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

[redacted] Study Statistician [redacted]

AZ Representative [redacted]

AstraZeneca

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BFI	Bowel Function Index
ATC	Anatomical-Therapeutic-Chemical
BM	Bowel movement
BMI	Body mass index
BSS	Bristol Stool Scale
CI	Confidence interval
CRF	Case report form
eCRF	Electronic case report form
ECG	Electrocardiogram
FAS	Full analysis set
MedDRA	Medical Dictionary for Regulatory Activities
LS Mean	Least Square Mean
OIC	Opioid-induced constipation
PEG 3350	Polyethylene glycol 3350
PGIC	Patient Global Impression of Change
PP	Per-protocol
PT	Preferred term
SAE	Serious adverse event
SBM	Spontaneous bowel movement
SD	Standard deviation
SE	Standard error
SOC	System organ class

1. Study Design

This is a prospective, multi-center, randomized, open-label, crossover study in subjects with chronic non-cancer pain to evaluate patients' preference for opioid-induced constipation (OIC) treatment (Movantik™ versus polyethylene glycol 3350 [PEG 3350]), and the reason for their preference. After a 1-week washout period, subjects will be randomized to one of two treatment sequences (either Movantik first and PEG 3350 second, or PEG 3350 first and Movantik second). The subject will then enter the first 2-week treatment period with study medication 1, followed by a second 1-week washout period, and then a second 2-week treatment period with study medication 2. Subject preference for study medication will be assessed at the end of treatment period 2.

The study plans to randomize approximately 256 total subjects, with 128 subjects per treatment sequence arm, for a non-completion rate of 20% for approximately 102 completed subjects per treatment sequence arm. The subjects were to be recruited and enrolled at approximately 80 sites in the United States. Due to rapid enrollment of subjects, the total number of sites that enrolled subjects was reduced from the target of 80 planned sites to 59 actual sites.

Study design and study scheduled assessments are included in Appendix sections 9.1 and 9.2, respectively.

2. Objectives

Primary Objective

- The primary objective is to determine the preferred treatment for managing OIC (Movantik versus PEG 3350) among subjects with chronic non-cancer pain.

Secondary Objectives

- To assess the reason(s) for patient preference of Movantik or PEG 3350 (only among subjects who indicate a preference).
- To compare the impact of Movantik and PEG 3350 on OIC symptoms.

Safety Objective

- To examine the safety of Movantik and PEG 3350 for treatment of OIC.

Exploratory Objective

- To examine the effect of Movantik and PEG 3350 on Bowel Movement (BM)/Spontaneous Bowel Movement (SBM) frequency and stool consistency.

3. Analysis Sets

3.1. Definition of analysis sets

3.1.1 Randomized Set

All subjects who were randomized at Visit 2 are included in the randomized set.

3.1.2 Full Analysis Set (FAS)

All subjects who satisfy inclusion and exclusion criteria, receive study medication, and attend at least one scheduled visit will be evaluated in the FAS. Data will be summarized according to the randomized treatment sequence (regardless of actual treatment sequence received). The analysis set for all but one secondary analyses and all exploratory analyses will be the FAS, unless otherwise indicated.

3.1.3 Per-protocol (PP) analysis set

The PP analysis set consists of the subset of FAS subjects who complete the patient preference assessment at Visit 5 (end of study), complete the treatment sequence in the order specified by the randomized treatment sequence, and are not excluded due to an important protocol deviation are included in the PP analysis set. The analysis set for the primary analysis and the secondary analysis of reason for preference will be the PP set.

3.1.4 Safety analysis set

There will be two 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 and will be used to list the occurrence of adverse events (AEs) prior to exposure to the study medications.

The Treatment-Emergent safety analysis set will include all subjects exposed to at least one dose of either study medication. For Treatment-Emergent safety analyses, subjects (including those who took the incorrect study treatment) will be summarized according to the actual treatment received during each study period. Each AE is also coded by the investigator according to its relationship (yes/no) to study medication (Movantik or PEG 3350) and/or rescue medication (bisacodyl).

The Treatment-Emergent safety analysis set will be used for AEs occurring after exposure to study medication, as well as for vital signs. Any treatment emergent AE that occurs from Visit 2 up to (but not including) Visit 4 (including washout period 2) will be summarized according to the actual treatment received in treatment period 1. Any treatment emergent AE that occurs from Visit 4 onward will be summarized according to the actual treatment received in treatment period 2.

4. Outcomes

4.1 Primary – Preference for OIC Treatment

The primary outcome will be the proportion of subjects in each preference category including: Prefer Movantik, No Preference, and Prefer PEG 3350. These three categories will be formed by collapsing the 7-point rating scale as follows: Prefer Movantik (includes Strong Preference for Movantik, Moderate preference for Movantik, Slight Preference for Movantik), No preference, and Prefer PEG 3350 (includes Strong Preference for PEG 3350, Moderate preference for PEG 3350, Slight Preference for PEG 3350).

4.2 Secondary

4.2.1 Reason for Preference

The influence of five medication characteristics (efficacy, tolerability, convenience, works quickly, and works predictably) on overall preference (Prefer Movantik, Prefer PEG 3350) as outlined, will be rated by the subject using a 4-point rating scale. The influence response levels include: 0 = No Influence, 1 = Mildly Influenced, 2 = Moderately Influenced, and 3 = Strongly Influenced. The reason for preference will only be completed by subjects who indicate a treatment preference at Visit 5.

4.2.2 Impact of Movantik and PEG 3350 on OIC symptoms

4.2.2.1 Bowel Function Index (BFI)

The impact of Movantik and PEG 3350 on OIC symptoms will be assessed using the BFI scores assessed at the end of each treatment period (Visits 3 and 5). The three items that comprise the BFI scale are: Ease of Defecation, Feeling of Incomplete Evacuation, and Personal Judgment of Constipation, with each item rated on a scale of 0 to 100. The overall BFI score will be computed as the mean of the three individual scale items. The overall score will be set to missing, if at least one of the three BFI item scores is missing. The BFI scores are obtained at each scheduled study visit, including Screening (Visit 1), the start of each treatment period (Visits 2 and 4), and the end of each treatment period (Visits 3 and 5).

4.2.2.2 Patient Global Impression of Change (PGIC)

The PGIC is completed once at the end of each treatment period (Visits 3 and 5), and measures a subject's global impression of change in OIC symptoms from the start of treatment on a 7-point scale. The response levels of the PGIC include: 1 = No change, 2 = Almost the same, 3 = A little better, 4 = Somewhat better, 5 = Moderately better, 6 = Better and a definite improvement, and 7 = A great deal better.

4.3 Exploratory

4.3.1 BM/SBM frequency

BM frequency will be summarized using information from the subject-completed daily diary. An SBM is defined as a BM that occurred without the use of rescue laxatives (bisacodyl) in the previous 24 hours.

4.3.2 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, ranging from 1 = Not at all, 2 = A little bit, 3 = A moderate amount, 4 = A great deal, and 5 = An extreme amount.

4.3.3 Bristol Stool Scale (BSS)

Stool consistency information will be summarized using information from the subject-completed daily diary. Subjects will provide a BSS score for each BM. The BSS is a 7-point scale measuring stool consistency (see Appendix B of the Clinical Study Protocol).

4.3.4 Rescue Medication

Usage of rescue medication for each treatment will be summarized using information from the subject-completed daily diary. Subjects will indicate the date and time that rescue medication was used, as well as the number of tablets taken.

4.4 Safety

4.4.1 Adverse Events

To compare the safety of Movantik and PEG 3350, descriptive analyses of AEs and serious adverse events (SAEs) will be presented for each treatment. The definition of AEs and SAEs is specified in Protocol sections 6.1 and 6.2.

4.4.2 Vital Signs

Vital signs (pulse, blood pressure, and respiratory rate) will be obtained at each scheduled study visit (Screening Visit 1, the start of each treatment period on Visits 2 and 4, and the end of each treatment period at Visits 3 and 5).

4.4.3 Opioid Medication

Opioid doses will be recorded for each subject, including both the maintenance dose and any breakthrough dose which results in a change in dose recorded on the eCRF. The daily opioid dose in morphine equivalents (mg/day) will be calculated using the equivalence information in Table 1 below (details provided in Appendix section 9.7).

