The SIM-study:

A RANDOMIZED CONTROLLED TRIAL OF SUBCUTANEOUS VERSUS INTRAVENOUS MORPHINE WHEN SWITCHING FROM ORAL TO PARENTERAL ROUTE IN PALLIATIVE CANCER PATIENTS

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ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical/Therapeutic/Chemical
CI	Confidence Interval
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
DAE	Discontinuation due to Adverse Event
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product (includes active comparator and placebo)
IND	Investigational New Drug
SOP	Standard Operating Procedure
ESAS	Edmonton symptom assessment scale
HRQoL	Health-related quality of life
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of life questionnaire - 30 items
SC	Subcutaneous
IV	Intravenous
PCA	Patient-controlled analgesia
NRS	Numeric rating scale
OME	Oral Morphine Equivalent

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1 Introduction

1.1 Background and Rationale

Adherence to the WHO analgesic ladder has in validation studies provided pain relief to the majority of patients with cancer pain (Ventafridda et al., 1985). However, it is well established that some patients need parenteral administration of opioids to achieve adequate pain (Radbruch et al., 2011). For the combination of continuous infusions and bolus doses of morphine, both the subcutaneous (SC) and intravenous (IV) routes have proven feasible and effective. However, few direct comparisons of the intravenous and subcutaneous routes have been performed (Radbruch et al., 2011). Thus, it is not known whether any of the two routes should be preferred as the first-line option when initiating parenteral opioid infusion combined with bolus doses of opioids (Caraceni et al., 2012).

1.2 Intervention(s)

Palliative care cancer patients with unsatisfactory pain control despite oral or transdermal opioid titration where opioid rotation to parenteral morphine is clinically indicated can be included in the study. Study participants will start morphine infusion via a patient-controlled analgesia (PCA) pump intravenously or subcutaneously. The study drug is Morphine diluted with normal saline to 5 mg/ml or 10 mg/ml in 100 ml drug containers suitable for CADD Solis PCA pump.

1.2.1 Brief description of the study intervention

The patient will have two PCA pumps. One connected to an IV line, one connected to a SC line. One infusion pump contains study drug (Morphine), one pump normal saline. Infusion rate and bolus doses are titrated equally from the two PCA pumps. The allocation procedure is randomized with a 1:1 ratio. Blinding is performed by the pharmacy producing the drug containers. Patients, staff, and study personnel are blinded during the 48-hour intervention period (Double-blinded, double-dummy study).

1.2.2 Control settings (if applicable)

All participants receive study drug (Morphine) either IV or SC. Comparisons will be performed between the two routes of administration. There will be no patients receiving only placebo and comparison to placebo is not part of this study.

1.3 Trial Objectives

The overall objective is to establish whether either the IV or SC route of administration has clinically significant advantages when parenteral administration of morphine is started with a combination of continuous infusion and bolus doses in palliative cancer patients.

1.3.1 Main study

1.3.1.1 Primary research question

a) Is there a difference between SC and IV administration of morphine in how quickly pain control is achieved after initiation of a continuous infusion?

1.3.1.2 Secondary research questions

b) Is there a difference in number of bolus doses after 24 and 48 hours between the groups
c) Is there a difference in pain score (NRS 0-10) between the groups
d) Is there a clinically significant difference between SC and IV administration of morphine in time from administration of bolus dose to clinically significant pain relief?

1.3.1.3 Pharmacokinetic study research question

e) What is the difference in the key pharmacokinetic parameters T_{max}, C_{max}, and AUC_{0-60} after SC and IV administration of morphine bolus doses during morphine infusion in palliative cancer patients?

1.3.2 Exploratory research question (if applicable)

Exploratory objectives include but are not restricted to following research questions:

i. Are there any group differences in change of ESAS score other than pain?
ii. What is the Patient Global Impression of Change in the two groups?
iii. Is there a difference between SC and IV group in morphine concentration in steady state*? (*>24 hours after start of infusion and >2 hours since last bolus dose)
iv. Is there a relationship between BMI and pharmacokinetic analyzes in the SC group?
v. How does respiration frequency (RF) and oxygen saturation change during the intervention? Are there any differences between the SC and IV group?
vi. What is the change in opioid side effect score in the two groups at 0, 24 and 48 hours
vii. What is the change in opioid dose (in OME) from start of titration to 48 hours
viii. What is the change in opioid dose (in OME) during follow up period
ix. What are the complications to SC line and IV line
x. What is the study population survival censored at 4 weeks

2 Trial Methods

2.1 Trial Design

Comparison of morphine infusion combined with bolus doses, administered subcutaneously or intravenously. The study is a single center phase III randomized controlled double blind, double dummy trial with open label follow-up.

