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

NCT Number: NCT02729909

Protocol Approve Date: 18 May 2015

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a 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.
- 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.

**PROTOCOL**

# 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

**Lubiprostone for the Treatment of Chronic Idiopathic Constipation**

| | | | |
|---|---|---|---|
| **Sponsor:** | Takeda Development Center Americas, Inc. (TDC Americas)<br>One Takeda Parkway<br>Deerfield, IL 60015 | | |
| **Study Number:** | Lubiprostone -3003 | | |
| **IND Number:** | Not applicable | **EudraCT Number:** | Not applicable |
| **Compound:** | Lubiprostone | | |
| **Date:** | 18 May 2015 | **Amendment Number:** | Not applicable |

# 1.0 ADMINISTRATIVE INFORMATION

## 1.1 Contacts

A separate contact information list will be provided to each site.

Takeda Development Center (TDC) sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

| Contact Type/Role | North America/Latin American Contact |
|---|---|
| Serious adverse event and pregnancy reporting | Contracted CRO contact<br>(Refer to the Study Team Contact list) |
| Medical Monitor<br>(medical advice on protocol and compound)<br><br>Responsible Medical Officer<br>(carries overall responsibility for the conduct of the study) | PPD |

## 1.2 Approval

### REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

### SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

PPD Date

PPD Date

PPD Date

## INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

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## 2.0 STUDY SUMMARY

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<tr><td>Title of Protocol: 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</td><td>IND No.:<br>Not Applicable</td><td>EudraCT No.:<br>Not applicable</td></tr>
<tr><td colspan="2">Study Number: Lubiprostone – 3003</td><td>Phase: 3</td></tr>
<tr><td colspan="3">Study Design:<br>This is a phase 3, parallel-group, comparison study with a 2-week Screening Period and subsequent 4-week (28 days) randomized, placebo-controlled, Double-Blind Treatment Period.<br>During the Screening Period, the defecation behavior of each subject will be recorded to confirm he/she has constipation. Use of all existing laxatives will be 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 study. When bisacodyl suppository does not improve constipation, glycerin enema (or equivalent drug) may be given. Subjects are instructed to complete the diary before using these rescue medications.<br>If these rescue medications fail to improve constipation, the investigator may decide to use another rescue medication. No rescue medication may be given from 24 hours before and until 48 hours after the first dose of 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).<br>Subjects whose constipation is confirmed during the Screening Period are randomized in the Double-Blind Treatment Period. Others whose constipation does not satisfy the criteria during the 2 week 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 will be excluded from the study. Subjects who satisfy the inclusion criteria and do not meet the exclusion criteria will be randomized to 1 of the treatment groups in the order of the number assigned. Approximately 204 subjects with chronic idiopathic constipation (CIC) will be randomized equally in a 1:1 manner into 2 groups (102 subjects each) in a double-blinded manner.</td></tr>
<tr><td colspan="3">Primary Objectives:<br>The primary objective is to evaluate the efficacy and safety of oral administration of 24 µg of lubiprostone twice daily (BID) for 4 weeks in subjects with CIC compared with placebo.</td></tr>
<tr><td colspan="3">Secondary Objectives:<br>None</td></tr>
<tr><td colspan="3">Subject Population: Male and nonpregnant, nonlactating female subjects 18 years of age and older with CIC.</td></tr>
<tr><td colspan="2">Number of Subjects:<br>Lubiprostone 24 µg group: Approximately 102 randomized<br>Placebo group: Approximately 102 randomized<br>Estimated total: Approximately 204 randomized</td><td>Number of Sites:<br>Estimated total: Approximately 10 sites in Mexico</td></tr>
<tr><td colspan="2">Dose Level(s):<br>24 µg lubiprostone capsule or matching placebo taken BID</td><td>Route of Administration:<br>Oral</td></tr>
</table>

| **Duration of Treatment:** | **Period of Evaluation:** |
|---|---|
| BID for 4 weeks | Up to 56 days |

**Main Criteria for Inclusion:**

Male and nonpregnant, nonlactating females aged 18 years or older who experience spontaneous bowel movement (SBM) frequency less than 3 times per week on average for the last 6 months or longer, including during the Screening Period. At the start of the Screening Period these subjects must also have been experiencing 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.

**Main Criteria for Exclusion:**

Subjects who have known mechanical obstruction, whose constipation is attributable to drug use or to whom a prohibited concomitant medication is required to be administered during the study; subjects having chronic constipation due to a secondary cause; subjects in whom there is sufficient criteria for irritable bowel syndrome (IBS) or functional defecation disorder, subjects whose SBM frequency is 3 or more per week, subjects whose SBM frequency has been less than 3 times per week for less than 6 months in duration or symptoms associated with SBM have been present for less than 6 months, subjects who receive treatment with an additional rescue medication within 24 hours of the first dose on Day 1 which is a standard laxative, glycerin enema or any other rescue medication; subjects who have megacolon/megarectum or have received a diagnosis of intestinal pseudo-obstruction, have hypersensitivity to lubiprostone or any of its excipients, a significant history of cardiovascular, liver, lung, kidney, neurological, or mental disease (including existing alcohol or drug abuse problem) or a systemic disease, or any significant clinical findings or clinical laboratory results as deemed by the investigator. Subjects with confirmed or suspected organic disorders of the large intestine (obstruction, stenosis, carcinoma, or inflammatory bowel disease), a polyp confirmed by total colonoscopy and requiring treatment, subjects who have been hospitalized for gastrointestinal or abdominal surgery within 3 months prior to screening.

**Main Criteria for Evaluation and Analyses:**

The primary endpoint for this study is SBM frequency in Week 1 of administration. Secondary endpoints for this study are SBM frequency (Weeks 2, 3, and 4), proportion of subjects who have a SBM within 24 hours after first dose, degree of straining (Weeks 1, 2, 3, and 4), stool consistency (Weeks 1, 2, 3, and 4), and abdominal symptoms (bloating and discomfort) (Weeks 1, 2, 3, and 4).

**Statistical Considerations:**

The primary efficacy variable will be analyzed using the van Elteren test stratified by pooled center. Secondary endpoints will also be analyzed by the van Elteren test (for ordinal data) or Cochran-Mantel-Haenszel (CMH) test (for binary data). Additionally logistic regression analyses will also be performed for binary and ordinal data. All analyses will account for pooled center either as a stratification factor or as a factor in the regression model.

**Sample Size Justification:**

Assuming equal allocation, a power of 90%, an alpha level of 0.05 for a 2-sided test, a placebo mean of 4, a treatment mean of 5.9 and a common standard deviation of 4 for SBM frequency at Week 1 and using the Wilcoxon-Mann-Whitney test, a total sample size of 198 is required. Assuming a drop-out rate of 3% by Day 4 a total of 204 subjects are needed.

# 3.0 STUDY REFERENCE INFORMATION

## 3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

## 3.2 Principal Investigator/ Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

## 3.3 List of Abbreviations

| | |
|---|---|
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANOVA | analysis of variance |
| AST | aspartate aminotransferase |
| BID | twice daily |
| BM | bowel movement |
| BPM | beats per minute |
| BUN | blood urea nitrogen |
| CIC | chronic idiopathic constipation |
| Cl- | chloride ions |
| ClC-2 | chloride channel |
| CMH | Cochran-Mantel-Haenszel |
| CRO | contract research organization |
| CRP | C-reactive protein |
| ECG | Electrocardiogram |
| eCRF | electronic case report form |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | gamma-Glutamyl Transpeptidase |
| GMP | Good Manufacturing Practice |
| hCG | human chorionic gonadotropin |
| HDPE | high-density polyethylene |
| IBS | irritable bowel syndrome |
| ICH | International Conference on Harmonisation |
| IEC | independent ethics committee |
| INR | international normalized ratio |
| IRB | institutional review board |
| IUD | intrauterine device |
| IVRS | interactive voice response system |
| IWRS | interactive web response system |
| LDH | lactic dehydrogenase |
| LFT | liver function tests |
| LOCF | last observation carried forward |
| LS | least squares |
| MAO | monoamine oxidase |
| MCH | mean corpuscular hemoglobin |

| | |
|---|---|
| MCV | mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MED ID | medication identification |
| OTC | over the counter |
| PAC-QOL | Patient Assessment of Constipation-Quality of Life Questionnaire |
| PED | pharmacologically effective dose |
| PK | Pharmacokinetic |
| PP | per protocol |
| PT | preferred term |
| PTE | pretreatment event |
| QD | Once daily |
| RBC | red blood cell |
| RDW | red (cell) distribution width |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS | Statistical analysis set |
| SBM | spontaneous bowel movement |
| SNRI | serotonin-norepinephrine reuptake inhibitor |
| SOC | system organ class |
| SOP | standard operating procedure |
| SSRI | serotonin reuptake inhibitor |
| SUSAR | suspected unexpected serious adverse reaction |
| $t_{1/2}$ | half-life |
| TID | 3 times daily |
| TMF | trial master file |
| TSH | thyroid stimulating hormone |
| UK | United Kingdom |
| ULN | upper limit of normal |
| US | United States |
| WBC | white blood cell |
| WHO | World Health Organization |

## 3.4 Corporate Identification

| | |
|---|---|
| TDC Japan | Takeda Development Center Japan |
| TDC Asia | Takeda Development Center Asia, Pte Ltd. |
| TDC Europe | Takeda Development Centre Europe Ltd. |
| TDC Americas | Takeda Development Center, Inc. Americas |
| TDC | TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable |
| Takeda | TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable |

# 4.0 INTRODUCTION

## 4.1 Background

### 4.1.1 Unmet Need—Burden of Disease

Constipation occurs when narrowing of the intestinal tract obstructs stool passage and intestinal propulsion decreases due to motion abnormality or defecation impairment occurs; it is pathologically classified into either idiopathic or secondary constipation, depending on the clinical condition of the patient. Most constipation can be associated with factors such as a diet low in soluble and insoluble fibers, inadequate exercise, medication use (in particular, opiate analgesics, anticholinergic antidepressants, antihistamines, and vinca alkaloids), bowel, neuromuscular, or metabolic disorders, or poor abdominal pressure or muscular atony. Constipation is considered idiopathic when its cause is unclear. Chronic idiopathic constipation (CIC) is defined by infrequent or difficult passage of stool and associated symptoms, such as abdominal bloating and discomfort, straining at defecation, and hard or lumpy stools. In CIC, these symptoms may be the result of abnormal colonic motility that can delay the transit of intestinal contents and impede the evacuation of rectal contents. One approach to the treatment of CIC is the stimulation of secretion of fluid into the abdominal lumen [1].

