Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a blue or black bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

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TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: LUBIPROSTONE-3002

A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Lubiprostone for the Treatment of Chronic Idiopathic Constipation

PHASE 3

Version**:** Final

Date**:** 12th April 2017

Prepared by:

███████, M.Sc.

████████████████, GI TAU

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1.0 APPROVAL SIGNATURES

Electronic signatures can be found on the last page of this document.

Study Title: A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Lubiprostone for the Treatment of Chronic Idiopathic Constipation

TDC Approvals:

███████████████████████████

13 APR 2017
Date

██████████████, GI TAU

██████████████████████████

13 Apr 2017
Date

████, M.Sc.

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Marketed Products Group Takeda Development Center INC –US

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2.0   TABLE OF CONTENTS

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3.0   LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
BID	bis in die (twice a day)
BM	bowel movement
BMI	body mass index
BUN	blood urea nitrogen
CIC	chronic idiopathic constipation
CPK	creatine phosphokinase
CRF	case report form
ECG	electrocardiogram
FAS	full analysis set
GGT	γ-glutamyl transferase
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IVRS	Interactive Voice Response System
LDH	lactate dehydrogenase
LLN	lower limit of normal
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
PAC-QoL	patient assessment of constipation – quality of life
PD	pharmacodynamics
PK	pharmacokinetics
QOL	quality-of-life
PPS	per protocol set
PRO	patient-reported outcome
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SBM	spontaneous bowel movement
SD	standard deviation
SDB	standard database
TLGs	tables, listings, and graphs
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary

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4.0   OBJECTIVES

4.1.   PRIMARY OBJECTIVES

The primary objective of this study is to evaluate the efficacy and safety of oral administration of lubiprostone 24 μg BID for 4 weeks in subjects with CIC compared with placebo.

4.2.   STUDY DESIGN

This is a phase 3, randomized, double-blind, parallel-group, placebo-controlled study in subjects with CIC as determined by the Rome III Diagnostic Criteria for Functional Constipation [4]. This study consists of a 14-day Screening Period,a subsequent 4-week (28 days) Double- Blind Treatment Period in which subjects will receive either lubiprostone or matching placebo BID and a 2 week follow-up period. Subjects will be randomized to either active lubiprostone or placebo in a 1:1 ratio. During the Screening Period, the defecation behavior of each subject is recorded in a diary to confirm he/she has constipation. The subject diary will be distributed on Study Days -15, -1, 8 and 15. Subjects will be instructed to keep the diary every day including on the morning of Visit 1 for the entire week.

Use of all existing laxatives is stopped at the beginning of the Screening Period (Visit 1). Subjects are instructed not to change their diet or lifestyle habits during the study. A total of 10 mg of bisacodyl suppository (or any equivalent drug) may be prescribed as a standard rescue medication if a subject has no adequate bowel movement for 3 consecutive days during the Screening Period of the study. When bisacodyl suppository does not improve constipation, glycerin enema (or equivalent drug) will be given. Subjects are instructed to complete their diaries before using rescue medications.

If the rescue medications fail to improve constipation, the investigator may decide to use another rescue medication. The recommendation may include a medication from the excluded medication list other than any form of polyethylene glycol, linaclotide, methylnaltrexone, or prucalopride, all of which are considered prohibited rescue medications. No rescue medication may be given 24 hours prior to and until 48 hours after the first dose of the study drug (Day 1). Subjects who use a rescue medication within 24 hours before the first dose of study drug on Day 1 should be withdrawn from the study. Those who use a rescue medication within 48 hours after dosing on Day 1 will be discontinued from the study by the investigator. The dose and mode of administration of rescue medications must be recorded in the electronic case report form (eCRF).

Approximately 150 subjects whose constipation is confirmed during the Screening Period will be randomized in the Double-Blind Treatment Period to receive either lubiprostone or matching placebo BID. Others whose constipation does not satisfy the criteria during the 14-day Screening Period or those who receive a rescue medication within 24 hours prior to the first dose on Day 1 are ineligible for randomization in the Double-Blind Treatment Period and therefore will be excluded from the study. Subjects who satisfy the inclusion criteria and do not meet the

