AstraZeneca

Clinical Study Protocol	
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A Phase IV, Randomized, Multi-Center, Open-Label, Prospective, Crossover Study to Evaluate Patient Preference of Movantik™ versus Polyethylene Glycol 3350 (PEG 3350) for Opioid-Induced Constipation (OIC) Treatment

Sponsor: AstraZeneca Pharmaceuticals LP
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VERSION HISTORY

Version 2.0, 26 January 2017

All major changes are detailed below, administrative changes such as the update of cross-references, spelling and abbreviations, and small changes to wording are not included here. Changes made to the body of the protocol are also reflected in the synopsis.

Section 2.4 (Exploratory Objective): Spontaneous Bowel Movement (SBM) frequency was added to the exploratory objective.

Section 3.3 (Subject Enrollment and Randomization): The reference to using prescription voucher cards for rescue medication was removed.

Section 3.5 (Methods for Assigning Treatment Groups): The section was updated to reflect that randomization will be performed using the Merge eClinical OS RAND module.

Section 4, Table 1 (Schedule of Assessments): The footnotes for Table 1 were updated to clarify that Screening and Visit 1 can occur up to 14 days before Visit 2, that Visit 2 is to occur after the first 1-week washout period, and that a subject's eligibility may be confirmed at Visit 1 or via telephone contact. The 'Confirm Eligibility' line was deleted and in its place, an 'X' was added to the Visit 2 column of 'Inclusion and exclusion'.

Section 4.1.1 (Enrollment and Washout Period 1): This section was updated to clarify that if a subject does not have the required lab and ECG results at Visit 1, the study site will notify them of their eligibility and instruct them to begin the 1-week washout period once lab and/or ECG results are available. Reference to the prescription voucher cards was removed from this section.

Section 5.1.4.1 (BM/SBM Frequency): The definition of an SBM (a Bowel Movement [BM] that occurred without the use of rescue laxatives in the previous 24 hours) was added to this section.

Section 7.1.1 (Rescue Medication): The reference to "commercially available" rescue medication was removed for consistency.

Section 8.4.4 (Exploratory Outcomes): SBM frequency was added as an exploratory outcome.

Section 8.5 (Methods for Statistical Analyses): A brief description of proposed subgroup analyses was added to this section.

Section 8.5.2 (Analysis of the Secondary Variable): A sentence describing the baseline measurement of Bowel Function Index scores for each time period was moved from Section 3.5 and expanded.

Section 8.5.5 (Exploratory Analysis): SBM frequency was added to this section. Section 9.3 (Study Timetable and End of Study): The expected start and end dates were updated. Section 9.4 (Data management): The drug dictionary to be used for medication classifications was changed to the WHO Drug Dictionary. Appendix B (Influence of Medication Characteristics on Overall Preference): Mildly Influenced and Moderately Influenced were added as headers for categories 1 and 2, respectively. Appendix B (Patient Global Impression of Change): The reference to the Investigator administering the PGIC was removed because the PGIC will be provided directly to the subjects. Appendix B (Bowel Function Index): All references to "study personnel" were changed to "study clinician" because the BFI may only be administered to the subject by a clinician.

Version 1.0, 06 October 2016
Initial creation.

This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

AstraZeneca

PROTOCOL SYNOPSIS

A Phase IV, Randomized, Multi-Center, Open-Label, Prospective, Crossover Study to Evaluate Patient Preference of Movantik™ versus Polyethylene Glycol 3350 (PEG 3350) for Opioid-Induced Constipation (OIC) Treatment

National Co-ordinating Investigators

[redacted]

[redacted]

Study site(s) and number of subjects planned

The study plans to randomize approximately 256 subjects total, 128 subjects per treatment sequence arm. The subjects are to be recruited and enrolled at approximately 80 sites in the United States allowing for a non-completion rate of 20% for approximately 102 completed subjects per treatment sequence arm. The anticipated accrual/enrollment will finish within approximately 9 months.

Study period		Phase of development
Estimated date of first subject enrolled	**Q1 2017**	**IV**
Estimated date of last subject completed	**Q1 2018**	**IV**

Study design

This is a prospective, multicenter, randomized, open-label, crossover study in patients with chronic non-cancer pain to evaluate preference for opioid-induced constipation (OIC) treatment and the reason for their preference.

At the enrollment visit (Visit 1) entry criteria will be assessed. Subjects who have met all eligibility criteria and consent to the study will be instructed on the use of the study diary, which they will complete daily throughout the study period and will, upon confirmation of eligibility from the site, immediately enter a 1-week (7 day) washout period during which they will discontinue use of all treatments for OIC. At Visit 1, subjects will also be provided with rescue medication to be used if a bowel movement (BM) does not occur within at least 72 hours from the start of washout period 1 or within 72 hours of the last recorded BM during the study. Following the initial 1-week washout period, at Visit 2, subjects' eligibility will be reassessed. Eligible subjects will be randomized to receive either Naloxegol (Movantik™) or Polyethylene glycol 3350 (PEG 3350) for the first 2-week treatment period, and will also complete the Bowel Function Index (BFI) as baseline for the treatment period 1 at Visit 2.

At the end of the first treatment period, subjects will attend Visit 3 where the Patient Global Impression of Change (PGIC) and BFI will be administered, and they will begin the second 1-week (7 day) washout period during which they will discontinue use of all treatments for OIC except for the rescue medication as needed. At the end of the second 1-week washout period, subjects will attend Visit 4 and complete the BFI, and the second 2-week treatment period will begin during which subjects will switch to either Movantik or PEG 3350 (whichever they did not use during treatment period 1). There will be a final clinic visit (Visit 5) for all subjects at the end of the second treatment period during which the primary outcome measure, preference for Movantik versus PEG 3350, will be assessed.

Objectives

Primary Objective:	**Outcome Measure:**
To determine the preferred treatment for managing OIC (Movantik versus PEG 3350) among patients with chronic non-cancer pain	Patient reported preference for Movantik or PEG 3350 measured using a 7-point preference scale (Strong preference for Movantik, Moderate preference for Movantik, Slight preference for Movantik, No preference, Slight preference for PEG 3350, Moderate preference for PEG 3350, and Strong preference for PEG 3350)

Secondary Objectives:	**Outcome Measures:**
To assess the reason(s) for patient preference of Movantik or PEG 3350 (only among subjects who indicate a preference)	Patient reported influence of each medication characteristic in contributing to their overall preference including efficacy, tolerability, convenience, works quickly, and works predictably using a 4-point rating scale
To compare the impact of Movantik and PEG 3350 on OIC symptoms	PGIC administered after each treatment period BFI measured at Day 1 and Day 14 of each treatment period

Safety Objective:	**Outcome Measure:**
To examine the safety of Movantik and PEG 3350 for treatment of OIC	Collection of adverse events (AEs) and serious adverse events (SAEs)

Exploratory Objective:	**Outcome Measure:**
To examine the effect of Movantik and PEG 3350 on BM/Spontaneous Bowel Movement (SBM) frequency and stool consistency	BM frequency reported in the daily diary Straining reported in the daily diary for each BM using a 5-point straining scale Stool consistency reported in the daily diary for each BM using the Bristol Stool Scale (BSS) Use of rescue medication reported in the daily diary

Target subject population

The target population includes patients (men or women) ≥18 and <85 years of age, who are experiencing self-reported active symptoms of OIC at screening and receiving a stable maintenance opioid regimen (daily dose ≥30 mg of oral morphine or equivalent) for chronic non-cancer pain and who are willing to use only study medications during the treatment periods and stop all laxatives during the screening and washout periods. A rescue medication, bisacodyl, will be available to participants throughout the study if they have not had a BM within 72 hours of their last recorded BM. Patients are not eligible for the study if they are receiving opioids for treatment of pain related to cancer, if their constipation is not primarily caused by or related to the use of opioids, if they have any acute or chronic conditions related to the gastrointestinal (GI) tract that could impose risk of obstruction or perforation, if they have any condition that may have affected the permeability of the blood-brain barrier, if they are pregnant, breastfeeding or planning a pregnancy during the study, if they are concomitantly using strong or moderate CYP3A4 inhibitors, or strong CYP3A4 inducers, if they have a known intolerance or sensitivity to PEG 3350, Movantik, or bisacodyl, or if they have any other significant and/or progressive medical, surgical, psychiatric, or mental health condition that could increase the risk of unsafe participation as judged by the Investigator.

