form, patient registration	X					
Demography, medical history	X					
Weight, Height (screening only), BMI	X	X		X		X
Physical examination	X			X		X
Vital signs	X	X		X		X
Hematology	X			X		X
Biochemistry	X			X		X
Pregnancy test[2]	X					
Urinalysis	X			X		X
Tests for HIV, hepatitis B and C	X					
Feces analysis for fecal calprotectin	X					
Colonoscopy [3]	X					
ECG	X					
Randomization		X				
Abdominal pain intensity on the NRS-11 scale[4]	X	X	X	X		X
Flatulence intensity on the NRS-11 scale[5]	X	X	X	X		X
Stool frequency	X	X	X	X		X
Bristol stool scale	X	X	X	X		X
Patient diary distribution	X	X				
Patient diary assessment[6]		X	X	X		X
Evaluate the quality of life (IBSQOL questionnaire)		X		X		X
Study drug dispense		X				
Study drug accountability and compliance assessment				X		X
Study drug return				X		
Adverse events	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X

ET – End of treatment, ED – Early discontinuation, TC – Telephone contact, D – day, V – Visit

1 Week -3 for patients undergo colonoscopy
2 For women of child-bearing potential (including those without history of surgical sterilization and women with <2 years post-menopause)
3 For patients older than 50 years old, in case it was not done during last 12 months. Colonoscopy will be performed not later than 10 days before randomization.
4 Daily recording of the worst pain episode for the last 24 hours
5 Daily recording of the worst bloating/flatulence episode for the last 24 hours
6 Including NRS-11, Bristol stool scale, stool frequency, drotaverine and concomitant medications intake assessment and menstrual bleeding days)

3.5. Study design rationale

This is a multicenter randomized open-label comparative clinical phase III study in parallel groups for assessment of efficacy and safety of Mebeverine+Simethicone fixed-dose combination versus Duspatalin® (mebeverine) and versus Espumisan® (simethicone) in patients with functional bowel disorders with abdominal pain and excess gas formation.

3.5.1. Assessment of superior efficacy of Mebeverine+Simethicone fixed-dose combination versus any of it's mono-component.

Investigated fixed-dose combination Mebeverine+Simethicone include well known drugs with favorable safety profile; these drugs have long history of successful use in clinical practice.

The bioequivalence of the FDC Mebeverine+Simethicone and Duspatalin® was confirmed in phase I clinical study.

In line with EEU Guideline on fixed dose combinations preclinical and clinical development the randomized controlled clinical study in three groups in purpose to evaluate the superioriority of efficacy and acceptability of safety profile of the FDC Mebeverine+Simethicone versus Duspatalin® (mebeverine) and versus Espumisan® (simethicone) is planned.

According to EMA Guidelines for development of pain medicines,[47] visual analogue scales (VAS), numeric rating scales (NRS) and verbal rating scales (VRS) are used to assess pain in clinical studies. To confirm the efficacy of investigational product over time as a primary endpoint, it is recommended to use mean pain intensity differences from baseline (PID). Moreover, it is indicated that for long-term studies it is recommended to use as a primary endpoint a parameter such as the average pain intensity per week in a daily measurement compared to the baseline value. This Guidelines also recommend the use of Sum of Pain Intensity Differences (SPID) and its associated area under the pain intensity-time curve in most cases, but this parameter is intended to assess the effect over time of classic analgesics, after a single dose of anaesthetic. In the case of functional bowel disorders, this parameter does not seem applicable, as the pain is wave-like and may not occur every day. None of the components of the fixed combination of Mebeverine+Simethicone is a classic analgesic.

For the self assessment of bloating/flatulence intensity by patient the numeric rating scale (NRS-11) will also be used. Such self assessment of bloating/flatulence intensity is being performed in clinical studies in patients with FBD.[46]

It is assumed that comcomitant use of mebeverine and simethicone as a fixed dose combination will possibly lead to potentiation of their effects. As the assessed symptoms (abdominal pain and bloating/flatulence) are interrelated and sensation of their intensity may be assessed variously by different patients, it is reasonably to use co primary end point –change of sum of NRS-11 abdominal pain and bloating/flatulence intensity scores. Such approach is widely used in clinical studies in patients with functional bowel disorders. For example the IBS symptom severity scale (IBSS-SSS), which is the sum scores of 5 visual analogue scales for 5 main IBS symptoms, is used for the assessment of the efficacy of drugs with pathogenic mechanism of action.[48]

Thus, according to the EMA's Guidelines for development of pain medicines[47] (2016) and Guidelines of EAEU for clinical and preclinical development of combined medicines, [49] and aslo in line with the previous clinical studies experience in patients with functional bowel disorders (FBD), the design and methods of assessment were chosen to study the efficacy and safety of Mebeverine+Simethicone fixed combination.

3.5.2. Study treatment duration and dosage regimen

To develop a fixed-dose combination, standard doses of Mebeverine and Simethicone studied in clinical trials and long used in clinical practice as per the Duspatalin® and Espumisan® prescribing information were used.

FDC Mebeverin+Simethicone is designed for symptomatic treatment of abdominal pain and bloating in patients with FBD. The FDC is used in this patient population for the purpose of symptoms relief, but not for the resolution of the main cause of the disease.

To improve the quality of life in patients with FBD it is necessary to decrease rapidly the main symptoms: abdominal pain and bloating. FDC Mebeverin+Simethicone is designed for relief of such symptoms as abdominal pain and bloating, and the quick therapeutic response is expected. The expectation of quick therapeutic response is based on the published data from clinical studies, which demonstrated that treatment with antispasmodic and simethicone in patients with IBS (in line with diagnostic criteria established before Rome IV classification, that is why this population includes not only patients with IBS but also patients with other functional bowel disorders as per Rome IV criteria) leads to the pain and bloating decrease as early as after 4 weeks of therapy.[50,51,52,53,54,55,56,57,58,59,60,61] These data are in consistence with published recommendations on clinical studies design in patients with functional GIT disorders, in which the minimal duration of study treatment for symptomatic drugs was defined as 4 weeks (but not for the drugs developed for the chronic long-term basic therapy.[62] As the FDC Mebeverin+Simethicone was developed as symptomatic drug for patients with functional GIT disorders, the 4 weeks duration therapy was chosen for the planned study. Abdominal pain and bloating relief with the FDC Mebeverin+Simethicone treatment are expected at the end of 4 weeks period. The long-term study treatment with the FDC in comparison with mebeverin monotherapy and simethicone monotherapy seems to be not rational as the therapeutic effect of each mono-component occurs after first dose already, and treatment with simethicone and mebeverin as mono-components does not allow to control symptoms of the disease sufficiently and increases the risk for postponed abdominal pain and bloating relief.

As a rescue therapy intake of droteverin in a dose of 80 mg 1-3 times a day will be allowed to stop intensive pain episode during one day after the episode. The drug effect is short, persists for 8-10 hours; the drug is completely eliminated within 72 hours and will not affect the assessment of the efficacy of study product.

3.5.3. Efficacy and safety assessment parameters

Mebeverine and Simethicone affect two different key symptoms in patients with functional diseases of the colon: pain and bloating/flatulence. As the assessed symptoms are interrelated it was decided to use a coprimary end point (change of sum of NRS-11 every symptom intensity scores) as such approach is widely used in clinical studies in patients with FBD.[48]

The study will also evaluate secondary efficacy parameters based on a numerical rating scale (NRS-11): the rate and degree of clinical symptoms relief, changes in the quality of life during treatment, need for additional antispasmodics.

Although the previous studies and the long-term use of Mebeverine and Simethicone in clinical practice demonstrated a favorable safety profile comparable to that of placebo, the study provides a detailed assessment of the product safety, including physical examination, vital signs, laboratory blood tests and urinalysis (hematology and clinical chemistry, urinalysis) before and after the study treatment. Women of child-bearing potential will undergo a urine pregnancy strip test before the study.

3.6. Previous experience

3.6.1. Mebeverine

3.6.1.1. Mechanism of action of mebeverine

Mebeverine has a pronounced direct spasmolytic effect on the smooth muscle cells of the gastrointestinal tract, reducing spasm without affecting the normal intestinal motility. The exact mechanism of action of mebeverine is not clear. However previous studies showed that mebeverine reduces the permeability of ion channels, inhibits the reuptake of norepinephrine, has a local analgesic effect and changes the absorption of water in the gastrointestinal tract[63, 64, 65, 66, 67, 68, 69, 70, 71,].

The direct antispasmodic effect of mebeverine on smooth muscle cells is not associated with impairment of gastrointestinal motility. The contraction of smooth muscle cells is mediated by an increase in intracellular calcium levels. Antispasmodics that act on smooth muscle cells inhibit the intracellular calcium currents in smooth muscle cells, blocking sodium channels. According to this mechanism of action, mebeverine reduces spasm and affects motility and sensitivity of the intestines[72]. Since the effect of mebeverine is not mediated by the autonomic nervous system, this drug does not have typical anticholinergic side effects [73].

3.6.1.2. Clinical studies to evaluate efficacy of mebeverine

Efficacy and safety of mebeverine used for symptomatic treatment of abdominal pain and spasms, dysfunction and discomfort in the intestine associated with FBD, as well as for treatment of secondary spasms in the gastrointestinal tract that occur in patients with chronic diseases were confirmed in many controlled clinical studies on more than 1500 patients.

Many patients noted a significant improvement in well-being during the treatment with mebeverine; this is clinically significant benefit for patients with pain. Noteworthy, the main data on the clinical efficacy of mebeverine was obtained in studies conducted in the 1970s and 1980s, when the requirements for the design of clinical studies differed significantly from modern requirements and diagnostic criteria for IBD were wider and included symptoms which were classified within other FBDs in the last version of Rome criteria.

Since 1965, in 9 placebo-controlled clinical studies the efficacy of mebeverine hydrochloride for treatment of IBS (in line with diagnostic criteria before Rome IV) was evaluated. In 4 of these studies [74, 75, 76, 77] 100 mg tablets were used: in 1 study[75] - in combination with 125 mg tablets), in 2 studies[78, 79] - 50 mg tablets, and in other 2 studies – 135 mg tablets[53, 80]. In 1 study[52] the dose and formulation was not reported. In these studies, mebeverine was administered orally; total daily dose was up to 810 mg.

In 8 of 9 these studies, the results were in favor of mebeverine; in 1 study[77] no significant differences between mebeverine and placebo were noted.

One placebo-controlled study was conducted with prolonged release capsules 200 mg [81]. In this 12-weeks study, 216 patients received treatment and ITT population was analyzed (106 patients received mebeverine, and 110 - placebo).

In 1994 г. Poynard et al[82] preformed meta-analysis of randomized controlled studies with antispasmodics for treatment of IBS (in line with diagnostic criteria before Rome IV), including mebeverine. This meta-analysis was performed by independent group and was not supported by pharmaceutical companies, federal agencies or any grants. Strict criteria were defined for inclusion to this meta-analysis: 1) the results are published as scientific articles; 2) randomization clearly described; 3) double-blind, placebo-controlled studies; 4) at least 51% patients with IBS included in the study; 5) at least 1 clinical endpoint of the following was used:

- Global assessment of symptoms by patient or physician;
- Abdominal pain;

- Constipation or
- Abdominal distension.

During the period from 1959 to 1992, a total of 148 clinical studies were found; 26 of them met inclusion criteria for this meta-analysis (total 8 drugs). Mebeverine was evaluated in 5 of these 26 studies[74, 76, 77, 80,83].

Mebeverine significantly improved global symptom score as compared to placebo (odds ratio 2.04, $p<0.01$). Mebeverine reduced abdominal pain; this result was not statistically significant due to relatively low number of mebeverine studies included to meta-analysis. Beneficial effect of mebeverine was similar to that for other antispasmodics.

After this meta-analysis of Poynard et al in 1994 other meta-analyses were published. These studies analyzed placebo-controlled studies in which antispasmodics (including mebeverine) that induce smooth muscle relaxation were used for treatment of IBS. In general, mebeverine showed good clinical efficacy and tolerability in patients with IBS.