In order to ensure blinding during the double-blind phase of the study, each participant will have both an intravenously and a subcutaneously administered PCA pump. One pump will contain morphine, the other placebo (saline).

The intervention period is 48 hours
Open label follow-up is four weeks

2.2 Randomization

The allocation ratio between treatments is 1:1 with no stratification. The randomization will be performed by using a computer-generated list of blocks of 6-8 patients. The randomization process is described in detail in *SIM-Study Procedure Manual version 1.3, 07.07.22*. Details of the randomization including the final random allocation list are held securely and unavailable to unauthorized trial personnel. Sequentially numbered, opaque, sealed envelopes containing information about patient allocation are located at the Department of Palliative Medicine for emergency and unblinding after 48-hour intervention period.

2.3 Statistical Framework

This trial is designed to establish the superiority of IV morphine PCA infusion compared to SC PCA infusion. The primary null hypothesis is that there is no difference in time from start of PCA infusion to last dose titration. The alternative hypothesis is that the time from start of infusion to final infusion rate titration differs between the two groups.

2.4 Hypothesis Test

2.4.1.1 Null-hypothesis:

Primary

a. There is no difference in time from start of a PCA pump until a titrated infusion rate that gives a clinically significant reduction in pain in the SC and IV group.

Secondary

b. There is no difference in number of bolus doses from PCA in the SC and IV group.
c. There is no difference in pain score as assessed by NRS for the whole 48-hour period
d. There is no difference in time from administration of a bolus dose to decrease in pain (change of 2 on 0-10 NRS) intensity and to acceptable pain relief between the SC and IV groups.

Pharmacokinetic study

e. There is no difference in T_{max}, C_{max}, and $AUC_{0\text{-}60}$ between the SC and IV groups

2.4.1.2 Alternative hypothesis

Primary

a. The time from start of infusion to final infusion rate titration differs between the SC and IV groups

Secondary

b. The number of bolus doses after 24 and after 48 hours in the two groups are different
c. The pain score in the groups differ during the 48-hour period
d. Time from bolus dose to clinically significant pain relief (change of 2 on 0-10 NRS) differ between the SC and IV group

Pharmacokinetic study

e. There is a difference in T_{max}, C_{max}, and AUC_{0-60} between the SC and IV groups

2.4.2 Confidence Intervals and p-values

All calculated p-values will be two-sided. The differences between the groups will be considered significant for p-values less than 0.05. All efficacy estimates will be presented with two-sided 95% confidence intervals. As there is only one primary null hypothesis to be tested in this trial, there will be no adjustments for multiple testing.

2.4.3 Decision Rule

This trial is designed to address a single primary outcome. Superiority is claimed if the primary null hypothesis is rejected on the significance level (alpha) of 0.05 (two-sided). That is, the 95% confidence interval of the difference between the two groups does not include zero.

2.5 Timing of Outcome Assessments

For all clinically planned measures, visits should occur within a window of the scheduled visit as described in Table 1. The exact time of a visit is also recorded.

Time of bolus titrations and time of bolus doses are registered with exact time.

Table 1 Schedule of assessment

	Screening Period	**Treatment Period**		
Time	**Within 24 hours of treatment**	**Baseline/start of treatment Between 11 am and 3 pm**	**12, 24, 36, and 48 +/- 2 hours**	**24 +/- 2; 48 +/- 2 hours**
Informed consent	X			

	Screening Period	**Treatment Period**		
Time	**Within 24 hours of treatment**	**Baseline/start of treatment Between 11 am and 3 pm**	**12, 24, 36, and 48 +/- 2 hours**	**24 +/- 2; 48 +/- 2 hours**
Inclusion/exclusion Evaluation	X			
Height, Weight	X			
Medical History	X			
Prior analgesic treatment	X			
Current medication	X			
Vital signs		X	X	
ESAS-revised		X	X	
EORCT QLQ-C30		X		X(at **48 +/- 2 hours)**
EAPC basic data set	X			
Opioid side effects		X		X
Patient Global Impression of Change				X (at **48 +/- 2 hours)**
Blood samples[2)]	X			
Treatment administration/dispensation		X	X	
Adverse event		X	X	X
Clinician's decision to continue ongoing treatment or to change treatment				X
Record of concomitant medication		X	X	X
Morphine dose		X	X	X
Hospitalization				
Survival				
Complications to IV line				
Need for switch SC to IV				
Reason for withdrawal				

1. Blood pressure, pulse, temperature, sedation level, respiratory rate
2. CRP, Hb, WBC (incl. differential counting), PLT, Na, K, Ca, creatinine, ASAT, ALP, γGT, INR, albumin, bilirubin

2.6 Statistical Interim Analysis and Stopping Guidance

There will be no interim analyses in this trial. The Data Monitoring and Safety Committee (DMSC) will recommend stopping the trial if there is a safety concern.

