# Statistical Analysis Plan (SAP):

## ENHANCE

A multi-centre, randomised, phase IV study to compare the efficacy of oxycodone/naloxone versus oxycodone prolonged release tablets in patients with advanced cancer

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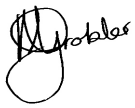
Based on Protocol Version 2.1 dated 28 August 2020

By signing this SAP I understand that the analysis of the trial data provided by the statistician will only include what is specified in this SAP. Changes to the SAP can be made until database lock and will be mutually agreed upon.

| | Signature | Date |
| --- | --- | --- |
| **Aaron Wong**<br>Coordinating Principal Investigator |  | 27/6/2022 |
| **Anneke Grobler**<br>Statistician (author) |  | 27/6/2022 |

**Document Version History**

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# LIST OF ABBREVIATIONS

| | |
| --- | --- |
| BPI-SF | Brief pain inventory – short form |
| BFI | Bowel function index |
| GEE | generalised estimating equations |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IRO | Immediate-release oxycodone |
| ITT | intention to treat |
| MAR | missing at random |
| NSAID | Non-steroidal anti-inflammatory drugs |
| oMEDD | oral morphine equivalent daily dose |
| OXN PR | Oxycodone/naloxone prolonged-release |
| Oxy PR | Oxycodone prolonged-release |
| PP | per protocol |
| SAP | statistical analysis plan |
| S-LANSS | Leeds Assessment of Neuropathic Symptoms & Signs – Self Reported |

# 1. CHANGES FROM THE PROTOCOL

The study protocol was written in 2019. In November 2019 the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) released an updated guideline on statistical principles for clinical trials introducing the estimand framework to align objectives, trial conduct, statistical analysis, and interpretation in randomised clinical trials (ICH, 2019). This framework was not taken into account when the protocol was written and is not reflected in the study protocol. However, the statistical analysis plan was written taking this guideline into account and the estimand for the primary outcome is defined in this statistical analysis plan even though it was not defined in the protocol.

Enrolment in the study was much slower than anticipated. Due to funding restrictions the study was terminated before the full sample size was enrolled. Because the sample size is much smaller than planned, most planned analyses will not have adequate power. For analyses where the sample size is small, we will merely provide descriptive analyses and not provide the full statistical analyses described in this document and the original protocol. We will only provide an intention to treat (ITT) analyses and not a per protocol analysis.

# 2. STUDY OBJECTIVES

## 2.1. PRIMARY OBJECTIVE

To demonstrate analgesic equivalence amongst cancer patients with pain who are taking Oxycodone/ naloxone prolonged-release (OXN PR) compared with patients taking Oxycodone prolonged-release (Oxy PR) over a 5-week period, based on average pain over last 24 hours as measured by the Brief Pain Inventory – Short Form (BPI-SF). The equivalence margin is defined as 1 point on the pain intensity scale.

## 2.2. SECONDARY OBJECTIVES

- To compare effects of OXN PR or Oxy PR on
  - Constipation, as measured by the Bowel Function Index (BFI) over a 5-week period.
  - Quality of life (nausea, vomiting, diarrhoea, appetite, functional activity, breathlessness, insomnia, fatigue, mood, memory), as measured by the EORTC-QLQ-C30 over a 5-week period
  - Rescue analgesia use
  - Total opioid dose
  - Total laxative use
- To demonstrate equivalence of OXN PR and Oxy PR on other pain measures, such as worst pain over preceding 24 hours, least pain over preceding 24 hours, and current pain at completing questionnaire (as measured by BPI-SF) over a 5-week period.
- To evaluate maintenance of analgesia and effect on bowel function in patients who switch from Oxy PR to OXN PR, and from OXN PR to OxyPR.

# 3. BACKGROUND / INTRODUCTION

## 3.1. STUDY DESIGN

This is a multi-centre, open-label, randomised, phase IV study of OXN PR or Oxy PR in patients with metastatic (Stage IV) or unresectable solid tumours or haematological malignancies with cancer-related pain.

Following randomisation to either OXN PR or Oxy PR, patients will enter the main study phase for 5 weeks. During the first week, the dose of Oxy PR or OXN PR will be titrated to analgesic effect. This is followed by a 4-week assessment period with Oxy PR or OXN PR doses adjusted only as necessary for ongoing analgesic titration at clinician discretion.

At the end of the main study phase (Week 5), patients will move into the continuation study phase. In the continuation study phase, patients originally in the Oxy PR arm of the main study phase may be switched to receive OXN PR and patients originally in the OXN PR arm of the main study phase may be switched to receive Oxy PR provided they are still able to swallow study medication, able to complete patient reported outcomes tools and willing to switch medications. OXN PR will be given at the equal dose of oxycodone (i.e.

Oxy PR 20mg will be switched to OXN PR 20mg/10mg). The continuation study will run for a further 6 weeks, with scheduled assessments occurring at 2-week intervals.

Immediate-release oxycodone (IRO) will be prescribed to be used 'as needed' for breakthrough pain. Oral IRO (up to 6 times per day where each dose is approximately 1/6$^{th}$ that of the total daily dose of study medication) will be prescribed for each patient with the instruction to only be used if pain actually occurs. IRO dosing details will be documented by the patient in a mediation diary.

### 3.2. TREATMENT GROUPS AND INTERVENTION

**Arm 1 (OXN PR):** Oxycodone/naloxone prolonged release for 5 weeks followed by optional switch to Oxy PR for a further 6 weeks
**Arm 2 (Oxy PR):** Oxycodone prolonged release for 5 weeks followed by optional switch to OXN PR for a further 6 weeks

### 3.3. STUDY POPULATION

Patients with a diagnosis of any metastatic (Stage IV) or unresectable solid tumours or haematological malignancies with cancer-related pain who meet all the inclusion and none of the exclusion criteria will be eligible for participation in this study.

