Statistical Analysis Plan

Version: V1, 30-Dec-2014

for

A Phase III, Randomized, Double-blind, Double-dummy, Parallel Group Study to Determine the Safety and Efficacy of Oxycodone / Naloxone Prolonged Release Tablets 5/2.5mg, 10/5mg, 20/10mg or 40/20mg compared to Oxycodone PR 5mg, 10mg, 20mg or 40mg in Subjects with Moderate to Severe, Chronic Cancer Pain

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ABBREVIATIONS

Term	Definition of Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical-Therapeutic-Chemical
BFI	Bowel Function Index
BMI	Body Mass Index
BPI-SF	Brief Pain Inventory Short-Form
CFDA	China Food and Drug Administration
CI	Confidence Interval
CRF	Case Report Form
CRO	Contracted Research Organization
DBP	Diastolic Blood Pressure
DOSEA	Determination of Subject Evaluability
ECG	Electrocardiogram
FAP	Full Analysis Population
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology
LOCF	Last Observation Carried Forward
LS means	Least Square Means
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
N	Number of Subjects
NA	Not Applicable
NAS	Numerical Analogue Scale
NIMP	Non-Investigational Medicinal Product
OXN PR	Oxycodone / Naloxone Prolonged Release Tablet
OXY PR	Oxycodone Prolonged Release Tablet
PPP	Per-Protocol Population
PT	Preferred Terms
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SOWS	Subjective Opiate Withdrawal Scale

1. SYNOPSIS

This study is designed as a Phase III, Randomized, Double-blind, Double-dummy, Parallel Group Study to Determine the Safety and Efficacy of Oxycodone / Naloxone Prolonged Release Tablets 5/2.5mg, 10/5mg, 20/10mg or 40/20mg compared to Oxycodone PR 5mg, 10mg, 20mg or 40mg in Subjects with Moderate to Severe, Chronic Cancer Pain.

The protocol and CRF version approved by CFDA are as follows:

- Protocol Version/date: V1.0/13 March 2013
- CRF Version/date: V2.0/08 May 2013

This study is composed of three phases: a screening phase (<7 days) and a 4-week double-blind phase and follow up phase (1 week after last dose). Approximately 230 subjects who qualify for entry into the Double-blind Phase of the study will be randomized to Oxycodone/naloxone PR (OXN PR) or Oxycodone PR (OXY PR) treatment in 1:1 ratio.

Summary statistics will be produced and sorted by treatment group and visit number where appropriate. Statistics to be reported for continuous variables are: number of subjects (N), mean, median, standard deviation (SD) and range (minimum and maximum). For categorical variables, number and percentage of subjects will be reported

For the superiority test (bowel function) the Full Analysis Population (FAP) will be used for the primary analysis and the Per Protocol Population (PPP) will be used for sensitivity analysis. For the non-inferiority test (pain), the PPP will be used for the primary analysis and the FAP will be used for sensitivity analysis. All secondary endpoints will be analyzed with the FAP only and all safety analysis will be based on Safety Population.

For the primary endpoints analyses including Bowel Function Index (BFI) and Brief Pain Inventory Short-Form (BPI-SF), ANCOVA will be used for comparing the treatments at final visit; method of Last Observation Carried Forward (LOCF) will be applied for missing values, adjust for baseline observation.

Additional sensitivity analyses will be performed. A MMRM model will be used that has fixed effects for visit, treatment within visit, baseline; random intercept over subjects; an unstructured covariance matrix over the visits. The comparison between treatments at final visit will be reported. A similar model will be estimated that assumes a constant treatment effect over visits. .

2. OBJECTIVES

This randomized, double-blind, double-dummy, parallel study is to assess the effectiveness in relieving cancer pain and the improvement of adverse reaction of opioid of Oxycodone / Naloxone prolonged release tablets 5/2.5mg, 10/5mg, 20/10mg or 40/20mg compared to Oxycodone prolonged release 5mg, 10mg, 20mg or 40mg in subjects with moderate to severe chronic cancer pain.

The **main** objectives are to

- Determine the improvement in symptoms of constipation in subjects with moderate to severe cancer pain receiving treatment with oxycodone/naloxone prolonged release tablets (OXN PR) compared to oxycodone prolonged release tablets (OXY PR) based on the Bowel Function Index (BFI).
- Demonstrate the non-inferiority (comparability) of oxycodone / naloxone prolonged release tablets (OXN PR) compared to oxycodone prolonged release tablets (OXY PR) for the management of chronic cancer pain as assessed by the average pain of the Brief Pain Inventory (BPI) recorded by subjects.

The **other** objectives are to

- Compare the improvement in symptoms of constipation in subjects receiving treatment with oxycodone/naloxone prolonged release tablets (OXN PR) to oxycodone prolonged release tablets (OXY PR) based on laxative use.
- Compare the management of chronic cancer pain of oxycodone / naloxone prolonged release tablets (OXN PR) compared to oxycodone prolonged release tablets (OXY PR) as assessed by rescue medication use recorded by subjects.
- Compare the management of chronic cancer pain of oxycodone / naloxone prolonged release tablets (OXN PR) compared to oxycodone prolonged release tablets (OXY PR) as assessed by Brief Pain Inventory Short-Form (BPI-SF) (Cleeland, 1991) recorded at each visit assesses subject's' pain (worst, least, right now), pain relief from medication and pain interference over the last 24 Hours. BPI will be assessed on V1, V2, V5, V6, V7 and V8.
- Assess safety of treatment with OXN PR compared with OXY PR based on the Modified Subjective Opiate Withdrawal Scale (SOWS), Adverse Events (AEs), Electrocardiograms (ECG) and laboratory tests.
- Assess quality of life based on EQ-5D

3. STUDY DESIGN

3.1 General Design and Plan

This is a multi-center, randomized, double-blind, double-dummy, active-controlled, parallel study using OXN PR 5/2.5mg, 10/5mg, 20/10mg or 40/20mg and OXY PR 5mg, 10mg, 20mg and 40mg to treat moderate to severe, chronic cancer pain.

