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**NCT05175131**

ABBOTT

**Statistical Analysis Plan**

**Module 1**
**(Non-standard data and analyses)**

Version 3.0, Date 09JUL2021

Study: 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

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## SIGNATURE PAGE

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# 1. ABBREVIATIONS

Standard Abbreviations

| | |
|---|---|
| AE | adverse event |
| ANCOVA | analysis of covariance |
| ATC | Anatomical Therapeutic Chemical (class) |
| AUC | area under the curve |
| BDR | blind data review |
| BMI | body mass index |
| bpm | beats per minute |
| CRF | case report form |
| CRO | contract research organization |
| CV | coefficient of variation |
| DARIUS | Document And Regulatory Information Universal System |
| DBP | diastolic blood pressure |
| DDT | data definition table |
| DSMB | data safety monitoring board |
| ECG | electrocardiogram |
| FA | Full Analysis |
| FDA | food and drug administration |
| Geo. mean | geometric mean |
| GOP | global standard operating procedure |
| HLGT | High Level Group Term |
| HLT | High Level Term |
| IBSQOL | Irritable bowel syndrome quality of life |
| ICH | International Conference on Harmonization |
| LDA | day number of the last day of drug administration |
| LLOQ | lower level of quantification |
| LLT | Lowest Level Term |
| LOCF | last observation carried forward |
| max | maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| min | minimum |
| N,n | number of observations |
| NA | not applicable |
| OC | observed cases |
| PD | pharmacodynamic |

| | |
|---|---|
| PK | pharmacokinetic |
| PP | Per Protocol |
| PT | Preferred Term |
| QOL | quality of life |
| S.I. | System International |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SOC | System Organ Class |
| SOP | standard operating procedure |
| TARC | Therapeutic Area Review Committee |
| TEAE | treatment-emergent adverse event |
| TESAE | treatment-emergent serious adverse event |
| TLF/T,L,F | tables, listings and figures |
| ULOQ | upper limit of quantification |
| URL | upper reference limit |
| WC | windowing convention |
| WHO-DD(E) | World Health Organization – Drug Dictionary (enhanced) |

## 2. INTRODUCTION

[redacted]

# 3. SUMMARY OF THE PROTOCOL

## 3.1 Overall Study Plan

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.

## 3.2 Study Flowchart

The flowchart of the study can be found in Appendix 9.1.

## 3.3 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 fixeddose combination versus Duspatalin® (mebeverin) and versus Espumisan® (simethicone) in patients with functional bowel disorders with abdominal pain and excess gas formation (bloating/flatulence:

- 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);

- 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.

# 4. STATISTICAL ANALYSIS

## 4.1 Subject samples

There will be five subject samples.

The **All Subjects Consented subject sample** will consist of all subjects who:

- gave their informed consent.

The **All Subjects Allocated to Treatment subject sample** will consist of all subjects who:

- are in the All Subjects Consented sample;
- were allocated to treatment (randomized).

The **Safety subject sample** will consist of all subjects who:

- are in the All Subjects Allocated to Treatment sample;
- received at least one dose of the study product.

The **Full Analysis (FA) subject sample** will consist of all subjects who:

- are included in the Safety subject sample;
- have at least one post-baseline assessment of the efficacy parameters.

The **Per Protocol (PP) subject sample** will consist of all subjects who:

- are included in the Full Analysis sample;
- had no significant protocol violations (consideration about exclusion of patients from the PP sample will be performed at the Blind Data Review before the Data Base Lock).

## 4.2 Efficacy analysis

The FA subject sample will be used for the analysis of the efficacy data. Additionally, primary efficacy results analysis will be conducted on the PP sample as the sensitivity analysis. Descriptive statistics will be presented by treatment arm for all planned efficacy endpoints.

The PP subject sample analyses will be based on available data only and no missing data will be imputed.

The FA subject sample analyses will be based ~~how~~ on available data only ~~so~~ and data following the last observation carried forward (LOCF) approach will be used.All parameters will be summarized using descriptive statistics and listed.