A total of 13 studies were conducted for evaluation of efficacy of standard tablets/capsules with active comparator. In 7 studies, 135 mg tablets were used, in 5 studies - 100 mg tablets, and in 1 study - 135 mg and 200 mg tablets. Treatment duration was from10 days to 12 weeks. In 7 studies, there were no statistically significant differences between the treatment groups; in 4 studies, the comparator was more effective, and in 2 studies mebeverine was more effective than active comparator[55,57].

In addition, efficacy of mebeverine in film-coated tablets was investigated in 8 non-controlled studies. In these studies, more than 1500 patients received therapy with mebeverine hydrochloride. Duration of the study treatment was from 15 days to 12 months. Different methods were used for assessment of efficacy; the results ranged 41% (no complaints) to 87% (general improvement)[84,85,86,87,88,89,90,91]). In 5 studies, mebeverine was administered in 100 mg tablets, in 2 studies - 135 mg tablets; in the study of Boisson et al, 1987[91] there is no data on formulation. Daiuly dose of mebeverine hydrochloride in these studies ranged from 300 mg/day to 600 mg/day.

Besides these 8 studies, in one study [92], only safety and tolerability were evaluated, without assessment of efficacy. In this study, mebeverine was administered to 7 healthy volunteers at 800 mg/dose for 4 weeks. Mebeverine was well tolerated; any abnormalities in hematology, biochemistry, ECG and electroencephalogram (EEG) was not observed.

In actively controlled studies, mebeverine, as well as different comparators, improved the symptoms, as compared to the baseline level. In most of the studies, improvements were similar in mebeverine and control groups. Open-label studies showed therapeutic efficacy of mebeverine assessed as clinical improvement from the baseline.

Ilchenko investigated the efficacy of mebeverine in treatment of functional disorder of Oddi's sphincter in 20 patients with gallstone disease who underwent surgical intervention.[93] The patients have complaints on pain in right hypochondrium, transient bitter taste in the mouth and nausea; therefore, the patients initially had pain and dyspepsia. All patients received mebeverine as monotherapy at 200 mg 2 times per day during 14 days. Clinical manifestations of disorder of Oddi's sphincter were assessed. In addition, the changes in biochemistry results and ultrasound examination were evaluated. Analysis of the results showed that treatment with mebeverine leads to a reduction in severity of pain or its complete disappearance, as well as a decrease in the manifestations of dyspepsia. Normalization of the function of Oddi's sphincter during the treatment with mebeverine was confirmed during an ultrasound study by narrowing of the common bile duct.

Another study conducted by Lipnitsky et al in 2008[93] showed that the use of mebeverine in a dose of 200 mg 2 times a day was effective in the long-term treatment and prevention of postcholecystectomy syndrome. The study assessed the clinical manifestations and quality of life, as well as the composition of the microflora of the duodenal and large intestine in patients with calculous cholecystitis who were subjected to cholecystectomy. The study included 40 patients, of whom 20 were patients with acute calculous cholecystitis and 20 patients with chronic calculous

cholecystitis. All patients complained of pain of moderate intensity in the right hypochondrium that occurred after eating, or manifestations of dyspeptic syndrome (60% of patients), and bowel disorders (40% of patients). Half of patients received standard therapy, the other half received mebeverine in addition to standard therapy at a dose of 200 mg 2 times a day for 7 days before surgery and 3 months after surgery. Analysis of the research results showed that mebeverine is effective in the treatment and prevention of postcholecystectomy syndrome and dyspepsia in 100% and 95% of cases, respectively. Normalization of motility and evacuation function of the intestine were noted in 85% of patients.

Mayev and co-authors in 2007[93] studied the efficacy of mebeverine in the treatment of patients with chronic non-calculous cholecystitis and primary functional disorders of the biliary tract. Patients (n = 191) were divided into three groups depending on the diagnosis: Group 1 - patients with non-calculous cholecystitis and functional disorders of the biliary tract; Group 2 - patients with a spastic primary functional disorder of the biliary tract; Group 3 - patients with primary gallbladder dysfunction (hypokinesia) without chronic non-calculous cholecystitis.

Efficacy was assessed by the change in pain and manifestations of dyspeptic syndrome according to a questionnaire filled out by patients. The use of mebeverine in the complex therapy of patients with chronic non-calculosis cholecystitis and primary functional disorders of the biliary tract resulted in a more rapid relief of abdominal pain than standard therapy. In almost all studies of mebeverine, an improvement in general well-being was observed, as well as a decrease in the severity of symptoms, especially abdominal pain.

It is important to stress that all of the above studies of the efficacy and safety of mebeverine were carried out in patients who were diagnosed with IBS in accordance with earlier versions of FBD diagnostic criteria and they certainly included patients who may be diagnosed with functional diarrhea, functional constipation and functional abdominal bloating by the current criteria of the fourth revision.

After the approval of the fourth edition of the Rome diagnostic criteria, some patients for whom mebeverine has been shown to be effective in clinical studies, may theoretically be left without symptomatic therapy capable of significantly improving their well-being. In practice, patients with functional diarrhea and functional constipation, in addition to stool regulators, receive both spasmolytics and simethicone that can improve their general symptoms (primarily pain and bloating). Therefore, it is reasonable to conduct a clinical study of a fixed combination of Mebeverine+Simethicone involving patient population with functional bowel disorders, suffering from abdominal pain and bloating, but already divided into groups of functional bowel disorders, according to Rome Criteria IV.

3.6.1.3. Safety of mebeverine

Mebeverine, when properly administered, has a favorable safety profile. The adverse events that occurred during the use of mebeverine in clinical trials do not differ in frequency and nature from those in placebo groups. The most frequent adverse events include headache, nausea and other gastrointestinal symptoms of mild or moderate severity. Allergic reactions were mainly represented by skin reactions. Significant risks associated with the use of mebeverine in clinical practice other than allergic reactions were not identified during 50 years (Instruction for medical use for Duspatalin®, Appendix 1)

In 2012, pooled analysis of adverse events was performed for clinical studies conducted in the period from 1968 to 2011[94]. In the course of these studies, 1354 patients received mebeverine (353 patients received mebeverine in studies with placebo control, 286 patients received placebo). In these studies, 121 healthy volunteers received mebeverine, and 11 healthy volunteers received placebo[94]

During the course of the study, no deaths have been reported. Serious adverse events (SAE) were reported in 7 patients who received mebeverine and 1 patient who received placebo; all

observed SAEs were considered by the Investigator as not related to the study drug. Similar proportions (%) of patients discontinued the study drug because of the occurrence of one or more AEs: 4.3% (n = 58) in mebeverine group and 3.5% (n = 10) in placebo group. [94]

A total of 474 (35.0%) AEs were reported in 1354 study subjects who received mebeverine; 61 of these AEs were assessed as related to the study drug (4.5%), while in the placebo group, AEs were recorded in 122 of 286 patients (42.7% / 15%); 43 of them were related to the study drug[94]

In the largest controlled pivotal study Meb003[95] mebeverine was administered in 200 mg capsules with prolonged release and film-coated tablets 135 mg. The information on the most frequent adverse events that were reported in this study is presented in Table 2 by preferred terms

Table 2 The most frequent (> 3%) adverse events (safety population, study MEB003)

Adverse event	**Mebeverine hydrochloride, 200 mg capsules, 2 times per day (N=106)**	**Mebeverine hydrochloride, 135 mg tablets, 3 times per day (N=107)**
Abdominal pain	16 (15%)	10 (9%)
Diarrhea	12 (11%)	4 (4%)
Headache	10 (9%)	7 (7%)
Vomiting	7 (7%)	2 (2%)
Rhinitis	6 (6%)	2 (2%)
Pain	6 (6%)	6 (6%)
Nausea	6 (6%)	9 (8%)
Constipation	6 (6%)	3 (3%)
Pharyngitis	4 (4%)	3 (3%)
Acne	3 (3%)	0 (0%)
Depression	3 (3%)	1 (1%)
Flatulence	3 (3%)	6 (6%)
Dyspepsia	3 (3%)	5 (5%)
Flu-like syndrome	3 (3%)	2 (2%)
Migraine	3 (3%)	3 (3%)
Bloating	3 (3%)	0 (0%)
Pain in the neck	1 (1%)	3 (3%)
Chest pain	1 (1%)	4 (4%)
Backache	0 (0%)	3 (3%)

The data provided in the table suggest that many of the AEs most frequently recorded in this study were associated with the gastrointestinal tract system and in fact were the usual symptoms of IBS.

The occurrence of gastrointestinal abnormalities (mainly abdominal pain, constipation, diarrhea and nausea) can be partially explained by the underlying disease, as well as by pharmacological action of mebeverine.

The results of clinical safety studies showed that the safety profile of mebeverine is comparable to that of placebo; therefore, mebeverine can be considered to have a favorable safety and tolerability profile for symptomatic treatment of IBS when used in accordance with recommendations.

For 50 years of use of mebeverine in clinical practice, any significant risks, except allergic reactions, were not identified. These allergic reactions were mainly limited to the skin: urticaria, angioedema, facial edema, exanthema, and hypersensitivity, including anaphylactic reactions. The frequency of allergic reactions that occur after treatment with mebeverine is impossible to estimate, since they have not been registered in clinical studies. Allergic reactions can appear after treatment with almost every drug and, therefore, are may not considered an important risk.

The most frequent adverse drug reactions include Gastrointestinal Disorders (26.3%), Skin and Subcutaneous Tissue Disorders (22.0%), General Disorders and Administration Site Conditions (20.2%), and also Nervous System Disorders (16.1%) (Meb003)[95].

Often recorded gastrointestinal reactions, as well as numerous symptoms from other system organ classes, are considered as not related to mebeverine; these reactions were explained by the underlying disease. In IBS, pain syndromes of other origin besides the gastrointestinal tract, such as chest and back pain, are also observed. Psychiatric and neurological symptoms were also frequently observed in patients with IBS.

Given the estimated cumulative effects of mebeverine in more than 233 million patients, the overall frequency of reported adverse events is very low.

Thus, mebeverine, when properly administered, has a favorable safety profile.

3.6.2. Simethicone

Simethicone is an oral anti-foaming agent with a long history of use in clinical practice and diagnostics [96, 97, 98, 99, 100].

3.6.2.1. Mechanism of action of Simethicone

Simethicone reduces the amount of gas in the intestine. Simethicone has surface activity and is able to reduce the surface tension at the liquid / gas interface. This leads to fusion of gas bubbles and destruction of the foam. Therefore, released gas can be absorbed or removed naturally due to intestinal motility[101] (Instruction for medical use for Espumisan®, Appendix 1).

As suggested by Debray and co-workers over 40 years ago, Simethicone acts as a local barrier that protects the mucosa from irritants, such as hydrochloric acid, acetylsalicylic acid or bile salts [102, 103]. Simethicone probably interacts with endogenous surface active substances, protecting the intestinal mucosa. The effect of Simethicone is mediated by its action in the intestinal lumen, since it is not absorbed and does not have a toxic effect[104].

3.6.2.2. Clinical efficacy of Simethicone

Some modern randomized prospective studies have shown the efficacy of Simethicone in patients with traveler's diarrhea [105] and functional dyspepsia [106, 107, 108, 109]. In addition, the efficacy of the drug in preparation for diagnostic procedures is well known [110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122].

According to the results of randomized, placebo-controlled studies, treatment with probiotics and Simethicone reduces the severity of flatulence and abdominal discomfort in patients with IBS to whom the diagnosis was made in line with previous versions of Rome criteria [123].

Anti-foaming effect is the main mechanism of action of Simethicone. As a result, patients who received Simethicone prior to the diagnostic procedure showed improved quality of visualization

during ultrasound examination of the gastrointestinal tract[110, 111,112] and endoscopy [113, 114, 115, 116] because Simethicone reduces bubbles and foam in the intestinal lumen. Addition of Simethicone in intestinal lavage or to laxatives also reduces the foam content in the colon and residual feces; this was confirmed by colonoscopy[117, 118, 119, 120, 121] and by ultrasound examination of rectum[122].

A literature search revealed 13 comparative studies and 6 double-blind studies that meet modern requirements for clinical studies. More than 3,000 patients who received Simethicone in various formulations were included in these clinical studies of therapeutic efficacy of Simethicone.