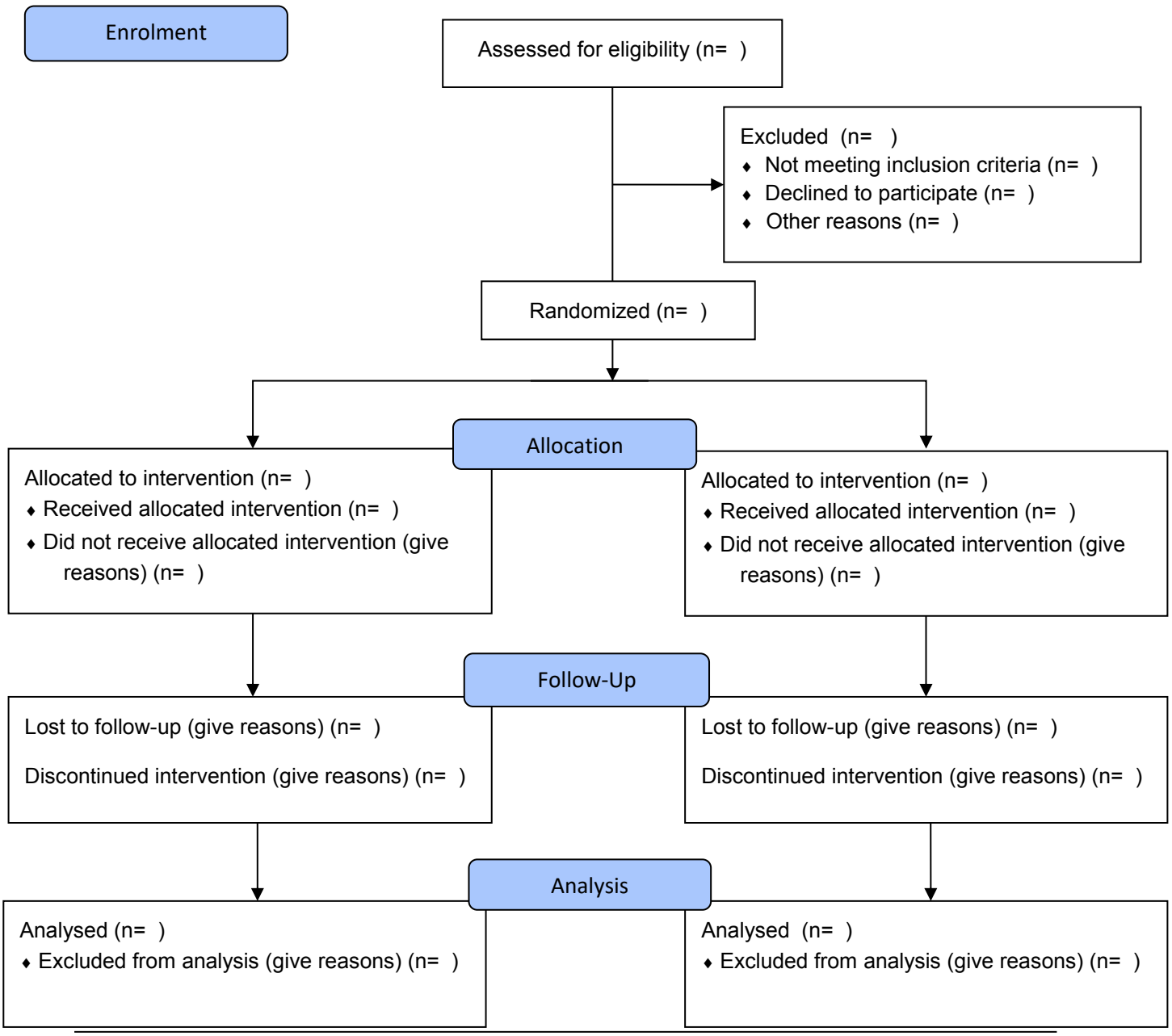
2.7 Timing of Main Analysis

The main analysis is planned when all patients have completed the 48-hour intervention period. Pharmacokinetics will be analyzed when morphine serum concentration is measured for 20 study participants.

3 Trial Population

3.1 Screening Data, Eligibility, and Recruitment

The "CONSORT" diagram comprisies the number of people screened, eligible, consented, randomized, receiving their allocated treatment, and withdrawing/lost to follow-up.