### 4.2.1 Primary Efficacy Analysis

The primary efficacy endpoint is:

- 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, in other words, the average of - 6 to 1 days). The Week 4 assessment is the same (data from last 7 days of the corresponding week in the case duration of treatment 28 days: 23 to 29 days or data from the last 7 days before the last treatment day inclusively in the case duration of treatment did not equal 28 days.

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.

ANCOVA analysis will be performed using SAS code for the analysis:

```
ods output LSmeans=LSMeans;
ods output Diffs=CL;
proc mixed data= <dataset_name> ;
        CLASS <treatment> <site>;
        MODEL <change from bl> = <treatment> <site> <baseline>;
  lsmeans <treatment> / pdiff cl;
run;
ods output close;
```

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 (Ha: 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, 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.

As a **Sensitivity analysis # 1**, PP subject sample will be used for analysis of the primary endpoint.

**Sensitivity analysis # 2**, LOCF method - one the FA subject sample will be used for analysis of the primary endpoint.

ANCOVA analysis will be performed using SAS code for the sensitivity analyses # 1 and # 2:

```
ods output LSmeans=LSMeans;
```

```
ods output Diffs=CL;
proc mixed data= <dataset_name> ;
        CLASS <treatment> <site>;
        MODEL <change from bl> = <treatment> <site> <baseline>;
  lsmeans <treatment> / pdiff cl;
run;
ods output close;
```

Missing values will be imputed using: the nearest previous post-baseline non-missing value for treatment period, the EoT or the nearest previous follow-up non-missing value for follow-up period. If patient has a missing value after such an imputation applying, his/her ALT response will be considered as failure.

***Source:*** *NST001, NSL010, NSL017.*

### 4.2.2 Secondary efficacy analysis

The secondary efficacy data are:

- 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 days 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 days over treatment period (NRS-11 0 assessment).
- Change in number of days per week during study treatment period when drotaverine was taken.
- Change in quality-of-life evaluation using IBS-QOL questionnaire versus baseline.

Secondary endpoints “Change from baseline of NRS-11 pain intensity after 4 weeks of treatment”, “Change from baseline of NRS-11 bloating/flatulence intensity after 4 weeks of treatment” and “Change in quality-of-life evaluation using IBS-QOL questionnaire versus

baseline" will be compared between the two treatment groups by means of analysis of covariance (ANCOVA), with treatment, site as fixed effects and baseline value (if available) as covariate. The same SAS code with MIXED procedure as for primary endpoint will be used for these endpoints.

Secondary endpoint "Change in number of days per week during study treatment period when drotaverine was taken" will be compared between the two treatment groups by means of analysis of variance (ANOVA), with treatment, site as fixed effects. To achieve full conformity with ANCOVA in case of missing's the ANOVA analysis will be performed using MIXED procedure as well:

```
ods output LSmeans=LSMeans;
ods output Diffs=CL;
proc mixed data= <dataset_name> ;
        CLASS <treatment> <site>;
        MODEL < change in number of days > = <treatment> <site>;
  lsmeans <treatment> / pdiff cl;
run;
ods output close;
```

The baseline abdominal pain and bloating/flatulence intensity will be determined as the average of daily episodes NRS-11 assessment during 7 days before randomization (last week of screening and run-in period, in other words, the average of daily episodes from - 6 to 1 days). The data from the 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 drotaverine intake. Week 1 (average of data 2 – 8 days), Week 2 (average of data 9 – 15 days), Week 3 (average of data 16 – 22 days) and Week 4 (average of data from the last 7 days of the corresponding week in the case duration of treatment 28 days: 23 to 29 days or data from the last 7 days before the last treatment day inclusively in the case duration of treatment did not equal 28 days).