According to clinical studies, the most relevant to modern requirements, the effect of Simethicone in the treatment of patients with functional dyspepsia significantly exceeds the effect of placebo, as well as the effect of cisapride, which was used as a comparator drug[106, 107, 108, 109].

Both functional dyspepsia and IBS are characterized by abdominal pain; however, in patients with IBS, there is also abnormal defecation pattern. Simethicone is usually prescribed to patients with IBS to reduce the feeling of bloating and flatulence[124], but there were no adequately conducted prospective comparative studies.

When analyzing the published literature data, only two studies were identified, in which 80 patients who received Simethicone and 54 patients who received placebo were included. Oswald et al. in 1961 published the results of a placebo controlled Simethicone study at a dose of 50 mg (tablets); the results showed that Simethicone was more effective than the comparators.[125] In 1974, Weiss[126] published a review and results of Simethicone study in 30 patients, also revealing the advantage of Simethicone. In more recent studies, the results of which are discussed below, in the section "Clinical studies of Simethicone as part of combination therapy," the efficacy and safety of Simethicone were evaluated in combination with other drugs in patients with IBS.

Urgesi R et al in 2014 published the results of a double-blind, randomized placebo -controlled study, which confirmed the efficacy of the combined use of probiotic and Simethicone. Patients were randomized to receive combination therapy with probiotic and Simethicone (n = 26) or placebo (n = 26); the duration of treatment was 4 weeks. Efficacy was evaluated at 2 weeks and 4 weeks from the start of therapy.[123].

Combination therapy with probiotics and Simethicone led to improvement in the main IBS symptoms (in line with diagnostic criteria before Rome IV), such as flatulence, abdominal discomfort and altered defecation pattern. Noteworthy, significant difference was found between the test group and placebo in the degree of reduction of flatulence and abdominal discomfort. The severity of abdominal pain statistically significantly decreased in the combination therapy group as compared to the baseline. More powerful clinical studies are need to identify the differences between the treatment groups in the degree of abdominal pain reduction.

Many patients with acute diarrhea, regardless of the cause, also complain on increased gas formation, cramps, abdominal pain, bloating, abdominal distension, flatulence, nausea and vomiting. In a double-blind placebo-controlled study, Kaplan et al compared the efficacy and safety of loperamide hydrochloride and Simethicone with Simethicone monotherapy, loperamide monotherapy and placebo in patients with acute diarrhea with abdominal discomfort caused by gas formation.[105] The duration of therapy was 48 hours. The study included 493 patients. 124 patients were randomized to the combination therapy group (loperamide 2 mg and Simethicone 125 mg), 123 patients were randomized loperamide 2 mg, 123 patients received Simethicone 125 mg, and 123 patients received placebo. After randomization, these patients received 2 tablets of the study drug, then patients took one tablet of the prescribed drug after each episode of liquid stool, up to 4 tablets for 24 hours.

The primary end points were the time until the last liquid stool and the time until resolution of abdominal discomfort disappeared. An analysis of the results revealed that patients who received the combined treatment with loperamide and Simethicone have significantly ($P < 0.001$) shorter time to the last liquid stool and abdominal discomfort disappears more quickly in comparison with both monotherapy group and the placebo group. Simethicone in monotherapy was significantly ($P < 0.01$) more effective than placebo in alleviating general symptoms, alleviating diarrhea,

abdominal discomfort, reducing the number of bowel movements with a liquid stool over a period of 36-48 hours.

In 2007, Hanauer et al published the results of a multicenter, double-blind study in patients with acute diarrhea[127]. The patients were randomized to receive two tablets, each contained either loperamide 2 mg and Simethicone 125 mg (n = 121), or loperamide 2 mg (n = 120), or Simethicone 125 mg (n = 123), or placebo (n = 121). The duration of therapy was 48 hours. As well, as in the study of Kaplan[105], the median time to the last liquid stool for group that received the combination therapy was significantly less than for loperamide, Simethicone and placebo groups (7.6 h, 11.5 h, 26.0 h and 29.4 h, respectively, p <0.0232). The time to complete resolution of discomfort was lower in the combination therapy group as compared to the monotherapy and placebo groups (all p = 0.0001).

Thus, co-administration of Simethicone and loperamide led to a more rapid resolution of acute nonspecific diarrhea and associated discomfort (abdominal pain, spasms, flatulence) in comparison with each drug as monotherapy or placebo; superiority of Simethicone monotherapy over placebo was also demonstrated[105].

Tolerability of the study treatment was good; none of the patients required rescue therapy.

Thus, a number of modern randomized prospective studies have shown efficacy of Simethicone in patients with traveler's diarrhea, functional dyspepsia. In additional, the efficacy of treatment with Simethicone during preparation to diagnostic procedures is well known.

According to randomized placebo controlled studies, therapy with a probiotic with Simethicone reduces the severity of flatulence and abdominal discomfort in patients with IBS (in line with diagnostic criteria before Rome IV).

3.6.2.3. Safety of Simethicone

Simethicone is usually well tolerated and has a favorable safety profile. No causal association of Simethicone with adverse events was found in published clinical studies. No systematic laboratory abnormalities, as well as laboratory abnormalities associated with Simethicone, have also been identified according to published data.

In 2007, Rémy Meier and Michael Steuerwald published a review of clinical studies with Simethicone and noted that the comparison of Simethicone with placebo, cisapride, loperamide, combination of loperamide with Simethicone, in terms of incidence of adverse events, serious adverse events and early withdrawals due to adverse events was in favor of Simethicone.[40] No causal relation of Simethicone with adverse events was found in published data from clinical studies. Systematic laboratory abnormalities, as well as laboratory abnormalities associated with Simethicone, were also not detected according to published data.

According to Espumisan Instruction for use (Simethicone is the active substance), no adverse effects have been reported after treatment with this drug; some allergic reaction to the excipients drug may be expected. There is low likelihood of overdose with Simethicone. In a safety study conducted by Nair et al. In 2003, healthy volunteers received Simethicone at a dose of 30 grams per day for several days without developing adverse events and without laboratory abnormalities in biochemical parameters[104].

3.7. Combined use of antispasmodics and Simethicone

In patients with FBD, a smooth muscle spasm of the gastrointestinal tract has an important role in the development of a pain symptoms.**Error! Bookmark not defined.** Antispasmodics are included in recommendations for the treatment of IBS as first-line line for the last decades [1, 35,36]

Simethicone is not currently included in recommendations for treatment of patients with IBS due to insufficient data from clinical studies. However, the results described above suggest that addition of Simethicone to the main therapy would be effective and would bring relief to a significant proportion of patients with FBD, because almost all of these patients suffer from flatulence.

Combined treatment with antispasmodic alverine and simethicone has lead to decrease in pain/discomfort intensity in patients with IBS, [39, 128] and also has lead to improvement in quality of life. It is important to note that in one study[39] in which the majority of patients took antispasmodics, addition of simethicone to alverine resulted in additional statistically significant improvement in quality of life and reducing symptoms such as abdominal pain and bloating/flatulence.

In 2011, Wittmann et al. published the results of a double-blind, randomized placebo-controlled study of the efficacy and safety of the combined use of myotropic antispasmodic alverine and Simethicone in patients with IBS (in line with diagnostic criteria before Rome IV.[39]

In this study, the patients with IBS (according to the Rome Criteria, revision III) were randomized to receive alverine citrate in combination with Simethicone or placebo. The treatment lasted 4 weeks. The primary endpoint was abdominal pain / discomfort intensity, assessed using Visual-Analogue Scale (VAS) after 4 weeks of therapy. In addition, the number of responders in both groups was compared. The response to treatment was defined as decrease in the number of points in the assessment of pain / discomfort on the VAS scale by 50% or more after 4 weeks of treatment. In the study, 207 patients were randomized to the combination therapy group and 205 patients to the placebo group. 399 (97%) patients completed the study. The results showed that the intensity of abdominal pain / discomfort after 4 weeks of therapy was significantly lower in the combination therapy group compared to the placebo group (median 40 mm versus 50 mm in the combination therapy and placebo groups, respectively, $p = 0.047$). In addition, the response rate to the treatment was also significantly higher in the combination therapy group compared to the placebo group (46.8% compared to 34.3%, OR = 1.3; $p = 0.01$). The patients who received the combined therapy significantly improved the general medical condition in comparison with patients from the placebo group.

The results on reduction in pain/discomfort after treatment with alverine and Simethicone showed that recovery rate was equal to 8; this is slightly less than the values obtained in previous studies for smooth muscles relaxants[44] In addition, an improvement in overall well-being was noted; it was significantly more pronounced in the combination therapy group as compared to the placebo group. The effect of combination therapy on abdominal distension was not evaluated. Since there is no data on the comparative efficacy of combination therapy, alverine and Simethicone in monotherapy, it is difficult to determine which component contributes mote to observed the therapeutic effect of the combination.

Thus, the use of antispasmodic combination therapy with alverine and Simethicone was effective in reducing the pain / discomfort in patients with IBS.

Ducrotte et al conducted a long (6 months of therapy) double-blind randomized study that compared the efficacy and safety of episodic use of combination therapy with alverine and Simethicone when a pain attack occurred and the standard therapy chosen by the attending doctor for each patient[128]. Patients in the combination therapy group (n = 222) were instructed to take a capsule with a combined preparation 3 times a day before meals if a pain attack occurs and until it resolves. In the control group (n = 214), the doctor chose the tactics of treatment, it was forbidden only to prescribe the combination therapy with alverine and Simethicone.

The primary endpoint in the study was the difference between groups in the change in the number of points on the questionnaire of quality of life from the initial to the end of therapy after 6 months.

Initially, the results of assessment of quality of life on a scale were comparable in both groups. Median dosing frequency in the combination therapy group was 75% days per month during the first month, 54% days per month for 2-3 months, and 45% days per month for 4-6 months. In the standard treatment group, 93.8% patients received at least one antispasmodic.

The improvement in the quality of life after assessing by Quality of Life scale during 6 months of therapy was significantly more pronounced in the combination therapy group (13.8 versus 8.4 with a difference between 5.4 groups (95% CI: 2.3 - 8, 6; p = 0.0008. The percentage of improvement was also greater in the combined treatment group (28.5% compared to the conventional treatment group 18.6%; p = 0.04). According to the VAS score, abdominal pain decreased by 76.1% in the combination therapy group and by 59.2% in the conventional therapy group (p = 0.0001). In patients suffering from flatulence when included in the study, the severity of symptoms in the combination therapy group decreased by 76.6% compared with 57% in the standard therapy group (p <0.0001).

Thus, the occasional use of combination therapy with alverine and Simethicone led to an improvement in the quality of life of patients with IBS (in line with diagnostic criteria before Rome IV), as well as to a reduction in the severity of symptoms, such as abdominal pain and flatulence, in comparison with standard therapy. In the comparison group, the vast majority of patients were treated with antispasmodics. Thus, addition of Simethicone to antispasmodics provides significant clinical advantage, improving the quality of life and reducing the severity of symptoms typical for FBD.

3.7.1. Conclusion on the combined use of antispasmodics and Simethicone

The use of antispasmodic combination therapy with altering and Simethicone led to a decrease in pain / discomfort in patients with IBS (in line with diagnostic criteria before Rome IV), as well as to an improvement in the quality of life of patients. Noteworthy, in one of the studies. in which the vast majority of patients received antispasmodics in the control group, addition of Simethicone to altering provided statistically significant advantage in improving the quality of life and reducing the severity of symptoms such as abdominal pain and flatulence.

Thus, addition of Simethicone to antispasmodics provides a clinically significant advantage, improving the quality of life and reducing the severity of main symptoms of FBD.

3.7.2. Approved combinations of Simethicone and antispasmodics

Fixed-dose combination, Meteospasmil, which includes altering 60 mg and Simethicone 300 mg, was approved in 1990 in Europe. The same combination of drugs was approved in the Russian Federation in 2007 (Meteospasmil). Meteospasmil is indicated for the treatment of functional disorders of the gastrointestinal tract, manifested by abdominal pain, increased gas formation, belching, nausea, constipation, diarrhea, or their alternation, as well as for preparation to X-ray, ultrasound or instrumental examination of the abdominal organs.