3.2 Baseline Patient Characteristics

Baseline characteristics (Tests of statistical significance will be performed for baseline characteristics but not included in the baseline tables in the article reporting the results; rather, the clinical importance of any imbalance between the two groups will be noted. The final table may be adjusted or abridged according to manuscript guidelines in the respective journal.

Table 2) will be summarized by treatment group and overall using descriptive statistics. Categorical data will be presented by numbers and percentages. Continuous data will be summarized by means, standard deviations (SDs), and min-max values if data are symmetrically distributed, and median, min-max values, and quartiles for skewed data. Tests of statistical significance will be performed for baseline characteristics but not included in the baseline tables in the article reporting the results; rather, the clinical importance of any imbalance between the two groups will be noted. The final table may be adjusted or abridged according to manuscript guidelines in the respective journal.

Table 2 Baseline characteristics

Characteristics		IV (n=xx)	SC (n=xx)	Overall (n=xx)
Age, mean/median	(SD, min-max)/(min-max,Q_1-Q_3)			
Sex	Female, n (%)			
Performance status	Karnofsky, median (min-max, Q_1-Q_3)			
ESAS, baseline	For each element mean (SD, min-max)			
EORTC-QLQ c 30, baseline	Function, mean (SD, min-max) Global health, mean (SD, min-max) Symptom burden, mean (SD, min-max)			
Weight, mean (SD, min-max)				
Height, mean (SD, min-max)				
BMI, mean (SD, min-max)				
Years with principal cancer diagnosis, median (min-max,Q_1-Q_3)				
Metastatic situation		n (%)	n (%)	n (%)
Localized/locally advanced disease only				
Metastatic disease				
Cancer diagnosis		n (%)	n (%)	n (%)
Malignant neoplasms of digestive organs				
Malignant neoplasms of respiratory and intrathoracic organs				
Malignant neoplasms of urinary tract				
Malignant neoplasms of male genital organs				
Malignant neoplasm of breast				
Malignant neoplasms of female genital organs				

Characteristics	IV (n=xx)	SC (n=xx)	Overall (n=xx)
Malignant neoplasms of ill-defined, secondary and unspecified sites Melanoma and other malignant neoplasms of skin Malignant neoplasms of eye, brain and other parts of central nervous system Malignant neoplasms, stated or presumed to be primary, of lymphoid, hematopoietic and related tissue Malignant neoplasms of lip, oral cavity and pharynx Malignant neoplasms of mesothelial and soft tissue Malignant neoplasms of bone and articular cartilage Malignant neoplasms of thyroid and other endocrine glands			
Any ongoing anti-cancer treatment Chemotherapy Immunotherapy Hormone therapy Radiotherapy	n (%)	n (%)	n (%)
Comorbidity Circulatory Musculoskeletal Endocrine Digestive Neurological Genitourinary Neoplasms Respiratory Behavioral Infection Eye Skin Blood	n (%)	n (%)	n (%)
Medication Non-opioid analgesics Opioids Antidiabetics Anticoagulants Antiepileptics Corticosteroids Antidepressants Antiemetics Neuroleptics	n (%)	n (%)	n (%)

Characteristics	IV (n=xx)	SC (n=xx)	Overall (n=xx)
Sedatives/anxiolytics Drug(s) for acid related disorders Laxatives Antibiotics Diuretics Hearth medication Antihypertensives Other			
Total 24-hour oral morphine equivalents (OME) at inclusion mean (SD, min-max) Regular opioid dose at inclusion in OME, mean (SD, min-max) Total (regular and as needed) opioid use at inclusion in OME, mean (SD, min-max)			
Biochemistry Mean (SD, min-max) CRP Hemoglobin WBC (and diff. counting Platelets Sodium Potassium Calcium Creatinine clearance ASAT ALAT ALP Gamma GT INR Albumin Bilirubin			

Abbreviations: Q quartile, SD standard deviation, ESAS Edmonton Symptom Assessment System, EORTC-QLQ c30 European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire, BMI body mass index, OME oral morphine equivalents, CRP C-reactive protein, WBC White blood cells, ASAT Aspartate aminotransferase, ALAT Alanine aminotransferase, ALP Alkaline phosphatase, INR International normalized ratio, GammaGT Gamma-glutamyl transferase.

3.3 Withdrawal/Follow-up

The status of eligible and randomized patients at trial end will be tabulated by treatment group according to:

- completed intervention and assessments.

- completed assessments but not intervention.
- completed intervention but not assessments.
- withdrew consent.
- lost to follow-up.

