Opioid Post-Marketing Requirement
(PMR) Consortium

MORPHINE SULFATE ER; OXYCODONE ER; OXYMORPHONE ER

{2065-5}

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CLINICAL TRIAL OF STRUCTURED OPIOID DISCONTINUATION VERSUS CONTINUED OPIOID THERAPY IN SUBOPTIMAL AND OPTIMAL RESPONDERS TO HIGH-DOSE LONG-TERM OPIOID ANALGESIC THERAPY FOR CHRONIC PAIN

Original Date: January 10, 2016

Amendment 1: July 7, 2016

Amendment 2: February 8, 2017

2. SUMMARY OF CHANGES

Any changes to the protocol after initial approval will be summarized in this section.

Amendment 1:

Section	Original Text	Revised Text
Title Page	*This document is the property of the Opioid PMR Consortium and may not—in full or part—be passed on, reproduced, published, distributed to any person, or submitted to any regulatory authority without the express written permission of the Opioid PMR Consortium.*	*The information contained in this document is proprietary and confidential and is the property of the member companies of the Opioid PMR Consortium. This document may not—in full or part—be passed on, reproduced, published, distributed to any person, or submitted to any regulatory authority without the express written permission of the member companies of the Opioid PMR Consortium, unless as permitted by a previously executed and effective Confidentiality Disclosure Agreement.*
3.0	Lead Principal Investigator	
Synopsis	(Note: Screening procedures are performed over 2 visits no more than 10 days apart.) Adverse events (AEs) will be recorded during this period. At the end of the 1-week Run-In Period, subjects will return to the clinic for the Tolerability Visit (Visit SR1) to determine whether they tolerated the standardized opioid regimen. Subjects who did not tolerate the standardized opioid regimen or do not have acceptable results on screening laboratory tests, including the UDT, will be discontinued; no dose adjustment of the ER medication will be permitted.	(Note: Screening procedures are performed over 2 visits no more than 14 days apart.) Adverse events (AEs) will be recorded during this period. At the end of the 1-week Run-In Period, subjects will return to the clinic for the Tolerability Visit (Visit SR1) to determine whether they tolerated the standardized opioid regimen. Subjects who did not tolerate the standardized opioid regimen will be discontinued; no dose adjustment of the ER medication will be permitted.
5.0 Table 2	2. Screening procedures will be performed over 2 visits no more than 10 days apart.	2. Screening procedures will be performed over 2 visits no more than 14 days apart.
5.0 Table 3	Telephone Calls[14]	Telephone Calls[15]
5.0 Table 3	3. Screening procedures will be performed over 2 visits no more than 10 days apart.	3. Screening procedures will be performed over 2 visits no more than 14 days apart.
10.1.1 Screening	(Note: Screening procedures will be performed over 2 visits no more than 10 days apart.)	(Note: Screening procedures will be performed over 2 visits no more than 14 days apart.)

Section	Original Text	Revised Text
10.1.2 For Suboptimal Responders Only	Subjects who did not tolerate the standardized regimen or do not have acceptable results on screening laboratory tests or UDT will be discontinued; no dose adjustment of the ER medication will be permitted.	Subjects who did not tolerate the standardized regimen will be discontinued; no dose adjustment of the ER medication will be permitted.
12.1.1 Screening Visit (Same for Suboptimal and Optimal Responders)	Screening assessments will be carried out over 2 visits that are not greater than 10 days apart.	Screening assessments will be carried out over 2 visits that are not greater than 14 days apart.
12.1.2 Suboptimal Responders Visits Only	• Discontinue subjects who did not tolerate the standardized regimen or have unacceptable laboratory results – no dose adjustment of the regimen is permitted (For study discontinuation procedures, see section 12.1.6.)	• Discontinue subjects who did not tolerate the standardized regimen – no dose adjustment of the regimen is permitted (For study discontinuation procedures, see section 12.1.6.)
12.1.6 Study Discontinuation	• Subjects who discontinue between Weeks 13 and 24 will complete Week 24 assessments and advance to the Follow-up period. At the completion of the Follow-up period, subjects will be discharged to their primary care physician who will manage their pain medication.	• Subjects who discontinue between Weeks 13 and 24 will complete Week 24 assessments and advance to the Follow-up period. For any subject who discontinues before Week 4, the Medical Monitor should be contacted to discuss that subject. At the completion of the Follow-up period, subjects will be discharged to their primary care physician who will manage their pain medication.
13.1	Under each digit the subject should write down the corresponding symbol as fast as possible.	Under each digit the subject should respond with the corresponding symbol as fast as possible.

Section	Original Text	Revised Text
14.5.1 Reporting Adverse Events	All AEs will be collected by the Investigator from the time of signing the informed consent through 3 days after the last dose of study medication; this includes any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 14 days after the subject's last study visit, whichever comes first.	Only SAEs will be collected starting at the time of signing the informed consent through Screening. Following Screening, all AEs will be collected by the Investigator through 3 days after the last dose of study medication; this includes any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 14 days after the subject's last study visit, whichever comes first.
Footer		Added: **Confidential and Proprietary Information**
Appendix B	**Optimal Responders: Open-label Taper and Titration Schedule** Optimal Responders will go through an open label taper phase to confirm their underlying pain state. Once a certain level of flare is confirmed they will titrate back to their original dose. Once back at their original dose, their baseline pin intensity scores will be assessed and if stabilized to ≤4 they will enter the Blinded Structured Discontinuation Period.	**Optimal Responders: Open-label Taper and Titration Schedule** Optimal Responders will go through an open label taper phase to confirm their underlying pain state. After a certain level of pain flare is confirmed they will titrate their dose to control their pain within the allowable dose range. Once the pain intensity score is ≤4 for 3 consecutive pain scores with satisfaction with pain and physical function and acceptable side effects, they will enter the Blinded Structured Discontinuation Period. Revisions were made to these tables to eliminate doses greater than 540 mg for MSER, 360 mg for OCER, and 180 mg for OMER.
Appendix K	Colombia	Columbia
Appendix L		Replaced EQ-5D-5L UK version with US version
Appendix R		Revised MADDERS forms incorporated
Appendix T		Revised advice to investigators provided

Section	Original Text	Revised Text
Appendix V	As a follow-up to the questions we just discussed, I want to ask you a few questions about the reasons why you are leaving this research study. People decide to leave research studies for many reasons. For each of the reasons listed below, indicate whether this contributed to your decision or not("Yes" or "No"). For those reasons where you answered "Yes", please check the box that best indicates how important that reason was for you.	As a follow-up to the questions we just discussed, I want to ask you a few questions about the reasons why you are leaving this research study. People decide to leave research studies for many reasons. For each of the reasons I will read to you, first indicate whether this contributed to your decision to leave the study or not ("Yes" or "No"). Second, for those reasons where you answered "Yes", please indicate whether the reason was "extremely important", "moderately important", "a little important", or "not that important" for you.

Amendment 2: changes are marked in **red bold** text in the revised text

Section	Original Text	Revised Text
Synopsis	**SCREENING** (Note: Screening procedures are performed over 2 visits no more than 14 days apart.) Subjects will be admitted into the study if they have non-radicular CLBP which can include Quebec Task Force Classification of Spinal Disorders Classes 1, 2, 9.2, and 10, for more than 12-months duration; have been taking extended-release (ER) or long-acting (LA) opioids for at least 12 months for their CLBP *Observation Period:…* their mean Average PI score over the 1 week of the period was ≤4 (with a minimum compliance of 4 out of 7 daily PI scores) *Taper Period (up to 2 weeks[+3 days]).* Subjects with a mean Average PI score ≥5 over ≥3 consecutive PI scores (excluding missing values), *Open-label Titration Period:…* The dose of index ER opioid will be increased as frequently as every 4 days (during telephone or office visits) until the mean Average PI score for	**SCREENING** (Note: Screening procedures are performed over 2 visits no more than 21 days apart.) Subjects will be admitted into the study if they have non-radicular CLBP which can include Quebec Task Force Classification of Spinal Disorders Classes 1, proximal radicular (above the knee) pain of 2, 9.2, and 10, for more than 12-months duration; have been taking extended-release (ER) or long-acting (LA) opioids (or doses of immediate-release opioids at least 4 times a day) for at least 12 months for their CLBP *Observation Period:…* their mean Average PI score over the 1 week of the period was ≤5 (with a minimum compliance of 4 out of 7 daily PI scores) *Taper Period (up to 2 weeks[+3 days]).* Subjects with a mean Average PI score >5 over ≥3 consecutive PI scores (excluding missing values), *Open-label Titration Period:…* The dose of index ER opioid will be increased as frequently as every 4 days (during telephone or office visits) until the mean Average PI score for

Section	Original Text	Revised Text
	at least 3 consecutive pain scores is ≤4 (qualify for randomization). *Randomization Visit for Optimal Responders* (Visit OR4). Subjects who have completed their titration, have achieved a mean Average PI score over 3 consecutive pain scores of ≤4… *Inclusion Criteria:* 2. Have a clinical diagnosis of non-radicular CLBP (pain that occurs in an area with boundaries between the lowest rib and the crease of the buttocks) of Class 1 or Class 2 based on the Quebec Task Force Classification for Spinal Disorders… *Inclusion Criteria:* 3. Have been taking ER/LA opioids for at least 12 months. *Exclusion Criteria:* 7. Have a body mass index (BMI) >40 kg/m^2. *Exclusion Criteria:* 8. Have clinically significant depression based on a score of ≥15 on the Patient Health Questionnaire (PHQ-8). ***Primary Endpoint…*** For Optimal Responders, the mean Average PI score including the Average PI scores during the Titration Period that meet the qualification criteria (Average PI score ≤4 for 3 consecutive non-missing values) plus any scores between the last qualification score and the Randomization Visit will count as the subject's baseline Average PI score for statistical analysis. Definition of Baseline… For Optimal Responders, the mean Average PI score including the Average PI scores during the Titration Period that meet the qualification criteria (Average PI score ≤4 for 3 consecutive non-missing values) plus any scores between the final qualification day and the Randomization Visit will count as the subject's baseline Average PI score for statistical analysis. • For Optimal Responders, the subject's mean Average PI score at the end of the Taper Period (with added variability based on the	at least 3 consecutive pain scores is ≤5 (qualify for randomization). *Randomization Visit for Optimal Responders* (Visit OR4). Subjects who have completed their titration, have achieved a mean Average PI score over 3 consecutive pain scores of ≤5… *Inclusion Criteria:* 2. Have a clinical diagnosis of non-radicular CLBP (pain that occurs in an area with boundaries between the lowest rib and the crease of the buttocks) of Class 1 or proximal radicular (above the knee) pain of Class 2 based on the Quebec Task Force Classification for Spinal Disorders… *Inclusion criteria:* 3. Have been taking ER/LA opioids or immediate release opioids (at least 4 times a day) for at least 12 months. *Exclusion Criteria:* 7. Have a body mass index (BMI) >45 kg/m^2. Anyone with a BMI > 40 but < 45 will complete a screening tool (STOPBang Questionnaire) to rule out high risk of obstructive sleep apnea. *Exclusion Criteria:* 8. Have clinically significant depression based on a score of ≥ 20 on the Patient health Questionnaire (PHQ-8). ***Primary Endpoint…*** For Optimal Responders, the mean Average PI score including the Average PI scores during the Titration Period that meet the qualification criteria (Average PI score ≤5 for 3 consecutive non-missing values) plus any scores between the last qualification score and the Randomization Visit will count as the subject's baseline Average PI score for statistical analysis. Definition of Baseline… For Optimal Responders, the mean Average PI score including the Average PI scores during the Titration Period that meet the qualification criteria (Average PI score ≤5 for 3 consecutive non-missing values) plus any scores between the final qualification day and the Randomization Visit will count as the subject's baseline Average PI score for statistical analysis. • For Optimal Responders, the subject's mean Average PI score at the end of the Taper Period (with added variability based on the

Section	Original Text	Revised Text
	variance of the data of the corresponding timepoint of missing data). This score will be the first 3 days of the mean Average PI score used to qualify the subject for entry into the Titration Period (i.e., where the mean Average PI score is ≥5 over ≥3 consecutive days, where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI score over the 7-day Observation Period).	variance of the data of the corresponding timepoint of missing data). This score will be the first 3 days of the mean Average PI score used to qualify the subject for entry into the Titration Period (i.e., where the mean Average PI score is >5 over ≥3 consecutive days, where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI score over the 7-day Observation Period).
Section 5 Figure 1	* Baseline PI scores=mean Average PI score including the Average PI scores during the Titration Period that meet the qualification criteria (Average PI score ≤4 for 3 consecutive non-missing values)	Added: ER/LA requirement can be satisfied by use of immediate-release opioid at least 4 times a day for at least 1 year * Baseline PI scores=mean Average PI score including the Average PI scores during the Titration Period that meet the qualification criteria (Average PI score ≤5 for 3 consecutive non-missing values)
Table 3 footnote 2	Screening procedures will be performed over 2 visits no more than 14 days apart.	Screening procedures will be performed over 2 visits no more than 21 days apart.
Table 3 footnote 5	At Screening: Height, weight, BMI, pulse rate, respiratory rate, and blood pressure. At subsequent visit: pulse rate, respiratory rate and blood pressure only.	At Screening: Height, weight, BMI, pulse rate, respiratory rate, and blood pressure. At subsequent visit: pulse rate, respiratory rate and blood pressure only. If BMI >40, complete STOPBang Questionnaire and record in source documents. Subject cannot continue if apnea risk is high.
Table 3 footnote 9	At end of Observation Period: Subjects must have had an index ER opioid medication use of ≥120 mg and ≤540 mg morphine equivalents/day (see table in protocol) on average and have had 80% to 120% compliance over the 1-week Observation Period; (ii) have a mean Average PI score over the 1 week of the period ≤4 (with a minimum compliance of 4 out of 7 daily PI scores); and (iii) still be satisfied with their pain and physical function. During or at the end of the Taper Period: Subjects must have a mean Average PI score ≥5 over ≥3 consecutive scores (non-missing values), where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI score over the 7-day Observation Period. Note that if these criteria are satisfied at Visit OR2, subject may skip OR2 and advance directly to Visit OR3. At the end of Titration Period: Subjects must have completed their titration and have achieved a mean Average PI score over at least 3 consecutive scores (non-missing values) ≤4 with acceptable side effects and a minimum dose of ≥120 mg and ≤540 mg morphine equivalents/day to continue on study.	At end of Observation Period: Subjects must have had an index ER opioid medication use of ≥120 mg and ≤540 mg morphine equivalents/day (see table in protocol) on average and have had 80% to 120% compliance over the 1-week Observation Period; (ii) have a mean Average PI score over the 1 week of the period ≤5 (with a minimum compliance of 4 out of 7 daily PI scores); and (iii) still be satisfied with their pain and physical function. During or at the end of the Taper Period: Subjects must have a mean Average PI score >5 over ≥3 consecutive scores (non-missing values), where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI score over the 7-day Observation Period. Note that if these criteria are satisfied at Visit OR2, subject may skip OR2 and advance directly to Visit OR3. At the end of Titration Period: Subjects must have completed their titration and have achieved a mean Average PI score over at least 3 consecutive scores (non-missing values) ≤5 with acceptable side effects and a minimum dose of ≥120 mg and ≤540 mg morphine equivalents/day to continue on study.

Section	Original Text	Revised Text
Section 10.1.1	(Note: Screening procedures will be performed over 2 visits no more than 14 days apart.) At the Screening Visit, a broad range of patients on long-term opioid analgesic therapy for CLBP will be evaluated for entry into the study based on medical history, physical examination, clinical laboratory testing, vital signs, electrocardiogram (ECG), PI, urine drug testing (UDT), and pregnancy test. Subjects will be admitted into the study if they have non-radicular CLBP which can include Quebec Task Force Classification of Spinal Disorders Classes 1, 2, 9.2, and 10, for more than 12-months duration; have been taking extended-release or long-acting opioids for at least 12 months for their CLBP; have been taking high doses as defined in the table below of one of the following "index ER opioids": morphine sulfate extended-release (MSER), oxycodone extended-release (OCER), or oxymorphone extended-release (OMER) for at least 3 consecutive months prior to the Screening Visit. (Subjects may also be taking additional ER opioids and/or immediate-release (IR) opioids, but the dose of any opioids beyond the index ER opioid will not be taken into account in the minimum or maximum required ER opioid dose for enrollment). For subjects taking multiple high-dose opioids, the Investigator will review all opioid use prior to enrollment and determine if the subject is still an appropriate candidate for the study based on the total amount of opioid the subject is receiving.	(Note: Screening procedures will be performed over 2 visits no more than 21 days apart.) At the Screening Visit, a broad range of patients on long-term opioid analgesic therapy for CLBP will be evaluated for entry into the study based on medical history, physical examination, clinical laboratory testing, vital signs, electrocardiogram (ECG), PI, urine drug testing (UDT), and pregnancy test. Subjects will be admitted into the study if they have non-radicular CLBP which can include Quebec Task Force Classification of Spinal Disorders Classes 1, proximal radicular (above the knee) pain of 2, 9.2, and 10, for more than 12-months duration; have been taking extended-release or long-acting opioids (or doses of immediate-release opioids at least 4 times a day) for at least 12 months for their CLBP; have been taking high doses as defined in the table below of one of the following "index ER opioids": morphine sulfate extended-release (MSER), oxycodone extended-release (OCER), or oxymorphone extended-release (OMER) for at least 3 consecutive months prior to the Screening Visit. (Subjects may also be taking additional ER opioids and/or immediate-release (IR) opioids, but the dose of any opioids beyond the index ER opioid will not be taken into account in the minimum or maximum required ER opioid dose for enrollment). For subjects taking multiple high-dose opioids, the Investigator will review all opioid use prior to enrollment and determine if the subject is still an appropriate candidate for the study based on the total amount of opioid the subject is receiving.
Section 10.1.3	***Observation Period (1 week)…*** Subjects will be confirmed as Optimal Responders and will be allowed to continue in the study if (i) their index ER opioid medication use was on average in the range shown in the table below and they had 80% to 120% compliance over the 1-week period; (ii) their mean Average PI score over the 1 week of the Observation Period was ≤4 (with a minimum compliance of 4 out of 7 daily PI scores); and (iii) they are still satisfied with their pain and physical function. ***Taper Period (up to 2 weeks)…*** Subjects with a mean Average PI score ≥5 over ≥3 consecutive PI scores (excluding missing values), where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI over the 7-day Observation Period,	***Observation Period (1 week)…*** Subjects will be confirmed as Optimal Responders and will be allowed to continue in the study if (i) their index ER opioid medication use was on average in the range shown in the table below and they had 80% to 120% compliance over the 1-week period; (ii) their mean Average PI score over the 1 week of the Observation Period was ≤5 (with a minimum compliance of 4 out of 7 daily PI scores); and (iii) they are still satisfied with their pain and physical function. ***Taper Period (up to 2 weeks)…*** Subjects with a mean Average PI score >5 over ≥3 consecutive PI scores (excluding missing values), where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI over the 7-day Observation Period,

Section	Original Text	Revised Text
	either off of the index ER opioid pain medication entirely or at a reduced dose, will be eligible to proceed to the Open-Label Titration Period. ***Open-Label Titration Period (up to 3 weeks)***… The dose of the index ER opioid will be increased as frequently as every 4 days (during telephone or office [OR3.1 – OR3.6] visits) until the mean Average PI score over at least 3 consecutive pain scores is ≤4 in order to qualify for randomization. ***Randomization Visit for Optimal Responders*** (Visit OR4). Subjects who have completed their titration, have achieved a mean Average PI score over 3 consecutive pain scores of ≤4 with satisfaction with their pain and physical function and acceptable side effects, and are taking a dose of index ER opioid shown in the table below will be allowed to continue on study.	either off of the index ER opioid pain medication entirely or at a reduced dose, will be eligible to proceed to the Open-Label Titration Period. ***Open-Label Titration Period (up to 3 weeks)***… The dose of the index ER opioid will be increased as frequently as every 4 days (during telephone or office [OR3.1 – OR3.6] visits) until the mean Average PI score over at least 3 consecutive pain scores is ≤5 in order to qualify for randomization. ***Randomization Visit for Optimal Responders*** (Visit OR4). Subjects who have completed their titration, have achieved a mean Average PI score over 3 consecutive pain scores of ≤5 with satisfaction with their pain and physical function and acceptable side effects, and are taking a dose of index ER opioid shown in the table below will be allowed to continue on study.
Section 10.3.2	• MSIR = Roxane brand of morphine sulfate (IR tablets)	• MSIR = West-Ward brand of morphine sulfate (IR tablets)
Section 10.3.3	For Optimal Responders, subjects will start the standardized regimen during the 2 week Taper Period during which study medication will be reduced every 3 days until the PI score increases as specified. The standardized regimen will continue during the 3-week Open-label Titration Period. During the Titration Period, the dose of the ER opioid will be increased as frequently as every 4 days (during telephone or office visits) until the mean Average PI score for at least 3 consecutive pain scores is ≤4.	For Optimal Responders, subjects will start the standardized regimen during the 2 week Taper Period during which study medication will be reduced every 3 days until the PI score increases as specified. The standardized regimen will continue during the 3-week Open-label Titration Period. During the Titration Period, the dose of the ER opioid will be increased as frequently as every 4 days (during telephone or office visits) until the mean Average PI score for at least 3 consecutive pain scores is ≤5.
Section 11.1 inclusion criterion 2	Have a clinical diagnosis of non-radicular CLBP (pain that occurs in an area with boundaries between the lowest rib and the crease of the buttocks) of Class 1 or 2 of the Quebec Task Force Classification for Spinal Disorders (subjects with previous surgery or chronic pain syndrome, i.e., classes 9.2 or 10, will be allowed if their pain does not radiate or radiates only proximally) for a minimum of 12 months and…	Have a clinical diagnosis of non-radicular CLBP (pain that occurs in an area with boundaries between the lowest rib and the crease of the buttocks) of Class 1 or proximal (above the knee) radicular pain of Class 2 of the Quebec Task Force Classification for Spinal Disorders (subjects with previous surgery or chronic pain syndrome, i.e., classes 9.2 or 10, will be allowed if their pain does not radiate or radiates only proximally) for a minimum of 12 months and…
Section 11.1 inclusion criterion 3	Have been taking ER/LA opioids for at least 12 months;	Have been taking ER/LA opioids (or immediate release opioids (at least 4 times a day) for at least 12 months;
Section 11.2 exclusion criterion 7	Have a body mass index (BMI) >40 kg/m^2.	Have a body mass index (BMI) >45 kg/m^2. Anyone with a BMI > 40 but ≤ 45 will complete a screening tool (STOPBang Questionnaire) to rule out high risk of obstructive sleep apnea (Appendix W).

Section	Original Text	Revised Text
Section 11.2 exclusion criterion 8	Have a clinically significant depression based on a score ≥15 on the Patient Health Questionnaire (PHQ-8).	Have a clinically significant depression based on a score ≥20 on the Patient Health Questionnaire (PHQ-8).
Section 12.1.1 sixth bullet	Screening assessments will be carried out over 2 visits that are not greater than 14 days apart. … • Collect vital signs (height, weight, BMI [calculated], pulse rate, respiratory rate, and blood pressure)	Screening assessments will be carried out over 2 visits that are not greater than 21 days apart. … • Collect vital signs (height, weight, BMI [calculated], pulse rate, respiratory rate, and blood pressure). Anyone with a BMI > 40 but ≤ 45 will complete a screening tool (STOPBang Questionnaire) to rule out high risk of obstructive sleep apnea.
Section 12.1.3 OR1 Visit (at Week -5) seventh bullet	• Subjects will be confirmed as Optimal Responders and will be allowed to continue in the study if: (i) their index opioid ER medication use was in the range shown in the table below and they had 80% to 120% compliance over the 1-week period; (ii) their mean Average PI score over the Observation Period was ≤4 (with a minimum compliance of 4 out of 7 daily PI scores); and (iii) they are still satisfied with their pain and physical function.	• Subjects will be confirmed as Optimal Responders and will be allowed to continue in the study if: (i) their index opioid ER medication use was in the range shown in the table below and they had 80% to 120% compliance over the 1-week period; (ii) their mean Average PI score over the Observation Period was ≤5 (with a minimum compliance of 4 out of 7 daily PI scores); and (iii) they are still satisfied with their pain and physical function.
Section 12.1.3 OR2 Visit (at Week -4) First bullet	• Check criteria for entry into the Titration Period: Subjects with a mean Average PI score ≥5 over ≥3 consecutive PI scores (non-missing values), where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI score over the 7-day Observation Period, either off of pain medication entirely or at a reduced dose, will immediately advance to Visit OR3 (skipping Visit OR2) and begin the Open-Label Titration Period	• Check criteria for entry into the Titration Period: Subjects with a mean Average PI score >5 over ≥3 consecutive PI scores (non-missing values), where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI score over the 7-day Observation Period, either off of pain medication entirely or at a reduced dose, will immediately advance to Visit OR3 (skipping Visit OR2) and begin the Open-Label Titration Period
Section 12.1.3 **OR3 Visit (at Week -3)** Ninth bullet	• Check criteria for entry into the Titration Period: Subjects with a mean Average daily PI score ≥5 over ≥3 consecutive PI scores (non-missing values), where this mean Average daily PI score has also increased by ≥1.5 points from the mean Average PI score over the 7-day Observation Period, either off of pain medication entirely or at a reduced dose, will be eligible to proceed to the Open-Label Titration Period. Subjects who do not meet these criteria will be discontinued from the study. (For study discontinuation procedures, see section 12.1.6.)	• Check criteria for entry into the Titration Period: Subjects with a mean Average daily PI score >5 over ≥3 consecutive PI scores (non-missing values), where this mean Average daily PI score has also increased by ≥1.5 points from the mean Average PI score over the 7-day Observation Period, either off of pain medication entirely or at a reduced dose, will be eligible to proceed to the Open-Label Titration Period. Subjects who do not meet these criteria will be discontinued from the study. (For study discontinuation procedures, see section 12.1.6.)

Section	Original Text	Revised Text
Section 12.1.3 **Telephone (or Office) Visits every 4 days (Up to 5 telephone or office visits from Week -3 to 0)** Sixth and seventh bullets	• If the subject does not have a mean Average PI score for at least 3 consecutive scores (non-missing values) that is ≤4, increase the subject's dose; increase dose as frequently as every 4 days (using Telephone or Office Visits) until the mean Average PI score over at least 3 consecutive scores (non-missing values) is ≤4 • When the subject's mean Average PI score over at least 3 consecutive scores (non-missing values) is ≤4, schedule the Randomization Visit as soon as possible (preferably the next day) and keep the subject on that ER opioid dose until that visit occurs	• If the subject does not have a mean Average PI score for at least 3 consecutive scores (non-missing values) that is ≤5, increase the subject's dose; increase dose as frequently as every 4 days (using Telephone or Office Visits) until the mean Average PI score over at least 3 consecutive scores (non-missing values) is ≤5 • When the subject's mean Average PI score over at least 3 consecutive scores (non-missing values) is ≤5, schedule the Randomization Visit as soon as possible (preferably the next day) and keep the subject on that ER opioid dose until that visit occurs
Section 12.1.3 Randomization Visit = OR4 (at Day 1) Seventh bullet	• Check the criteria for entry into the Randomization Period: To continue on study, subjects are required to have achieved a mean Average PI score ≤4 during the 3 consecutive scores (non-missing values) that triggered the randomization visit with satisfaction with their pain and physical function, and acceptable side effects, and be taking a dose of index ER opioid in the range listed in the table below.	• Check the criteria for entry into the Randomization Period: To continue on study, subjects are required to have achieved a mean Average PI score ≤5 during the 3 consecutive scores (non-missing values) that triggered the randomization visit with satisfaction with their pain and physical function, and acceptable side effects, and be taking a dose of index ER opioid in the range listed in the table below.
Section 12.2	Drugs that are allowed and not allowed as concomitant medications for either episodic or chronic use are described in this section. … **Prohibited Prior Medications** … **Prohibited and Allowed Concomitant Medications** … Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine and butorphanol), buprenorphine, methadone, barbiturates, and more than one benzodiazepine are prohibited throughout the study. Alcohol and other concomitant medications that are not to be taken in combination with opioid analgesics as well as non-prescribed controlled substances will NOT be permitted during the study except if determined to be appropriate by the Investigator.	Medications and procedures that are allowed and not allowed as concomitant medications for either episodic or chronic use are described in this section. … **Prohibited Prior Medications and Procedures** … **Prohibited and Allowed Concomitant Medications and Procedures** … Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine and butorphanol), buprenorphine, methadone, barbiturates, MAO inhibitors, investigational drugs, and more than one benzodiazepine are prohibited throughout the study. Alcohol and other concomitant medications that are not to be taken in combination with opioid analgesics as well as non-prescribed controlled substances will NOT be permitted during the study except if determined to be appropriate by the Investigator. Nerve or plexus block, including epidural steroid

Section	Original Text	Revised Text
		injections or facet blocks, botulinum toxin injection in the lower back region, chiropractic manipulation of the lower back, or any surgical procedure (including external or internal nerve stimulators) for lower back pain are not allowed during the study. Stimulators that are in place prior to study entry are allowed as long as the settings are not changed during the study. Massage therapy or exercise therapy may continue unchanged during the study but new massage therapy or exercise therapy is not allowed during the study.
Section 13.2	For Optimal Responders, the mean Average PI score during the Titration Period that meets the qualification criteria (Average PI score ≤4 for 3 consecutive non-missing values) plus any scores between the last qualification score and the Randomization Visit will count as the subject's baseline Average PI score for statistical analysis.	For Optimal Responders, the mean Average PI score during the Titration Period that meets the qualification criteria (Average PI score ≤5 for 3 consecutive non-missing values) plus any scores between the last qualification score and the Randomization Visit will count as the subject's baseline Average PI score for statistical analysis.
Section 17.5	For Optimal Responders, the mean Average PI score during the Titration Period that meets the qualification criteria (Average PI score ≤4 for 3 consecutive non-missing values) plus any scores between the last qualification score and the Randomization Visit will count as the subject's baseline Average PI score for statistical analysis.	For Optimal Responders, the mean Average PI score during the Titration Period that meets the qualification criteria (Average PI score ≤5 for 3 consecutive non-missing values) plus any scores between the last qualification score and the Randomization Visit will count as the subject's baseline Average PI score for statistical analysis.
Section 17.5.1	• For Optimal Responders, the subject's mean Average PI score at the end of the Taper Period (with added variability based on the variance of the data of the corresponding timepoint of missing data). This score will be the first 3 days of the mean Average PI score used to qualify the subject for entry into the Titration Period (i.e., where the mean Average PI score is ≥5 over ≥3 consecutive days, where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI over the 7-day Observation Period).	• For Optimal Responders, the subject's mean Average PI score at the end of the Taper Period (with added variability based on the variance of the data of the corresponding timepoint of missing data). This score will be the first 3 days of the mean Average PI score used to qualify the subject for entry into the Titration Period (i.e., where the mean Average PI score is >5 over ≥3 consecutive days, where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI over the 7-day Observation Period).
Section 18.1	• MSIR = Roxane brand of morphine sulfate (IR tablets)	• MSIR = West-Ward brand of morphine sulfate (IR tablets)

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td>Appendix B</td><td>Once the pain intensity score is ≤4 for 3 consecutive pain scores with satisfaction with pain and physical function and acceptable side effects, they will enter the Blinded Structured Discontinuation Period.
<table>
<tr><th>Patient group</th><th>Observation Period</th><th>Taper to Flare</th><th></th><th>Titration</th><th>Baseline to confirm stable pain ≤4</th></tr>
<tr><td>Optimal Responders</td><td>Current medication</td><td>Active Open Label taper doses (decreased every 3 days)</td><td>Flare established</td><td>Active Open Label titration doses back towards starting dose (increased every 4 days)</td><td>Active dose @ entry</td></tr>
</table>
Optimal Responders tables:
[in center] Establish flare: (Average daily PI score ≥5; increased by ≥1.5 points for >3 consecutive days from the mean Average PI). Then titrate to stable dose.

[last column] Highest titration dose which resulted in a mean Average daily PI score <4 for at least 3 consecutive days.</td><td>Once the pain intensity score is ≤5 for 3 consecutive pain scores with satisfaction with pain and physical function and acceptable side effects, they will enter the Blinded Structured Discontinuation Period.
<table>
<tr><th>Patient group</th><th>Observation Period</th><th>Taper to Flare</th><th></th><th>Titration</th><th>Baseline to confirm stable pain ≤5</th></tr>
<tr><td>Optimal Responders</td><td>Current medication</td><td>Active Open Label taper doses (decreased every 3 days)</td><td>Flare established</td><td>Active Open Label titration doses back towards starting dose (increased every 4 days)</td><td>Active dose @ entry</td></tr>
</table>
Optimal Responders tables:
[in center] Establish flare: (Average daily PI score >5; increased by ≥1.5 points for ≥3 consecutive days from the mean Average PI). Then titrate to stable dose.

[last column] Highest titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days.</td></tr>
<tr><td>Appendix W</td><td></td><td>NEW: STOPBang Questionnaire</td></tr>
</table>

3. SPONSOR CONTACT INFORMATION

This section will be completed when the information is available.

Table 1: Sponsor Contact Information

Role in Study	Name	Telephone and Email Address
Medical Monitor	Dr. David Schneider	919-745-2715 David.Schneider@INCResearch.com
SAE Reporting Pathway		FAX: 1-877-464-7787 E-Mail: INCDrugSafety@INCResearch.com

A list of other key study personnel and vendors will be provided separately for your reference.

4. SYNOPSIS

Name of Sponsor/Company The Opioid Post-Marketing Requirement Consortium (OPC)		**Name of Drug/Device** Morphine sulfate extended-release, oxycodone extended-release, or oxymorphone extended-release
Protocol Number	2065-5	
Title	A randomized, double-blind, placebo-controlled, clinical trial of structured opioid discontinuation versus continued opioid therapy in Suboptimal and Optimal Responders to high-dose long-term opioid analgesic therapy for chronic pain.	
Phase of Development	Phase 4	
Investigators and Study Centers	Assuming 5 Suboptimal Responder subjects and 5 Optimal Responder subjects are randomized (and 20 each screened) per site, this will be a multicenter study conducted at approximately 80-100 sites.	
Rationale	The clinical syndrome of poor response to high-dose long-term opioid therapy is not well characterized in the medical literature, but well recognized by the clinical pain management community. Characteristics of these patients include, in addition to the use of higher doses of opioids for extended periods of time, persistent severe pain intensity (PI) ratings, poor physical, psychological, and social function, frequent employment difficulties, and aberrant drug-taking behaviors that may or may not be sufficient to meet criteria for an addiction disorder. Patients often insist that despite their poor clinical status and the lack of an evident response to opioids, continued opioid treatment is essential. A traditional treatment for such patients is discontinuation of opioid therapy, in which patients have their opioid therapy gradually tapered off, in the context of psychological and physical rehabilitative support, often in a structured inpatient or outpatient program. Long-term clinical success has been noted in uncontrolled and unblinded observational studies, but the efficacy of removal from opioid therapy for a well-defined cohort of "Suboptimal Opioid Responders" has never been evaluated in a randomized, double-blind, controlled clinical trial. One proposed, but as yet unproven, explanation for the phenomenon of Suboptimal Responders to higher-dose opioid therapy is opioid-induced hyperalgesia (OIH). According to this hypothesis, some patients on long-term opioid therapy for chronic pain develop paradoxical hypersensitivity to pain caused by the very opioid treatment intended to reduce their pain, resulting in increasing doses, increasing pain intensity, increased sensitivity to painful stimuli (hyperalgesia), and according to many descriptions, spread of pain beyond the initially painful area. Under this hypothesis, removal of opioid therapy would result in improvement of experimental pain sensitivity, improvement in pain intensity, and potentially decreased spread of pain compared to patients in whom opioid therapy was continued. In addition, it would be expected that Suboptimal Responders to opioid therapy have greater experimental pain sensitivity and perhaps greater pain spread than Optimal Responders to opioid therapy (who presumably do not have OIH). Finally, it would be expected that in contrast to Suboptimal Responders, Optimal Responders to opioid therapy will worsen when their effective analgesics have been withdrawn, as with any other effective analgesic. From a clinical perspective, clinicians need to understand not only whether OIH underlies suboptimal responses to opioids in general, but how to identify, among patients who are responding poorly to opioids, which patients will improve after	

Name of Sponsor/Company The Opioid Post-Marketing Requirement Consortium (OPC)	**Name of Drug/Device** Morphine sulfate extended-release, oxycodone extended-release, or oxymorphone extended-release

Protocol Number	2065-5
	withdrawal of opioids. Therefore, it is important to attempt to identify predictors of benefit from withdrawal of opioids among Suboptimal Responders. The overarching purpose of this research program, which is being conducted to meet the U.S. Food and Drug Administration requirements and is one of the 5 Opioid Post Marketing Requirement Consortium (OPC) commitments, is to better characterize the contribution of OIH to suboptimal responses to opioid therapy. This goal will be approached in several different ways. Among a cohort of Suboptimal Responders to opioid therapy, the objective will be to evaluate the effect of structured discontinuation versus continuation of long-term opioid treatment on pain intensity, pain spread, and sensitivity to experimental pain. Predictors of a beneficial response to opioid discontinuation will be examined. The impact of structured opioid discontinuation (vs. continuation) among the Suboptimal Responders will be indirectly compared to the impact of structured opioid discontinuation (vs. continuation) among a cohort of Optimal Responders to opioid therapy in order to fully inform the objectives of the OPC commitment. Worsening of pain upon discontinuation of opioid therapy in the Optimal Responder group will confirm and extend previous observations of the efficacy of long-term opioid therapy. Baseline characteristics of Suboptimal and Optimal Responders will be compared, particularly with regard to experimental pain sensitivity.
Objectives	Primary Objective: To evaluate the effect on pain intensity (PI) of structured discontinuation of long-term opioid analgesic therapy compared to continuation of opioid therapy in Suboptimal and Optimal Responders to high-dose, long-term opioid analgesic therapy for chronic low back pain (CLBP). Secondary Objective: To evaluate the effect on additional clinical outcomes measures of structured discontinuation of long-term opioid analgesic therapy compared to continuation of opioid therapy for CLBP in Suboptimal and Optimal Responders to high-dose, long-term opioid analgesic therapy at multiple time points. Exploratory Objectives: • To compare experimental pain sensitivity in the opioid discontinuation vs. continuation groups in both Suboptimal Responders and Optimal Responders (subjects in substudy). • To determine subject characteristics that predict response to structured discontinuation of opioid therapy. • To determine the effect of opioid discontinuation on certain endocrine function tests, sexual function, and the relationship of changes in PI and endocrine function to changes in male and female sexual function. • To determine the effect of opioid discontinuation on neurocognitive function.
Study Design	This multicenter, randomized, double-blind, placebo-controlled study will consist of a common Screening Visit for all subjects, then different schedules for Optimal and Suboptimal Responders, followed by a common schedule for the Blinded Structured Opioid Discontinuation Period and Follow-up Period, as illustrated in Figure 1. The schedule of procedures for Suboptimal and Optimal Responders is shown in Table 2 and Table 3, respectively.