3.8. Fixed-dose combination Mebeverine+Simethicone

Fixed-dose combination Mebeverine + Simethicone, film-coated tablets 135 mg + 80 mg, is a new drug that contains mebeverine and Simethicone in one tablet. Currently, the drug has been

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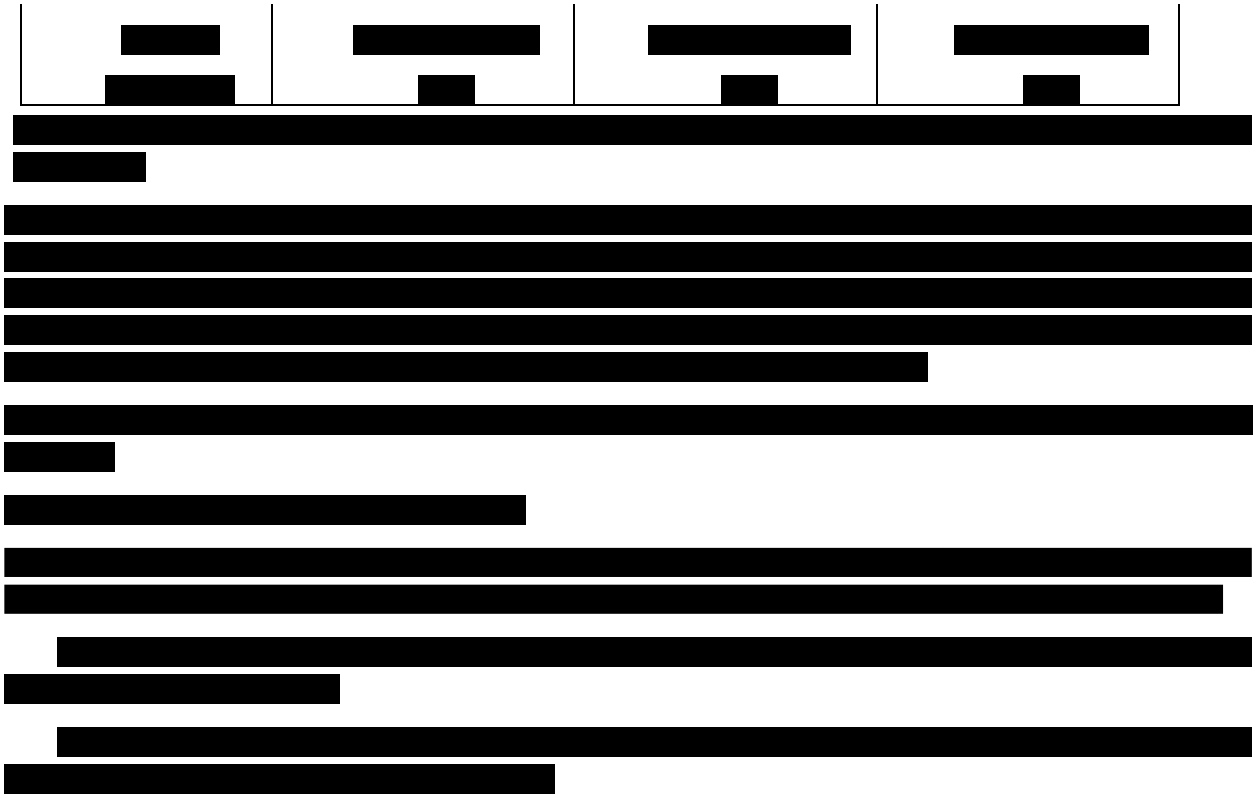


3.8.1. Risk/benefit ratio

The study is aimed at the evaluation of comparative efficacy and safety of the fixed-dose combination of Mebeverine + Simethicone film-coated tablets 135mg + 80mg versus Duspatalin® film-coated tablets 135mg and Espumisan®, 40mg capsules (2 capsules). The study will include patients with functional diseases of the colon with abdominal pain and bloating/flatulence.

Pain in patients with functional diseases of the colon is due to the spasm of intestine smooth muscles and excessive formation of gas. Spasmolytics being used for the decades are currently included into IBS treatment guideline as the first-line therapy. In accordance with the Clinical Guideline of Russian Association of Gastroenterology and Russian Association of Coloproctology on the diagnosis and treatment of irritable bowel syndrome, pain relief in IBS patients can be achieved with the use of various types of spasmolytics, i.e. blockers of M-cholinergic receptors, sodium and calcium channel blockers (Clinical Guideline of Russian Association of Gastroenterology, 2014). According to the IBS Treatment Guideline of the World Gastroenterology Association, the first-line therapy of this disease also includes spasmolytics, such as mebeverine, otilonium, hyoscine, cimetropium, pinaverium, and dicyclomine

Simethicone is not included into IBS treatment guidelines due to the absence of sufficient clinical data, although it is suggested that its addition to the basic therapy would be effective and alleviating in many patients, as far as almost all of FBD patients experience flatulence according to the data published. Many authors emphasize a strong negative effect of flatulence in the compromised well-being of FBD patients, because this symptom changes the intensity: it is the most prominent during the daytime, worsens after meal and generally abates at night[21,37,38]. Simethicone, as an antifoaming agent, helps to reduce flatulence, discomfort and abdominal pain due to the improved gas evacuation from the GI tract[39,40].

The contribution of each component will be proven in a clinical study by studying co primary endpoint that will provide data on the pharmacodynamic effects of the components, as well as by studying the relevant secondary endpoints.

The risk associated with the use of Mebeverine in clinical studies is considered low, comparable to placebo, and is mostly limited to rare anaphylactic reactions, mainly, but not exclusively, limited to the skin, such as urticaria, angioedema, facial edema, exanthema, and hypersensitivity, including anaphylactic reactions. The frequency of anaphylactic reactions due to mebeverine cannot be assessed, because no such reactions were reported in the clinical studies. Anaphylactic reactions may be caused by any drug and are not considered an important risk during its use.

Data of clinical safety studies show the comparability of safety profile of mebeverine to placebo, therefore, mebeverine can be considered to possess a favourable safety and tolerability profile for symptomatic treatment of FBD if used in accordance with the therapeutic guidelines.

The most common post-marketing adverse reactions were the gastrointestinal tract disorders (26.3%), skin and subcutaneous tissues disorders (22.0%), general disorders and injection site conditions (20.2%), as well as the nervous system disorders (16.1%).[92]

Common GIT reactions and multiple symptoms from other system and organ classes are not considered related to mebeverine and considered to be generally due to the underlying disease. IBS is often accompanied with other pain syndromes, besides gastrointestinal ones, such as back pain and chest pain. Moreover, IBS is frequently associated with psychiatric and neurological symptoms.

Therefore, if properly used, mebeverine generally demonstrates a favourable benefit-to-risk ratio.

The risk associated with the use of Simethicone is extremely low. The drug is not absorbed in the gastrointestinal tract, has a local effect, and is eliminated unchanged. In the published clinical studies data, a causal relation of adverse events to Simethicone has not been identified. According to the published data, no systemic laboratory abnormalities or laboratory abnormalities related to Simethicone have been observed.

According to the prescribing information for Espumisan® (simethicone), no adverse drug reactions have been reported; allergic reactions to the drug excepients are possible.

Risks associated with rescue medication drotaverin is also low.

The instruction on medical application for the No-spa® (drotaverin) is applied in Appendix 1.

Drotaverine is an antispasmodic drug which is a phosphodiesterase IV inhibitor, it increases the cyclic adenosine monophosphate, inactivates the kinase of light myosin chain which leads to smooth muscles relaxation. Its effect is shown within 45-60 minutes and lasts for 8-10 hours. The product will be allowed only as a rescue therapy to relief intensive pain episode in a dose of 80 mg 1 - 3 times a day during one day after the episode.

Contraindications to drotaverine intake are hypersensitivity, severe renal failure, severe hepatic failure, severe heart failure, hereditary galactose or fructose intolerance, total lactase deficiency, sucrase-isomaltose insufficiency, glucose-galactose malabsorption syndrome.

The side effects of drotaverin are rare, among them are: head ache, dizziness, insomnia, palpitation, hypotension, nausea, constipation, allergic reactions.

3.8.2. Clinical program for fixed dose combination Mebeverine+Simethicone development

The clinical program for the development of a fixed-dose combination of Mebeverine + Simethicone film-coated tablets 135 mg + 80 mg consists of a study of the pharmacokinetics and comparative bioavailability in healthy volunteers that confirmed the bioequivalence of the fixed-dose combination versus Duspatalin®, and a study of the efficacy and safety in patients with

functional bowel disorders followed by intestinal pain and bloating. The parallel three-group study of efficacy and safety is planned to compare, according to the EAEU Guidelines for the Development of Fixed-Dose Combinations, the reduction in abdominal pain and bloating, as well as the rate of adverse events, during treatment the fixed-dose combination of Mebeverine + Simethicone versus Duspatalin® and Espumisan® as a monotherapy.

4. SELECTION OF STUDY POPULATION

4.1. Study population

465 patients with functional bowel disorders with abdominal pain and bloating/flatulence from 18 to 75 years old will be randomized into the study. 665 patients will be screened (approximately 30% screen failure rate).

Patients will be randomized into three groups at the ration 1:1:1 (155 in every group):

- Mebeverine + Simethicone, film coated tablets, 135 mg + 80 mg, one tablets 3 times a day during 4 weeks;
- Duspatalin® film coated tablets, 135 mg, one tablets 3 times a day during 4 weeks;
- Espumisan® capsules 40 mg, 2 capsules 3 times a day during 4 weeks.

4.2. Inclusion criteria

Patients should corresponds to all inclusion criteria listed below:

1. Signed Informed Consent Form;
2. Males and females aged 18 to 75 years old (inclusive);
3. Abdominal pain and bloating/flatulence due to functional bowel disorder (including IBS, chronic functional constipation, chronic functional diarrhea or functional abdominal bloating);
4. Episodes of abdominal pain for at least 3 months, with a frequency of at least 3 times a month;
5. Abdominal pain intensity of 4 to 9 points (inclusive) when assessed on the NRS-11 scale (i.e. weekly average, with daily recording of the worst pain for the last 24 hours during last week of Screening and Run-in period);
6. Bloating/flatulence intensity of of 4 to 9 points (inclusive) when assessed on the NRS-11 scale (i.e. weekly average, with daily recording of the worst bloating episode for the last 24 hours during last week of Screening and Run-in period);
7. Patients' consent to use adequate contraception methods throughout the study. Adequate contraception methods include:
    a. oral contraceptives or contraceptive patches,
    b. condom or diaphragm (barrier method) with spermicide, or
    c. an intrauterine device

4.3. Exclusion criteria

Patients will be not eligible for participation in this study if he/she will meet at least one of the criteria described below:

1. Hypersensitivity to mebeverine, simethicone, drotaverin, excipients of the studied products, or contraindications;
2. Intake of tricyclic antidepressants, eluxadoline, linaclotide, selective serotonin re-uptake inhibitors, rifaximin, lubriprostone within the last week before screening;
3. New prescription or any change in probiotic drug therapy (including change in the drug or dosage regimen) during the last month before screening;
4. History of intestinal obstruction, stricture, toxic megacolon, GI (gastro-intestinal)

perforation, fecal impaction, gastric banding, bariatric surgery, adhesions, ischemic colitis, or impaired intestinal circulation (e.g. aorto-iliac disease);

5. History of major gastric, hepatic, pancreatic or intestinal surgery (appendectomy, hemorrhoidectomy, or polypectomy allowed as long as occurred > 3 months prior to trial screening; uncomplicated laparoscopic or open cholecystectomy is allowed if no history of post-operative biliary tract pain and surgery occurred > 3 months prior to screening);
6. Significant and progressive enlargement of the liver, spleen, lymph nodes; ascites; palpable tumor formation in the abdominal cavity / pelvis according to physical examination, hepatic cirrhosis;
7. Significant concomitant acute or chronic disease (cardiovascular, gastrointestinal, endocrine, immunological, metabolic, bronchopulmonary, urinary system) or any condition that, according to Investigator, is a contraindication for the patient to participate in the study if interference with the study performance;
8. Any inflammatory bowel disease (Crohn's disease, ulcerative colitis, any infection including bacterial, viral, protozoa, helminthosis);
9. Elevated fecal calprotectin level 1 month before or at screening which indicates the presence of inflammatory GIT disease;
10. Unexplained GI bleeding within 3 months prior to screening;
11. Confirmed diagnosis of bile acids malabsorption;
12. History of any malignant disease except basal cell carcinoma of skin and vesical cervix carcinoma in situ which were cured ≥ 5 years ago;
13. Confirmed diagnosis of celiac disease;
14. Confirmed hereditary galactose or fructose intolerance , total lactase deficiency, sucrase-isomaltose insufficiency, glucose-galactose malabsorption syndrome;
15. Diet changes (e.g, switching to fermented foods, a gluten-free diet) within the 1 months prior to screening;
16. Planned elective surgery during the study;
17. Pancreatic exocrine insufficiency or acute pancreatitis;
18. Endometriosis in women;
19. Positive results of tests for HIV, hepatitis B or C, at the moment of screening;
20. Drugs or alcohol abuse at screening or in the past, which, in the Investigator's opinion, makes the patient not eligible for participation in the study;
21. Participation in another clinical study or another study drug administration within 30 days prior to screening;
22. Pregnant or lactating women, or women planning to get pregnant during the clinical study; women of child-bearing potential (including those without history of surgical sterilization and women with <2 years post-menopause) not using adequate contraception methods;
23. Inability to read or right; unwillingness to understand and comply with Protocol procedures; non-compliance with medication dosing regimen or procedures which, in the Investigator's opinion, may affect study results or the patient's safety and prevent the patient's participation in the study; any other concomitant diseases or severe mental disorders, which make the patient ineligible for study participation, limit the legal basis for Informed Consent procedure, or may affect the patient's ability to participate in the study.