This study is composed of three phases: a screening phase (<7 days) and a 4-week double-blind phase and follow up phase (1 week after last dose).

Approximately 280 subjects may be screened to obtain 230 eligible subjects who will be randomized in a 1:1 ratio to OXN PR / OXY PR via an IRT system. Each group will have 115 subjects.

At the start of the double-blind phase (Randomization), subjects will discontinue their current (pre study) opioid and change to an effective dose of study medication (OXY PR/OXN PR). Subjects will also stop taking any pre study laxatives at the time of randomization and revert to the study laxative regime.

3.2 Treatment

There are Investigational Medicinal Products (IMPs) and Non-Investigational Medicinal Products (NIMPs) used in this study.

Investigational Medicinal Products (IMPs)

In double-blind phase, subjects randomized to test treatment group will take OXN PR and matching placebo of OXY PR. The dosage would be fixed and symmetrical (20/10, 30/15, 40/20, 60/30, 80/40,100/50 or 120/60 mg/day of oxycodone/naloxone)

Test Treatment Group (OXN PR)				
Treatment	**Dosage Form**	**Strength**	**Dosing Frequency**	**Mode of Administration**
Oxycodone /naloxone prolonged release (OXN PR)	Tablet	5/2.5, 10/5, 20/10 and 40/20mg OXN PR	Q12h	Oral
Matched placebo for OXY PR	Tablet	Matching placebos for 5, 10, 20 and 40 mg OXY PR tablets	Q12h	Oral

In double-blind phase, subjects randomized to reference treatment group will take OXY PR and matching placebo of OXN PR. The dosage would be fixed and symmetrical (20, 30, 40, 60,

80,100 or 120mg/day)

Reference Treatment Group (OXY PR)				
Treatment	**Dosage Form**	**Strength**	**Dosing Frequency**	**Mode of Administration**
Oxycodone Prolonged release (OXY PR)	Tablet	5, 10, 20 and 40 mg Oxy PR	Q12h	Oral
Matched placebo for OXN PR	Tablet	5/2.5, 10/5, 20/10 and 40/20 mg OXN PR placebo	Q12h	Oral

Non-Investigational Medicinal Products (NIMPs)

The rescue medications are not IMPs. Rescue medications include Analgesics and Laxative treatment.

During the double-blind treatment phase, all subjects can receive Morphine Sulphate Tablets as rescue medication up to 6 times a day at a dose

Rescue Medication (Pain)				
Treatment	**Dosage Form**	**Strength**	**Dosing Frequency**	**Mode of Administration**
Morphine Sulphate Tablets	Tablet	10 mg	P.R.N, q4-6h	Oral

Throughout the double-blind treatment phase subjects will be given bisacodyl tablets to take as a laxative medication.

Laxative Medication				
Treatment	**Dosage Form**	**Strength**	**Dosing Frequency**	**Mode of Administration**
Bisacodyl	Tablet	5 mg	q3d PRN (10mg/day)	Oral

3.3 Sample Size

Approximately 280 patients may be screened to obtain 230 patients who will be randomized in a 1:1 ratio to OXN PR group and OXY PR group. Each group will have 115 subjects randomized to ensure 105 patients in the FAP per group.

With 105 subjects in the FAP per treatment group, the study has a power of 90% to detect a treatment difference of 12, assuming a common standard deviation of 26, on the BFI on a two-sided level of significance level of 0.05.

3.4 Randomization

Subjects who have signed informed consent and meet all study criteria after screening period will be randomized to receive either OXN PR or OXY PR treatment. Randomization will be completed using a validated system by the Sponsor in a 1:1 ratio. An interactive response technology (IRT) system will be employed to manage study treatment supply.

3.5 Blinding

The study medication (OXN PR or OXY PR) will be packaged in a double-blind, double-dummy manner, rendering the active tablets indistinguishable from the matched placebo tablets. During the double-blind phase, the subject and all personnel involved with the conduct and the interpretation of the study, including the Investigators, investigational site personnel, and the Sponsor's and CRO's staff, will be blinded to the medication codes.

Randomization data will be kept strictly confidential, filed securely by the Sponsor, and accessible only to authorized persons per Sponsor's Standard Operating Procedures (SOPs) until the time of unblinding.

Emergency unblinding will be done via the IRT system. Unblinding is not to be done unless an actual emergency occurs and knowledge of the subject's randomization code may affect his/her medical treatment. If possible, before breaking the blind, the Investigator should consult with the Sponsor's Medical Monitor to ascertain the necessity of breaking the code. A record will be made of the date, time and reason for breaking the blind.

3.6 Laboratory Assessments

All scheduled clinical laboratory tests include hematology, blood chemistry and urinalysis will be performed by local laboratories.

4. STUDY POPULATIONS

4.1 Definition of Populations for Analysis

- **Enrolled Population**

The enrolled population is defined as all subjects who signed informed consent.

- **Randomized Population**

The randomized population is defined as all randomized subjects.

- **Full Analysis Population (FAP)**

The full analysis population is defined as all randomized subjects who receive at least one dose of study medication (IMP) and have at least one post-baseline primary efficacy endpoint.

- **Per Protocol Population (PPP)**

The Per Protocol Population is defined as all FAP subjects without major protocol violations.

Major protocol violations will be agreed at the Determination of Subject Evaluability meeting prior to database lock.

- **Safety Population**

The safety population is defined as all randomized subjects who receive at least one dose of IMP and with at least one post-baseline safety assessment.

