INCA

Temazepam or Melatonin Versus Placebo for the Treatment of **IN**somnia in Advanced **CA**ncer: A Three Arm, Double Blind, Phase III, Multicentre, Randomised Clinical Trial

Statistical Analysis Plan

Version 1
16 Feb 2023

Protocol number: 19/013

Authors: Anneke Grobler

CONTENTS

1. Administrative Information ... 3
1.1 Document Version History ... 3
1.2 Approvals ... 3

2. Study Synopsis ... 3
2.1. Primary Objective ... 4
2.2. Secondary Objectives ... 4
2.3. Optional Carer Component Objectives ... 5
2.4. Study Population ... 5
2.5. Intervention ... 6
2.6. Randomisation and Blinding ... 6
2.7. Sample Size ... 6
2.8. Study Procedures ... 6
2.9. Deviations from Protocol ... 7

3. General Statistical Methodology ... 8
3.1. Objectives of Analysis Plan ... 8
3.2. Analysis Software ... 8
3.3. Definition of analysis populations ... 8
3.4. Definitions related to Adverse Events ... 8
3.5. Adjustment for Multiplicity ... 8
3.6. Interim Analyses ... 8
3.7. Definitions Related to Estimands ... 8

4. Descriptive Statistics ... 9
4.1. Recruitment and Follow-up ... 9
4.2. Baseline Characteristics ... 9
4.3. Protocol Deviations ... 9
4.4. Compliance ... 9
4.5. Concomitant Therapies ... 9

5. Analysis of the Primary Outcome(s) ... 10

6. Secondary Outcomes ... 10
6.1 Comparing each of the treatments to placebo ... 10
6.1.1 Quality of life using EORTC QLQ-C15-PAL ... 10
6.1.2 Tolerability ... 11
6.1.3 Patient reported sleep quality as measured using the mPSQI on Day 8 ... 11
6.1.4 Patients' Global Impression of Change on Day 8 ... 14
6.2 Comparing the two treatments, temazepam and melatonin, to each other in terms of the primary and secondary objectives ... 14
6.3 Carer substudy ... 14

7. Safety Outcomes ... 14

8. Appendix A. Example Tables and Figures ... 15

9. References ... 18

List of Abbreviations

CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Event
ISI	Insomnia severity index
mPSQI	Modified Pittsburgh Sleep Quality Index
PR	Prolonged release

1. Administrative Information

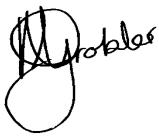
Protocol: Number 19/013; Version 1.0; 12 March 2020

1.1 Document Version History

Version Date	Version	Author	Change Description	Reason/Comment
	1.0		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		16/2/2023
Ruwani Mendis	Principal investigator	Western Health	Please see last page for signature	22/2/23

2. Study Synopsis

This is a multi-centre, double blind, placebo controlled, 3 arm, randomised, phase III study of temazepam (Arm A), melatonin prolonged release (PR, Arm B) or placebo (Arm C) in patients with advanced cancer of any aetiology.

Following randomisation, patients will enter the medication phase of the study for 7 days. The first dose of study medication will be taken on the evening of day 1, 30 minutes prior to sleep. At the end of the medication phase, patients will be assessed on day 8 (end of study).

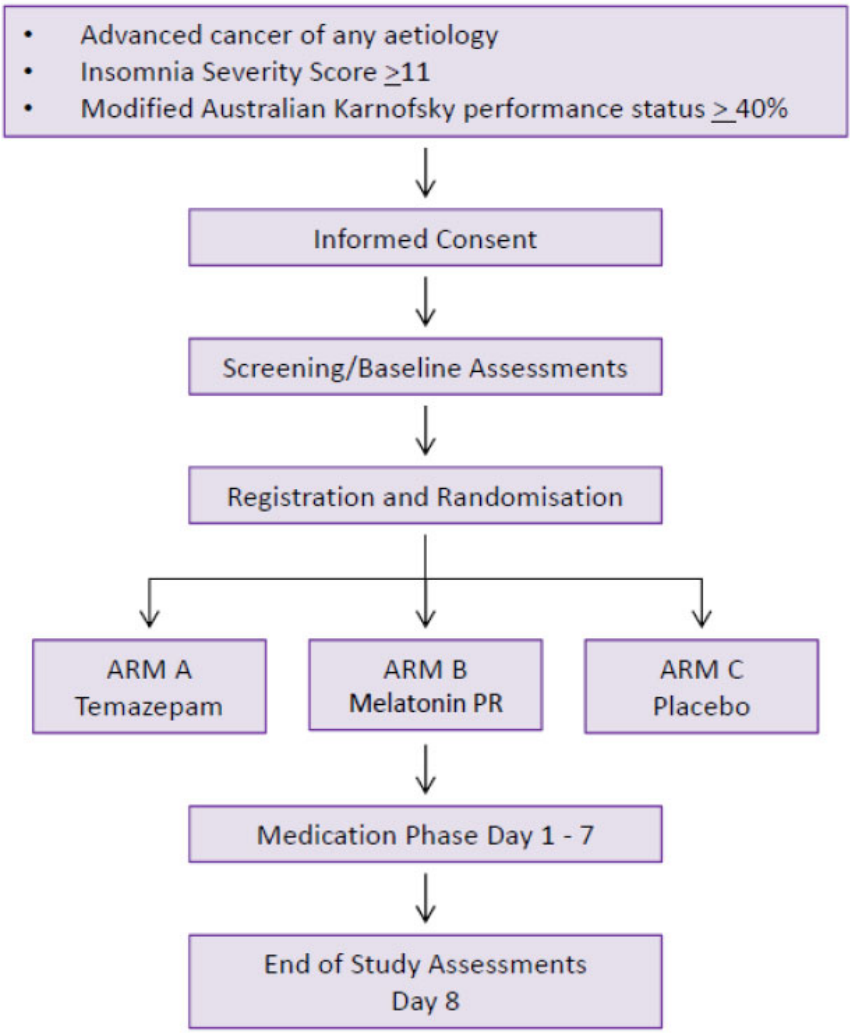
All study participants will be educated regarding good sleep hygiene by the consenting clinician and provided with a brochure on good sleep hygiene.