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exclusion criteria are randomized to 1 of the treatment groups in the order of the number assigned. Approximately 150 subjects with CIC will be randomized to 2 groups: active treatment or placebo in a 1:1 ratio (75 subjects each) in a double-blinded manner.
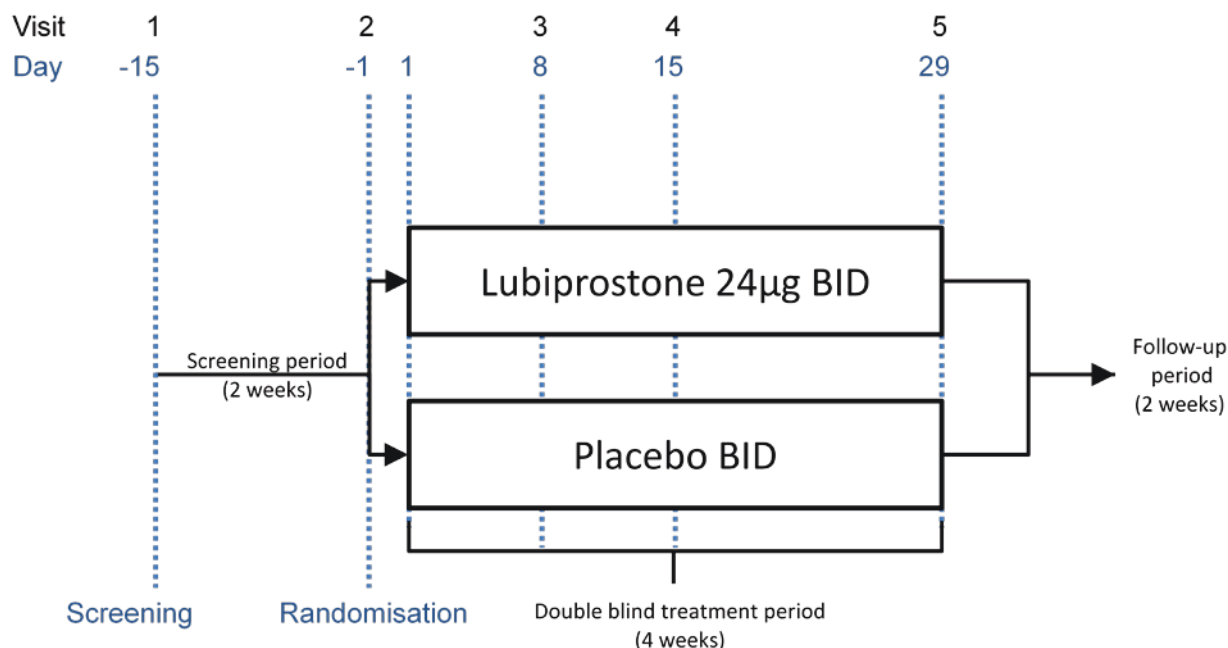
Subjects will be instructed to take 1 capsule BID, orally, at the same time of the day, preferably in the morning with breakfast and in the evening with dinner. Subjects are to begin their study drug treatment in the morning with breakfast following Visit 2.

Subjects will return to the study site on approximately Study Days 8, 15, and 29 during the 4 weeks of double-blind treatment and will be followed for an additional 2 weeks during the Follow-Up Period, in which no treatment will be administered.

At the investigator's discretion, with consideration to subject's bowel movement frequency and consistency, dose adjustments (dose reduction) may be made in a double-blind manner. Dose adjustment should be documented in the subject's source notes. Procedure for reduction of study drug dose due to Adverse Events is described in Section 7.7.

Subjects who withdraw prematurely will be seen within 1 week of discontinuation for an Early Termination Visit. A schematic of the study design is included as Figure 1. A schedule of assessments is listed in Appendix A.

Figure 1 Schematic of Study Design

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5.0   ANALYSIS ENDPOINTS

Primary Endpoint

Spontaneous bowel movement (SBM) frequency in Week 1 of study drug administration.

Secondary Endpoints

SBM frequency (Week 2, 3, and 4).

Proportion of subjects who have a SBM within 24 hours after first dose.

Mean degree of straining (Week 1, 2, 3, and 4).

Mean degree of stool consistency (Week 1, 2, 3, and 4).

Weekly abdominal symptoms score (bloating and discomfort) (Week 1, 2, 3, and 4).

Weekly responder rate (Week 1, 2, 3 and 4)

Additional Endpoints

Quality of life evaluation using the standard Patient Assessment of Constipation—Quality of Life (PAC-QOL) Questionnaire.

Safety

The safety of lubiprostone will be evaluated by the following parameters:
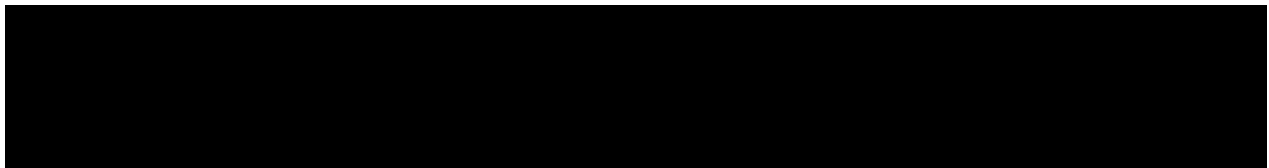
Adverse events (AEs)

Clinical laboratory values.

Vital signs, including body temperature, blood pressure, heart rate, and body weight.

Physical examination.

Exploratory Endpoints

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6.0   DETERMINATION OF SAMPLE SIZE

Assuming equal allocation, a power of 90%, an alpha level of 0.05 for a 2-sided test, a placebo mean of 4 (standard deviation of 2.7), and a treatment mean of 5.9 (standard deviation of 4) for SBM frequency at Week 1 and using the Wilcoxon-Mann-Whitney test [1], a total sample size of 146 is required. The Wilcoxon-Mann-Whitney test is a non-parametric test of the null hypothesis that the distribution is the same for both placebo and treatment responses against the alternative that there is a location difference between the two. The primary analysis will be conducted using the van Elteren test, which is a stratified version of the Wilcoxon-Mann-Whitney test, use of the Wilcoxon-Mann-Whitney test for sample size estimation will provide an approximate sample size for the van Elteren analysis. The estimates of placebo and treatment response are based on a previous study conducted by Sucampo Pharmaceuticals in the United States of America (Protocol No. RTU/0211SC0131).

The primary endpoint requires subjects to complete at least 4 days of the study diary, therefore assuming a non-evaluable rate of 3% by Day 4 an additional 4 subjects are required, giving a total of 150 subjects.

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7.0   METHODS OF ANALYSIS AND PRESENTATION

7.1   GENERAL PRINCIPLES [OR CONSIDERATIONS]

Continuous data will be summarized using number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum. Summary statistics for continuous data will only include subjects with a non-missing value for the data being summarized.