The proportion of patients with the *Scale* reduction of ≥A% versus baseline during at least 50% of treatment weeks over treatment period must be calculated as:

$$\frac{n_T}{N_T}$$

where $N_T$ is total number of patients in the treatment arm T, $n_T$ is number of patients in the treatment arm T who had reduction of ≥A% versus baseline (week 0) during at least 2 of treatment weeks over treatment period: week 1, week 2, week 3, week 4). Reduction of ≥A% must calculate as:

$$Reduction_i = \frac{\overline{Scale_{Week_i}} - \overline{Scale_{Week_0}}}{\overline{Scale_{Week_0}}} \times 100 \geq A\%$$

The transformation formula used for the IBS-QOL total and scale scores is:

$$\text{Score} = \frac{\text{The sum of the items} - \text{lowest possible score}}{\text{Possible raw score range}} \times 100$$

Where

$$\text{lowest possible score} = \text{number of questions} \times \text{lowest possible score of the items}$$

,

$$\text{possible raw score range} = \text{number of questions} \times (\text{upper possible score of the items} - \text{lowest possible score of the items})$$

The comparisons of treatment arms for secondary endpoints with "Proportion of patients with the…" type will be analyzed using Fisher exact test. The test will be performed by separately for for Mebeverine + Simethicone combination VS Duspatalin (mebeverin) and Mebeverine + Simethicone combination VS Espumisan (simethicone) comparisons.

Fisher exact test will be performed using following SAS code for the analysis:

```
PROC FREQ DATA = [dataset name];
  weight [frequency var] / ZEROS;
  tables [frequency var lvl 1/ frequency var lvl 2] * [Arm] / exact Fisher;
RUN;
```

If SAS code produces the "Row or column sum zero. No statistics computed for this table." output due to insufficient memory available to complete the Fisher exact computations, then the p-value should be assumed as equal 1.0000.

***Source:*** *NST002 – NST004, NSL010, NSL011, NSL012, NSL003, NSL014, NSL015.*

### 4.3 Safety analysis

The Safety subject sample will be used for the analysis of the safety data. In addition to this, three treatment groups will be used: "Mebeverine+Simethicone fixed-dose combination", "Espumisan® (simethicone)" and "Duspatalin® (mebeverin)".

The gap period is 7 days for adverse events, 7 days for vital signs, laboratory measurements and concomitant medications.

The following dictionaries are used for coding of medical terms:

| Medical term | Dictionary | Version |
|---|---|---|
| Concomitant medications | WHO DDE | March 2020, or later |
| Adverse events | MedDRA | 23.1 |
| Medical histories | MedDRA | 23.1 |

Treatment Emergent Adverse Events

An AE that starts during a unique treatment or that already exists before the start of that unique treatment but worsens during the treatment or post-treatment period (if no longer than 7 days after last dose of respective treatment) will be considered as treatment emergent for that unique treatment.

The following unique treatments are distinguished: Mebeverine + Simethicone, 135 mg+80 mg, three times a day; Duspatalin 135 mg three times a day; Espumisan, 80 mg (2 capsules 40 mg) three times a day. AEs will be reported on a per-subject basis, i.e., counting subjects rather than events. This means that if a subject suffers the same AEs repeatedly during the applicable study or treatment period, the event will be counted only once for that period. Repeated events per subject will be summarized according to the following rule: if a subject suffered the same AE more than once, the event will be assigned the worst severity, the closest relationship to the study drug and the earliest starting date. Only treatment emergent AEs (TEAE) will be reported. In the listings, however, all occurrences of the AEs will be presented.

For each unique treatment, TEAES will be summarized by MedDRA primary system organ class (SOC), high level term (HLT) within primary SOC and preferred term (PT) within HLT and primary SOC. Severity and drug-event relationship of adverse events are summarized separately.

In the listings, all occurrences of AEs will be presented together with all relevant information from the eCRFs. In addition, TEAEs will be flagged. Start and end day of the AE and the day of last dose of study drug will be also presented, relative to the start day of the treatment under which is started or worsened and relative to start of any study drug.

SAEs leading to death, non-fatal SAEs, TEAEs leading to study termination, TEAEs leading to discontinuation of study drug will be listed separately.

Vital signs, body weight, waist circumference and body mass index (BMI)

Vital signs include systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate.