As part of this study, an optional carer component is open to the primary carers of study patients. The primary carer is the person the study patient identifies as being most involved in his or her care. The carer component will explore the effectiveness of temazepam and melatonin PR taken by the patient in improving the sleep quality of carers as assessed by questionnaires. There will be no study medication administered to the carer as part of this study.

This study will be sponsored by Western Health, Melbourne, Victoria. Recruitment will take place over 24 months in approximately four Victorian Comprehensive Cancer Centre alliance (VCCC alliance) affiliated tertiary public hospital sites.

There will be 110 patients registered into the study. It is expected that it will take 2 years to accrue the required number of patients across the four sites at a rate of approximately one patient per site per month. Study participation for a patient is expected to be up to 11 days. Patient follow-up beyond the day 8 assessment is not required.

Figure 1: Trial schema:



2.1. Primary Objective

The primary objective is to study the effectiveness of temazepam and melatonin PR on patient reported sleep quality, using the Insomnia Severity Index, after 7 days. Each of the treatments will be compared to placebo.

2.2. Secondary Objectives

1. To study the impact of temazepam and melatonin PR on quality of life, using EORTC QLQ-C15-PAL

2. To study the tolerability of temazepam and melatonin PR. This will be measured by the Karolinska Sleepiness Score, frequency of falls, hospital admissions for delirium during the 7 days following randomisation
3. To study the effect of temazepam and melatonin PR on patient reported sleep quality as measured using the modified Pittsburgh sleep quality index (mPSQI) on Day 8
4. To study the impact of temazepam and melatonin PR on Patients' Global Impression of Change on Day 8
5. To compare the two treatments, temazepam and melatonin, to each other in terms of all of the primary and secondary objectives

2.3. Optional Carer Component Objectives

To study the effectiveness of temazepam and melatonin PR on the sleep quality of the carer on Day 8, using the Insomnia Severity Index and mPSQI.

2.4. Study Population

Hospital inpatients and outpatients with a diagnosis of an advanced cancer of any aetiology with insomnia who meet all the inclusion and none of the exclusion criteria will be eligible for participation in this study.

INCLUSION CRITERIA

Patients must meet all the following criteria for study entry:

1. Patient has provided written informed consent
2. Male or female patients aged ≥ 18 years
3. Presence of advanced cancer of any aetiology
4. Patient has an Insomnia Severity index (ISI) Score >11
5. Australian modified Karnofsky performance status ≥40% (see Appendix 1)
6. Patient is willing and able to comply with the protocol requirements for the duration of the study

EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from study entry:

1. Patient has pain or other unstable symptoms that the clinician and patient feels is directly contributing to poor sleep unless the symptom is optimally treated with no potential to change during the course of the study. Patients with unstable symptoms can be rescreened once the symptoms are stable
2. Patient who has taken any prescription medication for sleep within 3 days prior to randomisation. Patients on prescription medication for sleep can be rescreened once medication has been ceased for ≥3 days
3. Concurrent use of benzodiazepines for any indication
4. Patient has had > 2 falls in the past week
5. Patients on varying doses of corticosteroids for any reason during the intervention period or 3 days prior to randomisation
6. Plan for surgery during the study period
7. Formally diagnosed active and uncontrolled alcohol or substance abuse disorder
8. Intolerance to melatonin or temazepam
9. Patient is pregnant or lactating
10. Unstable psychiatric illness as assessed by the clinician
11. Any contraindication listed on the product description for temazepam or melatonin
12. The patient is on another clinical trial of an investigational agent that is likely to interfere with sleep