Categorical data will be summarized using the number and percent of subjects for each category where appropriate. Missing categories will be used for categorical data when missing data is present. The calculation of percentages will take into account missing responses.

All confidence intervals, statistical tests, and resulting p-values will be reported as 2-sided unless otherwise stated. P-values (when rounded to three decimals) less than or equal to α (=0.05) are reported as "statistically significant".

Means, LS means, and medians will be presented to 1 more decimal place than the recorded data. Where presented, SDs and standard errors will be presented to 2 more decimal places than the recorded data. Confidence intervals for parameter estimates will be presented using the same number of decimal places as those recorded for the parameter point estimate.

Alternative methods of analysis of the data may be considered prior to un-blinding should some of the assumptions underlying the proposed analyses not be met. However, the reasons for any departures from the planned approach and methods will be documented fully.

Centers may be pooled geographically if necessary for analysis purposes.

Version 9.4 or later of SAS®, will be used to provide all data summaries, statistical analyses, and data listings.

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Study Visit Windows

For BM data the assignment of data to each week (1, 2, 3 and 4) will be calculated from the date and time of the morning dose on Day 1. If no morning dose was taken on Day 1, then the date of Day 1 will be used and the time of the first recorded morning dose will be used. Weeks will be calculated as 168-hour intervals starting from this time. Note that any diary entries prior to this will be assigned to the screening period. Where missing dates or times do not allow the assignment of diary data to a treatment period (Screening or double blind) then it will be assumed that all data in the Screening booklet was recorded during Screening and all data in the remaining booklets were recorded after the booklets were provided to subjects. Abdominal symptom assessments will be assigned to the week as recorded in the diary. PAC-QOL is assessed at Day -1, Week 2 (Day 15) and Week 4 (Day 29). PAC-QOL assessments will be assigned to the time point relating to the visit at which they are recorded, regardless of actual study day. Assessments conducted at an Early Termination Visit will be assigned to the next scheduled visit that would have taken place if the subject had not discontinued, e.g. if the subject withdraws prior to Week 2 then the Early Termination Visit assessment will map to Week 2, whereas if the Early Termination Visit occurs after Week 2 then the assessment will be assigned to Week 4.

	Screening		Double Blind Treatment Period				Follow-up Phone Contact
Study Day/Week	**Screening**	**Randomization**	**First Dose**	**Week 1**	**Week 2**	**Final Visit / Early Termination Visit** **Week 4**	
Visit Number:	1	2	-	3	4	5	-
Day	-15	-1	1	8	15	29	43

7.2 ANALYSIS SETS

Total Set: The total set consists of all subjects who signed the informed consent form, including subjects withdrawn prior to randomization.

Full Analysis Set (FAS): This will consist of all subjects randomized to receive study treatment whether or not they received treatment. Subjects will be reported according to their randomized treatment group regardless of treatment received.

Per-Protocol Analysis Set (PPS): The PPS will consist of subjects in the FAS with the additional following criteria for exclusion:

- Did not receive study treatment as per randomization schedule (including not receiving any randomized treatment)
- Dose of randomized treatment was adjusted.

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- Violated inclusion criteria, such as:

  - Does not have a history of constipation defined as SBM frequency of less than 3 times per week on average for 6 months or longer (and observed during Screening Period).

  - Does not have SBMs with ≥1 of the following 3 symptoms for the last 6 months or longer, in at least 1 out of every 4 bowel movements: scybalum stool or hard feces, straining, or the sensation of incomplete evacuation.

  - The subject rarely has loose stools without the use of laxatives.

- Violated exclusion criteria, such as:

  - The subject has a history or clinical manifestations of significant mechanical obstruction (intestinal obstruction due to tumor, hernia etc).

  - Has chronic constipation due to a secondary cause (medications, diabetes mellitus, hypothyroidism, depression, etc).

  - Has sufficient criteria for IBS or there is a functional defecation disorder.

  - BM frequency is 3 or more per week.

  - SBM frequency has been less than 3 times per week for less than 6 months in duration or whose symptoms associated with SBM have been present for less than 6 months (hard feces, sensation of incomplete evacuation, or straining).

  - Received treatment with a rescue medication within 24 hours prior to the first dose on the morning of Day 1.

  - Has megacolon/megarectum or has received a diagnosis of intestinal pseudo-obstruction.

  - Has confirmed or suspected organic disorders of the large intestine (obstruction, stenosis, carcinoma, or inflammatory bowel disease). Any subject in whom total colonoscopy has detected a polyp requiring treatment is excluded from this study.

  - Has been hospitalized for gastrointestinal or abdominal surgery within 3 months before the start of this study.

  - Use of any excluded medications, procedures or treatments prior to the assessment of the primary endpoint.

Any other significant event interfering with efficacy evaluation of primary endpoint, to be decided at the Targeted Data Review Meeting, for example,. Definitions of criteria constituting major deviations will be provided, prior to unblinding.

Therefore subjects will be reported according to their treatment group.

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Safety Analysis Set (SAF): This will consist of all subjects who receive study treatment. Subjects will be assigned to the treatment group according to the actual treatment received.

The FAS will be used for efficacy analyses. Supportive analyses based on the PP will be performed for the primary efficacy variable. The SAF will be used for all safety analyses.

7.3 DISPOSITION OF SUBJECTS

A summary of screened subjects will display the number of subjects screened and the number of subjects in the Total Set, FAS, SAF and PPS; overall and at each center.   Reason for exclusion from each analysis population will also be presented.