4.2 Subject Disposition

A clear picture of subjects regarding screened, screen failure, primary reason of screen failure, randomized and completion status and the reason why subjects were withdrawn from study will be summarized in Figure 1.

The number and percentage of subjects in each population will be summarized by treatment group and overall for subjects in the enrolled set. Reasons for exclusion from the PPP will also be summarized.

The number and percentage of subjects enrolled and the primary reason for screen failure will be summarized for subjects in the enrolled population.

The number and percentage of subjects that complete the study and the primary reason for

discontinuation will be summarized for subjects in the randomized population.

The number and percentage of subjects enrolled from each site will be summarized for subjects in the randomized population.

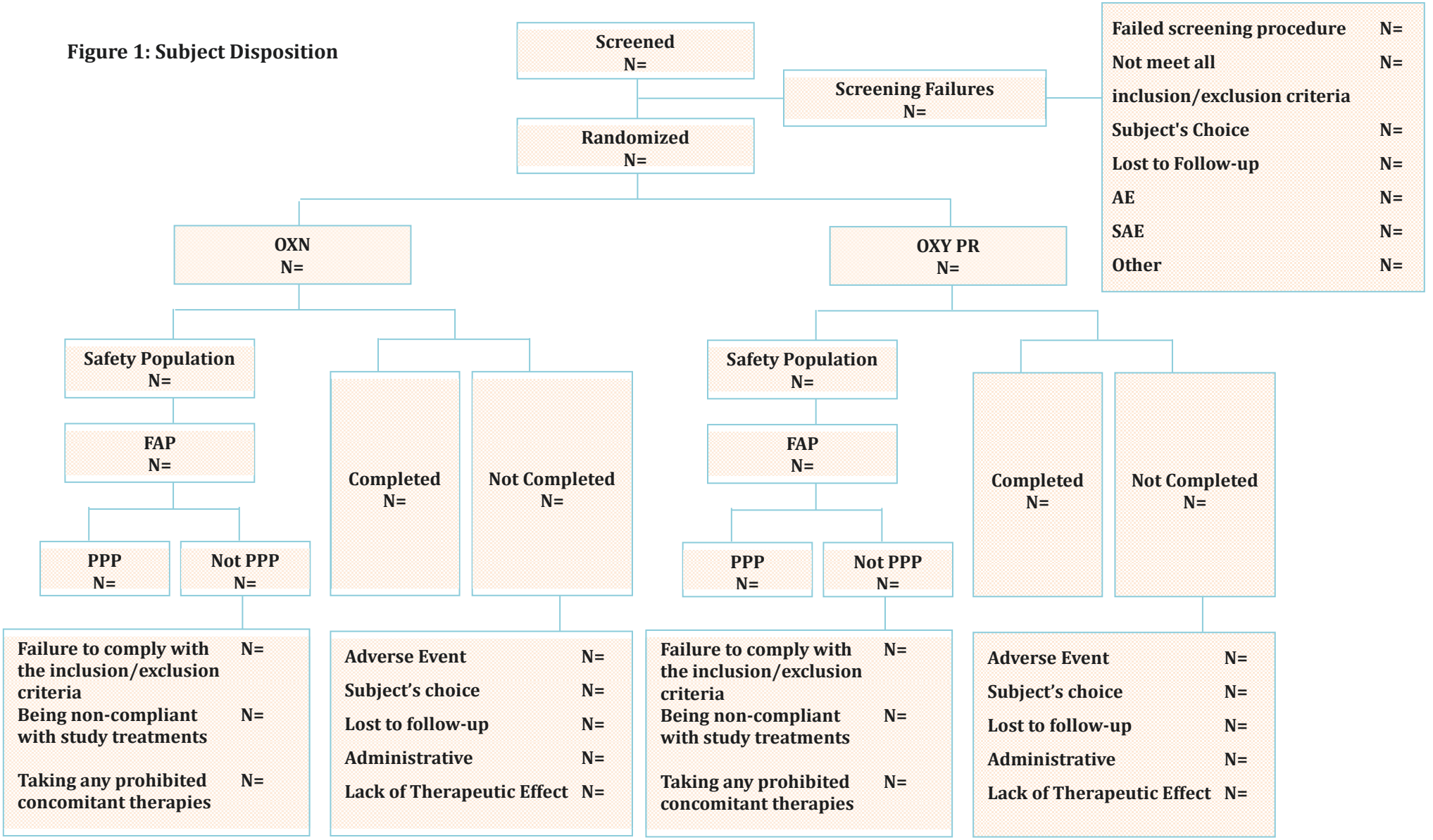
Details of analysis population will be tabulated as Table 1: Summary of Subject Disposition as appropriate.

Table 1: Summary of Subject Disposition

Variable	Status	OXN PR	OXY PR
Enrolled Population	Number of total screened		N
	Number of screen failure		N (%)
Major reason of screen failure	Failed screening procedure		N (%)
	Not meet all inclusion/exclusion criteria		N (%)
	Subject's Choice		N (%)
	Lost to Follow-up		N (%)
	AE		N (%)
	SAE		N (%)
	Other		N (%)
Randomized Population	Number of randomization	N (%)	N (%)
	Site1	N (%)	N (%)
	Site2	N (%)	N (%)
Safety Population	Number of Safety Population	N (%)	N (%)
FAP	Number of FAP	N (%)	N (%)
PPP	Number of PPP	N (%)	N (%)
Reason for PPP exclusion	Failure to comply with the inclusion/exclusion criteria	N (%)	N (%)
	Being non-compliant with study treatments	N (%)	N (%)
	Taking any prohibited concomitant therapies	N (%)	N (%)
Complete study	N	N	N
	Yes	N (%)	N (%)
	No	N (%)	N (%)
Reason for not complete study	Number of subject	N	N
	Adverse Event	N (%)	N (%)
	Subject's choice	N (%)	N (%)
	Lost to follow-up	N (%)	N (%)
	Administrative	N (%)	N (%)
	Lack of Therapeutic Effect	N (%)	N (%)

FAP: Full Analysis Population
PPP: Per Protocol Population

Figure 1: Subject Disposition



4.3 Protocol Deviations/Violations

The following protocol violations may exclude a subject from the PPP. Major protocol violations will be agreed at the Determination of Subject Evaluability (DOSEA) meeting prior to database lock.