2.5. Intervention

Table 1: Study Medication

ARM	Medication	Dose	Dose Frequency	Route of Administration
Arm A	Temazepam	10mg (1 capsule)	Day 1 -7	Oral
Arm B	Melatonin PR	2mg (1 capsule)	Day 1 -7	Oral
Arm C	Placebo	1 capsule	Day 1 -7	Oral

Patients will be instructed to take the study medication 30 minutes prior to sleep time on the evening of days 1 - 7. Study medication, regardless of Arm, should be taken at the same time every night. If vomiting occurs within 15 minutes after taking the study medication and expelled table(s) is still intact, another dose may be taken. Otherwise, no replacement dose is to be taken. In cases where a dose is missed or forgotten, the patient should be instructed not to take another dose until the next evening. Patients will need to complete a patient medication diary, recording daily doses taken and/or any missed doses. Sites must review the patient medication diaries on day 8. Any overdose or incorrect administration of study medication should be noted on the relevant eCRF. Adverse events associated with an overdose or incorrect administration of study medication should be recorded on the relevant eCRF.

2.6. Randomisation and Blinding

Patients deemed eligible by the investigator will be randomised in a 2:2:1 ratio to the 3 Arms (temazepam, melatonin PR or placebo). Patients will be randomised using permuted block randomisation, stratified by site.

Temazepam, melatonin PR and placebo will be blinded by encapsulation in identical gel capsules. The study medication assignments will not be known by any study personnel other than the site pharmacist(s) and the independent statistician who generated the randomisation list and will be unblinded, until unblinding occurs at the time of the final analysis.

2.7. Sample Size

In a previous study, the mean score on the ISI for cancer patients was 7, with a standard deviation of 6.3. The minimal clinically important difference for the ISI in patients with primary insomnia is 6.

A sample size of 44 patients in arm A, 44 patients in arm B and 22 patients in the placebo arm will give at least 90% power to compare each active arm to placebo assuming a difference of 6 points, and allowing for 10% loss to follow up. This sample size will also have 80% power to compare the two active arms assuming a difference of 4 points. The total sample size is 110 patients.

2.8. Study Procedures

SCREENING ASSESSMENTS

The following must be performed within 7 days prior to patient randomisation onto the study, unless otherwise stated.

- Written informed consent
- Confirmation patient met all of the inclusion criteria and none of the exclusion criteria
- Demographics
- Relevant medical history
- Cancer diagnosis stage
- Review of prior and concomitant medications
- Australian modified Karnofsky performance status

- Falls history within the last 7 days
- Patient Reported Outcomes:
- Insomnia Severity Index

BASELINE ASSESSMENTS
The following must be performed prior to the first dose the study, unless otherwise stated.

- Good sleeping hygiene handout and education
- Patient Reported Outcomes
- Karolinska Sleepiness Scale
- EORTC QLQ –C15-PAL
- Modified Patient Health Questionnaire-4
- Symptoms Assessment Scale
- Modified Pittsburgh Sleep Quality Index

MEDICATION PHASE ASSESSMENTS - DAYS 1 – 7
The following will be completed each day during the medication phase (day 1 - 7) unless otherwise specified

- Karolinska Sleepiness Scale
- Review of adverse events
- Patient Reported Outcomes on day 3: ISI, Patients' Global Impression of Change

END OF STUDY ASSESSMENTS - DAY 8
The end of study assessment will occur on day 8 after the last dose of study medication. The following assessments must be performed at this visit or over the telephone where necessary by the research officer or study nurse:

- Review of adverse events
- Review of medication diary
- Falls history within the last 7 days
- Patient Reported Outcomes:
    - Insomnia Severity Index
    - EORTC QLQ –C15-PAL
    - Modified Patient Health Questionnaire-4
    - Symptoms Assessment Scale
    - Modified Pittsburgh Sleep Quality Index
    - Karolinska Sleepiness Scale
    - Patients' Global Impression of Change

OPTIONAL CARER COMPONENT ASSESSMENTS
The following must be performed by the carer at baseline and on Day 8:

- Insomnia Severity Index
- Modified Pittsburgh Sleep Quality Index

2.9. Deviations from Protocol

The trial has been stopped early due to low enrolment and delays during the Covid-19 epidemic. The enrolled sample is smaller than planned.

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

3. General Statistical Methodology

3.1. Objectives of Analysis Plan

This analysis plan covers the analysis of the primary and secondary objectives and the optional carer component.

3.2. Analysis Software

All analyses will be done in Stata (version 17 or higher).

3.3. Definition of analysis populations

Data will be analysed according to the intention to treat principle which will include all patients who were randomised in the treatment arm they were randomised to.