Vital signs, body weight, waist circumference and BMI including changes from baseline will be summarized with descriptive statistics per treatment group.

Markedly abnormal values will be identified in accordance with pre-defined criteria, as presented in Table 5 in SAP Module 2.

The number and percentage of subjects with any post-baseline markedly abnormal value under treatment will be presented by variable, treatment. Percentages will be based on the total number of subjects with a baseline and post-baseline measurement of the specified variable in the analysis sample. All markedly abnormal values will be listed.

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

Laboratory data

Hematology and biochemistry values will be reported and analyzed in SI units (International System of Units).

Laboratory test results including changes from baseline will be summarized with descriptive statistics by treatment and cohort.

Each observed hematology and biochemistry value will be categorized whether it is lying below, within, or above the laboratory's reference range. These categories (low, normal, high) plus a category for missing values will be cross-tabulated (shift table) for baseline versus all time points. Only subjects with a value at baseline and the respective time point will be included in the shift table.

Markedly abnormal values will be identified in accordance with pre-defined criteria, as presented in Table 2 and 3 in SAP Module 2.

Additionally, a value of INR > 1.5 will be defined as markedly abnormal value.

The number and percentage of subjects with any post-baseline markedly abnormal value under treatment will be presented by laboratory test and treatment. Percentages will be based on the total number of subjects with a post-baseline measurement of the specified laboratory test in the analysis sample.

All markedly abnormal and/or clinically significant values will be listed.

***Analysis of safety endpoints:***

Safety variables will be summarized descriptively per treatment. Quantitative variables will be described by n, arithmetic mean, SD, minimum and maximum. Qualitative variables will be described by frequency tables containing counts and percentages.

For each unique treatment, treatment emergent AEs will be summarized per primary SOC, per HLT by primary SOC and per PT by HLT and primary SOC. Severity and drug-event relationship of treatment emergent AEs are summarized separately.

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

### 4.3.1 Demographic Data and Other Baseline Characteristics

***Source:*** *DMT002, DML002, VST003, VSL003, NSL016*

Patient distribution, demographic and baseline characteristics will be presented using descriptive statistics. The number and percentage of patients receiving concomitant medications will be presented in frequency tables according to the ATC classification and the generic name. The number of patients with prior medical conditions will be presented. Information on dosage, including daily doses, exposure time and the total dose, will be presented using descriptive

statistics for each treatment group, additionally baseline characteristics will be presented for subgroups (patients with IBS and other functional bowel diseases, patients with constipation, diarrhea, both constipation and diarrhea, neither of them)

All variables in this section will be reported on a by-subject data listing.

Such continuous characteristics as: age, height, weight, body mass index (BMI), body temperature, respiration rate, systolic blood pressure (in sitting position) (SBP), diastolic blood pressure (in sitting position) (DBP), pulse rate will be reported on tables grouped by treatment with the number (n), arithmetic mean, standard deviation (SD), median, minimum (min) and maximum (max) of unique subjects who have at least one measurement of the demographic data or other baseline characteristics.

For more detailed information about values calculations see Module 2

### 4.3.2 Medical History

***Source:*** *MHT001, MHL001, MHL002, NSL001, NST006*

Medical history will be presented in tables grouped by treatment, SOCs, HLTs, PTs and sorted by descending order of total incidence. SOCs, HLTs, PTs will be coded by the Medical Dictionary for Regulatory Activities version 24.0 ENG (MedDRA 24.0 ENG). In addition to this, the information will be reported on a by-subject data listing, for more detailed information see Module 2.

Additionally, the listing for disease information (index diagnosis and start date) and frequency table by index diagnosis will be presented.

An intergroup comparison for two treatment groups is not planned.

### 4.3.3 Physical Examinations

***Source:*** *NSL002*

Physical examinations will be reported on a by-subject data listing with the visits, visit dates of physical examinations.

### 4.3.4 Vital Signs, height and weight

***Source:*** *VST001, VST002, VSL004, VSL005*

All variables in this section will be reported on a by-subject data listing.