1) Failure to comply with the inclusion/exclusion criteria.
2) Being non-compliant with study treatments.
3) Taking any prohibited concomitant therapies.

Information regarding subject identification, reason for protocol deviations/protocol violation will be listed in the DOSEA Report which will be attached as appendix in statistical analysis report.

5. STATISTICAL ANALYSIS

5.1 Working platform

Statistical analysis programs will be generated with SAS 9.3 on Windows platform.

5.2 Time-Points for Analysis

Statistical analysis will be performed after database lock.

5.3 Methods for Handling Missing Data

For the primary analyses use ANCOVA comparing the treatments at final visit, method of Last Observation Carried Forward (LOCF) will be applied for missing values.

No imputation will be implemented for missing data in regard of secondary and other efficacy variables and safety analysis.

5.4 Statistical Analysis

5.4.1 Categorical Data

Categorical data will be summarized by treatment group with number and percentage of subject.

5.4.2 Continuous Data

Continuous data will be summarized by treatment group with number of subject (N), mean, median, SD and range (minimum and maximum).

For the primary efficacy endpoint LS means of the treatment difference with corresponding 95% confidence intervals will be provided as well.

5.4.3 Statistical Comparison

Significance tests (2-sided significance level of alpha=0.05) will be performed for the primary efficacy endpoint as appropriate and p-value will be rounded to three decimal places.

6. EVALUATION OF DEMOGRAPHICS/BASELINE CHARACTERISTICS

6.1 Demographics

FAP will be applied for the analysis of demographics. Age, weight, height, and body mass index (BMI) will be summarized as continuous data while gender and race will be summarized as categorical data and presented as Table 2: Summary of Demographic Data.

Table 2: Summary of Demographic Data

Parameter	Statistics	Total	OXN PR	OXY PR
Age (year)	N Mean (SD) Median (Min, Max)			
Weight (kg)	N Mean (SD) Median (Min, Max)			
Height (cm)	N Mean (SD) Median (Min, Max)			
BMI (kg/m^2)	N Mean (SD) Median (Min, Max)			
Gender	N Male Female	N N (%) N (%)	N N (%) N (%)	N N (%) N (%)
Race	N Caucasian Black Asian Other	N N (%) N (%) N (%) N (%)	N N (%) N (%) N (%) N (%)	N N (%) N (%) N (%) N (%)

6.2 Current Medical Condition (Baseline)

FAP will be applied for the summary of current medical condition. The current medical conditions will be coded with MedDRA version 15.0 and summarized by System Organ Class (SOC) and Preferred Term (PT). The results will be summarized by treatment group as categorical data as Table 3: Summary of Current Medical Conditions.

Table 3: Summary of Current Medical Conditions

SOC	PT	Total	OXN PR	OXY PR
Total		N, N (%)	N, N (%)	N, N (%)
SOC1	Total	N, N	N, N	N, N
	PT1	N, N (%)	N, N (%)	N, N (%)
	PT2	N, N (%)	N, N (%)	N, N (%)
	…	N, N (%)	N, N (%)	N, N (%)
SOC2	Total	N, N	N, N	N, N
	PT1	N, N (%)	N, N (%)	N, N (%)
	PT2	N, N (%)	N, N (%)	N, N (%)
	…	N, N (%)	N, N (%)	N, N (%)

N, N (%): Number of Event, Number of Subject (Percentage of Subject)

7. EFFICACY ANALYSIS

The efficacy analysis will be analyzed based on subjects in FAP and PPP as defined in the protocol.

Descriptive statistics of efficacy variables will be produced. These will be sorted by treatment group and visit where appropriate. Visit 2 measurements will be used as baseline data and Visit 1 measurements will be used when Visit 2 data is not available.

7.1 Primary Efficacy Assessments Analysis

There are 2 primary efficacy variables: one is Bowel Function Index (BFI) and the other is Brief Pain Inventory Short-Form (BPI-SF).

- **Bowel Function Index (BFI)**
  Bowel Function Index (BFI) is the mean of Numerical Analogue Scale (NAS) for the following items:
  – Ease of defecation
  – Feeling of incomplete bowel evacuation.
  – Personal judgment of constipation.

The analysis of the primary endpoint uses an ANCOVA comparing the treatments at final visit using LOCF for missing values, adjusted for baseline observation. The FAP is the primary population for this BFI analysis and the PPP will be analyzed as well. The result will be presented as Table 4: Summary of ANCOVA analysis for BFI LOCF data at final visit.

Table 4: Summary of ANCOVA analysis for BFI LOCF data at final visit

Variable	Statistics	OXN PR	OXY PR	P-value*
Bowel Function Index (BFI)	N Mean (SD) Median (Min, Max)			
Difference in BFI between OXN PR and OXY PR	LS Mean 95% CI			

* ANCOVA analysis

Additional sensitivity analyses will be performed in which LOCF will not be applied for missing values. A MMRM model will be used that has fixed effects for visit, treatment within visit, baseline; random intercept over subjects; an unstructured covariance matrix over the visits. The comparison between treatments at final visit will be reported. A similar model will be estimated that assumes a constant treatment effect over visits.

The comparison between treatments at final visit will be reported and the result will be presented as Table 5: Summary of Sensitivity analysis for BFI data at final visit.