3.4. Definitions related to Adverse Events

Adverse events were coding using the Common Terminology Criteria for Adverse Event (CTCAE) V5.0 dictionary.

3.5. Adjustment for Multiplicity

No adjustment for multiplicity will be made.

3.6. Interim Analyses

There was no interim analysis.

3.7. Definitions Related to Estimands

Section 5 and 6 report analytical approaches for the primary and secondary outcomes using the estimand framework. An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. It has 5 attributes: population, treatment, variable of interest e.g. outcome, summary measure, and possible intercurrent events (defined as an event that can occur post-randomisation and preclude or affect the interpretation of the variable of interest e.g. discontinuation of treatment).

Different approaches to handling intercurrent events can be taken and are described below:

i) **Hypothetica**l: a strategy which envisages a scenario in which the intercurrent event would not occur, e.g. if participants had not switched treatment or if death had not occurred
ii) **Treatment policy**: a strategy which seeks to understand the treatment effect on the variable regardless of the intercurrent event, i.e. an outcome is of interest whether or not the intercurrent event occurred prior to the outcome, e.g. the final outcome is of interest irrespective of whether the participant takes additional medication
iii) **Composite**: a strategy which considers the occurrence of the intercurrent event as informative about the participants outcome. Under this strategy the intercurrent event is included in the endpoint definition, e.g. classifying the use of rescue medication as failure, in addition to disease progression, in a time-to-event analysis
iv) **Principal Stratification**: a strategy wherein treatment effects are assessed in the stratum of participants who would have a specific status with respect to the intercurrent event e.g. examining the effect of treatment in participants who would not require rescue medication
v) **While-on-treatment**: a strategy which considers response to treatment prior to the occurrence of the intercurrent event to be of interest. For repeated measures, values up to the intercurrent event are of

interest but not values after the intercurrent event. Generally this strategy is only useful if the duration of treatment is not relevant either because it is not clinically *relevant* or because the rate of an event or outcome is constant over time e.g. the rate of adverse events, where one assumes a constant hazard.

4. Descriptive Statistics

4.1. Recruitment and Follow-up

The number of participants at each study visit will be reported using a CONSORT flowchart.

4.2. Baseline Characteristics

The following variables will be summarised at baseline by treatment group:
Advanced cancer
Cancer type
Primary site
Palliative treatment at study entry
Cancer stage
Age
Sex
Does carer participate in carer substudy
Inpatient or outpatient

Baseline characteristics will be summarised by mean and standard deviations (SDs) for continuous variables, and counts and percentages for categorical variables.

4.3. Protocol Deviations

Protocol deviations are defined as:

- Enrolment deviations
- Dosing deviations (overdose, missed doses)
- Assessment deviations (missed patient reported outcomes)
- Out of window visits
- Deviations for Good Clinical practice (GCP) and
- Other

Protocol deviations will be categorised as either major or minor. Minor deviations will comprise of less serious protocol non-compliance that does not significantly impact on the participants' rights, safety or well-being, or the completeness, accuracy and reliability of the trial data. All other protocol deviations are regarded as major deviations. Protocol deviations will be listed.

4.4. Compliance

Compliance to the study intervention is assessed via pill count. The following formula will be used: Compliance = 100*(number of tablets taken during the 7 days) / (number of tablets prescribed). Compliance will be summarised as the mean percentage compliance in each treatment arm as well as the proportion of patients who took more than 80% of the tablets they were prescribed.

4.5. Concomitant Therapies

Concomitant medications will be listed.

5. Analysis of the Primary Outcome(s)

Compare sleep quality, using the ISI, between the temazepam and placebo arms and between the melatonin PR and placebo arms on Day 8.

The Insomnia Severity Index has seven questions and the answers are added to get a total score. A high score indicated worse insomnia. The total score of the ISI ranges from 0-28 points, with a score above 15 being indicative of clinical insomnia. The ISI is measured at screening, Day 3 and Day 8.

Population: Patients with advanced cancer being treated for insomnia. Patients will be included in the treatment arm they were randomised to
Treatment: Temazepam once daily, or placebo, and any subsequent changes to treatment over the treatment period
Outcome: ISI score on Day 8
Summary measure: Mean difference (95% confidence interval [CI]) between treatment arms in the ISI score on Day 8
Potential intercurrent events: Treatment discontinuation without study withdrawal
Early study withdrawal
Participant unable to provide ISI score on Day 8
Death
Strategy for intercurrent event: Treatment policy strategy. All observed values will be used, regardless of whether or not the patient had experienced the intercurrent events. The only exception is that death will be handled by the while alive strategy, which means that patients who died prior to Day 8 will be excluded from the analysis.

The primary objective will be assessed by comparing the ISI score on Day 8 in each of the active arms, temazepam and melatonin PR, independently to the placebo arm using a linear regression model adjusted for the stratification variable site. The mean ISI score in each treatment arm will be calculated and given, as well as the mean difference between each of the active arms and placebo with a 95% CI. No adjustment for multiple testing will be done, since the two drugs are tested independently.