Time from randomization to treatment discontinuation and time from randomization to withdrawal/lost to follow-up will be presented in the CONSORT flow diagram.

3.4 Adherence and Protocol Deviations

3.4.1 Adherence to Allocated Treatment

Adherence will be defined as the percentage of subjects who have completed the 48-hour intervention period.

3.4.2 Protocol Deviations

The following pre-defined important protocol deviations are regarded to affect the efficacy of the intervention (See also Protocol Deviation Handling Plan):

- Subjects entered into the study even though they did not meet the entry criteria.
- Subjects who developed withdrawal criteria (from treatment or study) during the study but were not withdrawn.
- Subjects who received the wrong treatment or incorrect dose.
- Subjects who received an excluded concomitant treatment.
- Failure to register time from start of continuous IMP infusion until the last dose adjustment
- Withdrawn consent
- Other serious breaches according to the clinical trial protocol

The number (and percentage) of patients with major and minor protocol deviations will be summarized by treatment group with details of type of deviation provided. The patients that are included in the intention to treat analysis data set will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.

3.5 Analysis Populations

The enrolled set will include all patients who have provided informed consent and have been included in the study database.

The Full Analysis Set (FAS) will be defined as all patients randomly assigned to a treatment group regardless of whether they received any study treatment after randomization.

The Safety Analysis Set (SAS) will include all patients that receive any study treatment after randomization.

The Per Protocol (PP) population will include all randomized patients who meet the study eligibility criteria, and complete the study according to protocol with no major protocol deviations affecting the treatment efficacy.

The intention to treat (ITT) population will include all patients who were randomly assigned to a treatment group, regardless of whether they complete the treatment as planned: Main outcomes will be analyzed based on intention to treat principle. Supplemental PP analyses will be based on patients who completed the 48-hour double blind period.

3.5.1 Pharmacokinetic (PK) subgroup analysis set:

A subgroup of 20 participants that are enrolled in the study and meet eligibility criteria including the serum measurement specific criteria of Hb>9, and consent to blood sampling are considered for PK analyses.

The PK concentration population includes all study participants who have serum samples after bolus dose available for analysis.. The PK analysis population will be defined as all subjects who have PK data from minimum three concentration measurements.

4 Outcome Definitions

4.1 General Definitions and Derived Variables

4.1.1 NRS – Numeric Rating Scale

NRS is a widely used, standard one-dimensional scale from 0 to 10 for patient self-reporting of pain (Breivik et al., 2008). NRS is collected as part of ESAS at 0, 12, 24, 36, and 48 hours. Exact recording time is registered. NRS is also recorded before and after any bolus dose administration. A change of NRS of 2 or more after a bolus dose is considered as clinically significant change. A mean NRS score difference of 1-2 is typically considered clinically significant when treatment arms are compared.

4.1.2 ESAS - Edmonton Symptom Assessment System

A questionnaire used to rate the intensity of nine common symptoms experienced by cancer patients, including pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being and shortness of breath on an 11-point numeric rating scale mimicking the NRS scale (Bruera et al., 1991).

4.1.3 EORTC QLQ-C30 - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

Health-related QOL will be assessed using the cancer-specific EORTC QLQ-C30 (Aaronson et al., 1993), which contains 30 items across 5 functional scales, 9 symptom scales and a global health

status/QOL scale (Table 3). Items 1-28 have 4 response levels (not at all, a little, quite a bit, and very much) and items 29 and 30 are scored on a 7-point numeric rating scale. A summary score of EORTC QLQ-C30 will be calculated from the mean of the 15 EORTC QLQ-C30 subscales.

Descriptive statistics of observed values for the subscale scores of EORTC QLQ-C30 will be presented by treatment group.

Table 3 Definition of Subscale Scores of EORTC QLQ-C30

Subscale	Number of questions	Question range	Individual Items
Physical functioning	5	3	1-5
Role functioning	2	3	6-7
Emotional functioning	2	3	21-24
Cognitive functioning	4	3	20, 25
Social functioning	2	3	26-27
Fatigue	3	3	10, 12, 18
Nausea and vomiting	2	3	14-15
Pain	2	3	9, 19
Dyspnea	1	3	8
Insomnia	1	3	11
Appetite loss	1	3	13
Constipation	1	3	16
Diarrhea	1	3	17
Financial difficulties	1	3	28
Quality of life	2	6	29-30

Abbreviations: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
Every dimension (column 1) has a specific number of items assigned that are used to obtain the score. For instance, for Global health status (QL2) dimension, there are two items (number 29 and 30) used to obtain the score. The raw score for each dimension is calculated by averaging all the items assigned to the specific dimension.