Table 1 Dose Equivalents for Opioid Analgesics

Oral Dose (mg)	Analgesic	Parenteral Dose (mg)	Oral Morphine Equivalents (mg)
15	Morphine	5	15
100	Codeine[a]	60	15
-	Fentanyl[b]	0.1 (intravenous)	15
10	Hydrocodone	-	15
4	Hydromorphone	1.5	15
2	Levorphanol	1	15
150	Merperidine	50	15

10	Oxycodone	-	15
5	Oxymorphone	1	15
100	Propoxyphene	-	15
60	Tapentadol	-	15
67.5	Tramadol	-	15

Note: All doses listed in the above chart will be regarded as equianalgesic. For example, 10 mg of oral hydrocodone corresponds to 15 mg of oral morphine equivalents. And one mg of parenteral oxymorphone is considered to be equivalent to 15 mg of oral morphine.

[a] Dihydrocodeine is considered equipotent with codeine.

[b] For the 72 hr fentanyl patch (25 µg/hr), the equianalgesic daily dose of oral morphine will be considered to be 15 mg every 4 hh OR 45 mg BID of MS-Contin (i.e., 90 mg/day of morphine). For transmucosal fentanyl (i.e., the fentanyl "lollipop"), an 800 µg dose will be regarded as equivalent to 30 mg of oral morphine.

In order to calculate the duration of current opioid use partial start dates will be imputed. If only the year is available and the year is prior to 2017, the imputed start date will be 30-June-Year. If only the year and month is available and the year is prior to 2017, the imputed start date will be 15-Month of the corresponding year. If only the year is available and the year is 2017, the imputed start date will be 1. January 2017.

4.4.4 Study Medication Overdose

Information for any study medication overdose will be summarized in a listing which includes treatment sequence, medication, site, subject number, age, sex, start and stop date, intentional overdose (yes/no), form of medication, route, dose, total daily dose, dose unit, and any AE associated with overdose (yes/no).

5. Analysis Methods

5.1 General Principles

Unless otherwise indicated, descriptive statistics for categorical variables will include counts and percentages, and descriptive statistics for continuous variables will be presented as number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. For continuous variables, the mean and median will be reported to one more decimal place than the recorded value, the standard deviation (and standard error for LS Means) will be reported to two more decimal places than the recorded value, and the minimum and maximum will be reported to the same number of decimal places as the recorded value. For categorical variables, the percentage of subjects will be reported to one decimal place. P-values will be reported to 4 decimal places.

Summary tables will be presented by treatment, or by treatment sequence, where appropriate. In general, tables of baseline variables (e.g. subject disposition, demographics, prior medications including prior opioids, and medical history) will be presented by treatment sequence. Summary tables for the primary, secondary, exploratory and safety outcomes will be presented by treatment (Movantik and PEG 3350), both overall and by treatment sequence. For this crossover study, the overall summary will present results for each treatment for both time periods, whereas the summary by treatment sequence will present results by order of treatment presentation. In addition to summary tables, subject listings will be produced for all data collected for the study, and all summary tables will be cross listed with corresponding listings.

As stated in Section 4.4.3, in order to calculate the duration of current opioid use, partial start dates will be imputed. No other imputation will be performed for missing data, and all analyses will be performed on observed cases. The p-values for all secondary and exploratory measures will be considered descriptive only. All p-values are two-sided.

5.2 Subject Disposition

A summary table of subject disposition of all enrolled subjects (by treatment sequence and overall) will be presented for the number and percentage of subjects enrolled, screen failures, randomized, randomized and treated, completed Movantik, completed PEG 3350, completed period 1, completed period 2, completed both periods, and discontinued (with reasons for discontinuation). A summary table will also be presented for the number and percentage of FAS subjects by investigator (by treatment sequence and overall). In addition, a summary table of all enrolled subjects with important protocol deviations will be presented (by treatment sequence and overall) for categories listed below in Section 5.3. A separate table will also summarize the number and percentage of screen failures and all enrolled subjects in each analysis set (by treatment sequence and overall).

Listings related to subject disposition include: treatment assignment for each subject (including site, subject number, randomized treatment sequence, actual treatment sequence, informed consent date and randomization date, dates for visits 3,4 and 5, study completion status, and date of study completion); subjects discontinued from the study (including randomized treatment/treatment sequence, site, subject number, actual treatment, reason for discontinuation, date of last study medication, date discontinued/date of death, study day discontinued); study medication for each subject (including treatment sequence, site, subject number, age, sex, date medication taken, study day, whether study medication was entered in diary for each study day [yes/no], time taken, study medication taken, which study medication taken); subjects with protocol deviations (including treatment sequence, site, subject number, age, sex, race, treatment, protocol deviation date, visit, study day, protocol deviation, importance); screen failures (including site, subject number, age, sex, reason for screen failure, informed consent date, and discontinuation date); and randomization, evaluability and demographic data for all enrolled subjects (including treatment sequence, site, subject number, age, sex, ethnicity, race, and inclusion [yes/no] in each of the analysis sets of randomized subjects, FAS, PP, treatment-emergent safety, and pre-treatment safety).

5.3 Protocol Deviations

Protocol deviations are deemed important if they have the potential to influence the assessments of the true treatment effect. All protocol deviations will be listed and tabulated. The following important (major) protocol deviations are described in detail in Appendix section 9.6.

- Randomized but did not meet requirements for randomization
- Took prohibited laxative during the study period
- Took prohibited opioid antagonists and mixed agonists/antagonists during the study period
- Reason for discontinuation indicated as “Non-compliance with study drug” or “Protocol deviation” on the disposition form
- Randomized but not treated (did not receive any study medication)

- Errors in randomizations and treatment dispensing. An error in randomization is when a subject is not randomized or treated according to the treatment sequence schedule. It is envisaged there may be two sub-categories of this:
  - Subjects who receive no treatment whatsoever for a period of time due to errors in the dispensing of medication. Note, this is not due to tolerability issues where subjects may stop taking the drug.
  - The subject receives an incorrect study medication according to the treatment sequence specified in the randomization code.

The important protocol deviations will be reviewed and documented by the medical advisors and statisticians prior to database lock to help identify subjects to be excluded from the PP analysis set.

5.4 Subject Demographics and Baseline Characteristics

A subject demographics table will include age, age group (e.g. <50, ≥50 to <64, ≥65 years), sex, ethnicity, and race, by treatment sequence and overall. A summary table of baseline characteristics will include height, weight, body mass index (BMI), any abnormal physical exam results (yes/no), prior use of either Movantik or PEG 3350 within 1 year prior to the study, prior use of any laxatives within 2 weeks prior to the screen visit (with categories of: Any [at least 1 laxative]; Any [≥2 laxatives]; any laxative other than Movantik or PEG 3350; Movantik; PEG 3350; Both Movantik and PEG 3350; or Missing), pain scale (using number and percentage of subjects in each category, and n, mean, SD, median, minimum and maximum as continuous measures), duration of current opioid use in months, and morphine-equivalent opioid dose at screening (see Section 4.4.3 for conversion of reported opioid dose to morphine equivalents). A summary table will also be presented for prior medical history, with the number and percentage of subjects with and without any medical history, as well as the number and percentage of subjects by System Organ Class (SOC) and Preferred Term (PT). Tables will also be provided for prior medications (excluding opioids), as well as for prior opioid medications, with the number and percentage of subjects with any prior medications, as well as the number and percentage of subjects classified by Anatomical-Therapeutic-Chemical (ATC) code and PT. Further detail on prior medications is provided in Section 5.10.2.

Listings related to subject demographics and baseline characteristics are: baseline characteristics (including treatment sequence, site, subject number, age, sex, ECG reviewed, ECG type, ECG clinically significant, lab reviewed, lab type, lab clinically significant, any prior Movantik or PEG 3350 use [Movantik only, PEG 3350 Only, Both], pain scale, reason for pain, overall BFI score and individual BFI component scores at visits 1 and 2); physical exam (including treatment sequence, site, subject number, age, sex, height, weight, BMI, visit, date, general appearance, abdomen assessed, respiratory assessed, cardiovascular assessed); prior medications excluding opioids (including treatment sequence, site, subject number, age, sex, ATC, PT, investigator term, start and stop dates, duration, dose/unit, frequency, route and indication); prior opioid medications (including treatment sequence, site, subject number, age, sex, ATC, PT, investigator term, start and stop dates, duration, dose/unit, frequency, morphine-equivalent dose, route and indication); prior laxatives (including treatment sequence, site, subject number, age, sex. Movantik or PEG 3350 taken 1 year prior [yes/no], medication taken, stop dose, duration taken, duration unit, any prior laxative in last 2 weeks [yes/no], medication. Dose form, route, dose, total daily dose, dose unit, frequency, start and stop dates, ongoing [yes/no]); and medical history

(including treatment sequence, site, subject number, age, sex, SOC, PT, medical history term, start and stop dates, ongoing, controlled with mediation, any current medication for medical condition).