<table>
<tr><td colspan="2">Name of Sponsor/Company
The Opioid Post-Marketing Requirement Consortium (OPC)</td><td>Name of Drug/Device
Morphine sulfate extended-release, oxycodone extended-release, or oxymorphone extended-release</td></tr>
<tr><td>Protocol Number</td><td colspan="2">2065-5</td></tr>
<tr><td></td><td colspan="2">SCREENING
(Note: Screening procedures are performed over 2 visits no more than 21 days apart.)
At the Screening Visit, a broad range of patients on long-term opioid analgesic therapy for CLBP will be evaluated for entry into the study based on medical history, physical examination, clinical laboratory testing, vital signs, electrocardiogram (ECG), pain intensity (PI), urine drug testing (UDT), and urine pregnancy test. Subjects will be admitted into the study if they have non-radicular CLBP which can include Quebec Task Force Classification of Spinal Disorders Classes 1, proximal radicular (above the knee) pain of 2, 9.2, and 10, for more than 12-months duration; have been taking extended-release (ER) or long-acting (LA) opioids (or doses of immediate-release opioids at least 4 times a day) for at least 12 months for their CLBP; have been taking high doses as defined here of one of the following “index ER opioids” for their CLBP: morphine sulfate extended-release (MSER), oxycodone extended-release (OCER), or oxymorphone extended-release (OMER) within the dose range for each index ER opioid as shown in the table below, for at least 3 consecutive months prior to the Screening Visit.
<table>
<tr><td></td><td>Dose Range</td></tr>
<tr><td>Morphine sulfate extended-release</td><td>120-540mg</td></tr>
<tr><td>Oxycodone extended-release</td><td>80-360mg</td></tr>
<tr><td>Oxymorphone extended-release</td><td>40-180mg</td></tr>
</table>
Subjects may also be taking additional ER opioids and/or immediate-release (IR) opioids, but the dose of any opioids beyond the index opioid will not be taken into account in the minimum or maximum required ER opioid dose for enrollment. The goal will be to have a minimum representation of each index ER opioid, with a minimum of ~20% of randomized subjects for each index ER opioid. Subjects taking asymmetric dosing of index ER opioids (different dose in the morning and evening) will be allowed in the study as long as they meet the dose criterion of index ER opioid indicated above and can be converted to symmetric twice-daily dosing.
Subjects taking acetaminophen (or any acetaminophen-containing product after review of concomitant medications) prior to entering the study will be directed to stop taking it and only take the study-provided acetaminophen after entering the study.
Subjects will be classified as Suboptimal Responders or Optimal Responders at the Screening Visit as per the following criteria: Suboptimal Responder = Subject whose daily Average PI score is ≥6 and who is dissatisfied with his/her pain and physical function; Optimal Responder = Subject whose daily Average PI score is ≤4 and who is satisfied with his/her pain and physical function. The study design then differs for the Suboptimal and Optimal Responder populations as described below.
FOR SUBOPTIMAL RESPONDERS ONLY
The schedule of procedures for Suboptimal Responders is shown in Table 2. Visits specific for Suboptimal Responders are named SR1, SR2, etc.
Run-In Period (1 week). Subjects classified as Suboptimal Responders at the Screening Visit will enter the Run-in Period during which they will be required to discontinue all previously prescribed ER and immediate release (IR) opioid medications for the</td></tr>
</table>

Name of Sponsor/Company The Opioid Post-Marketing Requirement Consortium (OPC)	**Name of Drug/Device** Morphine sulfate extended-release, oxycodone extended-release, or oxymorphone extended-release
Protocol Number	2065-5
	remainder of the study and will receive a standardized regimen supplied as index ER opioid plus matching IR opioid depending on the index ER opioid they were taking at screening (i.e., either oxycodone extended-release [OCER], OxyContin®, plus oxycodone IR [OCIR] PRN, morphine sulfate extended-release [MSER], MS Contin®, plus morphine sulfate IR [MSIR] PRN, or oxymorphone extended-release [OMER], Opana® ER, plus oxymorphone IR [OMIR] PRN). In the standardized regimen, the dose of the ER opioid will be similar to the dose of the index ER opioid taken at screening and will remained fixed throughout the period. (Note: Subjects who were taking asymmetric doses of the index ER opioid at screening will be placed on a symmetric dosage [same dose in the morning and evening] of the standardized regimen.) The dose of the IR opioid will be limited to no more than twice daily PRN administration of OCIR 10 mg, MSIR 15 mg, or OMIR 5 mg, matching the index ER opioid each subject is receiving. The *maximum* dose of PRN IR opioid they are allowed per day will remain fixed. Subjects will also be provided acetaminophen as rescue medication (500 mg tablets, 1 to 2 tablets PRN every 4 to 6 hours, not to exceed 6 tablets/day) and will be encouraged to take acetaminophen to manage their pain before they use the IR opioid (i.e., only take the IR opioid if the maximum dose of acetaminophen is not effective). Subjects will be allowed to continue the non-opioid analgesics they had been taking before screening but will not be able to change the dose except for acetaminophen as described above. Adverse events (AEs) will be recorded during this period. At the end of the 1-week Run-In Period, subjects will return to the clinic for the Tolerability Visit (Visit SR1) to determine whether they tolerated the standardized opioid regimen. Subjects who did not tolerate the standardized opioid regimen will be discontinued; no dose adjustment of the ER medication will be permitted. *Baseline Period (1 week)*. Subjects will then enter a 1-week Baseline Period during which they will self-administer the standardized opioid regimen and record their opioid medication intake and PI scores (Average and Worst over past 24 hours on a 0-10 numerical rating scale (NRS)) daily before bed time. Each subject's 7-day daily PI scores will be averaged and used as the subject's baseline PI scores (with a minimum compliance of 4 out of 7 daily PI scores). At the *Randomization Visit for Suboptimal Responders* (Visit SR2), subjects will continue on study if they have (i) a mean Average PI score ≥6 on a 0-10 NRS over the 1 week of the Baseline Period (with a minimum compliance of 4 out of 7 daily PI scores); (ii) compliance with their index ER opioid medication between 80% and 120%; and (iii) are still dissatisfied with their pain and physical function. Subjects who had a baseline mean Average PI score of 10/10 (i.e., 10/10 score every day for the 1 week of the Baseline Period) will be discontinued. The rest of the study will then be similar for both Suboptimal Responders and Optimal Responders as described below.

<table>
<tr><td colspan="2">Name of Sponsor/Company
The Opioid Post-Marketing Requirement Consortium (OPC)</td><td>Name of Drug/Device
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<tr><td>Protocol Number</td><td colspan="2">2065-5</td></tr>
<tr><td></td><td colspan="2">FOR OPTIMAL RESPONDERS ONLY
The schedule of procedures for Optimal Responders is shown in Table 3. Visits specific for Optimal Responders are named OR1, OR2, etc.
Observation Period (1 week). Subjects meeting the common screening criteria at the end of the Screening Visit and classified as Optimal Responders at the Screening Visit will be sent home and told to continue their current medication (including non-index ER and IR opioid medications) for 1 week. (Note: Subjects who were taking asymmetric doses of the index ER opioid at screening will continue taking asymmetric doses of their index ER opioids during this period.) During this period, opioid medication intake and PI scores (Average and Worst over past 24 hours on a 0-10 NRS) will be captured daily before bed time. At the end of the period, subjects will return to the clinic (Visit OR1) and all opioid medication use and PI scores will be reviewed. Subjects will be confirmed as Optimal Responders and will be allowed to continue in the study if: (i) their index ER opioid medication use was, on average, in the range shown in the table below and they had 80% to 120% compliance over the 1-week period; (ii) their mean Average PI score over the 1 week of the period was ≤5 (with a minimum compliance of 4 out of 7 daily PI scores); and (iii) they are still satisfied with their pain and physical function.

<table>
<tr><td></td><td>Dose Range</td></tr>
<tr><td>Morphine sulfate extended-release</td><td>120-540mg</td></tr>
<tr><td>Oxycodone extended-release</td><td>80-360mg</td></tr>
<tr><td>Oxymorphone extended-release</td><td>40-180mg</td></tr>
</table>

Taper Period (up to 2 weeks[+3 days]). Subjects will be tapered with the same index ER opioid they were taking at screening (using study medication provided for the index ER opioid; i.e., either OxyContin®, MS Contin®, or Opana® ER); IR opioid will not be used during the Taper Period and any other opioid medication will be discontinued. (Note: Subjects who were taking asymmetric doses of ER index opioid at screening will be tapered with a symmetric dosage [same dose in the morning and evening] of the standardized regimen.) Tapering will start at Visit OR1. Subjects will self-administer a tapering dose of the standard index ER opioid matching the one they were taking for up to 2 weeks (+ 3 days) and will record PI scores daily. No other ER opioid will be allowed. At Visit OR2, the subjects' overall status (opioid medication dose, PI score, etc.) will be reviewed. If the minimum pain requirement has been met either before or at Visit OR2, the subject will immediately advance to Visit OR3 (skipping Visit OR2) and begin the Open-Label Titration Period. If the minimum pain requirement has not been met, the opioid taper will continue. By Visit OR3, subjects should be completely off of their opioid medication if they have not already met the minimum pain requirement. Subjects with a mean Average PI score >5 over ≥3 consecutive PI scores (excluding missing values), where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI score over the 7-day Observation Period, either off of their index ER opioid pain medication entirely or at a reduced dose, will be eligible to proceed to the Open-Label Titration Period. Subjects who do not meet these</td></tr>
</table>

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Protocol Number	2065-5

criteria, including those subjects who cannot tolerate the tapering of the index ER opioid, will be discontinued from the study.

Open-Label Titration Period (up to 3 weeks). Subjects will be titrated with the same index ER opioid they were taking during the Taper Period (supplied as index ER opioid plus matching IR opioid; i.e., either OCER (OxyContin®) plus OCIR PRN, MSER (MS Contin®) plus MSIR PRN, or OMER (Opana® ER) plus OMIR PRN). The dose of index ER opioid will be increased as frequently as every 4 days (during telephone or office visits) until the mean Average PI score for at least 3 consecutive pain scores is ≤5 (qualify for randomization). If the dose of the index ER opioid needs to be titrated above the baseline dose, the Titration Period may be extended 1 additional week (±3 days). The dose of the IR opioid will be limited to no more than twice daily PRN administration of OCIR 10 mg, MSIR 15 mg, or OMIR 5 mg, matching the index ER opioid each subject is receiving. Subjects will also be provided acetaminophen as rescue medication (500 mg tablets, 1-2 tablets PRN every 4 to 6 hours, not to exceed 6 tablets/day) and will be encouraged to take acetaminophen to manage their pain, before they use IR opioid (i.e., only take the IR opioid if the maximum dose of acetaminophen is not effective).

Randomization Visit for Optimal Responders (Visit OR4). Subjects who have completed their titration, have achieved a mean Average PI score over 3 consecutive pain scores of ≤5 with satisfaction with their pain and physical function and acceptable side effects, and are taking a dose of index opioid as shown in the table below will be allowed to continue on study.

	Dose Range
Morphine sulfate extended-release	120-540mg
Oxycodone extended-release	80-360mg
Oxymorphone extended-release	40-180mg

The rest of the study will then be similar for both Suboptimal Responders and Optimal Responders.

CONTINUING FOR BOTH SUBOPTIMAL AND OPTIMAL RESPONDERS

Blinded Structured Opioid Discontinuation Period (24 weeks). At the Randomization Visit (Visit SR2 or OR4), subjects meeting the criteria (described above for each population) to enter the Blinded Structured Opioid Discontinuation Period will then be randomized to either continue or discontinue opioid therapy, as follows.

For subjects whose index ER opioid is MSER, the groups will be:

- Morphine Group 1: MSER tablets + matching placebo tablets to maintain MSER dose, but appear as if tapering is occurring;
- Morphine Group 2: Placebo tablets to match MSER tablets + MSER tablets in decreasing dose to result in a tapering off of MSER.
- Both groups will be provided with MSIR and acetaminophen.

For subjects whose index ER opioid is OCER, the groups will be:

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Protocol Number	2065-5
	• Oxycodone Group 1: OCER tablets + matching placebo tablets to maintain OCER dose, but appear as if tapering is occurring; • Oxycodone Group 2: Placebo tablets to match OCER tablets + OCER tablets in decreasing dose to result in a tapering off of OCER. • Both groups will be provided with OCIR and acetaminophen. For subjects whose index ER opioid is OMER, the groups will be: • Oxymorphone Group 1: OMER tablets + matching placebo tablets to maintain OMER dose, but appear as if tapering is occurring; • Oxymorphone Group 2: Placebo tablets to match OMER tablets + OMER tablets in decreasing dose to result in a tapering off of OMER. • Both groups will be provided with OMIR and acetaminophen. Therefore, there will be a total of 4 groups in the Blinded Structured Opioid Discontinuation Period: • Suboptimal Responders, continuation arm • Suboptimal Responders, discontinuation arm • Optimal Responders, continuation arm • Optimal Responders, discontinuation arm Randomization will be stratified by responder status (Optimal Responder; Suboptimal Responder) and index ER opioid (morphine, oxycodone, or oxymorphone); subject recruitment into the study will be adjusted to ensure at least 20% of subjects are on oxycodone, at least 20% on morphine, and at least 20% on oxymorphone in the Blinded Structured Opioid Discontinuation Period within each cohort (Optimal Responders and Suboptimal Responders). The goal is to taper subjects in the discontinuation arms of both the Suboptimal Responder and Optimal Responder groups off their opioid treatment onto placebo over approximately 3-4 weeks (duration of taper will depend on the baseline dose of the index ER opioid). Subjects in the continuation arms will be on a fixed-regimen of ER opioid (i.e., the ER opioid dose will remain fixed and the maximum dose of PRN IR opioid dose they are allowed per day will remain fixed); note that the doses will vary across subjects based on their individualized standardized dose. Subjects will also be provided acetaminophen as rescue medication (500 mg tablets, 1-2 tablets PRN every 4-6 hours not to exceed 6 tablets/day) and will be encouraged to take acetaminophen to manage their pain before they use IR opioid. The dose of the IR opioid will be limited to no more than twice daily PRN administration of OCIR 10 mg, MSIR 15 mg, or OMIR 5 mg, matching the index ER opioid each subject is receiving. Subjects will return to the clinic at weeks 1, 2, 4, 6, 8, 12, 16, 20, and 24 (Visits BDP1 through BDP9). A series of assessments will be performed at each visit. *Follow-Up Period (4 weeks)*. Subjects completing the Blinded Structured Opioid Discontinuation Period will be required to advance to and complete the Follow-up Period. However, those subjects who discontinue from the Blinded Structured Opioid

<table>
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<tr><td>Protocol Number</td><td colspan="2">2065-5</td></tr>
<tr><td></td><td colspan="2">Discontinuation Period prior to Week 12 will complete Week 12 study procedures and those subjects who discontinue during Weeks 13-23 will complete Week 24 study procedures before proceeding to the Follow-Up Period. Subjects will self-administer a blinded tapering dose during the Follow-Up Period: Placebo taper for subjects who were in the discontinuation arm and active drug taper for subjects who were in the continuation arm. Subjects will be followed-up during 2 clinic visits (FUV1 and FUV2, and 2 phone calls (during the weeks between Follow-Up Visits). At the end of the Follow-up Period, subjects will be transitioned back to their primary care physician. Subjects will be instructed not to take any ER opioid medication until they have consulted with their primary care physician as they no longer will be opioid-tolerant at this time.</td></tr>
<tr><td>Number of Subjects (planned)</td><td colspan="2">Approximately 3280 subjects will be screened, 820 will be randomized into the Blinded Structured Opioid Discontinuation Period (205 subjects per arm per responder type will be needed), and it is assumed that approximately 60-70% will complete the study. The sample size is calculated to detect a between-group difference (between the opioid discontinuation group and the opioid continuation group within each responder type) of 0.8 points, assuming a standard deviation of 2.5, a 2-sided 5% significance level, and 90% power.</td></tr>
<tr><td>Entry Criteria at Screening</td><td colspan="2">Inclusion criteria: Subjects must meet all of the following inclusion criteria to be enrolled in the study:
1. Be male or non-pregnant, non-lactating female aged 18 to 75 years, inclusive.
2. Have a clinical diagnosis of non-radicular CLBP (pain that occurs in an area with boundaries between the lowest rib and the crease of the buttocks) of Class 1 or proximal radicular (above the knee) pain of Class 2 based on the Quebec Task Force Classification for Spinal Disorders (subjects with previous surgery or chronic pain syndrome, i.e., classes 9.2 or 10, will be allowed if their pain does not radiate or radiates only proximally) for a minimum of 12 months and
a. For the Suboptimal Responder group, pain must have been present for at least several hours a day and have an Average PI score of 6-9 on an 11-point NRS within the past 24 hours of screening.
b. For the Optimal Responder group, subjects must have an Average PI score of 1-4 on an 11-point NRS within the past 24 hours of screening.
3. Have been taking ER/LA opioids or immediate release opioids (at least 4 times a day) for at least 12 months.
4. Have been taking one of the 3 index ER opioid drugs around-the-clock at a twice-a-day frequency for at least 3 consecutive months at a total daily dose within the range shown in the table below.
<table>
<tr><td></td><td>Daily Dose Range</td></tr>
<tr><td>Morphine sulfate extended-release</td><td>120-540mg</td></tr>
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Name of Sponsor/Company The Opioid Post-Marketing Requirement Consortium (OPC)	**Name of Drug/Device** Morphine sulfate extended-release, oxycodone extended-release, or oxymorphone extended-release
Protocol Number	2065-5
	5. Be considered, in the opinion of the Investigator, to be in generally good health other than CLBP at screening based upon the results of a medical history, physical examination, 12-lead ECG, and laboratory profile. 6. Speak, read, write, and understand English (to reduce heterogeneity of data), understand the consent form, and be able to effectively communicate with the study staff. 7. Have access to the Internet (to access the patient support program). 8. Voluntarily provide written informed consent. 9. Be willing and able to complete study procedures. *Exclusion Criteria:* Subjects who have any of the following will not be enrolled in the study: 1. Have any clinically significant condition that would, in the opinion of the Investigator, preclude study participation or interfere with the assessment of pain and other symptoms of CLBP or increase the risk of opioid-related AEs. 2. Have a primary diagnosis of fibromyalgia, complex regional pain syndrome, neurogenic claudication due to spinal stenosis, spinal cord compression, acute nerve root compression, severe or progressive lower extremity weakness or numbness, bowel or bladder dysfunction as a result of cauda equina compression, diabetic amyotrophy, meningitis, diskitis, back pain because of secondary infection or tumor, or pain caused by a confirmed or suspected neoplasm. 3. Have undergone a surgical procedure for back pain within 6 months prior to the Screening Visit. 4. Have had a nerve or plexus block, including epidural steroid injections or facet blocks, within 1 month prior to the Screening Visit or botulinum toxin injection in the lower back region within 3 months prior to screening. 5. Have a history of confirmed malignancy within past 2 years, with exception of basal cell or squamous cell carcinoma of the skin that has been successfully treated. 6. Have uncontrolled blood pressure, i.e., subject has a sitting systolic blood pressure >180 mm Hg or <90 mm Hg, or a sitting diastolic blood pressure >110 mmHg or <40 mm Hg at screening. 7. Have a body mass index (BMI) >45 kg/m^2. Anyone with a BMI > 40 but ≤ 45 will complete a screening tool (STOPBang Questionnaire) to rule out high risk of obstructive sleep apnea. 8. Have clinically significant depression based on a score of ≥20 on the Patient Health Questionnaire (PHQ-8). 9. Have suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS). 10. Have a previous history of suicidal behaviors in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS. 11. Have any lifetime history of serious or recurrent suicidal behavior. (Non-

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Protocol Number	2065-5
	suicidal self-injurious behavior is not a trigger for a risk assessment unless in the Investigator's judgment it is indicated.) 12. Have clinically significant abnormality in clinical chemistry, hematology or urinalysis, including serum glutamic-oxaloacetic transaminase/aspartate aminotransferase or serum glutamic pyruvic transaminase/alanine aminotransferase ≥3 times the upper limit of the reference range or a serum creatinine >2 mg/dL at screening. 13. Have severe enough psychiatric or substance abuse disorder to compromise the subject's safety or scientific integrity of the study. 14. Have on-going litigation associated with back pain or pending applications for workers compensation or disability issues or subjects who plan on filing litigation or claims within the next 12 months; subjects with settled past litigations will be allowed as will subjects who have been on workers compensation or disability claims for at least 3 months. 15. Have used a monoamine oxidase inhibitor within 14 days prior to screening. 16. Are taking agonist-antagonists (pentazocine, butorphanol or nalbuphine), buprenorphine, methadone, barbiturates, or more than one type of benzodiazepine within 1 month prior to screening. 17. Have a positive UDT for illicit drugs (including marijuana), non-prescribed controlled substances (opioid or non-opioid), or alcohol at screening. 18. Have taken any investigational drug within 30 days prior to the Screening Visit or are currently enrolled in another investigational drug study.
Entry Criteria to Determine Responder Status	Following successful determination of eligibility, subjects will be assessed against the following criteria to determine responder status at the Screening Visit: • Subjects with an Average PI score ≤4 (as measured on the NRS) at Screening who are satisfied with their pain and physical function will be considered Optimal Responders • Subjects with an Average PI score ≥6 (as measured on the NRS) at Screening who are dissatisfied with their pain and physical function will be considered Suboptimal Responders
	• Subjects who do not fall into either category will be considered screen failures and discontinued from the study.
Assessments	• Roland-Morris Disability Questionnaire (RMDQ) • Average PI scores in the past 24 hours on 0-10 NRS • Worst PI scores in the past 24 hours on 0-10 NRS • Brief Pain Inventory – Short Form (BPI-SF) • Regional Pain Scale • Pain Quality Assessment Scale (PQAS) • Short-form health survey (EQ-5D-5L) • Patient Global Impression of Change (PGIC) • Patient Health Questionnaire-8 (PHQ-8) • Columbia-Suicide Severity Rating Scale (C-SSRS) • MOS Sleep Scale

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Protocol Number	2065-5
	• Digit Symbol Substitution Test (DSST) • Quantitative sensory testing (QST) for OIH to measure pain sensitivity to experimental thermal stimuli (for subjects enrolled at participating sub-study sites) • Endocrine function tests (eg, free and total testosterone, luteinizing hormone (LH), follicle-stimulating hormone [FSH], estradiol [women only], insulin growth factor-1 [IGF-1], cortisol, adrenocorticotropic hormone [ACTH], dehydroepiandrosterone sulfate [DHEAS], and thyroid-stimulating hormone [TSH] [baseline only]) and sexual function scales (International Index of Erectile Function [IIEF] for males and Female Sexual Function Index [FSFI] for females) • Subjective Opiate Withdrawal Scale (SOWS) • Clinical Opioid Withdrawal Scale (COWS) • Work productivity (Work Productivity and Activity Impairment [WPAI] scale) • AEs • Abuse-related events (using the MADDERS™ system) • Vital signs • Physical examination • ECG • Clinical laboratory parameters • Pregnancy test • Quantitative UDT

Name of Sponsor/Company The Opioid Post-Marketing Requirement Consortium (OPC)	**Name of Drug/Device** Morphine sulfate extended-release, oxycodone extended-release, or oxymorphone extended-release
Protocol Number	2065-5
Endpoints for Evaluation	***Primary Endpoint*** Change in the mean Average PI score on the 0-10 NRS from baseline to the 1 week period prior to the Week 12 visit. For Suboptimal Responders, the mean Average PI score over the 7-day Baseline Period will count as the subject's baseline Average PI score for statistical analysis. For Optimal Responders, the mean Average PI score including the Average PI scores during the Titration Period that meet the qualification criteria (Average PI score $\leq$4 for 3 consecutive non-missing values) plus any scores between the last qualification score and the Randomization Visit will count as the subject's baseline Average PI score for statistical analysis. ***Secondary Endpoints*** <u>Suboptimal Responders</u> • Change from baseline to Weeks 4, 8, 16, 20, and 24 in 0-10 NRS Average and Worst PI scores over 1 week prior to each visit. • Cumulative response function in percent improvement in PI score at Weeks 12 and 24 compared to baseline over 1 week prior to each visit. • Changes from baseline to Weeks 12 and 24 in physical function (RMDQ), impact of pain on function (BPI-SF), pain quality (PQAS), pain spread (Regional Pain Scale), neuropsychological function (DSST), sleep quality (MOS Sleep Scale), mood (PHQ-8), quality of life (EQ-5D-5L) and work productivity (WPAI). • Proportion of subjects with overall clinical benefit at Weeks 12 and 24 defined as a composite measure of key clinical endpoints: ≥30% improvement in Average PI score *and* ≥20% improvement in RMDQ *and* PGIC of moderately or better improvement. <u>Optimal Responders</u> • Change from the baseline to Weeks 4, 8, 16, 20, and 24 in 0-10 NRS Average and Worst PI scores over 1 week prior to each visit. • Cumulative response function in percent worsening in PI score at Weeks 12 and 24 over 1 week prior to each visit compared to baseline. • Changes from baseline to Weeks 12 and 24 in physical function (RMDQ), impact of pain on function (BPI-SF), pain quality (PQAS), pain spread (Regional Pain Scale), sleep quality (MOS Sleep Scale), mood (PHQ-8), quality of life (EQ5D), and work productivity (WPAI). ***Exploratory Endpoints*** • Change in sensitivity to thermal stimuli on QST (subjects in substudy) • Identification of baseline factors predictive of benefit of opioid discontinuation among Suboptimal Responders. • Changes from baseline in endocrine function and sexual function; relationship of changes in endocrine function to changes in PI; relationship of baseline endocrine status to efficacy of opioid discontinuation. • Changes from baseline in neurocognitive function as characterized in the DSST

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Protocol Number	2065-5
Safety and Tolerability	Safety will be assessed by: • AEs • Abuse-related events (using the Misuse Abuse Diversion Drug Event Reporting System [MADDERS™]) • Opioid-specific side effects • Vital signs • Clinical laboratory parameters • Physical examinations Additional safety measures will include UDT, C-SSRS, and opioid withdrawal effects (measured by COWS, SOWS and withdrawal AEs).
Statistical Methods	***Study Hypotheses*** Suboptimal Responders: In subjects with chronic pain on high-dose opioid therapy for at least 1 year who have a suboptimal response to opioid treatment, structured discontinuation results in an improvement in pain compared to continuation of opioid treatment. Optimal Responders: In subjects with chronic pain on high-dose opioid therapy for at least 1 year who have an optimal response to opioid treatment, structured discontinuation of opioid treatment results in worsening of pain compared to continuation of opioid treatment. Separate analyses will be conducted for Suboptimal Responders and Optimal Responders, at the 2-sided 0.05 alpha level for each of the 2 primary hypotheses, since these are considered 2 different study populations. ***Sample Size*** The primary endpoint is the change from baseline to Week 12 (mean Average PI score over the 1 week prior to the Week 12 visit) in 0-10 NRS Average PI score comparing the opioid discontinuation group to the opioid continuation group. To detect a between-group difference of 0.8 points, assuming a standard deviation of 2.5, 5% significance level, and 90% power, 205 randomized subjects per arm (410 total randomized) for each Responder type will be needed (820 total). Assuming a 3:1 screen failure rate, approximately 3280 subjects will need to be screened. ***Statistical Analyses*** A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP). All statistical comparisons will be 2-sided at the 0.05 alpha level. There will be no adjustments for multiplicity. Definition of Baseline: For Suboptimal Responders, the mean of the Average PI scores over the 7-day Baseline Period will count as the subject's baseline Average PI score for statistical analysis. Similarly, the mean of the Worst PI scores over the 7-day Baseline Period will count as the subject's baseline Worst PI score for statistical analysis. For all other assessments, the last non-missing observation prior to the first dose in the Blinded Structured Opioid Discontinuation Period will be used as the baseline observation.

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Protocol Number	2065-5
	For Optimal Responders, the mean Average PI score including the Average PI scores during the Titration Period that meet the qualification criteria (Average PI score ≤4 for 3 consecutive non-missing values) plus any scores between the final qualification day and the Randomization Visit will count as the subject's baseline Average PI score for statistical analysis. Similarly, the mean Worst PI score including the 3 qualification days (as defined above) during the Titration Period plus any days between the qualifications days and the Randomization Visit will count as the subject's baseline Worst PI score for statistical analysis. For all other assessments, the last non-missing observation prior to the first dose in the Blinded Structured Opioid Discontinuation Period will be used as the baseline observation. Subject Populations: All populations will be defined for Suboptimal Responders and Optimal Responders separately. Safety Population: Different Safety Populations will be defined to summarize data pre- and post-randomization. • For Suboptimal Responders, the Safety Population Pre-Randomization will include all subjects who were enrolled in the study and were switched to the standardized regimen (ie, who enter the Run-in Period) and took at least 1 dose of study drug. • For Optimal Responders, – The Safety Population Pre-Randomization (Observation Period) will include all Optimal Responder subjects who entered the Observation Period. – The Safety Population Pre-Randomization (Taper Period) will include all Optimal Responder subjects who were enrolled in the study and took at least 1 dose of study medication during the Taper Period. – The Safety Population Pre-Randomization (Titration Period) will include all subjects who were enrolled in the study and took at least 1 dose of study medication during the Titration Period (ie, who enter the Open-label Titration Period. For both Suboptimal Responders and Optimal Responders, the Safety Population Post-Randomization will include all subjects who were randomized and received at least one dose of double-blind treatment. Safety will be analyzed separately for these populations. Subjects who are randomized to one treatment group but mistakenly assigned the medication kit of the other treatment group will be reported "as treated". ITT Population: The ITT Population will include all subjects who were randomized and received at least one dose of study drug after randomization. All efficacy analyses will be performed using this population. Subjects will be reported in the treatment group to which they were randomly assigned. Per-protocol Population: The Per-Protocol Population is a subset of the ITT population, excluding subjects with protocol deviations that may have an impact on the results of the primary efficacy analyses. An additional analysis of the primary efficacy endpoint will be performed using this population.

Name of Sponsor/Company The Opioid Post-Marketing Requirement Consortium (OPC)	**Name of Drug/Device** Morphine sulfate extended-release, oxycodone extended-release, or oxymorphone extended-release
Protocol Number	2065-5

The number of subjects included in each study population will be summarized by treatment group. Demographic characteristics, including sex, age, age group, race, height, and weight, will be summarized by treatment group using descriptive statistics.

The analysis of the primary endpoint will be in two stages. First, multiple imputation will be used for missing data based on the reason for missing data. Missing data occurring between observed data points will be imputed using Markov Chain Monte Carlo methods to create monotone missing data patterns. For missing data caused by discontinuation due to Adverse Events, data will be imputed using

- For Suboptimal Responders, the subject's baseline Average PI score (with added variability based on the variance of the data of the corresponding timepoint of missing data).
- For Optimal Responders, the subject's mean Average PI score at the end of the Taper Period (with added variability based on the variance of the data of the corresponding timepoint of missing data). This score will be the first 3 days of the mean Average PI score used to qualify the subject for entry into the Titration Period (i.e., where the mean Average PI score is >5 over ≥3 consecutive days, where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI score over the 7-day Observation Period).

For missing data caused by discontinuation due to Lack of Efficacy, data will be imputed using the subject's last non-missing weekly mean Average PI score. For missing data caused by any other reason, data will be imputed using multiple imputation with a regression model for prior weekly Average PI scores and treatment group, and utilizing the subject's observed pain scores in the regression model. Ten imputation datasets will be used for this multiple imputation procedure.

Second, the multiple datasets will be analyzed using mixed model repeated measures (MMRM), and the individual imputation dataset results will be combined using standard methods. The MMRM analysis will include the fixed effects of treatment group, Index ER opioid (morphine, oxycodone, or oxymorphone) group, baseline NRS Average PI score, Week, and interaction between treatment group and Week as factors. Data up to Week 12 will be included in this analysis. The Restricted Maximum Likelihood estimation approach will be used, and the default covariance structure will be unstructured. Estimates of the primary endpoint will be shown by treatment group, and for the difference between groups (structured discontinuation treatment group compared to continuation treatment group), together with 95% confidence interval and p-value for the difference.

Safety Analyses:

Safety variables will include AEs, abuse-related events, laboratory parameters, vital signs, and physical examinations. For the Suboptimal Responders, each safety parameter will be assessed separately for the Safety Population Pre-Randomization and Post-Randomization, as appropriate. Likewise for the Optimal Responders, each safety parameter will be assessed separately for the Safety Population Pre-Randomization (Observation Period), the Safety Population Pre-Randomization (Taper Period), and the Safety Population Pre-Randomization (Titration Period), as well as the Safety Population Post-Randomization. Other safety parameters analyzed will be possible

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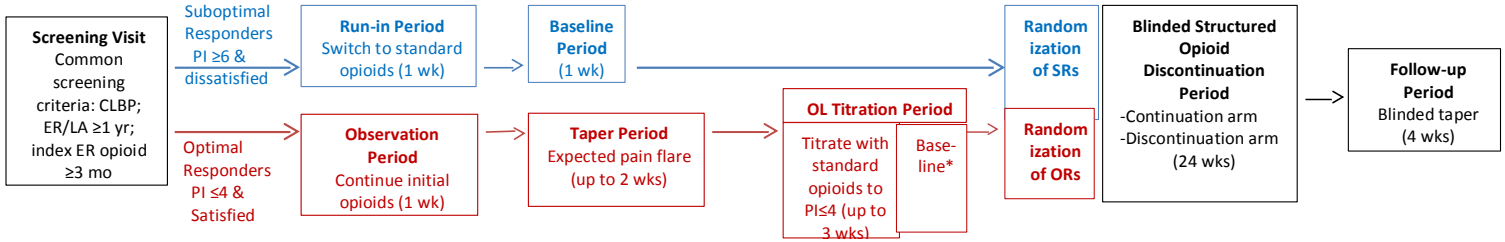
Protocol Number	2065-5	
	opioid withdrawal effects (summarized descriptively with COWS and SOWS scores), C-SSRS, and UDT.	

5. STUDY DESIGN AND SCHEDULE OF EVENTS

Figure 1: Study Design



wk=week, mo=month, SR=Suboptimal Responder; OR=Optimal Responder.

ER/LA requirement can be satisfied by use of immediate-release opioid at least 4 times a day for at least 1 year

* Baseline PI scores=mean Average PI score including the Average PI scores during the Titration Period that meet the qualification criteria (Average PI score ≤5 for 3 consecutive non-missing values) plus any scores between the final qualification day and the Randomization Visit.

Note: In the tables below, blue shading denotes periods of the study that are identical for Optimal and Suboptimal Responders.

Table 2: Schedule of Procedures for Suboptimal Responders

Period	Screening		Run-In Period (1 week)		Baseline Period (1 week)	Random-ization Visit	Blinded Structured Opioid Discontinuation Period[15] (24 weeks)									Follow-Up Period (4 weeks)	
Week			-2 to -1	-1	-1 to 0	0	1	2	4	6	8	12	16	20	24	26	28
Month						0		0.5	1	1.5	2	3	4	5	6	6.5	7
Visit Name[1]	Screening Visits[2]		--	SR1 Tolerabil-ity Visit	--	SR2	BDP 1	BDP 2	BDP 3	BDP 4	BDP 5	BDP 6	BDP 7	BDP 8	BDP 9	FUV1	FUV2
Informed consent	X																
Demographics	X																
Medical history	X																
Physical exam[3]	X											X			X		X
Vital signs[4]	X			X		X	X	X	X	X	X	X	X	X	X	X	X
ECG	X																
Clinical laboratory	X											X			X		
Pregnancy test[5]	X					X											X
Quebec Task Force Classification for Spinal Disorders	X																
Daily 24-hr Average and Worst PI score in past 24 hours on NRS [6]	X		←----------X----------→			X	←----------X----------→										
RMDQ	X					X						X			X		
Daily administration of ER and IR opioids (phone)	X[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Check entry or continuation criteria[8]	X	X		X		X											
Dispense Study Drugs[9]		X		X		X	X	X	X	X	X	X	X	X	X	X	
Collect Study Drugs & Drug Accountability[9]				X		X	X	X	X	X	X	X	X	X	X	X	X
BPI-SF	X					X						X			X		
Online Patient Support Program		Access Granted	←----------Encourage use of online patient support program----------→														
Regional Pain Scale						X						X			X		
PQAS						X						X			X		
EQ-5D-5L						X						X			X		
C-SSRS[10]	X									X					X		
PHQ-8	X											X			X		
MOS Sleep Scale						X						X			X		
DSST						X						X			X		

Table 2: Schedule of Procedures for Suboptimal Responders (Continued)

Period	Screening		Run-In Period (1 week)		Baseline Period (1 week)	Random-ization Visit	Blinded Structured Opioid Discontinuation Period[15] (24 weeks)									Follow-Up Period (4 weeks)	
Week			-2 to -1	-1	-1 to 0	0	1	2	4	6	8	12	16	20	24	26	28
Month						0		0.5	1	1.5	2	3	4	5	6	6.5	7
Visit Name[1]	Screening Visits[2]		--	SR1 Tolerabil-ity Visit	--	SR2	BDP 1	BDP 2	BDP 3	BDP 4	BDP 5	BDP 6	BDP 7	BDP 8	BDP 9	FUV1	FUV2
QST for OIH (for subjects enrolled at participating sub-study sites)						X						X			X		
Endocrine laboratory tests and sexual function questionnaire[11]	X											X			X		
Abuse-related events			←----------			----------X----------									----------→		
Opioid withdrawal (SOWS)						X		X	X	X						X	
Opioid withdrawal (COWS)						X		X	X							X	
PGIC												X			X		
UDT[12]	X								X			X			X		
Work productivity (WPAI)						X						X			X		
AEs[13]		X	←----------			---------- X ----------									----------→		
Telephone Calls[14]			←----------			---------- X ----------									----------→		
Prior/concomitant medications	←----------					---------- X ----------									----------→	X	X

1. Visit windows are ±3 days until BDP6, and ±5 days thereafter.
2. Screening procedures will be performed over 2 visits no more than 21 days apart.
3. Full physical exam at Screening and brief physical exam afterwards.
4. At Screening: Height, weight, BMI, pulse rate, respiratory rate, and blood pressure. At subsequent visit: pulse rate, respiratory rate and blood pressure only. If BMI >40, complete STOPBang Questionnaire and record in source documents. Subject cannot continue if apnea risk is high.
5. Serum pregnancy test at Screening and urine pregnancy test at randomization and final visit.
6. Captured once daily by phone at bedtime except at screening when captured in the office.
7. Daily dose of opioid and rescue medications at screening will be taken from medical records or medical history.
8. At Tolerability Visit (SR1): Subjects who did not tolerate the standardized regimen will be discontinued. At Randomization Visit: Subjects will be included if they have an Average PI score ≥6 on 0-10 NRS over the Baseline Period (with a minimum compliance of 4 out of 7 daily PI scores), not have an Average PI score each day of the 7-day Baseline Period equal to 10/10 and be dissatisfied with their pain and physical function.
9. Three (3) drugs will be dispensed, collected, and counted: ER opioids, IR opioids, and acetaminophen.
10. C-SSRS "Lifetime" will be done at Screening and the C-SSRS "Since Last Visit" will be done at 6 weeks and 24 weeks after randomization.
11. Blood for endocrine function tests will be drawn at Screening and sent to lab but only tested on Randomized subjects. Sexual function questionnaires will be administered when endocrine function tests are drawn.
12. Quantitative UDT for illicit drugs, non-prescribed controlled substances (opioid and non-opioid), and alcohol. To prevent unblinding, after randomization, results for the index opioid and its metabolites will not be provided to the investigator.
13. Only serious AEs will be collected in the eCRF during Screening.
14. Phone call every week of the study where a visit is not conducted to check for wellbeing, study drug compliance and safety issues. Changes in medications and AEs obtained during phone calls will be captured in the IRT or eCRF as appropriate. All other information will be captured in source documents.