### 4.1.2 Product Name and Chemical Name

Lubiprostone is chemically designated as: (−)-7-[(2R,4aR,5R,7aR)-2-(1,1-difluoropentyl)-2-hydroxy-6-xooctahydrocyclopenta[b]pyran-5-yl]heptanoic acid. It has been developed as a soft gelatin capsule containing 24 μg of liquid lubiprostone in a medium chain triglyceride for oral administration. Lubiprostone is a member of a class of compounds called prostones and directly activates the mammalian chloride channels, ClC-2 located in the apical membrane of the human intestinal epithelial cells. This activation causes an increase in chloride ions (Cl-) and subsequent secretion of intestinal fluid into the lumen without altering sodium and potassium concentrations in the serum. By increasing intestinal fluid secretion, lubiprostone facilitates the passage of stool and alleviates symptoms associated with CIC. Patch clamp cell studies in human cell lines have indicated that most of the beneficial biological activity of lubiprostone and its metabolites is observed only on the apical (luminal) portion of the gastrointestinal epithelium. Therefore, systemic absorption of lubiprostone and its only measurable active metabolite M3 is not required for pharmacological activity. Additionally, ClC-2 plays an important role in the restoration of the tight junction complexes and recovery of barrier function within the body [2]. Lubiprostone has been shown to stimulate the recovery of mucosal barrier function in ex vivo studies of the intestine and colon through the restoration of these tight junction complexes [3].

### 4.1.3 Summary of Nonclinical Data

#### *4.1.3.1 Pharmacology*

In in-vitro studies, lubiprostone selectively activated ClC-2 chloride ion channels. In-vivo studies in a number of animal models have shown that oral lubiprostone accelerates water and

electrolyte secretion in the intestinal tract with no effect on serum electrolyte concentrations. These findings suggest that lubiprostone increases secretion of intestinal fluids and improves the movement of feces in the intestine by activating ClC-2 in intestinal epithelial cells and increasing chloride ion secretion in the gastrointestinal lumen.

#### *4.1.3.2 Pharmacokinetics*

The pharmacokinetics (PK) of lubiprostone were evaluated using radiolabeled lubiprostone (3H-lubiprostone) in rats, mice, rabbits, dogs, and monkeys. The maximum plasma radioactivity was observed at 0.25 to 2 hours after oral dosing of 3H-lubiprostone in rats, within 15 minutes in mice, 0.5 to 3 hours in dogs, and 4 to 5 hours in rabbits and monkeys. The half-life ($t_{1/2}$) was about 2 to 3 hours in rats and mice, 2 to 13 hours in dogs, and about 9 hours in rabbits and monkeys. Very little unchanged lubiprostone was found in plasma of these animals, suggesting rapid metabolism of the drug after dose.

An evaluation of the effect of lubiprostone on enzyme induction and inhibition indicated that lubiprostone is unlikely to induce clinically significant drug interactions. On tissue distribution, tissue radioactivity concentration after dosing of 3H-lubiprostone was relatively high in the liver and gastrointestinal tract. Radioactivity in each tissue decreased over time, and was mostly below the detection limit at 48 hours after dosing. The amount of lubiprostone excreted in urine and feces was similar in rats. Urine was the main excretion route of the drug in mice, rabbits, dogs, and monkeys. The total excretion rate of the drug up to 48 hours after dosing was 73% to 95% relative to the dose in these animals.

#### *4.1.3.3 Safety Pharmacology, General Pharmacology, and Toxicity*

A safety and general pharmacological study has shown little effect of lubiprostone on the central nervous, cardiovascular, or respiratory systems; its effect on the smooth muscle was observed only at higher doses. Single- and repeat-dose toxicity studies revealed no significant toxicity findings relevant to dosing in humans. A reproductive toxicity study also reported that toxicities occurred only at doses much higher than the pharmacologically effective dose (PED). Lubiprostone did not induce abortion and showed no carcinogenic effect in these studies.

### 4.1.4 Summary of Clinical Data

Lubiprostone has been approved for use in patients with chronic idiopathic constipation (CIC) since January 2006 and been marketed in the United States (US) under the trade name Amitiza since April 2006 for CIC irritable bowel syndrome (IBS) with constipation and for opioid-induced constipation. Other approvals include: Japan, Switzerland, the United Kingdom, Ireland, Belgium, Luxembourg and the Netherlands.

Lubiprostone has been administered to humans in at least 30 clinical studies.

The pivotal phase 3 studies included 2 multicenter, double-blind, randomized, placebo-controlled, efficacy and safety studies (Studies SC0131 and SC0232) for the treatment

of occasional constipation conducted in the US, and 1 placebo-controlled study (Study SC0831) in subjects with CIC conducted in Japan.

In Studies SC0131 and SC0232, the efficacy and safety of a 24 µg twice daily (BID) dose of lubiprostone was compared with placebo. In both studies, following a 2-week Baseline/Washout Period, subjects received 4 weeks of double-blind medication. No dose escalation was permitted during either study. Each study was powered to detect a difference of 2 spontaneous bowel movements (SBMs) between the placebo and lubiprostone groups after 1 week of treatment. The primary and secondary efficacy endpoints were the same in both studies. The overall mean number of days on study drug was 27.1 days for SC0131 and 26.8 days for SC0232. The mean actual daily exposure was 1.9 capsules/day in both the placebo and lubiprostone groups in both studies. In terms of dose, the median actual daily exposure in the lubiprostone group was 46 µg in both SC0131 and SC0232.

Study SC0131 evaluated 242 subjects, and Study SC0232 evaluated 237 subjects. In the primary efficacy analysis in each study, the mean SBM frequency during Week 1 was significantly higher ($p<0.0001$) in the lubiprostone group than in the placebo group.

The overall treatment effect across all weeks was also significant ($p<0.0001$) in both studies. In SC0131, the median number of SBMs at Week 1 was 3.0 in the placebo group and 5.0 in the lubiprostone group; in SC0232, the values were 3.5 and 5.0, respectively. In both studies, the Baseline median number of SBMs in both treatment groups was 1.5.

In Study SC0831,124 Japanese subjects with CIC were randomly assigned to 24µg oral lubiprostone BID (62 subjects) or matching placebo (62 subjects) for a 4-week treatment duration. Eligibility criteria, endpoints and assessments were similar to the 2 previously conducted pivotal phase 3 trials in the US.

In Study SC0831, lubiprostone showed a highly similar efficacy and safety profile in Japanese patients when compared to data from previous pivotal US trials (Table 4.a).

**Table 4.a Summary of Efficacy of Lubiprostone 24 µg BID in Phase 3 Studies**

| Study No./Phase (Analysis Set, Analysis Method) Country | Treatment Group (Number of Subjects) | Baseline SBM (Mean±SD) (p-value) (a) | SBM at Week 1 (Mean±SD) (p-value) (a) |
|---|---|---|---|
| SC0131 Phase 3 (ITT, LOCF) US | Placebo (N = 122) | 1.47±1.32 | 3.46±2.28 |
| | Lubiprostone (N=129) | 1.47±1.32 (p=0.612) | 5.69±4.41 (P<0.001) |
| SC0232 Phase 3 (ITT, LOCF) US | Placebo (N=118) | 1.52±0.80 | 3.99±2.70 |
| | Lubiprostone (N=119) | 1.28±0.88 (p=0.012) | 5.89±4.02 (P<0.001) |
| SC0831 Phase 3 (FAS) Japan | Placebo (N=62) | 1.68±0.77 | 2.93±1.82 |
| | Lubiprostone (N=61) | 1.65±0.78 (p=0.873) | 5.37±2.78 (P<0.001) |

Source: Studies SC0131, SC0232, SC0831.
FAS=full analysis set, ITT=intent-to-treat, LOCF=last observation-carried-forward .
(a) Difference from placebo.
Note: SBM at Week 1 was the primary efficacy variable in Studies SC0131, SC0232, and SC0831.

## 4.2 Rationale for the Proposed Study

Lubiprostone has been approved for use in patients with CIC since January 2006 in the United States, November 2009 in Switzerland, September 2012 in the UK, and since February 2015 in Ireland, Belgium, Luxembourg and the Netherlands based on similarly designed phase 3 studies.