No sensitivity, supplementary or subgroup analyses are planned.

If the outcome on Day 8 is missing for more than 5% of participants, we will use multiple imputation, through chained equations to handle the missing data. Any appropriate auxiliary variables will be included.

6. Secondary Outcomes

6.1 Comparing each of the treatments to placebo

6.1.1 Quality of life using EORTC QLQ-C15-PAL

The EORTC QLQ-C15-PAL will be calculated following the standard scoring manual, using the Stata code developed by Bruun (2016). This Stata module can be installed by typing “ssc install qlqc15". All scales are scaled to range from 0 to 100, with a high score indicating high functioning.

Totals for the following scales will be calculated:

- Global health status/quality of life (QL2)

Functional scales

- Physical functioning (PF2)
- Emotional functioning (EF)

Symptom scales

- Fatigue (FA)
- Nausea and vomiting (NV)
- Pain (PA)
- Dyspnoea (DY)
- Insomnia (SL)
- Appetite loss (AP)
- Constipation (CO)

The same statistical method as described for the primary outcome will be used to compare temazepam and melatonin PR to placebo on quality of life on Day 8.

6.1.2 Tolerability

Tolerability will be measured by the following:

Karolinska Sleepiness Score
This is measured daily for 7 days as a single Likert scale, ranging from 1 to 9. We will calculate a mean score over the 7 or 8 days for each patient and compare these mean scores between the treatment using the same statistical methods as described for the primary outcome.

Frequency of falls
The number of falls a patient had in the previous 7 days will be reported.

Hospital admissions for delirium
Hospital admissions for delirium will be identified using the adverse events reported.

Delirium and falls will be compared between the two active arms and placebo, by giving the proportion of patients in each of the treatment arms who had these tolerability issues. Each of the active arms will be compared to placebo using binomial regression adjusted for site and a difference between the two proportions with 95% confidence interval will be given.

6.1.3 Patient reported sleep quality as measured using the mPSQI on Day 8

The PSQI is a tool used to evaluate subjective sleep quality over the previous month. The PSQI uses 19 self-rated questions to assess 7 sleep components. The seven components which are each scored between 0-3 are summed to give a total PSQI score between 0-21 with higher scores indicating worse sleep quality. In this study the PSQI has been modified (mPSQI) to assess sleep quality in the past week.

The 7 sleep components are scored as follows:

1. Sleep quality
   Use question 6 “During the past week, how would you rate your sleep quality overall?” and assign a score of 0 if answered “very good”
   1 if answered “fairly good”
   2 of answered “fairly bad”
   3 if answered “very bad”.
2. Sleep latency
   Use question 2 “During the past week, how long (in minutes) has it usually take you to fall asleep each night?
   Score it as follows: 0 if $\leq$ 15 min
   1 if 16-30 min
   2 if 21-60 min

3 if > 60 min

Use question 5a "During the past week, how often have you had trouble sleeping because you cannot get to sleep within 30 minutes?"

Score it as follows: 0 if not during the past week;
1 if less than once a week;
2 if once or twice a week;
3 if three or more times a week

Sum Question 2 and Question 5a.

If this sum is 0 set the score to 0
is 1 or 2 set the score to 1
is 3 or 4 set the score to 2
is 5 or 6 set the score to 3

3. Sleep duration

Use question 4 "During the past week, how many hours of actual sleep did you get at night? (this may be different than the number of hours you spend in bed)" using the values:

0 if > 7 hours
1 if 6-7 hours
2 if 5-6 hours
3 if <5 hours

4. Habitual sleep efficiency
   1. Write the number of hours slept (question 4).
   2. Calculate the number of hours spent in bed: getting up time (question 3) – bedtime (question 1).
   3. Calculate the habitual sleep efficiency as follows: (Number of hours slept/Number of hours spent in bed) x 100 = Habitual sleep efficiency (%)

Assign Component 4 score as follows:

0 if >85%
1 if 75-84%
2 if 65-74%
3 if <65%

5. Sleep disturbances

Questions 5b-5j are as follows:

5b: Wake up in the middle of the night or early morning
5c: Have to get up to use the bathroom
5d: Cannot breathe comfortably
5e: Cough or snore loudly
5f: Feel too cold
5g: Feel too hot
5h: Had bad dreams
5i: Have pain
5j: Other reason

Examine questions #5b-5j and assign scores for each question as follows:

0 if not during the past week
1 if less than once a week
2 if once or twice a week
3 if three or more times a week

The scores for questions 5b-5j are summed together. The component 5 score is assigned as follows:

0 if a score of 0
1 if a score of 1-9
2 if a score of 10-18
3 if a score of 19-27