15. The Early Discontinuation Assessment Tool will be administered to any subject who discontinues during the BDP.
BDP=Blinded Discontinuation Period; FUV=Follow-up Visit

Table 3: Schedule of Procedures for Optimal Responders

Period	Screen-ing		Observation Period (1 week)		Taper Period (up to 2 weeks)		OL Titration Period (up to 3 weeks)[1]	Random-ization Visit	Blinded Structured Opioid Discontinuation Period[16] (24 weeks)									Follow-Up Period (4 weeks)	
Week			-6 to -5	-5	-5 to -3	-3	-3 to 0	0	1	2	4	6	8	12	16	20	24	26	28
Month								0		0.5	1	1.5	2	3	4	5	6	6.5	7
Visit Name[2]	Screen-ing Visits[3]		--	OR1	OR2 (wk -4)	OR3	Telephone or office (OR3.1 – OR3.6) visits every 4 days	OR4	BDP 1	BDP 2	BDP 3	BDP 4	BDP 5	BDP 6	BDP 7	BDP 8	BDP 9	FUV1	FUV2
Informed consent	X																		
Demographics	X																		
Medical history	X																		
Physical exam[4]	X													X			X		X
Vital signs[5]	X			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
ECG	X																		
Clinical laboratory	X													X			X		
Pregnancy test[6]	X							X											X
Quebec Task Force Classification for Spinal Disorders	X																		
Daily 24-hr Average and Worst PI score in past 24 hours on NRS [7]	X		←-----X-----→		←-----X-----→		←---X---→	X	←----------X----------→										
RMDQ	X							X						X			X		
Daily dose or administration of ER and IR opioids and rescue meds taken (phone)	X[8]		←-----X[8]-----→		←-----X[8]-----→		←---X[8]---→	X[8]	←----------X[8]----------→									X[8]	X[8]
Check entry or continuation criteria	X	X		X[9]	X[9]	X[9]		X[9]											

Table 3: Schedule of Procedures for Optimal Responders (Continued)

Period	Screen-ing		Observation Period (1 week)		Taper Period (up to 2 weeks)		OL Titration Period (up to 3 weeks)[1]	Random-ization Visit	Blinded Structured Opioid Discontinuation Period[16] (24 weeks)									Follow-Up Period (4 weeks)	
Week			-6 to -5	-5	-5 to -3	-3	-3 to 0	0	1	2	4	6	8	12	16	20	24	26	28
Month								0		0.5	1	1.5	2	3	4	5	6	6.5	7
Visit Name[2]	Screen-ing Visits[3]		--	OR1	OR2 (wk -4)	OR3	Telephone or office (OR3.1 – OR3.6) visits every 4 days	OR4	BDP 1	BDP 2	BDP 3	BDP 4	BDP 5	BDP 6	BDP 7	BDP 8	BDP 9	FUV1	FUV2
Dispense Study Drugs[10]				X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Collect Study Drug & Drug Accountability[10]				X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
BPI-SF	X							X						X			X		
Online Patient Support Program		Access Granted			←----------Encourage use of online patient support program----------→														
Regional Pain Scale								X						X			X		
PQAS								X						X			X		
EQ-5D-5L								X						X			X		
C-SSRS[11]	X											X					X		
PHQ-8	X													X			X		
MOS Sleep Scale								X						X			X		
DSST								X						X			X		
QST for OIH (for subjects enrolled at participating sub-study sites)								X						X			X		
Endocrine laboratory tests and sexual function questionnarie[12]	X													X			X		
Abuse-related events			←---------- X ----------→																

Table 3: Schedule of Procedures for Optimal Responders (Continued)

Period	Screen-ing		Observation Period (1 week)		Taper Period (up to 2 weeks)		OL Titration Period (up to 3 weeks)[1]	Random-ization Visit	Blinded Structured Opioid Discontinuation Period[16] (24 weeks)									Follow-Up Period (4 weeks)	
Week			-6 to -5	-5	-5 to -3	-3	-3 to 0	0	1	2	4	6	8	12	16	20	24	26	28
Month								0		0.5	1	1.5	2	3	4	5	6	6.5	7
Visit Name[2]	Screen-ing Visits[3]		--	OR1	OR2 (wk -4)	OR3	Telephone or office (OR3.1 – OR3.6) visits every 4 days	OR4	BDP 1	BDP 2	BDP 3	BDP 4	BDP 5	BDP 6	BDP 7	BDP 8	BDP 9	FUV1	FUV2
Opioid withdrawal (SOWS)								X		X	X	X						X	
Opioid withdrawal (COWS)								X		X	X							X	
PGIC														X			X		
UDT[13]	X										X			X			X		
Work productivity (WPAI)								X						X			X		
AEs[14]		X	←----------					X											----------→
Telephone Calls[15]			←----------					X											----------→
Prior/concomitant medications	←----------							X										X	X ----------→

1 If the dose of the index ER opioid needs to be titrated above the baseline dose, the Titration Period may be extended by 1 additional week (+3 days).
2. Visit windows are ±3 days until BDP6, and ±5 days thereafter.
3. Screening procedures will be performed over 2 visits no more than 21 days apart.
4. Full physical exam at Screening and brief physical exam afterwards.
5. At Screening: Height, weight, BMI, pulse rate, respiratory rate, and blood pressure. At subsequent visit: pulse rate, respiratory rate, and blood pressure only. If BMI >40, complete STOPBang Questionnaire and record in source documents. Subject cannot continue if apnea risk is high.
6. Serum pregnancy test at Screening and urine pregnancy test at randomization and final visit.
7. Captured once daily by phone at bedtime except at Screening when captured in the office.
8. Daily dose of opioid and rescue medications at screening will be taken from medical records or medical history. Continuation of daily dose of opioid and rescue medications during the Observation Period will be confirmed by phone. Subsequently, confirmation of daily administration of ER and IR opioid study medications will be obtained by phone.
9. At end of Observation Period: Subjects must have had an index ER opioid medication use of ≥120 mg and ≤540 mg morphine equivalents/day (see table in protocol) on average and have had 80% to 120% compliance over the 1-week Observation Period; (ii) have a mean Average PI score over the 1 week of the period ≤5 (with a minimum compliance of 4 out of 7 daily PI scores); and (iii) still be satisfied with their pain and physical function. During or at the end of the Taper Period: Subjects must have a mean Average PI score >5 over ≥3 consecutive scores (non-missing values), where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI score over the 7-day Observation Period. Note that if these criteria are satisfied at Visit OR2, subject may skip OR2 and advance directly to Visit OR3. At the end of Titration Period: Subjects must have completed their titration and have achieved a mean Average PI score over at least 3 consecutive scores (non-missing values) ≤5 with acceptable side effects and a minimum dose of ≥120 mg and ≤540 mg morphine equivalents/day to continue on study.

10. The non-blinded ER opioid taper dose will be dispensed at OR1 and OR2; Open-label ER opioids, IR opioids, and acetaminophen will be dispensed starting at OR3 (for titration in the Titration Period); Double-blind ER opioid and open-label IR opioid and acetaminophen will be dispensed at OR4. Collection and counting of study medication will be done at all visits except OR1.
11. C-SSRS "Lifetime" will be done at Screening and the C-SSRS "Since Last Visit" will be done at 6 weeks and 24 weeks after randomization.
12. Blood for endocrine function tests will be drawn at Screening and sent to the lab but tested only on randomized subjects. Sexual function questionnaires will be administered when endocrine function tests are drawn.
13. Quantitative UDT for illicit drugs, non-prescribed controlled substances, and alcohol. To prevent unblinding, after randomization, results will not be provided to the investigator for the index opioid and its metabolites.
14. Only serious AEs will be collected in the eCRF during Screening.
15. Phone call every week of the study where a visit is not conducted to check for wellbeing, study medication compliance, and safety issues. Changes in medication and AEs obtained during phone calls will be captured in the IRT or eCRF as appropriate. All other information will be captured in source documents.
16. The Early Discontinuation Assessment Tool will be administered to any subject who discontinues during the BDP.

BDP=Blinded Discontinuation Period; FUV=Follow-up Visit

6. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

7. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation	Explanation
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANCOVA	Analysis of covariance
BMI	Body mass index
BPI-SF	Brief Pain Inventory- Short Form
CFR	Code of Federal Regulations
CLBP	Chronic low back pain
CMH	Cochran-Mantel-Haenszel (test)
COWS	Clinical Opioid Withdrawal Scale
CR	Controlled release
C-SSRS	Columbia-Suicide Severity Rating Scale
DHEAS	Dehydroepiandrosterone sulfate
DHHS	Department of Health and Human Services
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSST	Digit Symbol Substitution Test
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EQ-5D-5L	EuroQOL 5 dimensions (5 levels of response) instrument
ER	Extended release
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
IB	Investigator Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGF-1	Insulin-like growth factor-1
IR	Immediate release

Abbreviation	Explanation
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-Treat
LA	Long acting
LAR	Legally authorized representative
LH	Luteinizing hormone
LOCF	Last Observation Carried Forward
MADDERS	Misuse Abuse Diversion Drug Event Reporting System
MAO	Monoamine oxidase
mmHg	Millimeter of mercury
MMRM	Mixed model repeated measures
MSER	Morphine sulfate ER
MSIR	Morphine sulfate IR
NDA	New Drug Application
NRS	Numerical rating scale
OCER	Oxycodone ER
OCIR	Oxycodone IR
OIH	Opioid induced hyperalgesia
OMER	Oxymorphone ER
OMIR	Oxymorphone IR
OPC	Opioid Post-Marketing Requirement Consortium
OR	Optimal Responders
PCS	Potentially clinically significant
PGIC	Patient Global Impression of Change
PHQ-8	Patient Health Questionnaire-8
PI	Pain Intensity
PMR	Post-Marketing Requirement
PQAS	Pain Quality Assessment Scale
PRN	Pro re nata (as needed)
QST	Quantitative sensory testing
RMDQ	Roland-Morris Disability Questionnaire
SAE	Serious adverse event
SAP	Statistical Analysis Plan

Abbreviation	Explanation
SOWS	Subjective Opiate Withdrawal Scale
SR	Suboptimal Responders
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
UDT	Urine drug testing
URL	Uniform resource locator
WPAI	Work Productivity and Activity Impairment (questionnaire)

8. BACKGROUND AND RATIONALE

On September 10, 2013, U.S. Food and Drug Administration (FDA) announced class-wide safety labeling changes and new postmarketing study requirements for all extended-release and long-acting (ER/LA) opioid analgesics intended to treat pain (Department of Health and Human Services [DHHS]/FDA website).(1) As part of this announcement, the FDA is requiring approved New Drug Application (NDA) application holders for ER/LA opioid analgesics to conduct new postmarketing studies to "further assess the known serious risks of misuse, abuse, increased sensitivity to pain (hyperalgesia), addiction, overdose, and death". One of these requirements (2065-5) calls for approved ER/LA opioid analgesic NDA application holders to "Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain" (FDA announcement). The requirement "strongly encourages you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics" and requests that such studies "include an assessment of risk relative to efficacy".

The clinical syndrome of poor response to high-dose long-term opioid therapy is not well characterized in the medical literature, but recognized by the clinical pain management community. Characteristics of these patients include, in addition to the use of high doses of opioids for extended periods of time, persistent severe pain intensity (PI) ratings, poor physical, psychological, and social function, frequent employment difficulties, and aberrant drug-taking behaviors that may or may not be sufficient to meet criteria for an addiction disorder. Patients often insist that despite their poor clinical status and the lack of an evident response to opioids that continued opioid treatment is essential. A traditional treatment for such patients is discontinuation of opioid therapy, in which patients have their opioid therapy gradually tapered off, in the context of psychological and physical rehabilitative support, often in a structured inpatient or outpatient program. Long-term clinical success has been noted in uncontrolled and unblinded observational studies, but the efficacy of removal from opioid therapy for a well-defined cohort of "Suboptimal Opioid Responders" (designated as Suboptimal Responders in this protocol) has never been evaluated in a randomized, double-blind, controlled clinical trial.

One proposed, but as yet unproven, explanation for the phenomenon of suboptimal response to high-dose opioid therapy is opioid-induced hyperalgesia (OIH). According to this hypothesis, some patients on long-term opioid therapy for chronic pain develop paradoxical hypersensitivity to pain caused by the very opioid treatment intended to reduce their pain, resulting in increasing doses, increasing pain intensity, increased sensitivity to painful stimuli (hyperalgesia), and according to many descriptions, spread of pain beyond the initially painful area. Under this hypothesis, removal of opioid therapy would result in improvement of experimental pain sensitivity, improvement in pain intensity, and potentially decreased spread of pain compared to patients in whom opioid therapy was continued. In addition, it would be expected that Suboptimal Responders to opioid therapy have greater experimental pain sensitivity and perhaps greater pain spread than Optimal Responders (patients who require high doses of opioid therapy but have good pain control) to opioid therapy (who presumably do not have OIH). Finally, it would be expected that in contrast to Suboptimal Responders, Optimal Responders to opioid therapy will worsen when their effective analgesics have been withdrawn, as with any other effective analgesic.

From a clinical perspective, clinicians need to understand not only whether OIH underlies suboptimal responses to opioids in general, but how to identify, among patients who are responding poorly to opioids, which patients will improve after withdrawal of opioids. Therefore it is important to attempt to identify predictors of benefit from withdrawal of opioids among Suboptimal Responders.

The overarching purpose of this research program is to better characterize the contribution of OIH to suboptimal responses to opioid therapy. This goal will be approached in several different ways. Among a cohort of Suboptimal Responders to opioid therapy, the objective will be to evaluate the effect of structured discontinuation versus continuation of long-term high dose opioid treatment on pain intensity, pain spread, and sensitivity to experimental pain. Predictors of a beneficial response to opioid discontinuation will be examined. The impact of structured opioid discontinuation (vs. continuation) among the Suboptimal Responders will be indirectly compared to the impact of structured opioid discontinuation (vs. continuation) among a cohort of Optimal Responders to opioid therapy in order to fully inform the objectives of the Post-Marketing Requirement. Worsening of pain upon discontinuation of opioid therapy in the Optimal Responder group will confirm and extend previous observations of the efficacy of long-term opioid therapy. Baseline characteristics of Suboptimal and Optimal Responders will be compared, particularly with regard to experimental pain sensitivity.

9. OBJECTIVES AND HYPOTHESIS

9.1. Primary Objective

The primary objective is to evaluate the effect on PI of structured discontinuation of long-term opioid analgesic therapy compared to continuation of opioid therapy in Suboptimal and Optimal Responders to high-dose, long-term opioid analgesic therapy for treatment of chronic low back pain (CLBP).

9.2. Secondary Objectives

The secondary objective is to evaluate the effect on additional clinical outcomes measures of structured discontinuation of long-term opioid analgesic therapy compared to continuation of opioid therapy for CLBP in Suboptimal and Optimal Responders to high-dose, long-term opioid analgesic therapy at multiple time points.

9.3. Exploratory Objectives

The exploratory objectives are:

- To compare experimental pain sensitivity in the opioid discontinuation vs. continuation groups in both Suboptimal Responders and Optimal Responders (subjects in substudy)
- To determine subject characteristics that predict response to structured discontinuation of opioid therapy.
- To determine the effect of opioid discontinuation on certain endocrine function tests, sexual function, and the relationship of changes in PI and endocrine function to changes in male and female sexual function
- To determine the effect of opioid discontinuation on neurocognitive function.

9.4. Hypothesis

The study hypothesis in Suboptimal and Optimal Responders is as follows:

Suboptimal Responders: In subjects with CLBP on high-dose opioid therapy for at least 1 year who have a suboptimal response to opioid treatment, structured discontinuation results in an improvement in pain compared to continuation of opioid treatment.

Optimal Responders: In subjects with CLBP on high-dose opioid therapy for at least 1 year who have an optimal response to opioid treatment, structured discontinuation of opioid treatment results in worsening of pain compared to continuation of opioid treatment.

10. INVESTIGATIONAL PLAN

10.1. Study Design

This multicenter, randomized, double-blind, placebo-controlled study will consist of a common Screening Visit for all subjects, then different schedules for Optimal and Suboptimal Responders, followed by a common schedule for the Blinded Structured Opioid Discontinuation Period and Follow-up Period, as illustrated in Figure 1. The schedule of procedures for Suboptimal and Optimal Responders is shown in Table 2 and Table 3, respectively.

As a convention, whenever there is a requirement for the mean Average PI score to meet a certain criterion, the mean of the Average PI scores will be calculated to 1 decimal place prior to applying the qualification criterion.

10.1.1. Screening

(Note: Screening procedures will be performed over 2 visits no more than 21 days apart.)

At the Screening Visit, a broad range of patients on long-term opioid analgesic therapy for CLBP will be evaluated for entry into the study based on medical history, physical examination, clinical laboratory testing, vital signs, electrocardiogram (ECG), PI, urine drug testing (UDT), and pregnancy test. Subjects will be admitted into the study if they have non-radicular CLBP which can include Quebec Task Force Classification of Spinal Disorders Classes 1, proximal radicular (above the knee) pain of 2, 9.2, and 10, for more than 12-months duration; have been taking extended-release or long-acting opioids (or doses of immediate-release opioids at least 4 times a day) for at least 12 months for their CLBP; have been taking high doses as defined in the table below of one of the following "index ER opioids": morphine sulfate extended-release (MSER), oxycodone extended-release (OCER), or oxymorphone extended-release (OMER) for at least 3 consecutive months prior to the Screening Visit. (Subjects may also be taking additional ER opioids and/or immediate-release (IR) opioids, but the dose of any opioids beyond the index ER opioid will not be taken into account in the minimum or maximum required ER opioid dose for enrollment). For subjects taking multiple high-dose opioids, the Investigator will review all opioid use prior to enrollment and determine if the subject is still an appropriate candidate for the study based on the total amount of opioid the subject is receiving.

	Daily Dose Range
Morphine sulfate ER	120-540 mg
Oxycodone ER	80-360 mg
Oxymorphone ER	40-180 mg

The goal will be to have a minimum representation of each index ER opioid (a minimum of ~20% of randomized subjects for each index ER opioid). Subjects taking asymmetric dosing of index ER opioids (i.e., a different dose in the morning and evening) will be allowed in the study as long as they meet the dose criterion for their index ER opioid indicated in the table above, and can be converted to symmetric twice-daily dosing.

Subjects taking acetaminophen (or any acetaminophen-containing product after review of concomitant medications) prior to entering the study will be directed to stop taking it from their personal supply and only take the study-provided acetaminophen after entering the study.

Subjects will be classified as Suboptimal Responders or Optimal Responders at the Screening Visit as per the following criteria: **Suboptimal Responder** = Subject whose daily Average PI score is ≥6 and who is dissatisfied with his/her pain and physical function; **Optimal Responder** = Subject whose daily Average PI score is ≤4 and who is satisfied with his/her pain and physical function. The study design then differs for the Suboptimal and Optimal Responder populations; *for Suboptimal Responders only, see Section 10.1.2; for Optimal Responders only, go to section 10.1.3.*

10.1.2. For Suboptimal Responders Only

The schedule of procedures for Suboptimal Responders is shown in Table 2. Visits specific for Suboptimal Responders are named SR1, SR2, etc. As a convention, whenever there is a requirement for the mean Average PI score to meet a certain criterion, the mean of the Average PI scores will be calculated to 1 decimal place prior to applying the qualification criterion.

Run-In Period (1 week). Subjects classified as Suboptimal Responders at the Screening Visit will enter the 1-week Run-in Period during which they will be required to discontinue all previously prescribed opioid medications for the remainder of the study and will receive a standardized regimen of study medication consisting of index ER opioid plus the matching IR opioid depending on the index ER opioid they were taking at screening (i.e., OCER [OxyContin®] plus OCIR PRN, MSER [MS Contin®] plus MSIR PRN, or OMER [Opana® ER] plus OMIR PRN). In the standardized regimen, the dose of the ER opioid will be similar to the dose of the index ER opioid taken at screening and will remain fixed throughout the period. (Note: Subjects who were taking asymmetric doses of the index ER opioid at screening will be placed on a symmetric dosage [same dose in the morning and evening] of the standardized regimen at this time).

The dose of the IR opioid will be limited to no more than twice daily PRN administration of OCIR 10 mg, MSIR 15 mg, or OMIR 5 mg, matching the index ER opioid each subject is receiving. The maximum dose of PRN IR opioid they are allowed per day will remain fixed. Subjects will also be provided acetaminophen as rescue medication (500 mg tablets, 1-2 tablets PRN every 4-6 hours not to exceed 6 tablets/day) and will be encouraged to take study-provided acetaminophen to manage their pain before they use the IR opioid (i.e., only take the IR opioid if the maximum dose of acetaminophen is not effective). Personal supplies of acetaminophen should no longer be used for the duration of the study. Subjects will be allowed to continue the non-opioid, non-acetaminophen-containing analgesics they had been taking before screening, but will not be able to change the dose except for study-provided acetaminophen as described above.

During the Run-In Period, subjects will record daily before bedtime by phone their PI scores and their use of ER and IR opioid study medication. Adverse events (AEs) will be assessed during this period. At the end of the 1-week Run-In Period, subjects will return to the clinic for the Tolerability Visit (Visit SR1) to determine whether they tolerated the standardized opioid regimen. Subjects who did not tolerate the standardized regimen will be discontinued; no dose adjustment of the ER medication will be permitted.

Baseline Period (1 week). Subjects will then enter a 1-week Baseline Period during which they will self-administer the standardized opioid regimen and record their PI scores (Average and Worst over past 24 hours) on a 0-10 numerical rating scale (NRS) daily before bed time by phone. Each subject's 7-day daily PI scores will be averaged and used as the subject's baseline PI scores (with a minimum compliance of 4 out of 7 daily PI scores).

At the ***Randomization Visit for Suboptimal Responders*** (Visit SR2), subjects will continue on study if they have (i) a mean Average PI score (mean of average) ≥6 on 0-10 NRS over the 1 week of the Baseline Period (with a minimum compliance of 4 out of 7 daily PI scores); (ii) compliance with their index ER opioid medication between 80-120%; (iii) and are still dissatisfied with their pain and physical function. Subject who had a baseline mean Average PI score of 10/10 (i.e., 10/10 score every day for the 1 week of the Baseline Period) will be discontinued.

The rest of the study will then be similar for both Suboptimal Responders and Optimal Responders (as described in section 10.1.4).

10.1.3. For Optimal Responders Only

The schedule of procedures for Optimal Responders is shown in Table 3. Visits specific for Optimal Responders are named OR1, OR2, etc.

Observation Period (1 week). Subjects meeting the common screening criteria at the end of the Screening Visit and classified as Optimal Responders at the Screening Visit will be sent home and told to continue their current medication (including non-index ER and IR opioid medications) for 1 week. (Note: Subjects who were taking asymmetric doses of the index ER opioid at screening will continue taking asymmetric doses of their ER opioids during this period.) During this period, opioid medication intake and PI scores (Average and Worst over past 24 hours on 0-10 NRS) will be captured daily before bedtime by phone. At the end of the period, subjects will return to the clinic (Visit OR1) and all opioid medication use and PI scores will be reviewed. Subjects will be confirmed as Optimal Responders and will be allowed to continue in the study if (i) their index ER opioid medication use was on average in the range shown in the table below and they had 80% to 120% compliance over the 1-week period; (ii) their mean Average PI score over the 1 week of the Observation Period was ≤5 (with a minimum compliance of 4 out of 7 daily PI scores); and (iii) they are still satisfied with their pain and physical function.

	Daily Dose Range
Morphine sulfate ER	120-540 mg
Oxycodone ER	80-360 mg
Oxymorphone ER	40-180 mg

Taper Period (up to 2 weeks). Subjects will be tapered with the same index ER opioid they were taking at screening (using study medication provided for the index ER opioid; ie, either OxyContin®, MS Contin®, or Opana® ER). (Note: Subjects who were taking asymmetric doses of index ER opioid at screening will be tapered with a symmetric dosage [same dose in the morning and evening] of the standardized regimen.) Tapering will start at Visit OR1. For up to 2 weeks (+ 3 days), subjects will self-administer a tapering dose of the standard index ER opioid matching the one they were taking and will record PI scores daily before bedtime by phone. No other ER opioid will be allowed; IR opioids will not be allowed either during this period, i.e. all previously prescribed opioid medications will be discontinued. At Visit OR2 (week -4), the subjects' overall status (opioid medication dose, PI score, vital signs, etc.) will be reviewed. If the minimum pain requirement has been met (see below) either before or at Visit OR2, the subject will immediately advance to Visit OR3 (skipping Visit OR2) and begin the Open-Label Titration Period. If the minimum pain requirement has not been met, the opioid taper will continue. By Visit OR3, subjects should be completely off of their opioid medication if they

have not already met the minimum pain requirement. Subjects with a mean Average PI score >5 over ≥3 consecutive PI scores (excluding missing values), where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI over the 7-day Observation Period, either off of the index ER opioid pain medication entirely or at a reduced dose, will be eligible to proceed to the Open-Label Titration Period. Subjects who do not meet these criteria will be discontinued from the study (see Study Discontinuation Procedures, section 12.1.6).

Open-Label Titration Period (up to 3 weeks). Subjects will be titrated with the same index ER opioid they were taking during the Taper Period (supplied as index ER opioid plus matching IR opioid; i.e., either OCER [OxyContin®] plus OCIR PRN, MSER [MS Contin®] plus MSIR PRN, or OMER [Opana® ER] plus OMIR PRN). The dose of the index ER opioid will be increased as frequently as every 4 days (during telephone or office [OR3.1 – OR3.6] visits) until the mean Average PI score over at least 3 consecutive pain scores is ≤5 in order to qualify for randomization. If the dose of the index ER opioid needs to be titrated above the baseline dose, the Titration Period may be extended 1 additional week (+3 days). The dose of the IR opioid will be limited to no more than twice daily PRN administration of OCIR 10 mg, MSIR 15 mg, or OMIR 5 mg, matching the index ER opioid each subject is receiving. The maximum dose of PRN IR opioid they are allowed per day will remain fixed. Subjects will also be provided acetaminophen as rescue medication (500 mg tablets, 1-2 tablets PRN every 4-6 hours not to exceed 6 tablets/day) and will be encouraged to take study-provided acetaminophen to manage their pain before they use the IR opioid (i.e., only take the IR opioid if the maximum dose of acetaminophen is not effective). Personal supplies of acetaminophen should no longer be used for the duration of the study.

Randomization Visit for Optimal Responders (Visit OR4). Subjects who have completed their titration, have achieved a mean Average PI score over 3 consecutive pain scores of ≤5 with satisfaction with their pain and physical function and acceptable side effects, and are taking a dose of index ER opioid shown in the table below will be allowed to continue on study.

	Daily Dose Range
Morphine sulfate ER	120-540 mg
Oxycodone ER	80-360 mg
Oxymorphone ER	40-180 mg

The rest of the study will then be similar for both Suboptimal Responders and Optimal Responders (continued below).

10.1.4. Continuing for both Suboptimal and Optimal Responders

Blinded Structured Opioid Discontinuation Period (24 weeks). At the Randomization Visit (Visit SR2 or OR4, Day 1), subjects meeting the criteria (described above for each population) to enter the Blinded Structured Opioid Discontinuation Period will then be randomized to either continue or discontinue ER opioid therapy, as follows.

For subjects whose index ER opioid is MSER, the groups will be:

- Morphine Group 1: MSER tablets + matching placebo tablets to maintain MSER dose, but appear as if tapering is occurring;

- Morphine Group 2: Placebo tablets to match MSER tablets + MSER tablets in decreasing dose to result in a tapering off of MSER.
- Both groups will be provided with rescue MSIR and acetaminophen.

For subjects whose index ER opioid is OCER, the groups will be:

- Oxycodone Group 1: OCER tablets + matching placebo tablets to maintain OCER dose, but appear as if tapering is occurring;
- Oxycodone Group 2: Placebo tablets to match OCER tablets + OCER tablets in decreasing dose to result in a tapering off of OCER.
- Both groups will be provided with rescue OCIR and acetaminophen.

For subjects whose index ER opioid is OMER, the groups will be:

- Oxymorphone Group 1: OMER tablets + matching placebo tablets to maintain OMER dose, but appear as if tapering is occurring;
- Oxymorphone Group 2: Placebo tablets to match OMER tablets + OMER tablets in decreasing dose to result in a tapering off of OMER.
- Both groups will be provided with rescue OMIR and acetaminophen.

Therefore, there will be a total of 4 groups in the Blinded Structured Opioid Discontinuation Period:

- Suboptimal Responders, continuation arm
- Suboptimal Responders, discontinuation arm
- Optimal Responders, continuation arm
- Optimal Responders, discontinuation arm

Randomization will be stratified by responder status (Optimal Responder; Suboptimal Responder) and baseline ER opioid (morphine, oxycodone, or oxymorphone); subject recruitment into the study will be adjusted to ensure at least 20% of subjects are on oxycodone, at least 20% on morphine, and at least 20% on oxymorphone in the Blinded Structured Opioid Discontinuation Period within each cohort (Optimal Responders and Suboptimal Responders). The goal is to taper subjects (in the discontinuation arms of both the Suboptimal Responder and Optimal Responder groups) off their ER opioid treatment onto placebo over approximately 3-4 weeks depending on the baseline dose of index ER opioid. Subjects in the continuation arms will be on a fixed-regimen of ER opioid (i.e., the ER opioid dose will not change); note that the doses will vary across subjects based on their individualized standardized dose. Subjects will also be provided acetaminophen as rescue medication (500 mg tablets, 1-2 tablets PRN every 4-6 hours not to exceed 6 tablets/day) and will be encouraged to take acetaminophen to manage their pain, before they use IR opioid.

After randomization, the dose of the IR opioid for both Suboptimal Responders and Optimal Responders whether randomized to discontinuation or continuation will remain limited to no more than twice daily PRN administration of OCIR 10 mg, MSIR 15 mg, or OMIR 5 mg, matching the index ER opioid each subject is receiving. Subjects will return to the clinic at weeks 1, 2, 4, 6, 8, 12, 16, 20, and 24 (Visits BDP1 through BDP9). A series of assessments will be performed at each visit.

Follow-Up Period (4 weeks). Subjects completing the Blinded Structured Opioid Discontinuation Period will be required to advance to and complete the Follow-up Period. However, those subjects who

discontinue from the Blinded Structured Opioid Discontinuation Period prior to week 12 will complete Week 12 study procedures and those subjects who discontinue during weeks 13-23 will complete Week 24 study procedures. Subjects will self-administer a blinded tapering dose during the Follow-up Period: Placebo taper for subjects who were in the discontinuation arm and active drug taper for subjects who were in the continuation arm. Subjects will be followed-up during 2 clinic visits (at Weeks 26 [FUV1] and 28 [FUV2], and 2 phone calls (at Weeks 25 and 27). At the end of the Follow-up Period, subjects will be transitioned back to their primary care physician. Subjects will be instructed not to take any ER opioid medication until they have consulted with their primary care physician as they no longer will be opioid-tolerant at this time.

10.2. Selection of Doses

Selection of subjects based on the index ER opioid dose: Subjects will be selected on the basis of having taken either OCER, MSER, or OMER with a total daily dose as shown in the table below for ≥3 consecutive months for their CLBP. These doses have been selected because they represent high doses of opioids, which is one of the main criteria for selecting subjects for this study.

	Daily Dose Range
Morphine sulfate ER	120-540mg
Oxycodone ER	80-360mg
Oxymorphone ER	40-180mg

Standardized regimen: Prior to the Blinded Structured Opioid Discontinuation Period, subjects' opioid medication regimen will be standardized to study medication supplied as OCER (OxyContin®) plus OCIR PRN, or MSER (MS Contin®) plus MSIR PRN, or OMER (Opana® ER) plus OMIR PRN depending on which index ER opioid they were taking at screening. The reason for switching subjects to a standardized drug is to have more homogeneous treatment groups and reduce variability due to the use of different brands of products. The dose of the IR opioid will be limited to no more than twice daily PRN administration of OCIR 10 mg, MSIR 15 mg, or OMIR 5 mg, matching the index ER opioid each subject is receiving. (Note: Subjects who were taking asymmetric doses of the index ER opioid at screening will be placed on a symmetric dosage [same dose in the morning and evening] of the standardized regimen.) All subjects in the continuation arms will be on a fixed-regimen of ER opioid (i.e., the ER opioid dose will not change); note that the ER opioid doses will vary across subjects based on their individualized standardized dose.

Importantly, Suboptimal Responders will receive the standardized regimen *at a similar dose taken at screening* in order to maintain the high dose of opioids and the suboptimal response each subject has been screened for. No dose adjustments of the ER medication will be permitted during the Run-in Period. However, Suboptimal Responders will be discontinued from the study at the end of the Run-in Period if they have intolerable side effects.

For Optimal Responders, no dose adjustment of the ER medication will be permitted during the Observation Period. Dose adjustments (titration) will be made regularly in the Open-label Titration Period to return each subject to a mean Average PI score ≤4.

Rescue medication: Subjects will also be provided acetaminophen as rescue medication (500 mg tablets, 1-2 tablets PRN every 4-6 hours not to exceed 6 tablets/day) and will be encouraged to take acetaminophen to manage their pain before they use the IR opioid, (ie, only take the IR opioid if the maximum dose of acetaminophen is not effective).

10.3. Study Drug Administration

10.3.1. Study Medications

The study medications are FDA approved and will be provided by the Opioid Post-Marketing Requirement Consortium (OPC) as follows:

- OCER = OxyContin® (oxycodone hydrochloride ER tablets)
- MSER = MS Contin® (morphine sulfate ER tablets)
- OMER = Opana® ER (oxymorphone hydrochloride ER tablets)

Placebos for each of the abovementioned ER drugs will be manufactured by the respective manufacturer of the active ER medication and will be identical to the respective drugs in aspect, size, and color.

10.3.2. Study Prescribed Drugs

The following medications are commercially available and will be provided by the OPC in open-label fashion as study prescribed drugs:

- OCIR = Mallinckrodt brand of oxycodone IR tablets
- MSIR = West-Ward brand of morphine sulfate (IR tablets)
- OMIR = Opana® (Endo brand of oxymorphone hydrochloride IR tablets)
- Acetaminophen 500 mg tablets

10.3.3. Study Drug Administration and Dose

The standardized regimen in this study consists of: OCER (OxyContin®) plus OCIR PRN, or MSER (MS Contin®) plus MSIR PRN, or OMER (Opana® ER) plus OMIR PRN depending on which index ER opioid the subject was taking at screening. The dose of the IR opioid will be limited to no more than twice daily PRN administration of OCIR 10 mg, MSIR 15 mg, or OMIR 5 mg, matching the index ER opioid each subject is receiving.

For Suboptimal Responders, subjects will start the standardized regimen during the 1-week Run-in Period in an open-label fashion at a similar dose to the index ER opioid taken at screening. During the Baseline Period, subjects will continue to self-administer the standardized regimen at the same dose as in the Run-in Period (no dose adjustment will be permitted).

For Optimal Responders, subjects will start the standardized regimen during the 2 week Taper Period during which study medication will be reduced every 3 days until the PI score increases as specified. The standardized regimen will continue during the 3-week Open-label Titration Period. During the Titration Period, the dose of the ER opioid will be increased as frequently as every 4 days (during telephone or office visits) until the mean Average PI score for at least 3 consecutive pain scores is $\leq$4.

At the Randomization Visit, all eligible subjects will be randomized to one of the following groups:

For subjects whose ER opioid is morphine, the groups will be:

- Morphine Group 1: MSER tablets + matching placebo tablets to maintain MSER dose, but appear as if tapering is occurring;

- Morphine Group 2: Placebo tablets to match MSER tablets + MSER tablets in decreasing dose to result in a tapering off of MSER.

For subjects whose ER opioid is oxycodone, the groups will be:

- Oxycodone Group 1: OCER tablets + matching placebo tablets to maintain OCER dose, but appear as if tapering is occurring;
- Oxycodone Group 2: Placebo tablets to match OCER tablets + OCER tablets in decreasing dose to result in a tapering off of OCER.

For subjects whose ER opioid is oxymorphone, the groups will be:

- Oxymorphone Group 1: OMER tablets + matching placebo tablets to maintain OMER dose, but appear as if tapering is occurring;
- Oxymorphone Group 2: Placebo tablets to match OMER tablets + OMER tablets in decreasing dose to result in a tapering off of OMER.

Subjects in the continuation arms of both the Suboptimal Responder and Optimal Responder groups will be on a fixed-regimen of ER opioid (i.e., the ER opioid dose will not change).

Rescue medication: Subjects will also be provided acetaminophen as rescue medication (500 mg tablets, 1-2 tablets every 4-6 hours PRN, not to exceed 6 tablets/day) and will be encouraged to take acetaminophen to manage their pain before they use the IR opioid (ie, only take the IR opioid if the maximum dose of acetaminophen is not effective).

10.4. Discussion of Study Design, Including the Choice of Control Groups

For subjects on high-dose opioids possibly experiencing OIH, a traditional treatment is discontinuation of opioid therapy, in which subjects have their opioid therapy gradually tapered off in the structured context of psychological and physical rehabilitative support. Although the success of these programs has been noted in uncontrolled and unblinded observational studies, the efficacy of removal from opioid therapy for a well-defined cohort of "Suboptimal Opioid Responders" has never been evaluated in a randomized, double-blind, controlled clinical trial, which is the gold standard for the rigorous clinical evaluation of a treatment. Thus, this study uses a placebo-controlled, double-blind, parallel-arm study design to evaluate the effect of structured opioid discontinuation versus continuation of opioid therapy in Suboptimal Responders. A cohort of Optimal Responders is also included in this trial to determine the effect of continuation versus discontinuation of opioid therapy in Optimal Responders in order to fully inform the objectives of the Post-Marketing Requirement.