Duration of treatment

Following satisfactory completion of eligibility assessments during Visit 1, the subject will enter the first 1-week washout period followed by the first 2-week treatment period then a second 1-week washout period and the second 2-week treatment period. The entire planned duration of study participation is up to 7 weeks.

AstraZeneca medication, dosage and mode of administration

The product under study is Movantik (Naloxegol), and the comparator is PEG 3350.

All subjects will be asked to adhere to the dosing and frequency instructions on the drug label.

Statistical methods

The study design is a 2 by 2 AB/BA crossover study, where Prescott's test will be used for the analysis of the primary outcome endpoint of patient preference (Prefer Movantik, No Preference, and Prefer PEG 3350). The per-protocol (PP) dataset will be used for the primary outcome analysis.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
BFI	Bowel Function Index
BM	Bowel movement
BSS	Bristol Stool Scale
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
CSA	Clinical Study Agreement
FAS	Full Analysis Set
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
ICH	International Council for Harmonisation
ICF	Informed Consent Form
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
OIC	Opioid-induced constipation
OTC	Over-the-counter
PEG 3350	Polyethylene Glycol 3350
PGIC	Patient Global Impression of Change
PP	Per-protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
SBM	Spontaneous bowel movement
SD	Standard deviation
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Opioid-induced constipation (OIC) is a difficult-to-manage complication of chronic opioid use, which substantially compromises the patient's quality of life (Coyne et al. 2014 Argoff et al. 2015, Bell et al. 2009). The prevalence of OIC among patients taking opioids for non-cancer pain ranges from 41% to 81% (Nelson et al. 2015). In addition to modifying lifestyle and behavior to manage the symptoms of OIC, patients often incorporate over-the-counter (OTC) laxative therapies into their treatment regimen (Coyne et al. 2015). However, conventional laxatives are often only partially effective in managing OIC, because they fail to target the underlying pathophysiology, the activation of μ-opioid receptors of the gastrointestinal (GI) tract (Hurst 2004,. Holzer 2008, Johanson 2007, Kumar et al. 2014). There are limited clinical trial data to demonstrate the efficacy of OTC treatments for OIC (Camilleri et al. 2014, Xing et al. 2001).

Polyethylene glycol 3350 (PEG 3350), an osmotic laxative, is one of the most commonly used OTC laxatives among patients with chronic constipation including OIC (Coyne et al. 2015). The safety and efficacy of PEG 3350 has been well established for the treatment of chronic constipation (Johanson 2007). It works by increasing the osmotic pressure in the GI tract lumen, which leads to decreased straining, increased bowel movement (BM) frequency, improved stool formation, and reduced cramping and gas (Johanson 2007, McGraw 2016). Adverse drug reactions with PEG 3350 include nausea, abdominal fullness, and bloating (Panchal et al. 2007).

In contrast to the mechanism of action of traditional OTC laxatives, Naloxegol (Movantik™) is the first approved peripherally acting μ-opioid receptor antagonist, taken orally once daily by adult patients with OIC and chronic non-cancer pain. The efficacy of Movantik in the treatment of OIC among patients with non-cancer chronic pain was demonstrated in 2 large identical phase 3 double-blind placebo-controlled trials (Chey et al. 2014). In these studies which confirmed the benefit of 25 mg once daily oral Movantik compared with placebo, patients who received Movantik had a statistically significantly higher response rate of spontaneous bowel movements (SBM) than the placebo group. Movantik also significantly shortened the time to first post-dose SBM, and subjects experienced greater mean days per week with 1 or more SBM compared with the placebo. An open-label phase 3 long-term safety study revealed the most common adverse events (AEs) in the Movantik treatment groups were mild or moderate abdominal pain, diarrhea, nausea, headache, flatulence, and upper abdominal pain (Prescott 1981 Webster et al. 2014).

This open-label crossover study will assess patients' preference for Movantik or PEG 3350, as well as the real-world clinical effectiveness of each treatment in managing OIC symptoms and burden among patients using opioids for treatment of chronic non-cancer related pain. In addition to assessment of patient preference for Movantik or PEG 3350 and reason(s) for preference (if any), the study will utilize the Bowel Function Index (BFI), a validated tool that has been recommended by American Academy of Pain Medicine and endorsed by the American Gastroenterological Association to reliably screen for OIC and to evaluate the

progress of OIC while patients are on study medications (Argoff et al. 2015). Additionally, the Bristol Stool Scale (BSS) and the Patient Global Impression of Change (PGIC) will be used to assess the clinical effect and identify differences between treatments. Questionnaires will be administered to assess patient preference at the end of study participation.

1.2 Rationale for study design, doses and control groups

The primary objective of the study is to assess patients' preference for Movantik or PEG 3350, one of the most commonly utilized OTC laxatives for patients with constipation. The study is also designed to identify the reason(s) for this preference and to compare change in patient-reported OIC symptoms. This is a prospective, randomized, open-label crossover study consisting of a 1-week washout period, a 2-week treatment period, another 1-week washout and a final 2-week treatment period. The study design and procedures were chosen to allow time for the OIC treatments to affect symptoms, minimize risk of carry-over effects and ensure acceptability to participants.

The primary outcome under investigation is overall patient preference for Movantik versus PEG 3350. Secondary outcomes to be investigated include: 1) reasons for patient preference (only among subjects who indicate a preference), 2) patient reported impression of change measured by the PGIC, and 3) change in bowel function over the treatment periods measured using the BFI.

The study population includes patients with OIC who are taking a stable dose of opioids for chronic non-cancer related pain and are willing to discontinue use of laxatives during both the screening and washout periods. The approved rescue medication, bisacodyl, is to be used if a BM has not occurred within 72 hours of the last recorded BM. Patients will be prohibited from participating in the study if they are receiving opioids for treatment of pain related to cancer, if their constipation is not caused by or related to the use of opioids, if they have any acute or chronic conditions related to the GI tract that could impose risk, if they have any condition that may have affected the permeability of the blood-brain barrier, or if they have a known intolerance or sensitivity to PEG 3350 or Movantik. Additional requirements are further discussed in the sections on Inclusionary and Exclusionary Criteria.

Participants will be administered Movantik and PEG 3350 according to the standard dosing instructions in the Product Prescribing Information.

1.3 Benefit/risk and ethical assessment

The efficacy and safety profile of Movantik is well established for the treatment of OIC. The safety profile of PEG 3350 for the treatment of OIC has been deemed acceptable in clinical practice. There are no ethical concerns with the design of the study.

