A feasibility study of lorazepam for anxiety in palliative care (LORAZEPAM Study) Statistical Analysis Plan

Version 1
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List of Abbreviations

ADL   activities of daily living
AE   Adverse Event
AKPS   Australia-modified Karnofsky Performance Scale
CI   Confidence Interval
CPI   coordinating principal investigator
CRF   Case Report Form
ESAS-r   Edmonton Symptom Assessment Scale Revised
GCP   Good Clinical Practice
HADS-A   Hospital Anxiety and Depression Scale- anxiety
ITT   intent to treat
NCI CTCAE   common terminology criteria for adverse events
PGIC   Patient Global Impression of Change Scale
SAE   Serious Adverse Event

1.   ADMINISTRATIVE INFORMATION

Protocol: 19/016 LORAZEPAM Study; V1.1; 30th Nov 2021
ANZCTR Number: ACTRN12620001143910
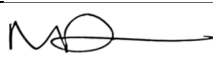
1.1   Document Version History

Version Date	Version	Author	Change Description	Reason/Comment
15Sep2022	1.0	AG. AR	Initial release.	Not applicable.

1.2   Approvals

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and confirm that this analysis plan was developed in a completely blinded manner (i.e. without knowledge of the effect of the intervention being assessed)

Name	Role on Study	Affiliation	Signature	Date
Anneke Grobler	Statistician	University of Melbourne		4/1/2023
Nicola Atkin	CPI	Peter MacCallum Cancer Centre, University of Melbourne		4/1/2023

2.   STUDY SYNOPSIS

Title	A Randomised, Double-Blind, Placebo Controlled Feasibility Study of Oral Lorazepam for Symptoms of Anxiety in Patients with Advanced Life-Limiting Disease
Short title	A feasibility study of lorazepam for anxiety in palliative care (LORAZEPAM Study)
Sponsor	Peter MacCallum Cancer Centre
Study design	Prospective, multi-centre, randomised, double-blind, placebo-controlled, parallel group feasibility study.
Study objectives	**Primary objective:** The primary objective is to demonstrate feasibility by: • Enrolling 21 participants within 12 months and • At least 80% of enrolled participants completing 1 week of intervention and at least 80% of scheduled study assessments up to and including End of Week 1 assessments. **Secondary objectives:** The secondary objectives are: • To assess participant retention and study assessment completion rates at 2 to 12 weeks. • To evaluate participant experience of participation in the study, including burden and the acceptability of the drug intervention and assessments. • To obtain preliminary data on the efficacy of lorazepam for anxiety. • To obtain preliminary data on the toxicity of lorazepam. • To obtain preliminary data on the effects of lorazepam on quality of life and performance status.
Number of sites	4
Expected sample size	21 participants
Recruiting period	12 months
Investigational Product	Lorazepam/placebo
Inclusion criteria	Participants must meet all the following criteria for study entry: 1. Provide written informed consent 2. Age ≥ 18 years. 3. Inpatient or outpatient receiving specialist palliative care input. 4. Advanced cancer (histological or clinical diagnosis) defined by intent of treatment no longer being curative or diagnosis of non-malignant advanced life-limiting illness. 5. Persistent or recurrent anxiety causing clinically significant distress or functional impairment, as determined by the Investigator through clinical interview as part of the medical assessment. 6. Able to tolerate oral medication. 7. Able to read and understand sufficient English to complete all required study questionnaires. 8. Capable of completing assessments and complying with the study procedures.
Exclusion criteria	Participants who meet any of the following criteria will be excluded from study entry: 1. Psychiatric disorder other than anxiety or depression, unless stable for past 3 months.

	2. Untreated depression, severe depression or suicidality as determined by the Investigator through clinical interview. 3. Current or recent history of alcohol abuse or substance misuse. 4. Formal diagnosis of severe respiratory failure (type 1 or 2). 5. Formal diagnosis of sleep apnoea. 6. Pregnant or breastfeeding. 7. Uncontrolled physical symptoms, as determined by medical assessment. 8. Hepatic dysfunction as defined as serum alanine aminotransferase or bilirubin >3.5 x upper limit of normal. 9. History of adverse reaction to benzodiazepine or constituents in the placebo. 10. Regular use of benzodiazepines (more than 2 doses within the past seven days). 11. Antidepressant medication commenced or dose changed within the past month. 12. Enrolment in another clinical trial with an investigational agent for anxiety or depression within 30 days of screening. 13. Clinician predicted survival less than 14 days.
Treatment duration	12 weeks

2.1.   Primary Objective

The primary objective is to demonstrate feasibility by:
- Enrolling 21 participants within 12 months and
- At least 80% of enrolled participants completing 1 week of intervention and at least 80% of scheduled study assessments up to and including the End of Week 1 assessments.

2.2.   Secondary Objectives

The secondary objectives are:
- To assess participant retention and study assessment completion rates at 2 to 12 weeks.
- To evaluate participant experience of participation in the study, including burden and the acceptability of the drug intervention and assessments.
- To obtain preliminary data on the efficacy of lorazepam for anxiety.
- To obtain preliminary data on the toxicity of lorazepam.
- To obtain preliminary data on the effects of lorazepam on quality of life and performance status.

2.3.   Tertiary/Exploratory Objectives

In order to guide the development of the Phase III RCT, additional exploratory objectives include:
- To describe maximum and maintenance doses of study drug per participant.
- To compare frequency of use of concomitant medications which may impact on anxiety (including alternative anxiolytic medications) between the two treatment arms.
- To evaluate perceived utility of anxiety action plan for acute episodes of anxiety.
- To describe frequency of use of non-pharmacological interventions for management of background anxiety levels.

2.4.   Study Population

Participants with advanced life-limiting disease receiving specialist palliative care input and experiencing symptoms of anxiety who meet all the inclusion and none of the exclusion criteria will be eligible for participation in this study.