To this end, subjects on a standardized regimen of high-dose opioids will be randomized to (i) continue on high-dose opioid (continuation arm) or (ii) taper off their high-dose opioid (discontinuation arm) in a double-blind manner.

In order to maintain the blind in both the continuation and discontinuation arms, the groups have been designed as follows:

- Continuation arm: ER opioid tablets+ placebo tablets during tapering to maintain the blind
- Discontinuation arm: Matching placebo tablets for the ER opioid + ER opioid tablets only during the first 3-4 weeks after randomization

Opioid Post-Marketing Requirement (PMR) Consortium

(The ER opioid is either OCER, MSER, or OMER; the IR opioid is either OCIR, MSIR, or OMIR matching the ER opioid). IR opioid will only be available at low dosage for infrequent use to manage pain not manageable by PRN acetaminophen.

11. SELECTION AND WITHDRAWAL OF SUBJECTS

11.1. Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be enrolled in the study:

1. Be male or non-pregnant, non-lactating female aged 18 to 75 years, inclusive;
2. Have a clinical diagnosis of non-radicular CLBP (pain that occurs in an area with boundaries between the lowest rib and the crease of the buttocks) of Class 1 or proximal (above the knee) radicular pain of Class 2 of the Quebec Task Force Classification for Spinal Disorders (subjects with previous surgery or chronic pain syndrome, i.e., classes 9.2 or 10, will be allowed if their pain does not radiate or radiates only proximally) for a minimum of 12 months and

– For the Suboptimal Responder group, pain must have been present for at least several hours a day and have an Average PI score of 6-9 on an 11-point NRS (as measured on the NRS) within the past 24 hours of screening.

– For the Optimal Responder group, subjects must have an Average PI score of 1-4 on an 11-point NRS (as measured on the NRS) within the past 24 hours of screening;

3. Have been taking ER/LA opioids (or immediate release opioids (at least 4 times a day) for at least 12 months;
4. Have been taking one of the 3 index opioid drugs around-the-clock at a twice-a-day frequency for at least 3 consecutive months at total daily doses shown in the table below.

	Daily Dose Range
Morphine sulfate ER	120-540 mg
Oxycodone ER	80-360 mg
Oxymorphone ER	40-180 mg

5. Be considered, in the opinion of the Investigator, to be in generally good health other than CLBP at screening based upon the results of a medical history, physical examination, 12-lead ECG, and laboratory profile.
6. Speak, read, write, and understand English (to reduce heterogeneity of data), understand the consent form, and be able to effectively communicate with the study staff.
7. Have access to the Internet (to access the patient support program).
8. Voluntarily provide written informed consent.
9. Be willing and able to complete study procedures.

Entry Criteria to Determine Responder Status: Following successful determination of eligibility, subjects will be assessed against the following criteria to determine responder status at the Screening Visit:

- Subjects with an Average PI score ≤4 (as measured on the NRS) at Screening who are satisfied with their pain and physical function will be considered Optimal Responders;

- Subjects with an Average PI score ≥ 6 (as measured on the NRS) at Screening who are dissatisfied with their pain and physical function will be considered Suboptimal Responders;
- Subjects who do not fall into either category will be considered screen failures and discontinued from the study.

11.2. Subject Exclusion Criteria

Subjects who have any of the following will not be enrolled in the study:

1. Have any clinically significant condition that would, in the opinion of the Investigator, preclude study participation or interfere with the assessment of pain and other symptoms of CLBP or increase the risk of opioid-related AEs.
2. Have a primary diagnosis of fibromyalgia, complex regional pain syndrome, neurogenic claudication due to spinal stenosis, spinal cord compression, acute nerve root compression, severe or progressive lower extremity weakness or numbness, bowel or bladder dysfunction as a result of cauda equina compression, diabetic amyotrophy, meningitis, diskitis, back pain because of secondary infection or tumor, or pain caused by a confirmed or suspected neoplasm.
3. Have undergone a surgical procedure for back pain within 6 months prior to the Screening Visit.
4. Have had a nerve or plexus block, including epidural steroid injections or facet blocks, within 1 month prior to the Screening Visit or botulinum toxin injection in the lower back region within 3 months prior to screening.
5. Have a history of confirmed malignancy within past 2 years, with exception of basal cell or squamous cell carcinoma of the skin that has been successfully treated.
6. Have uncontrolled blood pressure, i.e., subject has a sitting systolic blood pressure >180 mm Hg or <90 mm Hg, or a sitting diastolic blood pressure >110 mmHg or <40 mm Hg at screening.
7. Have a body mass index (BMI) >45 kg/m^2. Anyone with a BMI > 40 but ≤ 45 will complete a screening tool (STOPBang Questionnaire) to rule out high risk of obstructive sleep apnea (Appendix W).
8. Have a clinically significant depression based on a score ≥20 on the Patient Health Questionnaire (PHQ-8).
9. Have suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the Columbia-Suicide Severity Rating (C-SSRS).
10. Have a previous history of suicidal behaviors in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS.
11. Have any lifetime history of serious or recurrent suicidal behavior. (Non-suicidal self-injurious behavior is not a trigger for a risk assessment unless in the Investigator's judgment it is indicated.)

12. Have clinically significant abnormality in clinical chemistry, hematology or urinalysis, including serum glutamic-oxaloacetic transaminase/aspartate aminotransferase (AST) or serum glutamic pyruvic transaminase/alanine aminotransferase (ALT) ≥3 times the upper limit of the reference range or a serum creatinine >2 mg/dL at screening.
13. Have severe enough psychiatric or substance abuse disorder to compromise the subject's safety or scientific integrity of the study.
14. Have on-going litigation associated with back pain or pending applications for workers compensation or disability issues or subjects who plan on filing litigation or claims within the next 12 months; subjects with settled past litigations will be allowed as will subjects who have been on workers compensation or disability claims for at least 3 months.
15. Have used a monoamine oxidase (MAO) inhibitor within 14 days prior to the start of study medication.
16. Are taking agonist-antagonists (pentazocine, butorphanol or nalbuphine), buprenorphine, methadone, barbiturates, or more than one type of benzodiazepine within 1 month prior to screening.
17. Have a positive UDT for illicit drugs (including marijuana), non-prescribed controlled substances, or alcohol at screening.
18. Have taken any investigational drug within 30 days prior to the Screening Visit or are currently enrolled in another investigational drug study.

11.3. Replacement Procedures

Subjects who discontinue from the study will not be replaced.

12. TREATMENT OF SUBJECTS

12.1. Study Visits

The Schedule of Procedures to be performed at each visit is shown in Tables 2 and 3. Provided below are further details where additional instruction about the assessments that will be performed is deemed to be needed. Visit windows are ±3 days until BDP6, and ±5 days thereafter. A phone call will be conducted every week of the study where a visit is not conducted to check for wellbeing, study drug compliance, and safety issues. Changes in medications and AEs obtained during phone calls will be captured in the electronic Case Report Form (eCRF). All other information will be captured in source documents.

Investigators are encouraged to perform the study procedures at each visit in the order listed. The general rationale for the order of the procedures is the following:

- First, patient-reported outcomes, from the most important as regards to the endpoint measured (e.g., BPI-SF) to the least important (e.g., the Work Productivity and Activity Impairment [WPAI]), ending with quality of life measures (EQ-5D-5L) so that the subject has an overall view of his/her status when completing general health questionnaires
- Second, performance tasks (e.g., Digit Symbol Substitution Test [DSST]) as they may lead to subject fatigue and interfere with capture of the primary data
- Third, standard procedures associated with subject safety (e.g., recording of AEs, vital signs, physical exam, etc.)
- Fourth, study drug accountability and compliance, which is part of the process of identifying potentially abuse-related events
- Fifth, characterization of any abuse-related AEs, as this may be emotionally laden and consume time
- Sixth, drug dispensing, which may not be done if abuse-related events are identified

12.1.1. Screening Visit (Same for Suboptimal and Optimal Responders)

Investigators will be expected to maintain screening information on all potential study subjects. This will include limited information about the potential subject and the dates and outcome of the screening process (i.e., informed consent, demography, subject enrollment status, reason for ineligibility, and AEs [SAEs will be recorded in the eCRF]). Investigators will provide information about the study to subjects who appear to meet the criteria for participation in the study.

Screening assessments will be carried out over 2 visits that are not greater than 21 days apart.

Screening Visit 1

Determine Eligibility

- Obtain informed consent;
- Assign the subject identification number which will consist of 7 digits. The first 3 digits represent the study site number followed by ##01, ##02, and so on.
- Collect demographic data

- Collect medical history
- Obtain confirmation of the subject's pre-study ER opioid regimen. Confirmation may be documentation of verbal confirmation of regimen from a referring clinician, reviewing referring physician medical records, checking medical records for subjects of the Investigator, or other appropriate methods.
- Collect vital signs (height, weight, BMI [calculated], pulse rate, respiratory rate, and blood pressure). Anyone with a BMI > 40 but ≤ 45 will complete a screening tool (STOPBang Questionnaire) to rule out high risk of obstructive sleep apnea.
- Perform a full physical examination
- Perform an ECG
- Classify the subject according to the Quebec Task Force Classification for Spinal Disorders
- Check prior and concomitant medications
- Determine daily dose of index ER opioid (from the concomitant medication log)
- Assess PI using 0-10 NRS by phone
- Administer BPI-SF
- Administer the PHQ-8
- Administer the C-SSRS "Lifetime"
- Check entry criteria based on abovementioned assessments. A subject who gives written informed consent and who satisfies these criteria is considered preliminarily eligible for entry into the study.

Determine Responder Status

Following successful preliminary determination of eligibility, subjects will be assessed against the following criteria to determine responder status:

- Subjects with an Average PI score ≤4 at Screening (as measured on the NRS) who are satisfied with their pain and physical function will be considered Optimal Responders
- Subjects with an Average PI score ≥6 at Screening (as measured on the NRS) who are dissatisfied with their pain and physical function will be considered Suboptimal Responders

Subjects who do not fall into either category will be considered screen failures and discontinued from the study. (For study discontinuation procedures, see section 12.1.6.) The remaining subjects will continue as Preliminarily Eligible.

For All Preliminarily Eligible Subjects

- Perform clinical laboratory testing
- Perform a serum pregnancy test for all women of child-bearing age
- Perform a quantitative UDT for illicit drugs, non-prescribed controlled substances, and alcohol

- Draw blood for future endocrine testing and send to lab (will be tested later only for randomized subjects). Administer sexual function questionnaire (See Appendix S).
- Administer the Roland-Morris Disability Questionnaire (RMDQ)

Screening Visit 2

For all Preliminarily Eligible Subjects

- Review results from clinical laboratory testing and pregnancy testing
- Review results from quantitative UDT

Subjects who do not meet the entry criteria for the protocol will be considered screen failures and discontinued from the study. (For study discontinuation procedures, see section 12.1.6.)

All other subjects will continue according to their responder status:

For Suboptimal Responders Only:

- Provide training to the subject on how to use the phone response system
- Introduce the subject to the Online Patient Support Program (see description in Appendix U). The purpose of this program is to support subject retention in the trial as well as compliance with study medication, and to provide pain management support during medication regimen changes and during medication tapering. Subjects will be provided with an URL (uniform resource locator). Participation is not required but will be encouraged by the clinic staff.
- Determine standardized opioid regimen (Refer to the Run-in, Baseline, and Blinded Structured Opioid Discontinuation schedule in Appendix B – Dosing Schedule)
- Dispense open-label standard ER opioid
- Dispense matching IR opioid medication
- Discontinue all other opioid medications
- Discontinue using personal supply of acetaminophen
- Dispense study-provided acetaminophen
- Record drug supplied

For Optimal Responders Only:

- Provide training to the subject on how to use the phone response system
- Introduce the subject to the Online Patient Support Program (see description in Appendix U). The purpose of this program is to support subject retention in the trial as well as compliance with study medication, and to provide pain management support during medication regimen changes and during medication tapering. Subjects will be provided with an URL (uniform resource locator). Participation is not required but will be encouraged by the clinic staff.

- Direct optimal responders to continue to take their opioid analgesic medication regimen which they were previously taking without any changes until the next visit

12.1.2. Suboptimal Responders Visits Only

Run-in Period (1 week, from Weeks -2 to -1)

During the Run-in Period, subjects will:

- Self-administer the open-label standardized regimen of ER opioid
- Before bedtime, record via phone the daily Average PI and Worst PI scores in the past 24 hours
- Before bedtime, record via phone the daily use of ER opioid and IR opioid
- Participate in the on-line Patient Support Program

Tolerability Visit = SR1 (at Week -1)

At the Tolerability Visit (SR1), the following will be conducted in-clinic:

- Collect vital signs (pulse rate, respiratory rate, and blood pressure only)
- Collect AEs
- Collect concomitant medication data
- Determine whether any abuse-related events have occurred during the Run-in Period
- Review the data recorded via phone for daily Average PI and Worst PI scores recorded by the subject since the last visit
- Review the data recorded via phone for the daily use of ER and IR opioids taken by the subject since the last visit
- Collect study drug
- Perform a pill count for drug accountability (ER opioid, IR opioid, and acetaminophen)
- Discontinue subjects who did not tolerate the standardized regimen – no dose adjustment of the regimen is permitted (For study discontinuation procedures, see section 12.1.6.)
- Dispense study drug (ER opioid, IR opioid, and acetaminophen) for the Baseline Period

Baseline Period (1 week, from Week -1 to 0)

During the Baseline Period, the subject will:

- Self-administer the open-label standardized regimen of ER opioid
- Before bedtime, record via the phone the daily Average PI and Worst PI scores in the past 24 hours
- Before bedtime, record via the phone the daily use of ER opioid and IR opioid
- Participate in the on-line Patient Support Program

Randomization Visit = SR2 (Day 1)

At the Randomization Visit (SR2), the following will be conducted during a clinic visit:

- Collect vital signs (pulse rate, respiratory rate, and blood pressure only)
- Collect AEs
- Collect concomitant medication data
- Collect study drug
- Perform a pill count for drug accountability (ER opioid, IR opioid, and acetaminophen)
- Perform a urine pregnancy test for women of child-bearing age
- Review the data recorded via phone for daily Average and Worst PI scores by the subject since last visit
- Review the data recorded via phone for the daily use of ER and IR opioids taken by the subject since last visit
- Check the criteria for randomization into the Blinded Structured Opioid Discontinuation Period: To continue on study, subjects are required to have a mean Average PI score ≥6 on a 0-10 NRS over the 1 week of the Baseline Period (with a minimum compliance of 4 out of 7 daily PI scores) and to be dissatisfied with their pain and physical function. Subjects who had a baseline mean Average PI score of 10/10 (i.e., 10/10 score every day for the 1 week of the Baseline Period) will be discontinued. (For study discontinuation procedures, see section 12.1.6.)

For subjects eligible to continue on study, perform the following:

- Inform the lab to perform the endocrine parameter analysis drawn at Screening
- Administer the BPI-SF
- Administer the RMDQ
- Administer the Regional Pain Scale
- Administer the Pain Quality Assessment Scale (PQAS)
- Administer the MOS Sleep Scale
- Administer the WPAI
- Administer the EQ-5D-5L
- Administer the DSST
- Perform quantitative sensory testing (QST) for OIH (for subjects enrolled at participating sub-study sites)
- Administer the Subjective Opiate Withdrawal Scale (SOWS)
- Complete the Clinical Opioid Withdrawal Scale (COWS)
- Determine whether any abuse-related events have occurred during the Baseline Period
- Randomize the subject using IRT system

- Dispense blinded study drug (ER opioid) according to the IRT instructions and matching IR opioid and acetaminophen. Instruct the subject to begin treatment with the next scheduled dose.

12.1.3 Optimal Responders Visits Only

Observation Period (1 week, from Weeks -6 to -5)

During the Observation Period, subjects will

- Self-administer the same opioid analgesic regimen they have been taking at screening
- Before bedtime, record via phone the daily use of opioid analgesics and rescue medication taken over the past 24 hours
- Before bedtime, record via telephone the daily Average and Worst PI scores in the past 24 hours

OR1 Visit (at Week -5)

At the OR1 visit, the following will be conducted during a clinic visit:

- Collect vital signs (pulse rate, respiratory rate, and blood pressure only)
- Collect AEs
- Collect concomitant medication data
- Review the data recorded via phone for the daily Average and Worst PI scores by the subject since last visit
- Review the data recorded via phone for daily use of opioid and rescue medication taken by the subject since last visit
- Determine whether any abuse-related events have occurred during the Observation Period
- Subjects will be confirmed as Optimal Responders and will be allowed to continue in the study if: (i) their index opioid ER medication use was in the range shown in the table below and they had 80% to 120% compliance over the 1-week period; (ii) their mean Average PI score over the Observation Period was $\leq$5 (with a minimum compliance of 4 out of 7 daily PI scores); and (iii) they are still satisfied with their pain and physical function.

	Dose Range
Morphine sulfate ER	120-540 mg
Oxycodone ER	80-360 mg
Oxymorphone ER	40-180 mg

- Dispense open-label study medication (ER opioid dose cards and acetaminophen) for the Taper Period (Refer to the Optimal Responders: Open-label Taper and Titration schedule in Appendix B – Dosing Schedule)
- IR opioid is not allowed during the Taper Period
- Discontinue all other prescribed opioid medications prescribed for the subject
- Instruct the subject in the use of the Online Patient Support Program

Taper Period (up to 2 weeks, from Week -5 to -3)

During the Taper Period, subjects will:

- Self-administer the open-label ER opioid taper
- Before bedtime, record via phone the daily use of ER opioids (IR opioid rescue is not allowed during this period)
- Before bedtime, record via phone the daily Average PI and Worst PI scores in the past 24 hours
- Participate in the Online Patient Support Program

OR2 Visit (at Week -4)

At Visit OR2 (or before), the following will be conducted:

- Check criteria for entry into the Titration Period: Subjects with a mean Average PI score >5 over ≥3 consecutive PI scores (non-missing values), where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI score over the 7-day Observation Period, either off of pain medication entirely or at a reduced dose, will immediately advance to Visit OR3 (skipping Visit OR2) and begin the Open-Label Titration Period

For subjects continuing in the Taper Period, conduct Visit OR2:

- Collect vital signs (pulse rate, respiratory rate, and blood pressure only)
- Collect AEs
- Determine whether any abuse-related events have occurred since last visit
- Collect concomitant medication data
- Review the data recorded via phone for daily use of ER opioid taken by the subject since last visit
- Review the data recorded via phone for daily Average PI and Worst PI scores since last visit
- Collect study drug
- Perform a pill count for drug accountability (ER opioid and acetaminophen)
- Dispense additional open-label ER opioid taper medication and acetaminophen

OR3 Visit (at Week -3)

At Visit OR3, the following will be conducted:

- Collect vital signs (pulse rate, respiratory rate, and blood pressure only)
- Collect AEs
- Determine whether any abuse-related events have occurred since last visit
- Collect concomitant medication data

- Review the data recorded via phone for daily use of ER opioids taken by the subject since last visit
- Check the daily past 24 hour Average and Worst PI scores from the phone data since last visit
- Collect study drug
- Perform a pill count for drug accountability (ER opioid and acetaminophen)
- Check criteria for entry into the Titration Period: Subjects with a mean Average daily PI score >5 over ≥3 consecutive PI scores (non-missing values), where this mean Average daily PI score has also increased by ≥1.5 points from the mean Average PI score over the 7-day Observation Period, either off of pain medication entirely or at a reduced dose, will be eligible to proceed to the Open-Label Titration Period. Subjects who do not meet these criteria will be discontinued from the study. (For study discontinuation procedures, see section 12.1.6.)
- For subjects who are continuing into the Titration Period, dispense open-label titration medication of the standardized ER opioid corresponding to the subject's index ER opioid.
  - Also dispense rescue medication (corresponding IR opioid and acetaminophen) for the Titration Period

Open-label Titration Period (up to 3 weeks, from Week -3 to 0)

During the Open-label Titration Period, subjects will:

- Self-administer the open-label ER opioid titration regimen
- Before bedtime, record via phone the daily use of ER and IR opioids
- Before bedtime, record via phone the daily Average and Worst PI scores in the past 24 hours before bedtime
- Participate in the Online Patient Support Program

Telephone (or Office) Visits every 4 days (Up to 5 telephone or office visits from Week -3 to 0)

Note: Sites have the option of scheduling Office Visits (OR3.1, OR 3.2, etc.) during this time if they believe that is appropriate for the subject's wellbeing. Also, if the dose of the index ER opioid needs to be titrated above the baseline dose, the Titration Period may be extended by 1 additional week (+3 days).

At the Telephone (or Office) Visits, the following will be performed:

- Collect AEs
- Determine whether any abuse-related events have occurred since last visit
- Collect concomitant medication data
- Review the data recorded via phone for daily Average PI and Worst PI scores by the subject since the last visit

- Review the data recorded via phone for daily use of ER and IR opioids taken by the subject since the last phone call/visit
- If the subject does not have a mean Average PI score for at least 3 consecutive scores (non-missing values) that is ≤5, increase the subject's dose; increase dose as frequently as every 4 days (using Telephone or Office Visits) until the mean Average PI score over at least 3 consecutive scores (non-missing values) is ≤5
- When the subject's mean Average PI score over at least 3 consecutive scores (non-missing values) is ≤5, schedule the Randomization Visit as soon as possible (preferably the next day) and keep the subject on that ER opioid dose until that visit occurs

Randomization Visit = OR4 (at Day 1)

At the Randomization Visit (OR4), the following will be conducted during a clinic visit:

- Collect vital signs (pulse rate, respiratory rate, and blood pressure only)
- Collect AEs
- Collect concomitant medication data
- Perform a urine pregnancy test for women of child-bearing age
- Review the data recorded via phone for daily Average and Worst PI scores by the subject since last visit
- Review the data recorded via phone for daily use of ER and IR opioids taken by the subject since the last visit
- Check the criteria for entry into the Randomization Period: To continue on study, subjects are required to have achieved a mean Average PI score ≤5 during the 3 consecutive scores (non-missing values) that triggered the randomization visit with satisfaction with their pain and physical function, and acceptable side effects, and be taking a dose of index ER opioid in the range listed in the table below.

	Daily Dose Range
MS Contin ER	120-540 mg
OxyContin ER	80-360 mg
Opana ER	40-180 mg

For subjects eligible to continue on study, perform the following:

- Inform the lab to perform endocrine parameter analysis drawn at Screening
- Administer the BPI-SF
- Administer the RMDQ
- Administer the Regional Pain Scale
- Administer the PQAS
- Administer the MOS Sleep Scale
- Administer the WPAI

Opioid Post-Marketing Requirement (PMR) Consortium

- Administer the EQ-5D-5L
- Administer the DSST
- Administer the QST for OIH (for subjects enrolled at participating sub-study sites)
- Administer the SOWS
- Complete the COWS
- Determine whether any abuse-related events have occurred since last visit
- Randomize the subject using the IRT system
- Collect study drugs
- Perform a pill count for drug accountability (ER opioid, IR opioid, and acetaminophen)
- Dispense blinded study drug (ER opioids) according to the IRT instructions and matching IR opioid, and acetaminophen. Instruct the subject to begin treatment with the next scheduled dose.
- Encourage use of online Patient Support Program.

12.1.4 Continuing for both Suboptimal and Optimal Responders: Blinded Structured Opioid Discontinuation Period (24 weeks; from Week 1 to 24)

During the Blinded Structured Discontinuation Period, subjects will:

- Self-administer the double-blind standardized ER opioid regimen as directed
- Before bedtime, record via phone the daily use of ER and IR opioids
- Before bedtime, record via phone the daily Average and Worst PI scores in the past 24 hours
- Participate in the Online Patient Support Program

Clinic visits will occur at Weeks 1, 2, 4, 6, 8, 12, 16, 20, and 24 (BDP visits 1 through 9). A phone call will be conducted every week where a visit does not occur (i.e., Weeks 3, 5, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, and 23) to check for the subjects wellbeing, study medication compliance, and safety issues. Changes in study medication and AEs obtained during phone calls will be captured in the eCRF. All other information will be captured in source documents.

Conduct the following assessment at each clinic visit:

- Check vital signs (pulse rate, respiratory rate, and blood pressure only)
- Collect AEs
- Collect concomitant medication data
- Check the data recorded via phone for daily Average and Worst PI scores by the subject since last visit
- Determine whether any abuse-related events have occurred since last visit

Opioid Post-Marketing Requirement (PMR) Consortium

- Check the data recorded via phone for daily use of ER opioid and IR opioid taken by the subject since last visit
- Perform a pill count for drug accountability (ER opioid, IR opioid, and acetaminophen)
- Dispense study medication until next visit

Conduct the following assessments at specified visits:

- Conduct a brief physical exam, clinical laboratory testing, endocrine testing and sexual function questionnaire (see Appendix S) at Weeks 12 and 24
- Administer the BPI-SF, Regional Pain Scale, PQAS, WPAI, EQ-5D-5L, PHQ-8, and Patient's Global Impression of Change (PGIC) at Weeks 12 and 24
- Administer the RMDQ at Weeks 12 and 24
- Perform QST for OIH at Weeks 12 and 24 (for subjects enrolled at participating sub-study sites)
- Administer SOWS at Weeks 2, 4, and 6
- Administer the COWS at Weeks 2 and 4
- Administer the C-SSRS "Since Last Visit" at Weeks 6 and 24 (review results to determine if further risk assessment is necessary)
- Administer the MOS Sleep Scale and the DSST at Weeks 12 and 24
- Perform a quantitative UDT at Weeks 4, 12, and 24 for non-prescribed controlled substances, illicit drugs, and alcohol. The management of unexpected findings is described in the UDT Appendix (Appendix T). If an unexpected finding occurs after a repeat UDT, discontinue the subject from the study per the UDT algorithm. (For study discontinuation procedures, see section 12.1.6.)

During weeks without a visit, call the subject to assess subject wellbeing, study medication compliance, and safety (check for AEs). Changes in medications and AEs obtained during phone calls will be captured in the eCRF. All other information will be captured in source documents.

Full information about the reason(s) for dropout of any subject after randomization will be captured in the electronic case report form (eCRF) using a special questionnaire (Appendix V) as detailed in Section 12.1.6.

12.1.5 Follow-up Period (4 Weeks; from Week 25 to 28)

During the Follow-up Period, subjects will

- Self-administer the double-blind study medication as directed
- Before bedtime, record via phone the daily use of ER and IR opioids
- Participate in the Online Patient Support Program

There will be 2 clinic visits (at Weeks 26 and 28) and 2 phone calls (at Weeks 25 and 27).

Follow Up Visit 1 (FUV1; Week 26) and Follow Up Visit 2 (FUV2; Week 28 [final visit])

- Collect vital signs (pulse rate, respiratory rate, and blood pressure only)

Opioid Post-Marketing Requirement (PMR) Consortium

- Collect AEs
- Determine whether any abuse-related events have occurred since the last visit
- Check concomitant medications
- Check the data recorded via phone for daily use of ER opioid and IR opioid taken by the subject since last visit
- Perform a pill count for drug accountability (ER opioid, IR opioid, and acetaminophen)

At FUV1 only:

- Perform SOWS and COWS
- Dispense double-blind study medication until next visit (Week 28)
- Instruct the subject to discontinue ER study medication for the last 3 days prior to the final visit

At FUV2 only:

- Perform a urine pregnancy test for women of child-bearing age
- Conduct a brief physical exam
- Collect any remaining medication
- Discharge the subject at FUV2 to their primary care physician
  - Instruct the subject not to take any ER opioid medication until they see their primary care physician (as they are no longer opioid tolerant)

Phone Calls (Weeks 25 and 27):

- Check on the subject's wellbeing (AEs and potential withdrawal symptoms)
- Check the data recorded via phone for study drug use by the subject since the last visit
- Changes in medications and AEs obtained during phone calls will be captured in the eCRF. All other information will be captured in source documents.

12.1.6 Study Discontinuation Procedures

Subjects who do not meet the entry criteria for the protocol during Screening will be considered screen failures and discontinued from the study. Investigators will be expected to maintain screening information on all potential study subjects. This will include limited information about the potential subject and the dates and outcome of the screening process (i.e., informed consent, demography, subject enrollment status, reason for ineligibility, and AEs). Subjects will be discharged to their primary care physician. Opioid medication will be managed as appropriate by their primary care physician.

Subjects who discontinue the study after Screening but before the Randomization Visit will advance to the final visit (FUV2), complete all visit assessments, and will be discharged to their primary care physician. Opioid medication will be managed as appropriate by their primary care physician.

For subjects who discontinue the study during the Blinded Structured Opioid Discontinuation Period, the following should be performed:

- Subjects who discontinue before Week 12 will complete Week 12 assessments and advance to the Follow-up period. At the completion of the Follow-up period, subjects will be discharged to their primary care physician who will manage their pain medication.
- Subjects who discontinue between Weeks 13 and 24 will complete Week 24 assessments and advance to the Follow-up period. For any subject who discontinues before Week 4, the Medical Monitor should be contacted to discuss that subject. At the completion of the Follow-up period, subjects will be discharged to their primary care physician who will manage their pain medication.

Full information about the reason(s) for dropout of any subject after randomization will be captured in the eCRF using a special questionnaire (Appendix V). If the discontinued subject is unable or unwilling to come to the clinic for the discontinuation procedures, the staff will conduct a phone visit and complete the following assessments as best possible over the phone:

- PI according to NRS
- BPI-SF
- Regional Pain scale
- RMDQ
- EQ-5D-5L
- PGIC

12.2 Prior and Concomitant Medications and Procedures

Medications and procedures that are allowed and not allowed as concomitant medications for either episodic or chronic use are described in this section. Medication history, including the use of opioid analgesic medication during the previous 1 year and of any other medication during the previous 6 months, will be recorded at Screening in the eCRF. Thereafter, any changes in concomitant medications or new medications added will be recorded in the eCRF.

Medications taken for hormone replacement therapy including testosterone and estrogen/progesterone-containing products and erectile dysfunction medications will be recorded in the eCRF.

Medications and procedures permitted and not permitted during the study are described below:

Prohibited Prior Medications and Procedures

- Nerve or plexus block, including epidural steroid injections or facet blocks, within 1 month prior to the Screening Visit, or botulinum toxin injection in the lower back region within 3 months prior to screening
- MAO inhibitor within 14 days prior to screening
- Agonist-antagonists (pentazocine, butorphanol or nalbuphine), buprenorphine, methadone, barbiturates, or more than one type of benzodiazepine within 1 month prior to screening

- Positive UDT for illicit drugs (including marijuana), non-prescribed controlled substances, or alcohol at screening.
- Any investigational drug within 30 days prior to the Screening Visit

Prohibited and Allowed Concomitant Medications and Procedures

At Screening, Suboptimal Responder subjects will be required to discontinue all IR and ER opioids they had been taking including tramadol and tapentadol and will receive a standardized regimen supplied as ER opioid plus matching IR opioid. Optimal Responder subjects will continue to take their prescribed opioid regimen during the Observation Period after which those subjects advancing to the Taper Period will receive the standardized ER opioid.

Throughout the study, both Suboptimal Responder and Optimal Responder subjects will be allowed to continue the non-opioid, non-acetaminophen containing analgesics they had been taking prior to entering the study as concomitant medication at the dose they were taking at Screening.

Throughout the study (except during the Observation Period for the Optimal Responders), both Suboptimal Responder and Optimal Responder subjects will discontinue any personal acetaminophen and only take study-provided acetaminophen. The dose is 500 mg tablets, 1-2 tablets every 4-6 hours PRN, not to exceed 6 tablets/day, which provides for a total daily dose (3 grams), well within the accepted safety range (<4 grams daily).

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine and butorphanol), buprenorphine, methadone, barbiturates, MAO inhibitors, investigational drugs, and more than one benzodiazepine are prohibited throughout the study.

Alcohol and other concomitant medications that are not to be taken in combination with opioid analgesics as well as non-prescribed controlled substances will NOT be permitted during the study except if determined to be appropriate by the Investigator.

Nerve or plexus block, including epidural steroid injections or facet blocks, botulinum toxin injection in the lower back region, chiropractic manipulation of the lower back, or any surgical procedure (including external or internal nerve stimulators) for lower back pain are not allowed during the study. Stimulators that are in place prior to study entry are allowed as long as the settings are not changed during the study. Massage therapy or exercise therapy may continue unchanged during the study but new massage therapy or exercise therapy is not allowed during the study.

12.3 Study Drug Compliance

Treatment compliance will be calculated for ER opioids only (since IR opioids and acetaminophen are rescue medications taken PRN). Study drug compliance for ER opioids during each period will be calculated to determine treatment compliance. Compliance can be calculated using the following formula: Divide the number of doses of ER opioids taken by the subject by the number of doses required by the protocol for the given period and multiply by 100 to determine the percentage of compliance with the protocol. Subjects taking too much or too little study drug should be re-educated on the proper use of study drug. Repeated non-compliance (less than 80% or greater than 120%) should be evaluated for the need to withdraw the subject.

Accidental or intentional overdoses should be reported to the Sponsor/designee promptly (see section 14.6.1.2, Handling Reports of Overdose/Abuse/Misuse/Diversion/Withdrawal).

12.4 Blinding and Randomization

Following randomization, this study will be conducted as a double-blind investigation. Neither the Investigator nor the subject will know the identity of the assigned treatment. Supplies will be prepared using matching placebo tablets. Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups (continued opioid therapy or structured discontinuation of opioid therapy) in a 1:1 ratio based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by responder status (Optimal Responder; Suboptimal Responder) and Index ER opioid (morphine, oxycodone, or oxymorphone). A minimum of 20% of subjects will be randomized into each of the baseline ER opioid strata within each responder cohort. The IRT will assign a unique treatment code, which will dictate the treatment assignment and study medication for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IRT, and will then give the relevant subject details to uniquely identify the subject.

In the case of emergency, the Investigator will have the ability to break the blind at the clinical site for the welfare of the subject. Breaking the blind will be accomplished by using the IRT web interface. Before breaking the blind, the Investigator should attempt to contact the Medical Monitor to discuss the necessity of breaking the blind. The Investigator will be required to make a full written explanation of the reason for unblinding the subject and the date. In the event that a subject is unblinded prior to contacting the Medical Monitor, the Investigator must provide this information in writing to the Medical Monitor as soon as possible. The explanation for breaking the blind will be recorded in the eCRF. Breaking the blind at the investigative site will immediately disqualify the subject from further participation in the study. In addition, the event(s) leading to emergency unblinding must be reported as a SAE according to instructions in section 14.5.2.

Drug Safety will also have the ability to break the blind for individual subjects in order to fulfill regulatory reporting responsibilities. That information will not be shared with study operational personnel.

Electronic access to the randomization codes in the IRT system will be granted to Drug Supply only.

13 ASSESSMENT OF EFFICACY

13.1 Efficacy Measurements

Efficacy will be assessed by the following measurements:

- PI: Subjects will record the Average PI and Worst PI scores in the past 24 hours on 0-10 NRS before bedtime each day using the phone system.
- RMDQ: The RMDQ is an interviewer- or self-administered health status questionnaire that measures the level of physical function in subjects with CLBP.(2)
- BPI-SF: The BPI-SF is a self-administered questionnaire that measures pain severity and the impact of pain on daily function.(3)
- Regional Pain Scale: The Regional Pain Scale is a self-administered questionnaire that measures the location and intensity of pain in 38 articular and nonarticular regions.(4)
- PQAS: The PQAS assesses the different aspects and types of pain (sharp, dull, achy, hot, and cold) that a subject experiences. (5)
- EQ-5D-5L: The EQ-5D-5L is a self-administered general measure of health outcome applicable to a wide range of health conditions and treatments.(6)
- PGIC: The PGIC is a self-administered questionnaire that assesses the subject level of improvement/worsening from the beginning to the end of treatment.(7)
- PHQ-8: The PHQ-8 is an 8-item questionnaire that aims at assessing the level of depression of a subject. Each item is scored from 0 = "not at all" to 3= "nearly every day"; the total score, which is the sum of the score for each item, can be from 0 to 24. A score ≥10 is considered major depression and ≥20 is severe major depression. (8)
- MOS Sleep Scale: The MOS Sleep Scale is a questionnaire that assesses sleep quality.(9)
- DSST: Overall neuropsychological function will be assessed using the DSST, a test that is sensitive to brain damage, dementia, age, and depression, and is a widely used instrument for measuring the neuropsychological effects of opioid therapy. The DSST consists of a series of digit-symbol pairs followed by a list of digits. Under each digit the subject should respond with the corresponding symbol as fast as possible. The number of correct symbols within the allowed time (e.g., 90 or 120 sec) is measured.(10)
- Work productivity: Work productivity will be assessed by the WPAI questionnaire.(11)

13.2 Endpoints

The primary efficacy endpoint is:

Change in the mean Average PI score on the 0-10 NRS from baseline to the 1 week period prior to the Week 12 visit.

For Suboptimal Responders, the mean Average PI score over the 7-day Baseline Period will count as the subject's baseline Average PI score for statistical analysis.

For Optimal Responders, the mean Average PI score during the Titration Period that meets the qualification criteria (Average PI score <4 for 3 consecutive non-missing values) plus any scores

between the last qualification score and the Randomization Visit will count as the subject's baseline Average PI score for statistical analysis.

Secondary efficacy endpoints are:

For Suboptimal Responders:

- Change from baseline to Weeks 4, 8, 16, 20, and 24 in 0-10 NRS Average and Worst PI scores over 1 week prior to each visit.
- Cumulative response function in percent improvement in PI score at Weeks 12 and 24 compared to baseline over 1 week prior to each visit.
- Changes from baseline to Weeks 12 and 24 in physical function (RMDQ), impact of pain on function (BPI-SF), pain quality (PQAS), pain spread (Regional Pain Scale), sleep quality (MOS Sleep Scale), mood (PHQ-8), quality of life (EQ-5D-5L), and work productivity (WPAI).
- Proportion of subjects with overall clinical benefit at Weeks 12 and 24 defined as a composite measure of key clinical endpoints: ≥30% improvement in average daily PI score *and* ≥20% improvement in RMDQ *and* PGIC of moderately or better improvement.

For Optimal Responders:

- Change from baseline to Weeks 4, 8, 16, 20, and 24 in 0-10 NRS Average and Worst PI scores over 1 week prior to each visit.
- Cumulative response function in percent worsening in PI score at Weeks 12 and 24 over 1 week prior to each visit compared to baseline.
- Changes from baseline to Weeks 12 and 24 in physical function (RMDQ), impact of pain on function (BPI-SF), pain quality (PQAS), pain spread (Regional Pain Scale), sleep quality (MOS Sleep Scale), mood (PHQ-8), quality of life (EQ-5D-5L), and work productivity (WPAI).