6. Use of sleeping medication
   Examine question 7 "During the past week, how often have you taken medicine (prescribed or over the counter) to help you sleep?" and assign the score as follows:
   0 if not during the past week
   1 if less than once a week
   2 if once or twice a week
   3 if three or more times a week

7. Daytime dysfunction
   Examine question 8 "During the past week, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?" and assign the score as follows:
   0 if never
   2 if once or twice
   2 if once or twice each week
   3 if three or more times each week

   Examine question 9 "During the past week, how much of a problem has it been for you to keep up enough enthusiasm to get things done?" and assign the score as follows:
   0 if no problem at all
   1 if only a very slight problem
   2 if somewhat of a problem
   3 if a very big problem

Add the scores for Questions 8 and 9. Assign the Component 7 score as follows:
0 if a score of 0
1 if a score of 1-2
2 if a score of 3-4
3 if a score of 5-6

The global PSQI score is the seven component scores added together.

Questions 1 through 9 are not allowed to be missing except if:
- The sum of Question 5b, c, d, e, f, g, h, i, j is equal to 0 and Question 5j is missing, then the value of Q5j will be set to 0.
- If the sum of Question 5b-j is <u>> 1 and < 9 and Question 5j is missing, then the value of Q5j will be assigned the value 1.</u>
- If the sum of Question 5b-j is <u>> 9 and < 18 and Question 5j is missing, then the value of Q5j will be assigned the value 2.</u>
- If the sum of Question 5b-j is <u>> 18 and Question 5j is missing, then the value of Q5j will be assigned the value 3.</u>

If any of the above questions are missing (apart from the scenario described above), then any scores calculated using missing questions are also missing (which means the total PSQI score will be missing).
In the event that a range is given for an answer (for example, 30 to 60 is written as the answer for Question 2, minutes to fall asleep), the difference will be split and 45 will be used.

The same statistical method as described for the primary outcome will be used to compare temazepam and melatonin PR to placebo on daytime sleepiness on Day 8, for each of the scales and the total score.

6.1.4 Patients' Global Impression of Change on Day 8

Global impression of change is measured by one Likert scale question. We will use a cumulative logit model to compare temazepam and melatonin PR to placebo on patient's global impression of change on day 8. The common odds ratio will be reported.

6.2 Comparing the two treatments, temazepam and melatonin, to each other in terms of the primary and secondary objectives

If either of the treatment arms was shown to be superior to placebo, then the two active arms will be compared to determine whether any of the active treatment arms was superior to the other. If neither active arm was superior to placebo, the two active arms will not be compared.

The efficacy variables we will compare are:

1. ISI on Day 8
2. Quality of life using EORTC QLQ-C15-PAL (all scales) on Day 8
3. Patient reported sleep quality as measured using the mPSQI (all scales) on Day 8
4. Patients' Global Impression of Change on Day 8

Each of these variables will be assessed by comparing the score on Day 8 in the temazepam arm to the melatonin PR arm using a student t-test. The mean score in each treatment arm will be calculated and given, as well as the mean difference between the arms and placebo, with a 95% CI. All other elements of the analysis will be the same as for the primary outcome, for example the handling of intercurrent events and missing data will be the same as described for the primary outcome.

The tolerability variables we will compare are:

1. Karolinska sleepiness scale
2. Frequency of falls
3. Hospitalisation for delirium

The two active treatment arms will also be compared to each other using the method described above for the efficacy variables and for falls and hospitalization for delirium using binomial regression adjusted for site.

6.3 Carer substudy

The carer substudy is intended to study the effectiveness of temazepam and melatonin PR on the sleep quality of the carer on Day 8, using the ISI and mPSQI. The analyses that will be performed will be the same as for the main study (i.e. the analysis of the study participant's data) for the subset of carers who agreed to participate in the study.

The variables that will be analysed will be

- ISI
- All 7 scales and the global score of the mPSQI.

The analyses will be the same as described in Sections 5, 6.1.3 and 6.2 (Subsections 1 and 3).

7. Safety Outcomes

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.

8. Appendix A. Example Tables and Figures

Table 1: Summary of screening failures

Screening failures	Sunshine	Peter McCallum CC	Austin	St Vincent's	All
Reason for screening failure					
xxx					

Table 2: Patient disposition

	Temazepam n (%)	Melatonin PR n (%)	Placebo
Number of patients enrolled			
Overall			
By site			
Number of patients completed study			
Reason for trial discontinuation			
Reason for study treatment discontinuation			

Table 3: Baseline characteristics: Mean (95% confidence interval) or number and proportion

Variable	Temazepam	Melatonin PR	Placebo	Total
All variables listed in Section 4.2				

Table 4: Summary of protocol violations: Number reported

Protocol violation	Temazepam	Melatonin PR	Placebo
Major			
xxxx			
Minor			
xxxxx			

Listing 1: Listing of protocol violations

Table 5: Compliance to study treatment

	Temazepam	Melatonin PR	Placebo
Mean compliance (95% CI)			
Proportion with compliance > 80%			

Listing 2: Listing of concomitant medications

Table 6: Insomnia Severity Index on Day 8: mean with 95% CI

	Temazepam		Melatonin PR		Placebo		Difference	p-value
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	
Day 8	x	x	x	x	x	x		x
Temazepam - Placebo							x	x
Melatonin PR - Placebo							x	x
Temazepam – Melatonin PR							x	x

Table 7: Quality of life (EORTC QLQ-C15-PAL) on Day 8: mean with 95% CI

The same table outline as Table 6, repeated for each of the scales.