All baseline tables will be presented by treatment sequence and overall for the FAS.

5.5 Exposure and Compliance

A subject exposure table using the FAS will summarize the number of days subjects were exposed to each treatment medication, overall and by treatment sequence (including: n, mean, SD, median, minimum and maximum). Exposure for each treatment is calculated as the number of days from first dose date in case report form (CRF) start (Visits 2/4) to last dose date in CRF (Visits 3/5). In addition, a cumulative exposure table will tabulate the total number and percentage of subjects completing each week of the study by treatment, overall and by treatment sequence.

A compliance table using the FAS will summarize subjects' compliance to study medication by treatment and timepoint (treatment week 1, treatment week 2, and treatment weeks 1 and 2), overall and by treatment sequence. Study medication compliance is defined as the sum of the number of doses of study medication actually taken (as recorded in the subjects daily diary), divided by the number of theoretically due doses, multiplied by 100. The number of theoretically due doses is computed as the number of days from the start of treatment (Visits 2/4) to the last day of each treatment period.

5.6 Primary Analyses

5.6.1 Preference for OIC Treatment

The primary analysis will aim to determine the proportion of subjects in the PP analysis set in each preference category including: Prefer Movantik, No Preference, and Prefer PEG 3350. The three categories are collapsed from the 7-point preference scale (as described in Section 4.1).

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, 1981; Senn 2002). 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. The cell counts in the contingency table follow a hypergeometric probability distribution, and Prescott's test assesses the probability of obtaining a table with cell counts of equal or more extreme values. Prescott's test is only applicable for subjects who complete the entire treatment sequence, i.e., subjects in the PP analysis set. Prescott's test is computed as an exact 2-sided p-value. The SAS pseudo code for this analysis is presented in Appendix section 9.3.

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

A summary table of the counts and percentages of subjects' preference for OIC treatment will be presented. A detailed summary table, by treatment sequence, will also present the number and percentage of subjects in each of the seven categories of subject preference (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), as well as subjects' preference for Period 1 treatment, no preference, and preference for Period 2 treatment, and include the p-value from Prescott's test. An additional table will summarize subjects' preference for OIC treatment for specific subgroups, including laxative use in 2 weeks prior to screening, previous use of Movantik or PEG 3350 within 1 year prior to screening, age group (<50, ≥50 to <65, ≥65), and change in opioid medication from Visit 2 through Visit 5 (decrease, no change, or increase). Details on subgroups are provided in Section 5.9.

A listing of subjects who expressed a treatment preference (including treatment sequence, site, subject number, preferred treatment, and reasons for preferred treatment) will be provided.

5.7 Secondary Analyses

5.7.1. Reason for Preference

The subject-reported influence of each medication characteristic on overall preference will be summarized for the following characteristics: efficacy, tolerability, convenience, works quickly, and works predictably. A summary table will include the counts and percentages of subjects' ratings of the influence of each characteristic (measured on a 4-point scale) by preferred treatment. The influence score levels range from 0 = No Influence, 1 = Mildly Influenced, 2 = Moderately Influenced, and 3 = Strongly Influenced. In addition, a table of descriptive statistics (n, mean, SD, median, minimum, and maximum) will summarize the influence category scores for each medication characteristic by preferred treatment (overall and by treatment sequence). The analysis population will be the PP set.

5.7.2 Impact of Movantik and PEG 3350 on OIC symptoms

For analyses of secondary continuous variables, a linear regression model with terms for intercept, treatment (Movantik, PEG 3350, period (Period 1, Period 2), sequence (Movantik/PEG 3350, PEG 3350/Movantik) and subject within sequence will be used to assess the direct treatment effect as well as any effect of period (Senn, 2002). For the analysis of change scores, the baseline score at the start of each treatment period (Visits 2/4) will be included in an analysis of covariance (ANCOVA) model.

The mean score for the continuous variable will be tested for nominally significant differences between the two treatments by the following analysis of variance (ANOVA) model for cross-over designs:

$$Y_{ijkt} = \mu + SEQ_j + SUB_{i(j)} + PER_k + TRT_t + e_{ijkt}$$

Where,

Y_{ijkt} is the dependent continuous variable, measured at sequence j, for subject i at period k receiving treatment t.

μ is the overall mean,

SEQ_j is the sequence fixed effect (j = 1 to 2).

$SUB_{i(j)}$ is the random effect for subject i nested within sequence j, where $SUB_{i(j)} \sim N(0, \delta^2_s)$.

PER_k is the period fixed effect (k = 1 to 2).

TRT_t is the treatment fixed effect (t= 1 to 2).

e_{ijkt} is the residual random error, where $e \sim N(0, \delta^2_{e)}$.

The variation between subjects is assumed to be random. Sequence effects will be tested using the between-subjects, within-sequence mean square in the ANOVA model, and period and treatment effects will be tested using the error term. The treatment effect will be estimated using the difference in Least Square (LS) means, its standard error (SE), and the corresponding 95% confidence interval (CI). The SAS pseudo code for this analysis is presented in Appendix section 9.4.

The linear regression crossover model will be used for the following secondary variables:

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

5.7.2.1 Patient Global Impression of Change (PGIC)

A table summarizing the number and percentage of subjects in each category of the PGIC by treatment (overall and by treatment sequence), and the p-value will be computed using the Van Elteren test (where strata is the treatment sequence). The SAS pseudo code for the Van Elteren test analysis is presented in Appendix section 9.5.

In addition, a descriptive summary table will be presented (overall and by treatment sequence) for the PGIC measured at the end of the treatment period (Visits 3/5), and will include n, mean, median, SD, minimum, and maximum by treatment. A table of ANOVA results will also be presented, as well as a table of the estimated LS Means, difference in LS Means, SE and 95% CI of the difference in LS Means. The analysis population will be the FAS set.

A listing will include treatment sequence, site, subject number, age, sex, treatment, visit, visit date, and PGIC score.

5.7.2.2 Bowel Function Index (BFI)

For the BFI, a descriptive statistics summary table including n, mean, median, SD, minimum, and maximum will be presented for the observed score at screening (Visit 1), baseline (Visits 2/4), and end of treatment period (Visit 3/5) by treatment, overall and by treatment sequence. The descriptive statistics summary table will also include change from baseline (from Visits 2/4 to Visits 3/5). The BFI completed at Visit 2 will serve as the baseline for treatment period 1. The BFI completed at Visit 4 will be the baseline for treatment period 2. A table of ANCOVA results (including a term for baseline BFI score) will also be presented for the overall BFI score (computed as the mean of the 3 non-missing individual BFI measures stated in section 4.2.2.1), as well as a table of the estimated LS Means, difference in LS Means, SE and 95% CI of the difference in LS Means. The analysis population will be the FAS set.

A listing will include treatment sequence, site, subject number, age, sex, treatment, visit, visit date, overall BFI score and each component score (ease of defecation, feeling of incomplete evacuation, and personal judgment of constipation).

5.8 Exploratory Analyses

Exploratory outcomes include:

- 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.

5.8.1 Bristol Stool Scale (BSS)

For each subject, the most frequent BSS category for each treatment and time period (washout period prior to each treatment, and treatment period) will be classified. If the most common BSS category per time period cannot be determined for a given subject (in case of ties), the subject will be classified as "could not be determined". A summary table will present the number and percentage of subjects per the most common BSS category for each treatment and time period (previous washout and treatment period), overall and by treatment sequence.