2.5.   Intervention

The study drugs used in this trial are over-encapsulated lorazepam 0.5mg and a matched placebo capsule, both taken orally.

The study treatment will commence on Day 1, Week 1 and continue for up to 12 weeks, after which a weaning phase may be required. The 12-week study treatment phase will allow assessment of the sustained efficacy of lorazepam.

On Days 1 and 2 the study treatment will be taken as one capsule at night only (0.5mg lorazepam or matched placebo capsule).

On Day 3 dose toxicity will be reviewed via telephone or face-to-face using adverse event (AE) assessment and anxiety symptoms will be assessed using the Hospital Anxiety and Depression Scale-anxiety (HADS-A):
- For the purposes of dose titration, the study drug will be defined as 'not tolerated' if the participant experiences an AE of grade 2 severity or above (graded according to the NCI CTCAE v5.0) that is probably or definitely related to the study drug. In addition, if the participant has an AE of grade 1 severity that is probably or definitely related to the study drug, and this AE is unacceptable to the participant, this will also be deemed as 'not tolerated'.
- If the dose is not tolerated on Day 3, according to the above criteria, the study treatment will be ceased.
- If the dose is tolerated, the total daily dose will be increased by one capsule (i.e. take one capsule in the morning and one capsule in the evening, from the following morning Day 4). A weekly dose review will then occur (at End of Week 1, 2, 3, 4 etc.). Total daily dose can be adjusted in increments of 1 capsule (0.5mg) at each weekly assessment, as outlined below.

At weekly dose review toxicity will be assessed using AEs assessment and anxiety symptoms will be assessed using the HADS-A. The Investigator will conduct a clinical assessment and take these measures into account in order to determine whether the dose should be adjusted. These dose reviews may be conducted by telephone or face-to-face. Study drug prescriptions will be provided by the Investigator at baseline and Treatment Phase study assessment visits. The following guidance will be used to titrate the dose:
- On AE assessment, the study drug will be considered 'not tolerated' if the participant meets the criteria outlined above. The study drug will be considered 'tolerated' if the participant experiences no AEs or AEs of only grade 1 severity (unless they are probably or definitely related to the study drug and unacceptable to the participant).
- The Investigator will take the AEs assessment and HADS-A into account but supplement these with clinical assessment to determine whether or not the study drug dose is tolerated and anxiety symptoms are well-controlled.
- If the dose is tolerated and anxiety is well-controlled, no change will be made to study dose. In this event, the maintenance dose has been established. Weekly dose review will cease and dose will instead be reviewed with set assessments scheduled at end of Weeks 2, 4 and 8.
- If the dose is tolerated but anxiety is not well-controlled, the total daily dose will be increased by one capsule (0.5mg). The additional capsule will be added first at night. At the next dose increase, the additional capsule will be added in the morning. Subsequent additional capsules will alternate, added first at night and then in the morning. However, if anxiety symptoms are more severe in the daytime the investigator will have the option to instead add the additional capsule first in the morning rather than first at night. Weekly dose review will continue until anxiety is well-controlled or maximum dose of 4 capsules twice daily is reached (2mg twice daily). At that point no change will be made to the study dose, this will be the maintenance dose.

The dose will then be reviewed with set assessments scheduled at Weeks 2, 4 and 8. However, when the dose is increased to 4 capsules twice daily dose toxicity should still be reviewed one week later, unless a scheduled study assessment is planned within a week.

- If the dose is not tolerated, the total daily dose will be reduced by one capsule (0.5mg). The first reduction will be taken from the morning dose. The next dose reduction, if required, will be taken from the evening dose. Subsequent reductions will alternate. However, as with up-titration, the Investigator will have the option to instead reduce first from the evening dose if anxiety symptoms are more severe in the daytime. Weekly dose review will continue until the dose is tolerated and anxiety is well-controlled. However, if the study drug requires reduction to the minimum dose of 1 capsule at night and is still not tolerated, the study treatment will be ceased, as will weekly dose review. If the study drug is reduced to a dose that is tolerated but anxiety is not well-controlled, the dose should not be automatically increased back to the previous dose as this was not tolerated. Instead it will be at the Investigator's discretion whether they increase or decrease the dose by 1 capsule, maintain the current dose or discontinue the study treatment if criteria outlined in section 7.7 are met. Any of these circumstances should be documented on the relevant case report form (CRF). Dose review should then continue weekly, unless study treatment has been discontinued.

At any time a participant or member of the study team may request a dose review by the investigator, for example due to adverse effects or objective or subjective inadequate anxiety symptom control. The same options as outlined above will be available to the Investigator. This means the dose can be increased or decreased following the additional dose review, according to the specified options above.

At the end of Week 12, or following early discontinuation of study treatment, a weaning phase may be required.

Weaning schedule:
- Further pharmacological management following the Treatment Phase will be at the Investigator's discretion. However, to ensure safety a weaning regime may be required. Medical assessment will be conducted as part of the End of Treatment assessment (at the end of Week 12, or earlier in the case of early discontinuation of study drug). At this assessment the Investigator will have the option to either wean the study treatment (as outlined below), during or after which an alternative treatment may be commenced as deemed clinically appropriate, or the Investigator can opt to commence open-label lorazepam or another benzodiazepine immediately following the treatment phase without weaning the study treatment. However, the Investigator will remain blinded to whether the participant has received lorazepam or not and therefore open-label benzodiazepine will need to be commenced with appropriate re-titration. Rapid re-titration is possible with appropriate access to 'as required' doses of benzodiazepine. Open-label lorazepam or any alternative drug treatment prescribed will be obtained via commercial supply.
- For participants who have taken the study treatment for less than 4 weeks (27 days or less) no weaning is needed. However, if a participant is at risk of seizures weaning will be needed and the Investigator will tailor the regime depending on dose at the end of the treatment phase.
- For participants who have taken the study treatment for 4 or more weeks (28 days or more):
  - If dose at the end of treatment phase is more than 4 capsules per day, the study drug daily dose will be reduced by 2 capsules per week.
  - If dose at the end of the treatment phase is 4 capsules per day or less, the study drug daily dose will be reduced by 1 capsule per week.
  - Depending on dose at the end of treatment phase, the weaning phase will take up to 3 weeks.
- As part of safety monitoring, between the End of Treatment assessment and Follow-up