- Global health status/quality of life (QL2)

Functional scales

- Physical functioning (PF2)
- Role functioning (RF2)
- Emotional functioning (EF)
- Cognitive functioning (CF)
- Social functioning (SF)

Symptom scales

- Fatigue (FA)
- Nausea and vomiting (NV)
- Pain (PA)
- Dyspnoea (DY)
- Insomnia (SL)
- Appetite loss (AP)
- Constipation (CO)
- Diarrhoea (DI)
- Financial difficulties (FI)

Table 8: Karolinska sleepiness scale: mean with 95% CI

For each participant calculate the mean over the 7/8 days of the study.
The same table outline as Table 6

Table 9: Falls: Proportion with falls during the 7 day period (95% CI)

	Temazepam		Melatonin PR		Placebo		Difference in proportion (95% CI)	p-value
	N	Proportion (95% CI)	N	Proportion (95% CI)	N	Proportion (95% CI)		
	x	x	x	x	x	x		
Temazepam - Placebo							x	x
Melatonin PR - Placebo							x	x
Temazepam – Melatonin PR							x	x

Table 10: Hospitalisation for delirium: Proportion with delirirum during the 7 day period (95% CI)

The same table outline as Table 9

Table 11: Modified Pittsburgh sleep quality index (mPSQI) on Day 8: mean with 95% CI
The same table outline as Table 6, repeated for each of the scales.

- Sleep quality
- Sleep latency
- Sleep duration
- Habitual sleep efficiency
- Sleep disturbance
- Use of sleeping medication
- Daytime dysfunction
- Total

Table 12: Patient's global impression of change on Day 8: mean with 95% CI

	Temazepam N =	Melatonin PR N =	Placebo N =	Common odds ratio (95% CI) between temazepam and placebo (p-value)	Common odds ratio (95% CI) between Melatonin PR and placebo (p-value)
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)		
Day 8					
Category	**N(%)**	**N(%)**	**N(%)**		
No change or worse					
Almost the same					
A little better					
Somewhat better					
etc					

Table 13: Carer substudy: Insomnia Severity Index (ISI) on Day 8: mean with 95% CI
The same table outline as Table 6

Table 14: Carer substudy: Modified Pittsburgh sleep quality index (mPSQI) on Day 8: mean with 95% CI
The same table outline as Table 6, repeated for each of the scales.

- Sleep quality
- Sleep latency
- Sleep duration
- Habitual sleep efficiency
- Sleep disturbance
- Use of sleeping medication
- Daytime dysfunction
- Total

Table 15: Number of patients experiencing adverse events

Body system Adverse event lower level term	Temazepam	Melatonin PR	Placebo
Blood and lymphatic system disorders			
Cardiac disorders			

…

Table 16.1: Number of patients experiencing adverse events by severity grade: Temazepam
Table 16.2: Number of patients experiencing adverse events by severity grade: Melatonin PR
Table 16.3: Number of patients experiencing adverse events by severity grade: Placebo

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				
Injury, poisoning and procedural complications				
Investigations				
Metabolism and nutrition disorders				
Musculoskeletal and connective tissue disorders				
Neoplasms benign, malignant and unspecified				
Etc…..				