### 3.4. SAMPLE SIZE

The primary objective of this study is to show equivalence of OXN PR and Oxy PR, where the equivalence margin is defined as a difference of 1 point on the pain intensity scale. The standard deviation used in the sample size calculation was taken from Dupoiron et al (2017) and was taken as the largest standard deviation reported (1.4). When the sample size in each group is 43, a two group design will have 80% power to reject both the null hypothesis that the test mean minus the standard mean is below -1 and the null hypothesis that the test mean minus the standard mean is above 1, i.e. that the two treatment arms are not equivalent in favour of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0, the common standard deviation is 1.45 and that each test is made at the 5% level. This is adjusted for 10% loss to follow-up to 48 patients per arm.

This sample size would also provide adequate power to detect a difference between the two treatment arms in symptoms of constipation (secondary objective). A sample size of 43 (or 48 if adjusted for 10% loss to follow-up) in each group will have 80% power to detect a difference in means of 16 on the BFI, assuming that the common standard deviation is 26 using a two group t-test with a 0.05 2-sided significance level.

## 4. ANALYSIS POPULATIONS

### 4.1. STUDY POPUTATIONS AND ANALYSES SETS

The safety population will include all patients who received at least one dose of study medication and has any data collected post baseline. The safety population will be used to assess all safety outcomes.

The ITT population will include all patients who were randomised to one of the study arms. According to the ITT principle, patients will be analysed in the arm they were randomised to, regardless of actual treatment received, treatment compliance or withdrawal from the study.

The per protocol population (PP) is defined in the protocol as all patients who received study drug as indicated and did not have major protocol deviation. Because of the lower than planned enrolment in the trial, we have decided not to conduct an analysis using the PP population as defined in the protocol. However, the analysis described in this analysis plan following the estimand framework includes analyses that takes into account whether patients received study drug as indicated and whether they completed study follow-up as intended (which is similar to not having protocol violations). For this reason, the analysis described in the current document following the estimand framework will be done in place of the PP analysis defined in the protocol.

All analyses will be done for the main study period (Week 1 to Week 5), where the two randomised treatment arms are compared, unless stated otherwise.

### 4.2. BASELINE DESCRIPTION

The following variables will be summarised at baseline by treatment group:

**Demographics:** Age; Sex

**Medical history:**
Time since cancer diagnosis (where the day and month are unknown these will be replaced with the 6th of the month and the month June)
Time since metastatic diagnosis (where the day and month are missing these will be replaced with the 6th of the month and the month June)
Type of cancer (solid or haematological)
Primary site
Stage at trial entry
Metastatic site

## 5. OUTCOME VARIABLES (ENDPOINTS)

### 5.1. PRIMARY ENDPOINT

Average pain over last 24 hours as measured by the BPI-SF at each time point (Weeks 1, 3 and 5) over a 5-week period

### 5.2. SECONDARY ENDPOINTS

1. Degree of constipation as measured by the BFI over a 5-week period
2. Quality of life (global health status (Q29, Q30), dyspnea (Q8), insomnia (Q11), nausea and vomiting (Q14, Q15), pain (Q9, Q19), cognitive functioning (Q20, Q25) and social functioning (Q26, Q27)) as measured by the EORTC-QLQ-C30 over a 5-week period
3. Total daily dose of rescue analgesia over a 5-week period as measured by patient medication diary
4. Total dose of study medication over a 5-week period as measured by patient medication diary
5. Total laxative dose over a 5-week period
6. Worst pain over preceding 24 hours, least pain over preceding 24 hours and current pain at completing questionnaire (BPI-SF) at each time point (Weeks 1, 3 and 5) over a 5-week period

## 6. STATISTICAL METHODOLOGY

### 6.1. DEMOGRAPHY AND BASELINE

Baseline patient characteristics will be summarised by treatment arm using descriptive statistics and reported for continuous variables as number of patients with available data, mean, median, minimum and maximum; and for categorical variables as number of patients with available data, counts and percentages.

### 6.2. ANALYSIS OF PRIMARY OUTCOME

The objective of the trial is to demonstrate analgesic equivalence amongst cancer patients with pain who are taking two different formulations of slow-release opioids based on average pain over last 24 hours as measured by the BPI-SF over 5 weeks.

The primary estimand (ICH, 2019) corresponding to the primary endpoint is defined as:
**Treatment**: OXN PR vs Oxy PR regardless of any immediate release opioid (rescue medication) or other analgesics over a 5-week period
**Population**: Stage IV patients with cancer pain, as defined by the protocol inclusion/exclusion criteria
**Variable**: Average pain over last 24 hours as measured by the BPI-SF at Week 5
**Population level summary**: Difference in mean pain score at Week 5 between treatment arms, with a 95% confidence interval.
**Intercurrent events** under consideration:

a) Discontinuation of randomised treatment either for adverse events/harms or lack of efficacy
b) Discontinuation of randomised treatment for reasons other than adverse events/harms or lack of efficacy; for example administrative reasons or participant withdrawing consent
c) Withdrawal from the trial or loss-to-follow-up
d) Initiation of rescue medication, i.e., any use of immediate release opioids for pain relief
e) Unexpected intermittent (e.g. opioid toxicity) or permanent (e.g. disease progression/terminal phase) events preventing collection of participant data
f) Death

Two different estimands are defined:

***Estimand 1***: All intercurrent events will be handled following the **treatment policy strategy** and all randomised participants will be included in the analysis and all data collected will be included. Missing outcomes will be modelled through the use of a longitudinal mixed model. This estimand will be regarded as the ITT analysis described in the protocol.

***Estimand 2:*** **The intercurrent events will be handled as follows**:

a) The aim of this trial is to assess the ability of the study treatment to reduce pain by Week 5, therefore participants who prematurely discontinue treatment for lack of efficacy or adverse events/harms are considered treatment failures. For this reason, these intercurrent events will be handled by the **composite strategy**. We will replace the pain scores after these intercurrent events with the worst observed pain score in that arm, including after withdrawal from the trial. If this is done for > 10% of participants the method of analysis will be changed to evaluate the median pain score in stead of the mean pain score.