For each subject, the observed average BSS score will be computed as the mean of all non-missing BSS scores during a given time period (previous washout and treatment period). A descriptive statistics summary table for mean stool consistency (with n, mean, median, SD, minimum, and maximum) will also be presented by treatment and time period, using the average BSS score computed during the washout period prior to each treatment, and the average BSS scores during treatment week 1 period, treatment week 2 period, and treatment period for weeks 1 & 2. The table will be summarized overall, and by treatment sequence. A summary table of the average number of BMs for each category of the Bristol Stool Scale and timepoint (previous washout and treatment period) will be presented, overall and by treatment sequence.

For the BSS measure, the ANCOVA model described in section 5.7.2 will be used for the observed average BSS score computed for each treatment period. A linear regression model with terms for subject, baseline BSS score (computed as the average BSS score during the prior washout period), treatment sequence (Movantik/PEG 3350 or PEG 3350/Movantik), treatment period (Period 1, Period 2), treatment (Movantik, PEG 3350), and subject within treatment will be used to assess the direct treatment effect as well as any effect of the period. The average BSS score computed for the first washout period will be the baseline for treatment period 1, and the average BSS score computed for the second washout period will be the baseline for treatment period 2. A table of ANCOVA results will be presented for the average BSS score, as well as a table of the estimated LS Means, difference in LS Means, SE and 95% CI of the difference in LS Means. The analysis population will be the FAS set.

A listing will include treatment sequence, site, subject number, age, sex, treatment, date/study date/time of each BM, spontaneous BM [yes/no], and straining score.

5.8.2 Straining Sensation

For each subject, the most frequent straining scale category for each treatment and time period (washout period prior to each treatment, and treatment period) will be classified. If the most common straining scale category per time period cannot be determined for a given subject, the subject will be classified as "could not be determined". A summary table will present the number and percentage of subjects per straining scale category by treatment and time period (previous washout and treatment period), overall and by treatment sequence, and the p-value will be computed using the Van Elteren test (where strata is the treatment sequence).

For each subject, the observed average straining scale score will be computed as the mean of all non-missing straining scale scores during a given time period. A descriptive statistics summary table of the mean degree of straining (with n, mean, median, SD, minimum, and maximum) will be presented by treatment and time period, using the average straining scale score computed during the washout period prior to each treatment, and the average straining scale score during treatment week 1, treatment week 2, and treatment weeks 1 & 2. The table will be summarized overall, and by treatment sequence.

A summary table of the average number of BMs for each category of the straining scale and timepoint (previous washout and treatment period) will be presented, overall and by treatment sequence.

For the straining scale measure, the ANCOVA model described in Section 5.7.2 will be used for the observed average straining score computed for each treatment period. A linear regression model with terms for subject, baseline straining scale score (computed as the average straining scale score during the prior washout period), treatment sequence (Movantik/PEG 3350, PEG 3350/Movantik), treatment period (Period 1, Period 2), and treatment (Movantik, PEG 3350), will be used to assess the direct treatment effect as well as any effect of period. The average straining scale score during the first washout period will be the baseline for treatment period 1. The average straining scale score during the second washout period will be the baseline for treatment period 2. A table of ANCOVA results will be presented, as well as a table of the estimated LS Means, difference in LS Means, SE and 95% CI of the difference in LS Means. The analysis population will be the FAS set.

5.8.3 BM/SBM Frequency

The average number of BMs per week is computed for each subject as the total number of BMs divided by the total number of days the subject was in the time period, times 7. A table will summarize the BM average for each time period (washout, treatment week 1, treatment week 2, and treatment weeks 1 and 2) by treatment, overall and by treatment sequence. A similar table will be presented for SBMs. The analysis population will be the FAS set.

5.8.4 Rescue Medication

Usage of rescue medication by treatment will be summarized by the number of times (and percentage) that rescue medication was used per subject (none, 1 time, 2 times, 3 times, ≥4 times for each time point including washout prior to treatment, treatment week 1, and treatment week 2; and none, 1 time, 2 times, 3 times, 4 times, 5 times, 6 times, 7 times, and ≥8 times for treatment

weeks 1 and 2 combined), overall and by treatment sequence. The table will also summarize the mean bisacodyl use, defined as the sum of the bisacodyl dose (number of tablets x 5 mg per tablet) from each time period, divided by the number of days in the time period where the subject recorded diary data, multiplied by 7. The analysis population will be the FAS set.

5.9 Subgroups

A summary table of the counts and percentages of subjects' preference for OIC treatment in Section 5.7.1 will be presented for each of the following subgroups:

- Prior history of laxative use 2 weeks prior to screening (Any laxative use, No laxative use, Previous Movantik use, Previous PEG 3350 use)
- Previous Movantik and/or PEG 3350 use within 1 year prior to screening (Movantik only, PEG 3350 Only, Both, None)
- Age group (<50, ≥50 to <65, ≥65 years)
- Change in opioid medication from Visit 2 to Visit 5 (Increase, No change, Decrease)

The analysis population will be the PP set.

5.10 Safety

Safety outcomes include AEs, SAEs, vital signs, and concomitant medications.

5.10.1 Adverse Events

AEs and SAEs will be coded by SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. All summary tables will use the Treatment-Emergent Safety set. A listing will be provided for all Pre-Treatment AEs. All AEs will be tabulated according to the last treatment received prior to or at the time of onset. The actual treatment taken will be used for all AE summary tables (for any subject who may have received the incorrect study drug according to the randomized treatment sequence).

A general summary table will present the number and percentage of subjects with any AE, any treatment-related AE, any serious AEs, deaths, and any subjects with AEs leading to study drug discontinuation by treatment.

A summary table will also be presented for all AEs by SOC and PT. The table will summarize the number and percentage of subjects and the number of events, for any AE, as well as AEs classified by SOC and PT. If a subject has multiple occurrences of an AE, the subject is presented only once in the respective subject count column for the corresponding AE. Events are counted each time in the event column.

A similar table will summarize the incidence of AEs by SOC and PT, according to maximum intensity. If a subject has multiple occurrences of an AE, the subject is presented only once at the maximum intensity in the respective subject count column for the corresponding AE, whereas events are counted each time in the event column. Events with missing intensity are counted as severe.

A summary table will also be presented for the incidence of AEs by SOC and PT by relationship to treatment. Each AE is coded by the investigator according to its relationship to study treatment (either Movantik or PEG 3350, depending on study period) and/or rescue medication (bisacodyl). Each AE will be summarized according to one of the following mutually exclusive relationship categories (Related to treatment only, Related to bisacodyl only, Related to treatment and bisacodyl, Not related). Within each SOC and PT, a given subject can appear in multiple relationship categories. If a subject has multiple occurrences of an AE, the subject is presented only once in the respective subject count column for the corresponding AE, whereas events are counted each time in the event column. Events with a missing relationship are counted as related to study treatment (according to the last treatment received prior to or at the time of onset).

Separate summary tables will present the incidence of AEs by SOC and PT for events leading to study drug discontinuation, and for AE leading to study discontinuation. An additional table of key information for AEs leading to study drug discontinuation will include treatment sequence, subject number, actual treatment received, age, sex, investigator term, PT, number of days from start of treatment to onset of AE, number of days from start of treatment to discontinuation, serious AE (yes/no), outcome, and reasonable possibility that AE was caused by study drug (at least possibly related).

A table will also summarize the incidence of all serious AEs by SOC and PT. An additional table of key information for serious AEs will also be presented, which will include treatment sequence, subject number, actual treatment received, age, sex, investigator term, PT, number of days from start of treatment to onset of AE, number of days from last dose to onset of AE, number of days from start of treatment to AE becoming serious, outcome, and reasonable possibility that AE was caused by study drug (at least possibly related).

A listing of all AEs will include treatment sequence, site, age, sex, treatment at onset, SOC/PT/AE description, start and stop dates, onset day, onset period, duration, outcome, severity (or intensity), relationship to study medication(s), and action taken. A similar listing will be presented for SAEs, deaths, or other clinically significant AEs.

5.10.2 Vital Signs

A descriptive statistics summary table for vital signs (blood pressure, pulse and respiration rate) will also be presented with n, mean, median, SD, minimum, and maximum at each time point by treatment, overall and by treatment sequence. The table will also include change from baseline (Day 1 of each treatment period on Visits 2/4) to end of treatment period (Visits 3/5). Summary results will be based on the Treatment-Emergent Safety set. A listing of vital signs will include treatment sequence, site, subject number, age, sex, actual treatment, visit, visit date, systolic and diastolic blood pressure, pulse, and respiration rate,

5.10.3 Prior and Concomitant medications

All medications collected will be coded to ATC classification and PT using WHO drug version September 2016. A prior medication is defined as any medication taken by the subjects within 60 days prior to the screening visit (V1) and discontinued before the randomization visit (V2). A concomitant medication is defined as a medication that is ongoing at the randomization visit (V2), or a medication that starts on or after the randomization visit (V2).