13.3 Exploratory Measurements

Exploratory measurements include:

- Change in sensitivity to thermal stimuli on QST (subjects in substudy).
- Identification of baseline factors predictive of benefit of opioid discontinuation among Suboptimal Responders.
- Changes from baseline in endocrine function and sexual function as characterized in the male and female questionnaires; relationship of changes in endocrine function to changes in PI; relationship of changes in endocrine function to changes in male and female sexual function; and relationship of baseline endocrine status to efficacy of opioid discontinuation.
- Changes from baseline in neurocognitive function as characterized by the DSST

14 ASSESSMENT OF SAFETY

Safety will be assessed by:

- AEs
- Abuse-related events (using the Misuse Abuse Diversion Drug Event Reporting System [MADDERS™])
- Opioid-specific side-effects (defined as a subset of all AEs before the database is locked)
- Vital signs (heart rate and blood pressure only)
- Clinical laboratory parameters
- Physical examination

Additional safety measures will include:

- UDT
- C-SSRS
- Opioid withdrawal effects (measured by SOWS, COWS, and withdrawal AEs)

14.1 Definitions

14.1.1 Adverse Events

An adverse event (AE) is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (eg, chemistry, ECG, X-ray, etc.), or worsening of a pre-existing condition associated temporally with the use of the study medication whether or not considered related to the study medication. Adverse events will be captured once a subject has signed the informed consent. AEs include:

- Changes in the general condition of the subject
- Subjective symptoms offered by or elicited from the subject
- Objective signs observed by the Investigator or other study personnel
- All concurrent diseases that occur after the start of the study, including any change in severity or frequency of pre-existing disease
- All clinically relevant laboratory abnormalities or physical findings that occur during the study

A treatment-emergent AE (TEAE) is any condition that was not present prior to treatment with study medication but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

All AEs, including both observed or volunteered problems, complaints, signs or symptoms must be recorded on the AE page of the eCRF, regardless of whether associated with the use of study medication. This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states (excluding the disease under study). A condition present at baseline that worsens after initiation of study treatment will be captured as an AE; the onset

date will be the date the event worsened. The AE should be recorded in standard medical terminology when possible.

14.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that:

- Results in death
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death)
- Results in or prolongs an inpatient hospitalization (Note: a hospitalization for elective or pre-planned surgery, procedure, or drug therapy does not constitute an SAE)
- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect (in offspring of a subject using the study medication regardless of time to diagnosis)
- Is considered an important medical event

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.2 Monitoring Adverse Events

At each visit, subjects will be queried regarding any AEs that have occurred since the last visit. Subjects will be asked to volunteer information concerning AEs with a non-leading question such as, "How do you feel?" Study site personnel will then record all pertinent information in the source documents and the eCRF. The study drug compliance record should also be reviewed to detect potential overdoses (intentional/unintentional).

14.3 Relationship to Study Drug

The degree of "relatedness" of the AE to the study medication must be described using the following scale:

- **Not related** indicates that the AE is definitely not related to the study medication.
- **Unlikely related** indicates that there are other, more likely causes and study medication is not suspected as a cause.
- **Possibly related** indicates that a direct cause and effect relationship between study medication and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by the study medication.
- **Probably related** indicates that there is evidence suggesting a direct cause and effect relationship between the AE and the study medication.

It is the Sponsor's policy to consider "Probably related" and "Possibly related" causality assessments as positive causality. "Not related" and "Unlikely related" causality assessments are considered as negative causality.

Assessments will be recorded on the eCRF and must indicate clearly the relationship being assessed. For example, an AE that appears during a placebo run-in phase would be assessed with respect to the placebo treatment received and/or study procedures conducted during this phase. If the AE continued into an active treatment phase, the relationship would be assessed for the active treatment phase only if the AE worsened.

14.4 Intensity Assessment

The intensity (or severity) of AEs is characterized as mild, moderate, or severe:

- **Mild** AEs are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- **Moderate** AEs introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- **Severe** AEs interrupt a subject's usual daily activity and typically require systemic drug therapy or other treatment.

When the intensity category of an AE changes, the greatest intensity during that continuous episode should be recorded.

14.5 Reporting Adverse Events and Serious Adverse Events

14.5.1 Reporting Adverse Events

Throughout the study, AEs will be documented on the source document and on the appropriate page of the eCRF whether or not considered treatment-related. This includes any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness. Conditions existing prior to screening will be recorded as part of the subject's medical history. The Investigator is responsible for assessing the relationship of AEs to the study medication; relationship will be classified as not related, unlikely related, possibly related, or probably related.

Only SAEs will be collected starting at the time of signing the informed consent through Screening. Following Screening, all AEs will be collected by the Investigator through 3 days after the last dose of study medication; this includes any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 14 days after the subject's last study visit, whichever comes first.

14.5.2 Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study must be reported via email or fax by the Investigator using the OPC Clinical Trial Report Form for SAEs within 24 hours of first becoming aware of the SAE. SAEs will be collected by the Investigator from the time of signing the informed consent through 30 days after the last dose of study medication. SAEs that occur within 30 days following cessation of the study treatment, or within 30 days following premature discontinuation from the study for any reason, must also be reported within the same timeframe. Any SAE that is felt by the Investigator to be related to the study medication must

be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the Sponsor within 24 hours of receipt by the Investigator.

All SAEs will be followed until resolution, stabilization of condition, or until follow-up is no longer possible. **In the event discussion is necessary regarding treatment of a subject, call the Medical Monitor (see contact information in section 3).**

All SAEs should be sent via the email address, or faxed to the fax number, provided in section 3. The Sponsor will determine whether the SAE must be reported within 7 or 15 days to regulatory authorities in compliance with local and regional law. If so, the Sponsor (or the Sponsor's representative) will report the event to the appropriate regulatory authorities. The Investigator will report SAEs to the Institutional Review Board (IRB) per their IRB policy.

14.5.3 Follow-Up Procedures for Serious Adverse Events

To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, and the like should be obtained. In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and any autopsy report. These records should be reviewed in detail, and the Investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the follow-up SAE form and the Investigator should consider whether the event is related or not related to study drug. All events determined to be nonserious should be reported on the eCRF.

14.6 Events of Special Interest (EOSI)

14.6.1 Overdose/Abuse/Misuse/Diversion/Withdrawal

14.6.1.1 Terminology

Overdose is the accidental or intentional use of a drug or medicine in an amount that is higher than the maximum recommended dose.

Study Drug Overdose is any accidental or intentional use of study drug in an amount higher than the dose indicated by the protocol for that subject.

Abuse is defined as the taking of the drug for a non-therapeutic use or the use of an illicit drug (or substance).

Misuse is the taking of the drug for a therapeutic use, but not in accordance with the indication/dose/route of administration/frequency for which it was prescribed.

Diversion is any intentional act that results in transferring a prescription medication from lawful to unlawful distribution or possession

Withdrawal is an acute state caused by cessation or dramatic reduction of use of opioid drugs that has been heavy and prolonged (typically several weeks or longer). The physiologic reaction frequently includes sweating, shaking, headache, drug craving, nausea, vomiting, abdominal cramping, diarrhea, inability to sleep, confusion, agitation, depression, anxiety, and other behavioral changes.

14.6.1.2 Handling Reports of Overdose/Abuse/Misuse/Diversion/Withdrawal

Overdose: Study drug compliance (see section 12.3) should be reviewed to detect potential instances of overdose (intentional or accidental). Any study drug overdose during the study should be noted in the IRT.

All AEs associated with an **overdose** are considered EOSI and should be reported using the procedures detailed in section 14.6.1.3 Reporting and Classification of Events Using MADDERS. If an EOSI associated with an overdose does not meet seriousness criteria, the AE must still be reported within 24 hours of first becoming aware of the event using the AE form, which will trigger the MADDERS supplemental forms. Those AEs of overdose meeting the seriousness criteria will be handled according to the procedures of section 14.5.2 Reporting Serious Adverse Events and by completing the MADDERS supplemental forms.

Follow-up information for AEs associated with an overdose should be reported using the MADDERS forms for all events and the SAE forms for serious events.

Abuse: All incidents and AEs associated with **abuse** are considered EOSI and should be reported using the procedures detailed in section 14.6.1.3 Reporting and Classification of Events Using MADDERS. If an EOSI associated with abuse does not meet seriousness criteria, the AE must still be reported within 24 hours of first becoming aware of the event using the AE form, which will trigger the MADDERS supplemental forms. Those AEs of abuse meeting the seriousness criteria will be handled according to the procedures of section 14.5.2 Reporting Serious Adverse Events and by completing the MADDERS supplemental forms.

Follow-up information for AEs associated with abuse should be reported using the MADDERS forms for all events and the SAE forms for serious events.

Misuse: All AEs associated with **misuse** are considered EOSI and should be reported using the procedures detailed in section 14.6.1.3 Reporting and Classification of Events Using MADDERS. If an EOSI associated with misuse does not meet seriousness criteria, the AE must still be reported within 24 hours of first becoming aware of the event using the AE form, which will trigger the MADDERS supplemental forms. Those AEs of misuse meeting the seriousness criteria will be handled according to the procedures of section 14.5.2 Reporting Serious Adverse Events and by completing the MADDERS supplemental forms.

Follow-up information for AEs associated with misuse should be reported using the MADDERS forms for all events and the SAE forms for serious events.

Diversion: Even though instances of potential **diversion** are not considered adverse events, all incidences of diversion are considered EOSI and should be reported using the procedures detailed in section 14.6.1.3 Reporting and Classification of Events Using MADDERS. If there is an instance of potential diversion, the diversion must be reported within 24 hours of awareness using the appropriate MADDERS supplemental forms.

Follow-up information for instances of potential diversion should using the MADDERS forms.

Withdrawal: Signs and symptoms of **opioid withdrawal** are considered EOSI and should be reported using the procedures detailed in section 14.6.1.3 Reporting and Classification of Events Using MADDERS. If an EOSI associated with opioid withdrawal does not meet seriousness criteria, the AE must still be reported within 24 hours of first becoming aware of the event using the AE form, which will trigger the MADDERS supplemental forms. Those AEs of opioid withdrawal meeting the

seriousness criteria will be handled according to the procedures of section 14.5.2 Reporting Serious Adverse Events and by completing the MADDERS supplemental forms.

14.6.1.3 Reporting and Classification of Events Using MADDERS®

Potential abuse-related events will be tracked using the Misuse Abuse Diversion Drug Event Reporting System (MADDERS®), which is a clinician-based assessment to identify and classify such events based on selected AEs and drug accountability discrepancies. The MADDERS® classifies such events as abuse, misuse, suicide-related, therapeutic error, none of the above, and unknown.(12) Additional modifiers are available for severity of the event, route of administration, tampering, withdrawal, addiction-related, diversion, and overdose. Relevant adverse events and certain drug accountability discrepancies occurring during the study will trigger specific, detailed forms from the MADDERS system. The MADDERS® will be used to measure potentially abuse-related events throughout the study (Appendix R).

Follow-up information for AEs of special interest should be reported according to the instructions in section 14.5.2, Reporting Serious Adverse Events.

14.6.2 Pregnancy

Subjects should be instructed to immediately notify the Investigator of any pregnancies. Any uncomplicated pregnancy that occurs in a subject during this clinical study will be **reported for tracking purposes only**. All subject pregnancies that are identified during or after this study, where the estimated date of conception is determined to have occurred during study drug therapy or within 3 days of the last dose of study medication need to be reported, followed to conclusion, and the outcome reported, even if the subject is discontinued from the study. Pregnancies that occur in the partner of a treated subject (i.e., female partner of male subject) also need to be reported. The Investigator should report all pregnancies within 24 hours using the Initial Pregnancy Report Form, and any pregnancy-associated SAE using the SAE report form, according to the usual timelines and directions for SAE reporting provided in section 14.5.2. Monitoring of the pregnancy should continue until conclusion of the pregnancy; 1 or more Follow-up Pregnancy Report Form(s) detailing progress, and a Two-Month Follow-up Pregnancy Report Form detailing the outcome, should be submitted.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (e.g., congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE report form. Spontaneous miscarriages should also be reported and handled as SAEs.

A subject who becomes pregnant must be withdrawn from the study. Should a subject discontinue treatment due to pregnancy, alternative treatment (if available) should be arranged according to standard of care, as determined by the Investigator. Attempts to obtain the pregnancy follow-up and pregnancy outcome information detailed above are necessary even if a subject discontinues treatment because of pregnancy.

14.6.3 AEs/SAEs Experienced by Non-subjects Exposed to Study Medication

Non-subjects are persons who are not enrolled in the study but have been exposed to study medication, including instances of diversion of study medication. All such AEs/SAEs occurring in non-subjects from such exposure will be reported to the OPC Drug Safety Department (when the non-subject

agrees) on the appropriate form for serious adverse experiences regardless of whether the event is serious or not. Instructions for completing the form for events experienced by non-subjects will be provided. SAEs occurring in non-subjects exposed to study medication will be processed within the same SAE reporting timelines as described in section 14.5.2. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

14.7 Clinical Laboratory Determinations

Clinical laboratory tests will be conducted according to the Schedule of Events. Clinical laboratory tests will be performed by a designated central laboratory. Each site will be provided with instructions on specimen collection, preparation, packaging and transport. Refer to the central laboratory manual for further information regarding sample collection, handling, and labeling. The results of the tests will be returned to the investigational sites. Clinical laboratory parameters that will be measured in this study are listed in Table 4.

Clinical laboratory test data will be reviewed by the Investigator, or designee, and additional clinical laboratory tests may be ordered at his/her discretion (e.g., if the results of any clinical laboratory test falls outside the reference range or clinical symptoms necessitate additional testing to ensure safety). Any additional testing will be performed by the designated central laboratory.

Laboratory results will be sent electronically to the designated contract research organization for data management. The Investigator will review all abnormal lab results for clinical significance. Any abnormal clinical laboratory test result meeting the criteria for clinical significance (refer to central laboratory manual) will be recorded as an AE or SAE as appropriate (see sections 14.1.1 and 14.1.2).

Table 4: Clinical Laboratory Tests

Hematology	**Biochemistry**	**Urinalysis**
Hemoglobin	Glucose	Glucose
Hematocrit	Sodium	Protein
Red blood cell	Potassium	Specific gravity
White blood cell (WBC)	Calcium	pH
Platelets	Chloride	Ketones
WBC Differential	CO_2	Bilirubin
	Inorganic phosphate	Urobilinogen
	Blood urea nitrogen	Nitrite
	Creatinine	Blood*
	Creatinine clearance	Leukocytes*
	AST	
	ALT	
	Gamma-glutamyl transferase (GGT)	
	Total bilirubin (TBL) (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	
	Uric acid	

* Microscopic examination will be performed if blood or leukocytes are detected by dipstick.

Endocrine function will be assessed by measuring blood levels of free and total testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol [women only], insulin-like growth factor-1 (IGF-1), cortisol, adrenocorticotropic hormone (ACTH), dehydroepiandrosterone sulfate (DHEAS), and thyroid-stimulating hormone (TSH) [baseline only].(13)

For women of childbearing potential, a serum pregnancy test will be performed at Screening, and a urine pregnancy test will be performed at Randomization visit and Follow-up visit 2 or termination. If necessary, additional urine pregnancy tests can be performed at any time during the study at the discretion of the Investigator. Female subjects of childbearing potential must have a negative pregnancy test at Screening to be enrolled in the study. Pregnancy tests will be supplied by the Sponsor.

The Investigator will collect urine samples for the screening of (but not limited to) illicit drugs, opioids, other controlled prescription drugs, and alcohol.

14.8 Vital Signs

Vital sign measurements will be documented as described in the Schedule of Events. These parameters include height, body weight, BMI (calculated), pulse rate, respiratory rate, and systolic and diastolic blood pressure. All these parameters will be measured at Screening, while only pulse rate, respiratory rate, and blood pressure are measured at subsequent visits. Pulse rate, respiratory rate, and blood pressure readings will be taken after the subject has been sitting for 5 minutes. Subjects with systolic blood pressure greater than 180 mm Hg or less than 90 mm Hg or diastolic blood pressure greater than 110 mm Hg or less than 40 mm Hg at the Screening Visit or Randomization Visit should be excluded from study participation.

The Investigator will review all vital sign values for clinical significance. Any vital sign value meeting the Investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see sections 14.1.1and 14.1.2).

14.9 Physical Examination

A complete physical examination will be performed at Screening. Additional brief physical examinations will be performed at other times as described in the Schedule of Events. All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations.

The Investigator will review all physical exam findings for clinical significance. Any physical exam finding meeting the Investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see sections 14.1.1 and 14.1.2).

14.10 Other Safety Analyses

Other safety parameters analyzed will be:

- Withdrawal symptoms: The severity of withdrawal symptoms will be measured by the SOWS (14) and COWS (15). Withdrawal will also be assessed by the occurrence of typical withdrawal AEs, including chills, sweating, tremor, and muscle cramps.
- UDT: A quantitative UDT for illicit drugs, non-prescribed controlled substances, and alcohol will be conducted at Screening and Weeks 4, 12, and 24 after randomization. The UDT will be performed by liquid chromatography tandem mass spectrometry (LC-MS/MS)

technology. The management of unexpected findings is described in the UDT Appendix T. If an unexpected finding occurs after a repeat UDT, the subject will be discontinued from the study.

- C-SSRS: Risk of suicide will be measured at Screening using the C-SSRS "Lifetime". Subsequent assessments will be performed at Weeks 6 and 24 using C-SSRS "Since Last Visit".

15 ASSESSMENT OF PHARMACOKINETICS

Not applicable

16 ASSESSMENT OF PHARMACODYNAMICS

Not applicable.

17 STATISTICAL CONSIDERATIONS AND METHODS

A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

All statistical comparisons will be 2-sided at the 0.05 alpha level, with separate analyses for the Suboptimal Responders and the Optimal Responders. There will be no adjustments for multiplicity.

17.1 Determination of Sample Size

The primary endpoint is the change from baseline to Week 12 (mean Average PI score over the 1 week prior to the Week 12 visit) in 0-10 NRS Average PI score comparing the opioid discontinuation group to the continued opioid therapy group. To detect a between-group difference of 0.8 points with 90% power, assuming a standard deviation of 2.5, using the two-sided 5% significance level, 205 randomized subjects per arm for each responder type will be needed; thus a total of 820 subjects will need to be randomized into the Blinded Structured Opioid Discontinuation period. Assuming a 3:1 screen failure rate, approximately 3280 subjects will need to be screened.

17.2 Subject Populations

Separate analyses will be conducted for Suboptimal Responders and Optimal Responders since these are considered two different study populations. Therefore, all analysis populations will be defined for Suboptimal Responders and Optimal Responders separately.

17.2.1 Safety Population

Different Safety Populations will be defined to summarize data pre- and post-randomization.

- For Suboptimal Responders, the Safety Population Pre-Randomization will include all subjects who were enrolled in the study and were switched to the standardized regimen (i.e., who enter the Run-in Period) and took at least one dose of study drug.
- For Optimal Responders,
  - The Safety Population Pre-Randomization (Observation Period) will include all Optimal Responder subjects who entered the Observation Period.
  - The Safety Population Pre-Randomization (Taper Period) will include all Optimal Responder subjects who were enrolled in the study and took at least 1 dose of study medication during the Taper Period.
  - The Safety Population Pre-Randomization (Titration Period) will include all Optimal Responder subjects who were enrolled in the study and took at least 1 dose of study medication during the Titration Period (i.e., who entered the Open-label Titration Period).

For both Suboptimal Responders and Optimal Responders, the Safety Population Post-Randomization will include all subjects who were randomized and received at least one dose of double-blind treatment.

Safety will be analyzed separately for these populations. Subjects who are randomized to one treatment group but mistakenly assigned the medication kit of the other treatment group will be reported “as treated”.

17.2.2 ITT Population

The ITT Population will include all subjects who were randomized and received at least one dose of study drug after randomization. All efficacy analyses will be performed using this population. Subjects will be reported in the treatment group to which they were randomly assigned.

17.2.3 Per-protocol Population

The Per-Protocol Population is a subset of the ITT population, excluding subjects with protocol deviations that may have an impact on the results of the primary efficacy analyses. An additional analysis of the primary efficacy endpoint will be performed using this population. Further details of the Per-Protocol Population definition will be specified in the SAP.

17.3 Subject Disposition

The number of subjects included in each study population will be summarized by treatment group. Subjects excluded from the safety and efficacy populations will be listed by treatment group.

The number and percentage of subjects completed and prematurely discontinued during the Blinded Structured Opioid Discontinuation Period and up to the end of the study will be presented for each responder type and each treatment group. Screen failures (i.e., screened but not randomized subjects) and the associated failure reasons will be tabulated overall. Reasons for premature discontinuation as recorded on the termination page of the eCRF and collected in the special questionnaire will be summarized (number and percentage) by responder type and treatment group for all randomized subjects.

17.4 Demographics and Other Baseline Characteristics

Demographic characteristics, including sex, age, age group, race, height, and weight, will be summarized by responder type and treatment group using descriptive statistics. All screening characteristics and medical information, including type and duration of opioid use and duration since diagnosis of low back pain, will also be summarized by responder type and treatment group using descriptive statistics. The descriptive summaries will include frequency tables for all categorical response variables and number, mean, standard deviation, minimum and maximum for all continuous variables.

17.5 Efficacy Analyses

All efficacy analyses will be conducted separately for Suboptimal and Optimal Responders.

Definition of Baseline:

For Suboptimal Responders, the mean of the Average PI scores over the 7-day Baseline Period will count as the subject's baseline Average PI score for statistical analysis. Similarly, the mean of the Worst PI scores over the 7-day Baseline Period will count as the subject's baseline Worst PI score for statistical analysis.

For Optimal Responders, the mean Average PI score during the Titration Period that meets the qualification criteria (Average PI score $\leq$5 for 3 consecutive non-missing values) plus any scores between the last qualification score and the Randomization Visit will count as the subject's baseline Average PI score for statistical analysis. Similarly, the mean Worst PI score including the 3 qualification days (as defined above) during the Titration Period plus any days between the

qualifications days and the Randomization Visit will count as the subject's baseline Worst PI score for statistical analysis.

For all other assessments, the last non-missing observation prior to the first dose in the Blinded Structured Opioid Discontinuation Period will be used as the baseline observation.

17.5.1 Primary Efficacy Analysis

The primary endpoint is the change in the mean Average PI score on the 0-10 NRS from baseline to the 1 week period prior to the Week 12 visit.

The analysis of the primary endpoint will be in two stages. First, multiple imputation will be used for missing data based on the reason for missing data. Second, the multiple datasets will be analyzed using mixed model repeated measures (MMRM), and the individual imputation dataset results will be combined using standard methods (e.g., Little & Rubin, 2002) (16). The imputation and analysis are described below.

The imputation of missing data will be based on the reason for treatment discontinuation. Missing data occurring between observed data points will be imputed using Markov Chain Monte Carlo methods to create monotone missing data patterns. For missing data caused by discontinuation due to Adverse Events, data will be imputed using

- For Suboptimal Responders, the subject's baseline Average PI score (with added variability based on the variance of the data of the corresponding timepoint of missing data).
- For Optimal Responders, the subject's mean Average PI score at the end of the Taper Period (with added variability based on the variance of the data of the corresponding timepoint of missing data). This score will be the first 3 days of the mean Average PI score used to qualify the subject for entry into the Titration Period (i.e., where the mean Average PI score is >5 over ≥3 consecutive days, where this mean Average PI score has also increased by ≥1.5 points from the mean Average PI over the 7-day Observation Period).

For missing data caused by discontinuation due to Lack of Efficacy, data will be imputed using the subject's last non-missing weekly mean Average PI score. As PI data are collected electronically daily, this data will convey the level of pain as close as possible to the point of discontinuation. For missing data caused by any other reason, data will be imputed using multiple imputation with a regression model for prior weekly Average PI scores and treatment group, and utilizing the subject's observed pain scores in the regression model. Ten imputation datasets will be used for this multiple imputation procedure.

The analysis of the individual imputation datasets for the primary endpoint will use a MMRM analysis, which includes the fixed effects of treatment group, index ER opioid (morphine, oxycodone, or oxymorphone) group, baseline NRS Average PI score, Week, and interaction between treatment group and Week as factors. Data up to Week 12 will be included in this analysis. The Restricted Maximum Likelihood estimation approach will be used, and the default covariance structure will be unstructured. If there are convergence problems for this model, other variance-covariance matrix structures will be considered. Results from each of the ten imputation datasets will be combined using standard methodology, taking into account the within and between imputation components of variability. Estimates of the primary endpoint will be shown by treatment group, and for the difference between groups (structured discontinuation treatment group compared to continuation treatment group), together with 95% confidence interval and p-value for the difference.

17.5.2 Secondary Efficacy Analysis

Secondary analyses for the primary endpoint will include:

- A descriptive summary of the change in Average PI score from baseline to Week 12, by index ER opioid (morphine, oxycodone, or oxymorphone) group.
- The same analysis described in section 17.5.1 , using the Per-Protocol population.
- Sensitivity analyses for missing data: (i) Last observation carried forward with analysis of covariance (ANCOVA) (model terms of baseline NRS Average PI score, stratification parameters, and treatment group); (ii) MMRM of observed data up to Week 12 (with the same model terms as the primary analysis model).

The following endpoints will be analyzed using the same MMRM model as described above for the primary endpoint analysis (with corresponding baseline score and stratification parameters as covariates), using observed data (without multiple imputation). Data for these analyses will include all available timepoints up to Week 24:

- The change from baseline to Weeks 4, 8, 16, 20, and 24 in the 0-10 NRS Average PI score over 1 week prior to each visit
- The change from baseline to Weeks 4, 8, 12, 16, 20, and 24 in the 0-10 NRS Worst PI score over 1 week prior to each visit

The following endpoints will be analyzed using ANCOVA (with model terms of baseline score, stratification parameters, and treatment group) as described above for the primary endpoint analysis, using observed data (without multiple imputation):

- The change from baseline to Weeks 12 and 24 in the RMDQ total score
- The change from baseline to Weeks 12 and 24 in the BPI-SF Pain Interference Index (composite function score), and individual pain inference items (e.g., Pain Interference with General Activity, Walking Ability, Sleep, and Normal Work)
- The change from baseline to Weeks 12 and 24 in the PQAS specific aspects of pain (17 items), the Overall Unpleasantness of Pain, and the intensity of both Deep and Surface pain
- The change from baseline to Weeks 12 and 24 in the number of regions of any pain from the Regional Pain Scale
- The change from baseline to Weeks 12 and 24 in sleep quality using the MOS Sleep Scale
- The change from baseline to Weeks 12 and 24 in mood using the PHQ-8
- The change from baseline to Weeks 12 and 24 in work productivity in the WPAI.

The cumulative response function in percent improvement in Average PI score at Weeks 12 and 24 compared to baseline over 1 week prior to each visit, will be shown by treatment group. The categories used will include change from baseline of <0% (any improvement), and ≤10% to ≤50% in steps of 10%. In addition, the changes from baseline to Weeks 12 and 24 relating to worsening will be shown (including >0%, and ≥10% to ≥50% in steps of 10%).

The overall clinical benefit for the Suboptimal Responders is defined as ≥30% improvement in PI *and* ≥20% improvement in RMDQ *and* PGIC of moderately or better improvement. The proportion of

subjects in the Suboptimal Responder group with overall clinical benefit at Weeks 12 and 24 will be analyzed using logistic regression for binary endpoints with model terms for baseline Average PI score, baseline RMDQ, stratification variables, and treatment group.

The time to discontinuation due to lack of efficacy and for all reasons will be summarized by treatment group using Kaplan-Meier estimates.

The type of pain (intermittent, variable or stable) collected in the PQAS will be summarized at each timepoint, and changes will be summarized. The cumulative response function in percent improvement in RMDQ at Weeks 12 and 24 compared to baseline will also be summarized. The cumulative percent worsening in RMDQ will also be summarized at Weeks 12 and 24.

The PGIC scores will be analyzed using the Cochran-Mantel-Haenszel (CMH) row mean score test. The percentage of subjects with 'Much improved/very much improved' will be presented as descriptive statistics.

The average daily dose of opioid analgesic medication taken during the Blinded Structured Opioid Discontinuation Period and during the entire double-blind treatment period will be summarized with descriptive statistics by treatment group for each type of formulation (ER/CR and IR).

The baseline and post-baseline responses in the five dimensions of the EQ-5D-5L questionnaire (mobility; self-care; usual activity; pain/discomfort; anxiety/depression) will be summarized by treatment group. This summary will use observed data only (no imputation for missing data). An additional question, called the EQ-VAS asks the subject to rate their health today using a VAS scale from 0 (the worst health you can imagine) to 100 (the best health you can imagine). This will be summarized.

The change from baseline to Weeks 12 and 24 in the impairment endpoints of the WPAI for CLBP (WPAI:LBP) will be summarized by treatment group. These endpoints are Activity impairment, Overall Work Impairment, Impairment While Working, and Work Time Missed due to Low Back Pain. These data will be categorized (0%, >0-5%, >5-10%, >10-25%, >25-50%, >50-75%, >75-<100%, 100%) and analyzed using the CMH test. This summary will use observed data only (no imputation for missing data).

17.5.3 Exploratory Analyses

Exploratory analyses are:

- Change in sensitivity to thermal stimuli on QST (subjects participating in the substudy). This will be reported in a separate report of the substudy.
- Univariate and multivariate regression analyses with each subject characteristic as an independent variable to determine the subjects' characteristics that predict suboptimal or optimal response to structured discontinuation of opioid therapy
- Changes from baseline in endocrine function and sexual function as characterized in the male and female questionnaires; relationship of changes in endocrine function to changes in PI; relationship of changes in endocrine function to changes in male and female sexual function; and relationship of baseline endocrine status to efficacy of opioid discontinuation.
- Changes from baseline in neurocognitive function as characterized by the number of correct responses from the DSST will be analyzed using ANCOVA (with model terms of baseline

score, stratification parameters, and treatment group) as described above for the primary endpoint analysis, using observed data (without multiple imputation):

17.6 Safety Analyses

Safety will be assessed by

- Occurrence of AEs
- Occurrence of abuse-related events
- Occurrence of withdrawal AEs
- Occurrence of opioid-specific side effects
- Changes in vital signs
- Changes in physical examination findings
- Changes in clinical laboratory parameters

Additional safety measures will include:

- Occurrence of abnormal UDT findings
- Occurrence of C-SSRS findings
- Occurrence and severity of opioid withdrawal effects as measured by SOWS and COWS.

17.6.1 Adverse Events

Version 18.0 or newer of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs.

An AE (classified by preferred term) that started during the treatment period will be considered a TEAE if it was not present prior to the first dose of study drug, or was present prior to the first dose of study drug but increased in intensity during the treatment period. If more than 1 AE is reported prior to the first dose of study drug and coded to the same preferred term, then the AE with the greatest intensity will be used as the benchmark for comparison to the AEs occurring during the treatment period which were also coded to that preferred term. Any AE present prior to the first dose of study drug that increases in intensity during the treatment period will be re-entered with a new start date of the date of increased intensity.

Descriptive statistics (the number and percentage) for subjects reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug.

The distribution of TEAEs by severity and relationship to study drug will be summarized by treatment group. The incidence of common (≥5% of subjects in any treatment group) TEAEs will be summarized by preferred term and treatment group and sorted by decreasing frequency in the discontinuation arm. SAEs and AEs leading to premature discontinuation of study drug will be summarized by preferred term and treatment group, and sorted by decreasing frequency in the discontinuation arm. SAEs will be

displayed separately for those events occurring before the first study drug dosing date and all subsequent ones.

Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation, and subjects who die (if any).

Although abuse-related events will be reported as AEs, these AEs will be reported separately in a descriptive fashion for each group at each visit.

17.6.2 Vital Signs

Descriptive statistics for vital signs (i.e., systolic and diastolic blood pressure, pulse rate, respiratory rate, and body weight) and their changes from baseline at each visit and at the end of study will be presented by treatment group.

Vital sign values are potentially clinically significant (PCS) if they meet both the observed value criteria and the change from baseline criteria. The criteria for PCS vital sign values will be detailed in the SAP. The PCS percentages will be calculated relative to the number of subjects with baseline and at least one post-baseline assessment. The numerator will be the total number of subjects with at least one PCS post-baseline vital sign value. A supportive listing of subjects with post-baseline PCS values will be provided including the subject ID, study center, baseline and post-baseline values. A listing of all AEs for subjects with PCS vital signs will also be provided.

17.6.3 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline at each assessment time point will be presented by treatment group for each clinical laboratory parameter.

The number and percentage of subjects with PCS post-baseline clinical laboratory values will be tabulated by treatment group. The criteria for PCS laboratory values will be detailed in the SAP. The PCS percentages will be calculated relative to the number of subjects with available non-PCS baseline values and at least one post-baseline assessment. The numerator will be the total number of subjects with available non-PCS baseline value and at least one post-baseline PCS value. A supportive listing of subjects with post-baseline PCS values will be provided, including the subject ID, study center, baseline and post-baseline values. A listing of all AEs for subjects with PCS laboratory values will also be provided.

17.6.4 Physical Examination

For each body system, the number and percentage of subjects with transitions from normal or not done at baseline to abnormal post-baseline will be presented by treatment group. The percentages will be calculated relative to the number of subjects having normal or missing assessments at baseline who also had a post-baseline physical examination. A listing of physical examination data for all subjects will also be provided.

17.6.5 Other Safety Parameters

Other safety parameters analyzed will be:

- UDT findings will be summarized descriptively as the type of abnormal finding.
- Occurrence of C-SSRS findings after baseline.

- Possible opioid withdrawal effects will be summarized descriptively with SOWS scores at Weeks 2, 4, and 6 and with COWS scores at Weeks 2 and 4.

17.7 Pharmacokinetic Analyses

Not applicable

17.8 Pharmacodynamic Analyses

Not applicable

17.9 Other Data (e.g., Health Economics/QOL, Pharmacogenetics, etc)

Work productivity will be measured by the WPAI. Analysis of WPAI data are described in the secondary efficacy analyses.

17.10 Interim Analysis

No interim analysis is planned for this study.

17.11 Statistical Software

Statistical analyses will be performed using Version 9.2 (or higher) of SAS® (SAS Institute, Cary, NC).

18 STUDY DRUG MATERIALS AND MANAGEMENT

18.1 Study Drug Identity

Study medications will include blinded ER formulations of morphine sulfate, oxycodone HCl, and oxymorphone HCl.

Morphine Sulfate Extended Release (MSER) in strengths of 15, 30, 60, and 100 mg, and matching placebos will be supplied by Purdue Pharma L.P.

Oxycodone HCl Extended Release (OCER) in strengths of 10, 20, 30, 40, 60, and 80 mg, and matching placebos will be supplied by Purdue Pharma L.P.

Oxymorphone HCl Extended Release (OMER) in strengths of 5, 10, 15, 20, 30, and 40 mg, and matching placebo will be supplied by Endo Pharmaceuticals.

Study prescribed drugs that will be used as rescue pain medications will include commercial-image, IR formulations of morphine sulfate, oxycodone HCl, oxymorphone HCl, and acetaminophen.

Morphine sulfate (MSIR) 15 mg will be supplied by West-Ward Laboratories.

Oxycodone HCl (OCIR) 5 mg will be supplied by Mallinckrodt Pharmaceuticals.

Oxymorphone HCl (OMIR) 5 mg will be supplied by Endo Pharmaceuticals Inc.

Acetaminophen 500 mg tablets will be sourced commercially.

18.2 Study Drug Packaging and Labeling

Blinded ER study drug and matching placebos will be packaged in 20-count blister cards minimally labeled with protocol reference, contents (“oxymorphone ER or placebo”, “oxycodone ER or placebo”, or “morphine sulfate ER or placebo”), Schedule II designation, storage and appropriate caution statements. Additionally, the supplying company for each product will be listed as the sponsor.

Open-label MSIR, OCIR, and OMIR will be packaged in 15-count blister cards minimally labeled with protocol reference, contents, Schedule II designation, storage and appropriate caution statements. Additionally, the supplying company for each product will be listed.

Acetaminophen will be supplied in commercial bottles with the original manufacturer’s labeling. An auxiliary label will be added with protocol reference, use instructions, storage and appropriate caution statements.

18.3 Study Drug Storage

All study medications and study prescribed drugs that will be used as rescue medications will be provided by OPC representative. Since MSER, OCER, OMER, MSIR, OCIR, and OMIR are Schedule II controlled substances according to the Controlled Substances Act of 1970, all study medications and study prescribed drugs will be stored in a locked facility with restricted access that meets Drug Enforcement Agency requirements.

18.4 Study Drug Preparation

At the time of dispensing, the investigator or designee will use the IRT system to determine which material kit(s) for study drug and rescue to dispense to a given subject. The investigator or designee will complete the subject number field on the kit labels.

18.5 Study Drug Accountability

The principal investigator is responsible for ensuring accountability of all drugs supplied and appropriate storage and allocation of these supplies.

The investigator is responsible for ensuring that all study medications and study prescribed drug used as rescue medications received at the site are inventoried and accountability performed and that dispensed drug is recorded in both the CRF and the study drug logs. The investigator, or designee, will verify drug accountability with subjects during site visits.

18.6 Study Drug Handling and Disposal

The principal investigator will not supply study medications or study prescribed drugs used as rescue medication to any person except those named as sub-investigators on Form FDA 1572, designated staff, and subjects in this study and will not dispense study drug or rescue medication from any sites other than those listed on Form FDA 1572. Study drug and rescue medication may not be relabeled or reassigned for use by other subjects. Chain of custody will be followed in accordance with the individual site's standard procedures and will be documented by the site and provided to the Sponsor. All unused study drug will be returned, and unit counts will be performed whenever medication is returned. The site must account for all study drug received. At the end of the study, all unused drug supplies will be returned to the OPC's packaging vendor.

19 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

19.1 Source Documents

Source documents include but are not limited to original documents, data and records such as hospital/ medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.

19.2 Study Monitoring

A representative of the OPC will meet with the Investigator and his/her staff prior to the entrance of the first subject to review study procedures and methods of recording findings in the eCRF.

After enrollment of the first subject, an OPC representative will be assigned to periodically monitor each Investigator site for study progress and to verify that standards of Good Clinical Practice (GCP) were followed. The Investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed eCRFs, signed consent forms and other study related documents are readily available for review.

19.3 Audits and Inspections

The Investigator shall permit audits and inspections by the Sponsor, its representatives and members of regulatory agencies. The Investigator should immediately notify the Sponsor of an upcoming FDA or other regulatory agency inspection.

19.4 Institutional Review Board (IRB)

The Investigator shall permit members of the IRB/Independent Ethic Committee (IEC) to have direct access to source documents.

19.5 Data Recording and Documentation

All data recordings and source documentation (including electronic health records) must be made available to the Sponsor (or designee), FDA and any other regulatory agencies that request access to study records, including source documents, for inspection and copying, in keeping with federal and local regulations.

20 QUALITY CONTROL AND QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified principal Investigators and appropriate study centers, review of protocol procedures with the principal Investigators and associated personnel prior to start of the study, and periodic monitoring visits conducted by the Sponsor or Sponsor representative. Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in Investigator site termination and regulatory authority notification.