   The variable EOT_DSDECOD (Primary reason for treatment discontinuation) will be used to determine the reason for treatment discontinuation and the following will be regarded as discontinued due to lack of efficacy or adverse events/harms:
   - Trial treatment no longer sufficient to maintain adequate pain control
   - Patient unable to swallow or absorb study medication
   - Unacceptable toxicity
   - Any medical condition that the investigator determines may jeopardise the patient's safety
   - Where the "other" option was chosen, it will be reviewed to determine whether the reason related to lack of efficacy or adverse events

b + c) The outcomes of participants who prematurely discontinue randomised treatment for reasons other than lack of efficacy or adverse events/harms, including withdrawal, are of interest hence a **treatment policy strategy** will be used for these events. This will be accomplished by using all collected data on these participants, including data after treatment discontinuation.

   Missing data after treatment discontinuation and drop out will be handled via longitudinal mixed models of the data collected at Weeks 0, 1, 3 and 5. All participants will be included in the analysis according to the ITT principle and in accordance with the treatment policy strategy.

d) For participants initiating protocol-defined rescue medication **the treatment policy strategy** will be used. An implication of the treatment policy strategy is that the trial treatment definition is changed to include the use of rescue medication in addition to the treatment assigned at randomisation. Under this strategy, data collected after the initiation of rescue medication will be used as is. Missing data after the initiation of rescue medication will be handled as per b + c) above.

e) For this intercurrent event we want to estimate whether participants are benefitting from the trial treatment even when they are unable to provide trial information. For these events we follow the **hypothetical strategy**. We will estimate the values of the outcomes if the data could have been collected by using longitudinal modelling.

f) It makes no sense to make statements about treatment strategies for participants who have died, therefore death will be handled using the **while on treatment** strategy. Participants who died while on study will be excluded from the analysis.

**Estimand 2 will be replacing the PP analysis described in the protocol.** Pain scores observed after the intercurrent events will be handled as described above. Specifically, pain scores measured after discontinuation of study medication due to adverse events or lack of efficacy will be replaced by the highest pain score observed in that arm. Participants who died will be removed from the analysis. No other observed pain scores will be changed or removed. Missing outcomes will be handled via the longitudinal mixed model.

**Statistical analysis for both Estimand 1 and Estimand 2:**
Pain is measured at Weeks 0, 1, 3 and 5 during the main study phase. The primary analysis will be a generalised linear mixed effects model for repeated measurements, adjusted for the stratification variable (site), and including baseline variables associated with having missing outcome data with an identity link function. This model will include pain score (Weeks 0 to 5) as the dependent variable, include a random effect for patient to allow for the repeated measurements and fixed effects for treatment arm assigned, time (categorical variables), site and baseline variables associated with having missing outcome as independent variables. An interaction between treatment arm and time will also be included. If the sample size allows it, we will use an unstructured covariance matrix and allow a separate covariance structure for each treatment group. Model-based effect estimates (mean difference between treatment arms) over the 5 week period will be calculated, along with the 95% confidence interval. In addition, model-based mean difference between the treatment arms will be calculated for each of the time points (Week 1, 3 and 5) with a 95% CI.

If the proportion of participants for whom the pain score is replaced by the highest pain score observed in the arm is > 10%, we will fit a longitudinal quantile regression model, in stead of a linear regression model. The model will include treatment arm, time, site and baseline variables associated with having missing outcome site.

If the 95% confidence interval for the mean difference between treatment arms excludes the equivalence margin of 1, i.e. the 95% confidence interval lies within the equivalence margin (-1, 1), the two treatment arms will be declared equivalent in terms of pain management. It is recognised that the reduced sample size due to the early termination of the trial will make the confidence intervals wider, hence the trial may be underpowered to determine equivalence.

Since generalised linear mixed effects models for repeated measures provide unbiased analysis if some of the time points have missing data under the missing at random (MAR) assumption, no additional methods will be used to handle missing data in the outcome measures.

We will plot the model derived average pain scores at each week from the estimand 2 analysis.

## 6.3. ANALYSIS OF SECONDARY OUTCOMES

**Constipation**
Constipation is measured using BFI at the same time points as BPI-SF. However, the objective for this analysis is not to show equivalence of these outcomes, but to assess superiority of OXN PR.

The estimand of interest is:
**Treatment**: OXN PR vs Oxy PR regardless of any immediate release opioid (rescue medication) or other analgesics over a 5-week period
**Population**: Stage IV patients with cancer pain, as defined by the protocol inclusion/exclusion criteria
**Variable**: Constipation as measured using the BFI at Week 5
**Population level summary**: Difference in mean score at Week 5 between treatment arms, with a 95% confidence interval.
**Intercurrent events** under consideration:

a) Discontinuation of randomised treatment either for adverse events/harms or lack of efficacy
b) Discontinuation of randomised treatment for reasons other than adverse events/harms or lack of efficacy; for example administrative reasons or participant withdrawing consent
c) Withdrawal from the trial or loss-to-follow-up
d) Initiation of rescue medication, i.e., any use of immediate release opioids for pain relief
e) Unexpected intermittent (e.g. opioid toxicity) or permanent (e.g. disease progression/terminal phase) events preventing collection of participant data
f) Death

The same analysis as described in Section 6.2 for Estimand 2 will be done for BFI. The same treatment of the intercurrent events will be used as well. The model based mean difference between the two treatment arms, with 95% confidence interval and p-value comparing the two treatment arms will be reported.

**Quality of life as measured by the EORTC-QLQ-C30**
All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/quality of life represents a high quality of life, but a high score for a symptom scale/item represents a high level of symptomatology/problems.