4.4. Exclusion of patients from the study after randomization

The patient can withdraw the consent any time without any explanations. In the event of significant deviations, which, according to the Investigator, could impede the patient's participation in the study or interpretation of effectiveness or safety parameters, the patient should be excluded from the study. Criteria for early exclusion of patients from the study are provided in section 6.14

4.5. Re-tests and re-screening

In case of obtaining uncertain of doubtful results of laboratory testing during the screening examination repeated testing (re-test) may be conducted once in agreement with the Sponsor or its authorized representative

The patients, who do not meet the inclusion/exclusion criteria due to manageable medical condition, can pass repeated Screening Visit after agreement from the Sponsor or his representative (re-screening). In this case, all screening procedures will be repeated, including the procedure for obtaining informed consent and assigning a new identification number.

5. STUDY DRUG

5.1. Description of the investigated drugs

5.1.1. Fixed-dose combination Mebeverine + Simethicone

Study drug:	Mebeverine + Simethicone, film-coated tablets, 135 mg + 80 mg
Active substances:	Mebeverine hydrochloride and Simethicone
Pharmacological group	Analgesics and antispasmodics. ATC code: A03AX (or A03E)
Composition:	**Active substances:** Mebeverine hydrochloride 135.00 mg and Simethicone EP-100% 84.43 mg, corresponding to polydimethylsiloxane 80.00 mg [redacted]
Daily dose and dosing regimen:	Orally 1 tablet 3 times a day before meal
Package description:	100 tablets (10 tablets in 10 Blisters PVC/PE/PVDC/Alu)
Storage conditions	In a light-protected place at a temperature not above 25°C. Keep out of the reach of children.
Manufacturer:	[redacted]

5.1.2. Duspatalin ®

Study drug:	Duspatalin® coated tablets 135 mg
Active substance:	Mebeverine hydrochloride
Pharmacological group	Antispasmodics. ATC code: A03AA04
Composition:	Coated tablets **Active substance:** Mebeverine hydrochloride 135,0 mg [redacted]
Daily dose and dosing regimen:	Orally 1 tablet 135 mg three times a day before meals
Package description:	10 tablets in a blister from PVC / aluminum foil. 1 or 5 blisters in a carton pack with package insert.
Storage conditions	Store at a temperature not higher than 30˚C. Keep out of the reach of children.
Manufacturer:	Mylan Laboratories SAS, France

5.1.3. Espumisan®

Study drug:	Espumisan®, 40 mg capsules
Active substance:	Simethicone

Pharmacological group	Carminative ATH code: A03AH13
Composition:	**40 mg capsules** **Active substance:** Simethicone 40,0 mg [redacted]
Daily dose and dosing regimen:	Orally 2 capsules 3 times a day after or before meal
Package description:	25 capsules in a PVC / aluminum foil blister. 1, 2 and 4 blisters in a carton pack with Package Insert
Storage conditions:	Store at a temperature not higher than 30˚C. Keep out of the reach of children.
Manufacturer:	[redacted]

5.2. Administration of the study drug and randomization

At the visit 2 Week 0, Day 1, all eligible patients will be randomized into three equal groups (1:1:1):

- Mebeverine+Simethicone, 135 mg+80 mg, three times a day during 4 weeks
- Duspatalin® 135 mg three times a day during 4 weeks
- Espumisan®, 80 mg three times a day during 4 weeks

Patients will take the study drugs during 4 weeks: Mebeverine+Simethicone 1 tablet three times a day before meal, Duspatali® 1 tablet three times a day before meal, Espumisan ® 2 capsules 3 times a day after or before meal.

The last dose has to be taken at the evening before the Visit 3 (Week 4, Day 29).

The patients will register the study drug administration in the diary.

5.3. Compliance of the therapy conduction

The patient should take the first study drug dose at the Visit 2 day (Week 0). During telephone contact (TC 1, Week 2, Day 0), the Investigator checks the patient's treatment compliance and whether he/she follows the recommendations on the Patient's Diary filling, and, if necessary, conducts an additional conversation with the patient about the proper drug administration and filling out the Patient's Diary. At Visit 3 (Week 4, Day 29), the patient should return all used and unused study drug packagings. The Investigator will check compliance with the recommendations for study drug self-administration at Visit 3 (Week 4, Day 29) based on the results of accounting for the returned study drug and the patient's diary.

The study drug compliance will be calculated at Visit 3 using the formula:

$$\text{Compliance} = (\text{N dispensed.} - \text{N returned.}) / \text{N calc.} \times 100\%$$

where N dispensed. = number of tablets/capsules dispensed, N returned. = number of tablets/capsules returned, N calc. = estimated number of tablets/capsules the volunteer was to receive since the previous visit.

The compliance should be within the interval from 80% to 120%.

5.4. Packing and labeling of the study drugs

The study drug will be packed and marked in accordance with current law and applicable regulatory requirements, in particular, Federal Law # 61-FZ On Circulation of Pharmaceutical products" dd. April, 12 2010.

Label of investigational product is below:

Label of blister (Label 5829-L01)

Protocol no. MESI3001

Kit number: XXXXXX

Packaging batch number: 5829-BB

Tablet batch number: zzzzz

Contents: 10 film-coated tablets Mebeverine+Simethicone, 135 mg+80 mg

Sponsor: Abbott Product Operations AG

Label of secondary pack (Label 5829-L02)

FOR CLINICAL TRIAL USE ONLY

Protocol no. MESI3001

Kit number: XXXXXX

Instructions for use and route of administration: oral use, 1 tablet 3 times a day, before meal

Packaging batch number: [redacted]

Tablet batch number: zzzzz

Not to be used after: MM/YYYY

Contents:100 tablets (10 blisters with 10 tablets Mebeverine+Simethicone, 135 mg+80 mg each)

Storage conditions: store in a light-protected place at a temperature not above 25°C

Sponsor: Abbott Product Operations AG

CRO: [redacted]

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

For registered medication Duspatalin® in standard trade package and standard label additional label will be applied:

Label of blister (Label 5829-L03)

Protocol no. MESI3001

Kit number: XXXXXX

Packaging batch number: [redacted]

Contents: 10 tablets Duspatalin® 135 mg

Abbott Product Operations AG

Label of secondary pack (Label 5829-L04)

FOR CLINICAL TRIAL USE ONLY

Protocol no. MESI3001

Kit number: XXXXXX

Instructions for use and route of administration: oral use, 1 tablet 3 times a day, before meal

Packaging batch number: [redacted]

Not to be used after: MM/YYYY

Contents: 5 blisters with 10 tablets Duspatalin® 135 mg

Storage conditions: at a temperature below 30˚C

Abbott Product Operations AG

CRO: [redacted]

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

For registered medication Espumizan® in standard trade package and standard label additional label will be applied:

Label of blister (Label 5829-L05) (simple white label)

Protocol no. MESI3001

Kit number: XXXXXX

Packaging batch number: [redacted]

Contents: 25 capsules Espumisan® 40 mg

Abbott Product Operations AG

Label of secondary pack (Label 5829-L06) (simple white label)

FOR CLINICAL TRIAL USE ONLY

Protocol no. MESI3001

Kit number: XXXXXX

Instructions for use and route of administration: oral use, 2 capsules 3 times a day, after or before meal

Packaging batch number: [redacted]

Not to be used after: MM/YYYY

Contents: 1 blister with 25 capsules Espumisan® 40 mg

Storage conditions: store at a temperature below 30˚C

Abbott Product Operations AG

CRO: [redacted]

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

5.5. Accounting of the study drug

The Investigator will be responsible for proper accounting registration of the study drugs to provide their proper receiving, storage, distribution and return. The patients will be instructed to return all, both used and unused, packages of the study drugs to the investigational site at Visit 3. The returned materials will be checked, assessed the patient's compliance. In case the patient loses the study drug package, an appropriate note should be written in the source documentation and in the study drugs accountability log.

Upon completion of the study, all remaining study medications (Mebeverine+Simethicone, Duspatalin®, Espumisan®) should be returned to the local depot and destroyed.

5.6. Study drug storage in the study site

The Investigator will be responsible for the storage of the study drug in the study site throughout the entire period of the study. Restricted access and adequate temperature should be provided. Temperature monitoring should be carried out using thermometers, recording the minimum and maximum temperature during the reporting period. The temperature monitoring data should be recorded in the temperature registration log on a regularly basis. Upon the end of the study and the final calculation, the study drug Mebeverine+Simethicone is to be returned to the Sponsor or representatives.

5.7. Concomitant Medication

All the study drugs and concomitant medication including food supplements should be registered in the patient's source documentation and in the electronic Case Report Form (eCRF). The Concomitant Medication also include allowed by the protocol rescue therapy applied to relief intensive pain episodes - drotaverin in a dose of 80 mg 1 - 3 times a day during one day after the

episode. This includes all medicinal products and food supplements that are not study medication taken by patients at any time during the clinical study. The patient's source documentation and eCRF should contain the name (generic name of the active substance is preferable), dose, intake frequency, route of administration, indications for use (including the underlying disease, associated disease, adverse drug event or preventative treatment), date of the beginning and completion of a corresponding drug administration. Upon the study completion, the concomitant medication continues, a corresponding mark should be entered in the CRF

5.8. Prohibited medications

While taking part in the study, the patients are prohibited to take other study drugs, as well as medicines of the following groups:

- Antibacterial therapy;
- Systemic glucocorticosteroids;
- Treatment for HIV, hepatitis B or C;
- Treatment for HIV, hepatitis B or C;
- Eluxadoline;
- Linaclotid;
- Selective serotonin re-uptake inhibitors;
- Rifaximin;
- Lubriprostone;
- Antispasmodic therapy (including herbal, but excluding drotaverin to relief intensive pain episode in a dose of 80 mg 1 - 3 times a day during one day after the episode);
- other drugs, herbal or supplements to eliminate intestinal pain and bloating/flatulence, except for those provided by the study protocol;
- Any change in the dietary advise and probiotic drugs therapy (including the drug and dosage regimen).

Drotaverine hydrochloride will be allowed for intensive abdominal pain. Drotaverine administration should be recorder in the patient's diary (including a dosage).

5.9. Restrictions on the patient's diet and physical activity

Patients should maintain a pre-study food intake regimen and diet. There are no special restrictions on the physical activity.

Throughout the entire period of study the patient should use adequate contraceptive methods. Adequate contraceptive methods include:

- Oral contraceptives or contraceptive patches or
- Condoms or diaphragms (barrier method) together with a spermicide or
- Intrauterine devices.