Risks to subjects have been minimized in the following ways:

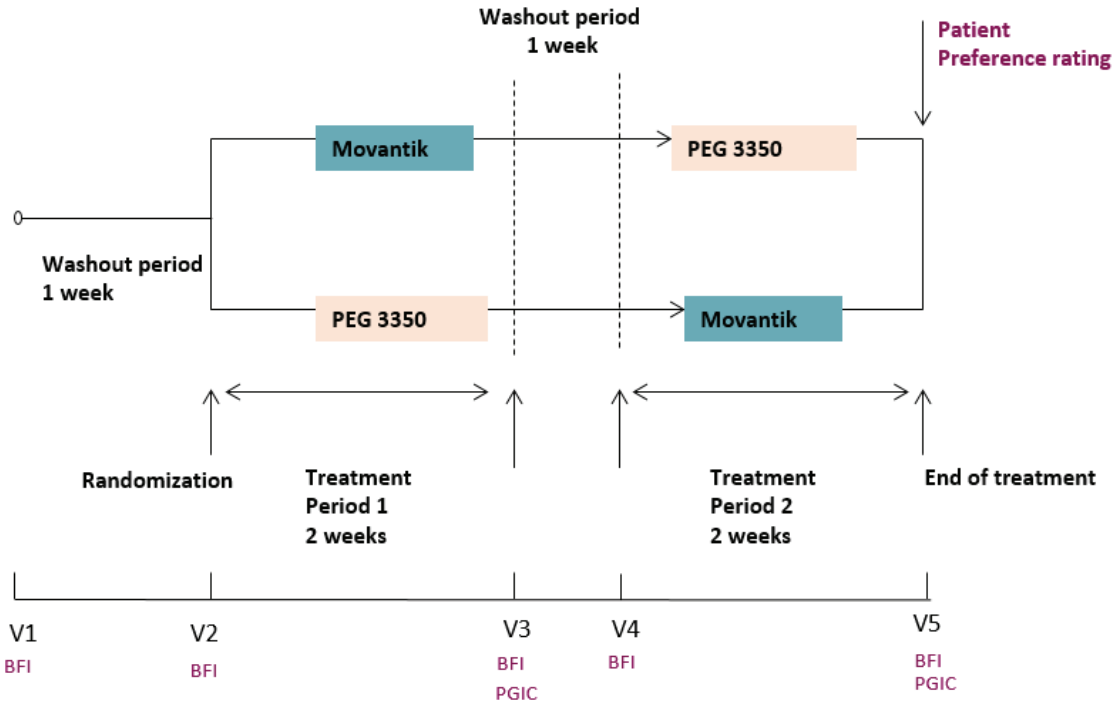
- All subjects will be screened and those with any chronic condition that could, in the judgement of the Investigator, represent a risk to safe participation, will be excluded.

- Subjects will be routinely monitored for AEs during clinic visits.

Each participating site will obtain Institutional Review Board (IRB) approval.

1.4 Study design

Figure 1 Study flow chart



2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To determine the preferred treatment for managing OIC (Movantik versus PEG 3350) among patients with chronic non-cancer pain	Patient reported preference for Movantik or PEG 3350 measured using a 7-point preference scale (Strong preference for Movantik, Moderate preference for Movantik, Slight preference for Movantik, No preference, Slight preference for PEG 3350, Moderate preference for PEG 3350, and Strong preference for PEG 3350)

2.2 Secondary objectives

Secondary Objectives:	Outcome Measures:
To assess the reason(s) for patient preference of Movantik or PEG 3350 (only among subjects who indicate a preference)	Patient reported influence of each medication characteristic in contributing to their overall preference including efficacy, tolerability, convenience, works quickly, and works predictably using a 4-point rating scale
To compare the impact of Movantik and PEG 3350 on OIC symptoms	PGIC administered after each treatment period BFI measured at Day 1 and Day 14 of each treatment period

2.3 Safety objective

Safety Objective:	Outcome Measure:
To examine the safety of Movantik and PEG 3350 for treatment of OIC	Descriptive summary of AEs and SAEs associated with each treatment

2.4 Exploratory objective

Exploratory Objective:	Outcome Measure:
To examine the effect of Movantik and PEG 3350 on BM/SBM frequency and stool consistency	BM frequency reported in the daily diary Straining reported in the daily diary for each BM using a 5-point straining scale Stool consistency reported in the daily diary for each BM using the BSS Use of rescue medication reported in the daily diary

3. SUBJECT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Subjects shall be recruited from approximately 80 sites including gastroenterology, internal medicine, pain medicine, and family medicine. Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study, subjects should fulfill the following criteria:

1. Provision of written informed consent prior to any study-specific procedures.

2. Men and women between the ages of ≥18 and <85 years.

3. Self-reported active symptoms of OIC based on components of the Rome IV criteria at screening. Patients should have at least 2 of the following new or worsening symptoms when initiating, changing, or increasing opioid therapy:

    - <3 SBMs per week;
    - Straining (>25% of defecations);
    - Sensation of incomplete evacuation (>25% of defecations);
    - Lumpy or hard stools (>25% of defecations);
    - Sensation of anorectal obstruction/blockage (>25% of defecations).

4. Confirmed OIC by BFI ≥30 at Visit 1 and Visit 2.

5. Receiving a stable maintenance opioid regimen consisting of a total daily dose of at least 30 mg of oral morphine, or equivalent of 1 or more other opioid therapies for a minimum of 1 month with stable dosing for at least 2 weeks prior to screening for non-cancer related pain with no anticipated change in opioid dose requirement over the proposed study period as a result of disease progression. The opioid regimen should be confirmed by a prescription or clearly labeled medication bottle.

6. Willingness to stop all laxatives and other bowel regimens including prune juice and herbal products except the period-specific study medications for the duration of the study. The only approved rescue medication is bisacodyl, to be used if a BM has not occurred within at least 72 hours of the last recorded BM.

7. Able to understand and comply with the requirements of the study, as judged by the Investigator (includes ability to read and write and complete the diary).

3.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Receiving opioid regimen for treatment of pain related to cancer or has a history of cancer within 5 years from the Screening Visit with the exception of fully treated basal cell cancer and squamous cell skin cancer.

2. Current constipation or chronic constipation (including functional constipation) not caused by or related to use of opioids.

3. History of rectal evacuation disorders (also known as pelvic floor dyssynergia or dysfunction), surgery or procedures that can potentially affect pelvic floor function; requirement of using manual maneuvers to facilitate a BM (e.g. digital evacuation or pelvic floor support) or patients who experienced 2 or more of the following as predominant symptoms:

    - Excessive straining (>90% of defecations);
    - Sensation of incomplete evacuation (>90% of defecations);
    - Sensation of anorectal obstruction/blockage (>90% of defecations).

4. Evidence of significant structural abnormalities of the GI tract (e.g., bowel obstruction and strictures), or any diseases/conditions that affect bowel transit (e.g., ileus and uncontrolled hypothyroidism).

5. Acute or chronic conditions related to the GI tract that could pose a risk to the patient or confound the study results including but not limited to current clinically diagnosed diarrhea, a history of fecal incontinence, irritable bowel syndrome or inflammatory bowel disease (e.g., ulcerative colitis and Crohn's disease).

6. Surgery that may affect GI motility or increase risk for bowel obstruction or perforation within 2 months prior to Visit 1, or who plan such surgery during the study.

7. Requirement of ongoing therapy with medications, other than opioids, that have contributed to the subjects' constipation in the judgement of the Investigator.