The scoring of the EORTC QLQ C30 will be done following the EORTC QLQ-C30 Scoring Manual (3rd Edition, Fayers, 2001). The principle for scoring these scales is the same in all cases: Estimate the average of the items that contribute to the scale; this is the raw score. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100. The Stata command qlqc30 (Bascoul-Mollevi et al, 2015) will be used to calculate the scale scores. The following scales will be analysed: global health status (Q29, Q30), dyspnea (Q8), insomnia (Q11), nausea and vomiting (Q14, Q15), pain (Q9, Q19), cognitive functioning (Q20, Q25) and social functioning (Q26, Q27).

The estimand of interest is:
**Treatment**: OXN PR vs Oxy PR regardless of any immediate release opioid (rescue medication) or other analgesics over a 5-week period
**Population**: Stage IV patients with cancer pain, as defined by the protocol inclusion/exclusion criteria
**Variable**: Quality of life as measured by the EORTC-QLQ-C30 Global health status (overall score)
**Population level summary**: Difference in mean score at Week 5 between treatment arms, with a 95% confidence interval.
**Intercurrent events**:

a) Discontinuation of randomised treatment either for adverse events/harms or lack of efficacy
b) Discontinuation of randomised treatment for reasons other than adverse events/harms or lack of efficacy; for example administrative reasons or participant withdrawing consent
c) Withdrawal from the trial or loss-to-follow-up
d) Initiation of rescue medication, i.e., any use of immediate release opioids for pain relief
e) Unexpected intermittent (e.g. opioid toxicity) or permanent (e.g. disease progression/terminal phase) events preventing collection of participant data
f) Death

The same analysis as described in Section 6.2 will be done. The same treatment of the intercurrent events will be used as well. The model based mean difference between the two treatment arms, with 95% confidence interval and p-value comparing the two treatment arms will be reported. The objective for this analysis is not to show equivalence of these outcomes, but to assess superiority of OXN-PR.

**Total rescue analgesia use**
Patients could be prescribed rescue pain medication. The total daily dose of rescue analgesia as measured by the patient medication diary will be calculated and converted to oral morphine equivalent daily dose (oMEDD) using the conversions from the Faculty of pain medicine, ANZCA (2021), see Table 1.

**Table 1: Opioid dose equivalence calculation table**

| CURRENT OPIOID | | CONVERSION FACTOR | PROPRIETARY NAMES |
|---|---|---|---|
| **ORAL (SWALLOWED) PREPARATIONS** *Note: Modified release formulations are marked MR* | | | |
| Morphine | mg/day | 1 | Anamorph, Kapanol (MR), MS Contin (MR), MS Mono (MR), Ordine, Sevredol |
| Oxycodone | mg/day | 1.5 | Endone, OxyContin (MR), OxyNorm, Targin (MR) |
| Hydromorphone | mg/day | 5 | Dilaudid, Jurnista (MR) |
| Codeine | mg/day | 0.13 | Aspalgin, Codalgin, Panadeine, Panadeine Forte, Mersyndol, Nurofen Plus, others |
| Dextropropoxyphene | mg/day | 0.1 | Di-Gesic, Doloxene |
| Tramadol | mg/day | 0.2 | Durotram-XR (MR) , Tramal, Tramadol SR (MR), Zydol, Zydol SR (MR), others |
| Tapentadol | mg/day | 0.3 | Palexia-SR (MR), Palexia-IR |
| **SUBLINGUAL PREPARATIONS** | | | |
| Buprenorphine | mg/day | 40 | Suboxone, Subutex, Temgesic |
| **RECTAL PREPARATION** *Note: Absorption from rectal administration is highly variable* | | | |
| Oxycodone | mg/day | 1.5 | Proladone |
| **TRANSDERMAL PREPARATIONS** | | | |
| Buprenorphine | mcg/hr | 2 | Norspan |
| Fentanyl | mcg/hr | 3 | Denpax, Durogesic, Dutran, Fenpatch, Fentanyl Sandoz |
| **PARENTERAL PREPARATIONS** | | | |
| Morphine | mg/day | 3 | DBL morphine sulphate injection, DBL morphine tartrate injection |
| Oxycodone | mg/day | 3 | OxyNorm FI |
| Hydromorphone | mg/day | 15 | Dilaudid FI, Dilaudid-HP FI |
| Codeine | mg/day | 0.25 | Codeine phosphate injection USP |
| Pethidine | mg/day | 0.4 | Pethidine injection BP |
| Fentanyl | mcg/day | 0.2 | DBL fentanyl injection, Sublimaze |
| Sufentanil | mcg/day | 2 | |
| **Faculty of Pain Medicine, ANZCA – June 2021** | | | |

Available at: Faculty of pain medicine ANZCA (2021) https://www.anzca.edu.au/getattachment/6892fb13-47fc-446b-a7a2-11cdfe1c9902/PS01(PM)-(Appendix)-Opioid-Dose-Equivalence-Calculation-Table

Additional conversions not in Table 1:
Fentanyl sublingual dose: oMEDD in mg = fentanyl sublingual dose in mcg*150/1000

The following pain medication will not be converted to oMEDD:

- Dexamethasone
- Cannabis
- Topical lidocaine
- Paracetamol
- Non-steroidal anti-inflammatory drugs (NSAIDs), ibuprofen, naproxen, celecoxib, parecoxib

These medications will be classed as adjuvant analgesics and recorded as being used or not used on a specific day, but a daily dose will not be calculated.

We will plot for each treatment arm the average daily dose of oMEDD (rescue medication only) used, from Days 0-35.

Two outcomes are defined:

1. We will calculate for each participant the average oMEDD taken during the 35 days, as the total oMEDD divided by the number of days on study. We will then calculate the mean per arm of these oMEDD averages and report this with a 95% CI. We will fit a linear regression model, with the average oMEDD as dependent variable and site, and treatment arm as independent variables to compare the rescue medication used between the treatment arms.