The Sponsor or its designee will utilize qualified monitors to review and evaluate activities conducted at Investigator Sites.

The data will be entered into the clinical study database and verified for accuracy, following procedures defined by the Sponsor (or designee). Data will be processed and analyzed following procedures defined by the Sponsor (or designee).

The study will be monitored and/or audited at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the Study Protocol; International Conference on Harmonisation (ICH), E6 consolidated guidelines; and other applicable regulations. The extent, nature, and frequency of monitoring and/or audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. At the conclusion of a program, a compliance statement will be generated by the Sponsor (or designee) listing all audit activities performed during the clinical study.

21 ETHICS

21.1 Ethics Review

Approval by the IRB/IEC prior to the start of the study will be the responsibility of the Investigator. A copy of approval documentation will be supplied to the OPC representative along with a roster of IRB members that demonstrates appropriate composition (a DHHS Assurance Number will satisfy this requirement).

The study protocol, the informed consent form, advertisements, materials being provided to subjects and amendments (if any) will be approved to IRB/IECs at each study center in conformance with ICH E6, the Code of Federal Regulations (CFR), Title 21, Part 56 and any other applicable local laws. The Investigator is responsible for supplying the IRB/IEC with a copy of the current Investigator's Brochure (IB), Package Insert, or Summary of Product Characteristics as well as any updates issued during the study. During the course of the study, the Investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB/IEC of SAEs or other significant safety findings, per the policy of the IRB/IEC. At the conclusion of the study, the Investigator will submit a final report or close out report to the IRB/IEC and provide a copy to the OPC representative.

Any amendment to this protocol will be provided to the Investigator in writing by the OPC representative. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB and the signature page, signed by the Investigator, has been received by the OPC representative. Where the protocol is amended to eliminate or reduce the risk to the subject, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment and approval obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the subject, and must be immediately reported to the OPC representative.

The Investigator will be responsible for supplying updated safety and/or study information to study subjects as it becomes available.

21.2 Ethical Conduct of the Study

This clinical study is designed to comply with the ICH Guidance on General Considerations for Clinical Trials (62 FR 6611, December 17, 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (62 FR 62922, November 25, 1997), Good Clinical Practice: Consolidated Guidance (62 FR 25692, May 9, 1997) and 21 CFR parts 50, 54, 56 and 312.

The study will be conducted in full compliance with ICH E6, the FDA guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki defined in 21 CFR, 312.120.

21.3 Subject Information and Consent

Subjects, after having the study explained to them and an opportunity to have their questions answered sufficiently, will give voluntary and written informed consent (in compliance with ICH E6, 4.8 and 21CFR Parts 50 and 312) before participating in any study-related procedures.

In addition to obtaining informed consent, the Investigator is responsible for obtaining any additional documentation to demonstrate compliance with local privacy laws applicable to activities performed.

The consent process shall be recorded in source documents. Signed copies of the informed consent will be given to the Subject and originals will be placed in the Investigator study files.

A unique Subject identification number will be assigned according to section at the time that the Subject signs the informed consent form.

22 DATA HANDLING AND RECORDKEEPING

22.1 Data Collection

Data collection will involve the use of an electronic data capture (EDC) system to which only authorized personnel will have access. The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement for a user login and password to enter or change data. The level of access to the EDC system will be dependent on the person's role in the study.

Study data will be collected from source documents and entered into an eCRF within the EDC system. The Investigator will be responsible for ensuring the eCRFs are completed in a timely manner relative to the subject's visit. In addition to periodic monitoring occurring within the system by a Sponsor monitor, programmatic edit checks will be used to review EDC data for completeness, logic, and adherence to the study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study sites and closed electronically by the monitor, data management staff or authorized staff at the study site. Additionally, the Investigator will review eCRFs, ensure all missing or corrected data is provided and will sign the eCRF pages with an electronic signature.

An electronic audit trail will be maintained in the EDC system to track all changes made to data entered in the eCRF. Data will be retrievable in such a fashion that all information regarding each individual subject is attributable to that subject. Unless otherwise indicated, all data captured in the eCRF must first be captured in source documents. Data that can be directly recorded in the eCRF will be clearly identified in the section(s) of the protocol that describes the assessment(s).

In addition, any contact with the subject via telephone or other means that provide significant clinical information must be documented in source documents as described above.

22.2 Study Documentation

Upon study completion, the complete eCRF, in portable document format (PDF), will be created from the EDC system. Study sites will be provided with the PDF of the eCRF for their subjects.

Upon study completion, the Investigator's copy of the paper CRF will be retained in each subject's file.

23 REPORTING AND PUBLICATION

All data generated in this study are the property of the OPC. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and the OPC.

24 INVESTIGATOR OBLIGATIONS

24.1 Regulatory Documents

The Investigator is responsible for creating and/or maintaining all study documentation required by 21CFR 50, 54, 56 and 312, ICH, E6 section 8, as well as any other documentation defined in the protocol or the Investigator Agreement. The Investigator must maintain the documentation relating to this study and permit the OPC representative or a member of a regulatory agency access to such records.

The Investigator must provide the following key documents to the OPC representative prior to the start of the study:

- A completed and signed Form FDA1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised Form FDA1572 must be completed and returned to the OPC representative for submission to the FDA. For studies executed outside the United States, documentation required by the governing regulatory authority may be substituted for the Form FDA 1572.
- A fully executed contract
- The Investigator's Statement page in this protocol signed and dated by the Investigator and any subsequent amendment signature pages
- The IB acknowledgment of receipt page
- Curricula vitae for the Principal Investigator and all Sub-Investigators listed on Form FDA 1572, including a copy of each physician's license (if applicable)
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals or shorter intervals defined by the IRB/IEC. All subsequent modifications must be submitted and approved by the IRB, as described in section 21.1
- A copy of the IRB/IEC-approved informed consent form
- A list of IRB/IEC members or DHHS Assurance Number
- Laboratory certifications and normal ranges (if local labs are required by the protocol)
- A financial disclosure agreement completed and signed by the Investigator and all Sub-Investigators listed on Form FDA 1572. Investigator site staff members who submitted an initial financial disclosure are also responsible for informing the OPC representative of any changes to their initial financial disclosure form 1 year after the completion of the study.

A complete list of required regulatory documents will be supplied by the OPC or its representative.

24.2 Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of

responsibilities. The Investigator is responsible for ensuring all delegated staff members have been properly trained on the protocol and their assigned study responsibilities.

24.3 Medical Care of Study Subjects

The Investigator and/or a qualified sub-Investigator shall be responsible for the subjects' medical care. Any unrelated medical condition discovered during the course of the study should be communicated to the subject so that they may seek appropriate medical care. The Investigator will report all AEs as required by the protocol (section 14.5). The Investigator will inform study subjects of new information regarding the study drug as it becomes available.

24.4 Use of Investigational Materials

The Investigator will acknowledge that the study drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Principal Investigator or Sub-Investigators listed on Form FDA1572 (or other regulatory document, depending on region). Study drug must be stored in a safe and secure location. At study initiation, a representative from the OPC will inventory the study drug at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. The OPC or its representative will supply forms to document total inventory as well as subject specific accountability. The Investigator is responsible for monitoring subject's use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to the OPC or its designee (this may include empty packaging such as bottles and blister cards). It is the Investigator's responsibility to ensure that subjects return their medication.

Study drug that has Schedule II designation must be stored in a double-locked area (secure enclosure within a locked, controlled access location).

24.5 Retention of Records

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study (e.g., informed consents, laboratory reports, source documents, study drug dispensing records) for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation

The OPC or its representative will notify Investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by the OPC or its representative that the entire clinical investigation (not merely the Investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application/Clinical Trial Authorization or request for marketing approval (NDA/Marketing Authorization Application).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The OPC or its representative must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with the OPC or its representative.

24.6 Subject Confidentiality

All subject records submitted to the OPC or its designee will be identified only by code number. Subjects' names are not to be transmitted to the OPC. The Investigator will keep a Master Subject List on which the identification number and the full name, address, and telephone number of each subject are listed. It is the Investigators' responsibility to inform study subjects that representatives of the Sponsor, FDA, or other regulatory agencies may review all records that support their participation in the study. The Investigator will adhere to all privacy laws to which he/she is subject.

25 TERMINATION OF STUDY

The Sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

26 INVESTIGATOR'S STATEMENT

I agree to conduct the study in accordance with the protocol, and with all applicable government regulations and Good Clinical Practice guidance.

_____ _____/_____/_____

Investigator's Signature Date

_____

Printed Name of Investigator

27 REFERENCES

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APPENDICES

Appendix A – Quebec Task Force on Spinal Disorders

Classification	Symptoms	Duration of symptoms from onset	Working status at time of evaluation
1	Pain without radiation	a (<7 days) b (7 days – 7 weeks) c (>7 weeks)	W (working) I (idle)
2	Pain + radiation to extremity, proximally		
3	Pain + radiation to extremity, distally*		
4	Pain + radiation to upper/lower limb, neurological signs		
5	Presumptive compression of a spinal nerve root on a simple roentgenogram (ie, spinal instability or fracture)		
6	Compression of a spinal nerve root confirmed by -Specific imaging techniques (ie, computerized axial tomography, myelography, or magnetic resonance imaging) -Other diagnostic techniques (eg, electromyography, venography)		
7	Spinal stenosis		
8	Postsurgical status, 1-6 months after intervention		
9	Postsurgical status, >6 months after intervention 9.1 Asymptomatic 9.2 Symptomatic		
10	Chronic pain syndrome		W (working) I (idle)
11	Other diagnoses		

* Not applicable to the thoracic segment

Reference: Spitzer WO, LeBlanc FE, Dupuis M. Scientific approach to the assessment and management of activity-related spinal disorders. A monograph for clinicians. Report of the Quebec Task Force on Spinal Disorders. *Spine*. 1987;12(7 Suppl):S1–S59.

Appendix B – Dosing Schedule

Optimal Responders: Open-label Taper and Titration Schedule

Optimal Responders will go through an open label taper phase to confirm their underlying pain state. After a certain level of pain flare is confirmed they will titrate their dose to control their pain within the allowable dose range. Once the pain intensity score is ≤5 for 3 consecutive pain scores with satisfaction with pain and physical function and acceptable side effects, they will enter the Blinded Structured Discontinuation Period.

Patient group	Observation Period	Taper to Flare	Flare established	Titration	Baseline to confirm stable pain ≤5
Optimal Responders	Current medication	Active Open Label taper doses (decreased every 3 days)		Active Open Label titration doses back towards starting dose (increased every 4 days)	Active dose @ entry

The tables below shows dosing paradigms for a variety of expected doses. Most probable doses in **BOLD** (doses achieved with same dosage strengths).

Optimal Responders: Morphine Sulfate ER (MSER) Open-label Taper and Titration Schedule

ER MORPHINE Tablet Strengths 15 mg 30 mg 60 mg 100 mg	Total Daily Dose @ entry	Patient group	Closest BID dose	Taper Days 1-3	Taper Days 4-6	Taper Days 7-9	Taper Days 10-12	Taper Days 13-14	Titration Step 1 (4 days)	Titration Step2 (4 days)	Titration Step 3 (4 days)	Titration Step 4 (4 days)	Titration Step 5 (4 days)	Titration Step 6 (4 days)	Titration Step 7 (4 days)	Baseline Period
	120mg - 149mg	Optimal Responders	**60A**	**30A/15A**	**30A**	**15A**	**No Drug**		**15A**	**30A**	**30A/15A**	**60A**	60A/30A	60A/60A	N/A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	150mg - 179mg	Optimal Responders	60A/15A	60A	30A/15A	30A	15A	No Drug	15A	30A	30A/15A	60A	60A/15A	100A	100A/30A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	180mg - 199mg	Optimal Responders	60A/30A	60A/15A	30A/15A	30A	15A	No Drug	15A	30A	30A/15A	60A/15A	60A/30A	60A/60A	100A/30A/15A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	200mg - 229mg	Optimal Responders	**100A**	**60A/15A**	**60A**	**30A**	**15A**	**No Drug**	**15A**	**30A**	**60A**	**60A/15A**	**100A**	100A/30A	100A/60A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	230mg - 259mg	Optimal Responders	**60A/60A**	**60A/30A**	**60A**	**30A**	**15A**	**No Drug**	**15A**	**30A**	**60A**	**60A/30A**	**60A/60A**	100A/30A/15A	60A/60A/60A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	260mg - 289mg	Optimal Responders	100A/30A	100A	60A/15A	30A/15A	15A	No Drug	15A	30A/15A	60A/15A	100A	100A/30A	100A/60A	100A/60A/30A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	290mg - 319mg	Optimal Responders	100A/30A/15A	100A/15A	60A/30A	60A	30A	No Drug	30A	60A	60A/30A	100A/15A	100A/30A/15A	60A/60A/60A	100A/100A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days

Establish Flare: (Average daily PI score >5; increased by ≥1.5 points for ≥3 consecutive days from the mean Average PI). Then titrate to stable dose.

All doses represent single BID dose in mg
A = Active; P = Placebo

Optimal Responders: Morphine Sulfate ER (MSER) Open-label Taper and Titration Schedule (Cont'd)

ER MORPHINE	Total Daily Dose @ entry	Patient group	Closest BID dose	Taper Days 1-3	Taper Days 4-6	Taper Days 7-9	Taper Days 10-12	Taper Days 13-14	Titration Step 1 (4 days)	Titration Step2 (4 days)	Titration Step 3 (4 days)	Titration Step 4 (4 days)	Titration Step 5 (4 days)	Titration Step 6 (4 days)	Titration Step 7 (4 days)	Baseline Period
	320mg - 349mg	Optimal Responders	100A/60A	60A/60A	60A/30A	60A	30A	No Drug	30A	60A	60A/30A	60A/60A	100A/60A	100A/60A/30A	100A/100A/15A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	360mg - 379mg	Optimal Responders	**60A/60A/60A**	**100A/30A**	**60A/30A**	**60A**	**30A**	**No Drug**	**30A**	**60A**	**60A/30A**	**100A/30A**	**60A/60A/60A**	100A/100A	100A/100A/30A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	380mg - 399mg	Optimal Responders	100A/60A/30A	100A/30A/15A	100A	60A/15A	30A	No Drug	30A	60A/15A	100A	100A/30A/15A	100A/60A/30A	100A/100A/15A	100A/100A/60A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	400mg - 429mg	Optimal Responders	**100A/100A**	**100A/60A**	**100A/15A**	**60A/15A**	**30A**	**No Drug**	**30A**	**60A/15A**	**100A/15A**	**100A/60A**	**100A/100A**	100A/100A/30A		Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	430mg - 459mg	Optimal Responders	100A/100A/15A	100A/60A/15A	100A/30A	60A/30A	30A	No Drug	30A	60A/30A	100A/30A	100A/60A/15A	100A/100A/15A	100A/100A/60A		Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	460mg - 519mg	Optimal Responders	100A/100A/30A	100A/60A/30A	100A/30A	60A/30A	30A	No Drug	30A	60A/30A	100A/30A	100A/60A/30A	100A/100A/30A	100A/100A/60A		Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	520mg - 540mg	Optimal Responders	100A/100A/60A	100A/100A	100A/60A	100A	30A	No Drug	30A	100A	100A/60A	100A/100A	100A/100A/60A			Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days

Establish Flare: (Average daily PI score >5; increased by ≥1.5 points for ≥3 consecutive days from the mean Average PI). Then titrate to stable dose.

All doses represent single BID dose in mg
A = Active; P = Placebo

Optimal Responders: Oxycodone ER (OCER) Open-label Taper and Titration Schedule

ER OXYCODONE Tablet Strengths	Total Daily Dose @ entry	Patient group	Closest BID dose	Taper Days 1-3	Taper Days 4-6	Taper Days 7-9	Taper Days 10-12	Taper Days 13-14	Titration Step 1 (4 days)	Titration Step2 (4 days)	Titration Step 3 (4 days)	Titration Step 4 (4 days)	Titration Step 5 (4 days)	Titration Step 6 (4 days)	Titration Step 7 (4 days)	Baseline Period
10 mg 20 mg 30 mg 40 mg 60 mg 80 mg	80mg - 99mg	Optimal Responders	**40A**	**30A**	**20A**	**10A**	**No Drug**		**10A**	**20A**	**30A**	**40A**	60A	80A	N/A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	100mg - 109mg	Optimal Responders	30A/20A	40A	30A	20A	10A	No Drug	10A	20A	30A	40A	30A/20A	40A/30A	60A/30A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	110mg - 139mg	Optimal Responders	**60A**	**40A**	**30A**	**20A**	**10A**	**No Drug**	**10A**	**20A**	**30A**	**40A**	**60A**	80A	60A/40A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	140mg - 149mg	Optimal Responders	40A/30A	30A/20A	40A	30A	10A	No Drug	10A	30A	40A	30A/20A	40A/30A	60A/30A	80A/30A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	150mg - 179mg	Optimal Responders	**80A**	**60A**	**40A**	**20A**	**10A**	**No Drug**	**10A**	**20A**	**40A**	**60A**	**80A**	60A/40A	60A/60A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	180mg - 199mg	Optimal Responders	60A/30A	40A/30A	40A	20A	10A	No Drug	10A	20A	40A	40A/30A	60A/30A	80A/30A	80A/60A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	200mg - 219mg	Optimal Responders	60A/40A	80A	60A	40A	20A	No Drug	20A	40A	60A	80A	60A/40A	60A/60A	80A/40A/30A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days

Establish Flare: (Average daily PI score >5; increased by ≥1.5 points for ≥3 consecutive days from the mean Average PI). Then titrate to stable dose.

All doses represent single BID dose in mg
A = Active; P = Placebo

Optimal Responders: Oxycodone ER (OCER) Open-label Taper and Titration Schedule (Cont'd)

ER OXYCODONE	Total Daily Dose @ entry	Patient group	Closest BID dose	Taper Days 1-3	Taper Days 4-6	Taper Days 7-9	Taper Days 10-12	Taper Days 13-14	Titration Step 1 (4 days)	Titration Step2 (4 days)	Titration Step 3 (4 days)	Titration Step 4 (4 days)	Titration Step 5 (4 days)	Titration Step 6 (4 days)	Titration Step 7 (4 days)	Baseline Period
	220mg - 239mg	Optimal Responders	80A/30A	80A	60A	40A	20A	No Drug	20A	40A	60A	80A	80A/30A	80A/60A	80A/80A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	240mg - 279mg	Optimal Responders	**60A/60A**	**60A/30A**	**40A/30A**	**40A**	**20A**	**No Drug**	**20A**	**40A**	**40A/30A**	**60A/30A**	**60A/60A**	80A/40A/30A	80A/80A/10A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	280mg - 299mg	Optimal Responders	80A/60A	60A/40A	40A/30A	40A	20A	No Drug	20A	40A	40A/30A	60A/40A	80A/60A	80A/80A	60A/60A/60A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	300mg - 319mg	Optimal Responders	80A/40A/30A	60A/60A	60A/30A	60A	30A	No Drug	30A	60A	60A/30A	60A/60A	80A/40A/30A	80A/80A/10A		Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	320mg - 339mg	Optimal Responders	**80A/80A**	**60A/60A**	**60A/30A**	**60A**	**30A**	**No Drug**	**30A**	**60A**	**60A/30A**	**60A/60A**	**80A/80A**	60A/60A/60A		Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	340mg - 359mg	Optimal Responders	80A/80A/10A	80A/60A	60A/40A	60A	30A	No Drug	30A	60A	60A/40A	80A/60A	80A/80A/10A			Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	360mg	Optimal Responders	**60A/60A/60A**	**80A/60A**	**60A/30A**	**60A**	**30A**	**No Drug**	**30A**	**60A**	**60A/30A**	**80A/60A**	**60A/60A/60A**			Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days

Establish Flare: (Average daily PI score >5; increased by ≥1.5 points for ≥3 consecutive days from the mean Average PI). Then titrate to stable dose.

All doses represent single BID dose in mg
A = Active; P = Placebo

Optimal Responders: Oxymorphone ER (OMER) Open-label Taper and Titration Schedule

ER OXYMORPHONE Tablet Strengths	Total Daily Dose @ entry	Patient group	Closest BID dose	Taper Days 1-3	Taper Days 4-6	Taper Days 7-9	Taper Days 10-12	Taper Days 13-14	Titration Step 1 (4 days)	Titration Step2 (4 days)	Titration Step 3 (4 days)	Titration Step 4 (4 days)	Titration Step 5 (4 days)	Titration Step 6 (4 days)	Titration Step 7 (4 days)	Baseline Period
5 mg 10 mg 15 mg 20 mg 30 mg 40 mg	40mg - 49mg	Optimal Responders	20A	Establish Flare: (Average daily PI score >5; increased by ≥1.5 points for ≥3 consecutive days from the mean Average PI). Then titrate to stable dose.										40A	N/A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	50mg - 59mg	Optimal Responders	15A/10A	Establish Flare: (Average daily PI score >5; increased by ≥1.5 points for ≥3 consecutive days from the mean Average PI). Then titrate to stable dose.										20A/15A	30A/15A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	60mg - 69mg	Optimal Responders	30A	Establish Flare: (Average daily PI score >5; increased by ≥1.5 points for ≥3 consecutive days from the mean Average PI). Then titrate to stable dose.										40A	30A/20A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	70mg - 79mg	Optimal Responders	20A/15A	Establish Flare: (Average daily PI score >5; increased by ≥1.5 points for ≥3 consecutive days from the mean Average PI). Then titrate to stable dose.										30A/15A	40A/15A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	80mg - 89mg	Optimal Responders	40A	Establish Flare: (Average daily PI score >5; increased by ≥1.5 points for ≥3 consecutive days from the mean Average PI). Then titrate to stable dose.										30A/20A	30A/30A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	90mg - 99mg	Optimal Responders	30A/15A	Establish Flare: (Average daily PI score >5; increased by ≥1.5 points for ≥3 consecutive days from the mean Average PI). Then titrate to stable dose.										40A/15A	40A/30A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	100mg - 109mg	Optimal Responders	30A/20A	Establish Flare: (Average daily PI score >5; increased by ≥1.5 points for ≥3 consecutive days from the mean Average PI). Then titrate to stable dose.										30A/30A	40A/40A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	110mg - 119mg	Optimal Responders	40A/15A	Establish Flare: (Average daily PI score >5; increased by ≥1.5 points for ≥3 consecutive days from the mean Average PI). Then titrate to stable dose.										40A/30A	40A/40A/10A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days

All doses represent single BID dose in mg
A = Active; P = Placebo

Optimal Responders: Oxymorphone ER (OMER) Open-label Taper and Titration Schedule (Cont'd)

ER OXYMORPHONE	Total Daily Dose @ entry	Patient group	Closest BID dose	Taper Days 1-3	Taper Days 4-6	Taper Days 7-9	Taper Days 10-12	Taper Days 13-14	Titration Step 1 (4 days)	Titration Step2 (4 days)	Titration Step 3 (4 days)	Titration Step 4 (4 days)	Titration Step 5 (4 days)	Titration Step 6 (4 days)	Titration Step 7 (4 days)	Baseline Period
	120mg - 129mg	Optimal Responders	**30A/30A**	**30A/15A**	**20A/15A**	**15A/10A**	**10A**	**No Drug**	**10A**	**15A/10A**	**20A/15A**	**30A/15A**	**30A/30A**	40A/40A	40A/40A/20A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	130mg - 139mg	Optimal Responders	30A/20A/15A	30A/20A	40A	15A/10A	10A	No Drug	10A	15A/10A	40A	30A/20A	30A/20A/15A	40A/20A/15A	40A/30A/15A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	140mg - 149mg	Optimal Responders	40A/30A	30A/20A	40A	15A/10A	10A	No Drug	10A	15A/10A	40A	30A/20A	40A/30A	40A/40A	30A/30A/30A	Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	150mg - 159mg	Optimal Responders	40A/20A/15A	60A	30A/15A	30A	15A	No Drug	15A	30A	30A/15A	60A	40A/20A/15A	40A/30A/15A		Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	160mg - 169mg	Optimal Responders	**40A/40A**	**60A**	**30A/15A**	**30A**	**15A**	**No Drug**	**15A**	**30A**	**30A/15A**	**60A**	**40A/40A**	30A/30A/30A		Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	170mg - 179mg	Optimal Responders	40A/30A/15A	40A/30A	30A/20A	30A	15A	No Drug	15A	30A	30A/20A	40A/30A	40A/30A/15A			Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days
	180mg	Optimal Responders	**30A/30A/30A**	**40A/30A**	**30A/20A**	**30A**	**15A**	**No Drug**	**15A**	**30A**	**30A/20A**	**40A/30A**	**30A/30A/30A**			Highest Titration dose which resulted in a mean Average daily PI score ≤5 for at least 3 consecutive days

Establish Flare: (Average daily PI score >5; increased by ≥1.5 points for ≥3 consecutive days from the mean Average PI). Then titrate to stable dose.

All doses represent single BID dose in mg
A = Active; P = Placebo

Run-in, Baseline and Blinded Structured Opioid Discontinuation Schedule

The Drug Supply Logistics Team is planning to package in blister cards by dose strength to afford the most flexibility for retaining patients on their dose at entry to the study and enabling a variety of taper schedules.
In general, the taper will be managed with a double-dummy design where patients maintaining dose get placebo doses added during the taper weeks. Patients being discontinued will switch to placebo versions of their dose at entry and will have active taper doses added.
This design ensures both the Maintain and the Discontinue arms will be dosed with the same number of identical tablets as they progress through the study, thus maintaining the blind.

Patient group	Baseline Period	Taper wks	Study Duration
Maintain	Active dose @ entry	Active dose @ entry PLUS Placebo taper doses	Active dose @ entry
Discontinue	Active dose @ entry	Placebo dose @ entry PLUS Active taper doses	Placebo dose @ entry

The tables below shows dosing paradigms for a variety of expected doses. Most probable doses in BOLD (doses achieved with same dosage strengths)

Blinded Structured Opioid Discontinuation Schedule - Morphine Sulfate ER

ER MORPHINE Tablet Strengths	Total Daily Dose @ entry	Closest BID dose @ entry	Patient group	Baseline Period	Taper wk 1	Taper wk 2	Taper wk 3	Taper wk 4	Study Duration
15 mg 30 mg 60 mg 100 mg	120mg - 149mg	**60**	Maintain	**60A**	**60A**	**60A**	**60A**	**60A**	**60A**
					30P/15P	**30P**	**15P**	**15P**	
			Discontinue	**60A**	**60P**	**60P**	**60P**	**60P**	**60P**
					30A/15A	**30A**	**15A**	**15P**	
	150mg - 179mg	75	Maintain	60A/15A	60A/15A	60A/15A	60A/15A	60A/15A	60A/15A
					60P	30P/15P	30P	15P	
			Discontinue	60A/15A	60P/15P	60P/15P	60P/15P	60P/15P	60P/15P
					60A	30A/15A	30A	15A	
	180mg - 199mg	90	Maintain	60A/30A	60A/30A	60A/30A	60A/30A	60A/30A	60A/30A
					60P/15P	30P/15P	30P	15P	
			Discontinue	60A/30A	60P/30P	60P/30P	60P/30P	60P/30P	60P/30P
					60A/15A	30A/15A	30A	15A	
	200mg - 229mg	**100**	Maintain	**100A**	**100A**	**100A**	**100A**	**100A**	**100A**
					60P/15P	**60P**	**30P**	**15P**	
			Discontinue	**100A**	**100P**	**100P**	**100P**	**100P**	**100P**
					60A/15A	**60A**	**30A**	**15A**	
	230mg - 259mg	**120**	Maintain	**60A/60A**	**60A/60A**	**60A/60A**	**60A/60A**	**60A/60A**	**60A/60A**
					60P/30P	**60P**	**30P**	**15P**	
			Discontinue	**60A/60A**	**60P/60P**	**60P/60P**	**60P/60P**	**60P/60P**	**60P/60P**
					60A/30A	**60A**	**30A**	**15A**	
	260mg - 289mg	130	Maintain	100A/30A	100A/30A	100A/30A	100A/30A	100A/30A	100A/30A
					100P	60P/15P	30P/15P	15P	
			Discontinue	100A/30A	100P/30P	100P/30P	100P/30P	100P/30P	100P/30P
					100A	60A/15A	30A/15A	15A	
	290mg - 319mg	145	Maintain	100A/30A/15A	100A/30A/15A	100A/30A/15A	100A/30A/15A	100A/30A/15A	100A/30A/15A
					100P/15P	60P/30P	60P	30P	
			Discontinue	100A/30A/15A	100P/30P/15P	100P/30P/15P	100P/30P/15P	100P/30P/15P	100P/30P/15P
					100A/15A	60A/30A	60A	30A	

All doses represent single BID dose in mg

A = Active; P = Placebo

Blinded Structured Opioid Discontinuation Schedule - Morphine Sulfate ER (Cont'd)

ER MORPHINE	Total Daily Dose @ entry	Closest BID dose @ entry	Patient group	Baseline Period	Taper wk 1	Taper wk 2	Taper wk 3	Taper wk 4	Study Duration
	320mg - 359mg	160	Maintain	100A/60A	100A/60A	100A/60A	100A/60A	100A/60A	100A/60A
					60P/60P	60P/30P	60P	30P	
			Discontinue	100A/60A	100P/60P	100P/60P	100P/60P	100P/60P	100P/60P
					60A/60A	60A/30A	60A	30A	
	360mg - 379mg	**180**	Maintain	**60A/60A/60A**	**60A/60A/60A**	**60A/60A/60A**	**60A/60A/60A**	**60A/60A/60A**	**60A/60A/60A**
					100P/30P	**60P/30P**	**60P**	**30P**	
			Discontinue	**60A/60A/60A**	**60P/60P/60P**	**60P/60P/60P**	**60P/60P/60P**	**60P/60P/60P**	**60P/60P/60P**
					100A/30A	**60A/30A**	**60A**	**30A**	
	380mg - 399mg	190	Maintain	100A/60A/30A	100A/60A/30A	100A/60A/30A	100A/60A/30A	100A/60A/30A	100A/60A/30A
					100P/30P/15P	100P	60P/15P	30P	
			Discontinue	100A/60A/30A	100P/60P/30P	100P/60P/30P	100P/60P/30P	100P/60P/30P	100P/60P/30P
					100A/30A/15A	100A	60A/15A	30A	
	400mg - 429mg	**200**	Maintain	**100A/100A**	**100A/100A**	**100A/100A**	**100A/100A**	**100A/100A**	**100A/100A**
					100P/60P	**100P/15P**	**60P/15P**	**30P**	
			Discontinue	**100A/100A**	**100P/100P**	**100P/100P**	**100P/100P**	**100P/100P**	**100P/100P**
					100A/60A	**100A/15A**	**60A/15A**	**30A**	
	430mg - 459mg	215	Maintain	100A/100A/15A	100A/100A/15A	100A/100A/15A	100A/100A/15A	100A/100A/15A	100A/100A/15A
					100P/60P/15P	100P/30P	60P/30P	30P	
			Discontinue	100A/100A/15A	100P/100P/15P	100P/100P/15P	100P/100P/15P	100P/100P/15P	100P/100P/15P
					100A/60A/15A	100A/30A	60A/30A	30A	
	460mg - 519mg	230	Maintain	100A/100A/30A	100A/100A/30A	100A/100A/30A	100A/100A/30A	100A/100A/30A	100A/100A/30A
					100P/60P/30P	100P/30P	60P/30P	30P	
			Discontinue	100A/100A/30A	100P/100P/30P	100P/100P/30P	100P/100P/30P	100P/100P/30P	100P/100P/30P
					100A/60A/30A	100A/30A	60A/30A	30A	
	520mg - 540mg	260	Maintain	100A/100A/60A	100A/100A/60A	100A/100A/60A	100A/100A/60A	100A/100A/60A	100A/100A/60A
					100P/100P	100P/60P	100P	30P	
			Discontinue	100A/100A/60A	100P/100P/60P	100P/100P/60P	100P/100P/60P	100P/100P/60P	100P/100P/60P
					100A/100A	100A/60A	100A	30A	

All doses represent single BID dose in mg

A = Active; P = Placebo

Blinded Structured Opioid Discontinuation Period – Oxycodone ER

ER OXYCODONE Tablet Strengths	Total Daily Dose @ entry	Closest BID dose @ entry	Patient group	Baseline Period	Taper wk 1	Taper wk 2	Taper wk 3	Taper wk 4	Study Duration
10 mg 20 mg 30 mg 40 mg 60 mg 80 mg	80mg - 99mg	40	Maintain	**40A**	**40A**	**40A**	**40A**	**40A**	**40A**
					30P	**20P**	**10P**	**10P**	
			Discontinue	**40A**	**40P**	**40P**	**40P**	**40P**	**40P**
					30A	**20A**	**10A**	**10P**	
	100mg - 109mg	50	Maintain	30A/20A	30A/20A	30A/20A	30A/20A	30A/20A	30A/20A
					40P	30P	20P	10P	
			Discontinue	30A/20A	30P/20P	30P/20P	30P/20P	30P/20P	30P/20P
					40A	30A	20A	10A	
	110mg - 139mg	60	Maintain	**60A**	**60A**	**60A**	**60A**	**60A**	**60A**
					40P	**30P**	**20P**	**10P**	
			Discontinue	**60A**	**60P**	**60P**	**60P**	**60P**	**60P**
					40A	**30A**	**20A**	**10A**	
	140mg - 149mg	70	Maintain	40A/30A	40A/30A	40A/30A	40A/30A	40A/30A	40A/30A
					30P/20P	40P	30P	10P	
			Discontinue	40A/30A	40P/30P	40P/30P	40P/30P	40P/30P	40P/30P
					30A/20A	40A	30A	10A	
	150mg - 179mg	80	Maintain	**80A**	**80A**	**80A**	**80A**	**80A**	**80A**
					30P/30P	**40P**	**20P**	**10P**	
			Discontinue	**80A**	**80P**	**80P**	**80P**	**80P**	**80P**
					30A/30A	**40A**	**20A**	**10A**	
	180mg - 199mg	90	Maintain	60A/30A	60A/30A	60A/30A	60A/30A	60A/30A	60A/30A
					40P/30P	40P	20P	10P	
			Discontinue	60A/30A	60P/30P	60P/30P	60P/30P	60P/30P	60P/30P
					40A/30A	40A	20A	10A	
	200mg - 219mg	100	Maintain	60A/40A	60A/40A	60A/40A	60A/40A	60A/40A	60A/40A
					80P	60P	40P	20P	
			Discontinue	60A/40A	60P/40P	60P/40P	60P/40P	60P/40P	60P/40P
					80A	60A	40A	20A	

All doses represent single BID dose in mg

A = Active; P = Placebo

Blinded Structured Opioid Discontinuation Period – Oxycodone ER (Cont'd)

ER OXYCODONE	Total Daily Dose @ entry	Closest BID dose @ entry	Patient group	Baseline Period	Taper wk 1	Taper wk 2	Taper wk 3	Taper wk 4	Study Duration
	220mg - 239mg	110	Maintain	80A/30A	80A/30A	80A/30A	80A/30A	80A/30A	80A/30A
					80P	60P	40P	20P	
			Discontinue	80A/30A	80P/30P	80P/30P	80P/30P	80P/30P	80P/30P
					80A	60A	40A	20A	
	240mg - 279mg	**120**	Maintain	**60A/60A**	**60A/60A**	**60A/60A**	**60A/60A**	**60A/60A**	**60A/60A**
					60P/30P	**40P/30P**	**40P**	**20P**	
			Discontinue	**60A/60A**	**60P/60P**	**60P/60P**	**60P/60P**	**60P/60P**	**60P/60P**
					60A/30A	**40A/30A**	**40A**	**20A**	
	280mg - 299mg	140	Maintain	80A/60A	80A/60A	80A/60A	80A/60A	80A/60A	80A/60A
					60P/40P	40P/30P	40P	20P	
			Discontinue	80A/60A	80P/60P	80P/60P	80P/60P	80P/60P	80P/60P
					60A/40A	40A/30A	40A	20A	
	300mg - 319mg	150	Maintain	80A/40A/30A	80A/40A/30A	80A/40A/30A	80A/40A/30A	80A/40A/30A	80A/40A/30A
					60P/60P	60P/30P	60P	30P	
			Discontinue	80A/40A/30A	80P/40P/30P	80P/40P/30P	80P/40P/30P	80P/40P/30P	80P/40P/30P
					60A/60A	60A/30A	60A	30A	
	320mg - 339mg	**160**	Maintain	**80A/80A**	**80A/80A**	**80A/80A**	**80A/80A**	**80A/80A**	**80A/80A**
					60P/60P	**60P/30P**	**60P**	**30P**	
			Discontinue	**80A/80A**	**80P/80P**	**80P/80P**	**80P/80P**	**80P/80P**	**80P/80P**
					60A/60A	**60A/30A**	**60A**	**30A**	
	340mg - 359mg	170	Maintain	80A/80A/10A	80A/80A/10A	80A/80A/10A	80A/80A/10A	80A/80A/10A	80A/80A/10A
					80P/60P	60P/40P	60P	30P	
			Discontinue	80A/80A/10A	80P/80P/10P	80P/80P/10P	80P/80P/10P	80P/80P/10P	80P/80P/10P
					80A/60A	60A/40A	60A	30A	
	360mg	**180**	Maintain	**60A/60A/60A**	**60A/60A/60A**	**60A/60A/60A**	**60A/60A/60A**	**60A/60A/60A**	**60A/60A/60A**
					80P/60P	**60P/30P**	**60P**	**30P**	
			Discontinue	**60A/60A/60A**	**60P/60P/60P**	**60P/60P/60P**	**60P/60P/60P**	**60P/60P/60P**	**60P/60P/60P**
					80A/60A	**60A/30A**	**60A**	**30A**	

All doses represent single BID dose in mg
A = Active; P = Placebo

Blinded Structured Opioid Discontinuation Period – Oxymorphone ER

ER OXYMORPHONE	Total Daily Dose @ entry	Single BID dose @ entry	Patient group	Baseline Period	Taper wk 1	Taper wk 2	Taper wk 3	Taper wk 4	Study Duration
Tablet Strengths	40mg - 49mg	**20**	Maintain	**20A**	**20A**	**20A**	**20A**	**20A**	**20A**
5 mg					**15P**	**10P**	**5P**	**5P**	
10 mg			Discontinue	**20A**	**20P**	**20P**	**20P**	**20P**	**20P**
15 mg					**15A**	**10A**	**5A**	**5P**	
20 mg	50mg - 59mg	25	Maintain	15A/10A	15A/10A	15A/10A	15A/10A	15A/10A	15A/10A
30 mg					20P	15P	10P	5P	
40 mg			Discontinue	15A/10A	15P/10P	15P/10P	15P/10P	15P/10P	15P/10P
					20A	15A	10A	5A	
	60mg - 69mg	**30**	Maintain	**30A**	**30A**	**30A**	**30A**	**30A**	**30A**
					15P/10P	**20P**	**10P**	**5P**	
			Discontinue	**30A**	**30P**	**30P**	**30P**	**30P**	**30P**
					15A/10A	**20A**	**10A**	**5A**	
	70mg - 79mg	35	Maintain	20A/15A	20A/15A	20A/15A	20A/15A	20A/15A	20A/15A
					30P	20P	10P	5P	
			Discontinue	20A/15A	20P/15P	20P/15P	20P/15P	20P/15P	20P/15P
					30A	20A	10A	5A	
	80mg - 89mg	**40**	Maintain	**40A**	**40A**	**40A**	**40A**	**40A**	**40A**
					30P	**20P**	**15P**	**10P**	
			Discontinue	**40A**	**40P**	**40P**	**40P**	**40P**	**40P**
					30A	**20A**	**15A**	**10A**	
	90mg - 99mg	45	Maintain	30A/15A	30A/15A	30A/15A	30A/15A	30A/15A	30A/15A
					20P/15P	15P/10P	15P	10P	
			Discontinue	30A/15A	30P/15P	30P/15P	30P/15P	30P/15P	30P/15P
					20A/15A	15A/10A	15A	10A	

All doses represent single BID dose in mg
A = Active; P = Placebo

Blinded Structured Opioid Discontinuation Period – Oxymorphone ER (Cont'd)

ER OXYMORPHONE	Total Daily Dose @ entry	Single BID dose @ entry	Patient group	Baseline Period	Taper wk 1	Taper wk 2	Taper wk 3	Taper wk 4	Study Duration
	100mg - 109mg	50	Maintain	30A/20A	30A/20A	30A/20A	30A/20A	30A/20A	30A/20A
					40P	30P	20P	10P	
			Discontinue	30A/20A	30P/20P	30P/20P	30P/20P	30P/20P	30P/20P
					40A	30A	20A	10A	
	110mg - 119mg	55	Maintain	40A/15A	40A/15A	40A/15A	40A/15A	40A/15A	40A/15A
					40P	30P	20P	10P	
			Discontinue	40A/15A	40P/15P	40P/15P	40P/15P	40P/15P	40P/15P
					40A	30A	20A	10A	
	120mg - 129mg	**60**	Maintain	**30A/30A**	**30A/30A**	**30A/30A**	**30A/30A**	**30A/30A**	**30A/30A**
					30P/15P	**20P/15P**	**15P/10P**	**10P**	
			Discontinue	**30A/30A**	**30P/30P**	**30P/30P**	**30P/30P**	**30P/30P**	**30P/30P**
					30A/15A	**20A/15A**	**15A/10A**	**10A**	
	130mg - 139mg	65	Maintain	30A/20A/15A	30A/20A/15A	30A/20A/15A	30A/20A/15A	30A/20A/15A	30A/20A/15A
					30P/20P	40P	15P/10P	10P	
			Discontinue	30A/20A/15A	30P/20P/15P	30P/20P/15P	30P/20P/15P	30P/20P/15P	30P/20P/15P
					30A/20A	40A	15A/10A	10A	
	140mg - 149mg	70	Maintain	40A/30A	40A/30A	40A/30A	40A/30A	40A/30A	40A/30A
					30P/20P	40P	15P/10P	10P	
			Discontinue	40A/30A	40P/30P	40P/30P	40P/30P	40P/30P	40P/30P
					30A/20A	40A	15A/10A	10A	
	150mg - 159mg	75	Maintain	40A/20A/15A	40A/20A/15A	40A/20A/15A	40A/20A/15A	40A/20A/15A	40A/20A/15A
					30P/30P	30P/15P	30P	15P	
			Discontinue	40A/20A/15A	40P/20P/15P	40P/20P/15P	40P/20P/15P	40P/20P/15P	40P/20P/15P
					30A/30A	30A/15A	30A	15A	
	160mg - 169mg	**80**	Maintain	**40A/40A**	**40A/40A**	**40A/40A**	**40A/40A**	**40A/40A**	**40A/40A**
					30P/30P	**30P/15P**	**30P**	**15P**	
			Discontinue	**40A/40A**	**40P/40P**	**40P/40P**	**40P/40P**	**40P/40P**	**40P/40P**
					30A/30A	**30A/15A**	**30A**	**15A**	
	170mg - 179mg	85	Maintain	40A/30A/15A	40A/30A/15A	40A/30A/15A	40A/30A/15A	40A/30A/15A	40A/30A/15A
					40P/30P	30P/20P	30P	15P	
			Discontinue	40A/30A/15A	40P/30P/15P	40P/30P/15P	40P/30P/15P	40P/30P/15P	40P/30P/15P
					40A/30A	30A/20A	30A	15A	
	180mg	**90**	Maintain	**30A/30A/30A**	**30A/30A/30A**	**30A/30A/30A**	**30A/30A/30A**	**30A/30A/30A**	**30A/30A/30A**
					40P/30P	**30P/20P**	**30P**	**15P**	
			Discontinue	**30A/30A/30A**	**30P/30P/30P**	**30P/30P/30P**	**30P/30P/30P**	**30P/30P/30P**	**30P/30P/30P**
					40A/30A	**30A/20A**	**30A**	**15A**	

All doses represent single BID dose in mg
A = Active; P = Placebo

Follow-Up Period

The Drug Supply Logistics Team is planning to package in blister cards by dose strength to afford the most flexibility for retaining patients on their dose at entry to the study and enabling a variety of taper schedules.