Subject disposition will be summarized for the Total Set and will include the frequency and percentage of subjects who completed each visit, the frequency and percentage of subjects who were screen failures, the frequency and percentage of subjects who discontinued prematurely from the study along with the frequency and percentage of subjects for each reason for screen failure/discontinuation. This information will be displayed by treatment.

The primary reason for screen failure should be recorded using the following categories:
1. Pretreatment event (PTE) or adverse event (AE),
2. Did not meet inclusion criteria or did meet exclusion criteria.
3. Significant protocol deviation.
4. Lost to follow-up.
5. Voluntary withdrawal (specify reason).
6. Study termination.
7. Other (specify reason).

The primary reason for discontinuation should be recorded using the following categories:
1. PTE or AE, including liver function test (LFT) abnormalities.
2. Significant protocol deviation.
3. Lost to follow-up.
4. Voluntary withdrawal.
5. Study termination.
6. Pregnancy.
7. Lack of efficacy.
8. Unblinding of subject treatment.
9. Other.

Significant protocol deviations for the FAS will be summarized according to the category of deviation, by site and treatment group.

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7.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will include age (years) at date of informed consent, race, ethnicity, smoking status, gender, height (cm), weight (kg) at Screening, body mass index (BMI) (kg/m2) at Screening.

Demographic and baseline characteristics will be summarized by randomised treatment group and total for the Total Set. Subjects in the Total Set who were screen failures will be included in a 'Screen Fail' group for presentation purposes and included in the total column.

7.5 MEDICAL HISTORY AND CONCURRENT MEDICAL CONDITIONS

Any significant relevant illness that was resolved before screening will be recorded as medical history. Any relevant illness that is present at the day of the screening visit will be documented as concomitant illness. Medical histories and concomitant illnesses will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), current version. Medical histories and concomitant illnesses will be summarized separately, by system organ class (SOC) and preferred term (PT). Frequencies and percentages will be displayed by treatment and in total.

7.6 MEDICATION HISTORY AND CONCOMITANT MEDICATIONS

Medication history information includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 1 month prior to signing of informed consent.

Concomitant medication is any medication other than the IMP that is administered during the trial including screening. Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug). Concomitant medications and medication history will be summarized separately for the SAF as the frequency and percentage of patients taking each medication. If a patient took a particular coded medication more than once, the patient will be counted only once for that medication total. If a patient took more than one medication in a particular therapeutic class, the patient will be counted only once in that therapeutic class total.

A total of 10 mg of bisacodyl suppository (or an equivalent drug) may be prescribed as a standard rescue medication if a subject has no adequate BM for 3 consecutive days during the study. When bisacodyl suppository does not improve constipation, glycerin enema (or equivalent drug) may be given. Rescue treatment will be summarized for the FAS by the frequency and percentage of patients for each applied type and time to active rescue treatment.

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7.7 STUDY DRUG EXPOSURE AND COMPLIANCE

Study drug exposure and compliance will be summarized by randomised treatment group for the SAF and FAS respectively. No inferential statistics will be presented. Subject diary compliance will be presented summarized by randomised treatment group and total for the FAS for both screening and double blind periods separately.

Duration of exposure to drug (days) will be calculated as the number of days from the date of first dose to the date of last dose of study drug inclusive. So that exposure = date of last dose-date of first dose + 1. Exposure will be summarised as a continuous variable. Doses taken after Day 28 will be included in the calculation of compliance, as specified compliance is calculated up to the date of the last dose taken,

Study drug is dispensed to subjects on Day -1 only. Subjects are supplied with a bottle containing enough drug for 28 days + 2 extra days. Subjects will be required to bring their study drug bottle with them for each visit of the double blind treatment period; Day 8 (visit 3), Day 15(visit 4) and Day 29 (visit 5). Subjects also record their daily medication intake in their diary.

Study drug compliance will be calculated by:

$$100 \times \left(\frac{\text{number of capsules taken}}{\text{number of capsules expected to be taken}} \right)$$

Overall compliance calculation is considered to indicate compliance with the dosing regimen rather than dosing duration, e.g. if a subject takes all expected doses whilst in the study but withdraws early then compliance will be considered 100%.

Overall compliance will be calculated using:

The number of capsules taken is defined as the difference between the total number of capsules dispensed and the total number of capsules remaining at the last visit.

The number of capsules expected to be taken is defined as the number of capsules prescribed per day (BID dosing) multiplied by the number of days from Day 1 to the date of last dose (last dose date – Day 1 date). If the last dose was a morning dose then this will be increased by 1, if the last dose was an evening dose then this number will be increased by 2. This is to account for the fact that the subject may stop dosing in the morning or evening of the last dose date.

Week 1 compliance will be calculated using:

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The number of capsules taken is derived from the subject diary and will be calculated as the number of completed dosing entries in the diary for the first 7 days following randomization (i.e. Day 1 to Day 7 inclusive). This should be 2 per day, a morning and evening dosing record).

The number of expected capsules to be taken will be calculated as 14 (7 days of BID dosing) if the subject has not withdrawn prior to completing 7 days of dosing. If the subject has withdrawn early (less than 7 days on treatment) then this number will be calculated as for overall compliance.

Overall study drug compliance should also be calculated from the subject's diary, where the number of tablets taken is derived from the number of completed entries (there should be 2 per day, a morning and evening record). The number of expected capsules is calculated as before. If there is a discrepancy between calculated compliance values then unless there is a recorded comment explaining the discrepancy and indicating that the diary value is correct (e.g. a comment may have been recorded indicating that some tablets were lost) the overall compliance calculated using capsule counts will be taken as the correct value.