2. The second analysis will not assess the dose of the rescue medication, but will merely assess whether any rescue medication, either oMEDD or adjuvant analgesics was used on a specific day. For each participant we will calculate the proportion of study days where rescue medication was used. We will then calculate the mean proportion of days of rescue medication use per arm and report this with a 95% CI. We will fit a linear regression model, with the proportion of days as dependent variable and site, and treatment arm as independent variables to compare the rescue medication used between the treatment arms.

**Total opioid dose**

Total daily opioid dose consists of rescue medication (converted to oMEDD) and study medication converted to oMEDD. Since study medication use is recorded weekly and not daily, the weekly average oMEDD will be calculated for each study week for patients by adding total daily rescue medication for the week to the study medication consumed in the week, converted to a daily dose by dividing by 7.

We will calculate for each participant the average daily dose for the week oMEDD taken during the 5 weeks. We will then calculate the mean per arm of these oMEDD averages and report this with a 95% CI. We will fit a linear regression model, with the average daily dose for the week oMEDD as dependent variable and site, and treatment arm as independent variables to compare the total opioid dose between the treatment arms.

We will plot for each treatment arm the average daily dose oMEDD, from weeks 0-5.

Where data on drug accountability were not collected the weekly study drug dose will be set to missing and excluded from the calculations. Where patients were hospitalized the data will be included due to drug accountability being done in hospital.

In addition, to the total opioid dose specified in the protocol, we will also summarise the total dose of study medication used during the study.

**Total laxative dose**

Patients could be prescribed any laxative and total daily laxative dose will be calculated as follows:
1 dose is equal to:

- 1 coloxyl/senna tablet
- 50 mg coloxyl/ 8 mg senna tablet
- 1 movicol sachet
- 1 macrogol sachet
- 1 macrovic sachet
- 20 mL lactulose
- 20 mL or 15 mL Duphalac
- 20 mL Agarol
- 1 suppository
- 1 enema

We will plot for each treatment arm the average daily number of laxative doses received, from Days 0-35.

We will calculate for each participant the total number of laxative doses received during the study period divided by the number of days on study, giving the average laxative doses per day. We will then calculate the mean per arm of these averages and report this with a 95% CI. We will fit a linear regression model, with the average daily laxative doses as dependent variable and site, and treatment arm as independent variables to compare the laxative doses used between the treatment arms.

**Worst pain over preceding 24 hours, least pain over preceding 24 hours and current pain at completing questionnaire (BPI-SF) as measured by the BPI-SF over 5 weeks**
Worst pain, least pain and current pain will have estimand 1 and 2 defined in the same wat and will be analysed in the same manner for the same time points as described for the primary outcome (average pain) in Section 6.2.

**To evaluate maintenance of analgesia and effect on bowel function in patients who switch from Oxy PR to OXN PR, and from OXN PR to OxyPR**
The analyses for this secondary objective will be descriptive only.

4 groups will be defined:
Started with OXN PR, stayed with OXN PR
Started with OXN PR, switched to OXy PR
Started with OXy PR, stayed with OXy PR
Started with OXy PR, switched to OXN PR

The number of participants, mean and 95% CI (average, worst, least and current) pain scores and BFI will be given for Week 5, 7, 9 and 11 for each of the 4 groups.

## 6.4. ANALYSIS OF OTHER OUTCOMES

Variables collected but not described under the primary and secondary objectives will be summarised as means with 95% CIs in the treatment arms at each time point from Week 0 to Week 5. These include:

- Australia-modified Karnofsky Performance Status
- BPI: Percentage of pain relief in last 24 hours
- BPI: During the past 24 hours, pain has interfered with your general activity
- BPI: During the past 24 hours, pain has interfered with your mood
- BPI: During the past 24 hours, pain has interfered with your walking ability
- BPI: During the past 24 hours, pain has interfered with your normal work
- BPI: During the past 24 hours, pain has interfered with your relations with other people
- BPI: During the past 24 hours, pain has interfered with your sleep
- BPI: During the past 24 hours, pain has interfered with your enjoyment of life

**Adverse events**
Adverse events will be listed and summarised per treatment arm, overall and per grade. Serious adverse events will be listed and summarised similarly. A listing of all deaths will be provided.

# 7. STATISTICAL ISSUES

All analyses will be done in Stata (version 17 or higher) and all confidence intervals and p-values will be 2-sided.

The study did not reach the intended sample size. Some of the analyses described in this statistical analysis plan relies on fitting data intensive models. If it is not possible to fit the intended models due to small sample size, we will revert to providing descriptive statistics at each time point by treatment arm only.

## 7.1. HANDLING OF MISSING DATA

The majority of the statistical analyses will use longitudinal models applied to the data collected at each time point simultaneously. This approach enables participants with data at one or more time points to be included in the analysis hence naturally handles missing data. The description of the various estimands details how missing data will be handled in certain instances.

## 7.2. SUBGROUP ANALYSES

A subgroup analysis of the pain outcomes will be done in patients identified as having neuropathic pain according to the S-LANSS score at baseline.