assessment, additional AEs assessment will be conducted weekly by telephone, whether or not a weaning regime is used. Any participant with suspected withdrawal will be reviewed by the Investigator and treatment initiated as clinically appropriate. The Follow-up assessment 4 weeks after cessation of study drug will include a review of compliance and AEs to ascertain whether the participant has successfully weaned off or ceased the study treatment.

2.6.   Randomisation and Blinding

Registered participants will be randomised in a 2:1 ratio to the two medication arms (lorazepam or placebo).

A master randomisation list will be prepared by an independent statistician and provided to pharmacies at each participating site. The clinical trial pharmacist(s) at sites will be responsible for assigning study medication to participants using the unique code (randomisation code) provided at the time of registration and the master randomisation list, and thus will be unblinded. The responsible pharmacist(s) will ensure the study medication is labelled in accordance with regulatory requirements and the blind maintained. In addition, the responsible pharmacist(s) will ensure the randomisation list is held in a secure place within the pharmacy and will not communicate this information to any members of the study team.

Treatment allocations will not be disclosed to participants, study staff, Investigators or any other healthcare professionals involved in the participants' care. Only the site pharmacist(s) and the independent statistician will be unblinded. The blind will only be broken in cases of extreme emergency. In cases of medical need, where urgent medical decisions will be influenced by knowledge of the treatment assignment, the site Investigator must discuss with the coordinating principal investigator (CPI) or delegate to determine the urgency and need for unblinding and will be informed by the CPI of follow-up actions. Unblinding will be the responsibility of site Investigator and the site pharmacist(s). If the blind is broken for any reason, the Investigator must immediately notify the Sponsor of the unblinding incident without revealing the participant's study medication assignment. In addition, the Investigator must record the date and reason for revealing the blinded study medication assignment for that participant in the relevant eCRF.

2.7.   Sample Size

The sample size of 21 participants is based on anticipated recruitment of one participant per fortnight and not on any statistical criteria.

2.8.   Deviations from Protocol

The Investigator(s) is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations.

A protocol deviation is defined as any change, divergence, or departure from the requirements or procedures of this protocol or from ICH good clinical practice (GCP). Efforts should be made to limit deviations. The Investigator is responsible for promptly reporting protocol deviations to the Sponsor. The Sponsor will determine the effect of the protocol deviation on the scientific soundness of the clinical study and patient safety and determine whether additional reports or actions are required.

Full details of the background to the trial and its design are presented in the protocol.

2.9.   Study Procedures

Trial Phase	Screening	Baseline	Treatment Phase (Week 1 – 12)	End of Treatment	Follow-up
Assessments and Events/Windows	Within 14 days prior to randomisation	Within 1 day or on the day of randomisation [1]	End of Week[2] 1, 2, 4, 8 and 12 (± 2 days) [3]	Within 2 days after last dose of treatment in treatment phase [4]	4 weeks after End of Treatment (± 7 days)
Clinical/Administrative Assessments					
Written informed consent	X				
Review of inclusion/exclusion criteria	X	X			
Medical assessment[5]	X	X		X	X
Demographics	X				
Diagnosis of life-limiting illness	X				
Comorbidities	X				
Prior and concomitant medications	X	X	X	X	X
Provision of non-pharmacological management strategies & tailored anxiety action plan		X			
Dose review[6]			X		
Assessment of compliance with study treatment by capsule count			X[7]	X[7]	X[7]
Adverse events assessment[6]		X	X	X	X
Review of non-pharmacological interventions for anxiety		X	X	X	X
Australia-modified Karnofsky Performance Scale (AKPS)		X	X	X	X
Survival status			X	X	X
Documentation of weaning regime				X	
Documentation of alternative anxiolytic medication regime				X	X
Patient Reported Outcomes					
Hospital Anxiety and Depression Scale-anxiety (HADS-A)[6]		X	X	X	X
PROMIS Short Form – Anxiety 7a		X	X	X	X

Trial Phase	Screening	Baseline	Treatment Phase (Week 1 – 12)	End of Treatment	Follow-up
Assessments and Events/Windows	Within 14 days prior to randomisation	Within 1 day or on the day of randomisation [1]	End of Week[2] 1, 2, 4, 8 and 12 (± 2 days) [3]	Within 2 days after last dose of treatment in treatment phase [4]	4 weeks after End of Treatment (± 7 days)
Patient Global Impression of Change Scale (PGIC)			X	X	X
Edmonton Symptom Assessment Scale Revised (ESAS-r)		X	X	X	X
5-level EQ-5D version (EQ-5D-5L)		X	X	X	X
Epworth Sleepiness Scale		X	X	X	X
Brief semi-structured interview			X[8]	X[8]	
PRO CoMiDa[9]		X	X	X	X
Laboratory Procedures/Assessments: analysis performed by local laboratory					
Liver function tests[10]	X				

Footnotes:

1. Screening and Baseline assessments can be completed on the same day. In such cases, baseline assessments do not need to be repeated provided the required assessments have been performed within protocol-defined window.
2. End of Week refers to the 7th day of that week.
3. Treatment Phase assessments may be conducted by face-to-face review in clinic or by telephone. However, face-to-face assessments are required for End of Week 2, 4, 8 and 12 if the participant is still taking the study drug.
4. To be completed within 2 days after the last dose of treatment in the Treatment Phase or as soon as the study team are informed of early discontinuation. If a participant completes 12 weeks of treatment, End of Week 12 Treatment Phase and End of Treatment visits can be combined into one visit provided all required assessments listed for both time points are performed.
5. Medical assessment: In screening this will include a clinical interview to establish diagnosis of anxiety.
6. Dose reviews, which include clinical assessment by the Investigator, HADS-A and AE assessment, will also take place telephonically on day 3 of Week 1, End of Week 3, 5, 6 and 7 or until maintenance dose is established (refer to section 8.3). In between End of Treatment and Follow-up, an additional AE assessment will be conducted weekly by telephone.
7. Capsule count will be performed at End of Week 2, 4, 8, 12 and End of Treatment visits. If a weaning regime is required, compliance with the weaning regime will be assessed via capsule count at the follow-up visit.
8. Brief semi-structured interview with participant to be performed within 7 days of the last dose of treatment in the Treatment Phase and within 7 days of End of Week 12 Treatment Phase Assessment. Semi-structured interview only required once if a participant completes 12 weeks of treatment.
9. PRO CoMiDa to be completed by study personnel at each PRO time point.
10. Liver function tests: Alanine aminotransferase (ALT) and bilirubin. Obtained at screening unless sample available from the previous 14 days and clinical picture has not otherwise changed.

3.   GENERAL STATISTICAL METHODOLOGY

3.1.   Objectives of Analysis Plan

To provide an outline of how the primary and secondary outcomes will be analysed.

3.2.   Analysis Software

Stata Standard Edition V17 will be used to analyse the data.

3.3.   Definition of Baseline

Baseline assessments are to be completed post-screening but both screening and baseline assessments may be performed on the same day. If conducted on the same day, assessments already completed as part of screening do not need to be repeated as part of baseline assessment. Baseline assessments should be performed within 1 day prior to or on the day of randomisation, unless otherwise specified.

3.4.   Definition of analysis populations

An intent to treat (ITT) analysis will be used. All participants randomised will be included in the intent to treat analysis.

3.5.   Definitions related to Adverse Events (AEs)

It is the responsibility of the site Investigator to assess AEs and serious adverse events (SAE)s for severity. Severity will be graded according to the NCI CTCAE v5.0. The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below:

Grade	Severity	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care ADL
Grade 4	Life threatening	Life-threatening consequences; urgent intervention indicated
Grade 5	Fatal	Death related to AE

The Investigator will assess the causal relationship between the investigational product and the AE. Each AE/SAE will be evaluated for a casual code as per the table below to the question *"is there at least a reasonable possibility that the event may have been caused by the investigational product?"*

CODE	CAUSAL RELATIONSHIP		DESCRIPTION
1	Unrelated	Unrelated	The AE is clearly NOT related to the intervention
2	Unlikely		The AE is doubtfully related to the intervention
3	Possible	Related	The AE may be related to the intervention
4	Probable		The AE is likely related to the intervention
5	Definite		The AE is clearly related to the intervention

4.   DESCRIPTIVE STATISTICS

4.1.   Recruitment and Follow-up

Patient status will be based on treatment phase assessments completed. During the treatment phase, formal study assessments will occur at the End of Week 1, 2, 4, 8 and 12 (± 2 days). These may be conducted face-to-face or by telephone. An End of Treatment visit will occur within 2 days of the last dose of treatment taken by the participant in the treatment phase and a follow-up assessment will take place 4 weeks (± 7 days) later.

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                    ┌──────────────────────────────────┐
                    │  Informed consent & Screening    │
                    └──────────────────────────────────┘
                                    ↓
                    ┌──────────────────────────────────┐
                    │       Baseline Assessments       │
                    │       Non-pharmacological        │
                    │  management strategies provided  │
                    └──────────────────────────────────┘
                                    ↓
                    ┌──────────────────────────────────┐
                    │    Registration and Randomisation│
                    │      (allocation ratio 2:1)      │
                    └──────────────────────────────────┘
                        ↙                       ↘
    ┌────────────────────────────┐    ┌────────────────────────────┐
    │           ARM A            │    │           ARM B            │
    │  Oral lorazepam with dose  │    │  Matched placebo with dose │
    │      titration (n=14)      │    │      titration (n=7)       │
    └────────────────────────────┘    └────────────────────────────┘
                        ↘                       ↙
                    ┌──────────────────────────────────┐
                    │         Treatment Phase          │
                    │  Daily for 12 weeks unless criteria│
                    │  for early discontinuation of study│
                    │       treatment are met          │
                    │                                  │
                    │    Treatment Phase Assessments   │
                    │   At end of Weeks 1, 2, 4, 8 and 12│
                    └──────────────────────────────────┘
                                    ↓
                    ┌──────────────────────────────────┐
                    │    End of Treatment Assessment   │
                    └──────────────────────────────────┘
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                    │          Weaning Phase           │
                    └──────────────────────────────────┘
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                    ┌──────────────────────────────────┐
                    │            Follow-up             │
                    │    Within 4 weeks of the End of  │
                    │         treatment Visit          │
                    └──────────────────────────────────┘
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4.2.   Baseline Characteristics

These baseline characteristics will be reported by treatment group as either number and proportion or mean and 95% confidence interval.

- Age
- Sex
- AKPS
- Primary life limiting diagnosis (cancer/non-malignant)

- Type of non-malignant diagnosis
- Cancer type (solid/haematological)
- Primary Site of cancer (Bladder, Bone and soft tissue, Breast, etc)
- Palliative treatment (systemic/radiation therapy/best supportive care
- Cancer stage (I/II/III/IV)
- Patient receiving disease-directed treatment at trial entry
- HADS-A
- PROMIS Anxiety 7a
- ESAS-r
- EQ-5D-5L
- Epworth Sleepiness scale
- Review of non-pharmacological interventions being used for anxiety

4.3.   Protocol Deviations

Protocol deviations will be listed and summarised.