This phase 3, randomized, double-blind, placebo-controlled study is aimed at scientifically and objectively evaluating the efficacy and safety of lubiprostone in subjects with CIC and confirming that data on efficacy and safety from previously conducted studies in the US population is consistent with that in the Mexican population. The study design allows for independent assessment of efficacy and safety in these subjects to support registration.

# 5.0 STUDY OBJECTIVES AND ENDPOINTS

## 5.1 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.

## 5.2 Endpoints

### 5.2.1 Primary Endpoints

#### *5.2.1.1 Efficacy*

SBM frequency in Week 1 of administration.

### 5.2.2 Secondary Endpoints

#### *5.2.2.1 Efficacy*

- 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).

### 5.2.3 Additional Endpoints

#### *5.2.3.1 Efficacy*

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

#### *5.2.3.2 Safety*

The safety of lubiprostone will be evaluated by the following parameters:

- Adverse events.
- Clinical laboratory values.
- Vital signs, including body temperature, blood pressure, and heart rate.
- Body weight and height.
- Physical examination.

### 5.2.4 Exploratory

CCI

[redacted]

# 6.0 STUDY DESIGN AND DESCRIPTION

## 6.1 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 and a subsequent 4-week (28 days) Double-Blind Treatment Period in which subjects will receive either lubiprostone or matching placebo twice a day. 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. 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.

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.

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 (PEG), 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 204 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 exclusion criteria are randomized to 1 of the treatment groups in the order of the number assigned. Approximately 204 subjects with CIC will be randomized to 2 groups: active treatment or placebo in a 1:1 ratio (102 subjects each) in a double-blinded manner.

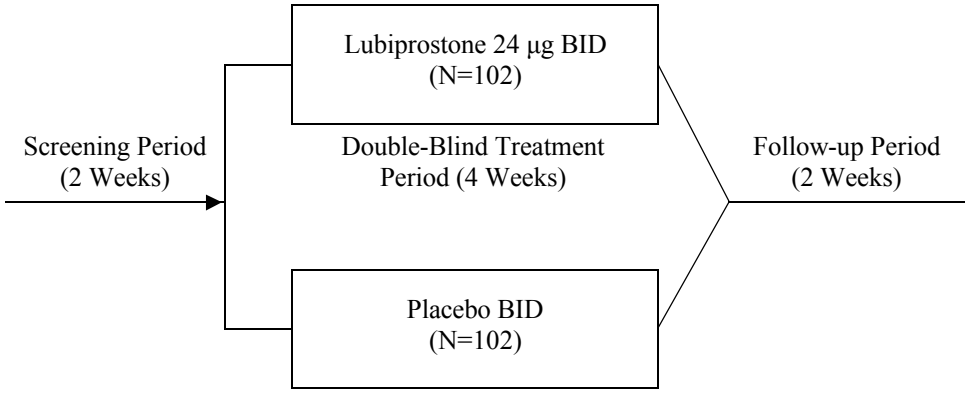
Subjects are to begin their study drug treatment twice daily (after breakfast and dinner) in the morning following Visit 2.

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 6.a. A schedule of assessments is listed in Appendix A.

**Figure 6.a Schematic of Study Design**




Note: Randomization occurs on Day -1 of the Screening Period. The first dose of study drug is administered the next day, on Day 1 of the Double-Blind Treatment Period.
Note: There is no treatment during the Follow-up Period.

## 6.2 Justification for Study Design, Dose, and Endpoints

Constipation is generally considered as infrequent and difficult passage of stool. It is typically defined as a condition of having fewer than 3 BMs a week [1]. However, stool shape and the subject's own perception other than stool frequency need to be considered for evaluation of disturbance in bowel movement [5].

The Rome Foundation, an international organization that classifies functional gastrointestinal disorders, published the definition of functional constipation in 2006 ("constipation without gastrointestinal tract abnormalities") as shown in Table 6.a.The Rome Foundation requires use of multiple indices for diagnosis of functional constipation. The definition is characterized by the "criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis" [4].

## Table 6.a Rome III Diagnostic Criteria for Functional Constipation

| **C3. Functional Constipation (*)** |
|---|
| 1. Satisfies at least 2 of the following: |
| a) Straining in at least 1 out of every 4 bowel movements. |
| b) Scybalum stool or hard feces in ≥25% of defecations. |
| c) Sensation of incomplete evacuation in ≥25% of defecations. |
| d) Sensation of anorectal obstruction/blockade in ≥25% of defecations. |
| e) Manual maneuvers to facilitate defecation (eg, digital evacuation, support of the pelvic floor) in ≥25% of defecations. |
| f) Fewer than 3 defecations per week. |
| 2. Loose stool rarely present without use of laxatives. |
| 3. Does not satisfy the diagnostic criteria for IBS. |

Source: Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders [4].
*At least 2 of the criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

The major symptom of CIC is a decrease in SBM frequency. SBM has been assessed in previous studies in CIC, and is typically calculated by stool frequency in a week (SBM denotes a bowel movement occurring without the use of a laxative, suppository, or enema within the preceding 24 hours) [6,7].

This phase 3, randomized, double-blind, placebo-controlled study is aimed at scientifically and objectively evaluating the efficacy and safety of lubiprostone in subjects with CIC. The study design allows for independent assessment of efficacy and safety in these subjects to support registration.

SBM at week 1 is proposed as the primary endpoint in this bridging study. Lubiprostone is expected to improve stool frequency within a short period of treatment.

In a late phase 2 study and 2 phase 3 studies supporting applications, subjects treated with lubiprostone showed a significant increase in SBM frequency relative to subjects treated with placebo using this endpoint as the primary efficacy endpoint. Use of the same primary endpoint allows for direct comparison of efficacy data in the Mexican population.

SBM frequency at other time points during the study will be evaluated to support the continuous effect of lubiprostone.

Drug effect on straining, stool consistency, and abdominal symptoms (bloating and discomfort) are selected as secondary endpoints because these are common symptoms of CIC. Addition of these endpoints to frequency of bowel movement assessment provides a comprehensive evaluation of the effect of treatment.

The phase 1 Study 99101 examined single oral doses of lubiprostone ranging from 6 µg to 96 µg; the results of this study demonstrated that there was a noticeable increase in pharmacodynamic effects when the lubiprostone dose was increased from 24 µg to 48 µg, and the maximum tolerated single dose based on the results of this study was determined to be 96 µg. The phase 1 study 99102 examined daily doses of lubiprostone ranging from 72 µg (24 µg 3

times daily [TID]) to 108 µg (36 µg TID); the results of this study showed a lack of additional pharmacodynamic effects at doses above 24 µg TID, suggesting a saturation effect of lubiprostone pharmacodynamics at this dose level. The phase 2b study SC9921 examined lubiprostone doses of 24 µg (24 µg QD), 48 µg (24 µg BID), and 72 µg (24 µg TID) over a 3-week double-blind treatment period. Results from this study showed that all 3 doses of lubiprostone were more effective than placebo in relieving constipation, with the 48 µg and 72 µg doses having similar effects on constipation. The overall tolerability of the 48 µg dose was considered better than the 72 µg dose, so it was chosen for further development in the Phase 3 studies conducted in the United States.

A Japanese phase 2b dose-finding study (CC0721) was conducted to verify validity of preceding data generated in the US population for Japanese patients. CC0721 examined lubiprostone doses of 16 µg (8 µg BID), 32 µg (16 µg BID), and 48 µg (24 µg BID) over a 2-week double-blind treatment period. Results from this study showed that the two higher doses of lubiprostone were more effective than placebo in relieving constipation, with the 48 µg dose providing best effects on constipation. The overall tolerability of the 48 µg dose was considered well suited, so this dose was chosen for further development in the Phase 3 studies conducted in Japan, confirming preceding data generated in study SC9921 in the United States.

The efficacy and safety of the lubiprostone 24 µg BID dose has been demonstrated in previously conducted phase 3 studies in CIC. The 24 µg BID dose will be used in this study for 4 weeks in subjects with CIC.

## 6.3 Premature Termination or Suspension of Study or Investigational Site

### 6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for lubiprostone, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

### 6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

### 6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

## 7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to dispensing of study medication on Day -1.

### 7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject has a history of constipation defined as having SBM frequency of less than 3 times per week on average for 6 months or longer and for whom the same SBM frequency is observed during the Screening Period.
4. The subject has had 1 or more of the symptoms associated with SBM (described below) for 6 months or longer at the start of screening:
   a) Scybalum stool or hard feces in at least 1 out of every 4 bowel movements.
   b) Sensation of incomplete evacuation in at least 1 out of every 4 bowel movements.
   c) Straining in at least 1 out of every 4 bowel movements.
5. The subject rarely has loose stools without the use of laxatives.
6. The subject is willing and able to keep a diary on his/her own and willing and able to complete a questionnaire.
7. The subject is male or female and aged 18 years or older, at the time of signing an informed consent.
8. A female subject of childbearing potential* who is sexually active agrees to use routinely adequate contraception* from signing of informed consent throughout the duration of the study and 14 days after the last dose of study drug.

> *Definitions and acceptable methods of contraception are defined in Section 9.1.13 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.14 Pregnancy.