Table 5: Summary of Sensitivity analysis for BFI data at final visit

Variable	Statistics	OXN PR	OXY PR	P-value*
Bowel Function Index (BFI)	N Mean (SD) Median (Min, Max)			
Difference in BFI between OXN PR and OXY PR	LS Mean 95% CI			

* MMRM model applied

To observe trend, BFI will also be summarized by visit.

- **Brief Pain Inventory Short-Form (BPI-SF)**

Brief Pain Inventory Short-Form (BPI-SF) (Cleeland, 1991) recorded at each visit assesses subjects' average pain over the last 24 Hours. For average pain uses an ANCOVA comparing the treatments at final visit using LOCF for missing values, adjusted for baseline observation. The PPP is the primary population for this pain analysis. FAP will be analyzed as well. The result will be presented as Table 6: Summary of ANCOVA analysis for BPI-SF LOCF data at final visit.

Table 6: Summary of ANCOVA analysis for BPI-SF LOCF data at final visit

Variable	Statistics	OXN PR	OXY PR	P-value*
Brief Pain Inventory Short-Form (BPI-SF)	N Mean (SD) Median (Min, Max)			
Difference in BFI between OXN PR and OXY PR	LS Mean 95% CI			

* ANCOVA analysis

7.2 Secondary Efficacy Assessments Analysis

Only FAP will be used for secondary efficacy analysis.

- **To compare the improvement in symptoms of constipation based on laxative use.**

Amount of laxative medication use recorded at each assessment visit. Total number of bisacodyl tablets used per week, and the number of Bisacodyl tablets used per day will be calculated using the data recorded on CRF in section "Study Laxative (Bisacodyl) Use" section. The results will be summarized as continuous data as Table 7: Summary of use of Laxative

Medication (Bisacodyl).

Table 7: Summary of use of Laxative Medication (Bisacodyl)

Parameter	Visit	Statistics	OXN PR	OXY PR
Number of laxative tablets took during the last 7 days (per week)		N Mean (SD) Median (Min, Max)		
Daily number of laxative tablets took during the last 7 days (per day)		N Mean (SD) Median (Min, Max)		

* Daily tablets = Total tablets took / Number of days with medication

- **To compare the management of chronic cancer pain as assessed by rescue medication use recorded by subjects.**

Amount (mg) of rescue medication used per day (24 hours) recorded on the OXY IR wallet. Average rescue medication (Morphine Sulphate) used per day will be summarized as continuous data as Table 8: Summary of Rescue Medication (Morphine Sulphate).

Table 8: Summary of Rescue Medication (Morphine Sulphate)

Parameter	Visit	Statistics	OXN PR	OXY PR
Average rescue medication used per day (mg)		N Mean (SD) Median (Min, Max)		

- **Brief Pain Inventory Short-Form (BPI-SF) (Cleeland, 1991) recorded at each visit assesses subjects' pain (worst, least, right now), pain relief from medication in percentage and pain interference over the last 24 Hours.**

The 11 individual items regarding subjects' pain (worst, least, right now), pain relief from medication and pain interference will be summarized as continuous data as Table 9: Summary of BPI-SF.

Table 9: Summary of BPI-SF for Individual Items

Parameter	Visit	Statistics	OXN PR	OXY PR
Pain at its worst in the last 24 hours …		N Mean (SD) Median (Min, Max)		

In addition, BPI pain interference will be scored as the mean of the seven interference items

and summarized as continuous data as Table 10: Summary of BPI-SF for Pain Interference.

Table 10: Summary of BPI-SF for Pain Interference

Parameter	Visit	Statistics	OXN PR	OXY PR
Mean of seven interference items		N Mean (SD) Median (Min, Max)		

- **Modified Subjective Opiate Withdrawal Scale (SOWS).**

SOWS will be scored as the total of the 15 symptoms and, change from baseline to visit 3 and visit 9 will be summarized as continuous data as Table 11: Summary of SOWS.

Table 11: Summary of SOWS

Parameter	Visit	Statistics	OXN PR	OXY PR
Total of the 15 items		N Mean (SD) Median (Min, Max)		

Scatter plots will be produced for SOWS comparing baseline and Visit 3 values as well.

- **To assess quality of life based on EQ-5D.**

The scale of health state will be summarized as continuous data as Table 12: Summary of EQ-5D.

Table 12: Summary of EQ-5D

Parameter	Visit	Statistics	OXN PR	OXY PR
EQ-5D		N Mean (SD) Median (Min, Max)		

- **Number of bowel movements the subject has had in the last 7 days before the study visit and number of days the subject had a bowel movement in the last 7 days before the study visit.**

Number of bowel movements and number of days the subject had a bowel movement in the last 7 days before the study visit will be summarized as continuous data as Table 13: Summary of Bowel Movement.

Table 13: Summary of Bowel Movement

Parameter	Visit	Statistics	OXN PR	OXY PR
Number of bowel movement		N		
…		Mean (SD)		
		Median		
		(Min, Max)		

8. SAFETY ANALYSIS

The safety analysis will be summarized by treatment group and overall based on subjects in Safety population and the assessments include adverse events, vital signs, laboratory test, electrocardiogram (ECG) and physical examination.

8.1 Adverse Event

AEs will be coded with MedDRA version 15 and summarized by SOC and PT for each event. Only treatment emergent AEs will be summarized. A treatment emergent AE will be defined as any AE with an onset date on or after the first dose of IMP if the AE was absent before the first dose of IMP, or worsened after the first dose of IMP. This will also include AEs with an onset date up to and including 7 days after the last dose of IMP.

The overall AE information including incidence, severe AE, AE related to IMP and SAE will be summarized as Table 14: Summary of Overall Adverse Events information.