Study drug compliance will be summarized, for overall compliance and for compliance during Week 1, as a continuous variable and additionally, as a categorical variable, with the following categories:

- Compliance < 70%

- Compliance ≥ 70% and < 90%

- Compliance ≥ 90% and < 110%

- Compliance >110%

Compliance with the diary will also be assessed. During the double blind period there should be 2 records of study drug intake per day, note that if a dose was missed then 'Not taken' should be ticked, therefore there should be 2 entries per day, regardless of actual doses taken. Also for each day there are two questions requiring an answer (Yes/No): "Did you have bowel movement today?" and "Did you use rescue medication today?" A diary shall be considered compliant for that day if all expected entries for that day are recorded. At a minimum this will mean both questions have been answered and two drug accountability records (either time or 'Not taken'). If 'Yes' has been answered to any question then at least one related entry should be present for that day, with all expected data fields completed. Compliance during the screening period will be similar, except that no study drug intake is recorded and bowel movement is captured either as 'I did not have a bowel movement today" ticked or at least one completed bowel movement record. Subject Diaries are dispensed on Day -15 (visit 1) Day -1, Day 8 and Day 15. Diary compliance checks are conducted at each visit, except screening and follow-up. Diary compliance should be calculated as:

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$$100 \times \left(\frac{\text{number of days completed}}{\text{number of days expected to be completed}} \right)$$

Subject diary compliance will be summarized, for overall compliance during the double blind period and Week 1, as a continuous variable and additionally, as a categorical variable, with the following categories:

- Compliance < 70%

- Compliance ≥ 70% and < 80%

- Compliance ≥ 80% and < 90%

- Compliance ≥ 90% and < 100%

- Compliance = 100%

7.8 EFFICACY ANALYSIS

The primary and secondary endpoints will be derived from the daily diary data entered by patients.

Two-sided tests at a significance level of α=5% will be used throughout unless otherwise stated. The null hypothesis is that lubiprostone is equal to placebo against the alternative that lubiprostone is different to placebo. All analyses will be performed using the FAS. Analyses specified for the PP are to be regarded as supportive evidence. There will be no adjustment for multiplicity.

All efficacy endpoints will be summarized by treatment and visit. If baseline measures are also defined and collected for an efficacy endpoint then change from Baseline at each visit will also be presented by summary statistics by treatment and visit. Change from baseline will be calculated as (post-baseline value) – (baseline value). Baseline is defined as the last recorded measurement prior to treatment.

For diary data, baseline values will be the average of all diary data from the screening period (Days –14 through –1, inclusive, relative to day of first dose). If more than 14 days of diary data are collected during the screening period only the data from Day -14 onwards will be used. If fewer than 8 days are available then the baseline value will be set to missing.

Centers may be pooled geographically if necessary for analysis purposes. This will be determined before database lock.

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For weekly SBM frequency, at least 4 days of diary data are required to compute a weekly estimate, if there are less than 4 days recorded in a week then the SBM frequency for that week will be set to missing.

As the primary endpoint is within the first week of study treatment and only 4 days of diary collection are required it is not anticipated that missing values should be a cause of concern therefore the LOCF technique will be used to impute missing values for efficacy analysis purposes only. For a given subject, the most recent nonmissing data point will be carried forward to the subsequent week where data are missing. Details for each efficacy parameter are given below. It is expected, based on previous studies, that the number of subjects with in-sufficient post baseline data for the primary endpoint will be small therefore a simple approach to handling missing data will be used. Where there is no post baseline efficacy data then the baseline value will be used, it is expected that the number of SBMs should increase for those on treatment, therefore using a baseline value for missing post baseline data assumes no treatment effect, this approach can be considered conservative,. To examine the effect of the requirement to have at least a minimum of 4 days post baseline efficacy data for the primary endpoint an additional analysis, stratified by centre, of the primary endpoint, using the stratified van Elteren test [2], will be conducted using all valid SBM data post baseline even when less than 4 days data is present, only where there is no post baseline data will baseline be used in this analysis.

An SBM is defined as any BM that does not occur within 24 hours after rescue medication use. Certain periods after taking rescue medication will be defined as "blackout periods" during which BMs are considered as non-spontaneous. Blackout periods, including those with missing or partial times for rescue medication use in the diary, will be handled as follows:

0-24 hours post rescue medication intake if the time is fully specified.

0-24 hours post rescue medication intake if the hour is present, but the minute is missing. The blackout time will commence from the imputed time. If the minutes are incomplete or missing from either the rescue medication or bowel movement entry then it is assumed that the missing values are zero and an imputed time will be calculated. e.g.

1	5	_	_	=	1	5	0	0
2	1	5	_	=	2	1	5	0

0-48 hours, beginning from midnight on the day the rescue medication intake is recorded for, if the hour is missing from the time entry for the rescue medication.

Box plots will be produced for each weekly measure (SBM frequency, mean degree of straining, mean degree of stool consistency and weekly abdominal symptoms scores) by treatment over time from baseline to Week 4. Additionally graphs presenting histograms of SBM frequency will also be produced by treatment for each week.

7.8.1   Primary Efficacy Endpoint(s)

The primary efficacy endpoint is SBM frequency at Week 1; an SBM is defined as any BM that does not occur within 24 hours after rescue medication use. Since rescue medication use will be disallowed during Week 1, the SBM frequency should equal the BM frequency. In the case of protocol violators, the analysis will be based on SBMs.