8. Receiving opioid medication on less than daily dosing schedule prior to enrollment or throughout the duration of the study period, or exhibiting significant opioid withdrawal symptoms.

9. Any condition that may have affected the permeability of the blood-brain barrier.

10. Severe background pain (e.g., typical average daily pain intensity rating of 9 to 10 on an 11-point Numeric Rating Scale) that is refractory to opioid therapy.

11. Current or previous severe hepatic impairment.

12. Calculated creatinine clearance <60 ml/min (i.e., patients with moderate, severe, or end-stage renal impairment or on dialysis treatment) prior to enrollment.

13. Any other significant and/or progressive medical, surgical, psychiatric, or mental health condition or any significant laboratory findings that could increase the risk of participation in the study or affect the interpretation of study data as determined by the Investigator (e.g., uncontrolled hypothyroidism, inadequately controlled clinical depression, prolonged QT interval, history of myocardial infarction within 6 months before randomization, symptomatic congestive heart failure despite treatment, unstable angina, or symptomatic peripheral vascular disease, etc.).

14. Currently using methadone or buprenorphine or other opioid antagonists.

15. Pregnancy, breast feeding, or planned pregnancy during the study; fertile women not using acceptable contraceptive measures, as judged by the Investigator. Female subjects who are not post-menopausal or surgically sterile must have a negative urine pregnancy test (urine dipstick test only) prior to randomization and must comply with contraceptive methods.

16. Concomitantly using strong (e.g., ketoconazole, itraconazole, clarithromycin) or moderate (e.g., diltiazem, erythromycin, verapamil) CYP3A4 inhibitors and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, St. John's Wort).

17. Known history of intolerance or hypersensitivity to PEG 3350, Naloxegol, bisacodyl, or to any of their excipients.

18. Active substance or alcohol use that, in the opinion of the Investigator, may compromise the patient's ability to comply with the study instructions.

19. Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff, [redacted] staff, [redacted] staff, [redacted] staff, staff at the study site, and third-party vendors).

20. Any receipt of an investigational medication within 30 days of screening. Was currently participating in or had participated in another clinical study within 30 days prior to screening for this study.

For procedures for withdrawal of incorrectly enrolled subjects see Section 3.4.

3.3 Subject enrollment and randomization

Investigator(s) should keep a record of the subject screening log of subjects who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject before any study specific procedures are performed.

2. Assign each potential subject a unique enrollment number, beginning with 'E#'.

3. Determine subject eligibility. See Section 3.

4. Provide rescue medication to all subjects eligible for the study.

If a subject withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

Randomization codes will be assigned strictly sequentially as subjects become eligible for randomization.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the study physician immediately, and a discussion should occur between the study physician and the Investigator regarding whether to continue or discontinue the subject from treatment. The study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Subjects who meet all inclusion criteria and none of the exclusion criteria for this study will be enrolled and will begin the first 1-week (7 day) washout period before treatment period 1.

Following the 1-week washout period, at Visit 2, subjects will complete the BFI and confirm that no change in eligibility has occurred and will be randomized to receive either Movantik or PEG 3350 for the first 2-week treatment period.

A statistician will generate the randomization scheme, where the treatment sequences are randomly allocated to subjects in a permuted block design using the RAND module of Merge eClinicalOS, which will then be incorporated into the Electronic Data Collection system.

3.6 Methods for ensuring blinding

Not applicable.

3.7 Methods for unblinding

Not applicable.

3.8 Restrictions

Refer to Exclusion Criteria in Section 3.2.

3.9 Discontinuation of study medication(s)

Subjects may be discontinued from the study medications in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment;
- Safety or tolerability reasons warranting discontinuation as judged by the Investigator and/or AstraZeneca representative;
- Severe non-compliance with the study protocol.

3.9.1 Procedures for discontinuation of a subject from study medication(s)

At any time, subjects are free to discontinue the study medications or withdraw from the study (i.e., study medications and assessments – see Section 3.10), without prejudice to further treatment. A subject who decides to discontinue will always be asked about the reason(s) and the presence of any AE. If possible, they will be seen and assessed by an Investigator(s). AEs will be followed up (See Section 6) and all study medications should be returned by the subject.

If a subject is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

Subject participation in this study may be discontinued for any of the following reasons:

1. Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subjects to adhere to the requirements of the protocol.
2. Any spontaneously reported AE, intercurrent illness, or other medical condition where the Investigator determines that continued participation is not in the best interest of the subjects. For definitions and additional information regarding SAE and AE, please refer to Section 6.
3. Subject’s decision to withdraw.
4. Subject discontinues opioid use.
5. Severe non-compliance with the protocol requirements or study related procedures.

6. Termination of the study by the Investigator, Sponsor, Food and Drug Administration, or other regulatory authorities.

The clinical report will include reason(s) for subject withdrawals as well as details relevant to the subject withdrawal. If a subject is withdrawn from the study prior to study completion, the subject will undergo all procedures scheduled for study completion (end of treatment evaluations) as the situation allows. Any subject withdrawn due to an AE (whether serious or non-serious, with or without a study medication) will be evaluated by the Investigator and will be treated and/or followed up until the symptoms return to normal or acceptable levels as judged by the Investigator.

3.10.1 Screen failures

Screening failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be randomized.

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (study medication and assessments), without prejudice to further treatment.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow up AEs outside of the clinical study.

If a subject withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca or an AstraZeneca representative, study subjects are placed at undue risk because of clinically significant findings that are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the subject at the time of discontinuation must be recorded in the electronic Case Report Form (eCRF). All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1- Schedule of Assessments

	Screening		Treatment Period 1				Treatment Period 2		
Procedure/Scale	**Visit 1**		**Visit 2**		**Visit 3**		**Visit 4**		**Visit 5**
	Consenting/ Screening		Randomization /Dispense Treatment 1		End of Treatment Period 1		Dispense Treatment 2		End of Treatment Period 2
	Day -14 to Day 1[a]		Day 1 (±2)[b]		Day 15 (-2)		Day 22 (±2)[c]		Day 36 (-2)
Informed consent	X	1-week (7 day) Washout Period 1[e]		2-week Treatment Period 1 begins the day after Visit 2		1-week (7 day) Washout Period 2		2-week Treatment Period 2 begins the day after Visit 4	
Inclusion and exclusion	X		X						
Demographic information	X								
Medical history	X								
Complete physical exam	X								
Brief physical exam			X		X		X		X
Vital signs	X		X		X		X		X
Blood sample collection and 12-lead ECG review[d]	X								
Pain scale- 11 point Numeric Rating Scale	X								
Urine pregnancy test (WOCBP)	X								
Concomitant medication review	X		X		X		X		X
Confirm ongoing opioid use			X		X		X		
Query change in medical status			X		X		X		X
Provide diary & training	X		X						
Provide study medication			X				X		
Provide rescue medication	X								
Study drug collection and accountability					X				X
Rescue medication review and accountability			X		X		X		X
Diary review			X		X		X		X
Adverse Event collection & review			X		X		X		X
Overdose information collection			X		X		X		X
Bowel Function Index (BFI)	X		X		X		X		X
Patient Global Impression of Change (PGIC)					X				X
Patient Preference Assessment[f]									X
Bristol Stool Scale (BSS)[g]	To be completed by the patient in the daily diary for each BM								
Straining scale[g]	To be completed by the patient in the daily diary for each BM								

[a] Screening process and Visit 1 can occur up to 14 days prior to Visit 2
[b] Visit 2 to occur after 1-week Washout Period 1
[c] Visit 4 to occur after 1-week Washout Period 2
[d] Blood test results from no more than 30 days and ECG results from no more than 60 days prior to Visit 1 will be abstracted from medical records. If labs have not been completed within 30 days (blood) or 60 days (ECG) local labs will be ordered by the Investigator
[e] Subjects will begin the 1-week (7 day) Washout Period 1 after the study site confirms eligibility and informs patient to begin washout (this can be done at Visit 1 or via telephone contact after Visit 1)
[f] Patient preference is assessed on a 7-point scale, reasons for preference are also assessed
[g] BSS and straining scale are collected in the daily diary for each bowel movement throughout the study including during screening and washout periods

4.1 Enrollment/screening period

Procedures will be performed according to the Study Plan (Table 1).