6. DESCRIPTION OF THE PROCEDURES

All the study procedures will be conducted in accordance with the requirements of International Conference on Harmonization Good Clinical Practice Guideline (ICH GCP(E6)) and Eurasian Economic Union (EEU), principles provided in Helsinki Declaration, as well as in accordance with the applicable legislation and regulations of the Russian Federation. The Investigator should agree to monitoring, audits and inspections in the study site and provide direct

access to the study for the Sponsor and representatives thereof, Independent Ethics Committee and regulatory authorities.

6.1. Informed consent

Written Informed consent will be obtained during the screening before any procedures related to the study are performed.

6.2. Patient Registration

Each patient, who has signed the Patient Information Form and the informed consent form, will be assigned an individual registration number, which consists of five digits: ☐☐-☐☐☐ the first two digits indicate the number of the site, the other three refer to the sequence number of the patient in this site (001, 002, 003…010 etc.). The Investigator will be provided the instructions on the registration of patients prior to the study.

6.3. Demographic data and medical history

To assess the eligibility/ non-eligibility of patients, demographic data (gender, age, race) and a complete medical history, including significant acute and chronic diseases and conditions (i.e. menopause), surgical procedures and allergic reactions should be collected. It is also necessary to ask the patient about any hospitalizations/surgical interventions scheduled for the period of study (if applicable). All new diagnoses and conditions identified in the screening should be included in the patient's medical history.

6.4. Physical examination

Physical examination includes an assessment of general appearance, condition of the skin and mucous membranes, neck (including the thyroid gland), eyes, ears, nasopharynx, lungs, heart, abdomen, back, lymph nodes and neurologic status

Any relevant findings from physical examination are to be recorded on the Medical History form in the eCRF (for findings from the screening evaluation that occurred prior to allocation to treatment). Any change versus baseline evaluation data considered to be an AE, should be registered appropriately in the eCRF and source documents.

6.5. Vital signs, height and weight

This examination includes measurement of body temperature in the armpit, blood pressure in a sitting position, heart rate and respiration rate. Assessment of vital signs will be performed after 10 minutes of rest.

Weight and height of volunteer are measured without shoes. Height are measured only at Screening. Index body weight (BMI) is calculated according to the formula:

BMI = weight / height2 (kg / m2).

Changes in the vital signs regarding the data of the initial examination, regarded as AEs, should be recorded accordingly in the primary documentation and in CRFs.

6.6. Electrocardiography

Electrocardiography (ECG) in 12 leads will be performed in a supine position. The Investigator will examine ECG records, evaluate possible abnormalities, and then sign and date the conclusion. Changes on the ECG vs. baseline, regarded as AEs, should be recorded accordingly in primary documentation and in CRFs. The nest ECG parameters will be evaluated: heart rate, RR, PQ, QT, QRS and QT_C.

6.7. Colonoscopy

Colonoscopy will be performed during screening in patients over 50 years of age who do not have a colonoscopy report on the absence of significant pathology in the last 12 months.

Colonoscopy should be performed after confirmation of the patient's full compliance with other selection criteria. The procedure and the relevant preparation should be performed as per the standards adopted in the medical diagnostic center. The screening and induction period in the case of colonoscopy is to be extended to 3 weeks.

6.8. Numeric range scale (NRS-11)

NRS-11 is a Visual Analog Scale version (Visual Analog Scale for pain). The scale is a horizontal 10 cm line with the numbers from 0 to 10 located on it, where 0 is "no pain/bloating", 10 is "most severe pain/bloating you can imagine". During Visit 1 (screening and run-in period), the Investigator will train the patient to select a number from 0 to 10 that corresponds to his/her worst pain in the last 24 hours and the greatest bloating/flatulence. Abdominal pain and bloating/flatulence according to the NRS-11 scales will be evaluated at the screening visit, then daily throughout the screening/run-in and study treatment periods (in the Patient's Diary). The Patient's Diary is to be returned to the Site at Visit 3 (Week 4) and stored along with the primary patient's documents. The Investigator should enter the diary data into the eCRF. The baseline parameters of abdominal pain intensity and bloating/flatulence severity for the inclusion criteria assessment will be determined as the average daily NRS-11 scales scores 7 days before randomization (last week of the run-in period).

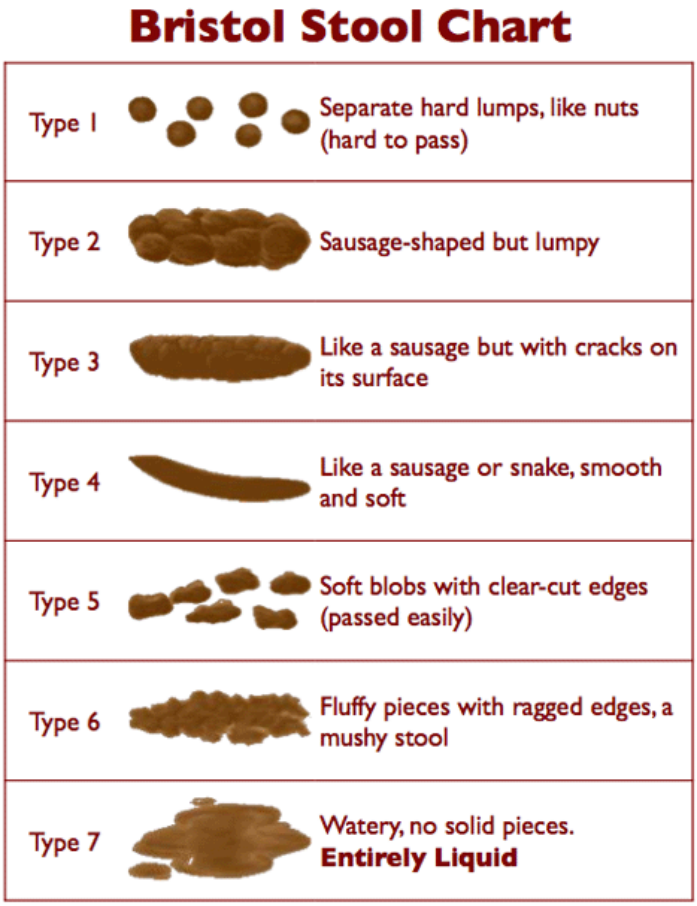
NRS-11 scales for abdominal pain and bloating/flatulence are provided in Appendix 2.

6.9. Bristol Stool Chart (BSC)

Classification of stools according to the BSC is easily understood by patients and makes it possible to quickly identify the nature of stool disorders. In accordance with BSC, hard stool includes types 1 and 2, loose stool—types 6 and 7 (Table 5)

At Visit 1 (Week -1), the Investigator will train patients to assess stool consistency using BSC. Assessment of stool consistency starts at Visit 1, then it is performed for every bowel movement daily until Visit 3 (Week 4).

Table 5. Bristol Stool Chart.



6.10. Quality of life evaluation using the IBSQOL questionnaire

Patients will be asked to evaluate the quality of life using the IBSQOL questionnaire at baseline at Visit 2 (Week 0) and at the end of the study treatment at Visit 3 (Week 4). A sample questionnaire is provided in Appendix 3.

6.11. Laboratory parameters

All laboratory tests under the protocol will be performed at the study sites local laboratories as per the approved standards. Testing for faecal calprotectin will be performed in the local laboratory or central laboratory (if test is not performed or delayed in local laboratory) if there is no result in 1 month before screening. Women of child-bearing potential will undergo a pregnancy strip test (including less than 2-year postmenopause).

Before the study start, the local and central laboratories will provide the necessary certificates and laboratory standards. The laboratory is responsible for providing laboratory reports to the study sites. The Investigator will analyze the results of laboratory tests as per standard clinical practice.

The required laboratory tests will be performed during visits in accordance with the study procedures schedule (TableTable 1). The table below (TableTable 6) provides laboratory parameters to be evaluated in the clinical study. Clinical relevance of the values outside the normal range (or abnormal results) is to be evaluated by the Investigator.

Table 6 Laboratory tests

Hematology	Biochemistry tests			Urinalysis	Feces analysis	Serology
	General	Liver function	Renal function			
Hemoglobin Hematocrit Red blood cells White blood cells Neutrophils * Lymphocytes * Monocytes * Eosinophils * Basophils * Platelets	Glucose Total protein Sodium Potassium Chloride	Total bilirubin Direct bilirubin Alkaline phosphatase ALT AST GGT	Blood Urea Nitrogen Serum creatinine	General properties: color, transparency, specific gravity, pH, protein, glucose, bilirubin, urobilinogen, ketone bodies, nitrites, hemoglobin Sediment microscopy: epithelium, red blood cells, white blood cells, cylinders, bacteria, salts	Fecal calprotectin	Anti-HIV antibodies Anti-HCV HBsAg

Abbreviations: ALT - alanine aminotransferase, AST - aspartate aminotransferase, GGT - γ-glutamyltransferase; HIV - human immunodeficiency virus, Anti-HCV - antibodies to hepatitis C virus, HBsAg - surface antigen of hepatitis B virus.

The Investigator must review the laboratory report, evaluate possible abnormalities, and then sign and date the conclusion. Hematology (including absolute values of leukocyte formula) and blood chemistry results should be transferred into eCRF.

Urinalysis results has to be accessed as normal/abnormal registered into eCRF. Clinical significance should be also evaluated. Clinically significant laboratory abnormalities should be recorded as AE. Laboratory reports should be kept with primary patient documentation.

6.12. Requirements for Collecting, Recording and Reporting of Adverse Events

Each subject is to be evaluated at every visit. Should any AE be identified at termination visit, the investigator will continue to follow the subject as described in section 6.12.1.6.

The reference safety information of Mebeverine+Simethicone, Duspatalin® and Espumisan® for the expectedness assessment is contained in the Investigators' Brochure, Instructions for medical use and section 1.5.3.

Investigator will be notified by Sponsor's representative in case any updates of IB or comparators labels (Instructions for medical use) become available.

6.12.1. Adverse events

6.12.1.1. Definition of Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom (including an AE occurring from drug abuse, an AE occurring from drug withdrawal and any failure of expected pharmacological action), or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.12.1.2. Recording of Adverse Events

Any AE should be recorded on the Adverse Events form in the eCRF and source documents. In order to avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words. Whenever possible, the Investigator should group together into a single term signs and symptoms which constitute a single diagnosis.

The existence of or change in an AE may be concluded due to the necessity to administer a concomitant medication, from a spontaneous report of the subject, from the physical examination or from special tests like laboratory assessments or other study specified tests (source of AE).

For each subject that has signed the informed consent and prior to study drug allocation at any dose any change to medical status should be recorded in patient's medical file in accordance to local requirements and the medical history eCRF only.

Any change to medical status, which occurs after study drug allocation at any dose in the specified study AE collection period will be handled as an (S)AE.

For each subject that has signed the informed consent but does not qualify for allocation to treatment, i.e. Screen Failure, any change to medical status (from the time of ICF signature until determination of non-qualification for the study) should be recorded in patient's medical file according to local requirements. The related medical status change information will not be reviewed by Abbott or delegated staff, and will not qualify as a study (S)AE.

The post-therapy AE collection period is defined as 30 days after the subject's termination of study drug after the subject's termination of study drug (collection of (S)AEs should be passive in this period unless otherwise specified)

Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the investigational drug. The action taken with study drug, the concomitant treatment/therapy introduced and the outcome as well as whether the event led to study termination will also be recorded.

6.12.1.3. Severity

The severity of the AE should be characterized as "mild, moderate or severe" according to the following definitions:

- Mild events are usually transient and do not interfere with the subject's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
- Severe events interrupt the subject's usual daily activity

6.12.1.4. Drug-Event Relationship

The causal relationship between the study drug and the AE should be characterized according to the following:

- Unrelated – there is not a reasonable possibility that the study drug caused the AE.

- Unlikely – suggests that only a remote connection exists between the study drug and the event. Other conditions, including concurrent illness, progression or expression of the disease state or reaction to concomitant medication, appear to explain the AE.
- Possible – suggests that the association of the AE with the study drug is unknown, however the event is not reasonably supported by other conditions.
- Probable – suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of the disease state, or concomitant medication reactions) do not appear to explain the AE.
- Certain - clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals.