### 7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 30 days prior to Screening.

2. The subject has received lubiprostone in a previous clinical study or as a therapeutic agent.
3. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has, in the judgment of the investigator, clinically significant abnormal hematological parameters of hemoglobin, hematocrit, or erythrocytes at Screening**.**
5. The subject has a history or clinical manifestations of significant mechanical obstruction (intestinal obstruction due to tumor, hernia etc).
6. The subject has a history of hypersensitivity or allergies to lubiprostone or any of its excipients.
7. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to the Screening Visit.
8. The subject is required to take excluded medications as listed in Section 7.3.1.
9. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period.
10. Subject whose constipation is considered to be due to drugs or to whom a prohibited concomitant medication has been administered.
11. Subject having chronic constipation due to a secondary cause (medications, diabetes mellitus, hypothyroidism, depression, etc.
12. Subject in whom there is sufficient criteria for irritable bowel syndrome (IBS) or functional defecation disorder.
13. Subject whose SBM frequency is 3 or more per week.
14. Subject whose 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).
15. Subject who received treatment with a rescue medication within 24 hours prior to the first dose on the morning of Day 1: bisacodyl suppository, which is a standard laxative, glycerin enema, or any other rescue medication.
16. Subject who has megacolon/megarectum or has received a diagnosis of intestinal pseudo-obstruction.
17. Subject with confirmed or suspected organic disorders of the large intestine (obstruction, stenosis, carcinoma, or inflammatory bowel disease). Organic disorders of the large intestine can be confirmed or ruled out using the results of enema X-ray examination or total colonoscopy performed in the previous 2 years. If the subject has no history or shows no current evidence of weight loss, anemia, or rectal bleeding, organic disorders may be ruled

out based on the results of such testing performed in the past 3 years. Any subject in whom total colonoscopy has detected a polyp requiring treatment is excluded from this study.

Note - Subject should not be screened unless at least 7 days have passed since an enema X-ray examination, sigmoidoscopy or total colonoscopy have been performed. See Section 7.3.3 and 7.4.

18. Subject who has been hospitalized for gastrointestinal or abdominal surgery within 3 months prior to Screening.
19. Subject who has a significant cardiovascular, liver, lung, kidney, neurological, or mental disease (including existing alcohol or drug abuse problem) or a systemic disease.
20. Subject who has significant clinical findings or in whom a significant abnormality has been found in hematology test, serum chemistry, or urinalysis.
21. Subject in whom noncompliance with the study protocol (administration schedule, visit schedule, diary completion or other study procedure) is expected.
22. The subject has a history of malignant disease (except basal cell carcinoma) within 5 years prior to Screening.
23. The subject has any Screening abnormal laboratory value that suggests a clinically significant underlying disease or condition that may prevent the subject from entering the study; or the subject has: creatinine >1.5 mg/dL, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN), or total bilirubin >2.0 mg/dL with AST/ALT elevated above the limits of normal values.
24. Subject who the investigator/subinvestigator has determined ineligible to participate in this study for any reason other than the above.

## 7.3 Excluded Medications and Procedures

### 7.3.1 Excluded Medications

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

Due to the potential influence on the efficacy evaluation of lubiprostone, the following medications are to be excluded during the course of the study and must be discontinued no later than Day -15 of the Screening period through the Final Visit or Early Termination Visit:

- Anticholinergic drugs or drugs with anticholinergic effect (except ipratropium bromide or any inhaled or nasal-spray forms of this medication).
- Opioids.
- Antispasmodics.
- Cholinesterase inhibitors.

- Antidiarrheal medications.
- Anticonstipation medications (eg, linaclotide).
- Gastrointestinal prokinetic agents.
- Laxative agents (eg, PEG 3350), including homeopathic remedies.
- Tricyclic antidepressants.
- Any medications at the discretion of the investigator known to relieve or cause constipation or constipation symptoms.

The use of excluded medications listed above should be documented as concomitant medications. The Medical Monitor must be notified in advance (or as soon as possible thereafter) of any instances in which excluded medications are taken, or to be taken. Continued participation of the subject will be at the discretion of the Sponsor.

### 7.3.2 Drugs Permitted with Condition

*7.3.2.1 Exceptions to Excluded Medications*

If subject has a confirmed diagnosis of clinical depression and he/she has been treated with selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or monoamine oxidase (MAO) inhibitors, treatment must have been at a stable dose for at least 30 days prior to the Screening Visit and not likely to change during the study. Antidepressants must not be suddenly stopped or reduced as doing so may provoke withdrawal symptoms or other untoward symptoms. The investigator determines how to handle subjects using antidepressants on an individual subject basis without compromising the safety of the subject.

Rescue medication use is determined and prescribed depending on the subject's clinical condition. 10 mg of bisacodyl suppository may be prescribed as a standard rescue medication if a subject has no adequate bowel movement for 3 consecutive days during the study. When bisacodyl suppository does not improve constipation, glycerin enema (or any equivalent drug) may be given.

Subjects are instructed to complete their diaries before taking rescue medications. No rescue medication may be used within 24 hours before and 48 hours after the start of the Double-Blind Treatment Period (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 eCRF.

The use of excluded medications with exceptions mentioned above should be documented as concomitant medications, as applicable. The Sponsor's medical monitor or designee must be notified in advance (or as soon as possible thereafter) of any instances in which any drugs

permitted with condition are taken, or to be taken. Continued participation of the subject will be at the discretion of the Sponsor.

### 7.3.3 Excluded Procedures

Invasive procedures such as enema X-ray, total colonoscopy and sigmoidoscopy are not allowed 7 days prior to screening until the Final Visit as these procedures could affect bowel habits observed subsequently. Subject should not be screened (including diary keeping) unless at least 7 days have passed since an enema X-ray examination or sigmoidoscopy or total colonoscopy have been performed.

The Medical Monitor must be notified in advance (or as soon as possible thereafter) of any instances of excluded procedures being performed. Continued participation of the subject will be at the discretion of the Sponsor.

## 7.4 Diet, Fluid, Activity Control

The investigator, subinvestigator, and study coordinator should advise subjects to comply with the following instructions:

The following instructions are given to each subject.

- Discontinuation of all laxatives and prohibited drugs (including dietary fiber supplement).
- No change in diet or lifestyle habits during the study. Subjects should maintain their usual caffeine and alcohol intake during the study.

The subject diary will be distributed, and subjects will be instructed to keep the diary every day including on the morning of Visit 1. The data to capture in the diary include the following: time of defecation, stool consistency [every time], degree of straining during defecation, degree of sensation of complete evacuation, and abdominal symptoms such as bloating and discomfort. Subjects will be instructed to begin taking study drug twice daily, beginning the morning after Visit 2 (1 capsule in the morning with breakfast and 1 capsule in the evening with dinner and about 240 mL of water with each administration). Subjects will be instructed to record the date and time of consumption of the study drug in the diary.

Note – Subjects should not be screened unless at least 7 days have passed since an enema X-ray examination or sigmoidoscopy or total colonoscopy have been performed.

## 7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.15.

1. Pretreatment event (PTE) or adverse event (AE). The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk

to the subject's health or the subject is unwilling to continue because of the PTE or AE (this includes when there are safety concerns in a subject after dose reduction).

- Liver function test (LFT) abnormalities.

  Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.12), if the following circumstances occur at any time during study medication treatment:

  – ALT or AST >8 × ULN, or

  – ALT or AST >5 × ULN and persists for more than 2 weeks, or

  – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or

  – ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

2. Significant protocol deviation. The discovery after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy).
5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.14.
7. Lack of efficacy. The investigator has determined that the subject is not benefiting from investigational treatment; and, continued participation would pose an unacceptable risk to the subject.
8. Unblinding of subject treatment.
9. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

## 7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit, with a follow up telephone contact 14 days later. Discontinued or withdrawn subjects will not be replaced.

## 7.7 Procedure for Reduction of Study Drug Dose Due to Adverse Events

If a subject experiences an adverse event during the Treatment Period (Double-Blind Period), the investigator may decide to reduce the dose or discontinue treatment as needed based on the type and severity of the adverse event.

For a dose reduction, either the morning (with breakfast) or evening (with dinner) dose is discontinued. As a general rule, **the investigational drug blind shall not be broken by the investigator,** even when the dose in a subject is reduced.

If the report of an adverse event from a subject calls for dose reduction at a point other than the scheduled visit, the investigator determines whether to reduce the dose in the subject. If dose reduction is determined necessary, the investigator must instruct the subject how to reduce the dose.

If the dose is reduced or treatment discontinued in a subject, the reason for dose reduction or discontinuation as well as relevant details should be recorded in the eCRF of the subject. The lubiprostone dose cannot be increased after reduction.

# 8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

## 8.1 Study Medication and Materials

### 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to all or any of the drugs defined below.

- Lubiprostone 24 μg capsules.
- Placebo capsules to match Lubiprostone 24 μg.

Investigational material is encapsulated in clear orange soft gelatin capsules and packaged into 60 count high-density polyethylene (HDPE) bottles, including a rayon filler, induction sealed and closed with a child-resistant cap. Each bottle contains enough capsules to treat subjects for 28 days + a 2-day window during the Double-Blind Treatment Period, and will be labeled with a single-panel label including pertinent study information. As this study is double-blind, all study medication will be packaged, labeled, and dispensed in a blinded manner.

The bottle will contain a unique medication identification (MED ID) number and will be dispensed via the InteractiveVoice/ Web Response System (IVRS/IWRS), with 1 bottle dispensed per subject.

An IVRS/IWRS program will be used to manage inventory, assist the site in dispensing the proper investigational drug to the subjects, record accountability and support the return to sponsor or designee of these investigational drugs after study completion.