4.1.1 Enrollment (Visit 1) and washout period 1

At the initial visit, informed consent must be signed prior to any study specific procedures. Consenting subjects are assessed to ensure that they meet all of the eligibility criteria.

The following information is obtained and procedures are performed to support the completion of screening and eligibility assessment: demographics, complete physical examination including vital signs, medical history, BFI, medication use, urine pregnancy test (among WOCBP [women of childbearing potential] only), pain scale, and review of most recent blood sample laboratory results and 12-lead electrocardiogram (ECG) results. If blood sample collection has not been completed within 30 days, or 12-lead ECG has not been completed within 60 days prior to study enrollment, the Investigator will order the appropriate tests from a local lab.

Subjects who do not meet the eligibility criteria must not proceed to the treatment period. If all test results support eligibility at Visit 1, the subject will be informed by the study site to proceed to the initial 1-week washout period. Otherwise, the patient will be notified of their eligibility by the study site once the lab and/or ECG results are available and instructed to begin the 1-week washout period if they are eligible for the study. During the 1-week washout period, subjects will discontinue use of all current laxatives. If a patient takes dietary fiber supplements and/or has any regular exercise routines, these practices should be maintained at a stable level for at least 1 month prior to the enrollment and continued throughout the study duration. All subjects who initiate the washout period will be trained in the use of the diary, including instructions on how to assess stool consistency with the BSS and how to complete the straining score. Subjects will be provided with rescue medication (to be used if a BM does not occur within at least 72 hours of the last recorded BM) at Visit 1.

4.2 Treatment period

The treatment period for this study consists of two 2-week treatment periods separated by a 1-week washout period, as depicted in Figure 1.

4.2.1 Randomization/dispense treatment 1 (Visit 2)

At the beginning of treatment period 1, upon confirmation of BFI score and study eligibility, subjects will be randomized to receive either Movantik or PEG 3350 for Treatment Period 1 as described in Section 3.5. At Visit 2, the following information is obtained and procedures are performed: brief physical examination (including vital signs), concomitant medication review, diary review, AE collection, and BFI. The appropriate medication for Treatment Period 1 will be distributed by the Investigator to subjects who meet the inclusion and do not meet the exclusion criteria at Visit 2.

4.2.2 End treatment period 1 (Visit 3)

At the end of treatment period 1 (Visit 3), the following information is obtained and procedures are performed: brief physical examination (including vital signs), concomitant medication review, diary review, AE collection, collection of Treatment Period 1 medication, BFI, rescue medication review, and PGIC.

4.2.3 Washout period 2

During this washout period, subjects will continue to withhold use of all laxatives except the rescue medication, as needed, if the patient has not experienced a BM in the last 72 hours.

4.2.4 Dispense treatment 2 (Visit 4)

At the beginning of Treatment Period 2 (Visit 4), subjects will receive the appropriate treatment from the Investigator. At Visit 4, the following information is obtained and procedures are performed: brief physical examination (including vital signs), concomitant medication review, diary review, AE collection, and BFI.

4.2.5 End treatment period 2 (Visit 5)

At the end of treatment period 2 (Visit 5), the following information is obtained and procedures are performed: brief physical examination (including vital signs), concomitant medication review, diary review, AE collection, collection of Treatment Period 2 medication, BFI, rescue medication review, PGIC, overall preference for Movantik versus PEG 3350, and reason for preference.

4.3 Follow-up period

This study has a relatively short duration and will not have a follow-up period. Both study drugs are approved in the US, and their safety profiles are well characterized. No delayed toxicity is anticipated. In addition, no safety signal was detected in the Movantik pivotal studies during the follow-up period. Please see Section 6 for additional post-study safety-related procedures.

5. STUDY ASSESSMENTS

The Investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Outcome assessments

5.1.1 Primary outcome endpoint

5.1.1.1 Patient reported preference for Movantik or PEG 3350

Patient reported preference for Movantik or PEG 3350 will be assessed at the end of treatment period 2 using a 7-point preference scale: Strong preference for Movantik, Moderate preference for Movantik, Slight preference for Movantik, No preference, Slight preference for PEG 3350, Moderate preference for PEG 3350, Strong preference for PEG 3350. For statistical analysis, the 7-point scale will be collapsed into 3 categories: Prefer Movantik, No preference, and Prefer PEG 3350.

Only per-protocol (PP) subjects who have completed both treatment periods will be eligible for this analysis.

5.1.2 Secondary outcome endpoints

5.1.2.1 Reason for preference (among subjects who indicated a preference)

The reason for preference will be assessed by summarizing the patient-reported influence of each medication characteristic in contributing to their overall preference including efficacy, tolerability, convenience, works quickly, and works predictably using a 4-point rating scale.

Only PP subjects who have completed both treatment periods and have indicated a preferred treatment will be eligible for this analysis.

5.1.2.2 Impact of Movantik and PEG 3350 on OIC symptoms

The impact of Movantik and PEG 3350 on OIC symptoms will be assessed using the change in BFI scores between Day 1 and Day 14 of each treatment and the difference in PGIC (Hurst 2004) measured at the end of treatment period 1 and the end of treatment period 2.

5.1.3 Safety outcome endpoint

5.1.3.1 Adverse event and serious adverse events

Descriptive characteristics of AEs and SAEs will be presented for each treatment. See Sections 6.1 and 6.2 for a description of AEs and SAEs.

5.1.4 Exploratory outcome endpoints

5.1.4.1 BM/SBM frequency

BM frequency will be summarized using information from the subject-completed daily diaries. An SBM is defined as a BM that occurred without the use of rescue laxatives (bisacodyl) in the previous 24 hours. Unless otherwise specified, the term BM is used hereafter to refer to both SBMs and non-spontaneous BMs.

5.1.4.2 Straining sensation

Straining sensation will be summarized using information from the subject-completed daily diary. Subjects will report straining sensation for each BM using a 5-point straining scale.

5.1.4.3 Stool consistency

Stool consistency information will be summarized using information from the subject-completed daily diaries. Patients will provide a BSS score for each BM.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Not applicable.

5.2.2 Physical examination

Complete and brief physical examinations will be performed in accordance with the Study Plan provided in Section 4, Table 1. The physical examinations will include an assessment of the following: general appearance; abdomen; respiratory and cardiovascular symptoms; weight and height.

5.2.3 ECG

Not applicable.

5.2.4 Vital signs

Vital signs (pulse, blood pressure, and respiratory rate) will be obtained in accordance with the Study Plan provided in Section 4, Table 1.

5.2.5 Other safety assessments

Not applicable.

5.3 Other assessments

Not applicable.

5.4 Pharmacokinetics

Not applicable.

5.5 Pharmacodynamics

Not applicable.