5.10.3.1 Non-Opioid Medication

A summary table will be presented for concomitant medications (excluding opioids and prohibited medications), with the number and percentage of subjects with and without any concomitant medications, as well as the number and percentage of subjects with medications classified by ATC classification and PT. All concomitant medication tables will be presented by treatment and overall for the FAS.

A summary table of any prohibited/restricted medications (as defined by medical advisers) taken during the treatment and washout periods only, will be presented. The tables will summarize the number and percentage of subjects with prohibited medications by ATC and PT.

A listing of all concomitant medications (excluding opioids) will be provided, including treatment sequence, site, subject number, subject age and sex, ATC and PT classification, investigator term, start and stop dates, ongoing (yes/no), dose/unit, frequency, route and indication.

In addition, a listing of any overdose in study medication (bisacodyl, Movantik or PEG 3350) will include treatment sequence, treatment, site, subject number, age, sex, start and stop dates, intentional overdose [yes/no], form of medication, route, total daily dose, and any AE associated with overdose [yes/no].

5.10.3.2 Opioid Medication During Treatment

Opioid medication and doses will be recorded for each subject at screening and during the study, including both the maintenance dose and any change in dose recorded on the eCRF, and the daily opioid dose in morphine equivalents (mg/day) will be calculated using the equivalence information in Table 1 (Section 4.4.3).

Daily opioid dose is computed as the sum of the morphine-equivalent dose for all opioid medications per day per subject (including the maintenance dose and any breakthrough opioid dose). The mean daily opioid dose (mg/day) for an interval will be calculated as the sum of daily opioid doses (mg/day) for the interval divided by the number of days within the interval in which the data were collected. Change from baseline in mean daily opioid dose will be calculated for each day of the study period, computed as the post-baseline value minus the baseline value, where baseline is the daily opioid dose recorded at Visit 2. Positive changes from baseline indicate an increase in opioid dose. A table will summarize the number of subjects with any decrease in opioid dose, no change in dose, or any increase in dose post baseline during the treatment phase from Visit 2 though Visit 5. If a subject has both an increase and a decrease during the treatment phase, an increase will be used. In addition, the table will summarize the number and percentage of subjects who have any decrease in daily opioid dose of ≥10%, and the number and percentage of subjects who have any increase in daily opioid dose of ≥10%.

A table will also be presented for all concomitant opioid medications classified by ATC and PT. A listing of all concomitant opioid medications will be provided, including treatment sequence, site, subject number, subject age and sex, ATC and PT classification, investigator term, start and stop dates, visit, dose change from baseline, ongoing (yes/no), dose/unit, oral morphine-equivalent, frequency, route and indication.

6. Interim Analyses

No interim analyses are planned.

7. Changes from Protocol Specified Analyses

This statistical analysis plan specifies that the comparison of treatment groups for PGIC should use the Van Elteren test (Stokes, 1995) in addition to the ANOVA specified in the protocol.

The protocol originally stated that Wilcoxon signed rank test would be used for the straining scale analysis. This was revised to use Van Elteren test for both PGIC and straining scale measures to provide test of difference between the treatments.

8. References

Senn, S, Cross-over Trials in Clinical Trial Research, Second Edition, 2002

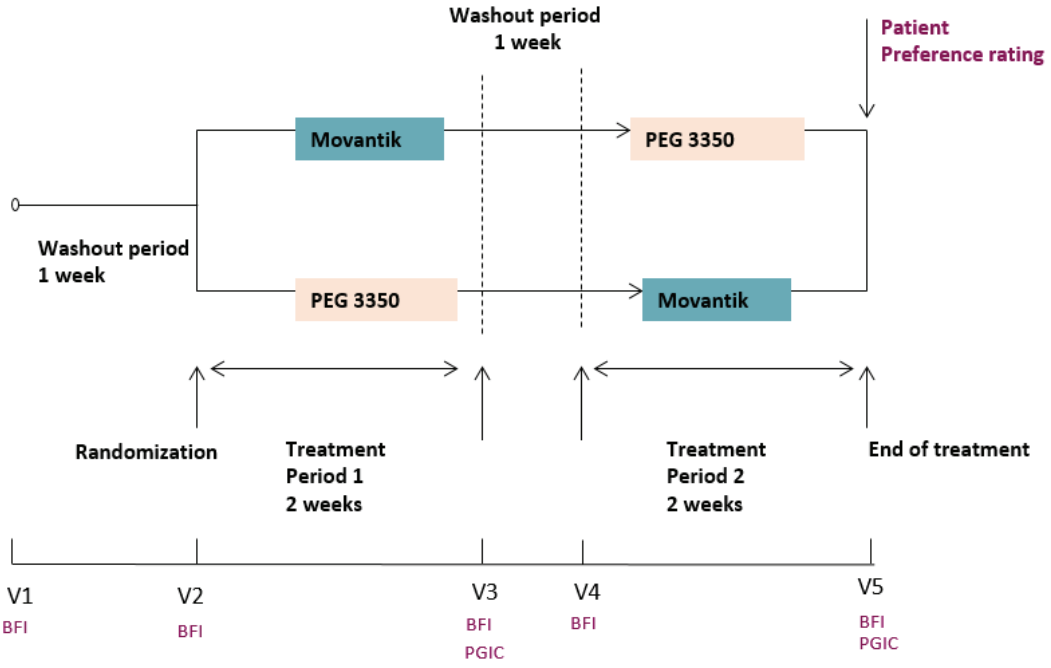
Prescott, R.J. (1981) The comparison of success rates in cross-over trials in the presence of an order effect, Applied Statistics, Vol. 30, 9-15.

Stokes, M.E., Davis, C.S., Koch, G.G. (1995) Categorical Data Analysis Using the SAS System, Cary, NC: SAS Institute.

Feng, W. W., Ding, D. (2014) Paper SP02 SAS@ Application In 2 * 2 Crossover Clinical Trial, Cary, NC: SAS Institute.

9. Appendix

9.1 Study Flow Chart



BFI = Bowel Function Index; PGIC = Patient Global Index of Change; V1 – V5 = Visit1 – Visit 5

9.2 Schedule of Assessments

	Screening		Treatment Period 1			Treatment Period 2		
Procedure/Scale	**Visit 1**		**Visit 2**		**Visit 3**	**Visit 4**		**Visit 5**
	Consenting/ Screening	1-week (7 day) Washout Period 1[e]	Randomization /Dispense Treatment 1	2-week Treatment Period 1 begins the day after Visit 2	End of Treatment Period 1	Dispense Treatment 2	2-week Treatment Period 2 begins the day after Visit 4	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							
Inclusion and exclusion	X							
Demographic information	X							
Medical history	X							
Complete physical exam	X							
Confirm eligibility			X					
Brief physical exam			X		X	X		X
Vital signs	X		X		X	X		X
Blood sample collection and 12-lead ECG review	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
Subject questionnaires- BFI	X		X		X	X		X
Subject questionnaires- PGIC					X			X
Patient Preference Assessment								X
Subject daily diary- BSS[g]	To be completed by the subject in the daily diary for each BM							
Subject daily diary- Straining[g]	To be completed by the subject in the daily diary for each BM							

[a] Screening process and V1 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 subject to begin washout (this can be done at V1 or via telephone contact after V1)
[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

9.3 Sample SAS code for Section 5.5 Prescott's Test

```
*data from Feng and Ding;
data fishers;
input seq pref count;
cards;
1 1 7
1 2 11
1 3 2
2 1 2
2 2 10
2 3 8
;
run;

title4 'fishers';
proc print data=fishers;  run;

data fishers2;
set fishers;
do i = 1 to count;
  sequence = seq;
  preference = pref;
  outcome = 1;
  output;
  end;
run;



proc freq data=fishers2;
tables sequence*preference / fisher exact norow nocol nopercent ;
run;
```