In order to adjust for early withdrawals or those with less than 7 days diary data, weekly SBM frequency will be calculated as follows:

7 x (Number of SBMs / Number of days)

Where the number of days is the number of days during the week that the subject was in the study. Weeks will be calculated as 168-hour intervals starting from the day after randomization (Day1), if there is no time recorded for the morning dose on Day1 then the time of the first recorded morning dose will be used. The number of days will generally be 7 unless a subject drops out during a treatment week. If the number of days is less than 4, then the data will be considered insufficient and the frequency will be missing.

Primary Analysis

Since outliers are commonly observed in these data, parametric models may not be robust. The efficacy data will therefore be analyzed by a van Elteren test stratified by center. If necessary, small centers will be pooled as mentioned above. This procedure will test the null hypothesis of equal SBM rates between treatments at the end of Week 1 versus the alternative hypothesis of non-equality between the 2 groups; the test will be conducted at a 2-sided significance level of 0.05. A related 95% confidence interval and point estimate will be provided for the treatment difference; the confidence interval will be estimated by inverting the hypothesis test. This endpoint will be analyzed for the FAS.

Sensitivity Analyses

The primary analysis as described above will be repeated using the PP rather than the FAS. An additional sensitivity analysis using the FAS assuming a 'worse-case' scenario approach will also be conducted, where missing values, including those with < 4 days diary data, are assigned the worst case values (the lowest SBM frequency for week 1) recorded in the study by any subject for that endpoint at that time.

Additionally the endpoint will be analyzed using robust analysis of variance (ANOVA) models (by M-estimation [3] using PROC ROBUSTREG in SAS) with center and treatment in the model as a sensitivity analysis using the FAS. The interaction between treatment and center will also be examined in a separate model, using robust ANOVA methods as previously described.

To examine the effects of any permanent dose reduction in response to an AE (as recorded on the eCRF) an additional sensitivity analysis will also be performed. This will be performed on the

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FAS where data from those subjects with a dose reduction will be excluded from the time of dose reduction (taken as date of last BID dose + 12 hours, e.g. if the evening dose is removed then the time will be from the morning dose + 12 hours, if the morning dose is removed then it will be from the previous day's evening dose + 12 hours) and subjects will be treated as a drop-out from this time point onwards. This will be implemented using robust ANOVA. Additionally, another factor will be added to the robust ANOVA model to examine the effect of dose reduction (), this will be performed on the FAS. This analysis will not be carried out if the number of subjects with a dose reduction within the first week is less than 5%.

7.8.2   Secondary Efficacy Endpoint(s)

The interaction of treatment and center and the effect of dose reduction will not be examined for any secondary endpoints. All secondary endpoints will be analyzed for the FAS only.

<u>SBM frequency at Week 2, 3 and 4</u>

The secondary endpoint will be analyzed as specified for the primary endpoint separately for each week.

Additionally for patients with a missing Week 2 frequency estimate (where diary days < 4 in Week 2) the Week 1 estimate will be carried forward, if available. For the worse-case analysis all missing Week 2 values will be assigned the lowest SBM frequency for week 2.

<u>Proportion of subjects with an SBM within 24 hours after first dose</u>

The 24 hour period will be taken from the time of the first recorded dose in the patient diary. If the efficacy data is missing for the first 24 hours following this dose then it will be assumed that the patient did not experience any BM (including SBMs) during this period, this is based on the assumption that a patient is more likely to complete the diary on any particular day if they experience a BM than if they did not. The proportion of subjects with an SBM within 24 hours after first dose in Week 1 will be analyzed by a Cochran-Mantel-Haenszel (CMH) test stratified by center. Additionally a logistic regression model will be used with treatment and center as factors as a sensitivity analysis. The estimated odds ratio and associated 95% CI for both methods will be presented to aid interpretation of the clinical effect.

<u>Mean Degree of Straining (Week 1, 2, 3, and 4)</u>

For each BM patients should indicate the degree of straining associated with that BM. The degree of straining is a 5 point scale:

0 = No straining

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1 = Mild straining
2 = Moderate straining
3 = Strong straining
4 = Very strong straining

For each subject, the mean degree of straining will be averaged for all SBMs in a given week. The mean degree of straining will then be analyzed by van Elteren tests, stratified by center, at Weeks 1, 2, 3, and 4 separately. A related 95% confidence interval and point estimate will be provided for the treatment difference; the confidence interval will be estimated by inverting the hypothesis test.

Additionally the endpoint will be analyzed using robust analysis of variance (ANOVA) models with center and treatment in the model as a sensitivity analysis.

If there are no SBMs during the week or if there are SBMs but all ratings are missing, then the LOCF method will impute the average from the average used for the most recent week. For Week 1 analysis where there is no value to carry forward then a value of 4 will be assumed. This assumption will be carried into later weeks if LOCF does not provide an estimate.

Mean Degree of Stool Consistency (Week 1, 2, 3, and 4)

For each BM patients should indicate the type of stool consistency associated with that BM. The degree of stool consistency is assessed using the Bristol Stool Scale [3]; a 7 point scale, where decreasing values indicate harder stools:

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool

Type 7		Watery, no solid pieces, entirely liquid

Stool consistency will be analyzed in the same manner described for the degree of straining. For Week 1 analysis where there is no value to carry forward then a value of 1 will be assumed. This assumption will be carried into later weeks if LOCF does not provide an estimate.

Weekly Abdominal Symptoms Score (Bloating and Discomfort) (Week 1, 2, 3, and 4)

The abdominal symptom score should be completed by patients in their diary, every 7 days on the last day of each treatment week upon waking in the morning. Patients should indicate the degree of abdominal bloating and discomfort experienced over the past week.