5.6 Pharmacogenetics

Not applicable.

5.7 Biomarker analysis

Not applicable.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver), or the abnormal results of an investigation (e.g., laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, and washout), that fulfills 1 or more of the following criteria:

- Results in death;
- Is immediately life-threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital abnormality or birth defect;
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent 1 of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs will be collected from the time of signature of informed consent throughout the treatment period. If the Investigator becomes aware of any SAEs that occur after study completion and considers them to be caused by Movantik, the Investigator may report the SAEs to AstraZeneca as a spontaneous report by calling the AstraZeneca information center [redacted]

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca and its representatives retain the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim);
- The date when the AE started and stopped;
- Intensity rating scale (intensity, maximum intensity or changes in intensity)
    - Mild
    - Moderate
    - Severe;
- Whether the AE is serious or not;
- Investigator causality rating against the study medication (yes or no);
- Action taken with regard to the study medication;
- Whether the AE caused subject's withdrawal from study (yes or no);
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE;
- Date Investigator became aware of serious AE;

- The reason AE is serious;
- If hospitalization or prolongation of hospitalization:
    - Date of hospitalization;
    - Date of discharge;
- If death:
    - Probable cause of death;
    - Date of death;
    - Autopsy performed; (yes or no) and conclusion of cause of death from autopsy;
- Causality assessment in relation to study medication;
- Causality assessment in relation to study procedure(s);
- Causality assessment in relation to other medication;
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between the study medication and each AE, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the study medication?’

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as ‘yes’.

A guide to the interpretation of the causality question is found it Appendix B to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the study medication, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to AstraZeneca Patient Safety via email to [redacted] **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

For SAEs related to PEG 3350, an AstraZeneca representative will send all SAE information to the manufacturer.

6.4.1 Overdose

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module;
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on a study medication occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

The following information should be provided in the event of an overdose:

- Details of the patient who was dispensed study medication (randomization code)
- Details of the patient who took the overdose (demographic information, was patient a study participant?)
- Details of the drug overdose (total daily dose, route, formulation, overdose start and stop dates)
- Was the overdose accidental or intentional?
- Was the overdose associated with an AE (serious or non-serious)
- Provide an AE description (use same wording as in the eCRF). Provide start and stop dates of the event, or indicate if the event is ongoing.

6.5 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to an AstraZeneca representative.

6.5.1 Maternal exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study medication may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.5.2 Paternal exposure

There is no restriction on fathering children or donating sperm during the study.

6.6 Management of IP related toxicities

Not applicable

7. ASTRAZENECA MEDICATION AND OTHER TREATMENTS

7.1 Identity of study medications

Study Medications	Dosage form and strength	Manufacturer
Movantik™	25 mg tablet taken once daily on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal	AstraZeneca
Polyethylene Glycol 3350	17 g of powder to be dissolved in 4 to 8 oz of water, juice, soda, coffee, or tea to be taken once daily	Breckenridge Pharmaceutical Inc.

7.1.1 Rescue medication

Subjects will be provided bisacodyl to be taken as needed if a BM has not occurred within 72 hours of the start of washout period 1 or 72 hours from the last recorded BM. Rescue medication will be prescribed at Visit 1 and will be available throughout the study.

Rescue Medication	Dosage form and strength	Manufacturer
Bisacodyl	1 to 3 tablets (5 mg) taken with a glass of water in a single daily dose	Commercially available

7.2 Dose and treatment regimens

For each 2-week treatment period, subjects will use the appropriate treatment (Movantik or PEG 3350) as described on the drug label. The first dose of each treatment period should be taken the morning after receipt of the treatment from the Investigator.

7.3 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language.

7.4 Storage

All study medications should be kept in a secure place under appropriate storage conditions as stated on the labels provided with the study medications.

7.5 Compliance

Adherence to the recommended dosage for all study medications including the rescue medication will be reported by participants in the daily diary.

7.6 Accountability

The study medications provided for this study will be used only as directed in the study protocol.

7.7 Concomitant and other treatments

As stated in the Exclusion Criteria (Section 3.2), concomitant use of strong or moderate CYP34A inhibitors, strong CYP3A4 inducers, and other opioid antagonists is prohibited.

7.7.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

Analyses will be performed by an AstraZeneca representative.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first subject randomized and any subsequent amendments will be documented.

8.2 Sample size estimate

For the primary endpoint of patient preference, the 7-point preference scale will be condensed into 3 categories (Prefer Movantik, No Preference, Prefer PEG 3350) and analyzed using Prescott's test. When the sample size in each of the 2 sequence groups is 102, a 0.050 level Chi-square test will have 88% power to distinguish between the groups when the proportions in the 3 categories are characterized by an Effect size, $D^2 = S(p2j-p1j)^2/[2(p2j+p1j)]$, of 0.0588, as in the following table (which shows a 20% difference in preference for treatment 1 over treatment 2, and assumes 25% of subjects with no preference). The sample size calculation was performed with nQuery Advisor version 7.0 using Table PTT3.

Sequence	First Treatment	No Preference	Second Treatment
AB	0.48	0.25	0.27
BA	0.27	0.25	0.48

Assuming a non-completion rate of 20%, 256 subjects will need to be randomized in order to have 102 subjects per treatment sequence for the primary analysis.

8.3 Definitions of analysis sets

8.3.1 Per-protocol analysis set

The analysis set for the primary analysis will be the PP set. All subjects who satisfy inclusion and exclusion criteria, receive study medication, and complete the patient preference assessment at Visit 5 will be evaluated in the PP set.

8.3.2 Full analysis set

The analysis set for all secondary and exploratory analyses will be the Full Analysis Set (FAS), unless otherwise indicated. All subjects who receive study medication and complete at least 1 scheduled visit will be evaluated in the FAS.

8.3.3 Safety analysis set

There will be 2 safety analysis sets – the pre-treatment safety analysis set and the treatment emergent safety analysis set. The pre-treatment safety analysis set will include all subjects who consent to participate in the study. The pre-treatment safety analysis set will be the set used to summarize the occurrence of adverse experiences prior to exposure to the study medications.

The treatment-emergent safety set will include all subjects exposed to at least 1 dose of either study medication. The treatment-emergent safety analysis set will be used for each of the safety endpoints and AEs occurring after exposure study medication. For treatment-emergent safety analyses, subjects will be categorized according to the actual treatment received. Subjects who took incorrect study treatment will be included in the group corresponding to the actual treatment received.

8.4 Outcome measures for analyses

8.4.1 Primary outcome

- To determine the proportion of patients in the PP analysis set in each preference category including: Prefer Movantik, No Preference, and Prefer PEG 3350. The 3 categories are collapsed from the 7-point preference scale as described in Section 5.1.1.1.

8.4.2 Secondary outcomes

- To assess the influence of each medication characteristic in contributing to overall preference for Movantik or PEG 3350 (only among subjects who indicate a preference in the PP analysis set), this outcome will use a 4-point scale ranging from 0 for No influence to 3 for Strongly influenced;

- To compare the impact of Movantik and PEG 3350 on OIC symptoms;

    - Overall impression of symptom change: PGIC measured at the end of each treatment period;

- OIC symptoms: BFI measured at the first and last day of each treatment period.

8.4.3 Safety outcome

- To examine the safety of Movantik and PEG 3350 for treatment of OIC Exploratory Outcomes;
  - Descriptive characteristics of AEs and SAEs.