9.4 Sample SAS code for Section 5.6.2 linear regression model.

```
 data ab;
input obs subject $ month treatment sequence $ outcome;
cards;
1  CK  1 0 AW 6
2  CK  2 1 AW 6
3  DH  2 0 WA 10
4  DH  1 1 WA 8
5  DP  1 0 AW 24
6  DP  2 1 AW 16
7  DS  2 0 WA 20
8  DS  1 1 WA 16
9  DS2 2 0 WA 14
10 DS2 1 1 WA 16
11 EM  1 0 AW 14
12 EM  2 1 AW 16
;
run;


data ab2;
set ab;
trt=treatment;
seq = sequence;
period = month;
DV = outcome;
patient=subject;
run;



title4 'Crossover Proc Mixed';
proc mixed data=ab2 covtest;
class SEQ PATIENT PERIOD TRT  ;
model DV = TRT PERIOD SEQ
/ solution ddfm=kenwardroger; ***recommended for crossover;
random intercept / subject = PATIENT v vcorr  ;
lsmeans TRT / pdiff cl;
run;
```

9.5 Sample SAS code for Sections 5.6.2.1 and 5.7.2 Van Elteren test.

```
*******************************************;
data ab;
input obs subject $  treatment sequence $ outcome;
cards;
1  CK   0 AW 4
2  CK   1 AW 6
3  DH   0 WA 5
4  DH   1 WA 7
5  DP   0 AW 1
6  DP   1 AW 2
7  DS   0 WA 3
8  DS   1 WA 3
9  DS2  0 WA 4
10 DS2  1 WA 7
11 EM   0 AW 1
12 EM   1 AW 4
;
run;


proc freq data=ab;
table sequence*treatment*outcome / cmh scores=modridit noprint;
run;
```

9.6 Important (Major) Protocol Deviations

The important (major) protocol deviations will be the following:

- Randomized but did not meet requirements for randomization.
  - Confirmed OIC by BFI ≥30 at Visit 1 and Visit 2.
  - 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 results of disease progression. The opioid regiment should be confirmed by a prescription or clearly labeled medication bottle.
- Took prohibited laxative during the study period.

  All medications for each subject will be reviewed to determine if any prohibited laxatives were taken after the start of study drug and prior to the follow-up period. The list of prohibited laxatives other than bisacodyl includes the following: milk of magnesia or magnesium citrate, non-absorbable phosphate, cascara, senna, castor oil/mineral oil, epsom salt, lactulose, docusate, enemas, tegaserod, lubiprostone (Amitiza®), drugs blocking fat absorption with an associated laxative effect, Prucalopride, prune juice, herbal preparations for constipation, bulk laxatives, such as psyllium and

methylcellulose. Other prohibited laxatives include any agent that is used in an off-label fashion to treat constipation (e.g., colchicine, misoprostol, erythromycin, cholinesterase inhibitors such as donezepil), and any experimental constipation therapy.

- Took prohibited opioid antagonists and mixed agonists/antagonists during the study period.

  All medications for a subject will be reviewed by the study physician before database lock to determine if any prohibited opioid antagonists and mixed agonists/antagonists were taken after the start of study drug which might have a significant impact on efficacy. The list of prohibited opioid antagonists and mixed agonists/antagonists includes the following: 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), methadone or buprenorphine or other opioid antagonists.

- Reason for discontinuation indicated as "Non-compliance with study drug" or "Protocol deviation" on the disposition form.

  Subjects who discontinue the study for whom "Non-compliance with study drug" is indicated on the disposition form will be included in this category, as well as subjects with "Protocol deviation" indicated on the disposition form who have documented non-compliance with study medication.

- Randomized but not treated (did not receive any study medication).

- Errors in randomization or treatment dispensing. An error in randomization occurs when a subject is not randomized or treated according to the treatment sequence schedule specified in the randomization code. It is envisaged there may be two sub-categories of this:

  - Subjects who receive no treatment whatsoever for a period of time due to errors in dispensing of medication. Note, this is not due to tolerability issues where subjects may stop taking drug.

  - The subject receives a treatment medication that differs from that associated with their treatment sequence randomization code.

9.7 Data handing conventions for opioid doses (morphine equivalents)

Reported frequency of administration of opioid dosing will be mapped to the number of daily doses (example table is presented below). Because dosing frequency can be reported on a free text field, the frequency factor will be determined based on a medical review of the data. For transdermal opioid patches (e.g., fentanyl, buprenorphine), a continuous around-the-clock release of the drug substance will be assumed. Daily dose for the transdermal opioids will be

calculated based on the dose released per hour (i.e., 24 x dose/h). Frequency of 1 will therefore be used for the daily dose.

MEDFREQ	Analysis Frequency	ROUTE
1 EVERY 3 DAYS TOPICALLY	1	CUTANEOUS
TID	3	ORAL
1 BID	2	ORAL
1 EVERY 4-6 HOURS	4	ORAL
1 EVERY 4HRS	6	ORAL
1 EVERY 6 HRS	4	ORAL
1 PATCH FOR 72 HOURS	1	CUTANEOUS
1 PATCH Q 72 HOURS	1	CUTANEOUS
1 TAB EVERY 4 HOURS	6	ORAL
1 TABLET 4 TIMES A DAY	4	ORAL
1 TABLET 4 TIMES A DAY FOR PAIN	4	ORAL
1 TABLET BY MOUTH AT BEDTIME	1	ORAL
1 TABLET EVERY 4 HOURS	6	ORAL
1 TABLET EVERY 4 TO 6 HOURS	4	ORAL
1 TABLET EVERY 6 HOURS	4	ORAL
1 TABLET EVERY 6 HOURS FOR PAIN	4	ORAL
1 TABLET QD	1	ORAL
1 TABLET THREE TIMES DAILY	3	ORAL
1 TABLET TID	3	ORAL
1 THREE TIMES A DAY	3	ORAL
1 THREE TIMES DAILY	3	ORAL
1-2 EVERY 4-6 HOURS	4	ORAL
1-2 TABS EVERY 4-6 HOURS	4	ORAL
1-2 TABS EVERY 6-8 HOURS	3	ORAL
1-2 TABS Q 6 HOURS	4	ORAL
1/2 TAB TID	1.5	ORAL
1X	1	INTRAMUSCULAR
1X	1	INTRAVENOUS
2 - 60MG TABS Q A.M. AND 1-60MG TAB Q P.M.	3	ORAL
2 BID	4	ORAL

MEDFREQ	Analysis Frequency	ROUTE
2 FOUR TIMES DAILY	8	ORAL
2 Q 4-6 HRS	8	ORAL
2 Q3DAYS	2	CUTANEOUS
2 QID	8	ORAL
2 TABLETS EVERY 12 HOURS	4	ORAL
2 TABS BID	4	ORAL
2 TABS EVERY 6 HOURS	8	ORAL
2 TABS Q4HRS	12	ORAL
2 TABS QD	2	ORAL
2 TABS QID	8	ORAL
2 TABS TID	6	ORAL
2 X DAILY 10 MG	2	ORAL
2/DAY	2	ORAL
24 HOUR PATCH/EVERY 3 DAYS	1	CUTANEOUS
3 A DAY	3	ORAL
3 DAILY	3	ORAL
3 Q12HRS	6	ORAL
3 TABLETS IN AM, TWO AT LUNCH TIME, THREE AT DINNER, AND TWO AT BEDTIME	10	ORAL
3 TABS (150MG) IN A.M. 2 TABS (100MG) AT NOON, 3 TABS (150MG) IN P.M.	8	ORAL
3 TIMES DAILY	3	ORAL
3 X DAILY	3	ORAL
3,2,3 TABS 3X DAILY	8	ORAL
4 TABS DAILY	4	ORAL
4 TABS TID	12	ORAL
4 TIMES A DAY	4	ORAL
4 TIMES DAILY	4	ORAL
4-6 HRS	4	ORAL
4/DAY	4	ORAL
4QD	4	ORAL
5 ML (20 MG) BY MOUTH EVERY 4 HOURS	6	ORAL
5 PER DAY	5	ORAL
5 TABLETS A DAY	5	ORAL
5 TIMES A DAY	5	ORAL
5 TIMES DAILY	5	ORAL
5 TIMES PER DAY	5	ORAL
5 TIMES/DAY	5	ORAL
5 X DAILY	5	ORAL