4.4.   Compliance

Compliance with study treatment will be assessed at each face-to-face assessment visit via capsule counts taking into account the number of capsules prescribed, dispensed and returned. Capsule counts will be documented on the relevant CRF. Unused study drug will be returned at the assessment visit and new supply will be dispensed. Compliance will be assessed prior to dispensing of each additional bottle of study drug to the participant. As an exception to this, compliance will not be assessed by capsule count at the End of Week 1 assessment as the participant will be provided on Day 1 with an adequate supply of study drug to cover Week 1 and Week 2. However, they will be asked at the End of Week 1 assessment if they have missed any doses. Compliance will then be assessed fully at the End of Week 2 assessment when the first bottle of study drug will be returned. When assessments are completed by telephone rather than face-to-face, compliance assessments can be delayed until the participant or their delegate is next able to return unused study drug and bottles. During telehealth appointments initiated during Covid-restrictions patient reported capsule counts were used.

We will add the number of tablets the patients should have taken in the morning and the evening, multiplied by the number of days they should have taken this dose, for all the dose levels. Then we will calculate the number dispensed minus the number returned (what they took). We then calculate percentage compliance by dividing the number they took by the number they should have taken multiplied by 100.

Compliance will be summarised as percentage compliance (number of capsules taken/number of capsule prescribed) for each visit. If both returned capsule count (i.e. returned and counted by nurse or pharmacy) and patient reported capsule count were collected, we will use returned capsule count performed by nurse or pharmacy for the calculation of adherence.

4.5.   Concomitant Therapies

Any over the counter or prescription medications, vitamins and/or herbal supplements taken by the participant from 1 month prior to screening through to the final study assessment will be reported by the participant. Those medications which may impact on anxiety symptoms or interact with the study drug will be recorded on the relevant eCRF with the name of the medication, dosage information including dose, route and frequency, date(s) of administration including start and end dates, and reason for use.

5.   ANALYSIS OF THE PRIMARY OUTCOME(S)

5.1.   Main Analysis

The following will be calculated:
- Number of participants enrolled within enrolment period (12 months). Enrolment into this study will be deemed feasible if 21 participants were enrolled within 12 months.
- Participant retention on study and on study treatment at End of Week 1. This will be measured as
    - The number and proportion of enrolled participants who are still taking the study treatment at the end of 1 week.
    - The number and proportion of enrolled participants who are still in the study at the end of Week 1.
    - The number (and proportion) of enrolled participants who complete at least 80% of scheduled study assessments up to and including the End of Week 1 assessments. These scheduled assessments will include: AKPS, HADS-A, PROMIS-Short form anxiety, PGIC, ESAS-r, EQ-5D-5L, Epworth sleepiness scale at Week 1.

5.2.   Missing Data

As this is a feasibility study missing data will be noted but not imputed.

6.   SECONDARY OUTCOMES

6.1   Feasibility

- Participant retention on study and on study treatment at 2, 4, 8 and 12 weeks. This will be given as a number and proportion as for the primary endpoint.
- Number of enrolled participants who complete at least 80% of scheduled study assessments at 2, 4, 8 and 12 weeks. This will be given as a number and proportion for each of Weeks 2, 4, 8 and 12 using the same list of assessments as for the primary endpoint.
- The number of participants who are known alive, know dead or survival status is unknown will be summarised at 12 weeks.

6.2   Acceptability, burden and participant experience

- The number and proportion of enrolled participants who respond 'yes' to the question 'If you were given the choice again, would you still choose to participate in this study?'
  Patients who came off study treatment early will have been asked to do semi-structured interview at end of treatment and also at week 12 assessment. For participants who have answered these questions twice, the second answer (end of week 12) will be taken as the response as this reflects the acceptability and burden when they have participated in the full length of the trial.
- The mean score on the 11-point (0-10) numerical rating scale for burden.
- (The experience of participation in the study as evaluated by qualitative analysis of semi-structured interviews is one of the secondary outcomes, but it will be analysed using qualitative analysis methods and will not form part of this statistical analysis plan.)

6.3   Efficacy

- Anxiety as measured by
    - HADS-A
      The HADS-A will be scored as follows:
      The questions, their answers and the number assigned to each answer:

I feel tense or "wound up": 3 = most of the time, 2 = a lot of the time, 1 = occasionally, 0 = not at all

I get a sort of frightened feeling like "butterflies" in the stomach: 0 = not at all, 1 = occasionally, 2 = quite often, 3 = very often

I get a sort of frightened feeling as if something awful is about to happen: 3 = very definitely and quite badly, 2 = yes, but not too badly, 1 = a little, but it doesn't worry me, 0 = not at all

I feel restless as I have to be on the move: 3 = very much indeed, 2 = quite a lot, 1 = very much, 0 = not at all

Worrying thoughts go through my mind: 3 = a great deal of the time, 2 = a lot of the time, 1 = from time to time, but not too often, 0 = only occasionally

I get sudden feelings of panic: 3 = very often indeed, 2 = quite often, 1 = not very often, 0 = not at all

I can sit at ease and feel relaxed: 0 = definitely, 1 = usually, 2 = not often, 3 = not at all

The score will be added up to provide a score between 0 and 21. A score of 0-7 is interpreted as normal, 8-10 as borderline and 11-21 as anxious.

o PROMIS Anxiety 7a

Each question has 5 response options ranging from 1-5. If all questions are answered, sum the value of the response to each question. The scores will range from 8 to 40. The raw scores will be translated into a standardised T-score with a mean of 50 and a standard deviation of 10. The raw scores will then be converted to a T-score using the following table:

Anxiety 7a - Adult v1.0						
Short Form Conversion Table						
Raw Score	T-score	SE*		21	61.3	2.2
7	36.3	5.4		22	62.6	2.2
8	42.1	3.4		23	63.8	2.2
9	44.7	2.9		24	65.1	2.2
10	46.7	2.6		25	66.4	2.2
11	48.4	2.4		26	67.7	2.2
12	49.9	2.3		27	68.9	2.2
13	51.3	2.3		28	70.2	2.2
14	52.6	2.2		29	71.5	2.2
15	53.8	2.2		30	72.9	2.2
16	55.1	2.2		31	74.3	2.2
17	56.3	2.2		32	75.8	2.3
18	57.6	2.2		33	77.4	2.4
19	58.8	2.2		34	79.5	2.7
20	60.0	2.2		35	82.7	3.5
				SE* = Standard Error on T-Score		

o PGIC

The PGIC is recorded as a number from 1 to 7, with 7 indicating very much worsening and 1 very much improvement.

o ESAS-r

The ESAS-r requires participants to complete a scale numbered 0 to 10. It allows participants to rate the severity of nine symptoms (pain, tiredness, nausea, depression, anxiety, drowsiness,

appetite, wellbeing, shortness of breath) at the time of the assessment. The higher the number selected on the scale, the more severe the symptom. A physical score is calculated as the total of the 6 physical symptoms (pain, tiredness, nausea, drowsiness, appetite, shortness of breath) to provide a score randing from 0-60. We will summarise the mean for each of the symptoms at baseline. At the later visits, we will provide the mean for the anxiety scale and the physical symptoms scale.

All measures will be summarised as a mean score with 95% confidence interval at each of the assessment periods for each of the treatment arms.

All scores will be compared between the two treatment arms using a t-test at 1, 2, 4, 8 and 12 weeks.

Frequency of use of non-pharmacological interventions was reported by participants. This will be summarised by giving the proportion of participants in each category for the following questions:
- In the past week how many times have you used the anxiety action plan?
- What self-management non-drug strategies have you used to improve or maintain your overall anxiety levels?
- How many times have you used these strategies in the past week?
- What non-drug therapies have you received?
- Mean of average frequency of therapy per week

6.4   Toxicity

- Epworth Sleepiness Scale total score will be calculated by adding up the 8 questions to create a score from 0-24, with a high score indicating excessive sleepiness. A score above 10 indicates excessive sleepiness. It will be summarised per treatment arm by giving a mean and 95% confidence interval.
- The number of participants who report AEs will be summarised according to lower level term by body system. We will report both the number of participants who reported the AEs and the number of AEs. In addition, AEs will be summarised by toxicity grade.
- Listing of all SAEs will be provided

6.5   Quality of life and performance status

- EQ-5D-5L

The EQ-5D-5L assesses 5 dimensions of impairment (mobility, self-care, usual activities, pain/ discomfort, anxiety/depression) with each dimension having 5 levels of severity. We will compute the EQ-5D index using the English (ENG) Devlin value set Version 1.1 (Updated 01/12/2020), since a value set for Australia has not been published. The coding to use this value set is provided in Appendix B. Overall health status is also measured on a visual analogue scale.

- AKPS

EQ-5D index, overall health status and AKPS will be summarised as a mean score with 95% confidence interval at each of the assessment periods for each of the treatment arms and compared between the two treatment arms using t-tests at each visit.

6.6   Subgroup Analyses

No subgroup analyses are planned.

7.   EXPLORATORY OUTCOMES
- Dose of study drug received over time. The mean, maximum and minimun dose of study drug taken

at each week in the study will be summarised by treatment arm. In addition, the maintenance dose (defined as the final dose for each participant) in each arm will be given.

- All concomitant medication and alternative anxiolytic medication used that may impact on anxiety will be summarised and listed by treatment arm
- Utility of Anxiety Action Plan as evaluated by participants will be summarised as the proportion of answers in each category to the following question: How helpful have you found the anxiety action plan?
- Frequency of use of other non-pharmacological interventions as reported by participants. The analysis of this is described in Section 6.3.

8.   REFERENCES

A feasibility study of lorazepam for anxiety in palliative care (LORAZEPAM Study). Clinical Trial Protocol Version 1.1 05th October 2021.

9.   APPENDIX A. EXAMPLE TABLES AND FIGURES

Table 1: Baseline characteristics: Mean (95% confidence interval) or number and proportion

Variable	Lorazepam	Placebo	Total
All variables listed in Section 4.2			

Range will be given for age and AKPS

Table 2: Summary of protocol violations: Number reported

Protocol violation	Lorazepam	Placebo

Table 3: Primary outcome: Number and proportion

	Lorazepam	Placebo	Total
Participants enrolled within 12 months	-	-	
Enrolled participants who are still taking the study treatment at the end of Week 1			
Enrolled participants who are still in the study at the end of Week 1.			
Enrolled participants who complete at least 80% of scheduled study assessments up to and including the End of Week 1. These scheduled assessments will include: AKPS, HADS-A, PROMIS-Short form anxiety, PGIC, ESAS-r, EQ-5D-5L, Epworth sleepiness scale at Week 1			
Enrolled participants who complete at least 80% of scheduled study assessments up to and including the End of Week 1. These scheduled assessments will include: AKPS, HADS-A, PROMIS-Short form anxiety, PGIC, ESAS-r, EQ-5D-5L, Epworth sleepiness scale at screening, baseline and Week 1			