All characteristics will be reported on tables grouped by treatment with the number (n), mean, standard deviation (SD), median, minimum (min) and maximum (max) of unique subjects who have at least one measurement of the vital signs (other baseline characteristics).

Also, abnormal vital signs from the module 1 and markedly abnormal vital signs criteria will be reported on table grouped by treatment with the number (n) and percentage (%) of unique subjects with at least one type of measurement of the parameter.

For more detailed information about norms, value calculation etc. see Module 2.

### 4.3.5 Visual Analogue Scales

***Source:*** *NST002, NSL003, NSL014, NSL015*

The results of assessment by visual analogue scales (NRS-11) at screening/run-in and study treatment periods will be presented in by-subject data listing with the name of a scale, time of assessment, units and result of assessment and summarized by treatment group and scale. The number (n), mean, standard deviation (SD), median, minimum (min) and maximum (max) of unique subjects with at least one scale measurement will be presented in the table.

### 4.3.6 Safety Laboratory Data

***Source:*** *LBT001, LBT002, LBT003, LBT004, LBT005, LBL002, LBL003, LBL007, LBL008*

All variables in this section will be reported on a by-subject data listings.

Safety laboratory information will be collected as quantitative (hematology and biochemistry assessments only) and qualitative (all laboratory tests) data. The quantitative data will be reported on listings and tables with the following statistics: the number (n), arithmetic mean, standard deviation (SD), median, minimum (min) and maximum (max) of unique subjects who have at least one measurement of safety laboratory data. In contrast to this, the qualitative data will be reported on shift-tables with the following statistics: the number (n) and percentage (%) of unique subjects with safety laboratory measurement. There are will be presented such characteristics of values as “Low”, “Normal” and “High”.

Each center uses its own safety laboratory norms for hematology and biochemistry assessments and normal values for urinalysis are not defined centrally. Investigators will choose the most appropriate answer (“Normal” or “Abnormal”) for a value. In case an investigator chooses the point “Abnormal” he/she has to define whether the deviation is clinically significant (“Yes” or “No”).

For more detailed information see Module 2.

### 4.3.7 Adverse Events

***Source:*** *AET001, AET002, AET003, AET005, AET006, AET007, AET008, AET009, AET010, AEL002, AEL008, AEL009, AEL010, AEL011, AEL012, AEL013*

Adverse Events will be presented in tables grouped by treatment, SOCs, HLTs, PTs and sorted by descending order of total incidence. SOCs, HLTs, PTs will be coded by the Medical Dictionary for Regulatory Activities version 23.1 ENG (MedDRA 23.1 ENG). In addition to this, the information will be reported on a by-subject data listing.

Adverse Events (TEAEs) started after the last administration of study drug but within the Gap Period after the last administration will also be attributed to the Treatment Period. For more detailed information see Module 2.

An intergroup comparison for two treatment groups is not planned.

### 4.3.8 Time of administration (patient diary)

***Source:*** *NSL004*

Time of administration collected in patient diary will be presented in a by-subject data listing with the date and treatment day of assessment and also time of each administration per day.

### 4.3.9 Concomitant Medication

***Source:*** *CMT001, CML001, CML002*

Concomitant Medication will be presented in tables grouped by treatment, ATC 3rd level or ATC 4th level, preferred name WHO DD and sorted by descending order of total incidence. All parameters except treatment group will be coded by the World Health Organization-Drug Dictionary (WHO-DD) of the latest version. In addition to this, the information will be reported on a by-subject data listing.

Medications started after the last administration of study drug but within the Gap Period (7 days) after the last administration will also be assigned to the Treatment Period. For more detailed information see Module 2.

An intergroup comparison for two treatment groups is not planned.

### 4.3.10 Drug Accountability, Treatment Compliance and Exposure

***Source:*** *DAT001, DAL001, NST005, NSL04*

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:

**Compliance = (N dispensed. – N returned.) / N calc. * 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 calculated percentage compliance will be categorized as:

- Too Low: < 80% compliance.
- Adequate: ≥ 80% to ≤ 120% compliance.
- Too High: > 120% compliance.