MEDFREQ	Analysis Frequency	ROUTE
5 X/ DAY	5	ORAL
5X DAY	5	ORAL
5X PER DAY	5	ORAL
5X QD	5	ORAL
6 PER DAY	6	ORAL
6 TABLETS PER DAY	6	ORAL
6 TIIMES PER DAY	6	ORAL
6 TIMES A DAY	6	ORAL
6 TIMES DAILY	6	ORAL
6 TIMES PER DAY	6	ORAL
6 X DAY	6	ORAL
6/DAY	6	ORAL
6X DAILY	6	ORAL
75 MCG/HR	1	CUTANEOUS
8 DAILY	8	ORAL
8 QD	8	ORAL
8 TIMES A DAY	8	ORAL
ALL 3 DAYS	1	CUTANEOUS
APPLY 1 PATCH Q 48 HOURS	1	CUTANEOUS
APPLY 1 PATCH TO SKIN EVERY 72 HOURS	1	CUTANEOUS
APPROXIMATELY ONCE MONTHLY, FOR BREAKTHROUGH PAIN	0.033	ORAL
B.D.	2	ORAL
BD	2	ORAL
BID	2	ORAL
BID (10/325MG)	2	ORAL
BID - 10 MG IN AM, 20 MG IN PM	3	ORAL
BID TWICE DAILY	2	ORAL
BID-TWICE DAILY	2	ORAL
CONTINUOUS	1	INTRAMUSCULAR
DAILY	1	INTRAVENOUS
DAILY	1	NOT APPLICABLE
DAILY	1	ORAL
DAILY DOSE IS 6.5 MG. PER DAY	1	PARENTERAL
DAILY IN AM	1	ORAL
DAILY IN PM	1	ORAL
EVERY 12 HOURS	2	ORAL
EVERY 2 DAYS	1	CUTANEOUS

MEDFREQ	Analysis Frequency	ROUTE
EVERY 2 HOURS	12	INTRAVENOUS
EVERY 3 DAY	1	CUTANEOUS
EVERY 3 DAYS	1	CUTANEOUS
EVERY 3 HOURS	8	INTRAVENOUS
EVERY 4 HOURS	6	ORAL
EVERY 4-6 HOURS	4	ORAL
EVERY 6 HOURS	4	INTRAVENOUS
EVERY 6 HOURS	4	ORAL
EVERY 6HR	4	ORAL
EVERY 72 HOURS	1	CUTANEOUS
EVERY 8 HOURS	3	ORAL
EVERY FOUR HOURS	6	ORAL
EVERY FOUR HOURS.	6	ORAL
EVERY HOUR	1	CUTANEOUS
EVERY OTHER DAY	1	CUTANEOUS
EVERY SIX HOURS DAILY	4	ORAL
EVERY SIX HOURS.	4	ORAL
EVERY TWO DAYS	1	CUTANEOUS
FIVE TIMES DAILY	5	ORAL
FOUR TIMES A DAY	4	ORAL
FOUR TIMES DAILY	4	ORAL
FOUR TIMES PER DAY	4	ORAL
FOUR TIMES PER DAY.	4	ORAL
HS	1	ORAL
HYDROCODONE/ACETAMINOPHEN 10-500 MG TO TAKE 1 TABLET THREE TIMES DAILY	3	ORAL
ONCE	1	INTRAMUSCULAR
ONCE	1	INTRAVENOUS
ONCE A WEEK	1	CUTANEOUS
ONCE DAILY	1	ORAL
ONCE EVERY 2 DAYS	1	CUTANEOUS
ONCE PATCH FOR 72 HOURS	1	CUTANEOUS
ONE DAILY	1	ORAL
ONE PATCH EVERY 72 HRS	1	CUTANEOUS
ONE PATCH WEEKLY	1	CUTANEOUS
ONE PILL TID	3	ORAL
ONE TAB EVERY 4 HOURS	6	ORAL
ONE TABLET BY MOUTH THREE TIMES DAILY	3	ORAL

MEDFREQ	Analysis Frequency	ROUTE
ONE TABLET FIVE TIMES A DAY	5	ORAL
ONE TABLET THREE TIMES A DAY	3	ORAL
ONE TIME	1	INTRAMUSCULAR
ONE TIME	1	INTRAVENOUS
ONE TIME	1	ORAL
ONE TIME ONLY	1	INTRAVENOUS
PATCH IS CHANGED EVERY OTHER DAY	1	CUTANEOUS
Q 12 HOURS	2	ORAL
Q 12 HR	2	ORAL
Q 12H	2	ORAL
Q 3 DAYS	1	CUTANEOUS
Q 3-4 HR	6	ORAL
Q 4 HOURS	6	ORAL
Q 4 HOURS DAILY	6	ORAL
Q 4 HRS	6	ORAL
Q 4-6 HR	4	ORAL
Q 4-6H	4	ORAL
Q 48 HOURS	1	CUTANEOUS
Q 6 HOURS	4	ORAL
Q 6 HOURS, QID	4	ORAL
Q 6 HRS	4	ORAL
Q 6HRS	4	ORAL
Q 72 HOURS	1	CUTANEOUS
Q 8 HOURS	3	ORAL
Q 8 HRS	3	ORAL
Q.I.D	4	ORAL
Q12H	2	ORAL
Q12H-EVERY 12 HOURS	2	ORAL
Q2D	1	CUTANEOUS
Q2H	12	ORAL
Q3 DAYS	1	CUTANEOUS
Q36 HOURS	1	CUTANEOUS
Q3D	1	CUTANEOUS
Q3H	8	ORAL
Q4	6	ORAL
Q4 HOURS	6	ORAL
Q4-6 HR	4	ORAL
Q48 HOURS	1	CUTANEOUS
Q48 HRS	1	CUTANEOUS

MEDFREQ	Analysis Frequency	ROUTE
Q4H	6	ORAL
Q4HOURS	6	ORAL
Q4HRS	6	ORAL
Q4HS	6	ORAL
Q5HOURS	5	ORAL
Q6	4	ORAL
Q6 HOURS	4	ORAL
Q6 HR	4	ORAL
Q6 HRS	4	ORAL
Q6H	4	ORAL
Q6H EVERY SIX HOURS	4	ORAL
Q6HOURS	4	ORAL
Q6HRS	4	ORAL
Q72HR	1	CUTANEOUS
Q72HRS	1	CUTANEOUS
Q8 HOURS	3	ORAL
Q8H	3	ORAL
Q8HRS	3	ORAL
QAM	1	ORAL
QD	1	INTRAVENOUS
QD	1	NOT APPLICABLE
QD	1	ORAL
QD	1	SUBCUTANEOUS
QD (PATIENT TAKES 30MG QAM AND 15MG QHS)	1	ORAL
QD - AT 1200	1	ORAL
QH-EVERY HOUR	1	CUTANEOUS
QHR	1	CUTANEOUS
QHS	1	ORAL
QID	4	ORAL
QID FOUR TIMES DAILY	4	ORAL
QID-FOUR TIMES DAILY	4	ORAL
QOD	0.5	ORAL
QPM	1	ORAL
SIX TIMES PER DAY	6	ORAL
TAKE ONE TABLET (5/325MG) BY MOUTH EVERY 8 HOURS	3	ORAL
TAKE ONE TABLET BY MOUTH 2-3 TIMES DAILY	2	ORAL