The relationship with COVID-19 will also be registered (in case it is ongoing at the moment of the study treatment phase).

6.12.1.5. Outcome

The outcome of the adverse event should be classified according to the following definitions:

- Recovered / resolved: the event has resolved (no further symptoms are present and no treatment is being received by the subject).
- Recovered / resolved with sequelae: the event has resolved but there may be lingering effects present (e.g., a scar following a cut or abrasion).
- Fatal: the subject died as a result of the event. This code should only be used for the event that caused the death, not any event that was present at the time of the subject's death. Fatal events require immediately reporting to the Sponsor (or an authorized representative).
- Unknown: may only be used in the event that the subject is lost to follow-up and no reliable data can be obtained.

All efforts should be made to classify the AE according to the above categories.

Note: when the AE is ongoing, the outcome will remain blank on the Adverse Events form in the eCRF.

6.12.1.6. Follow-up of Adverse Events

All AEs occurring during the study are to be followed up in accordance with good medical practice until resolved or judged no longer clinically significant, or if a chronic condition, until fully characterized. All follow-up results are to be reported to the Sponsor (or an authorized representative).

6.12.1.7. Serious Adverse Events (SAEs)

Definitions of Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death,

- Is life-threatening (an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- Requires inpatient hospitalization or prolongation of an existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect,
- Is any suspected transmission via a medicinal product of an infectious agent,
- Is considered an important medical event (an event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse as well as spontaneous or elective abortions, stillbirths and ectopic pregnancies)

6.12.1.8. Reporting Serious Adverse Events

Any SAE (fatal or life-threatening SAE and other SAEs), whether or not related to the study drug, must be reported immediately within 24 hours of the investigator's awareness of the event by telephone, faxing and email the appropriate SAE forms to the following numbers:

Study Medical Monitor

[redacted]

After office hours, the emergency telephone number is: [redacted]

6.12.2. Pregnancy

If a subject should become pregnant during the study, the event will be reported within 1 day of the investigator's knowledge of the pregnancy.

[redacted]

If pregnancy occurs in a subject from the time of ICF signature who does not qualify for allocation to treatment, i.e. Screen Failure, the pregnancy should be recorded in patient's medical file only, in accordance to local requirements. The pregnancy related medical status change information will not be reviewed by Abbott or delegated staff. The pregnancy will not qualify as a study (S)AE.

If pregnancy occurs in a subject from the time of ICF signature who is not disqualified for allocation to treatment, the pregnancy should be recorded in patient's medical file in accordance to local requirements and in Abbott's pregnancy from. The pregnancy related medical status

change information will be reviewed by Abbott or delegated staff. The pregnancy will not qualify as a study (S)AE.

The pregnancy evolution and outcome, i.e., the health status of the newborn, is to be reported on the Pregnancy Outcome Form [redacted]

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth, ectopic pregnancy or congenital anomaly is considered a SAE and must be reported to [redacted] within 24 hours of the investigator becoming aware of the event and followed-up as described in Section 6.12.2

6.13. Emergency Situation Procedures

The Investigator is responsible for obtaining information on all the patient's emergency medical conditions in the course of the study. The text of the Patient Information Sheet and Informed Consent Form should contain the Investigator's contact information. The patients will be recommended to contact the Investigator in the event of any emergency conditions occurring during the study.

6.14. Subject Withdrawal from the Study

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the subject is otherwise entitled.

The Study Termination form must be completed for all subjects who did not fail screening.

In case of premature termination of the subject from the study, the primary reason for this premature termination is to be indicated according to the following definitions:

- Adverse event: discontinuation due to any adverse event (AE) with a corresponding entry reflected on the Adverse Events form in the eCRF
- Lack of efficacy: subject fails to respond to the study drug at an acceptable level where the subject or the Investigator feels it is in the best interests of the subject to seek another treatment.
- Lost to follow-up: the subject fails to return to the study site for scheduled visits and does not respond to telephone or written attempts to contact.
- Withdrew consent: subject decides to stop his/her participation in the study for any reason other than an AE, or is unable to complete the study as described in the clinical study protocol (e.g., subject is relocating to another location).
- Administrative: the Sponsor decides to discontinue the study (either at the study site or the entire study), e.g., general safety problems leading the Sponsor to entirely stop the study.
- Protocol violation – anything which is in direct violation of the clinical study protocol (e.g., inclusion/exclusion violation)

If possible, the Investigator must first discuss the discontinuation with the Medical Monitor. Otherwise, the Investigator should discuss the issue of discontinuation with the Medical Monitor within 24 hours after discontinuation.

The reason for the patient's discontinuation should be specified in the source documentation and on the electronic Case Report Form. If the patient discontinues participating in the study for more than one reason, the main reason should be given. Occurrence of an AE or SAE should be specified as the reason for the withdrawal of the patient's consent due to such AE or SAE.

In addition, the Sponsor shall be entitled to terminate the study at any time. The Investigator is entitled to terminate the study at any time for medical or regulatory reasons. Termination of the study should be done after mutual consultations between the Investigator and the Sponsor only.

If the study is terminated ahead of time, all patients should undergo early termination visit procedures, and all study documents must be returned to the Sponsor or its representative.

Follow-up of AE, SAE and pregnancy continuing at the time of the study termination should be performed as per the Protocol, unless another procedure for the safety follow-up is agreed between the Investigator and the Sponsor.

6.15. The validity of measurements

Evaluations of the efficacy and safety of therapy in patients with functional diseases of the colon are standard and well known. A randomized, controlled, parallel-group clinical study will evaluate the safety and efficacy of the study drug versus reference drugs.

Due to the COVID-19 pandemic, visits to the study site can be replaced by home visits by the site's employees or the use of telemedicine opportunities. These changes, including the permissible amount of missing data, should be approved by the Sponsor and IEC and do not require amendments to the protocol (in case it is ongoing at the moment of the study treatment phase).

7. STUDY PROCEDURES

7.1. Screening and run-in period (Visit 1, Week – 1,[1] Day -7)

Visit window day -21….-7

- The procedure for obtaining the informed consent
- Patient Registration
- Collection of demographic data, medical history and concomitant medication data
- Physical examination
- Assessment of vital signs
- Measuring height, weight, BMI
- Abdominal pain intensity on the NRS-11 scale evaluation (worst pain for the latest 3 months)
- Bloating/Flatulence intensity on the NRS-11 scale evaluation (worst bloating episode for the latest 3 months)
- ECG
- Blood sampling for safety laboratory tests (hematology and blood chemistry, tests for HIV, hepatitis B and C)
- Urine collection for urinalysis
- Feces sampling for Fecal calprotectin analysis (if there is no result in 1 month before screening)
- The urine pregnancy test is carried out on women with child-bearing potential (including women in the menopausal period of less than two years)

[1] Week -3, Day -21 in case of colonoscopy

- Assessment of inclusion/non-inclusion criteria
- Patient diary dispense
- Colonoscopy should be performed in patients over 50 years of age who do not have a colonoscopy report on the absence of significant colon pathology in the last 12 months who meet all inclusion/exclusion criteria (excluding Inclusion Criteria 5 and 6 that are to be evaluated at a randomization visit). Colonoscopy should be performed not later than 10 days before the randomization visit.

Patient questionnaires, tests, and scales should be completed according to the adopted clinical practice by the certified trained member of the Site study team before dosing.

In case of ambiguous or controversial results of laboratory tests, a single repeated test (retest) may be performed, as agreed with the Sponsor or its representative.

Patients that do not meet all inclusion/exclusion criteria will not be included in the study. Patients not enrolled in the study due to conditions which may be corrected may be re-screened one time, as agreed upon with the Sponsor or its representative.

From this date intake of drugs prohibited by the protocol are not allowed. Intake of drotaverin in a dose of 80 mg 1-3 times a day will be allowed to stop intensive pain episode during one day after the episode.

7.2. Treatment period

7.2.1. Randomization (Visit 2 Week 0, Day 1).

- Assessment of AE and concomitant medication
- Measuring, weight, BMI
- Assessment of vital signs
- Abdominal pain and bloating/flatulence intensity on the NRS-11 scale evaluation
- Patient diary assessment (Including stool consistency in line with the Bristol stool scale, stool frequency, drotaverine intake and menstrual bleeding days)
- Assessment of inclusion/non-inclusion criteria
- Randomization
- Evaluate the quality of life (IBSQOL questionnaire)
- Study drug dispense

7.2.2. Telephone contact 1 (Week 2, Day 15)

Visit window ± 1 day

- Assessment of AE and concomitant medication, study drug intake, interrogation for correctness of patient diary filling

7.2.3. End of treatment (Visit 3, Week 4, Day 29)

Visit window ± 1 day

- Assessment of AE and concomitant medication
- Measuring, weight, BMI
- Physical examination

- Assessment of vital signs
- Blood sampling for safety laboratory tests (hematology and blood chemistry)
- Urine collection for urinalysis
- Patient diary assessment (daily data for 4 weeks, including abdominal pain and bloating/flatulence intensity, stool consistency in line with the Bristol stool scale, stool frequency, drotaverine intake and menstrual bleeding days)
- Evaluate the quality of life (IBSQOL questionnaire)
- Study drug return, accountability and compliance assessment

At this point the period of the study therapy is completed. The patient will be given recommendations for further treatment as part of standard therapy

7.3. Follow-up period

7.3.1. Telephone contact 2 (Week 5, Day 36)

Visit window +1 day

- Assessment of AE and concomitant medication

7.4. Unscheduled visits

At the discretion of the Investigator, the patients may be invited for an unscheduled visit at any time in the course of the clinical study for safety reasons, in case a re-examination or repeated procedure is required, or to provide additional quantity of the study drug. During unscheduled visits, the Investigator may conduct the necessary procedures. Unscheduled visits should be registered in the source documentation and CRF. Unscheduled visits should not affect the schedule of planned visits provided by the Protocol of this clinical study

7.5. Early discontinuation visit

In case of early termination of participation, after Visit 2 (Week 0, Day 1) and before Visit 3 (Week 4, Day 29), the patient should be invited to the study site to undergo an early discontinuation Visit (ED) assessments. The Investigator should make every effort to conduct ED

ED Visit should include all procedures of Visit 3 (Week 4, Day 29). If ED Visit cannot be carried out in full, the Investigator should coordinate their actions with the Medical Monitor. On ED Visit the patient should return all used and unused packages of the study drug. The patient will be given recommendations for further treatment as part of standard therapy.

If possible, the Investigator should discuss the patient's early discontinuation from the study with the Medical Monitor in advance. Otherwise, the Investigator should contact the Medical Monitor within 24 hours after the early discontinuation of the patient

8. QUALITY ASSURANCE

This clinical study will be conducted in accordance with Standard Operating Procedures (SOP) of the Sponsor and/or representatives thereof, the requirements of International Conference on Harmonization Good Clinical Practice Guidelines (ICH GCP(E6)) and Eurasian Economic Union (EEU), principles provided in Helsinki Declaration, as well as in accordance with the applicable legislation and regulations of the Russian Federation. Compliance with the requirements will be provided by audits of the study site and the data obtained in the study.

The Investigator will enter the data required in accordance with this Protocol into the eCRF, provided by the Sponsor or the representative thereof. The monitors shall visit each study site at a frequency described in the monitoring plan to check the eCRFs for completeness and accuracy of

filling. Specifying question shall be asked concerning any differences between the source documentation and completed eCRFs, which the Investigator should answer and/or eliminate these inconsistencies. When all the information required had been entered and all the specifying questions clarified, the Investigator should sign and date the eCRF of each patient. The completed pages of the eCRF will be checked during the monitoring visits..

Due to the COVID-19 pandemic, a centralized and remote monitoring model can be used in the study. All applicable principles will be described in the monitoring plan.

9. STATISTICAL METHODS PLANNED

9.1. General provisions

This is clinical study to evaluate efficacy and safety of Mebeverine+Simethicone fixed-dose combination versus Duspatalin® (mebeverine) and versus Espumisan® (simethicone) in patients with functional bowel disorders with abdominal pain and excess gas formation.

Statistical analysis, described in the following subsections, will be performed as specified in the Statistical analysis plan, which will be created and finalized before closing the database. The Statistical analysis plan will be included in the report on the clinical study for this Protocol.