#### *8.1.1.1 Investigational drug*

Lubiprostone 24 μg and placebo will be supplied by the sponsor. All drugs supplied by the sponsor will be manufactured, tested, and released according to Good Manufacturing Practice (GMP).

#### *8.1.1.2 Rescue Medication*

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. Subjects are instructed to complete their diaries before using these drugs. No rescue medication may be used within 24 hours before and 48 hours after the start of the Double-Blind Treatment Period (Day1).

### 8.1.2 Storage

Investigational drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drug must be stored under the conditions specified on the label, and remain in the original bottle until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

Temperature excursion must be reported to the sponsor or designee.

### 8.1.3 Dose and Regimen

Subjects will be dispensed 1 bottle of study medication at Visit 2 (Day -1) and will be required to take 2 capsules daily, 1 in the morning and 1 in the evening with food and approximately 240 mL of water. Subjects will be instructed to start study medication in the morning of the following day (Day 1).

Table 8.a describes the dose and regimen as it will be administered to each subject in each treatment group during the 4 weeks of the Double-Blind Treatment Period.

**Table 8.a Dose and Regimen**

| | | Timing of Dose and Regimen | |
|---|---|---|---|
| **Treatment Group** | **Dosage** | **Morning (AM)** | **Evening (PM)** |
| Placebo | 1 placebo capsule taken by mouth BID for 4 weeks | Administered orally at breakfast with food and 240 mL of water | Administered orally at dinner with food and 240 mL of water |
| Lubiprostone | 1 lubiprostone 24 µg capsule taken by mouth BID for 4 weeks | | |

### 8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF according to Section 10.0, Pretreatment Events and Adverse Events.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated symptomatically.

## 8.2 Investigational drug Assignment and Dispensing Procedures

The investigator or investigator's designee will access the IVRS/IWRS at Screening/ Visit 1 to obtain the subject study number.

After study eligibility is confirmed (ie, At Visit 2), the investigator or the investigator's designee will utilize the IVRS/IWRS to randomize the subject into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening. The MED ID number of the investigational drug to be dispensed will then be provided by the IVRS/IWRS.

If the investigational drug is lost or damaged, the site can request a replacement from IVRS/IWRS. (Refer to IVRS/IWRS manual provided separately.)

If a dose was missed, the subject is to leave the capsule in the bottle and resume regular administration at the next scheduled dose time. The subject is instructed to note the missing dose in the daily diary.

Instructions for subjects on how to store investigational drug will be provided by the investigator or investigator's designee.

Unused medication should be returned at Visit 5.

## 8.3 Randomization Code Creation and Storage

The sponsor or designee will generate the randomization schedule prior to the start of the study; IVRS/IWRS will be used in a centralized fashion for subject randomization and study medication assignments. All randomization information will be stored in a secured area, accessible only by authorized personnel.

## 8.4 Investigational Drug Blind Maintenance

The investigational drug blind will be maintained using the IVRS/IWRS.

## 8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by the investigator, by accessing the IVRS/IWRS.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, investigational drug must be stopped immediately and the subject must be withdrawn from the study.

## 8.6 Accountability and Destruction of sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects randomized in the study. To document appropriate use of sponsor-supplied drug (lubiprostone and matching placebo), the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by recording in IVRS/IWRS. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates (if the expiry date is provided to the investigator).
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the MED ID.
- Verifying that all containers/ bottles used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IVRS/IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs lubiprostone and matching placebo on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry date, date and amount dispensed including initials or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

In the event of expiry date extension of sponsor-supplied drug already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

# 9.0 STUDY PLAN

## 9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

### 9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2 and Appendix C.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

### 9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include age, sex, race as described by the subject, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.11).

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within1 month prior to signing of informed consent.

### 9.1.3 Physical Examination Procedure

A Baseline physical examination (defined as the assessment prior to first dose of investigational drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) genitourinary system; and (12) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

### 9.1.4 Weight, Height

A subject should have weight and height measured while wearing indoor clothing and with shoes off. Height will be measure at Visit 1 and weight will be measured at Visit 1 and 5.The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place.

### 9.1.5 Vital Sign Procedure

Vital signs will include body temperature, respiratory rate, sitting blood pressure (resting more than 5 minutes), and pulse (bpm).

### 9.1.6 Primary Efficacy Endpoint

The primary efficacy endpoint is SBM frequency at Week 1, the data for which will be collected in a subject diary; see Appendix E. Subjects will be given a diary to complete at home, where they will record the date and time of each BM.

### 9.1.7 Secondary Efficacy Endpoints

#### *9.1.7.1 SBM Frequency at Weeks 2, 3 and 4*

This secondary endpoint will be collected as specified for the primary analysis.

#### *9.1.7.2 Proportion of Subjects Who Have a SBM Within 24 Hours After First Dose*

The proportion of subjects with an SBM within 24 hours after first dose in Week 1 will be assessed and derived from the data on SBMs collected in the subject diary.

#### *9.1.7.3 Degree of Straining*

For each subject, the degree of straining will be scored on a 5-point scale, with a higher score indicating more severe straining, and averaged for all SBMs at Weeks 1, 2, 3, and 4. The degree of straining for each SBM will be collected in the subject diary.

#### *9.1.7.4 Stool Consistency*

Stool consistency will be scored using the Bristol Stool Chart (see Appendix E) and the mean provided for all SBMs at Weeks 1, 2, 3 and 4. Stool consistency will be collected in the subject diary for each SBM recorded.

#### *9.1.7.5 Assessments of Abdominal Symptoms*

The abdominal symptoms (bloating and discomfort upon waking in the morning) will be scored weekly on a 5-point scale, with a higher score indicating more severe symptoms. This will be assessed at Baseline and at Weeks 1, 2, 3, and 4. Subjects will be instructed to record weekly abdominal symptoms assessment in the diary. Diary entries will be reviewed at each Study Visit as per protocol schedule.

### 9.1.8 Additional Endpoints

#### *9.1.8.1 Quality of Life Evaluation*

The PAC-QOL is a health related QOL instrument designed specifically to evaluate an adult subject's assessment of constipation over time. It is self -administered assessment consisting of

28 items and is designed to cover the 2 weeks prior to the questionnaire being completed. Each item is scored from 0 to 4; a lower score is better. The 28 items are grouped into 4 subscales: physical discomfort, psychosocial discomfort, worries and concerns, and satisfaction.

The PAC-QOL will be assessed at Day -1 (prior to the start of study drug), mid-way through the Double-Blind Treatment Period on Day 15, and at the end of the Double-Blind Treatment Period, on Day 29.

#### *9.1.8.2 Safety Endpoints*

Safety endpoints include adverse events, vital signs, clinical laboratory tests, physical examinations, and body weight.

### 9.1.9 Exploratory Endpoint

CCI [redacted]

### 9.1.10 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

### 9.1.11 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at the screening examination. The condition (ie, diagnosis) should be described.

### 9.1.12 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 8 mL, and the approximate total volume of blood for the study is 24 mL.

Details of these procedures will be provided in the Central Laboratory Manual.

Table 9.a presents the clinical laboratory tests that will be utilized during this study.

## Table 9.a Clinical Laboratory Tests

| Hematology | Serum Chemistry | Urinalysis |
|---|---|---|
| RBC<br>WBC with differential<br>Hemoglobin<br>Hematocrit<br>Platelets<br>MCV<br>MCH<br>RDW | ALP<br>Albumin<br>ALT<br>AST<br>Total bilirubin<br>Direct bilirubin<br>Total protein<br>Total Cholesterol<br>Triglyceride<br>Glucose<br>Creatinine<br>BUN<br>Creatine kinase<br>Uric acid<br>GGT<br>LDH<br>Potassium<br>Sodium<br>Chloride<br>Calcium<br>Phosphorous<br>Magnesium<br>TSH (Visit 1)<br>CRP (Visit 1) | Qualitative urinalysis (a)<br><br>Microscopic analysis (only if positive dipstick results) (b) |

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

BUN=blood urea nitrogen, CRP= C-reactive protein, GGT= gamma-Glutamyl Transpeptidase, hCG=human chorionic gonadotropin, hpf=high-power field, LDH= lactic dehydrogenase, MCH=mean corpuscular hemoglobin, MCV=mean corpuscular volume, RBC= red blood cell, RDW=red (cell) distribution width, TSH= thyroid-stimulating hormone, WBC=white blood cell.
(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.

Blood is collected for hematology and blood biochemistry, and urine is collected for urinalysis at Visit 1 (screening), and Visit 5 (at the completion of the Double-Blind Treatment Period), and, if applicable, at an Early Termination Visit. Women of childbearing potential undergo pregnancy test by serum at Visit 1 and 5 (or Early Termination Visit) and by urine at Visit 2. No pregnancy test is performed on women who have not menstruated for a year or longer.

The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis (excluding pregnancy tests). The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted.

(Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

### 9.1.13 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 14 days after last dose of study medication, female subjects of childbearing potential* who are sexually active with a non-sterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:

**Table 9.b Acceptable Methods of Contraception**

| Barrier Methods (a) | Intrauterine Devices (IUDs) | Hormonal Contraceptives |
|---|---|---|
| • Male condom PLUS spermicide.<br>• Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.<br>• Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide. | • Copper T PLUS condom or spermicide.<br>• Progesterone T PLUS condom or spermicide. | • Implants.<br>• Hormone shot/injection.<br>• Combined pill.<br>• Minipill.<br>• Patch.<br>• Vaginal ring PLUS male condom and spermicide. |

IUD=intrauterine device.
(a) Barrier methods: to be used each time the subject has intercourse.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova during the course of the study.