Table 4: Retention on study and on study treatment: Number and proportion

	Week 2	Week 4	Week 8	Week 12
Enrolled participants who are still taking the study treatment at the end of Week				
Lorazepam				
Placebo				
Total				
n				
Enrolled participants who are still in the study at the end of Week				
Lorazepam				
Placebo				
Total				
n				
Enrolled participants who complete at least 80% of scheduled study assessments up to and including the End of Week (including AKPS, HADS-A, PROMIS-Short form anxiety, PGIC, ESAS-r, EQ-5D-5L, Epworth sleepiness scale)				
Lorazepam				
Placebo				
Total				
n				

Listing 1: End of study

Patient ID Treatment arm End of study date Primary reason for trial discontinuation Specify other

This listing will be sorted by treatment arm

Listing 2: End of treatment

Patient ID Treatment arm Complete the full course of treatment Date of last treatment Primary reason for treatment discontinuation Other specify Specify adverse event Specify medication Specify protocol deviation Outcome from medical assessment

This listing will be sorted by treatment arm

Table 5: End of study and study treatment

	Lorazepam	Placebo	Total
Completed full course of study treatment			
Reason for treatment discontinuation			
Withdrawal of consent			
Investigator beliefs it is in the best interest of the patient			
Medical condition			
Etc			
Decision at end of study treatment			
Study treatment weaned			
Study treatment ceased without weaning			
Commenced open-label lorazepam			
Commenced other benzodiazepine			
Commenced alternative anxiolytic medication			
No new anxiolytic medication commenced			
Other regime			
Not assessed			
Reason for study discontinuation			
Completed			
Death			
Loss to follow-up			
Etc			
Weaning regimen scheduled			
Yes			
No			
Reason not scheduled			
Adverse event			
Patient forgot			
Other			
New anxiolytic medication since End of Treatment visit			
Not on any anxiolytic medication			
Same anxiolytic medication prescribed at End of Treatment			
Open label lorazepam			
Other benzodiazepine			
Alternative anxiolytic medication			
Other			

Table 6: Mortality: Number and proportion

	Lorazepam	Placebo	Total
Participants alive			
Dead			
Unknown			

Table 7: Acceptability, burden and experience

	Lorazepam	Placebo	Total
Number and percentage saying yes to: If you were given the choice again, would you still choose to participate in this study?'			
Mean and 95% confidence interval: Numerical rating scale for burden			
Interview not done at Week 12 (for patients who completed Week 12 visit)			
Interview not done at end of treatment (for patients who completed end of treatment visit)			
Reason interview not done			

Table 8: Efficacy: HADS-A mean with 95% CI

Table 9: Efficacy: PROMIS Anxiety 7a mean with 95% CI

Table 10: Efficacy: PGIC mean with 95% CI

Table 11: Efficacy: ESAS-r mean with 95% CI

	Lorazepam		Placebo		Difference	p-value
	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	
Baseline						
Week 1						
Week 2						
Week 4						
Week 8						
Week 12						
Follow-up						

Table 12: Non-pharmacological interventions for anxiety: Number and proportion

	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12
In the past week how many times have you used the anxiety action plan?						
Lorazepam						
Never						
1-4 times						
5-9 times						
10-15 times						
> 15 times						
Placebo						
Never						
1-4 times						
5-9 times						
10-15 times						
> 15 times						
Total						
Never						
1-4 times						
5-9 times						
10-15 times						
> 15 times						
What self-management non-drug strategies have you used to improve or maintain your overall anxiety levels?						
Lorazepam						
Strategies provided as part of study						
None						

	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12
Self-management techniques recommended in written information resources						
Relaxation CD						
Internet based application						
Other						
None						
Aromatherapy						
Breathing techniques						
etc						
Other						
Placebo						
Strategies provided as part of study						
None						
Self-management techniques recommended in written information resources						
Relaxation CD						
Internet based application						
Other						
None						
Aromatherapy						
Breathing techniques						
etc						
Other						
Total						
Strategies provided as part of study						
None						
Self-management techniques recommended in written information resources						
Relaxation CD						
Internet based application						
Other						
None						
Aromatherapy						
Breathing techniques						
etc						
Other						
How many times have you used these strategies in the past week?						
Lorazepam						
Never						
1-4 times						
5-9 times						
10-15 times						
> 15 times						
Placebo						
Never						
1-4 times						
5-9 times						
10-15 times						
> 15 times						
Total						
Never						

	Baseline	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**
1-4 times 5-9 times 10-15 times > 15 times						
What non-drug therapies have you received?						

Lorazepam
  None
  Cognitive behavioral therapy
  Counselling
  etc
  Other
 Placebo
  None
  Cognitive behavioral therapy
  Counselling
  etc
  Other
 Total
  None
  Cognitive behavioral therapy
  Counselling
  etc
  Other						

Mean of average frequency per week, since the last assessment						
Lorazepam Placebo Total						
How helpful have you found the anxiety action plan?						

Lorazepam
   Not at all helpful
   Slightly helpful
   Moderately helpful
   Very helpful
   Extremely helpful
 Placebo
   Not at all helpful
   Slightly helpful
   Moderately helpful
   Very helpful
   Extremely helpful
 Total
   Not at all helpful
   Slightly helpful
   Moderately helpful
   Very helpful
   Extremely helpful						

Table 13: Epworth sleepiness scale: mean with 95% CI

	Lorazepam		Placebo		Difference	p-value
	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	
Baseline						
Week 1						
Week 2						
Week 4						
Week 8						
Week 12						
Follow-up						

Table 14: Number of patients experiencing adverse events

Body system Adverse event lower level term	Lorazepam	Placebo
Blood and lymphatic system disorders Cardiac disorders …		

Table 15: Number of adverse events

Body system Adverse event lower level term	Lorazepam	Placebo
Blood and lymphatic system disorders Cardiac disorders …		