9.2. Sampling size identification

In first amendment to protocol the pre-specified interim analysis was removed. However, as already all subjects were recruited no change in sample size was made. Note that a design without the interim analysis needs less patients to achieve the same power, so that deleting the interim did not have negative consequences to the power of the study while maintaining still the usual type 1 error rate of 5% (two-sided). For sake of completeness below the original sample size rationale is given.

There are no published data on bloating/flatulence and abdominal pain assessment with NRS-11 for simethicone versus placebo and mebeverin versus placebo. Comparison of Linaclotide treatment versus placebo for bloating decrease in chronic constipation patients was assessed with NRS-11 and found out 1.0 point difference between groups with approximately 2.5 standard deviation.[2]Comparison of B. coagulans Unique IS2 treatment versus placebo for pain decrease in IBS patients was assessed with NRS-11 and found out 3.2 point difference between groups with 2.5 standard deviation. [3]

An assumption was taken that Mebeverin+Simethicone fixed dose combination will decrease the sum of pain and bloating/flatulence scores on average at least 1.0 point more than simethicone or mebeverine as monotherapy.

For primary endpoint to demonstrate the superiority of the FDC versus separately each mono-component assuming an expected 1.0 point difference between the two treatment groups and standard deviation 2.5 with type I error $\alpha = 0.05$ (two-sided) and a power 90% for each comparison individually in a group-sequential design with one interim stage at information fraction 40%, about 132patients should be included in both groups. The overall power to demonstrate superiority for both comparisons (FDC vs mebeverine monotherapy and FDC vs simethicone monotherapy) is about 80%.

Thus, 396 should be included into the analysis

3. mebeverin	superiority /sum NRS-11 scores for pain and bloating/flatulene intensity	$\alpha = 0.05$ (two-sided) $\beta = 0.1$ Power = 90% Mean diff. = 1.0 SD = 2.5 Alpha spending function: O'Brien-Fleming	n1 = n2 = 132

		Beta spending function (non-binding): O'Brien-Fleming Max. num, of stages = 2 Info. proportion at Interim stage = 0.40	
4. simethicone	superiority /sum NRS-11 scores for pain and bloating/flatulene intensity	$\alpha = 0.05$ (two-sided) $\beta = 0.1$ Power = 90% Mean diff. = 1.0 SD = 2.5 Alpha spending function: O'Brien-Fleming Beta spending function (non-binding): O'Brien-Fleming Max. num, of stages = 2 Info. proportion at Interim stage = 0.40	n1 = n2 = 132

Thus, taking into account a 15% drop-out rate, about 155 patients should be included in each group. A total of 465 patients should be randomized..

9.3. Randomization

Randomization will take place at Visit 2 (Week 0) with IWRS system which is described in the eCRF. Patients will be randomized into three equal groups (1:1:1) using the IWRS system (155 patients per group).

9.4. Statistical methods

Statistical analysis will be performed according to the Statistical Analysis Plan created and finalized before the database lock.

The Safety Population will consist of all randomized patients who received at least one dose of the study product.

The Full Analysis Set (FAS) will consist of all randomized patients who received at least one dose of the study product and have at least one post-baseline assessment of the efficacy parameters.

Per Protocol set (PP) will consist of all FAS patients who completed study treatment and had no significant protocol violations.

Also, secondary endpoint analysis will be performed in the following subgroups:

- Patients with IBS
- Patients with other functional bowel diseases
- Patients with constipation
- Patients with diarrhea
- Patients with both constipation and diarrhea
- Patients with neither constipation nor diarrhea

9.5. Patient distribution, demographic and baseline characteristics

Patient distribution, demographic and baseline characteristics will be presented using descriptive statistics. The number and percentage of patients receiving concomitant medication will be presented in frequency tables according to the ATC class level 2 and 4. The number and percentage of patients with comorbidities and preceding conditions will also be specified.

9.6. Study drug intake

Information on dosage, including daily doses, duration of effect and total doses, will be presented in a descriptive way for each treatment group.

9.7. Efficacy analysis

9.7.1. Primary efficacy end point

- Change from baseline of sum of NRS-11 abdominal pain and bloating/flatulence intensity scores after 4 weeks of treatment.

The baseline abdominal pain and bloating/flatulence intensity will be determined as the average of the NRS-11 daily assessment during 7 days before randomization (weekly average of last week of screening and run-in period). The Week 4 assessment is the same (data from last 7 days of the corresponding week)..

9.7.2. Primary end points analysis

The FAS will be the main sample for efficacy assessment in this study performed to confirm superiority. Additional analysis of the primary efficacy endpoint will be performed in the per protocol (PP) set.

For the difference of changes in sum scores of NRS-11 pain and bloating/flatulence intensities after 4 weeks of treatment versus baseline between the groups Mebeverine+Simethicone versus Duspatalin® and Mebeverine+Simethicone versus Espumisan®, a two-sided 95% confidence interval (CI) will be constructed, which is equivalent to a 97.5% one-sided CI. The confidence interval will be constructed using ANCOVA, which will include treatment and site as fixed effect, and baseline parameter will be included in the model as covariate. To test the hypothesis of superiority of the FDC Mebeverine+Simethicone versus every comparator (Duspatalin® and Espumisan®), the upper confidence limit will be used. The null hypothesis (H_0: no difference in change from baseline of sum of bloating/flatulence and pain scores between the FDC and corresponding comparator, will be rejected in favor of the alternative hypothesis (H_a: larger change from baseline of sum of bloating/flatulence and pain scores in the fixed-dose combination Mebeverine+Simethicone group) only if the upper limit of two-sided 95% CI does not contain the value 0. In addition the study will be considered successful in case both superiority hypothesizes are proven, i. e. upper limit of two-sided 95% CI does not contain the value 0 for both constructed confidence intervals. In this case, the conclusion will be drawn on the fixed-dose combination of Mebeverine+Simethicone to be superior versus Duspatalin® (mebeverin) and Espumisan® (simethicone) for the decrease of both pain and bloating/flatulence intensity.

9.7.3. Secondary efficacy end points

- Change from baseline of NRS-11 pain intensity after 4 weeks of treatment
- Proportion of patients with the NRS-11 pain intensity reduction of ≥30% versus baseline during at least 50% of treatment weeks over treatment period
- Proportion of patients with the NRS-11 pain intensity reduction of ≥ 50% versus baseline during at least 50% of treatment weeks over treatment period.
- Proportion of patients with the abdominal pain assessed in the Patient Dairy completely resolved during at least 50% of treatment weeks over treatment period (NRS-11 0 assessment).
- Change from baseline of NRS-11 bloating/flatulence intensity after 4 weeks of treatment
- Proportion of patients with the NRS-11 bloating/flatulence intensity reduction of ≥30% versus baseline during at least 50% of treatment weeks over treatment period.
- Proportion of patients with the NRS-11 bloating/flatulence intensity reduction of ≥ 50% versus baseline during at least 50% of treatment weeks over treatment period.

- Proportion of patients with the bloating/flatulence assessed in the Patient Dairy completely resolved during at least 50% of treatment weeks over treatment period (NRS-11 0 assessment).
- For patients with constipation: proportion of patients with any increase in number of CSBM per week versus baseline during at least 50% of treatment weeks.
- For patients with diarrhea : proportion of patients with any decrease in the number of days per week with at least one stool consistency of Type 6 or Type 7 BSS versus baseline during at least 50% of treatment weeks.
- Change in number of days per week during study treatment period when drotaverine was taken.
- Change in quality of life evaluation using IBSQOL questionnaire versus baseline.

The baseline abdominal pain and bloating/flatulence intensity will be determined as average of the worst daily episodes NRS-11 assessment during 7 days before randomization (last week of screening and run-in period). The data from last week of screening and run-in period will be also used for baseline assessment of stool frequency and consistency and number of days of drotaverin intake. Week 1, Week 2, Week3 and Week 4 assessments are the same (data from the last 7 days of the corresponding week).

9.7.4. Secondary efficacy end points analysis

Intergroup comparisons will also be performed for secondary efficacy endpoints using the χ^2/Fisher exact test and 95% confidence intervals for differences in proportions will be given. Additionally, the proportion of patients with reduced severity of pain in the bowel region and bloating/flatulence during each week of the 4-week treatment period charts will be constructed.

ANCOVA model, which will include treatment and site as fixed effect, and baseline value as covariate, will be used for continuous covariates comparison presenting treatment effect estimates and associated 95% CIs.

9.8. Safety analysis

9.8.1. Safety end points:

- Safety will be assessed per treatment arm, based on the incidence and severity of AE and SAE, physical examination, vital signs and lab results.

9.8.2. Safety end points analysis

The safety sample will be used for the analysis of the safety and tolerability data.

Treatment Emergent Adverse Events (TEAEs) including AE and SAE will be presented by frequencies (number of patients with AEs and number of events) and are summarized by unique treatment (Mebeverine+Simethicone, Duspatali®, Espumisan®), primary System Organ Class (SOC) and Preferred terms (PT) and relation to the study drug and severity. Severity and drug-event relationship of the treatment emergent AEs are summarized separately.

Laboratory values and vital signs by visit and their changes from baseline will be summarized in tables of descriptive statistics. Abnormal values (according to the reference ranges) will be presented in frequency tables (low, normal and high values).

9.9. Procedures to record missing, not subject to analysis and dubious data

No missing data will be added. To analyze the efficacy endpoints the last observation carry forward (LOCF) will be used. To determine the sensitivity of the evaluation: first the patients with

missing data will be analyzed, then the patients will be analyzed without replacing the missing data.

9.10. Reporting of any deviations from the original statistical plan

In case of any deviation from the planned statistical analysis all the changes compared to the methods described in the Protocol should be identified. Similarly, if there is a need for any additional changes, upon the completion of the analysis they should be specified in the Study report.

10. ADMINISTRATIVE PROCEDURES

[redacted]

[redacted]

10.5. Ethical aspects

10.5.1. Independent Ethics Committee

Prior to the clinical study initiation, all study sites will obtain written approvals of independent Ethics committees (IECs) in accordance with International Conference on Harmonization Good Clinical Practice Guideline (ICH GCP(E6 R2)) and Eurasian Economic Union (EEU), principles provided in Helsinki Declaration, as well as in accordance with the applicable legislation and regulations of the Russian Federation. The following documents shall be submitted for IEC's review: study protocol with amendments, patient's information list and the informed consent form, written materials to be submitted to the patients, investigator's brochure, information of safety of the study drug application, information on payments and other remunerations to the patients, investigator's scientific biography and other documents at request.

The list of IEC's members and the statement of its organization and operations compliance with the standards of the Good Clinical Practice and regulatory requirements shall be submitted to the Sponsor.

10.5.2. Ethical conduct of clinical study

The procedures described in the Protocol of clinical studies related to its conduct, assessment and documentation of the findings have been designed to ensure that the Sponsor and the Investigator followed the requirements of the Good Clinical Practice guidance of International Conference on Harmonization (ICH GCP(E6 R2)) and the Eurasian Economic Union (EEU). This clinical study will also be conducted in accordance with applicable law and applicable regulatory requirements. This includes the possibility of conducting audits and inspections by representatives of the Sponsor and/or competent authorities. The Investigator should give their consent to monitoring, audits and inspections in study site and at any time on demand providing direct access to the study for the Sponsor and representatives thereof, Independent Ethics Committee and competent authorities

10.5.3. Informed Consent

Prior to the clinical study, the Investigator shall obtain IEC's written approval of the patient's information sheet and the informed consent form, as well as any other written information, which will be provided to the study subjects. IEC's written approval and approved documents shall be filed with the Study Record.

The procedure for obtaining the informed consent shall comply with the requirements of International Conference on Harmonization Good Clinical Practice Guideline (ICH GCP(E6)) and Eurasian Economic Union (EAU), principles provided in Helsinki Declaration, as well as in accordance with the applicable legislation and regulations of the Russian Federation. The informed consent form shall be signed and dated by the patient before beginning of any study procedures. The process of obtaining the informed consent shall be described in detail in the primary documentation, including the fact of patient's consent to take part in this clinical study and the date of signing; the version of the informed consent form should be specified

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