During the course of the study, regular serum and urine hCG pregnancy tests will be performed for women of childbearing potential only, and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A). In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test prior to dispensing of study medication at Visit 2.

### 9.1.14 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug (lubiprostone or matching placebo) should be immediately discontinued.

If the pregnancy occurs during administration of active study medication, eg, after Visit 2 or within 14 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received.

All pregnancies in subjects on active study drug including comparator will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted (first well baby visit).

### 9.1.15 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible at this visit, the investigator should complete the eCRF. The IVRS/IWRS should be contacted as a notification of screen failure.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

Subject numbers assigned to subjects who fail screening should not be reused.

### 9.1.16 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the Double-Blind Treatment Period.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

If the subject is found to be eligible the subject will be randomized to either lubiprostone or placebo using IVRS/IWRS. Instructions on accessing and using the IVRS/IWRS will be provided in a separate manual. Blinded details of subject treatment allocation (MED ID numbers) will be provided via the IVRS/IWRS.

### 9.1.17 Subject Diary

The Study Diary will be a paper diary distributed to each subject on Study Days -15, -1, 8, and 15.

Subjects will be instructed to record in the diary every day, including the morning of Visit 1 (Day -15, the first day of the Screening Period). Subjects will continue to record their defecation behavior in the diary to confirm he/she has constipation. Use of all laxatives will be stopped at

the beginning of the Screening Period (Visit 1), and subjects will be instructed not to change their diets or lifestyle habits during the study.

Study Diary will be collected and reviewed for completeness on Study Days -1, 8, 15, 29 and any unscheduled visit. The authorized study personnel will transcribe all data collected from the diary into the eCRF. All information collected from the diary will be analyzed for primary and secondary endpoints in the study.

All subjects should be instructed about diary completion at every study visit.Documentation that subjects are appropriately instructed (and re-instructed as necessary) on diary completion should be recorded in the subject's source notes.

Subjects who are not consistent or thorough with Study Diary completion may receive phone reminders if deemed necessary by the investigators. The authorized study personnel providing phone reminders must document the phone contact process in the subject's source notes.

A sample of the diary is located in Appendix E; it provides a sample of the types of questions that the diary asks as a way of helping the subject to record defecation behavior.

## 9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study medication bottles/unused medications to each dispensing site visit.

If a subject is persistently noncompliant with the study medication, it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

## 9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s). The recommended visit windows for Visits 2, 3, 4, and 5 are within 2 days of the required visit.

### 9.3.1 Screening Period

Subjects will be screened within 2 weeks prior to Randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.15 for procedures for documenting screening failures.

Procedures to be completed at Screening (Visit 1) include:

- Sign informed consent.
- Record demographics, medical history, and medication history. The results of enema X-ray examination or total colonoscopy performed in the past 2 years are referred to in order to confirm organic disorders have been ruled out. For subjects who have no history or show no

current evidence of weight loss, anemia, or rectal bleeding, the examination results of the past 3 years may be used to rule out organic disorders.

- Perform physical examination.
- Measure vital signs, weight, and height.
- Record concomitant medications, including previous use of laxatives/drugs used for constipation.
- Instruct subject to stop use of all existing laxatives/drugs used for constipation.
- Document concurrent medical conditions.
- Pretreatment adverse events assessment.
- Collect blood and urine samples for laboratory tests and urine drug screen. Serum hCG pregnancy test is required for women of child-bearing potential only.
- Dispense study diary and provide instructions on diary completion.
- Distribute rescue medications prescription.
- Eligibility assessment (review Inclusion/Exclusion criteria).
- Access IVRS/IWRS to obtain subject number.
- Guidance on the avoidance of pregnancy and ova donation.

### 9.3.2 Study Entrance/Randomization

Randomization will take place on Day -1. The following procedures will be performed and documented during Randomization:

- Review diary entries for completeness and compliance. Evaluate the need for providing phone reminders to subjects who are not consistent or thorough with study diary completion.
- Check the use of rescue medication (by diary).
- Measurement of vital signs.
- Record use of concomitant medications.
- Urine hCG pregnancy test (for females of childbearing potential only).
- Abdominal symptom assessment review (by diary).
- Pretreatment Adverse Events assessment.
- PAC-QOL Questionnaire.
- Eligibility assessment (review Inclusion/ Exclusion criteria).
- Access IVRS/IWRS for Randomization and MED ID.

- Dispensing of study medication via IVRS/IWRS.
- Dispense study diary. Re-instruct subject on diary completion.
- Distribute rescue medications prescription as necessary.
- Schedule next visit 7 days from first dose of study medication.
- Instruct subject to bring the study medication bottle and the completed diary at Visit 3.
- Guidance on the avoidance of pregnancy and ova donation.

No rescue medication may be used within 24 hours before and 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).

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IVRS/IWRS as described in Section 9.3.2. Subjects will be instructed to start study medication the following day (Day 1) as described in Section 6.1. Subjects will be instructed to take 1 capsule twice a day, orally, at the same time of day, preferably in the morning with breakfast and in the evening with dinner. The procedure for documenting Screening failures is provided in Section 9.1.15.

### 9.3.3 Double-Blind Treatment Period

The following tests and procedures will be performed and documented during the Double-Blind Treatment Period (First Dose/ Day 1 through Visit 5/ Day 29).

- Record use of concomitant medications.
- Adverse Events assessment.
- Document dose adjustment (dose reduction) when applicable.
- Calculate and document study medication return, accountability and compliance.
- Review diary entries for completeness and compliance. Evaluate the need for providing phone reminders to subjects who are not consistent or thorough with study diary completion (Visit3/Day8 and Visit 4/Day 15). Abdominal symptom assessment review (by diary).
- Check the use of rescue medication (by diary).
- PAC-QOL Questionnaire (Visit 4/Day 15).
- Dispense study diary (Visit 3/ Day 8 and Visit 4/ Day 15). Re-instruct subject on diary completion.
- Distribute rescue medications prescription at Visit 3/ Day 8 and Visit 4/ Day 15 as necessary.

- Instruct subject to bring the study medication bottle and the completed diary at next scheduled visit.
- Guidance on the avoidance of pregnancy and ova donation.

The investigator may reduce the dose due to adverse events, based on the type and severity of the adverse event. As a general rule, the investigational drug blind shall not be broken by the investigator for dose adjustment.

### 9.3.4 Final Visit or Early Termination Visit

The Final Visit will be performed at the end of Week 4 (Day 29) or at the Early Termination Visit. For all subjects receiving study medication, the investigator must complete the End of Study eCRF page. Subjects who withdraw prematurely will be seen within 1 week of discontinuation for an Early Termination Visit.

The following tests and procedures will be performed:

- Perform physical examination including weight.
- Measurement of vital signs.
- Record use of concomitant medications.
- Collect blood and urine samples for laboratory tests. Serum hCG pregnancy test is required for women of child-bearing potential only.
- Calculate and document study medication return, accountability and compliance.
- Abdominal symptom assessment review (by diary).
- PAC-QOL Questionnaire.
- Check the use of rescue medication (by diary).
- Review diary entries for completeness and compliance.
- Adverse Events Assessment.
- Guidance on the avoidance of pregnancy and ova donation.
- Access IVRS/IWRS to update subject status.

### 9.3.5 Follow-up Period

Follow-up period will begin the first day after the Final Visit/ Early Termination Visit and will continue up to 14 Days.

Subjects who completed the study will be contacted through phone for Follow Up interview 14 days after the Final Visit. Subjects will answer questions about adverse events and concomitant medication use (including rescue medications). This will include any pregnancy reporting in female subjects.

Subjects who are withdrawn prematurely should return to the site within 1 week after the last taken dose for all procedures scheduled for Early Termination Visit. Efforts should be made to follow up with a telephone contact 14 days after the last dose of study medication or Early Termination visit.

### 9.3.6 Post Study Care

The study medication will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

# 10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

## 10.1 Definitions

### 10.1.1 PTEs

A 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.

### 10.1.2 AEs

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.

### 10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values:

- A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

### 10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

**Table 10.a Takeda Medically Significant AE List**

| Term | |
|---|---|
| Acute respiratory failure/acute respiratory distress syndrome | Hepatic necrosis |
| Torsade de pointes / ventricular fibrillation / ventricular tachycardia | Acute liver failure |
| | Anaphylactic shock |
| Malignant hypertension | Acute renal failure |
| Convulsive seizure | Pulmonary hypertension |
| Agranulocytosis | Pulmonary fibrosis |
| Aplastic anemia | Confirmed or suspected endotoxin shock |
| Toxic epidermal necrolysis/Stevens-Johnson syndrome | Confirmed or suspected transmission of infectious agent by a medicinal product |
| | Neuroleptic malignant syndrome / malignant hyperthermia |
| | Spontaneous abortion / stillbirth and fetal death |

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

### 10.1.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

| | |
|---|---|
| Mild: | The event is transient and easily tolerated by the subject. |
| Moderate: | The event causes the subject discomfort and interrupts the subject's usual activities. |
| Severe: | The event causes considerable interference with the subject's usual activities. |

### 10.1.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

| | |
|---|---|
| Related: | An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible. |
| Not Related: | An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments. |

### 10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

### 10.1.8 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

### 10.1.9 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

### 10.1.10 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

### 10.1.11 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Dose Reduced – the dose was reduced due to the particular AE.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE.