Abdominal Bloating	0 = None: No abdominal distension 1 = Mild: Slight abdominal distension 2 = Moderate: Abdominal distension clearly felt 3 = Severe: Severe abdominal distension 4 = Very severe: Extremely strong abdominal distension
Abdominal Discomfort	0 = None: No abdominal discomfort 1 = Mild: Slight abdominal discomfort 2 = Moderate: Abdominal discomfort clearly felt 3 = Severe: Abdominal discomfort with pain 4 = Very severe: Abdominal discomfort with severe pain

The abdominal symptoms (bloating and discomfort) will be analyzed separately by van Elteren tests, stratified by center, at Weeks 1, 2, 3, and 4. A related 95% confidence interval and point estimate will be provided for the treatment difference; the confidence interval will be estimated by inverting the hypothesis test.

Additionally a cumulative logistic regression model will be used with treatment and center as factors as a sensitivity analysis. The estimated odds ratio and associated 95% CI will also be presented to aid interpretation of the clinical effect. The interaction between treatment and center will also be examined in a separate model.

If the assessment ratings are missing, then the LOCF method will impute the value from the value used for the most recent week. For Week 1 analysis where there is no value to carry forward then a value of 4 will be assumed. This assumption will be carried into later weeks if LOCF does not provide an estimate.

Weekly Responder Rate (Weeks 1, 2, 3, and 4)

Weekly responder rate will be assessed at each week and will be derived from the data on SBMs collected in the subject diary. Responder analysis will be performed at each week. A non-

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responder will be defined as any subject with a spontaneous BM frequency rate of less than 3 for a given week, any subject who dropped out during or prior to the given week due to lack of efficacy, or any subject who used rescue medication during or within 24 hours prior to the given week. Otherwise, the subject will be considered a responder. A responder with a spontaneous BM frequency rate $\geq$ 3 but <4 will be
considered a moderate responder. Otherwise, the subject will be a full responder ($\geq$ 4 SBM).

Weekly responder rate (non-responder/ moderate responder/ full responder) will be analyzed by van Elteren tests, stratified by center, at Weeks 1, 2, 3, and 4 separately. Additionally a cumulative logistic regression model will be used with treatment and center as factors as a sensitivity analysis. The estimated odds ratio and associated 95% CI will also be presented to aid interpretation of the clinical effect. The interaction between treatment and center will also be examined in a separate model.

7.8.3   Additional Efficacy Endpoint(s)

PAC-QOL Questionnaire:

The PAC-QOL will be analyzed separately for the first 24 items that comprise the Dissatisfaction Index and for the last 4 items that comprise the Satisfaction Subscale at Baseline, and at Weeks 2 and 4. As the PAC-QoL is performed during the visit missing data should only occur when the entire questionnaire is missing, rather than individual items. When the PAC-QoL is missing then LOCF will be used to carry forward the nearest previous value.

The Dissatisfaction Index will be analyzed using van Elteren's test stratified by center to examine the difference between lubiprostone and placebo. Additionally the endpoint will be analyzed using ANOVA models with center and treatment in the model as a sensitivity analysis. The estimated LS means, related mean difference and associated 95% CI will also be presented to aid interpretation of the clinical effect.

The Satisfaction Index will be categorized by combined scores of the 4 items as either poor (0-4), fairly good (5-8), good (9-12), or excellent (13-16) and will be analyzed by van Elteren tests, stratified by center, at Baseline, and at Weeks 2 and 4 separately. Additionally a cumulative logistic regression model will be used with treatment and center as factors as a sensitivity analysis. The estimated odds ratio and associated 95% CIs will also be presented to aid interpretation of the clinical effect.

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7.9 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

Not applicable.

7.10 OTHER OUTCOMES

Not applicable.

7.11 SAFETY ANALYSIS

Safety analyses include AEs, clinical laboratory values, vital signs, and other safety parameters. All safety summaries will be based on the SAF. The analysis of safety data will be restricted to descriptive statistics only unless otherwise specified.

7.11.1 Adverse Events

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug. AEs are captured from when informed consent has been given until last follow-up visit.

Treatment-emergent adverse events (TEAEs) will be defined as any AE that occurs after the first dose of study drug and up to the last dose or early termination plus applicable follow up (two weeks). An AE with a completely or partially missing onset date will be counted as a TEAE, unless the partial date information available clearly indicates that the event happened out of the treatment period (e.g. a stop date earlier than the date of first dose).Only TEAEs will be included in summary tables.

There are no AEs of special interest defined for the study.

The MedDRA dictionary, current version, will be used to code all AEs reported during the trial by SOC and PT.

All TEAE summaries will be arranged in alphabetical order of SOC then by descending frequency (subject frequency) of the preferred term (PT) within the lubiprostone treatment group.

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AEs with missing intensity will be listed as such in the AE listings, however, will be summarized as severe in summary tables. If the relationship of an event is missing, the relationship for the event will be considered to have been related. In the cases where a subject has multiple AEs with the same SOC or PT the AE with the maximum intensity or strongest relationship will be summarized. When calculating the frequency and percentage of subjects who reported TEAEs, a subject will be counted only once for each SOC or PT when multiple TEAEs are coded to the same SOC or preferred term. Thus, if a subject has two distinct AEs, each of which corresponds to a distinct preferred term but both of which correspond to the same SOC, then that subject will be counted once at that SOC subject-count summary level and once at each of the two preferred-term subject-count summary levels.