Sum dose of study drug (mg), duration of taken study drug (days) and average dose taken per day (mg) will be calculated for each subject. Data is collected in **patient diaries**.

*Duration of taken study drug (days)* will be calculated as sum of days where at least one dose were taken by subject.

*Average dose taken per day (mg)* will be calculated with the following formula:

$$\textbf{Average dose taken per day (mg)} = \frac{\textbf{Sum dose of study drug (mg)}}{\textbf{Duration of taken study drug (days)}}$$

All data of drug accountability, treatment compliance and exposure will be presented in subject data listings and by-treatment group tables.

### 4.3.11 Compliance with selection criteria assessments.

***Source:*** *NSL006, NSL007, NSL008, NSL009*

Pregnancy test, test for HIV, hepatitis B and C, feces analysis for fecal calprotectin and colonoscopy results will be listed only.

## 4.4 Interim Analysis

Interim analysis was removed after amendment. The reason for this was a very steep increase of patients' recruitment over last weeks before interim analysis. Therefore, even if the interim analysis resolution would have been to stop the study, all screened patients would have already completed the study per the protocol. So, conduct of the interim analysis would have been futile.

## 4.5 Data Safety Monitoring Board

Not applicable.

## 4.6 Safety Management Team

Not applicable.

# 5. DESCRIPTION OF NON-STANDARD DATA COLLECTED AND DERIVED VARIABLES

## 5.1 Other Non-Standard Baseline Characteristics

Not applicable.

## 5.2 Non-Standard Disease History

Not applicable.

## 5.3 Efficacy data

The efficacy data collected are:

Efficacy data collected in the study are: assessment of pain abdominal pain and bloating/flatulence intensity as measured by NRS-11 scale.

## 5.4 Non-standard Safety Data

The following non-standard safety data are collected*: Exposure*.

## 5.5 Drug Accountability and Exposure

Drug accountability and exposure variables collected in the study is: number of tablets per day.

Drug accountability and exposure variables calculated during the analysis are: sum dose of study drug (mg), duration of taken study drug (days), average dose taken per day (mg), compliance.

# 6. FURTHER SPECIFICATIONS TO THE STANDARD ANALYSES IN MODULE 2

## 6.1 Trial Design [2]

### 6.1.1 Trial Periods

| | ***Screening and run-in period*** | ***Treatment Period*** | ***Follow up*** |
|---|---|---|---|
| *Mebeverine + Simethicone* | *Screening (Days -21 - 1)* | *Investigational Treatment (Days 1-29)* | *Follow up (Day 36)* |
| *Duspatalin* | *Screening (Days -21 - 1)* | *Investigational Treatment (Days 1-29)* | *Follow up (Day 36)* |
| *Espumisan* | *Screening (Days -21 - 1)* | *Investigational Treatment (Days 1-29)* | *Follow up (Day 36)* |

### 6.1.2 Trial Elements

| *Trial Element* | *Description of Element* | *Rule for Start of Element* | *Rule for End of Element* | *Planned Duration of Element* |
|---|---|---|---|---|
| *Screen* | *Screening and Randomization* | *Informed consent obtained* | *First dose of treatment* | |
| *Treatment "Mebeverine+ Simethicone"* | *Investigational Treatment of taken study drug "Mebeverine + Simethicone"* | *First administration of "Mebeverine + Simethicone"* | *6 days after first administration of "Mebeverine + Simethicone"* | *7 days* |
| *Treatment "Duspatalin"* | *Investigational Treatment of taken study drug "Duspatalin"* | *First administration of "Duspatalin"* | *6 days after first administration of "Duspatalin"* | *7 days* |
| *Treatment "Espumisan"* | *Investigational Treatment of taken study drug "Espumisan"* | *First administration of "Espumisan"* | *6 days after first administration of "Espumisan"* | *7 days* |
| *FOLLOW UP* | *Follow-up period* | *Date of last study drug administration* | *Last Contact with Subject* | *1 day* |