Table 14: Summary of Overall Adverse Events information

Category	Total	OXN PR	OXY PR
Number of AEs	N	N	N
Number of subjects with AEs	N (%)	N (%)	N (%)
Number of related AEs	N	N	N
Number of subjects with related AEs	N (%)	N (%)	N (%)
Number of Severe AEs	N	N	N
Number of subjects with Severe AEs	N (%)	N (%)	N (%)
Number of SAEs	N	N	N
Number of subjects with SAEs	N (%)	N (%)	N (%)
Number of related SAEs	N	N	N
Number of subjects with related SAEs	N (%)	N (%)	N (%)

AEs leading to death, AEs leading to discontinuation from study, AEs requiring additional therapy, AEs leading to dose reduction, and AEs leading to dose interruption and SAE not related to IMP will be summarized as Table 15: Summary of Incidence of Deaths, Other SAE and Other Significant EventsTable 14: Summary of Overall Adverse Events information.

Table 15: Summary of Incidence of Deaths, Other SAE and Other Significant Events

Category	Total	OXN PR	OXY PR
AEs leading to Deaths	N (%)	N (%)	N (%)
AEs leading to withdraw from study	N (%)	N (%)	N (%)
AEs requiring treatment given	N (%)	N (%)	N (%)
AEs leading to dose decrease	N (%)	N (%)	N (%)
AEs leading to withheld transiently	N (%)	N (%)	N (%)
SAE not related to IMP	N (%)	N (%)	N (%)

The number and percentage of subjects reporting any AE and the number of reported AEs will be summarized by PT nested within SOC

AEs will also be summarized by PT nested within SOC for worst severity, relationship to IMP, IMP action taken, other action taken and outcome.

Serious AE will be summarized by PT nested within SOC as Table 16: Summary of Serious Adverse Events.

Table 16: Summary of Serious Adverse Events

SOC	PT	Total	OXN PR	OXY PR
Total		N, N (%)	N, N (%)	N, N (%)
SOC1	Total	N, N	N, N	N, N
	PT1	N, N (%)	N, N (%)	N, N (%)
	PT2	N, N (%)	N, N (%)	N, N (%)
	…	N, N (%)	N, N (%)	N, N (%)
SOC2	Total	N, N	N, N	N, N
	PT1	N, N (%)	N, N (%)	N, N (%)
	PT2	N, N (%)	N, N (%)	N, N (%)
	…	N, N (%)	N, N (%)	N, N (%)

N, N (%): Number of Event, Number of Subject (Percentage of Subject)

The most frequent AEs (PT ≥ 5% in any treatment group) will be summarized for the double-blind phase as Table 17: Summary of Adverse Events ≥ 5% in Double-Blind phase.

Table 17: Summary of Adverse Events ≥ 5% in Double-Blind phase

SOC	PT	Total	OXN PR	OXY PR
Total	N	N, N (%)	N, N (%)	N, N (%)
SOC1	N	N, N	N, N	N, N
	PT 1	N, N (%)	N, N (%)	N, N (%)
	PT 2	N, N (%)	N, N (%)	N, N (%)
…				

N, N (%): Number of Event, Number of Subject (Percentage of Subject)

These will also be presented graphically using a dot plot and a caterpillar plot within which the percentage of subjects reporting each of the most common AEs will be presented alongside the odds ratio (and associated 95% CI) for comparing the incidence of AEs.

8.2 Laboratory Assessment

Safety population will be used for the analysis of laboratory assessments including blood chemistry, hematology and urinalysis. Laboratory results recorded at each visit and change from baseline to each visit will be summarized as continuous or categorical data as appropriate for each parameter by treatment group and overall. P-values will not be provided.

Each parameter will be assigned an LNH classification according to whether the value is lower than (L), within (N) or higher than (H) the reference range for that parameter. Results will be summarized using shift tables to evaluate categorical changes from baseline to end of study with respect to reference range values (lower than, within, higher than) as Table 18: Shift table of Laboratory Assessments for OXN PR /OXY PR treatment-Blood Chemistry/Hematology/Urinalysis. For those tests with qualitative results which cannot be categorized to LNH level, will only be summarized according to abnormality.

Table 18: Shift table of Laboratory Assessments for OXN PR /OXY PR treatment-Blood Chemistry/Hematology/Urinalysis

Parameter	Baseline	Final Visit		
		L	N	H
Hemaglobin	**L**			
…	**N**			
	H			

L: Lower than
N: Within
H: Higher than

Laboratory values after first dose of IMP will be evaluated for markedly abnormal value. The number and percentage of subjects reporting markedly abnormal value with or without clinical significance will be summarized for each parameter by treatment group and overall as Table 19: Summary of Laboratory Assessment Abnormality-Blood Chemistry/Hematology/Urinalysis.

Table 19: Summary of Laboratory Assessment Abnormality-Blood Chemistry/Hematology/Urinalysis

Parameter	Visit	Status	Total	OXN PR	OXY PR
Hemaglobin		N	N	N	N
…		Normal	N (%)	N (%)	N (%)
		Abnormal, NCS	N (%)	N (%)	N (%)
		Abnormal, CS	N (%)	N (%)	N (%)

Scatter plots will be produced for each laboratory parameter comparing baseline (Visit 2) and end of study values.

8.3 Vital Signs

Safety population will be used for the analysis of vital sign parameters to be summarized include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiration rate, and temperature. Vital sign results recorded at each visit and change from baseline to each visit will be summarized as continuous data for each parameter by treatment group and overall. P-values will not be provided

Each parameter will be assigned an LNH classification according to whether the value is lower than (L), within (N) or higher than (H) the reference range for that parameter. Results will be summarized using shift tables to evaluate categorical changes from baseline to end of study with respect to reference range values (lower than, within, higher than) as Table 20: Shift table of Vital Signs for OXN PR /OXY PR Treatment .