Repeat this table for each treatment arm

Table 17: Number of patients experiencing serious adverse events

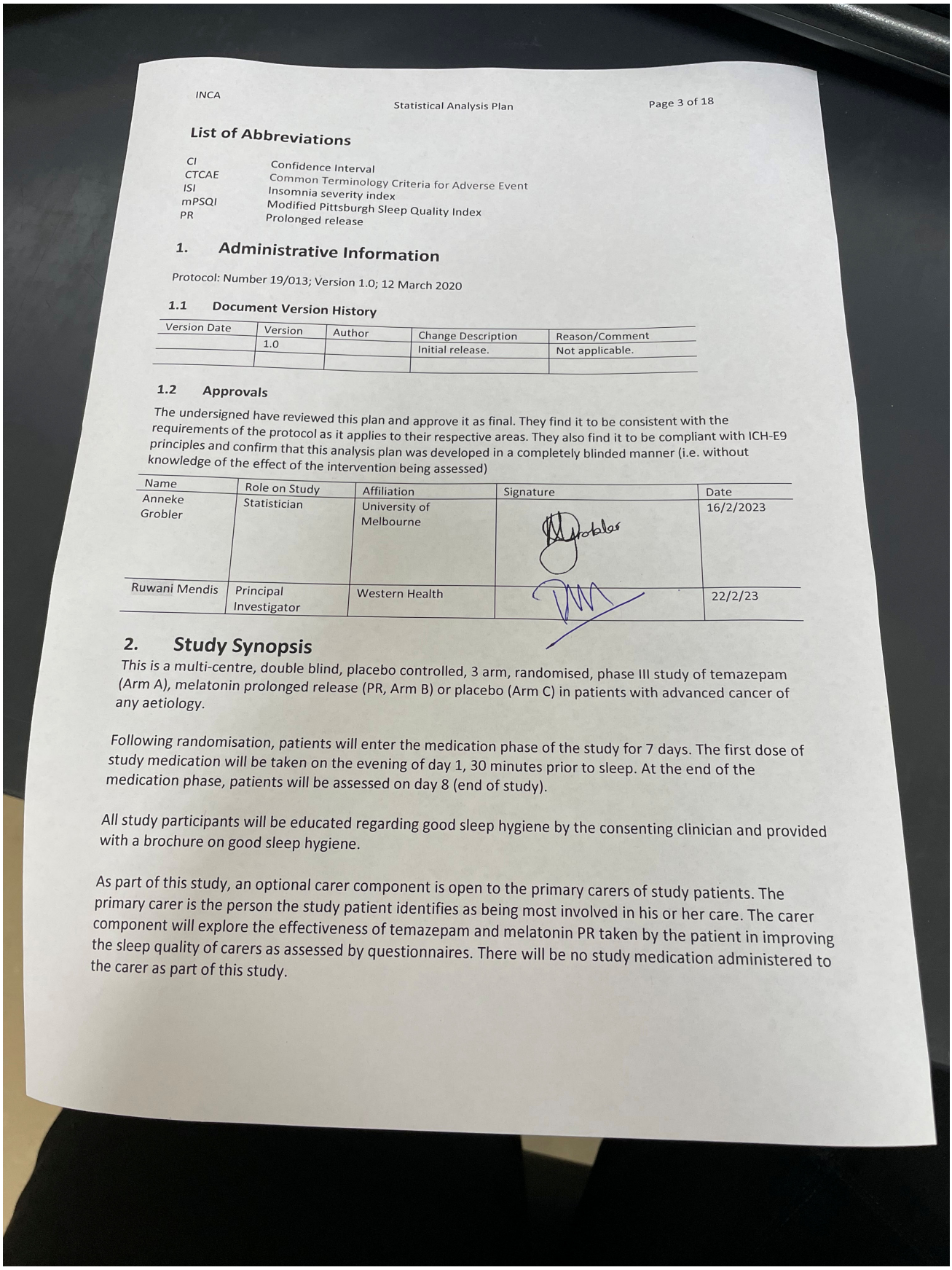
Body system **Adverse event lower level term**	**Temazepam**	**Melatonin PR**	**Placebo**
Blood and lymphatic system disorders			
Cardiac disorders			
…			

Listing 3: Serious adverse events

Listing 4: Deaths

9. References

Niels Henrik Bruun, 2016. "QLQC15: Stata module for scoring of the EORTC QLQ-C15-PAL," Statistical Software Components S458284, Boston College Department of Economics.



List of Abbreviations

CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Event
ISI	Insomnia severity index
mPSQI	Modified Pittsburgh Sleep Quality Index
PR	Prolonged release

1. Administrative Information

Protocol: Number 19/013; Version 1.0; 12 March 2020

1.1 Document Version History

Version Date	Version	Author	Change Description	Reason/Comment
	1.0		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		16/2/2023
Ruwani Mendis	Principal Investigator	Western Health		22/2/23

2. Study Synopsis

This is a multi-centre, double blind, placebo controlled, 3 arm, randomised, phase III study of temazepam (Arm A), melatonin prolonged release (PR, Arm B) or placebo (Arm C) in patients with advanced cancer of any aetiology.

Following randomisation, patients will enter the medication phase of the study for 7 days. The first dose of study medication will be taken on the evening of day 1, 30 minutes prior to sleep. At the end of the medication phase, patients will be assessed on day 8 (end of study).

All study participants will be educated regarding good sleep hygiene by the consenting clinician and provided with a brochure on good sleep hygiene.

As part of this study, an optional carer component is open to the primary carers of study patients. The primary carer is the person the study patient identifies as being most involved in his or her care. The carer component will explore the effectiveness of temazepam and melatonin PR taken by the patient in improving the sleep quality of carers as assessed by questionnaires. There will be no study medication administered to the carer as part of this study.