The S-LANSS will be scored as follows:

### The S-LANSS Pain Score

| | | |
| --- | --- | --- |
| 1. | **In the area where you have pain, do you also have "pins and needles", tingling or prickling sensations?** | |
| | ☐ NO – I don't get these sensations | 0 |
| | ☐ YES – I get these sensations | 5 |
| 2. | **Does the painful area change colour (perhaps look mottled or more red) when the pain is particularly bad?** | |
| | ☐ NO – The pain does not affect the colour of my skin | 0 |
| | ☐ YES – I have noticed that the pain does make my skin look different from normal. | 5 |
| 3. | **Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations or pain when lightly stroking the skin might describe this.** | |
| | ☐ NO – The pain does not make my skin abnormally sensitive to touch. | 0 |
| | ☐ YES – My skin in that area is particularly sensitive to touch. | 3 |
| 4. | **Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Words like "electric shocks", jumping and bursting might describe this.** | |
| | ☐ NO – My pain doesn't really feel like this. | 0 |
| | ☐ YES – I get these sensations often. | 2 |
| 5. | **In the area where you have pain, does your skin feel unusually hot like a burning pain?** | |
| | ☐ NO – I don't have burning pain | 0 |
| | ☐ YES – I get burning pain often | 1 |
| 6. | **Gently rub the painful area with your index finger and then rub a non-painful area (for example, an area of skin further away or on the opposite side from the painful area). How does this rubbing feel in the painful area?** | |
| | ☐ The painful area feels no different from the non-painful area | 0 |
| | ☐ I feel discomfort, like pins and needles, tingling or burning in the painful area that is different from the non-painful area. | 5 |
| 7. | **Gently press on the painful area with your finger tip and then gently press in the same way onto a non-painful area (the same non-painful area that you chose in the last question). How does this feel in the painful area?** | |
| | ☐ The painful area does not feel different from the non-painful area. | 0 |
| | ☐ I feel numbness or tenderness in the painful area that is different from the non-painful area. | 3 |
| | **Total score:** | |

**Scoring a score of 12 or more suggests pain of predominantly neuropathic origin**

Source: Bennett, M *et al* J Pain, Vol 6, No 3 March, 2005 pp 149–158 The S-LANSS Score for Identifying Pain of Predominantly Neuropathic Origin: Validation for Use in Clinical and Postal Research.

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Where a score of 12 or more will be used to determine whether a patient has neuropathic pain.

The analysis described in Section 6.2 for the primary outcome will be repeated for the subgroup of patients who have neuropathic pain at baseline. In addition, the interaction term between presence of neuropathic pain at baseline and treatment arm will be included in the model and the p-value associated with the interaction term will be estimated.

### 7.3. INTERIM ANALYSIS

No interim analyses were planned or conducted.

## 8. NOTE

A peer reviewed paper has been published describing the application of the addendum to the ICH guidelines (ICH, 2019) to estimands in a palliative care trial. The manuscript provides more detail about the implications of the various decisions made regarding the definition of the estimands and the handling of the intercurrent events in this trial. The example study referred to in that manuscript is the ENHANCE trial. Readers of this SAP might be interested in also reading the manuscript (Grobler et al, 2022).

## 9. REFERENCES

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# 10. TABLES, FIGURES AND LISTINGS

### Table 1: Summary of screening failures

| Screening failures | Austin | Peter McCallum CC | Western health | St Vincent's | All |
| --- | --- | --- | --- | --- | --- |
| Cirrhosis, portal hypertension or liver metastasis<br>Appropriate/willing for randomisation to either Oxy PR 2 or OXN PR<br>Pain score <4<br>Not able to complete study assessments<br>Radiotherapy to site of pain<br>Not adequate organ function by lab test<br>Patient refused<br>New chemotherapy starting within 14 days<br>Not able to take oral medication<br>Not metastatic (Stage 4) or unresectable solid tumour or haematological malignancy<br>Life expectation < 12 weeks<br>Clinically significant gastrointestinal disease<br>AKPS < 50<br>Other<br>Not able to provide informed consent<br>Enrolled in another pain trial | | | | | |

### Table 2: Patient disposition

| | OXN PR n (%) | Oxy PR n (%) |
| --- | --- | --- |
| Number of patients screened<br>Overall<br>By site<br>Number of patients enrolled<br>Overall<br>By site<br>Number of patients completed 5 weeks on study<br>Number of patients completed 5 weeks of study treatment<br>Number of patients died prior to week 5<br><br>Reason for trial discontinuation<br>Reason for study treatment discontinuation<br><br>Number of patients entered continuation phase | | |

### Table 3: Retention: Number of patients who attended each visit

| | Week 0 | Week 1 | Week 3 | Week 5 | Week 7 | Week 9 | Week 11 |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Overall**<br>**OXN PR**<br>**Oxy PR** | | | | | | | |

**Table 4: Baseline demographics**

| | OXB PR<br>Mean (SD) or n (%) | Oxy PR<br>Mean (SD) or n (%) |
| --- | --- | --- |
| Variables per Section 4.2<br><br>S-LANSS score<br>Number of patients with neuropathic pain | | |

Oxycodone/naloxone prolonged-release (OXN PR); Oxycodone prolonged-release (Oxy PR)

**Listing 1: Protocol deviations**

Treatment arm, Site, Patient ID, Deviation, Type, Timepoint, Minor or major

**Table 5: Primary outcome: Pain over last 24 hours as measured by the BPI-SF at Week 5**

| | Mean (95% CI) | | Mean difference |
| --- | --- | --- | --- |
| **Pain over last 24 hours** | **OXN PR** | **Oxy PR** | |
| **ITT analysis**<br>Average pain<br>Worst pain<br>Least pain<br>Pain now<br><br>**Estimand described**<br>Average pain<br>Worst pain<br>Least pain<br>Pain now | | | |

**Table 6: Subgroup analysis of primary outcome: Pain over last 24 hours as measured by the BPI-SF at Week 5 in patients who have neuropathic pain according to the S-LANSS score at baseline**

| | Mean (95% CI) | | Mean difference |
| --- | --- | --- | --- |
| **Pain over last 24 hours** | **OXN PR** | **Oxy PR** | |
| **ITT analysis**<br>Average pain<br>Worst pain<br>Least pain<br>Pain now<br><br>**Estimand described**<br>Average pain<br>Worst pain<br>Least pain<br>Pain now<br><br>Interaction between presence of neuropathic pain and treatment arm | | | |

**Table 7: Mean pain score as measured by the BPI-SF**

| | OXN PR | | | | Oxy PR | | | |
|---|---|---|---|---|---|---|---|---|
| | **Week 0** | **Week 1** | **Week 3** | **Week 5** | **Week 0** | **Week 1** | **Week 3** | **Week 5** |
| Average pain<br>Worst pain<br>Least pain<br>Pain now | | | | | | | | |