### 6.1.3 Trial Arms

| ***Trial Arm*** | ***Elements*** | | | | |
|---|---|---|---|---|---|
| | ***Screen*** | ***Treatment "Mebeverine + Simethicone"*** | ***Treatment "Duspatalin"*** | ***Treatment "Espumisan"*** | ***FOLLOW UP*** |
| *Mebeverine + Simethicone* | *Screening and Randomization* | *Investigational Treatment of taken study drug "Mebeverine + Simethicone"* | – | – | *Follow-up period* |
| *Duspatalin* | *Screening and Randomization* | – | *Investigational Treatment of taken study drug "Duspatalin"* | – | *Follow-up period* |
| *Espumisan* | *Screening and Randomization* | – | – | *Investigational Treatment of taken study drug "Espumisan"* | *Follow-up period* |

### 6.1.4 Unique Treatments

The trial arms for this study are made up of the following unique treatments*:*

| ***Unique treatment*** | | ***Arm*** | ***Elements*** | | | | |
|---|---|---|---|---|---|---|---|
| ***Description*** | ***Label*** | | ***Screen*** | ***Treatment "Mebeverine + Simethicone"*** | ***Treatment "Duspatalin"*** | ***Treatment "Espumisan"*** | ***FOLLOW UP*** |
| *Mebeverine + Simethicone, 135 mg+80 mg, three times a day* | *Mebeverine + Simethicone* | *Mebeverine + Simethicone* | *Screening and Randomization* | *Investigational Treatment of taken study drug "Mebeverine + Simethicone"* | – | – | *Follow-up period* |
| *DuspatalinDuspatalin–* | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Duspatalin 135 mg three times a day* | *Duspatalin* | *Duspatalin* | *Screening and Randomization* | – | *Investigational Treatment of taken study drug "Duspatalin"* | – | *Follow-up period* |
| *Espumisan, 80 mg (2 capsules 40 mg) three times a day* | *Espumisan* | *Espumisan* | *Screening and Randomization* | – | – | *Investigational Treatment of taken study drug "Espumisan"* | *Follow-up period* |

### 6.1.5 Visits and related definitions

| ***Test / Examination*** | ***Visit name*** | ***Visit Label*** | ***Visit Number*** | ***Reference Start Date/Time*** | ***Relative Day Number*** |
|---|---|---|---|---|---|
| *Informed Consent Form, patient registration* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| *Demography, medical history* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| *Weight, Height (screening only), BMI* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| | *Visit 1* | *Visit 1 (week 0)* | *2* | *Date of first Drug Adminitration* | *1* |
| | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |

| ***Test / Examination*** | ***Visit name*** | ***Visit Label*** | ***Visit Number*** | ***Reference Start Date/Time*** | ***Relative Day Number*** |
|---|---|---|---|---|---|
| *Physical examination* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |
| *Vital signs* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| | *Visit* | *Visit 1 (week 0)* | *2* | *Date of first Drug Adminitration* | *1* |
| | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |
| *Hematology* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |
| *Biochemistry* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |

| ***Test / Examination*** | ***Visit name*** | ***Visit Label*** | ***Visit Number*** | ***Reference Start Date/Time*** | ***Relative Day Number*** |
|---|---|---|---|---|---|
| *Pregnancy test* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| *Urinalysis* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |
| *Tests for HIV, hepatitis B and C* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| *Feces analysis for fecal calprotectin* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| *Colonoscopy* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| *ECG* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| *Randomization* | *Visit 1* | *Visit 1 (week 0)* | *2* | *Date of first Drug Administration* | *1* |
| *Abdominal pain intensity on the NRS-11 scale* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |

| ***Test / Examination*** | ***Visit name*** | ***Visit Label*** | ***Visit Number*** | ***Reference Start Date/Time*** | ***Relative Day Number*** |
|---|---|---|---|---|---|
| | *Visit 1* | *Visit 1 (week 0)* | *2* | *Date of first Drug Administration* | *1* |
| | *Visit 2 (Telephone Call)* | *Visit 2 (Telephone Call)* | *3* | *Date of Telephone Call* | *15 (+-1)* |
| | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |
| *Flatulence intensity on the NRS-11 scale* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| | *Visit 1* | *Visit 1 (week 0)* | *2* | *Date of first Drug Adminitration* | *1* |
| | *Visit 2 (Telephone Call)* | *Visit 2 (Telephone Call)* | *3* | *Date of Telephone Call* | *15 (+-1)* |
| | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |
| *Stool frequency* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| | *Visit 1* | *Visit 1 (week 0)* | *2* | *Date of first Drug Adminitration* | *1* |
| | *Visit 2 (Telephone Call)* | *Visit 2 (Telephone Call)* | *3* | *Date of Telephone Call* | *15 (+-1)* |

| ***Test / Examination*** | ***Visit name*** | ***Visit Label*** | ***Visit Number*** | ***Reference Start Date/Time*** | ***Relative Day Number*** |
|---|---|---|---|---|---|
| | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |
| *Bristol stool scale* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| | *Visit 1* | *Visit 1 (week 0)* | *2* | *Date of first Drug Adminitration* | *1* |
| | *Visit 2 (Telephone Call)* | *Visit 2 (Telephone Call)* | *3* | *Date of Telephone Call* | *15 (+-1)* |
| | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |
| *Patient diary distribution* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| | *Visit 1* | *Visit 1 (week 0)* | *2* | *Date of first Drug Adminitration* | *1* |
| *Patient diary assessment* | *Visit 1* | *Visit 1 (week 0)* | *2* | *Date of first Drug Adminitration* | *1* |
| | *Visit 2 (Telephone Call)* | *Visit 2 (Telephone Call)* | *3* | *Date of Telephone Call* | *15 (+-1)* |
| | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |

| ***Test / Examination*** | ***Visit name*** | ***Visit Label*** | ***Visit Number*** | ***Reference Start Date/Time*** | ***Relative Day Number*** |
|---|---|---|---|---|---|
| *Evaluate the quality of life (IBSQOL questionnaire)* | *Visit 1* | *Visit 1 (week 0)* | *2* | *Date of first Drug Adminitration* | *1* |
| | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |
| *Study drug dispense* | *Visit 1* | *Visit 1 (week 0)* | *2* | *Date of first Drug Adminitration* | *1* |
| *Study drug accountability and compliance assessment* | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |
| *Study drug return* | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discontinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |
| *Adverse events* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| | *Visit 1* | *Visit 1 (week 0)* | *2* | *Date of first Drug Adminitration* | *1* |
| | *Visit 2 (Telephone Call)* | *Visit 2 (Telephone Call)* | *3* | *Date of Telephone Call* | *15 (+-1)* |
| | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |
| | *Follow up* | *Follow up* | *5* | *Date of Follow up* | *36 (+1)* |

| ***Test / Examination*** | ***Visit name*** | ***Visit Label*** | ***Visit Number*** | ***Reference Start Date/Time*** | ***Relative Day Number*** |
|---|---|---|---|---|---|
| *Concomitant medications* | *Screening* | *Screening* | *1* | *Date of Informed consent obtained* | *-21…-7* |
| | *Visit 1* | *Visit 1 (week 0)* | *2* | *Date of first Drug Adminitration* | *1* |
| | *Visit 2 (Telephone Call)* | *Visit 2 (Telephone Call)* | *3* | *Date of Telephone Call* | *15 (+-1)* |
| | *Visit 3 (End of Trial)* | *Visit 3 End of Trial or Early Discantinuation visit* | *4* | *Date of last Drug Administration* | *29 (+-1)* |
| | *Follow up* | *Follow up* | *5* | *Date of Follow up* | *36 (+1)* |

## 6.2 Further Specifications to the Standard Tables in Module 2

Not applicable

## 6.3 Other Further Specifications

Not applicable