### 10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining “Not recovered/not resolved”.

- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

## 10.2 Procedures

### 10.2.1 Collection and Reporting of AEs

#### *10.2.1.1 PTE and AE Collection Period*

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Study Visit 1, Day -15) or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication (Day 1). Routine collection of AEs will continue until Final Visit or Early Termination Visit).

A follow-up phone contact will be made to each subject 14 days following the last dose of study drug to collect any AEs that may have occurred. The stop date of the AE/serious PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

#### *10.2.1.2 PTE and AE Reporting*

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date {and time}.

3. Severity.
4. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
5. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
6. Action concerning study medication (not applicable for PTEs).
7. Outcome of event.
8. Seriousness.

PAC-QOL and subject diary will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the subject for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

### 10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

### 10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be

completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.12 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

## 10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

### 10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to Mexican regulatory authorities, including investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. At each site, the Investigator is responsible to communicate any safety matters to its corresponding IRB/IE committee. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

## 11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

## 12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

### 12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will provide investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

### 12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms),

electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

# 13.0 STATISTICAL METHODS

## 13.1 Statistical Analysis Plan

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

### 13.1.1 Analysis Sets

*Total Set*

The total set consists of all subjects who signed the informed consent form including subjects withdrawn prior to randomization (defined as not randomized subjects).

*Full Analysis Set*

This will consist of all subjects randomized to receive study treatment whether or not they received treatment. Subjects will be assigned to the randomized treatment group regardless of treatment received.

*Per-protocol analysis set*

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

- Did not receive study treatment as per randomization schedule.
- Dose of randomized treatment was not adjusted.
- 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.
- SBM 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.

Subjects will be assigned to the treatment group dependent upon the actual treatment randomized and received.

*Safety Analysis Set*

This will consist of all subjects who receive study treatment. Subjects will be assigned to the treatment group dependent upon the actual treatment received.

The analysis populations must be identified before database lock by the Responsible Medical Officer, the Coordinating Study Manager and the Study Statistician. The reason(s) for exclusion of subjects from the analysis populations must be documented, signed and filed in the Trial Master File (TMF).

The FAS will be used for efficacy analyses. Supportive analyses based on the PP will be performed for the primary efficacy variable. Definitions of criteria constituting major deviations will be provided, prior to unblinding.

### 13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and other Baseline characteristics will be summarized descriptively.

### 13.1.3 Efficacy Analysis

Two-sided tests at a significance level of $\alpha$=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. Baseline is defined as the last recorded measurement prior to treatment. For parameters based on diary data, Baseline values will be derived using the data from the Screening Period.

Centers may be pooled geographically if necessary for analysis purposes.

The last observation carried forward (LOCF) technique will be used to impute missing values. For a given subject, the most recent nonmissing treatment-period data point will be carried forward to the subsequent week where data are missing. Supportive analyses will be conducted without missing value imputation (ie, without LOCF) and with a 'worse-case' scenario where missing values are assigned the worst case values recorded in the study by any subject for that endpoint at that time.

#### *13.1.3.1 Primary Endpoint*

The primary endpoint for the study is the frequency of SBM at Week 1. An SBM is defined as any BM that does not occur within 24 hours after rescue medication use. The SAP will contain more details on the handling of rescue medication and missing or partial data.

In order to adjust for early withdrawals, weekly SBM frequency rates will be calculated as follows:

$$(\text{Number of SBMs} / \text{Number of Days}) \times 7$$

The number of days in the denominator above is the number of days during the week that the subject was in the study. Weeks will be calculated as 168-hour intervals starting with the exact time of the first intake of study drug. 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 rate will be set to missing.

The primary endpoint 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 analysis of variance (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 interaction between treatment and center will also be examined in a separate ANOVA model.

This endpoint will be analyzed for the FAS. A sensitivity analysis using the PP will also be presented.

To examine the effects of any dose reduction in response to an AE an additional sensitivity analysis will also be performed. This will be performed on the FAS where data from those subjects with a dose reduction will be excluded from the time of dose reduction and subjects will be treated as a drop-out from this time point onwards. Additionally, another factor will be added to the ANOVA model to examine the effect of dose reduction, this will be performed on the FAS, with no subjects excluded.

*13.1.3.2 Secondary Endpoints*

All secondary endpoints will be analyzed for the FAS only.

*SBM Frequency at Week 2, 3 and 4*

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

*Proportion of Subjects With an SBM Within 24 hours After First Dose*

The proportion of subjects with an SBM within 24 hours after first dose in Week 1 will be analyzed by a 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 will also be presented to aid interpretation of the clinical effect. The interaction between treatment and center will not be examined in a separate model.

*Mean Degree of Straining (Week 1, 2, 3, and 4)*

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

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

Stool consistency will be analyzed in the same manner described for the degree of straining.

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

The abdominal symptoms (bloating and discomfort upon waking in the morning) will be analyzed separately by van Elteren tests, stratified by center, at Weeks 1, 2, 3, and 4. 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.

*13.1.3.3 Additional Endpoints*

*Efficacy*

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.

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.

*Safety*

Adverse events will be summarized using the safety analysis set. No statistical testing or inferential statistics will be generated.

All AEs will be coded using the MedDRA. Data will be summarized using preferred terms (PTs) and primary system organ class (SOC).

Vital signs, clinical laboratory values, and body weight will be summarized by treatment group for both actual and change from baseline values.

*13.1.3.4 Exploratory Endpoint*

CCI [redacted]

## 13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

## 13.3 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, a treatment mean of 5.9 and a common standard deviation of 4 for SBM frequency at

Week 1 and using the Wilcoxon-Mann-Whitney test, a total sample size of 198 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 2. The estimates of placebo and treatment response are based on a previous study conducted by Sucampo Pharmaceuticals in the US (Protocol No. RTU/0211SC0131).

The primary endpoint requires subjects to complete at least 4 days of the study diary, therefore assuming a drop-out rate of 3% by Day 4 an additional 6 subjects are required, giving a total of 204 subjects.

# 14.0 QUALITY CONTROL AND QUALITY ASSURANCE

## 14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (contract research organization [CRO]) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

## 14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

## 14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution

guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

## 15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

### 15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable Mexican regulations (Guidance from Comisión Nacional de Bioética). The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor or designee will only ship drug once the adequacy of site regulatory documentation and, permission from competent authority to begin the trial has been confirmed. Until the site receives drug/notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

## 15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

## 15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRFs).

## 15.4 Publication, Disclosure, and Clinical Trial Registration Policy

### 15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

### 15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

### 15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

## 15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

## 16.0 REFERENCES

1. National Institute of Diabetes and Digestive and Kidney Diseases. Constipation. National Institute of Diabetes and Digestive and Kidney Diseases. Accessed 16 February 2015. Available at: http://www.niddk.nih.gov/health-information/health-topics/digestive-diseases/constipation/Documents/Constipation_508.pdf.
2. Nighot PK, Blikslager AT. Chloride channel ClC-2 modulates tight junction barrier function via intracellular trafficking of occludin. Am J Physiol Cell Physiol 2012;302(1):C178-87.
3. Moeser AJ, Nighot PK, Engelke KJ, Ueno R, Blikslager AT. Recovery of mucosal barrier function in ischemic porcine ileum and colon is stimulated by a novel agonist of the ClC-2 chloride channel, lubiprostone. Am J Physiol Gastrointest Liver Physiol 2007;292(2):G647-56.
4. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006;130(5):1480-91.
5. National Institute of Diabetes and Digestive and Kidney Diseases. Bristol Stool Form Scale. National Institute of Diabetes and Digestive and Kidney Diseases. Accessed 16 February 2015. Available at: http://en.wikipedia.org/wiki/Bristol_stool_scale.
6. Mueller-Lissner S, Kamm MA, Wald A, Hinkel U, Koehler U, Richter E, et al. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of sodium picosulfate in patients with chronic constipation. Am J Gastroenterol 2010;105(4):897-903.
7. Kamm MA, Muller-Lissner S, Talley NJ, Tack J, Boeckxstaens G, Minushkin ON, et al. Tegaserod for the treatment of chronic constipation: a randomized, double-blind, placebo-controlled multinational study. Am J Gastroenterol 2005;100(2):362-72.

# Appendix A Schedule of Study Procedures

| | Screening | Randomization | Treatment | | | | Follow-up Period |
|---|---|---|---|---|---|---|---|
| **Study Day/Week** | **Day -15** | **Day -1 (a)** | **First Dose Day 1 (b)** | **Week 1** | **Week 2** | **Final Visit or Early Termination Visit Week 4 (c)** | **Follow-up Phone Contact Week 6 (o)** |
| **Visit Windows (Days):** | **-15 to -1** | **-1** | **1** | **8** | **15** | **29** | **43** |
| **Visit Number:** | **1** | **2** | **N/A** | **3** | **4** | **5** | **N/A** |
| Informed consent | X | | | | | | |
| Demographics and medical history (d) | X | | | | | | |
| Inclusion/exclusion criteria (e) | X | X | | | | | |
| Medication history | X | | | | | | |
| Physical examination | X | | | | | X | |
| Vital signs (f) | X | X | | | | X | |
| Weight and height (g) | X | | | | | X | |
| Concomitant medications | X | X | X | X | X | X | X |
| Concurrent medical conditions | X | | | | | | |
| Clinical laboratory tests (h) | X | | | | | X | |
| Pregnancy test (i) | X | X | | | | X | |
| Urine drug screen | X | | | | | | |
| Access IVRS/IWRS for Subject ID/MED ID/Subject Status | X | X | | | | X | |
| Dispense investigational drug | | X | | | | | |
| Distribute rescue medications prescription, as necessary | X | X | | X | X | | |
| Drug return/accountability/compliance | | | | X | X | X | |
| Distribution diaries to subjects | X | X | | X | X | | |
| **Efficacy:** | | | | | | | |
| Abdominal symptom assessment review (by diary) | | X | | X | X | X | |
| PAC-QOL | | X | | | X | X | |
| Use of rescue medication (by diary) | | X | | X | X | X | |
| Diary-keeping by subjects (j) | X | X | X | X | X | X | |
| Diary collection/ compliance check (k) | | X | | X | X | X | |
| **Safety:** | | | | | | | |
| Guidance on avoidance of pregnancy and ova donation | X | X | | X | X | X | |
| Pretreatment adverse events (l) | X | X | | | | | |
| Adverse events (m) | | | X | X | X | X | X |
| Dose reduction (optional) (n) | | | | X | X | | |
| Phone interview | | | | | | | X |

Footnotes are on last table page.