8.4.4 Exploratory outcomes

- To examine the effect of Movantik and PEG 3350 on BM/SBM frequency and stool consistency;
  - Stool consistency: BSS reported in diary for each BM;
  - Straining sensation: 5-point straining scale reported in diary for each BM;
  - BM frequency: reported in diary;
  - SBM frequency: based on diary-reported BM frequency and rescue medication use;
  - Usage of rescue medication as reported in the diary.

8.5 Methods for statistical analyses

All computations and generation of tables, listings, and figures will be performed using SAS version 9.2 or higher.

The SAP will be generated to provide details of the planned analyses.

Summary measures of all continuous variables will include the mean, standard deviation (SD), median, minimum, and maximum by treatment and sequence, as indicated.

Summary measures for all discrete variables will include the frequency and percentage by treatment and sequence, as indicated.

Descriptive summary measures will be presented for demographic and baseline characteristics, including medical history, physical exam, laboratory measures and ECG results at screening from medical, concomitant medications, and changes in medical status.

Additional subgroups will be analyzed including, but not limited to, age groups, subjects with and without prior history of laxative medication use, and subjects with and without a significant change in opioid dose.

8.5.1 Analysis of the primary variable

The analysis for the primary outcome of patient's preference (Prefer Movantik, No Preference, Prefer PEG 3350) will use Prescott's test to assess the difference in preference for the two treatments. Prescott's test analyzes the difference between the 2 treatment sequences

in a 2 (treatment sequence AB, treatment sequence BA) by 3 (Prefer First Treatment Received, No Preference, Prefer Second Treatment Received) contingency table (Prescott 1981). The cell counts in the contingency table follow a hypergeometric probability distribution, and Prescott's test assesses the probability of obtaining a table with cells counts of equal or more extreme values.

Prescott's test is only applicable for subjects who complete the entire treatment sequence in the PP analysis set; thus, subjects who do not complete both treatments will be missing from the primary analysis. Unless otherwise specified in the SAP, no imputation will be performed for missing data, and the analysis will be performed on observed cases.

There is only a single primary outcome variable at the end of the study, thus no adjustment for multiplicity is needed.

Additional sensitivity analyses will be conducted for the primary variable as described in the SAP.

8.5.2 Analysis of the secondary variables

For analyses of secondary continuous variables, a linear regression model with terms for subject, treatment sequence (AB/BA), treatment period (Period 1, Period 2), and treatment (Movantik, PEG 3350), will be used to assess the direct treatment effect as well as any carry-over effect. In addition, other potential covariates may be added to the model (e.g., age group, gender) for secondary analyses. P-values for all secondary measures will be considered descriptive only.

The linear regression crossover model will be used for variables including:

- PGIC, using a 7-point scale;
- BFI, a numeric analogue scale from 0 to 100, using the mean of 3 variables (ease of defecation, feeling of complete evacuation, and personal judgment of constipation).

Descriptive summary tables will be presented for the PGIC by treatment medication at Day 14, including mean, median, SD, minimum and maximum. For the BFI, a summary table including mean, median, SD, minimum and maximum will be presented for the observed score at baseline, Day 1 and Day 14 by treatment medication. In addition, summary measures will be presented for change from baseline, and percentage change from baseline at Day 14 by treatment medication. The BFI completed at Visit 2 will serve as the baseline for treatment period 1. The BFI completed at Visit 3 will be the baseline for treatment period 2. The descriptive summary tables will be presented overall and by treatment sequence.

A summary of the patient-reported influence of each medication characteristic on overall preference including: efficacy, tolerability, convenience, works quickly, and works predictably, will be performed. A summary table for each characteristic by treatment will include the mean, SD, median, minimum, and maximum for patients in the PP analysis set, overall and by treatment sequence. In addition, the number and percentage of subjects in each

category (see Appendix B) will be summarized overall and by treatment sequence. An additional factor analysis may be performed to assess the specific items that cluster together for patient preference.

8.5.3 Interim analysis

No interim analysis is planned for this study.

8.5.4 Safety analysis

Safety analysis will include a summary of the frequencies and percentages of AEs and SAEs and frequency and percentage of subjects experiencing the AEs and SAEs presented by system organ class and preferred term according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

8.5.5 Exploratory analysis

For analyses of exploratory outcomes, the methods described in section 8.5.2 will be used for the measures including:

- BSS, using a 7-point scale of stool consistency measured for each BM;
- Straining sensation, using a 5-point straining scale reported for each BM;
- BM frequency;
- SBM frequency;
- Usage of rescue medication.

For the BSS, a linear regression model with terms for patient, treatment sequence (AB/BA), treatment period (Period 1, Period 2), and treatment (Movantik, PEG 3350), will be used to assess the direct treatment effect as well as any carry-over effect. In addition, other potential covariates may be added to the model (e.g., age groups 18-55 and >55 years, and gender) for exploratory analyses. P-values for all exploratory measures will be considered descriptive only. A summary table will also be presented with mean, median, SD, minimum, and maximum BSS score at baseline, as well as Days 1 to 14 by study medication. Results will be presented overall and by treatment sequence.

The average score of straining sensation is the quotient of the sum of each BM rating occurring during a given period (i.e., 1-week screen period, treatment period 1, washout, and treatment period 2) and the number of BMs within a given period. The average straining sensation score during the 1-week screen period is the baseline score for the average straining sensation score in treatment period 1 and the average straining sensation score for the between treatment washout period is the baseline score for the average straining sensation score in treatment period 2. The differences in the change from baseline and treatment periods will be assessed via a Wilcoxon signed-rank test.

For BM frequency, a summary table of the counts and percentages of BM frequency per week will be presented by treatment medication. Results will be presented overall and by treatment sequence.

Usage of rescue medication by treatment period will be summarized by the number and percentage of patients requiring rescue medication, as well as the number of times rescue medication was used per subject, overall and by treatment.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and system(s) utilized.

The Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contact with the study site, including visits to:

- Provide information and support to the Investigator(s);
- Confirm that facilities remain acceptable;
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in a timely fashion on the eCRFs, that biological samples are handled in accordance with the Laboratory Manual, and that study medication accountability checks are being performed;
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts).

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the center need information and advice about the study conduct.

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The Investigator at each site/the center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

Agreements between AstraZeneca or their representatives and the Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study is expected to start in Q1 2017 and to end by Q1 2018.

The study may be terminated at individual centers if the study procedures are not being performed according to International Council for Harmonisation/Good Clinical Practice (ICH/GCP), or if recruitment is slow. AstraZeneca or their representative may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with Movantik.

9.4 Data management

Data management will be performed by an AstraZeneca representative, according to the Data Management Plan. AEs and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the WHO Drug Dictionary. Classification coding will be performed by an AstraZeneca representative.

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible, or missing values. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and

responsibilities of the various functions and personnel involved in the data management process

When all data have been coded, validated, and locked, a clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

SAE Reconciliation

SAEs are reconciled as agreed upon in the SAE reconciliation plan. Generally, specific SAE fields are reconciled between the clinical trial database and the safety database.

Data Management of genotype data

Not applicable.

Data associated with human biological samples

Not applicable.

Management of external data

Not applicable.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The Informed Consent Form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An IRB should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable IRB and to the study site staff.

The opinion of the IRB should be given in writing. The Investigator should submit the written approval to an AstraZeneca representative before enrollment of any subject into the study.

The IRB should approve all advertising used to recruit subjects for the study.

An AstraZeneca representative should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB annually.

An AstraZeneca representative will handle the distribution of any of these documents to the national regulatory authorities.