The taper will be managed in a blinded fashion. Patients on active study drug will be switch through active taper doses while patients on placebo during the study will receive a placebo taper pack.

Taper applied at end of study or at any point when a patient chooses to discontinue after being randomized to study drug.

Patient group	Study Period (after structured discontinuation)	Taper wks 25-28	End of Study
Maintain	Active dose @ entry	Active taper doses	No drug
Discontinue	Placebo dose @ entry	Placebo taper doses	No drug

The tables below shows dosing paradigms for a variety of expected doses. Most probable doses in BOLD (doses achieved with same dosage strengths)

Follow-Up Period - Morphine Sulfate ER

ER MORPHINE Tablet Strengths	Single BID dose in study	Patient group	Study Period	Taper wk 25	Taper wk 26	Taper wk 27	Taper wk 28	End of Study - Off Drug
15 mg 30 mg 60 mg 100 mg	**60**	Maintained	**60A**	**30A/15A**	**30A**	**15A**	**15P**	
		Discontinued	**60P**	**30P/15P**	**30P**	**15P**	**15P**	
	75	Maintained	60A/15A	60A	30A/15A	30A	15A	
		Discontinued	60P/15P	60P	30P/15P	30P	15P	
	90	Maintained	60A/30A	60A/15A	30A/15A	30A	15A	
		Discontinued	60P/30P	60P/15P	30P/15P	30P	15P	
	100	Maintained	**100A**	**60A/15A**	**60A**	**30A**	**15A**	
		Discontinued	**100P**	**60P/15P**	**60P**	**30P**	**15P**	
	120	Maintained	**60A/60A**	**60A/30A**	**60A**	**30A**	**15A**	
		Discontinued	**60P/60P**	**60P/30P**	**60P**	**30P**	**15P**	
	130	Maintained	100A/30A	100A	60A/15A	30A/15A	15A	
		Discontinued	100P/30P	100P	60P/15P	30P/15P	15P	
	145	Maintained	100A/30A/15A	100A/15A	60A/30A	60A	30A	
		Discontinued	100P/30P/15P	100P/15P	60P/30P	60P	30P	
	160	Maintained	100A/60A	60A/60A	60A/30A	60A	30A	
		Discontinued	100P/60P	60P/60P	60P/30P	60P	30P	

All doses represent single BID dose in mg

A = Active; P = Placebo

Follow-Up Period - Morphine Sulfate ER (Cont'd)

ER MORPHINE	Single BID dose in study	Patient group	Study Period	Taper wk 25	Taper wk 26	Taper wk 27	Taper wk 28	End of Study - Off Drug
	180	Maintained	**60A/60A/60A**	**100A/30A**	**60A/30A**	**60A**	**30A**	
		Discontinued	**60P/60P/60P**	**100P/30P**	**60P/30P**	**60P**	**30P**	
	190	Maintained	100A/60A/30A	100A/30A/15A	100A	60A/15A	30A	
		Discontinued	100P/60P/30P	100P/30P/15P	100P	60P/15P	30P	
	200	Maintained	**100A/100A**	**100A/60A**	**100A/15A**	**60A/15A**	**30A**	
		Discontinued	**100P/100P**	**100P/60P**	**100P/15P**	**60P/15P**	**30P**	
	215	Maintained	100A/100A/15A	100A/60A/15A	100A/30A	60A/30A	30A	
		Discontinued	100P/100P/15P	100P/60P/15P	100P/30P	60P/30P	30P	
	230	Maintained	100A/100A/30A	100A/60A/30A	100A/30A	60A/30A	30A	
		Discontinued	100P/100P/30P	100P/60P/30P	100P/30P	60P/30P	30P	
	260	Maintained	100A/100A/60A	100A/100A	100A/60A	100A	30A	
		Discontinued	100P/100P/60P	100P/100P	100P/60P	100P	30P	

All doses represent single BID dose in mg

A = Active; P = Placebo

Follow-Up Period - Oxycodone ER

ER OXYCODONE Tablet Strengths 10 mg 20 mg 30 mg 40 mg 60 mg 80 mg	Single BID dose in study	Patient group	Study Period	Taper wk 25	Taper wk 26	Taper wk 27	Taper wk 28	End of Study - Off Drug
	40	Maintained	**40A**	**30A**	**20A**	**10A**	**10P**	
		Discontinued	**40P**	**30P**	**20P**	**10P**	**10P**	
	50	Maintained	30A/20A	40A	30A	20A	10A	
		Discontinued	30P/20P	40P	30P	20P	10P	
	60	Maintained	**60A**	**40A**	**30A**	**20A**	**10A**	
		Discontinued	**60P**	**40P**	**30P**	**20P**	**10P**	
	70	Maintained	40A/30A	30A/20A	40A	30A	10A	
		Discontinued	40P/30P	30P/20P	40P	30P	10P	
	80	Maintained	**40A/40A**	**30A/30A**	**40A**	**20A**	**10A**	
		Discontinued	**40P/40P**	**30P/30P**	**40P**	**20P**	**10P**	
	90	Maintained	60A/30A	40A/30A	40A	20A	10A	
		Discontinued	60P/30P	40P/30P	40P	20P	10P	

All doses represent single BID dose in mg

A = Active; P = Placebo

Follow-Up Period - Oxycodone ER (Cont'd)

ER OXYCODONE	Single BID dose in study	Patient group	Study Period	Taper wk 25	Taper wk 26	Taper wk 27	Taper wk 28	End of Study - Off Drug
	100	Maintained	60A/40A	80A	60A	40A	20A	
		Discontinued	60P/40P	80P	60P	40P	20P	
	110	Maintained	80A/30A	80A	60A	40A	20A	
		Discontinued	80P/30P	80P	60P	40P	20P	
	120	Maintained	**60A/60A**	**60A/30A**	**40A/30A**	**40A**	**20A**	
		Discontinued	**60P/60P**	**60P/30P**	**40P/30P**	**40P**	**20P**	
	140	Maintained	80A/60A	60A/40A	40A/30A	40A	20A	
		Discontinued	80P/60P	60P/40P	40P/30P	40P	20P	
	150	Maintained	80A/40A/30A	60A/60A	60A/30A	60A	30A	
		Discontinued	80P/40P/30P	60P/60P	60P/30P	60P	30P	
	160	Maintained	**80A/80A**	**60A/60A**	**60A/30A**	**60A**	**30A**	
		Discontinued	**80P/80P**	**60P/60P**	**60P/30P**	**60P**	**30P**	
	170	Maintained	80A/80A/10A	80A/60A	60A/40A	60A	30A	
		Discontinued	80P/80P/10P	80P/60P	60P/40P	60P	30P	
	180	Maintained	**60A/60A/60A**	**80A/60A**	**60A/30A**	**60A**	**30A**	
		Discontinued	**60P/60P/60P**	**80P/60P**	**60P/30P**	**60P**	**30P**	

All doses represent single BID dose in mg

A = Active; P = Placebo

Follow-Up Period - Oxymorphone ER

ER OXYMORPHONE	Single BID dose in study	Patient group	Study Period	Taper wk 25	Taper wk 26	Taper wk 27	Taper wk 28	End of Study - Off Drug
Tablet Strengths 5 mg 10 mg 15 mg 20 mg 30 mg 40 mg	**20**	Maintained	**20A**	**15A**	**10A**	**5A**	**5P**	
		Discontinued	**20P**	**15P**	**10P**	**5P**	**5P**	
	25	Maintained	15A/10A	20A	15A	10A	5A	
		Discontinued	15P/10P	20P	15P	10P	5P	
	30	Maintained	**30A**	**15A/10A**	**20A**	**10A**	**5A**	
		Discontinued	**30P**	**15P/10P**	**20P**	**10P**	**5P**	
	35	Maintained	20A/15A	30A	20A	10A	5A	
		Discontinued	20P/15P	30P	20P	10P	5P	
	40	Maintained	**40A**	**30A**	**20A**	**15A**	**10A**	
		Discontinued	**40P**	**30P**	**20P**	**15P**	**10P**	
	45	Maintained	30A/15A	20A/15A	15A/10A	15A	10A	
		Discontinued	30P/15P	20P/15P	15P/10P	15P	10P	
	50	Maintained	30A/20A	40A	30A	20A	10A	
		Discontinued	30P/20P	40P	30P	20P	10P	
	55	Maintained	40A/15A	40A	30A	20A	10A	
		Discontinued	40P/15P	40P	30P	20P	10P	

All doses represent single BID dose in mg
A = Active; P = Placebo

Follow-Up Period - Oxymorphone ER (Cont'd)

ER OXYMORPHONE	Single BID dose in study	Patient group	Study Period	Taper wk 25	Taper wk 26	Taper wk 27	Taper wk 28	End of Study - Off Drug
	60	Maintained	**30A/30A**	**30A/15A**	**20A/15A**	**15A/10A**	**10A**	
		Discontinued	**30P/30P**	**30P/15P**	**20P/15P**	**15P/10P**	**10P**	
	65	Maintained	30A/20A/15A	30A/20A	40A	15A/10A	10A	
		Discontinued	30P/20P/15P	30P/20P	40P	15P/10P	10P	
	70	Maintained	40A/30A	30A/20A	40A	15A/10A	10A	
		Discontinued	40P/30P	30P/20P	40P	15P/10P	10P	
	75	Maintained	40A/20A/15A	30A/30A	30A/15A	30A	15A	
		Discontinued	40P/20P/15P	30P/30P	30P/15P	30P	15P	
	80	Maintained	**40A/40A**	**30A/30A**	**30A/15A**	**30A**	**15A**	
		Discontinued	**40P/40P**	**30P/30P**	**30P/15P**	**30P**	**15P**	
	85	Maintained	40A/30A/15A	40A/30A	30A/20A	30A	15A	
		Discontinued	40P/30P/15P	40P/30P	30P/20P	30P	15P	
	90	Maintained	**30A/30A/30A**	**40A/30A**	**30A/20A**	**30A**	**15A**	
		Discontinued	**30P/30P/30P**	**40P/30P**	**30P/20P**	**30P**	**15P**	

All doses represent single BID dose in mg

A = Active; P = Placebo

Appendix C – Roland-Morris Disability Questionnaire (RMDQ)

When your back hurts, you may find it difficult to do some of the things you normally do.

This list contains some sentences that people have used to describe themselves when they have back pain. When you read them, you may find that some stand out because they describe you *today*. As you read the list, think of yourself *today*. When you read a sentence that describes you *today*, mark the box next to it. If the sentence does not describe you, then leave the space blank and go on to the next one. **Remember, only mark the sentence if you are sure that it describes you *today***.

1. I stay at home most of the time because of the pain in my back.
2. I change position frequently to try and make my back comfortable.
3. I walk more slowly than usual because of the pain in my back.
4. Because of the pain in my back, I am not doing any of the jobs that I usually do around the house.
5. Because of the pain in my back, I use a handrail to get upstairs.
6. Because of the pain in my back, I lie down to rest more often.
7. Because of the pain in my back, I have to hold on to something to get out of a reclining chair.
8. Because of the pain in my back, I ask other people to do things for me.
9. I get dressed more slowly than usual because of the pain in my back.
10. I only stand up for short periods of time because of the pain in my back.
11. Because of the pain in my back, I try not to bend or kneel down.
12. I find it difficult to get out of a chair because of the pain in my back.
13. My back hurts most of the time.
14. I find it difficult to turn over in bed because of the pain in my back.
15. My appetite is not very good because of the pain in my back.
16. I have trouble putting on my socks (or stockings) because of the pain in my back.
17. I only walk short distances because of the pain in my back.
18. I sleep less because of the pain in my back.
19. Because of the pain in my back, I get dressed with help from someone else.
20. I sit down for most of the day because of the pain in my back.
21. I avoid heavy jobs around the house because of the pain in my back.
22. Because of the pain in my back, I am more irritable and bad tempered with people.
23. Because of the pain in my back, I go upstairs more slowly than usual.
24. I stay in bed most of the time because of the pain in my back.

Note to users:

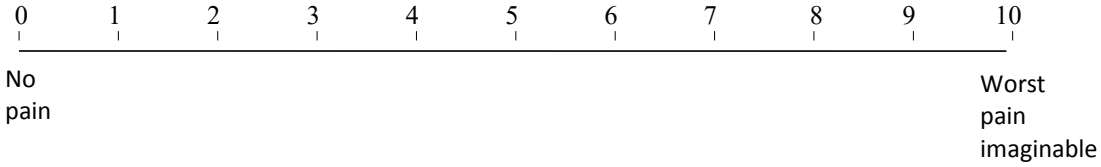
The score of the RDQ is the total number of items checked – i.e. from a minimum of 0 to a maximum of 24.

It is acceptable to add boxes to indicate where patients should mark each item.

The questionnaire may be adapted for use on-line or by telephone.

Reference: Roland MO, Morris RW. A study of the natural history of back pain. Part 1: Development of a reliable and sensitive measure of disability in low back pain. *Spine*. 1983;8:141-144.

Appendix D – Pain Intensity on 0-10 NRS



Appendix E – Brief Pain Inventory- Short Form (BPI-SF)

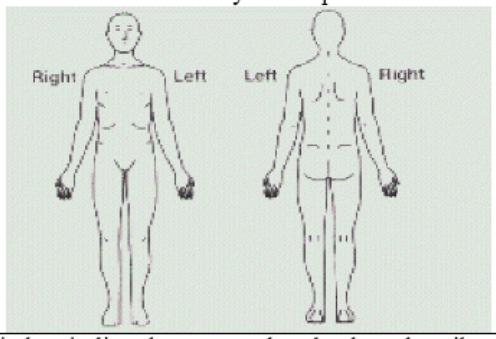
The BPI-SF is shown in its entirety. However, for this study, questions 2 and 7 are not relevant and that information will not be collected.

Date: ___ ___ /___ ___ /___ ___ Subject Initials: ___ ___ ___ I.D. ___ ___ ___

BRIEF PAIN INVENTORY (SHORT FORM)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?
   ☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at it worst in the last 24 hours.
   0 1 2 3 4 5 6 7 8 9 10
   No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.
   0 1 2 3 4 5 6 7 8 9 10
   No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average
   0 1 2 3 4 5 6 7 8 9 10
   No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.
   0 1 2 3 4 5 6 7 8 9 10
   No Pain — Pain as bad as you can imagine

7. What treatments or medications are your receiving for your pain
   _____
   _____
   _____
   _____

Date: ___ ___ /___ ___ /___ ___ Subject Initials: ___ ___ ___ I.D. ___ ___ ___

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

---

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

Reference: Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain*. 1983;17:197-210.

Appendix F – Regional Pain Scale

Please indicate below the amount of pain and/or tenderness you have had over THE PAST 7 DAYS in each of the joint and body areas listed below. Please make an X in the box that best describes your pain or tenderness. Be sure to mark both right side and left side separately. If you have had no pain or tenderness in a particular joint or body part, mark "None." *There should be an answer for every joint or body part listed.*

JOINTS	None	Mild	Mod	Severe
Shoulder, Lt.	☐	☐	☐	☐
Shoulder, Rt.	☐	☐	☐	☐
Elbow, Lt.	☐	☐	☐	☐
Elbow, Rt.	☐	☐	☐	☐
Wrist, Lt.	☐	☐	☐	☐
Wrist, Rt.	☐	☐	☐	☐
Hand knuckles, Lt.	☐	☐	☐	☐
Hand knuckles, Rt.	☐	☐	☐	☐
Finger knuckles, Lt.	☐	☐	☐	☐
Finger knuckles, Rt.	☐	☐	☐	☐
Hip, Lt.	☐	☐	☐	☐
Hip, Rt.	☐	☐	☐	☐
Knee, Lt.	☐	☐	☐	☐
Knee, Rt.	☐	☐	☐	☐
Ankle, Lt.	☐	☐	☐	☐
Ankle, Rt.	☐	☐	☐	☐
Ball of foot, Lt.	☐	☐	☐	☐
Ball of foot, Rt.	☐	☐	☐	☐
Heel, Lt.	☐	☐	☐	☐
Heel, Rt.	☐	☐	☐	☐
Foot arch, Lt.	☐	☐	☐	☐
Foot arch, Rt.	☐	☐	☐	☐

OTHER BODY AREAS	None	Mild	Mod	Severe
Jaw, Lt.	☐	☐	☐	☐
Jaw, Rt.	☐	☐	☐	☐
Lower Back	☐	☐	☐	☐
Upper Back	☐	☐	☐	☐
Neck	☐	☐	☐	☐
Upper arms, Lt.	☐	☐	☐	☐
Upper arms, Rt.	☐	☐	☐	☐
Lower arms, Lt.	☐	☐	☐	☐
Lower arms, Rt.	☐	☐	☐	☐
Upper leg, Lt.	☐	☐	☐	☐
Upper leg, Rt.	☐	☐	☐	☐
Lower leg, Lt.	☐	☐	☐	☐
Lower leg, Rt.	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Chest	☐	☐	☐	☐
Abdomen	☐	☐	☐	☐

Reference: Wolfe F. Pain extent and diagnosis: development and validation of the regional pain scale in 12,799 subjects with rheumatic disease. *J Rheumatol*. 2003;30:369-378.

Appendix G – Pain Quality Assessment Scale (PQAS)

Instructions: There are different aspects and types of pain that patients experience and that we are interested in measuring. Pain can feel sharp, hot, cold, dull, and achy. Some pains may feel like they are very superficial (at skin-level), or they may feel like they are from deep inside your body. Pain can also be described as unpleasant.

The Pain Quality Assessment Scale© helps us measure these and other different aspects of your pain. For one patient, a pain might feel extremely hot and burning, but not at all dull, while another patient may not experience any burning pain, but feel like their pain is very dull and achy. Therefore, we expect you to rate very high on some of the scales below and very low on others.

Please use the 19 rating scales below to rate how much of each different pain quality and type you may or may not have felt OVER THE PAST WEEK, ON AVERAGE.

Place an "X" through the number that best describes your pain. For example:

0	1	2	3	4	X	6	7	8	9	10

1. Please use the scale below to tell us how **intense** your pain has been over the past week, on average.

No pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense** pain sensation imaginable

2. Please use the scale below to tell us how **sharp** your pain has felt over the past week. Words used to describe sharp feelings include "like a knife," "like a spike," or "piercing."

Not sharp	0	1	2	3	4	5	6	7	8	9	10	The most **sharp** sensation imaginable ("like a knife")

3. Please use the scale below to tell us how **hot** your pain has felt over the past week. Words used to describe very hot pain include "burning" and "on fire."

Not hot	0	1	2	3	4	5	6	7	8	9	10	The most **hot** sensation imaginable ("burning")

4. Please use the scale below to tell us how **dull** your pain has felt over the past week.

Not dull	0	1	2	3	4	5	6	7	8	9	10	The most **dull** sensation imaginable

5. Please use the scale below to tell us how **cold** your pain has felt over the past week. Words used to describe very cold pain include "like ice" and "freezing."

Not cold	0	1	2	3	4	5	6	7	8	9	10	The most **cold** sensation imaginable ("freezing")

6. Please use the scale below to tell us how **sensitive** your skin has been to light touch or clothing rubbing against it over the past week. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."

Not sensitive	0	1	2	3	4	5	6	7	8	9	10	The most **sensitive** sensation imaginable ("raw skin")

7. Please use the scale below to tell us how **tender** your pain is when something has pressed against it over the past week. Another word used to describe tender pain is "like a bruise."

Not tender	0	1	2	3	4	5	6	7	8	9	10	The most **tender** sensation imaginable ("like a bruise")

8. Please use the scale below to tell us how **itchy** your pain has felt over the past week. Words used to describe itchy pain include "like poison ivy" and "like a mosquito bite."

Not itchy	0	1	2	3	4	5	6	7	8	9	10	The most **itchy** sensation imaginable ("like poison ivy")

9. Please use the scale below to tell us how much your pain has felt like it has been **shooting** over the past week. Another word used to describe shooting pain is "zapping."

Not shooting	0	1	2	3	4	5	6	7	8	9	10	The most **shooting** sensation imaginable ("zapping")

10. Please use the scale below to tell us how **numb** your pain has felt over the past week. A phrase that can be used to describe numb pain is "like it is asleep."

Not numb	0	1	2	3	4	5	6	7	8	9	10	The most **numb** sensation imaginable ("asleep")

11. Please use the scale below to tell us how much your pain sensations have felt **electrical** over the past week. Words used to describe electrical pain include "shocks," "lightning," and "sparking."

Not electrical	0	1	2	3	4	5	6	7	8	9	10	The most **electrical** sensation imaginable ("shocks")

12. Please use the scale below to tell us how **tingling** your pain has felt over the past week. Words used to describe tingling pain include "like pins and needles" and "prickling."

Not tingling	0	1	2	3	4	5	6	7	8	9	10	The most **tingling** sensation imaginable ("pins and needles")

13. Please use the scale below to tell us how **cramping** your pain has felt over the past week. Words used to describe cramping pain include "squeezing" and "tight."

Not cramping	0	1	2	3	4	5	6	7	8	9	10	The most **cramping** sensation imaginable ("squeezing")

14. Please use the scale below to tell us how **radiating** your pain has felt over the past week. Another word used to describe radiating pain is "spreading."

Not radiating	0	1	2	3	4	5	6	7	8	9	10	The most **radiating** sensation imaginable ("spreading")

15. Please use the scale below to tell us how **throbbing** your pain has felt over the past week. Another word used to describe throbbing pain is "pounding."

Not throbbing	0	1	2	3	4	5	6	7	8	9	10	The most **throbbing** sensation imaginable ("pounding")

16. Please use the scale below to tell us how **aching** your pain has felt over the past week. Another word used to describe aching pain is "like a toothache."

Not aching	0	1	2	3	4	5	6	7	8	9	10	The most **aching** sensation imaginable ("like a toothache")

17. Please use the scale below to tell us how **heavy** your pain has felt over the past week. Other words used to describe heavy pain are "pressure" and "weighted down."

Not heavy	0	1	2	3	4	5	6	7	8	9	10	The most **heavy** sensation imaginable ("weighted down")

18. Now that you have told us the different types of pain sensations you have felt, we want you to tell us overall how **unpleasant** your pain has been to you over the past week. Words used to describe very unpleasant pain include "annoying," "bothersome," "miserable," and "intolerable." Remember, pain can have a low intensity but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how **unpleasant** your pain feels.

Not unpleasant	0	1	2	3	4	5	6	7	8	9	10	The most **unpleasant** sensation imaginable ("intolerable")

19. Finally, we want you to give us an estimate of the severity of your deep versus surface pain over the past week. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.

HOW INTENSE IS YOUR *DEEP* PAIN?

No **deep** pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense deep** pain sensation imaginable

HOW INTENSE IS YOUR *SURFACE* PAIN?

No **surface** pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense surface** pain sensation imaginable

20. Pain can also have different time qualities. For some people, the pain comes and goes and so they have some moments that are completely without pain; in other words the pain "comes and goes". This is called **intermittent** pain. Others are never pain free, but their pain types and pain severity can vary from one moment to the next. This is called **variable** pain. For these people, the increases can be severe, so that they feel they have moments of very intense pain ("breakthrough" pain), but at other times they can feel lower levels of pain ("background" pain). Still, they are never pain free. Other people have pain that really does not change that much from one moment to another. This is called **stable** pain. Which of these best describes the time pattern of your pain (please select only one):

( ) I have **intermittent** pain (I feel pain sometimes but I am pain-free at other times).
( ) I have **variable** pain ("background" pain all the time, but also moments of more pain, or even severe "breakthrough pain or varying types of pain).
( ) I have **stable** pain (constant pain that does not change very much from one moment to another, and no pain-free periods).

Note: The NPS© and PQAS© are distributed by the MAPI Research Trust, and there is no cost for use by unfunded academic researchers. Both measures can be accessed via the MAPI website (http://www.mapi-research.fr).

Reference: Victor T, Jensen M, Gammaitoni A, Gould E, White R, Galer BS. The dimensions of pain quality: factor analysis of the Pain Quality Assessment Scale. *Clin J Pain*. 2008;24:550-555.

Appendix H – MOS Sleep Scale

1. How long did it usually take for you to fall asleep during the past 4 weeks?

(Circle One)

0-15 minutes……..…1

16-30 minutes……..2

31-45 minutes……..3

46-60 minutes……..4

More than 60 minutes …….5

---

2. On the average, how many hours did you sleep each night during the past 4 weeks?

Write in number
of hours per night: ☐☐

How often during the past 4 weeks did you…

	(Circle One Number On Each Line)					
	All of the Time ▼	Most of the Time ▼	A Good Bit of the Time ▼	Some of the Time ▼	A Little of the Time ▼	None of the Time ▼
3. feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	1	2	3	4	5	6
4. get enough sleep to feel rested upon waking in the morning?	1	2	3	4	5	6
5. awaken short of breath or with a headache?	1	2	3	4	5	6
6. feel drowsy or sleepy during the day?	1	2	3	4	5	6
7. have trouble falling asleep?	1	2	3	4	5	6
8. awaken during your sleep time and have trouble falling asleep again?	1	2	3	4	5	6
9. have trouble staying awake during the day?	1	2	3	4	5	6
10. snore during your sleep?	1	2	3	4	5	6
11. take naps (5 minutes or longer) during the day?	1	2	3	4	5	6
12. get the amount of sleep you needed?	1	2	3	4	5	6

Reference: Hays RD, Stewart AL. Sleep measures. In Stewart AL & Ware JE. (eds.), Measuring Functioning and Well-being: The Medical Outcomes Study Approach. Durham, NC: Duke University Press, 1992, pp. 235-259.

Appendix I – Work Productivity and Activity Impairment (WPAI)

WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: LOW BACK PAIN (WPAI-LBP) - Page 1 of 2

☐ (1) NOT DONE

The following questions ask about the effect of your LOW BACK PAIN on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ☐ (2) No ☐ (1) Yes
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your LOW BACK PAIN? *Include hours you missed on sick days, times you went in late, left early, etc., because of your LOW BACK PAIN. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: LOW BACK PAIN (WPAI-LBP) - Page 2 of 2

5. During the past seven days, how much did your LOW BACK PAIN affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If LOW BACK PAIN affected your work only a little, choose a low number. Choose a high number if LOW BACK PAIN affected your work a great deal.

Consider only how much LOW BACK PAIN affected productivity while you were working.

LOW BACK PAIN had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	LOW BACK PAIN completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your LOW BACK PAIN affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If LOW BACK PAIN affected your activities only a little, choose a low number. Choose a high number if LOW BACK PAIN affected your activities a great deal.

Consider only how much LOW BACK PAIN affected your ability to do your regular daily activities, other than work at a job.

LOW BACK PAIN had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	LOW BACK PAIN completely prevented me from doing my daily activities

CIRCLE A NUMBER

Reference: Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics*. 1993;4:353-365

Appendix J – Patient Health Questionnaire Depression Scale (PHQ-8)

Over the **last 2 weeks**, how often have you been bothered by any of the following problems?
*(circle **one** number on each line)*

How often during the past 2 weeks were you bothered by...	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3

Scoring

If two consecutive numbers are circled, score the higher (more distress) number. If the numbers are not consecutive, do not score the item. Score is the sum of the 8 items. If more than 1 item missing, set the value of the scale to missing. A score of 10 or greater is considered major depression, 20 or more is severe major depression.

Reference: Kroenke K, Strine TW, Spritzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord*. 2009;114:163-73.

Appendix K – Columbia Suicide Severity Rating Scale (C-SSRS)

C-SSRS Lifetime:

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime: Time He/She Felt Most Suicidal
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

C-SSRS Since Last Visit:

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes No ☐ ☐ Total # of Attempts _____ Yes No ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of interrupted _____
Aborted or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of aborted or self-interrupted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes No ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes No ☐ ☐
Completed Suicide:	Yes No ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Reference: Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin G, Greenhill L, Shen S, Mann JJ. The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psych.* 2011;168:1266-1277.

Appendix L – EuroQOL 5 Dimensions (EQ-5D-5L)

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

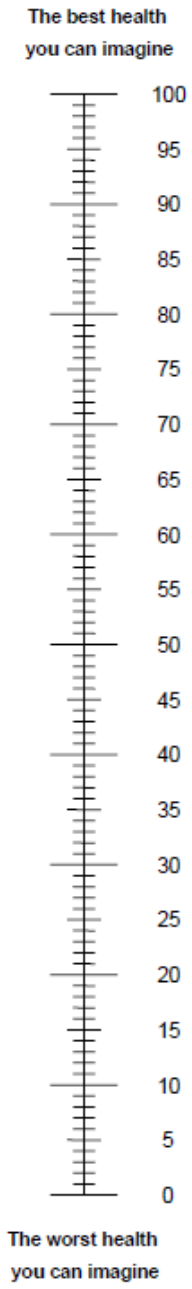
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Reference: The EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199-208.

Appendix M – Patient Global Impression of Change (PGIC)

√ (Check) the box you feel most closely describes any change you have experienced in your low back pain since you entered the study. Choose only ONE response.

☐ 1. Very Much Improved

☐ 2. Much Improved

☐ 3. Minimally Improved

☐ 4. No Change

☐ 5. Minimally Worse

☐ 6. Much Worse

☐ 7. Very Much Worse

Reference: John T. Farrara JT, Young JP, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149-158.

Appendix N – Subjective Opiate Withdrawal Scale (SOWS)

Instructions to patient: Based on the way you feel now, rate each of the 16 symptoms on a scale for 0 to 4, where:

0 = not at all
1 = a little
2 = moderately
3 = quite a bit
4 = extremely

_____

1. I feel anxious
2. I feel like yawning
3. I'm perspiring
4. My eyes are tearing
5. My nose is running
6. I have goose flesh
7. I am shaking
8. I have hot flashes
9. I have cold flashes
10. My bones and muscles ache
11. I feel restless
12. I feel nauseous
13. I feel like vomiting
14. My muscles twitch
15. I have cramps in my stomach
16. I feel like shooting up now

_____

Scoring: the sum of the scores on each item is the total SOWS score. The minimum SOW score is 0 and the maximum is 64.

Reference: Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse*. 1987;13:293-308.

Appendix O – Clinical Opiate Withdrawal Scale (COWS)

For each item, write in the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date: _____

Item	Score
Resting Pulse Rate: _____ (record beats per minute) *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	
Sweating: *over past ½ hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	
Restlessness: *Observation during assessmen*t 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds	
Pupil size: 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	
Bone or Joint aches: *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	
Runny nose or tearing: *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	

Item	Score
GI Upset: *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting	
Tremor: *observation of outstretched hands* 0 No tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching	
Yawning: *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute	
Anxiety or Irritability: 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult	
Gooseflesh skin: 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection	
Total scores **with observer's initials**	

Score:
5-12 = mild;
13-24 = moderate;
25-36 = moderately severe;
More than 36 = severe withdrawal

Reference: Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*. 2003;35:253-259.

Appendix P – Digit Symbol Substitution Test (DSST)

Digit Symbol Substitution Test

Baseline and after any head injury. Time for 90 seconds and record score (number of correct substitutions).

Name: Date: Score:

Digit	1	2	3	4	5	6	7	8	9
Symbol	—	†	Π	L	Γ	o	^	X	=

Example

Digit	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4	5	6	3	1
Symbol	—	Π	^	†	L	X																	

Digit	4	5	4	2	7	6	3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4
Symbol																							

Digit	7	3	2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7
Symbol																							

Reference: Wechsler D. The measurement and appraisal of adult intelligence (1st ed.). Baltimore: Williams and Wilkins Corporation, 1939.

Appendix Q – Quantitative Sensory Testing

Background

In addition to clinical outcomes, opioid-induced hyperalgesia (OIH) will be evaluated in a sub-study at interested and qualified sites by using quantitative sensory testing (QST) methods to assess pain sensitivity during certain study visits. The procedure is described in detail in the study specific procedure manual for the OIH QST Algorithm. All study staff participating in the QST sub-study will be trained on the QST procedure. Subjects will sign a separate informed consent for participation and are not required to participate after being informed of the risks, benefits, and requirements of the sub-study.

The QST Procedure

The procedure is based on 4 tests, in which thermal stimuli will be administered via a thermode to the subject's hand or arm by using the Q-Sense CPM Device (Medoc, Ramat Yishai, Israel). Subjects will report the pain they perceive from each stimulus, and the study staff will capture these reports on source documents. The 4 QST tests are: (1) Phasic heat Pain Intensity (PPI); (2) Tonic heat Pain Intensity (TPI); (3) Conditioned Pain Modulation (CPM) and (4) Temporal Summation (TS).

Training Session

At the beginning of the study visit, participants will be exposed to a short training session. The training session, lasting approximately 10 minutes, will allow participants to practice the use of the scoring scale and to address questions regarding the procedure. The training session will include a detailed description of the study tests and instructions on how to rate pain intensity during the procedure. The results of the training session will be captured in the system but not entered into the data capture system or used for the statistical analysis.

Phasic Heat Pain Intensity

In order to assess pain intensity in response to a phasic (short) heat pain stimulus, the thermode will be attached to the thenar eminence of the non-dominant hand. The temperature will be increased gradually from baseline until it reaches the destination temperature of 47°C, which will then be maintained consistently for a duration of 3 seconds. The maximal pain intensity reported by the subject will be recorded.

The Phasic Heat Pain Intensity test outcome is a single pain score.

Tonic Heat Pain Intensity

In order to assess pain intensity in response to tonic (long) heat pain stimulation, the thermode will be attached to the volar aspect of the dominant arm. The thermode temperature will be increased to 46°C and will remain constant for 60 seconds, after which the temperature will be reduced back to baseline. During the 60-second stimulus, subjects will report their pain intensity (0–100 on the Numerical Pain Scale [NPS]) every 20 seconds (at 0, 20, 40, and 60).

The Tonic Heat Pain Intensity test outcomes are recorded as four pain ratings, collected at times 0, 20, 40, and 60 seconds.