Table 16: Number of adverse events by severity grade

Body system Adverse event lower level term	Number of events			
	Grade 1	Grade 2	Grade 3	Grade 4
Blood and lymphatic system disorders Cardiac disorders				
Congenital, familial and genetic disorders				
Ear and labyrinth disorders				
Endocrine disorders				
Eye disorders				
General disorders and administration site conditions				
Infections and infestations				

This table will be repeated by treatment arm

Listing 3: Serious adverse events
This listing will be sorted by treatment arm

Table 17: EQ-5D-5L: mean with 95% CI

	Lorazepam		Placebo		Difference	p-value
	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	
Overall health status						
Baseline						
Week 1						
Week 2						
Week 4						
Week 8						
Week 12						
Follow-up						
Repeat for EQ-5D index						

Table 18: AKPS: mean with 95% CI

	Lorazepam	Placebo	p-value
Baseline			
Week 1			
Week 2			
Week 4			
Week 8			
Week 12			
Follow-up			

Table 19: Dose of study drug: mean with 95% CI

	Lorazepam	Min, max	Placebo	Min, max
Week 1				
Week 2				
Week 4				
Week 8				
Week 12				
Follow-up				
Maintenance dose				

Table 20: Compliance: mean with 95% CI

	Lorazepam	Min, max	Placebo	Min, max
Week 1				
Week 2				
Week 4				
Week 8				
Week 12				
Follow-up				

Table 21: Dose changes and reasons for dose change

	Dose reduced (n)			Dose increased			Maintained	Discontinued
	All	AE[1]	Anxiety[2]	All	AE[1]	Anxiety[2]		
Week 1								
Week 2								
Week 4								
Week 8								
Week 12								

1: Dose not tolerated
2: Anxiety not well controlled

Table 22: Reason PRO forms were not completed

Reason	Baseline	Week 1 D 3	Week 1	Week 2	Week 4	Week 8	Week 12	Follow-up
Lorazepam								
Assessments not completed								
Patient received the questionnaires but did not return them								
Patient refused to complete questionnaires								
Patient missed appointment								
Patient withdrew consent								
Forgot to administer questionnaire								
Administered incorrect questionnaire								
Passed away								
Other								
Reason related to patient's illness								
Repeat for placebo								

Listing 4: Concomitant medication and alternative anxiolytic medication

Listing sorted by treatment arm

Add an additional column whether this is prescribed/ongoing at the end of treatment visit

Add an additional column whether this is prescribed between the end of treatment visit and Follow-up

Listing 5: Anxiety medication

A listing of all concomitant medication with indication "anxiety", with start and stop dates

Add an additional column whether this is prescribed/ongoing at the end of treatment visit

Add an additional column whether this is prescribed between the end of treatment visit and Follow-up

This listing will be sorted by treatment arm

10.   APPENDIX B STATA CODING FOR EQ-5D-5L INDEX VALUES

https://euroqol.org/support/analysis-tools/index-value-set-calculators/

Computing EQ-5D-5L index values with Stata using the English (ENG) Devlin value set Version 1.1 (Updated 01/12/2020)

The variables for the 5 dimensions of the EQ-5D-5L descriptive system should be named 'mobility', 'selfcare', 'activity', 'pain', and 'anxiety'. If they are given different names the syntax code below will not work properly. The 5 variables should contain the values for the different dimensions in the EQ-5D health profile (i.e. 1, 2, 3, 4 or 5). The variable 'EQindex' contains the values of the EQ-5D-5L index values on the basis of the ENG set of weights.

```
************************************************************
*STATA syntax code for the computation of index*
*values with the English value set*
************************************************************;
```

```
gen disut_mo= .
 replace disut_mo= 0 if missing(disut_mo) & mobility == 1
replace disut_mo= 0.058 if missing(disut_mo) & mobility == 2
replace disut_mo= 0.076  if missing(disut_mo) & mobility == 3
replace disut_mo= 0.207 if missing(disut_mo) & mobility == 4
replace disut_mo= 0.274  if missing(disut_mo) & mobility == 5

 gen disut_sc= .
 replace disut_sc= 0 if missing(disut_sc) & selfcare == 1
replace disut_sc= 0.050 if missing(disut_sc) & selfcare == 2
replace disut_sc= 0.080  if missing(disut_sc) & selfcare == 3
replace disut_sc= 0.164 if missing(disut_sc) & selfcare == 4
replace disut_sc= 0.203  if missing(disut_sc) & selfcare == 5

 gen disut_ua= .
 replace disut_ua= 0 if missing(disut_ua) & activity == 1
replace disut_ua= 0.050 if missing(disut_ua) & activity == 2
replace disut_ua= 0.063  if missing(disut_ua) & activity == 3
replace disut_ua= 0.162 if missing(disut_ua) & activity == 4
replace disut_ua= 0.184  if missing(disut_ua) & activity == 5

 gen disut_pd= .
 replace disut_pd= 0 if missing(disut_pd) & pain == 1
replace disut_pd= 0.063 if missing(disut_pd) & pain == 2
replace disut_pd= 0.084  if missing(disut_pd) & pain == 3
replace disut_pd= 0.276 if missing(disut_pd) & pain == 4
replace disut_pd= 0.335  if missing(disut_pd) & pain == 5

 gen disut_ad= .
 replace disut_ad= 0 if missing(disut_ad) & anxiety == 1
replace disut_ad= 0.078 if missing(disut_ad) & anxiety == 2
replace disut_ad= 0.104  if missing(disut_ad) & anxiety == 3
replace disut_ad= 0.285 if missing(disut_ad) & anxiety == 4
replace disut_ad= 0.289  if missing(disut_ad) & anxiety == 5

gen disut_total=disut_mo+disut_sc+disut_ua+disut_pd+disut_ad

gen EQindex=.
replace EQindex=1-disut_total
replace EQindex=round(EQindex,.001)
```