An AstraZeneca representative will provide Regulatory Authorities, Ethics Committees, and Principal Investigators with safety updates/reports according to local requirements.

Each Investigator is responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study medications. An AstraZeneca representative will provide this information to the Investigator so that he or she can meet these reporting requirements.

10.4 Informed consent

The Investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study;
- Ensure each subject is notified that they are free to discontinue from the study at any time;
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided;
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study;
- Ensure the original, signed ICF is/are stored in the Investigator's Study File;
- Ensure a copy of the signed ICF is given to the subject;
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB.

10.5 Changes to the protocol and ICF

Study procedures will not be changed without the mutual agreement of the National Co-ordinating Investigators, AstraZeneca, and their representatives.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

An AstraZeneca representative will distribute any subsequent amendments and new versions of the protocol to each Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a protocol amendment requires a change to a center's ICF, an AstraZeneca representative and the center's Ethics Committee are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH/GCP, and any applicable regulatory requirements. The Investigator will contact an AstraZeneca representative immediately if contacted by a regulatory agency about an inspection at the center.

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Clinical Study Protocol Appendix A

Drug Substance	Movantik
Study Code	D3820L00017
Edition Number	1.0
Date	06 October 2016

Appendix A
Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality, consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug:

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host, or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of ‘related’ is made if following a review of the relevant data, there is evidence for a ‘reasonable possibility’ of a causal relationship for the individual case. The expression ‘reasonable possibility’ of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as ‘not related’.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix B

Drug Substance	Movantik
Study Code	D3820L00017
Edition Number	2.0
Date	26 January 2016

Appendix B
Questionnaires

Overall patient preference

Overall patient preference for Movantik or Polyethylene Glycol 3350 (PEG 3350) will be assessed at Visit 5 among subjects who completed both treatment periods using a 7-point preference scale designed for this study. The question is provided below:

"Please rate your preference for Movantik or PEG 3350 to treat your opioid-induced constipation (OIC) by choosing one of the following:"

- Strong preference for Movantik
- Moderate preference for Movantik
- Slight preference for Movantik
- No preference
- Slight preference for PEG 3350
- Moderate preference for PEG 3350
- Strong preference for PEG 3350

Influence of medication characteristics on overall preference

The influence of medication characteristics will be assessed at Visit 5 among subjects who completed both treatment periods and who reported a preferred treatment for their OIC. Subjects will be asked to evaluate the degree that each characteristic of the medications influenced their specific treatment preference (efficacy, tolerability, convenience, works quickly, works predictably) individually using a 4-point rating scale. The questions are provided below, the medication name that appears in the brackets will be adjusted based on the patient's overall medication preference:

"Please indicate how much each of the factors below influenced your preference for [MOVANTIK or PEG 3350]:"

	No Influence 0	Mildly influenced 1	Moderately Influenced 2	Strongly Influenced 3
[MOVANTK or PEG 3350] worked better to relieve my opioid-induced constipation (OIC)				
I tolerated [MOVANTIK or PEG 3350] better				
[MOVANTIK or PEG 3350] was more convenient				
[MOVANTIK or PEG 3350] worked quickly				
[MOVANTIK or PEG 3350] worked predictably				

Patient Global Impression of Change (PGIC)

The PGIC will be given to the subjects at the conclusion of each treatment period, Visits 3 and 5. The PGIC is designed to assess a patient's belief about the efficacy of a particular treatment. See below for the PGIC question:

"Since the beginning of this treatment period, how would you describe the change (if any) in activity limitations, symptoms, emotions, and overall quality of life related to your opioid-induced constipation (OIC)?"

Choose ONE.

1. No change (or condition has gotten worse)
2. Almost the same, hardly any change at all
3. A little better, but no noticeable change
4. Somewhat better, but the change has not made any real difference
5. Moderately better, and a slight but noticeable change
6. Better and a definite improvement that has made a real and worthwhile difference
7. A great deal better and a considerable improvement that has made all the difference

Bowel Function Index (BFI)

The Bowel Function Index (BFI) is a 3-item questionnaire to measure constipation from the patient's perspective. A study clinician should ask subjects the BFI questions. The BFI is not intended to be given to the subject for completion on their own (self-administration), not even if a study clinician explains how the measure should be completed. The BFI should always be administered to the subject by a study clinician.

Instructions for administering each item of the BFI are indicated in the grey sections below each item.

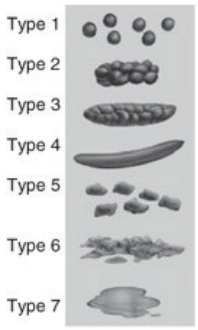
Ask subjects each question. If the subject does not understand the question, a study clinician may provide clarification as indicated below each question in the grey sections of the measure below. A study clinician should enter each answer provided by the subject in the appropriate section of the case report form (CRF). To avoid any form of response bias, study clinicians must not lead the subjects in their answers (e.g., study clinicians should not provide examples of answers to a given question).

Bowel Function Index (BFI)
Please complete all items in this assessment.
1. Ease of defecation (NAS) during the last 7 days according to patient assessment: 0 = easy / no difficulty 100 = severe difficulty ***Ask the subject:*** *"During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"* ***If the subject requires clarification, ask:*** *"During the last 7 days, how easy or difficult was it to have a bowel movement on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"*
2. Feeling of incomplete bowel evacuation (NAS) during the last 7 days according to patient assessment: 0 = not at all 100 = very strong ***Ask the subject:*** *""During the last 7 days, how would you rate any feeling of incomplete bowel evacuation on a scale from 0 to 100, where 0 = no feeling of incomplete evacuation and 100 = a very strong feeling of incomplete evacuation?"* ***If the subject requires clarification, ask:*** *"During the last 7 days, how strongly did you feel that you did not empty your bowels completely? Please indicate how strong this feeling was on a scale from 0 to 100, where 0 = not at all and 100 = very strong"*
3. Personal judgement of patient (NAS) regarding constipation during the last 7 days: 0 = not at all 100 = very strong ***Ask the subject:*** *"During the last 7 days, how would you rate your constipation on a scale from 0 to 100, where 0 = not at all and 100 = very strong"* ***If the subject requires clarification, ask:*** *"During the last 7 days, how would you rate how constipated you felt on a scale from 0 to 100, where 0 = not at all and 100 = very strong"*

Bristol Stool Scale (BSS)
Subjects will rate stool consistency through completion of the BSS after each BM.

The BSS is a medical aid designed to classify the form of human feces into 7 categories. The 7 stool types are represented by words and pictures for ease of classification:

1. *Separate hard lumps, like nuts (hard to pass)*
2. *Sausage-shaped but lumpy*
3. *Like sausage, but with cracks on its surface*
4. *Like a sausage or snake, smooth and soft*
5. *Soft blobs with clear cut edges (passed easily)*
6. *Fluffy pieces with ragged edges, a mushy stool*
7. *Watery, no solid pieces*



Straining scale

The degree of straining with each BM will be recorded at the time of the BM. A single-item straining question will be asked via the patient diary. The question is provided below:

"How much did you strain during your bowel movement?"

Patients will be asked to respond on a 5-point Likert scale choosing one of the following options:

1=Not at all

2=A little bit

3=A moderate amount

4=A great deal

5=An extreme amount.

11-point pain scale

Typical average daily pain intensity will be measured at Visit 1 using the 11-point Numeric Rating Scale below:

"Please rate your typical average daily pain level from 0 (no pain) to 10 (worst pain imaginable)."