**Table 8: Mean pain score as measured by the BPI-SF**

| | Did not switch OXN PR | | | | Did not switch Oxy PR | | | |
|---|---|---|---|---|---|---|---|---|
| | **Week 5** | **Week 7** | **Week 9** | **Week 11** | **Week 5** | **Week 7** | **Week 9** | **Week 11** |
| Average pain<br>Worst pain<br>Least pain<br>Pain now | | | | | | | | |
| | **Started with OXN PR, switched to OXy PR** | | | | **Started with OXy PR, switched to OXN PR** | | | |
| | **Week 5** | **Week 7** | **Week 9** | **Week 11** | **Week 5** | **Week 7** | **Week 9** | **Week 11** |
| Average pain<br>Worst pain<br>Least pain<br>Pain now | | | | | | | | |

**Figure 1: Average pain over last 24 hours as measured by the BPI-SF per treatment arm**
x-axis: Study weeks (From 0 to 11)
y-axis: Mean average pain
Line graph, with a line for each treatment arm – 2 randomised arms up to week 5. 4 lines with the groups:
Started with OXN PR, stayed with OXN PR; Started with OXN PR, switched to OXy PR
Started with OXy PR, stayed with OXy PR; Started with OXy PR, switched to OXN PR
Observed data only, no statistical models

**Figure 2: Worst pain over last 24 hours as measured by the BPI-SF per treatment arm**
Same as Figure 1

**Figure 3: Least pain over last 24 hours as measured by the BPI-SF per treatment arm**
Same as Figure 1

**Figure 4: Current pain over last 24 hours as measured by the BPI-SF per treatment arm**
Same as Figure 1

**Table 9: Constipation: Bowel function index at Week 5**

| | Mean (95% CI) | | Mean difference | p-value |
|---|---|---|---|---|
| | **OXN PR** | **Oxy PR** | | |
| ITT analysis<br>Estimand analysis | | | | |

**Table 10: Constipation: Mean bowel function index**

| OXN PR | | | | Oxy PR | | | |
|---|---|---|---|---|---|---|---|
| **Week 0** | **Week 1** | **Week 3** | **Week 5** | **Week 0** | **Week 1** | **Week 3** | **Week 5** |
| | | | | | | | |

**Table 11: Constipation: Mean bowel function index**

| Did not switch OXN PR | | | | Did not switch Oxy PR | | | |
|---|---|---|---|---|---|---|---|
| **Week 5** | **Week 7** | **Week 9** | **Week 11** | **Week 5** | **Week 7** | **Week 9** | **Week 11** |
| | | | | | | | |
| **Started with OXN PR, switched to OXy PR** | | | | **Started with OXy PR, switched to OXN PR** | | | |
| **Week 5** | **Week 7** | **Week 9** | **Week 11** | **Week 5** | **Week 7** | **Week 9** | **Week 11** |
| | | | | | | | |

**Figure 5: BFI per treatment arm**
Same as Figure 1

**Table 12: Quality of life: EORTC-QLQ-C30**

| | Mean (95% CI) | | Mean difference | p-value |
|---|---|---|---|---|
| | **OXN PR** | **Oxy PR** | | |
| Global health status (overa score)<br>ITT analysis<br>Estimand analysis<br>Dyspnea<br>ITT analysis<br>Estimand analysis<br>Insomnia<br>ITT analysis<br>Estimand analysis<br>Nausea and vomiting<br>ITT analysis<br>Estimand analysis<br>Pain<br>ITT analysis<br>Estimand analysis<br>Cognitive functioning<br>ITT analysis<br>Estimand analysis<br>Social functioning<br>ITT analysis<br>Estimand analysis | | | | |

**Table 13: Quality of life: EORTC-QLQ-C30**

| | OXN PR | | | | Oxy PR | | | |
|---|---|---|---|---|---|---|---|---|
| | **Week 0** | **Week 1** | **Week 3** | **Week 5** | **Week 0** | **Week 1** | **Week 3** | **Week 5** |
| Global health status (overal score)<br>Dyspnea<br>Insomnia<br>Nausea and vomiting<br>Pain<br>Cognitive functioning<br>Social functioning | | | | | | | | |

**Table 14: Quality of life: EORTC-QLQ-C30**

| | Did not switch OXN PR | | | | Did not switch Oxy PR | | | |
|---|---|---|---|---|---|---|---|---|
| | **Week 5** | **Week 7** | **Week 9** | **Week 11** | **Week 5** | **Week 7** | **Week 9** | **Week 11** |
| Global health status (overal score)<br>Dyspnea<br>Insomnia<br>Nausea and vomiting<br>Pain<br>Cognitive functioning<br>Social functioning | | | | | | | | |
| | **Started with OXN PR, switched to OXy PR** | | | | **Started with OXy PR, switched to OXN PR** | | | |
| | **Week 5** | **Week 7** | **Week 9** | **Week 11** | **Week 5** | **Week 7** | **Week 9** | **Week 11** |
| Global health status (overal score)<br>Dyspnea<br>Insomnia<br>Nausea and vomiting<br>Pain<br>Cognitive functioning<br>Social functioning | | | | | | | | |

**Figure 6: Quality of life per treatment arm**
Same as Figure 1

**Table 15: Opioid use**

| | Mean (95% CI) | | Mean difference | p-value |
|---|---|---|---|---|
| | **OXN PR** | **Oxy PR** | | |
| Total oMEDD (rescue medication + study drug)<br>Total oMEDD (rescue medication)<br>Total oMEDD (study drug)<br>Proportion of days with rescue medication | | | | |