4.1.4 Opioid side effect score

A questionnaire used to rate the intensity of 10 common symptoms experienced when on opioid treatment, including nausea, vomiting, constipation, drowsiness, disorientation, hallucinations, and spasticity on an 11-point numeric rating scale mimicking the NRS scale will be used (Fallon et al., 2022)

4.1.5 Global impression of change

The Patient Global Impression of Change (PGI-C) is a single item designed to capture the subject's perception of change in overall symptom severity from randomization until the time of completion

(Guy, 1976). Change in severity is captured using a 7-point scale: 1-Very much improved, 2-Much improved, 3-Minimally improved, 4-No change, 5-Minimally worse, 6-Much worse, 7-Very much worse. The number and percentage of patients with each PGI-C score will be summarized by treatment group for the ITT population.

4.2 Primary Outcome Definition

a) The time (hours and minutes) from start of continuous infusion until the last dose adjustment within the 48-hour period.

4.3 Secondary Outcomes Definitions

b) The share of patients not reaching adequate pain relief within 48 hours.
c) Comparison of pain score every 12 hours during the 48 hour period.
d) Number of bolus doses the first 24- and 48 hours (assessed every 12 hours.)
e) Time from bolus administration of morphine to clinically significant pain relief (reduction of 2 on NRS 0-10)

Pharmacokinetic study

f) Difference in the key pharmacokinetic parameters T_{max}, C_{max}, and AUC_{0-60} after SC and IV administration of morphine bolus doses in steady state* morphine infusion in palliative cancer patients. (*>24 hours after start of infusion and >2 hours since last bolus dose.)

Analysis Methods

4.4 Methods for Primary Outcome

The time (hours and minutes) from start of continuous infusion until the last dose adjustment within the 48-hour period. (Outcome a)

As primary analysis, an independent samples t-test will be used for comparison of primary outcome between SC and IV groups. Since the outcome is censored at 48 hours, the same comparison will also be performed by a tobit regression model. In the case of violation of model assumptions, a suitable transformation of data or a non-parametric alternative will be considered for sensitivity analysis.

4.4.1 Assumption Checks and Alternative Analyses

Primary outcome will be assessed for normality within the two treatment arms. Levene's test for equal variances will be performed. Standard residual diagnostics (normality, homoscedasticity) after *tobit* regression model will be performed. In the case of serious deviations, either non-parametric tests will be considered or transformation of the outcome, or both.

4.4.2 Missing Data

Patients will be excluded from analyses of primary outcome if data on the outcome variable is missing.

4.4.3 Sensitivity Analyses

None.

4.4.4 Subgroup Analyses

None planned for primary outcome.

4.5 Methods for Dichotomous Secondary Outcomes

The share of patients not reaching adequate pain relief within 48 hours (Outcome b)

This outcome is assessed by whether physician and patient conclude that further adjustments in pain medication are required after 48 hours. Physicians may for convenience reasons during follow-up period convert from SC to IV for patients who have a long-term venous catheter. This will not be seen as an adjustment unless the intention is to improve pain treatment or infusion rate and/or bolus dose also is changed.

4.5.1 Descriptive Statistics

Categorical data will be presented by numbers and percentages.

4.5.2 Primary Inferential Analysis

Z-test for proportions will be applied to compare the secondary outcome (b) between the groups.

4.5.3 Effect Estimates

Difference in proportions will be presented together with the corresponding 95% CIs.

4.5.4 Assumption Checks and Alternative Analyses

Including 30 participants in each arm implies large enough groups to assume approximately normal distribution of z-statistics.

4.5.5 Missing Data

The patients who are considered not to have achieved pain control at the end of 48-hour double blind treatment will be excluded from PP analyses but included in ITT analyses.

4.5.6 Sensitivity Analyses

None.

4.5.7 Subgroup Analyses

None.

4.6 Methods for Continuous Secondary Outcomes

4.6.1.1 The pain score recorded every 12 hours during the 48 hours period. (Outcome c)

Linear mixed model with random effects for patients and slopes will be estimated to assess the difference between the groups in overall trend in pain score. The model will include fixed effects for (possibly non-linear polynomial for) time, group dummy and the interaction between the two. Post hoc analyses will be performed to assess between-group differences at each time point as well as within-group changes.

4.6.1.2 Number of bolus doses the first 24- and 48 hours (Outcome d)

Number of bolus doses after the first 24- and 48 hours will be compared between the treatment arms by an independent samples t-test. In addition, linear mixed model with the same random and fixed effects as for outcome c will be estimated to assess a difference between the groups in overall trend in number of boluses. Post hoc analyses will be performed to assess between-group differences at each time point as well as within-group changes.