Table 20: Shift table of Vital Signs for OXN PR /OXY PR Treatment

Parameter	Baseline	Final Visit		
		L	N	H
SBP	**L**			
…	**N**			
	H			

L: Lower than
N: Within
H: Higher than

Vital sign values after first dose of IMP will be evaluated for clinically notable abnormalities according to Appendix 7 of protocol and each subject can be counted once in the parameter high and low categories as applicable. The number and percentage of subjects reporting clinically notable abnormalities will be summarized for each parameter by treatment group as Table 21: Summary of Clinically Notable Abnormality of Vital Signs.

Table 21: Summary of Clinically Notable Abnormality of Vital Signs

Parameter	Visit	Clinically Notable Abnormal	Total	OXN PR	OXY PR
SBP		N	N	N	N
…		High	N (%)	N (%)	N (%)
		Normal	N (%)	N (%)	N (%)
		Low	N (%)	N (%)	N (%)

Scatter plots will be produced for each vital sign parameter comparing baseline (Visit 2) and end of study values.

8.4 Electrocardiogram

Safety population will be applied for the analysis of Electrocardiogram assessment. Electrocardiogram assessment will be summarized by treatment and visit as Table 22: Summary of Electrocardiogram Assessments.

Table 22: Summary of Electrocardiogram Assessments

Characteristics	Visit	Statistics	Total	OXN PR	OXY PR
Electrocardiogram		N	N	N	N
		Normal	N (%)	N (%)	N (%)
		Abnormal, NCS	N (%)	N (%)	N (%)
		Abnormal, CS	N (%)	N (%)	N (%)

9. OTHER ANALYSIS

9.1 IMP Analysis

Safety population will be applied for the analysis of IMP. Treatment exposure will be defined as the number of days on IMP which will be calculated as the number of days between the first and last dose of IMP. Treatment exposure will be summarized by treatment group as continuous data and summarized as Table 23: Summary of IMP Exposure.

Table 23: Summary of IMP Exposure

Parameter	Statistics	OXN PR	OXY PR
IMP exposure (Day)	N Mean (SD) Median (Min, Max)		

9.2 Concomitant Medication Analysis

FAP will be applied for concomitant medication analysis. Concomitant medications will be coded with World Health Organization Drug Dictionary of version Q4/2012.

The number and percentage of subjects taking concomitant medications will be summarized by ATC class level 1 and level 4 for treatment group as Table 24: Summary of Concomitant Medication by ATC

Table 24: Summary of Concomitant Medication by ATC

ATC class	OXN PR	OXY PR
Alimentary...	N, N (%)	N, N (%)
Level 4	N, N (%)	N, N (%)
...	N, N (%)	N, N (%)
	N, N (%)	N, N (%)
Blood ...	N, N (%)	N, N (%)
Level 4	N, N (%)	N, N (%)
...	N, N (%)	N, N (%)
	N, N (%)	N, N (%)

9.3 Physical Examination

Safety population will be applied for the analysis of physical examination. Summary of physical examination will be summarized as categorical data in Table 25: Summary of Physical Examination.

Table 25: Summary of Physical Examination

Parameter	Visit	Status	OXN PR	OXY PR
Any clinical significant finding		N	N	N
		No	N (%)	N (%)
		Yes	N (%)	N (%)

9.4 Pregnancy Test

Safety population will be applied for the analysis of pregnancy test. Pregnancy test result will be summarized as categorical data in Table 26: Summary of Pregnancy Test.

Table 26: Summary of Pregnancy Test

Parameter	Visit	Result	OXN PR	OXY PR
Pregnancy Test		N	N	N
		No	N (%)	N (%)
		Yes	N (%)	N (%)
		ND	N (%)	N (%)

10. LIST OF TABLES

Tables will be presented for Enrolled, Randomized, FAP, PPP and Safety population as appropriate.

Table 14.1.1: Summary of Subject Disposition (All subjects)
Table 14.1.2: Summary of Demographic Data (FAP)
Table 14.1.3: Summary of Current Medication Conditions (FAP)

Table 14.2.1: Summary of ANCOVA analysis for BFI LOCF data at final visit (FAP)
Table 14.2.2: Summary of ANCOVA analysis for BFI LOCF data at final visit (PPP)
Table 14.2.3: Summary of Sensitivity analysis for BFI data at final visit – MMRM model (FAP)
Table 14.2.4: Summary of Sensitivity analysis for BFI data at final visit - MMRM model constant treatment effect over visits (FAP)
Table 14.2.5: Summary of BFI (FAP)
Table 14.2.6: Summary of ANCOVA analysis for BPI-SF LOCF data at final visit (PPP)
Table 14.2.7: Summary of ANCOVA analysis for BPI-SF LOCF data at final visit (FAP)
Table 14.2.8: Summary of use of Laxative Medication (Bisacodyl) (FAP)
Table 14.2.9: Summary of Rescue Medication (Morphine Sulphate) (FAP)
Table 14.2.10: Summary of BPI-SF (FAP)
Table 14.2.11: Summary of BPI-SF for Pain Interference (FAP)
Table 14.2.12: Summary of SOWS (FAP)
Table 14.2.13: Summary of EQ-5D (FAP)
Table 14.2.14: Summary of Bowel Movement (FAP)

Table 14.3.1: Summary of Overall Adverse Events information (Safety)
Table 14.3.2: Summary of Incidence of Deaths, Other SAE and Other Significant Events (Safety)
Table 14.3.3: Summary of Adverse Events (Safety)
Table 14.3.4: Summary of Serious Adverse Events (Safety)
Table 14.3.5: Summary of Adverse Events by Outcome (Safety)
Table 14.3.6: Summary of Adverse Events by Severity (Safety)
Table 14.3.7: Summary of Adverse Events by Relationship (Safety)
Table 14.3.8: Summary of Adverse Events by Action Taken (Safety)
Table 14.3.9: Summary of Adverse Events by Other Action Taken (Safety)
Table 14.3.10: Summary of Adverse Events $\geqslant$ 5% in Double-Blind phase (Safety)
Table 14.3.11: Summary of Laboratory Assessments-Blood Chemistry (Safety)
Table 14.3.12: Summary of Laboratory Assessments-Hematology (Safety)
Table 14.3.13: Summary of Laboratory Assessments-Urinalysis (Safety)

11. LIST OF LISTINGS

All subject data will be presented in subject data listings.