**Table 16: Opioid use**

| | OXN PR | | | | Oxy PR | | | |
|---|---|---|---|---|---|---|---|---|
| | **Week 0** | **Week 1** | **Week 3** | **Week 5** | **Week 0** | **Week 1** | **Week 3** | **Week 5** |
| Total oMEDD (rescue medication + study drug)<br>Total oMEDD (rescue medication)<br>Total oMEDD (study drug)<br>Proportion of days with rescue medication | | | | | | | | |

**Table 17: Opioid use**

| | Did not switch OXN PR | | | | Did not switch Oxy PR | | | |
|---|---|---|---|---|---|---|---|---|
| | **Week 5** | **Week 7** | **Week 9** | **Week 11** | **Week 5** | **Week 7** | **Week 9** | **Week 11** |
| Total oMEDD (rescue medication + study drug)<br>Total oMEDD (rescue medication)<br>Total oMEDD (study drug)<br>Proportion of days with rescue medication | | | | | | | | |
| | **Started with OXN PR, switched to OXy PR** | | | | **Started with OXy PR, switched to OXN PR** | | | |
| | **Week 5** | **Week 7** | **Week 9** | **Week 11** | **Week 5** | **Week 7** | **Week 9** | **Week 11** |
| Total oMEDD (rescue medication + study drug)<br>Total oMEDD (rescue medication)<br>Total oMEDD (study drug)<br>Proportion of days with rescue medication | | | | | | | | |

**Figure 7: Daily oMEDD (rescue medication + study drug) used per treatment arm**
Same as Figure 1

**Figure 8: Daily oMEDD (rescue medication) used per treatment arm**
Same as Figure 1

**Figure 9: Daily oMEDD (study drug) used per treatment arm**
Same as Figure 1

### Table 18: Laxative use

| | Mean (95% CI) | | Mean difference | p-value |
|---|---|---|---|---|
| | OXN PR | Oxy PR | | |
| Average daily laxative doses<br>Proportion of days used | | | | |

### Table 19: Laxative use

| | OXN PR | | | | Oxy PR | | | |
|---|---|---|---|---|---|---|---|---|
| | Week 0 | Week 1 | Week 3 | Week 5 | Week 0 | Week 1 | Week 3 | Week 5 |
| Average daily laxative doses<br>Proportion of days used | | | | | | | | |

### Table 20: Laxative use

| | Did not switch OXN PR | | | | Did not switch Oxy PR | | | |
|---|---|---|---|---|---|---|---|---|
| | Week 5 | Week 7 | Week 9 | Week 11 | Week 5 | Week 7 | Week 9 | Week 11 |
| Average daily laxative doses<br>Proportion of days used | | | | | | | | |
| | Started with OXN PR, switched to OXy PR | | | | Started with OXy PR, switched to OXN PR | | | |
| | Week 5 | Week 7 | Week 9 | Week 11 | Week 5 | Week 7 | Week 9 | Week 11 |
| Average daily laxative doses<br>Proportion of days used | | | | | | | | |

### Figure 10: Average daily laxative use per treatment arm

Same as Figure 1

### Table 21: Number of patients experiencing adverse events

| Body system<br>Adverse event lower level term | OXN PR | Oxy PR |
|---|---|---|
| Blood and lymphatic system disorders<br>Cardiac disorders<br>… | | |

**Table 22: Number of patients experiencing adverse events by severity grade**

| Body system<br>Adverse event lower level term | Number of events | | | |
|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Blood and lymphatic system disorders<br>Cardiac disorders | | | | |
| Congenital, familial and genetic disorders | | | | |
| Ear and labyrinth disorders | | | | |
| Endocrine disorders | | | | |
| Eye disorders | | | | |
| General disorders and administration site conditions | | | | |
| Infections and infestations | | | | |
| Injury, poisoning and procedural complications | | | | |
| Investigations | | | | |
| Metabolism and nutrition disorders | | | | |
| Musculoskeletal and connective tissue disorders | | | | |
| Neoplasms benign, malignant and unspecified<br>Etc….. | | | | |

**Table 23: Number of patients experiencing serious adverse events**

| Body system<br>Adverse event lower level term | OXN PR | Oxy PR |
|---|---|---|
| Blood and lymphatic system disorders<br>Cardiac disorders<br>… | | |

## Listing 2: Serious adverse events

## Listing 3: Deaths

Treatment arm, Site, Patient ID, Registration date, Date of death, Primary cause of death, secondary cause of death

**Table 24: Additional variables: Mean (95% CI) at study visits per treatment arm**

| | OXN PR | | | | Oxy PR | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Week 0 | Week 1 | Week 3 | Week 5 | Week 0 | Week 1 | Week 3 | Week 5 |
| Australia-modified Karnofsky Performance Status<br>Percentage of pain relief in last 24 hours<br>During the past 24 hours, pain has interfered with general activity<br>During the past 24 hours, pain has interfered with mood<br>During the past 24 hours, pain has interfered with walking<br>During the past 24 hours, pain has interfered with normal work<br>During the past 24 hours, pain has interfered with relations<br>During the past 24 hours, pain has interfered with sleep<br>During the past 24 hours, pain has interfered with enjoyment of life | | | | | | | | |

**Table 25: Additional variables: Mean (95% CI) at study visits per treatment arm**

| | Did not switch OXN PR | | | | Did not switch Oxy PR | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Week 5 | Week 7 | Week 9 | Week 11 | Week 5 | Week 7 | Week 9 | Week 11 |
| Same variables as Table 24 | | | | | | | | |
| | Started with OXN PR, switched to OXy PR | | | | Started with OXy PR, switched to OXN PR | | | |
| | Week 5 | Week 7 | Week 9 | Week 11 | Week 5 | Week 7 | Week 9 | Week 11 |
| Same variables as Table 24 | | | | | | | | |

## Listing 4: Concomitant medication

Treatment arm, Site, Patient ID, Medication, Indication, Start date, end date, ongoing, Dose, Unit, Frequency, Route