Conditioned Pain Modulation (CPM) Test

CPM is conducted by the administration of two types of stimuli, a test stimulus and a conditioning stimulus. At the beginning, the test stimulus is administered alone, and the pain intensity reported by the subject is recorded. This test is followed by the administration of the conditioning stimulus to a separate, remote part of the body. While the conditioning stimulus is administered, another test stimulus is given and the pain intensity reported by the subject is recorded.

The test-pain stimulus is a 30-second stimulus delivered to the volar aspect of the dominant forearm and set at 45.6°C. Pain intensity (NPS) will be recorded at seconds 0, 15, and 30. After a 60-second break, the conditioning stimulus, lasting approximately 40 seconds, will be administered to the volar aspect of the non-dominant forearm at of 46.3°C. A few seconds after initiation of the conditioning stimulus, the test-pain stimulus will be repeated, and pain intensity (NPS) will be recorded in the same manner.

The CPM outcomes to be collected are 6 pain scores, 3 for each test stimulus (at time 0, 15, and 30 seconds, for each test stimulus).

Temporal Summation (TS) test

The TS test will be induced by applying a rapid set of 4 identical stimuli, each lasting 0.1 second, at 46.5°C intensity to the ventral section of the non-dominant forearm. Thermode temperature will oscillate between 46.5°C and 44°C a total of 4 times, and stimuli will be separated by 2.5 seconds. The thermode temperature will decline to the device baseline temperature (32 °C) after reaching the last peak temperature. Following each stimulus, participants will rate their pain using the NPS (0–100).

The TS outcomes are 4 pain scores, one per stimulus.

Appendix R – Abuse-Related Adverse Events (MADDERS)

Description

Potentially abuse-related events will be identified, assessed, and quantified using the Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS™), which identifies and characterizes such events according to a classification system developed in the context of the FDA-ACTTION initiative (Smith 2013).

Events are identified for further evaluation on the occurrence of specific adverse events (such as abuse, overdose, respiratory arrest, etc.), or significant drug accountability discrepancies. Events triggering will be outlined in the MADDERS™ User's Manual. When such an event occurs, investigators and study staff, having been trained on the system, complete a clinician-based assessment to capture information and classify whether the event was abuse, misuse, suicide-related, therapeutic error, unknown, or none of the above, with further supplemental designations for tampering, withdrawal, addiction-related, diversion, and overdose.

The output of the system is count data for each type of event and their total, which can be compared between groups in a study, as well as the event characteristics as captured by the supplemental forms. The result of the process is a more accurate classification of potentially abuse-related events than can be achieved by standard methods, to avoid either overestimation, underestimation, or mischaracterization of product risks.

The system components consist of:

- Triggering Adverse Events List
  - A list of specific adverse event terms and definitions that, if documented by the investigator, lead to completion of a "Supplemental Adverse Event Form"
- Drug Accountability Discrepancy Threshold
  - A criterion for drug accountability discrepancies that, if documented during a study visit, lead to completion of a "Supplemental Drug Accountability Form"
- Supplemental Adverse Event Form
  - A clinician-reported assessment that directs the clinician on what information to capture at the time of a triggering adverse event to inform the correct classification of the event
- Supplemental Drug Accountability Form
  - A clinician-reported assessment that directs the clinician on what information to capture at the time of a drug accountability discrepancy to inform the correct classification of the event
- Medication Use Survey
  - A clinician-reported assessment that directs the clinician on what information to capture at the end of study or at an early termination visit to inform of any potential MADDERS™ events that might not have been captured

The 3 forms that will need to be completed are presented in the following pages. The remaining information will be provided in the User's Manual.

Reference: Smith SM, Dart RC, Katz NP, Paillard F, Adams EH, Comer SD, Degroot A, Edwards RR, Haddox JD, Jaffe JH, Jones CM, Kleber HD, Kopecky EA, Markman JD, Montoya ID, O'Brien C, Roland CL, Stanton M, Strain EC, Vorsanger G, Wasan AD, Weiss RD, Turk DC, Dworkin RH; Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. *Pain*. 2013;154:2287.

Supplemental Adverse Event Form

	MADDERS™ Supplemental Adverse Event Form
ANALGESIC SOLUTIONS	**Site #** ☐☐☐ **Subject ID #** ☐☐☐ - ☐☐☐☐
	Adverse Event ID # _____

General Instructions: *When Triggering Adverse Events (AEs) of interest (i.e., events that are considered abuse liability in the Investigator's opinion) are identified by the clinical site, trained site personnel should interview the patient and discuss the Triggering AE of interest in order to answer each of the questions below and to appropriately classify the event.*

- ***This form should be completed only by certified study personnel.***
- ***"Study medication"*** *refers only to the medication that is the subject of the protocol (Active or Placebo), not to any other supplemental medications the patient may be using.*
- ***"Explain"*** *– An explanation should be provided for any response selection (unless indicated otherwise).*
- ***All free text field entries*** *should be limited to 200 characters.*

Form Completion Date: ☐☐-☐☐☐-20☐☐ (**dd-mmm-yyyy,** *e.g. 01-JAN-2016*)
Form Completion Time: ☐☐:☐☐ (**hh:mm,** *24-hour clock, e.g. 1:36pm = 13:36*)
Study drug name:
Dosage form:
Triggering AE (as described verbatim by the patient):
Please describe the Triggering AE (in the case of a serious adverse event, leave blank): _____ _____ _____ _____
☐ **FORM NOT COMPLETED.** ***If this box is checked, please provide a reason why this form was not completed:*** _____ _____ _____ _____

ANALGESIC SOLUTIONS	**MADDERS™ Supplemental Adverse Event Form** **Site #** ☐☐☐ **Subject ID #** ☐☐☐ - ☐☐☐☐ **Adverse Event ID #** _____

Interview guide (Ask the patient questions that will allow you to answer each of the questions below.)	**Information collected from the patient** (Answer to the best of your ability, in light of patient responses, and add written explanation for any response selection.)	**Classification** (Check the box only if applicable.)
1. Did the patient alter the route of administration with his/her study medication in association with this Triggering AE?	☐ Yes (select classification in column to the right) ☐ No ☐ Uncertain Explain: _____ _____ _____	**Administration Method** (check one box only in case the patient altered the route of administration) ☐ ***Oral*** ☐ ***Sublingual*** ☐ ***Nasal insufflation*** ☐ ***Inhaled*** ☐ ***Injected*** ☐ ***Unknown*** ☐ ***Other, please specify:*** _____
2. In the period leading up to the Triggering AE, how much study medication did the patient take compared to his/her usual dose?	☐ More than usual ☐ About the same ☐ Less than usual ☐ Other Explain: _____ _____ _____	
If "More than usual" or "Less than usual" for question 2, complete question 2a.		
2a. Did the patient change his/her dose intentionally or unintentionally?	☐ Intentionally ☐ Unintentionally ☐ Uncertain Explain: _____ _____ _____	

ANALGESIC SOLUTIONS	**MADDERS™ Supplemental Adverse Event Form** **Site #** ☐☐☐ **Subject ID #** ☐☐☐ - ☐☐☐☐ **Adverse Event ID #** ___

Interview guide (Ask the patient questions that will allow you to answer each of the questions below.)	**Information collected from the patient** (Answer to the best of your ability, in light of patient responses, and add written explanation for any response selection.)	**Classification** (Check the box only if applicable.)
If "Less than usual" for question 2, also complete question 2b.		
2b. Does the Triggering AE meet criteria for a withdrawal syndrome?	☐ Yes (select classification in column to the right) ☐ No ☐ Uncertain Explain: _____	☐ ***Withdrawal:*** Symptoms or signs due to the decline in blood concentration of a drug substance (e.g., after dose reduction, at the end of a dosing interval, or after discontinuing treatment) or due to the administration of an antagonist.
3. Does the Triggering AE meet criteria for an overdose?	☐ Yes (select classification in column to the right) ☐ No ☐ Uncertain Explain: _____	☐ ***Overdose:*** Any act that results in drug exposure exceeding that which is generally recommended or medically accepted.
4. Did the patient tamper with his/her study medication in association with this Triggering AE?	☐ Yes (select classification in column to the right) ☐ No ☐ Uncertain Explain: _____	☐ ***Tampering:*** The inappropriate manipulation of a drug product (includes cutting or crushing a tablet or vial, dissolving it, etc.).
5. Is it likely that the study drug passed into the possession of someone other than the subject?	☐ Yes (select classification in column to the right) ☐ No ☐ Uncertain Explain: _____	☐ ***Diversion:*** Any intentional act that results in transferring a drug product from lawful to unlawful distribution or possession.

ANALGESIC SOLUTIONS	**MADDERS™ Supplemental Adverse Event Form** **Site #** ☐☐☐ **Subject ID #** ☐☐☐ - ☐☐☐☐ **Adverse Event ID #** ____

Interview guide (Ask the patient questions that will allow you to answer each of the questions below.)	**Information collected from the patient** (Answer to the best of your ability, in light of patient responses, and add written explanation for any response selection.)	**Classification** (Check the box only if applicable.)
6. Did the patient indicate that the Triggering AE was pleasant or unpleasant?	☐ Pleasant ☐ Unpleasant ☐ Uncertain Explain: _____	☐ ***Addiction-related indicator:*** **(check based on responses to items 6 - 8)** Behavioral, cognitive, and physiological phenomena that may develop after exposure to a substance. May include a strong desire to take the drug, difficulties in controlling drug use, persistent drug use despite harmful consequences, intractable and distracting thoughts about the drug, or placing a higher priority on drug use than other activities and obligations.
7. Would the patient take the drug again just to re-create the effect?	☐ Yes ☐ No ☐ Uncertain Explain: _____	
8. Has the patient shown a constellation of behaviors consistent with a substance use disorder?	☐ Yes ☐ No ☐ Uncertain Explain: _____	
9. How likely is the Triggering AE to be related to study drug?	Select classification in column to the right. Explain: _____	**Check one box only:** ☐ ***Definitely related*** ☐ ***Probably related*** ☐ ***Possibly related*** ☐ ***Unrelated*** ☐ ***Uncertain***

ANALGESIC SOLUTIONS	**MADDERS™ Supplemental Adverse Event Form** **Site #** ☐☐☐ **Subject ID #** ☐☐☐ - ☐☐☐☐ **Adverse Event ID #** ____

Interview guide (Ask the patient questions that will allow you to answer each of the questions below.)	**Information collected from the patient** (Answer to the best of your ability, in light of patient responses, and add written explanation for any response selection.)	**Classification** (Check the box only if applicable.)
10. What was the patient's intent when taking the last dose(s) of study drug prior to the onset of the Triggering AE?	**What was the patient's intent?** (Check one box only)**:** ☐ Unintentional ☐ To relieve pain or to achieve another therapeutic goal (e.g., relieve insomnia, cramps) ☐ To "get high" or induce other psychological feelings ☐ To attempt to end his/her life ☐ Other Explain: _____ _____ _____	**Classification** (Check one box only): ☐ ***Therapeutic Error:*** A mistake in a therapeutic regimen, that is, unintentional errors made by the prescriber or patient (e.g., erroneous prescription or instructions from healthcare provider; wrong medication dispensed; taking the medication not according to directions). ☐ ***Misuse-Event Indicator:*** Any intentional, therapeutic use of a drug product in an inappropriate way (i.e., use of drug other than for treatment of pain). Misuse specifically excludes those events that meet the definition of an Abuse-Event Indicator (see below). ☐ ***Abuse-Event Indicator:*** Any intentional, nontherapeutic use of a drug product or substance, even once, for the purpose of achieving a desirable psychological or physiological effect. ☐ ***Suicide-Related Event:*** A self-injurious or potentially self-injurious behavior associated with at least some intent to die or that resulted in death. Evidence that the individual intended to kill him/herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury. ☐ ***None of the Above:*** Sufficient information exists to determine that none of the previous categories apply. ☐ ***Unknown:*** Insufficient information exists to determine which category applies.

ANALGESIC SOLUTIONS	**MADDERS™ Supplemental Adverse Event Form** **Site #** ☐☐☐ **Subject ID #** ☐☐☐ - ☐☐☐☐ **Adverse Event ID #** _____

Interview guide (Ask the patient questions that will allow you to answer each of the questions below.)	**Information collected from the patient** (Answer to the best of your ability, in light of patient responses.)
11. Indicate any physical examination observations that inform the nature of the Triggering AE.	☐ Physical examination not done ☐ Physical examination done; no relevant findings ☐ Physical examination done; Explain relevant findings: _____ _____
12. Indicate any additional laboratory information obtained that could provide information on the Triggering AE.	☐ Labs not done ☐ Labs done; Explain relevant findings: _____ _____ _____

Certified individual who has completed the form		
Print Name	**Print Title**	**Signature & Date (dd-mmm-yyyy)**
Principal Investigator		
Print Name	**Signature & Date (dd-mmm-yyyy)**	

Thank you for completing the form!

Supplemental Drug Accountability Form

ANALGESIC SOLUTIONS	MADDERS™ Supplemental Drug Accountability Form
	Site # ☐☐☐ **Subject ID #** ☐☐☐ - ☐☐☐☐
	Visit # _____

General Instructions: *When Triggering Drug Accountability Discrepancies are identified by the clinical site, either by automated notification (e.g., IVRS) or by manual drug counts indicating missing study medication, trained site personnel are to discuss these discrepancies in a non-leading manner with the patient and complete the form below on the basis of that interview.*

- ***This form should be completed only by certified study personnel.***
- ***"Study medication"*** *refers only to the medication that is the subject of the protocol (Active or Placebo), not to any other supplemental medications the patient may be using.*
- ***"Explain"*** *– An explanation should be provided for any response selection (unless indicated otherwise).*
- ***All free text field entries*** *should be limited to 200 characters.*

Form Completion Date: ☐☐-☐☐☐-20☐☐ (**dd-mmm-yyyy,** *e.g. 01-JAN-2016*)
Form Completion Time: ☐☐:☐☐ (**hh:mm,** *24-hour clock, e.g. 1:36pm = 13:36*)
Study drug name:
Dosage form:
Did the patient return lower amounts of study drug than expected based on protocol-prescribed amounts? ☐ **Yes** ☐ **No** **If yes, please describe the event:** _____ _____ _____ _____
Amount of drug missing: _____ _____ _____
☐ **FORM NOT COMPLETED.** ***If this box is checked, please provide a reason why this form was not completed:*** _____ _____ _____

ANALGESIC SOLUTIONS	**MADDERS™ Supplemental Drug Accountability Form** **Site #** ☐☐☐ **Subject ID #** ☐☐☐ - ☐☐☐☐ **Visit #** _____

Interview guide (Ask the patient questions that will allow you to answer each of the questions below.)	**Information collected from the patient** (Answer to the best of your ability, in light of patient responses, and add written explanation for any response selection.)	**Classification** (Check the box only if applicable.)
1. Did the patient alter the route of administration of the study medication?	☐ Yes (select classification in column to the right) ☐ No ☐ Uncertain Explain: _____ _____ _____ _____ _____	**Administration Method** (check one box only in case the patient altered the route of administration) ☐ ***Oral*** ☐ ***Sublingual*** ☐ ***Nasal insufflation*** ☐ ***Inhaled*** ☐ ***Injected*** ☐ ***Unknown*** ☐ ***Other, please specify:*** _____
2. Did the patient experience withdrawal syndrome?	☐ Yes (select classification in column to the right) ☐ No ☐ Uncertain Explain: _____ _____ _____	☐ ***Withdrawal:*** Symptoms or signs due to the decline in blood concentration of a drug substance (e.g., after dose reduction, at the end of a dosing interval, or after discontinuing treatment) or due to the administration of an antagonist.
3. Did the patient experience adverse events that might be overdose-related?	☐ Yes (select classification in column to the right) ☐ No ☐ Uncertain Explain: _____ _____ _____	☐ ***Overdose:*** Any act that results in drug exposure exceeding that which is generally recommended or medically accepted.

ANALGESIC SOLUTIONS	**MADDERS™ Supplemental Drug Accountability Form** **Site #** ☐☐☐ **Subject ID #** ☐☐☐ - ☐☐☐☐ **Visit #** _____

Interview guide (Ask the patient questions that will allow you to answer each of the questions below.)	**Information collected from the patient** (Answer to the best of your ability, in light of patient responses, and add written explanation for any response selection.)	**Classification** (Check the box only if applicable.)
4. Is there evidence of tampering with the study medication?	☐ Yes (select classification in column to the right) ☐ No ☐ Uncertain Explain: _____ _____ _____	☐ ***Tampering:*** The inappropriate manipulation of a drug product (includes cutting or crushing a tablet or vial, dissolving it, etc.).
5. Is it likely that the study drug passed into the possession of someone other than the subject?	☐ Yes (select classification in column to the right) ☐ No ☐ Uncertain Explain: _____ _____ _____	☐ ***Diversion:*** Any intentional act that results in transferring a drug product from lawful to unlawful distribution or possession.
6. Has the patient shown a constellation of behaviors consistent with a substance use disorder?	☐ Yes (select classification in column to the right) ☐ No ☐ Uncertain Explain: _____ _____ _____	☐ ***Addiction-related indicator:*** Behavioral, cognitive, and physiological phenomena that may develop after exposure to a substance. May include a strong desire to take the drug, difficulties in controlling drug use, persistent drug use despite harmful consequences, intractable and distracting thoughts about the drug, or placing a higher priority on drug use than other activities and obligations.
7. How likely is the event related to study drug?	Select classification in column to the right. Explain: _____ _____ _____	**Check one box only:** ☐ ***Definitely related*** ☐ ***Probably related*** ☐ ***Possibly related*** ☐ ***Unrelated*** ☐ ***Uncertain***

ANALGESIC SOLUTIONS	**MADDERS™ Supplemental Drug Accountability Form** **Site #** ☐☐☐ **Subject ID #** ☐☐☐ - ☐☐☐☐ **Visit #** _____

Interview guide (Ask the patient questions that will allow you to answer each of the questions below.)	**Information collected from the patient** (Answer to the best of your ability, in light of patient responses, and add written explanation for any response selection.)	**Classification** (Check the box only if applicable.)
8. Please discuss with the patient the reason for returning a lower-than-expected amount of medication.	**Reason for lower amount returned?** (Check one box only): ☐ Used additional study medication unintentionally ☐ Used additional study medication to relieve pain or to achieve another therapeutic goal (e.g., relieve insomnia, muscle spasms) ☐ Used additional study medication to "get high" or induce other psychological feelings ☐ Used additional study medication in attempt to end his/her life ☐ Transferred study medication to someone other than the patient ☐ Unknown, no explanation ☐ Other Explain: _____ _____ _____ _____ _____	**Classification** (check one box only): ☐ ***Therapeutic Error:*** A mistake in a therapeutic regimen, that is, unintentional errors made by the prescriber or patient (e.g., erroneous prescription or instructions from healthcare provider; wrong medication dispensed; taking the medication not according to directions). ☐ ***Misuse-Event Indicator:*** Any intentional, therapeutic use of a drug product in an inappropriate way (i.e., use of drug other than for treatment of pain). Misuse specifically excludes those events that meet the definition of an Abuse-Event Indicator (see below). ☐ ***Abuse-Event Indicator:*** Any intentional, nontherapeutic use of a drug product or substance, even once, for the purpose of achieving a desirable psychological or physiological effect. ☐ ***Suicide-Related Event:*** A self-injurious or potentially self-injurious behavior associated with at least some intent to die or that resulted in death. Evidence that the individual intended to kill him/herself can, at least to some degree, be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury. ☐ ***None of the Above:*** Sufficient information exists to determine that none of the previous categories apply. ☐ ***Unknown:*** Insufficient information exists to determine which category applies.

ANALGESIC SOLUTIONS	**MADDERS™ Supplemental Drug Accountability Form** **Site #** ☐☐☐ **Subject ID #** ☐☐☐ - ☐☐☐☐ **Visit #** _____

Interview guide (Ask the patient questions that will allow you to answer each of the questions below.)	**Information collected from the patient** (Answer to the best of your ability, in light of patient responses.)
9. Indicate any physical examination observations that inform the nature of Drug Accountability Discrepancy.	☐ Physical examination not done ☐ Physical examination done; no relevant findings ☐ Physical examination done; Explain relevant findings: _____ _____ _____
10. Indicate any additional laboratory information obtained that could provide information on the Drug Accountability Discrepancy (e.g., urine drug screen).	☐ Labs not done ☐ Labs done; Explain relevant findings: _____ _____ _____

Certified individual who has completed the form		
Print Name	**Print Title**	**Signature & Date (dd-mmm-yyyy)**
Principal Investigator		
Print Name	**Signature & Date (dd-mmm-yyyy)**	

Thank you for completing the form!

Medication Use Survey

ANALGESIC SOLUTIONS	MADDERS™ Medication Use Survey
	Site # ☐☐☐ Subject ID # ☐☐☐ - ☐☐☐☐

Instructions: **This form is to be filled out by the clinician or certified study staff for all subjects during an interview with each subject, either at end of study visit or early termination visit.**

1. Remind subject that answers to these questions will be kept strictly confidential and the subject's identity will be unknown to those assessing the answers.
2. All questions should be answered in relation to study medication, not any other medications the subject may be taking.
3. All questions should be answered in relation to the time since first enrolling in the study.

Form Completion Date: ☐☐-☐☐☐-20☐☐ **(dd-mmm-yyyy,** *e.g. 01-JAN-2016***)**

Form Completion Time: ☐☐:☐☐ **(hh:mm,** *24-hour clock, e.g. 1:36pm = 13:36***)**

☐ **FORM NOT COMPLETED.** ***If this box is checked, please provide a reason(s) for why this form was not completed:***

_____

_____

_____

Please check only 1 response per question.	Never	Seldom	Sometimes	Often
1. How often did the subject use more medication than instructed? *If "never" skip to Section 2; otherwise continue with the questions below*	☐	☐	☐	☐
1a. How often did the subject take more medication than instructed with the intent of improving relief of pain or to treat symptoms other than pain?	☐	☐	☐	☐
1b. How often did the subject take more medication than instructed with the intent of getting "high" (intoxicated/drunk) or just feeling good?	☐	☐	☐	☐
1c. How often did the subject take more medication than instructed by accident (i.e. unintentionally)?	☐	☐	☐	☐
	Never	Seldom	Sometimes	Often
2. How often did the subject take additional study medication for the purposes of ending his/her life?	☐	☐	☐	☐
	Never	Seldom	Sometimes	Often
3. How often did the subject experience craving for the study medication, difficulties in controlling drug use, distracting thoughts about the drug, or placing a higher priority on drug use than on other activities and obligations?	☐	☐	☐	☐

ANALGESIC SOLUTIONS	MADDERS™ Medication Use Survey Site # ☐☐☐ Subject ID # ☐☐☐ - ☐☐☐☐

	Never	Seldom	Sometimes	Often
4a. How often did the subject take study medication by any route other than instructed (for example, inhaling medication meant for swallowing, swallowing a medication in a skin patch, etc.)?	☐	☐	☐	☐
4b. How often did the subject tamper with study medication (for example, crush a pill or dissolve a skin patch)?	☐	☐	☐	☐
	Never	Seldom	Sometimes	Often
5. How often did the subject experience a constellation of symptoms after stopping or substantially reducing the dosage of study medication (i.e. more than just skipping a dose) that might be withdrawal related?	☐	☐	☐	☐
	Never	Seldom	Sometimes	Often
6. How often did the subject's study medication pass into the possession of someone other than the subject contrary to instructions in the protocol? (Do not count situations in which caregivers are expected to control study medication.)	☐	☐	☐	☐

Certified individual who has completed the form		
Print Name	**Print Title**	**Signature & Date (dd-mmm-yyyy)**
Principal Investigator		
Print Name	**Signature & Date (dd-mmm-yyyy)**	

Appendix S – Endocrine Function and Sexual Function

Endocrine function will be assessed at screening, and 12 and 24 weeks post-randomization, in all participants. Participants will be encouraged to attend the clinic and have blood drawn as early in the morning as practical, and to fast prior to their morning blood draw. Data will be captured on customary time to bed, customary awakening time, and time blood is drawn, to account for variability in actual blood drawing time. In female patients, data will be captured on type of birth control (including IUDs, implants, etc.), menopausal status, the date the last menstrual period began, and during the study the onset dates of all menstrual periods. The timing of blood draws will be performed according to the study schedule irrespective of the timing of the menstrual cycle.

The endocrine endpoints will be as follows:

- HPG axis: Total testosterone, free testosterone (assayed using the equilibrium dialysis method), FSH, LH, and, in women, estradiol
- HPA axis: ACTH, cortisol, dehydroepiandrosterone sulfate (DHEAS)
- Growth hormone axis: IGF-1
- Thyroid function: TSH (only at screening)

Questionnaires (following this description) regarding sexual function (International Index of Erectile Function [IIEF] in males and Female Sexual Function Index [FSFI] in females) will be obtained at the same time that endocrine blood samples are drawn. Changes in sexual function will be correlated to changes in endocrine function.

Procedure:

At a morning visit in fasted subjects (who ideally have been seated and resting quietly for 30 min), obtain blood for total testosterone, free testosterone, FSH, LH, estradiol (women only), IGF-1, cortisol, ACTH, DHEAS, and TSH (baseline only).

Anticipated results:

Participants who stop opioids, compared to those continued on opioids, will:

1) Show increases in testosterone and free testosterone (and estradiol in women). The increases in these hormones will likely be accompanied by increases in FSH/LH, suggesting that opioids act at the hypothalamic level to affect gonadal function. Improvements in gonadal function may correlate with improved sexual function.
2) Show increases in cortisol, ACTH and DHEAS
3) Show increases in IGF-1

Potential Confounders:

Potential confounders include any steroid use (inhaled steroids, topical steroids, oral steroids, injected into joints--effects will suppress the HPA axis for up to a year), phase of the menstrual cycle, whether a woman is pre- versus post-menopausal, use of hormones or oral contraceptives, smoking, age, sex, other medical illnesses, body mass index (particularly important in interpreting IGF-1), duration of opioid use, and specific opioid being used. These factors should be assessed in a detailed history.

IIEF Questionnaire Assessment

Circle one answer for each question

1. Over the past 4 weeks, how often were you able to get an erection during sexual activity?
   0 No sexual activity
   1 Almost always or always
   2 Most times (much more than half the time)
   3 Sometimes (about half the time)
   4 A few times (much less than half the time)
   5 Almost never or never

2. Over the past 4 weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?
   0 No sexual stimulation
   1 Almost always or always
   2 Most times (much more than half the time)
   3 Sometimes (about half the time)
   4 A few times (much less than half the time)
   5 Almost never or never

3. Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
   0 Did not attempt intercourse
   1 Almost always or always
   2 Most times (much more than half the time)
   3 Sometimes (about half the time)
   4 A few times (much less thanhalf the time)
   5 Almost never or never

4. Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
   0 Did not attempt intercourse
   1 Almost always or always
   2 Most times (much more than half the time)
   3 Sometimes (about half the time)
   4 A few times (much less than half the time)
   5 Almost never or never

5. Over the past 4 weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
1 Did not attempt intercourse
2 Almost always or always
3 Most times (much more than half the time)
4 Sometimes (about half the time) 0 A few times (much less than half the time)
5 Almost never or never

6. Over the past 4 weeks, how many times have you attempted sexual intercourse?
0 No attempts
1 1-2 attempts
2 3-4 attempts
3 5-6 attempts
4 7-10 attempts
5 11 or more attempts

7. Over the past 4 weeks, when you attempted sexual intercourse how often was it satisfactory for you?
0 Did not attempt intercourse
1 Almost always or always
2 Most times (much more than half the time)
3 Sometimes (about half the time)
4 A few times (much less than half the time)
5 Almost never or never

8. Over the past 4 weeks, how much have you enjoyed sexual intercourse?
0 No intercourse
1 Very highly enjoyable
2 Highly enjoyable
3 Fairly enjoyable
4 Not very enjoyable
5 Not enjoyable

9. Over the past 4 weeks, when you had sexual stimulation or intercourse how often did you ejaculate?
0 Did not attempt intercourse
1 Almost always or always
2 Most times (more than half the time)
3 Sometimes (about half the time)
4 A few times (much less than half the time)
5 Almost never or never

10. Over the past 4 weeks, when you had sexual stimulation or intercourse how often did you have the feeling of orgasm or climax (with or without ejaculation)?
0 No sexual stimulation or intercourse
1 Almost always or always
2 Most times (much more than half the time)
3 Sometimes (about half the time)
4 A few times (much less than half the time)
5 Almost never or never

11. Over the past 4 weeks, how often have you felt sexual desire?
1 Almost always or always
2 Most times (much more than half the time)
3 Sometimes (about half the time)
4 A Few times (much less than half the time)
5 Almost never or never

12. Over the past 4 weeks, how would you rate your level of sexual desire?
1 Very high
2 High
3 Moderate
4 Low
5 Very low or none at all

13. Over the past 4 weeks, how satisfied have you been with you overall sex life?
1 Very satisfied
2 Moderately satisfied
3 About equally satisfied and dissatisfied
4 Moderately dissatisfied
5 Very dissatisfied

14. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?
1 Very satisfied
2 Moderately satisfied
3 About equally satisfied and dissatisfied
4 Moderately dissatisfied
5 Very dissatisfied

15. Over the past 4 weeks, how do you rate your confidence that you can get and keep your erection?
1 Very high
2 High
3 Moderate
4 Low
5 Very low

Female Sexual Function Index (FSFI) ©

Subject Identifier _____ Date _____

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

   ☐ Very high
   ☐ High
   ☐ Moderate
   ☐ Low
   ☐ Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very high confidence
- ☐ High confidence
- ☐ Moderate confidence
- ☐ Low confidence
- ☐ Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

Thank you for completing this questionnaire

Appendix T – Urine Drug Testing (UDT)

Appendix: Urine Drug Testing Procedures and Management of Unexpected Findings

General Procedure

Urine Drug Testing (UDT) will be performed according to the Schedule of Procedures of the protocol. Testing will be performed for the presence of the following drugs:

- Illegal drugs
- Non-prescribed controlled substances (opioid and non-opioid)
- Alcohol

Following randomization, index drugs and their metabolites will NOT be tested to avoid unblinding of the subject or the investigator.

Management of Unexpected Findings

Unexpected finding will be managed according to the following table:

	Unexpected Result/Report	Possible Explanation	Recommended Action	Comment
1	UDT *positive* for non-study opioid medication	• If not prescribed, patient acquired opioids from other sources (doctor shopping, street)	• Report indicates detection of non-study opioid. Details of the non-study opioid are provided. Investigator to determine whether result is appropriate based on patient's prescribed rescue regimen and phase of study. • Unscheduled visit: Investigator performs "Supplemental Evaluation" (see below) if result is not appropriate. • Since repeated consumption of prohibited medications against instructions creates a patient safety issue, patient is terminated from study per sponsor guidelines upon second event	• Example: patient has codeine in his urine. Report indicates presence of codeine. Investigator understands that after randomization codeine is inappropriate and follows unscheduled visit and related procedures. • Example: patient on oxycodone ER and codeine rescue at Screening has codeine in their urine. Investigator understands that this is acceptable and takes no action.
2	UDT *positive* for *non-opioid* controlled medication	• If not prescribed, patient acquired non-opioids from other sources (doctor shopping, street)	• Report indicates detection of "non-opioid controlled substance." Identity of substance is provided. • Unscheduled visit: Investigator performs "Supplemental Evaluation" (see below) if this is a non-prescribed medication. • Since repeated consumption of prohibited or non-prescribed non-opioid controlled medications is against instructions creates a patient safety issue, patient is terminated from study per sponsor guidelines upon second event.	• Example: patient on any regimen has diazepam in urine. Investigator reviews prescribed concomitant medications to determine if patient was prescribed diazepam

	Unexpected Result/Report	Possible Explanation	Recommended Action	Comment
3	UDT *positive* for illicit drugs (e.g., cocaine, heroin) or alcohol (not cannabis; see below)	• Patient is abusing the detected substance • Cannabis is positive for dronabinol (Marinol®) or medical marijuana	• Report indicates detection of specified illicit substance. • Unscheduled visit: Investigator performs "Supplemental Evaluation" (see below) • Counsel patient that repeated similar results may lead to discontinuation from study • Since repeated consumption of prohibited medications against instructions creates a patient safety issue, patient is terminated from study per sponsor guidelines upon second event	• Example: patient has cocaine in urine.
4	UDT positive for cannabis	• Medical marijuana • Recreational marijuana	• Report indicates detection of cannabis • Unscheduled visit: Investigator performs "Supplemental Evaluation" (see below) • Counsel patient based on investigator judgment • Termination from study based on investigator judgment	•
5	Failed specimen validity test (e.g. creatinine, specific gravity)	• Patient added water to sample	• Send report to investigator, indicating that "urine specimen was not valid", suggesting adulteration • Unscheduled visit: Investigator performs "Supplemental Evaluation" (see below) • Review treatment agreement and counsel patient that repeated similar results may lead to discontinuation from study. • Consider supervised collection or temperature testing • Since repeated masking of urine testing raises the likelihood of a patient safety issue, patient is terminated from study per sponsor guidelines upon second event	• Algorithm constructed to be general in terms of the type of specimen validity test result that will generate this report, since specimen validity testing may vary across lab vendors

Supplemental Evaluation and Intervention

- Bring patient in for unscheduled visit to discuss test results in non-judgmental manner.
- Take a detailed history of the patient's medication use for the preceding 7 days (e.g., could learn that patient ran out of study medication several days prior to test or that a legitimate supplemental prescription had been provided).
- Ask patient if they took any non-prescribed medications, and if so, which ones, doses, etc.
- Ask about medical prescription of dronabinol or medical marijuana if cannabis detected.
- Ask patient if they've given the drug to others.
- Monitor compliance with pill counts.
- Check Prescription Monitoring Program (PDMP) data if available for recent non-study pain medication prescriptions.
- Repeat UDT is not required but may be performed at discretion of investigator if that will improve management of subject.
- Review treatment agreement (brief form to be used) and counsel patient that repeated similar results may lead to discontinuation from study.
- If patient is terminated from the study, advance subject to follow-up period.

Appendix U – Online Patient Support Program

Unfortunately, several barriers stand in the way of **face-to-face** pain treatment for millions of people, including inadequate finances, reluctance to seek treatment, and reduced access in rural areas. A highly cost-effective avenue for making inroads into this problem is the use of technology as a **supplement to the traditional administration of services**. Technology-based programs are affordable, self-paced, and are available 24 hours a day to people with reduced access to traditional treatment, such as people living in rural areas, with communication or other disabilities, with busy or inflexible schedules, or who lack child care, transportation, or insurance coverage.

The Online Patient Support Program uses easy-to-use computer-based tools **to aid in treatment for chronic pain and depression**. These tools help people manage psychological, social, and health-related problems that are often treated in health care settings and in during clinical trials. The tools provide a uniquely **dynamic foundation for learning** such as online assessments and the scoring and reporting of data, interactive learning, electronic messaging, in-stream video, online discussion forums, as well as online data tracking and graphing. Features such as self-assessment, homework exercises, and self-monitoring can be created to suit the specific goals of a program. The program was created by two psychologists, Dr. Linda Ruehlman and Dr. Paul Karoly.

Reference: Ruehlman LS, Karoly P, Enders C. A randomized controlled evaluation of an online chronic pain self-management program. *Pain*. 2012;153:319-30.

Appendix V – Early Discontinuation Assessment Tool

As a follow-up to the questions we just discussed, I want to ask you a few questions about the reasons why you are leaving this research study. People decide to leave research studies for many reasons. For each of the reasons I will read to you, first indicate whether this contributed to your decision to leave the study ("Yes" or "No"). Second, for those reasons where you answered "Yes", please indicate whether the reason was "extremely important", "moderately important", "a little important", or "not that important" for you.

	Each question is initially answered "Yes" or "No" by circling the word. If "Yes" is chosen, then indicate the importance		Extremely important	Moderately important	A little important	Not that important
1)	Too much pain	*Yes No*	□	□	□	□
2)	Side effects from medications	*Yes No*	□	□	□	□
3)	Feeling sick from medication withdrawal	*Yes No*	□	□	□	□
4)	Anxiety or nervousness	*Yes No*	□	□	□	□
5)	Trouble sleeping	*Yes No*	□	□	□	□
6)	Transportation problems	*Yes No*	□	□	□	□
7)	Study procedures are too uncomfortable	*Yes No*	□	□	□	□
8)	Study procedures require too much of my time	*Yes No*	□	□	□	□
9)	Cannot take time from work or other obligations	*Yes No*	□	□	□	□
10)	Do not like not knowing what medication I am on	*Yes No*	□	□	□	□
11)	Prefer to receive medical care elsewhere	*Yes No*	□	□	□	□
12)	Need treatment that is not allowed in this study	*Yes No*	□	□	□	□
13)	Moving too far from the research center	*Yes No*	□	□	□	□
14)	Developed a new medical condition	*Yes No*	□	□	□	□
15)	Do not want to be in an experiment any longer	*Yes No*	□	□	□	□
16)	Want to go back on opioid medications	*Yes No*	□	□	□	□
17)	Do not like the research center	*Yes No*	□	□	□	□

Please add any additional comments:

_____

_____

How has your pain changed during this study?	**Increased**	**Remained the same**	**Decreased**
Severity of pain	□	□	□
Area of pain	□	□	□
Sensitivity to pain	□	□	□

Appendix W – STOPBang Questionnaire

Please answer the following questions below to determine if you are at risk for obstructive sleep apnea (OSA):

Yes ○ No ○	**S**noring? Do you **Snore Loudly** (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?
Yes ○ No ○	**T**ired? Do you often feel **Tired, Fatigued, or Sleepy** during the daytime (such as falling asleep during driving)?
Yes ○ No ○	**O**bserved? Has anyone **Observed** you **Stop Breathing** or **Choking/Gasping** during your sleep?
Yes ○ No ○	**P**ressure? Do you have or are being treated for **High Blood Pressure**?
Yes ○ No ○	**B**ody Mass Index more than 35 kg/m^2?
Yes ○ No ○	**A**ge older than 50 year old?
Yes ○ No ○	**N**eck size large? (Measured around Adams apple) For male, is your shirt collar 17 inches/43 cm or larger? For female, is your shirt collar 16 inches/41 cm or larger?
Yes ○ No ○	**G**ender = Male?

Scoring Criteria:

For general population

Low risk of OSA: Yes to 0 - 2 questions

Intermediate Risk of OSA: Yes to 3 - 4 questions

High Risk of OSA: Yes to 5 - 8 questions
or Yes to 2 or more of 4 STOP questions + male gender
or Yes to 2 or more of 4 STOP questions + BMI > 35kg/m^2
or Yes to 2 or more of 4 STOP questions + neck circumference 17 inches / 43cm in male or 16 inches / 41cm in female

Modified from Chung F et al. Anesthesiology 2008; 108:812-21, Chung F et al Br J Anaesth 2012; 108:768–75, Chung F et al J Clin Sleep Med Sept 2014
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