Bolus doses will be categorized and summarized as

- Total number of bolus doses.
- Bolus dose without effect (change in NRS less than 2) but without need of further titration.
- Bolus doses without effect (change in NRS less than 2) and the need for further titration (repeated bolus dose within one hour).

4.6.1.3 Difference in the key pharmacokinetic parameters T_{max}, C_{max}, and AUC_{0-60} after SC and IV administration of morphine bolus doses in steady state morphine infusion in palliative cancer patients (Outcome f)

Pharmacokinetic parameters will be assessed by drawing IV blood samples for assessment of morphine serum concentrations from a peripheral venous catheter at 0 (baseline), 2, 5, 7, 10, 12, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, and 120 minutes after a bolus dose when the patient is assumed to be in a pharmacological steady state*. *(*>24 hours after start of infusion and >2 hours since last bolus dose) .*
Detailed sampling procedure is described *in SIM-Study Procedure Manual version 1.3, 07.07.22*.
The actual time of pharmacokinetic sampling will be used for the determination of all pharmacokinetic parameters. Concentration values will be considered as missing if they cannot be measured due to analytical or clinical issues. AUC_{0-60} values will not be determined if fewer than three consecutive concentration values are obtained.

In summary statistics and figures plasma concentrations, C_{max} and area under the curve (AUC) will, if fitted, be adjusted to a normalized 5 mg morphine bolus dose (actual dose in the study: 2.5–20 mg). Morphine concentration at t=0 during steady state before bolus dose will be standardized.

The main absorption and disposition parameters will be calculated for individual concentration time profiles using, if fitted, a noncompartmental model. An independent samples t-test will be used for comparison of C_{max} and AUC_{0-60} between SC and IV groups. T_{max} will be compared using Wilcoxon rank-sum test.

Linear mixed model with random effects for patients and slopes will be estimated to assess the difference between the groups. The model will include fixed effects for time, dose, age, sex, and weight. Post hoc analyses will be performed to assess between-group differences at each time point as well as within-group changes.

T_{max}: The mean (and median) morphine T_{max} for each mode of administration will be calculated as the average of the protocol-specified time points at which the plasma morphine is highest in each patient. T_{max} will be reported in the unit of minutes.

C_{max} : Maximum observed concentration, to be reported in the unit of nmol/l (morphine). The geometric mean for each mode of administration will be calculated.

AUC_{0-60}: Area under the curve from the time of dosing to 60 minutes will be calculated using a log-linear trapezoidal method. The geometric mean for each group will be reported in the unit of nmol/l/hr.

4.6.2 Descriptive Statistics

Continuous data will be summarized by means, standard deviations (SDs), and min-max values if data are symmetrically distributed, and median, min-max values and quartiles for skewed data

4.6.3 Primary Inferential Analysis

Independent samples t-test for outcomes d) and f). In addition, linear mixed model for outcome c) and f).

4.6.4 Effect Estimates

Mean differences between the groups at each time point with the corresponding 95% CIs.

4.6.5 Assumption Checks and Alternative Analyses

Assumptions for independent sample t-test (normality and homoscedasticity) and linear mixed models (homoscedasticity and normality of residuals) will be assessed by standard methods.

4.6.6 Missing Data

All patients with at least one measurement will be included in the analysis of secondary outcomes (b, c, and d), as the linear mixed model includes all available information, also from dropouts.

4.6.7 Sensitivity Analyses

If larger deviations from the assumptions of linear mixed model will be identified, transformation of outcome variable or model with robust errors, or both, will be considered.

4.6.8 Subgroup Analyses

None planned.

4.7 Methods for Time to Event Secondary Outcomes

4.7.1.1 Time from bolus administration of morphine to clinically significant pain relief (Reduction of 2 on NRS0-10) (Outcome e)

Time (minutes) from administration of a bolus dose until effect is registered for each bolus dose.

All bolus doses with a minimum of one hour since last bolus dose will be included in the statistical analysis. If a patient is asleep after bolus dose this will count as effect of bolus, but will not be quantified with change in NRS.

Total number of bolus doses and subgroups of bolus doses without effect are summarized as dichotomous variables as part of outcome b) and described in 4.*5 Methods for Dichotomous Secondary Outcomes*

4.7.2 Descriptive Statistics

Outcome within treatment groups will be presented by medians and 95% CIs. Robust standard errors will be used to account for possible within-patient correlations due to recurrent events (multiple achieved effects in the observation time).

4.7.3 Primary Inferential Analysis

Outcome between the groups will be compared by Cox proportional hazards model with robust standard errors to account for correlated within-patient data due to recurrent events.