Listing 16.1.1.: Listing of Subjects' Population
Listing 16.1.2: Listing of Eligibility Evaluation
Listing 16.1.3: Listing of Screening Result at V1 & V2
Listing 16.1.4: Listing of Study completion / Early Study Termination
Listing 16.1.5: Listing of Protocol Deviations/Violations
Listing 16.1.6: Listing of Subjects Excluded from the FAP
Listing 16.1.7: Listing of Subjects Excluded from the PPP
Listing 16.1.8: Listing of Informed Consent and Visit Dates

Listing 16.2.1: Listing of Demographics
Listing 16.2.2: Listing of Medical History and Current Medical Conditions
Listing 16.2.3: Listing of Prior and Current Medication/Therapies

Listing 16.3.1: Listing of Rescue Medication dosing (Morphine Sulphate)
Listing 16.3.2: Listing of Laxatives Rescue Medication dosing (Bisacodyl)
Listing 16.3.3: Listing of Investigational Medicinal Product dosing
Listing 16.3.4: Listing of Questions on Bowel Movements and Study Laxative (Bisacodyl) Use
Listing 16.3.5: Listing of Bowel Function Index (BFI)
Listing 16.3.6: Listing of Brief Pain Inventory Short Form (BPI-SF)
Listing 16.3.7: Listing of EuroQol EQ-5D
Listing 16.3.8: Listing of Modified Subjective Opiate Withdrawal Scale (SOWS)

Listing 16.4.1: Listing of Adverse Event
Listing 16.4.2: Listing of Serious Adverse Event
Listing 16.4.3: Listing of Laboratory Tests Results - Hematology
Listing 16.4.4: Listing of Laboratory Tests Results - Blood Chemistry
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Listing 16.4.6: Listing of Pregnancy Test
Listing 16.4.7: Listing of Physical Examination
Listing 16.4.8: Listing of Vital Signs
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12. LIST OF FIGURES

13. Appendix

13.1 Flow chart

Phase Period	Pre-Randomization	Double-blind phase							Safety Phase
	Screening period	Treatment period							Safety Phase
Duration	< 10 days	4 weeks							1 week
Study visit	V1	V2[10]	V3	V4	V5	V6	V7	V81	V9
Study day[2]	-10 to 0	0	1	3	7± 3	14± 3	21± 3	28± 3	35+ 3
Informed consent	X								
Assess inclusion/ exclusion criteria	X	(X)							
Demography	X								
Physical examination	X							X	
Vital signs measurements	X	(X)			X	X	X	X	
Medical history	X	(X)							
Assess prior and current medication use	X	(X)							
Clinical laboratory tests (hematology, chemistry, urinalysis)	X							X	
pregnancy[3]	X							X	
12-lead ECG	X							X	
Clinic visit	X	(X)			X	X	X	X	
Telephone visit[4]			X	X					X
Laxative medication use[5]		X			X	X	X	X	
Question on bowel movements x2[6]	X	(X)			X	X	X	X	
Rescue medication use[7]		daily							
Assess concomitant medication use		X			X	X	X	X	
Bowel function index(BFI)[8]	X	(X)			X	X	X	X	
Brief pain inventory (BPI-SF)	X	(X)			X	X	X	X	
Modified SOWS	X		X						X

Phase Period	Pre-Randomization	Double-blind phase							Safety Phase
	Screening period	Treatment period							Safety Phase
Duration	< 10 days	4 weeks							1 week
EuroQol EQ-5D	X							X	
Adverse events (Non-elicited reporting)		X	X	X	X	X	X	X	X
Call IRT to enter/update subject status information	X	X			X	X	X	X	
Study medication dosing[9]		X			X	X	X	X	
Study medication dispensation		X			X	X	X		
Drug accountability					X	X	X	X	
Randomization		X							
Discontinuation/ end of study								X	

1. End of the double-blind phase completed at visit 8 or as soon as possible after early discontinuation from study medication.
2. The study visit window for Visit 1 ± 3 days and ± 3 days for Visits 5, 6, 7, 8 , +3 days for visit 9 Further visits to the study site will be conducted if considered necessary for the subject's welfare.
3. Urine test. Women of childbearing potential must have a negative pregnancy test prior to first dose of study medication.
4. Visits 3 & 4 are scheduled as telephone visits but can be completed as a clinic visit if required.
5. Laxative use in the last week to be recorded (total number of tablets per week and number of tablets per day)
6. Question 1. Number of bowel movements the subject has had in the last 7 days before the study visit
   Question 2. Number of days the subject had a bowel movement in the last 7 days before the study visit.
7. Recorded throughout the day for the rescue medication at the time of occurrence.
8. Includes subject assessments; ease of defecation, feeling of incomplete bowel evacuation, and personal judgment of constipation over the past 7 days.
9. If a subject needs to be titrated for adequate pain control the visit should be documented in the subject's source notes and the change in study medication dose will be recorded on the dosing CRF page at the next clinic visit
10 If screening visit and visit 2 are on the same day, do not duplicate the assessment completed on visit 1.