The number and percentage of subjects with TEAEs will be summarized in several different tables:

- Overview of TEAEs (including number and percentage of patients and events)
- All TEAEs by SOC and PT.
- All TEAEs by SOC.
- All TEAEs by PT.
- Most frequent TEAEs by PT (occurring in ≥5% of subjects within one treatment group).
- Most frequent non-serious TEAEs by PT (occurring in ≥5% of subjects within one treatment group).
- Relationship of TEAEs to Study Drug by SOC and PT(not related, related).
- Drug-Related TEAEs by SOC and PT
- Intensity of TEAEs by SOC and PT
- Intensity of Drug-Related TEAEs by SOC and PT
- TEAEs Leading to Study Drug Discontinuation by SOC and PT
- Serious TEAEs by SOC and PT
- Pretreatment Events by SOC and PT
- Pretreatment Serious Events by SOC and PT
- Listing of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Subject mappings will also be produced for:
- TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs

A list of PTEs by subject number and MedDRA coding will be presented separately. PTEs will be summarized by SOC and PT.

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7.11.2   Clinical Laboratory Evaluations

Laboratory values will be summarized, for absolute and change from baseline values (the last recorded value prior to randomization, including any values recorded at unscheduled visits) and will be presented by parameter and scheduled visit for the SAF. All recorded laboratory tests will be performed at a central laboratory, except for pregnancy tests. All laboratory test parameters will be displayed in individual subject data listings in standard international (SI) units and as reported. Shifts in laboratory test values will be presented as cross-tabulations (baseline versus post-baseline) of numbers of subjects with low, normal and high values relative to the normal range used at the central laboratory. This classification will be based on the low, normal and high alert flags reported by the central laboratory. If a subject has multiple values post baseline (e.g. values from scheduled and unscheduled visits), the most extreme result will be used for shift tables. Shift tables will be produced for all clinical laboratory tests with reference ranges. Individual results for clinical hematology and chemistry laboratory tests that meet the predefined criteria for markedly abnormal values (MAV) (Appendix 1) will be summarized in tables, MAV tables will include values recorded at scheduled and unscheduled visits..

The following tables will be produced:

- Summary of Laboratory Test Results and Change from Baseline by Study Visit

- Number and Percent of Subjects in Categories of Urine Laboratory Parameters by Visit

- Summary of Shifts of Laboratory Test Results

- Number and Percent of Subjects With MAVs of Laboratory Parameters

- Number and Percent of Subjects With Elevated Liver Enzyme Laboratory Parameters

Subject mappings will also be produced for:

- The Number and Percent of Subjects With MAVs of Laboratory parameters

- Subjects With Elevated Liver Enzyme Laboratory Parameters

Listings of all clinical safety laboratory data will be provided for all subjects. Listings will be produced for each of hematology, serum chemistry and urinalysis categories. Laboratory data outside of the normal reference range will be indicated in the listings. In addition, MAVs will also be flagged.

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Table 7.a   **Clinical Laboratory Tests**

Hematology	Serum Chemistry	Urinalysis
Red blood cells (RBC) White blood cells (WBC) with differential Hemoglobin Hematocrit Platelets mean corpuscular volume (MCV) mean corpuscular hemoglobin (MCH) red (cell) distribution width (RDW)	ALP ALT Albumin AST Total bilirubin Direct bilirubin Total protein Total Cholesterol Triglyceride Glucose Creatinine Blood urea nitrogen (BUN) Creatine kinase Uric acid Gamma GT (GGT) Lactic dehydrogenase (LDH) Potassium Sodium Chloride Calcium Phosphorous Magnesium Thyroid Stimulating Hormone (TSH) (Visit 1) C Reactive Protein (CRP) (Visit 1)	Qualitative urinalysis (a) Microscopic analysis (only if positive dipstick results) (b)

Other:	
Serum:	**Urine:**
Female subjects of childbearing potential only: Beta hCG (for pregnancy) Visits 1 and 5	Female subjects of childbearing potential only: hCG for pregnancy Visit 2. Drug screen for drugs of abuse at Visit 1.

(a) Qualitative urinalysis: pH, specific gravity, protein, glucose, occult blood, urobilinogen, bilirubin, ketone and leukocyte esterase.
(b) Microscopic analysis: RBC/hpf, WBC/hpf, epithelial cells, casts, etc.

7.11.3 Vital Signs

Vital signs, including body temperature (℃), respiratory rate (breaths per minute), sitting blood pressure (mmHg) and pulse (bpm), will be measured at Day -15 (Screening), Day -1 (Randomization), and Day 29 (Final Visit or Early Termination). Weight (kg) and height (cm) will also be measured at Screening. Measures taken on Day -1 will be considered as baseline values. Vital signs will be summarized by scheduled visit and treatment group for the SAF. Change from baseline ((the last recorded value prior to randomization, including any values

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recorded at unscheduled visits)) will also be summarized for Day 29. No statistical analysis will be performed on vital signs data. Individual results for vital signs parameters that meet the predefined criteria for MAVs will be summarized in tables, MAV tables will include values recorded at scheduled and unscheduled visits.

The following tables and subject mappings will be produced:

- Summary of Vital Signs Parameters and Change from Baseline by Visit

- Number and Percent of Subjects With MAVs of Vital Signs Parameters

- Subject Mappings for the Number and Percentage of Subjects With MAVs of Vital Signs Parameters

Listings of all vital signs will be provided for all subjects. MAVs will also be flagged in the listings.

7.11.4 12-Lead ECGs

Not applicable.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 INTERIM ANALYSIS

Not applicable.

7.13 CHANGES IN THE STATISTICAL ANALYSIS PLAN

This SAP provides more details for the protocol specified analyses and includes additional analysis not presented in the protocol..

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