MEDFREQ	Analysis Frequency	ROUTE
TAKE ONE TABLET BY MOUTH EVERY 6 HOURS	4	ORAL
TAKE ONE TABLET BY MOUTH FOUR TIMES DAILY	4	ORAL
TAKE ONE TABLET BY MOUTH THREE TIMES DAILY	3	ORAL
TAKE ONE TABLET BY MOUTH TWICE DAILY	2	ORAL
TAKEN AT BEDTIME	1	ORAL
TAKEN EVERY 12 HOURS	2	ORAL
TAKEN EVERY 48 HOURS.	1	CUTANEOUS
TAKEN EVERY DAY AT BEDTIME	1	ORAL
TAKEN EVERY EIGHT HOURS.	3	ORAL
TAKEN EVERY FOUR HOURS	6	ORAL
TAKEN EVERY FOUR HOURS EVERY DAY	6	ORAL
TAKEN EVERY FOUR HOURS PER DAY.	6	ORAL
TAKEN EVERY SIX HOURS	4	ORAL
TAKEN EVERY SIX HOURS DAILY.	4	ORAL
TAKEN EVERY SIX HOURS PER DAY.	4	ORAL
TAKEN FOUR TIMES PER DAY	4	ORAL
TAKEN FOUR TIMES PER DAY.	4	ORAL
TAKEN SIX TIMES A DAY	6	ORAL
TAKEN THREE TIMES PER DAY	3	ORAL
TAKEN THREE TIMES PER DAY.	3	ORAL
TAKEN TWICE PER DAY	2	ORAL
TAKEN TWICE PER DAY.	2	ORAL
TAKES ONE 10/325MG TABLET BY MOUTH TWICE DAILY	2	ORAL
THREE TIMES A DAY	3	ORAL
THREE TIMES DAILY	3	ORAL
THREE TIMES PER DAY	3	ORAL
TID	3	INTRAMUSCULAR
TID	3	ORAL
TID-QID	3	ORAL
TID-THREE TIMES DAILY	3	ORAL
TQ 4 HOURS (QID)	6	ORAL
TWICE	2	INTRAVENOUS
TWICE A DAY	2	ORAL
TWICE DAILY	2	ORAL
TWICE PER DAY	2	ORAL

MEDFREQ	Analysis Frequency	ROUTE
TWICE PER DAY.	2	ORAL
TWICE TIMES PER DAY	2	ORAL
TWO TIMES PER DAY	2	ORAL
TWO TO THREE TIMES PER DAY	2	ORAL
UP TO 3 X DAILY	3	ORAL

Reported opioid medications will be converted to oral morphine equivalent doses as presented below in the table. The conversion factors are derived from Table 1 in the SAP (Section 4.4.3). A 1:100 equipotency ratio between buprenorphine and oral morphine is used to calculate morphine equivalent dose. The conversion factor for intravenous oxycodone, is derived from literature (iv oxycodone : iv morphine 2:3). The conversion factors presented below assume microgram units for fentanyl and buprenorphine and milligram units for other opioids. Route = "not applicable" refers to cases in which the subject is receiving opioids via intrathecal pump. Intrathecal opioids are not included in the daily opioid dose." In the rare instances in which a fentanyl patch is recorded as a breakthrough medication, a continuous release of the drug substance for 72h is assumed and used in calculating the daily opioid dose.

MEDPREF	ROUTE	MEDFORM	Analgesic	Multiplier
BUPRENORPHINE	CUTANEOUS		Buprenorphine	2.4
CODEINE	ORAL		Codeine	0.15
CODEINE	ORAL	Tablets	Codeine	0.15
CODEINE+PARACETAMOL	ORAL		Codeine	0.15
CODEINE+PARACETAMOL	ORAL	Tablets	Codeine	0.15
DIHYDROCODEINE	ORAL		Dihydrocodeine	0.15
DIHYDROCODEINE BITARTRATE	ORAL		Dihydrocodeine	0.15
FENTANYL	CUTANEOUS		Fentanyl	3.6
FENTANYL	CUTANEOUS	Patches	Fentanyl	3.6
FENTANYL	INTRAVENOUS		Fentanyl	0.15
FENTANYL	CUTANEOUS		Fentanyl	3.6
FENTANYL CITRATE	CUTANEOUS	Patches	Fentanyl	3.6
FENTANYL CITRATE	OROMUCOSAL (INCL. SUBLINGUAL)	Lollipops	Fentanyl	0.0375
HYDROCODONE	ORAL		Hydrocodone	1.5

MEDPREF	ROUTE	MEDFORM	Analgesic	Multiplier
HYDROCODONE	ORAL	Caplets	Hydrocodone	1.5
HYDROCODONE	ORAL	Capsules	Hydrocodone	1.5
HYDROCODONE	ORAL	Tablet	Hydrocodone	1.5
HYDROCODONE	ORAL	Tablets	Hydrocodone	1.5
HYDROCODONE+PARACETAMOL	ORAL		Hydrocodone	1.5
HYDROCODONE+PARACETAMOL	ORAL	Caplets	Hydrocodone	1.5
HYDROCODONE+PARACETAMOL	ORAL	Tablets	Hydrocodone	1.5
HYDROCODONE+PARACETAMOL	ORAL	tablet	Hydrocodone	1.5
HYDROMORPHONE	INTRAVENOUS		Hydromorphone	10
HYDROMORPHONE	ORAL		Hydromorphone	3.75
HYDROMORPHONE HYDROCHLORIDE	INTRAMUSCULAR		Hydromorphone	10
HYDROMORPHONE HYDROCHLORIDE	INTRAVENOUS		Hydromorphone	10
HYDROMORPHONE HYDROCHLORIDE	NOT APPLICABLE		Hydromorphone	0
HYDROMORPHONE HYDROCHLORIDE	ORAL		Hydromorphone	3.75
HYDROMORPHONE HYDROCHLORIDE	ORAL	Caplets	Hydromorphone	3.75
HYDROMORPHONE HYDROCHLORIDE	ORAL	Tablets	Hydromorphone	3.75
METHADONE	ORAL		Methadone	3
METHADONE	ORAL	Tablets	Methadone	3
METHADONE HYDROCHLORIDE	ORAL		Methadone	3
MORPHINE	INTRAMUSCULAR		Morphine	3
MORPHINE	INTRAMUSCULAR	Injection	Morphine	3
MORPHINE	INTRAVENOUS		Morphine	3
MORPHINE	NOT APPLICABLE		Morphine	0
MORPHINE	ORAL		Morphine	1
MORPHINE	ORAL	Tablet	Morphine	1
MORPHINE	PARENTERAL		Morphine	3

MEDPREF	ROUTE	MEDFORM	Analgesic	Multiplier
MORPHINE	SUBCUTANEOUS		Morphine	3
MORPHINE SULFATE	INTRAMUSCULAR		Morphine	3
MORPHINE SULFATE	ORAL		Morphine	1
MORPHINE SULFATE	ORAL	Capsules	Morphine	1
MORPHINE SULFATE	ORAL	Tablets	Morphine	1
NALOXONE+OXYCODONE	ORAL		Oxycodone	1.5
OXYCODONE	ORAL		Oxycodone	1.5
OXYCODONE	ORAL	Tablet	Oxycodone	1.5
OXYCODONE	ORAL	Tablets	Oxycodone	1.5
OXYCODONE	ORAL	tablet	Oxycodone	1.5
OXYCODONE HYDROCHLORIDE	INTRAVENOUS		Oxycodone	4.55
OXYCODONE HYDROCHLORIDE	ORAL		Oxycodone	1.5
OXYCODONE HYDROCHLORIDE	ORAL	Tablets	Oxycodone	1.5
OXYCODONE+PARACETAMOL	ORAL		Oxycodone	1.5
OXYCODONE+PARACETAMOL	ORAL	Caplets	Oxycodone	1.5
OXYCODONE+PARACETAMOL	ORAL	Tablets	Oxycodone	1.5
OXYMORPHONE	ORAL		Oxymorphone	3
OXYMORPHONE HYDROCHLORIDE	ORAL		Oxymorphone	3
OXYMORPHONE HYDROCHLORIDE	ORAL	Tablets	Oxymorphone	3
PARACETAMOL+TRAMADOL	ORAL		Tramadol	0.2222
PARACETAMOL+TRAMADOL	ORAL	Tablets	Tramadol	0.2222
PERCODAN	ORAL		Oxycodone	1.5
PETHIDINE HYDROCHLORIDE	INTRAMUSCULAR		Pethidine	0.3

MEDPREF	ROUTE	MEDFORM	Analgesic	Multiplier
PETHIDINE HYDROCHLORIDE	INTRAMUSCULAR	ml	Pethidine	0.3
TAPENTADOL	ORAL		Tapentadol	0.25
TAPENTADOL	ORAL	Tablets	Tapentadol	0.25
TRAMADOL	ORAL		Tramadol	0.2222
TRAMADOL	ORAL	Capsules	Tramadol	0.2222
TRAMADOL HYDROCHLORIDE	ORAL		Tramadol	0.2222
TRAMADOL HYDROCHLORIDE	ORAL	Capsules	Tramadol	0.2222
TRAMADOL HYDROCHLORIDE	ORAL	Tablets	Tramadol	0.2222