4.7.4 Effect Estimates

Hazard ratio with corresponding 95% CI will be presented.

4.7.5 Assumption Checks and Alternative Analyses

Proportional hazards assumption will be assessed by global test and by examining Shoenfeld's residuals. If this assumption is not met, a model with time-dependent treatment arm variable will be considered.

4.7.6 Missing Data

Each patient is supposed to contribute data on all bolus use. If any patients do only contribute data on one or two episodes these episodes will still be included in the analyses, as linear mixed model handles missing data by including all available information from all patients.

4.7.7 Sensitivity Analyses

As outcome comprises correlated survival data due to possible recurrent events, frailty model will be estimated to compare the outcome between the treatment arms.

4.7.8 Subgroup Analyses

None planned.

4.8 Additional Analyses

Any further future analyses not specified in the analysis protocol will be exploratory in nature and will be documented in a separate statistical analysis plan.

4.9 Sample size

The estimation of sample size is performed for primary outcome, time from start of continuous infusion until the last dose adjustment within the 48-hour period, and is based on the following assumptions: normal distribution within each treatment arm, difference in time from start of infusion to final dose adjustment between the IV and SC treatment arm of minimum 12 hours (assumed clinically significant), and SD of 12 hours in each arm. To show that the difference between the groups is statistically significant at the significance level of 5% with 90% power, using a two-sided independent samples t-test, the minimum number of patients is estimated to be 23 in each arm, total 46. Expecting a 25% dropout rate, 30 subjects need to be included in each group.

5 Safety Analyses

The number (and percentage) of patients experiencing each AE/SAE will be presented for each treatment group categorized by severity. For each patient, only the maximum severity experienced of each type of AE will be displayed. The number (and percentage) of occurrences of each AE/SAE will also be presented for each treatment arm.
The Data Monitoring and Safety Committee (DMSC) will be informed of serious adverse events. The committee will if necessary, make decisions about terminating the trial before completed inclusion.

Study-specific safety measurement during intervention period:
Repeated measurement of saturation (every 12 hours), sedation level and respiration frequency (every 2 hour and after each bolus dose) will be assessed by linear mixed models mirroring the approach used for the analysis of secondary outcome c).

Opioid side effects score, mean (SD) at 24 and 48 hours will be presented for each treatment group and compared by an independent samples t-test

5.1 Adverse Events

In the study population declining function, development of cachexia, increasing symptoms, worsening of laboratory results (including blood cells, inflammatory markers, measures of organ function, electrolytes), re-hospitalization, and even death are expected in the course of the disease. Such events will be recorded by the investigator as disease-related events. Such disease-related events will not be classified and handled as AE/SAE even if the event meets the definition of an SAE. If events are of greater intensity, frequency or duration than expected for the individual patient, the investigator considers there is a reasonable possibility that the event is related to the intervention, the event will be recorded as an AE/SAE.

The intensity of the adverse event will be classified as Mild / Moderate / Severe according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE).

The number (and percentage) of subjects with any AE leading to study drug withdrawal will be summarized by treatment group. The number of events and number (and percentage) of subjects with adverse events by system organ class (SOC) and preferred term (PT) will be summarized by treatment group, overall, for severe AEs and for AEs leading to study discontinuation. In addition, a summary table of AEs reported by >= 20% of all patients will be presented by SOC and PT. A detailed patient narrative will be given for any serious adverse event in the clinical study report in addition to listing. Sub-tabulations by diagnosis will also be presented.

5.2 Clinical Laboratory Parameters

Safety clinical laboratory parameters are collected and assessed but only used to identify exclusion criteria or adverse events. Clinical laboratory parameters will be summarized by treatment group and time point.

5.3 Vital Signs

Changes in vital signs (including systolic and diastolic blood pressure [mmHg], heart rate [beats per minute], will be summarized by treatment group and time point. No formal statistics is planned. Respiration frequency and saturation will be analysed as described in 5.0 Safety Analyses

6 Statistical Software

All statistical analyses will be done in Stata v17.0 or later (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX, USA). For estimation of pharmacokinetic parameters standard software for pharmacokinetic modelling such as the Phoenix WinNonlin software v.8.3 or later or package for noncompartmental analysis in R Statistical Software v4.1.2 or later may be applied as a supplement.

7 References

7.1 Literature References

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7.2 Reference to Data Handling Plan

SIM-Study Procedures Manual version 1.3, 07.07.22

7.3 Reference to the Trial Master File and Statistical Documentation

Protocol version 1.1.1 18.11.22

7.4 Reference to other Standard Operating Procedures or Documents