N/A= not applicable.
(a) Subjects will be randomized on Day -1, the last day of the Screening Period. They will also receive their bottle of dispensed investigational study drug on Day -1, although they will be instructed to take the first dose the next day, on Day 1.
(b) Day 1 is the first day of study drug administration. Subjects are to take 1 capsule of lubiprostone 24 µg or placebo in the morning with 240 mL of water in the morning with breakfast and again in the evening with dinner. Repeat this regimen for 4 weeks.
(c) Conduct Final Visit procedures for subjects discontinued early per Section 7.6. Subjects who withdraw prematurely should return within 1 week of discontinuation for an Early Termination Visit.
(d) Includes the results of screening for IBS. The results of enema X-ray examination or total colonoscopy performed in the past 2 years are referred to in order to determine organic disorders that can be ruled out. For subjects who have no history or show no current evidence of weight loss, anemia, or rectal bleeding, the examination results of the past 3 years may be used to rule out organic disorders.
(e) Subject eligibility is to be reconfirmed for all criteria on Day -1, Randomization Day, including diary data.
(f) Vital signs=blood pressure (systolic and diastolic), body temperature, and pulse rate.
(g) Height will be measured at Visit 1 and weight will be measured at Visit 1 and 5.
(h) Hematology: hemoglobin, hematocrit, RBC, WBC with differential, platelets, MCV, MCH, RDW.
Serum chemistry: ALP, Albumin, ALT, AST, Total bilirubin, Direct bilirubin, Total protein, Total Cholesterol, Triglyceride, Glucose, Creatinine, BUN, Creatine kinase, Uric acid, GGT, LDH, Na, K, Cl, Ca, P, Mg, (TSH [performed to exclude hypothyroidism] and CRP levels are measured at Visit 1 only).
Urinalysis: pH, specific gravity, protein, glucose, occult blood, urobilinogen, bilirubin, ketone and leukocyte esterase. Microscopic analysis (only if positive dipstick results).
(i) In women of childbearing potential only. Serum hCG pregnancy test conducted at Screening and at Final Visit (Early Termination Visit), and urine hCG pregnancy test conducted at Visit 2.
(j) Diary-keeping by subjects will be continuous from Day -15 throughout the Screening Period and the Double-Blind Treatment Period to Day 29 (Final Visit). There will be no diary-keeping in the Follow-up Period.
(k) Subjects who are not consistent or thorough with Study Diary completion may receive phone reminders if deemed necessary by the investigators. The authorized study personnel providing phone reminders must document the phone contact process in the subject's source notes.
(l) Pretreatment adverse events: an adverse event in subjects who have signed informed consent to participate in the study that occurs prior to administration of any study medication; the event does not necessarily have to have a causal relationship with study participation. The pretreatment adverse events are assessed from Day -15 to hour 0 on Day 1, when study drug is administered.
(m) Pregnancy reporting in Follow-Up Period occurs at 2 weeks after the last dose of study drug.
(n) The investigator may reduce the dose due to adverse events depending on the type or severity of the adverse event. As a general rule, the investigational drug blind shall not be broken by the investigator for dose adjustment. Reasons for dose reduction or discontinuation as well as relevant details are recorded in the eCRFs.
(o) Efforts should be made to follow up with a telephone contact 14 days after the last dose of study medication or Early Termination visit for subjects who are withdrawn from the study prematurely.

## Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non-routine/non-standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

## Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) That personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) It is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) That personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) That subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

e) That the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, non-sterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study medication will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

## Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

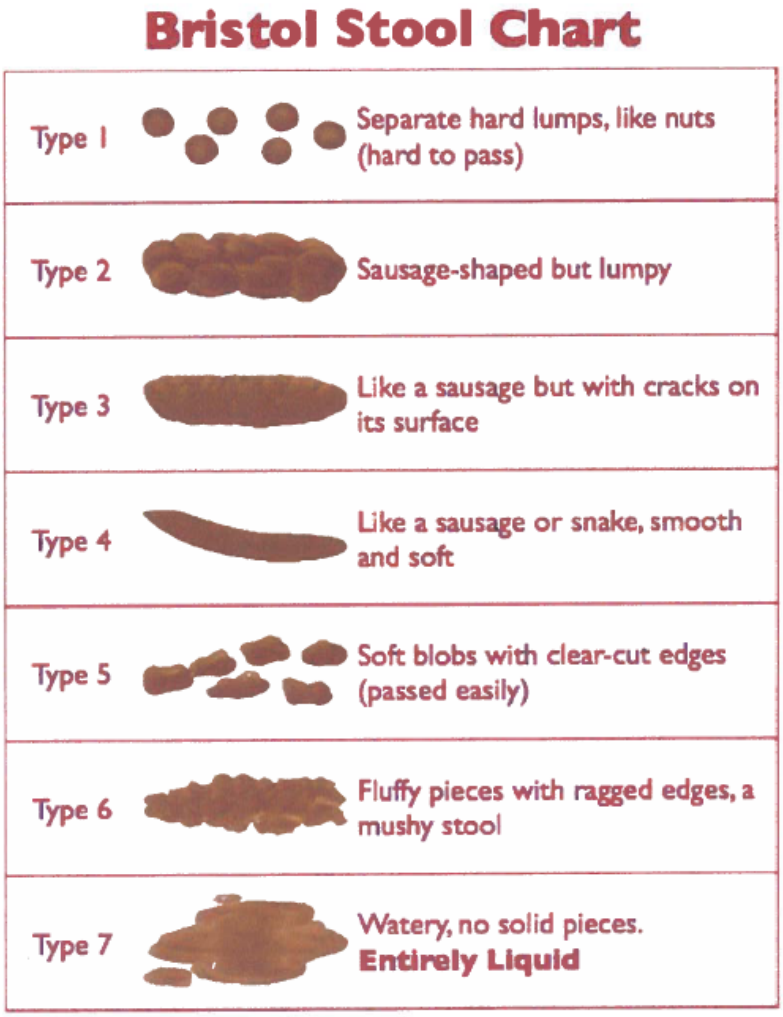
Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

## Appendix E Sample of Subject Diary and The Bristol Stool Scale

This table provides a sample of the subject diary, which will be provided to subjects on Day -15 of the Screening Visit and in which they are to record every defecation event from Day -15 until Day 29. The diary prompts the subject to record all details of each event including the consistency of the stool and the difficulty they have in passing it. The second page of the appendix is the Bristol Stool Scale, which will be supplied to the subjects as an aid.

| |
|---|
| A. Date and time they take the study drug |
| B. After a bowel movement: |
| a. Date and time |
| b. Stool consistency |
| 1 = Hard and round (difficult-to-pass) stool like those of rabbits |
| 2 = Sausage-shaped but hard stool |
| 3 = Sausage-shaped stool with cracks on the surface |
| 4 = Sausage-shaped, soft stool with smooth surface, or coiled stool (like a snake) |
| 5 = Soft, half-solid (and easy-to-pass) stool with clear crease |
| 6 = Unshaped, loose stool with small, irregular-shaped pieces, or mushy stool |
| 7 = Watery stool without solid pieces (entirely liquid) |
| c. Degree of straining: |
| 0 = No straining |
| 1 = Mild straining |
| 2 = Moderate straining |
| 3 = Strong straining |
| 4 = Very strong straining |
| d. CCI [redacted] |
| CCI [redacted] |
| CCI [redacted] |
| C. Abdominal symptom (bloating and discomfort) |
| Abdominal bloating: |
| 0 = None (no abdominal distention) |
| 1 = Mild (Slight abdominal distention) |
| 2 = Moderate (Abdominal distention 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) |
| D. Date and time a rescue medication was used (if applicable) |
| E. Concomitant drugs (if applicable) |

The investigator or clinical research coordinator will instruct the subjects to keep the diary throughout the study. If the investigator or coordinator asks a subject about diary entries and adds a note or corrects the diary for clarification, each note/correction will be marked with the date and signature and the reason for the correction. The investigator will maintain the diaries as part of the subject's file at the site.




Source: National Institute of Diabetes and Digestive and Kidney Diseases. [5]

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

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm) |
|---|---|---|
| PPD | Clinical Science Approval | 20-May-2015 08:21 |
| | Statistical Approval | 20-May-2015 10:53 |
| | Clinical Science Approval | 20-May-2015 11:52 |