Statistical analysis plan (SAP) for the OMAMA study: a multicenter, open-label, non-inferiority trial comparing magnesium hydroxide with macrogol/electrolytes for prevention of opioid-induced constipation in patients with advanced cancer

Version of this SAP: 1.0; 6-NOV-2026

Full title of the study: *OMAMA-study - prevention of opioid-induced constipation in patients with advanced cancer*
Short title of the study/acronym (optional): *OMAMA-study*
ABR number: *80508*
Research protocol: ID/number: NL.08440012010002 Protocol version: 22 dd 07-SEP-2026
Trial registration number: ClinicalTrials.gov: NCT05216328 NTR: NTR80508

Content

Section 1. Administrative information. 3
Section 2. Introduction. 5
Section 3. Study Methods. 6
Section 4. Statistical Principles. 8
Section 5. Study populations. 10
Section 6. Analysis. 12
Section 7. References. 16
Section 8. Appendix. 17

Section 1. Administrative information.

1.1. Names and Signatures

Role of contributor	Name and full affiliation	Signature	Date of signature
Principal investigator	Prof.dr. M.A.H. Steegers, department of Anesthesiology, Amsterdam UMC		
Researcher who will perform the statistical analysis	K.R.J. Kistemaker, departments of Anesthesiology and Medical Oncology, Amsterdam UMC		
Senior statistician consulted	P.M. van de Ven, department of Data Science and Biostatistics,Julius Center, UMC Utrecht		
Contributor to statistical analysis plan	K.R.J. Kistemaker, departments of Anesthesiology and Medical Oncology, Amsterdam UMC		

1.2. Revision history

Updated statistical analysis plan version	Protocol version	Section number(s) changed	Description of and reason for changes	Date of approval

1.3. How is the trial registered?

This study is registered in the WHO-approved OMON (Overview of Medical Research in the Netherlands) under reference NTR80508 and on clinicaltrials.gov under reference NCT05216328.

*URL: *Prevention of opioid-induced constipation in patients with advanced cancer* | Research with human participants*

URL: Study Details | NCT05216328 | Prevention of Opioid-induced Constipation in Patients With Advanced Cancer | ClinicalTrials.gov

1.4. What is the planned period of observation?

The date of the inclusion of the first patient is 02-DEC-2022.
The expected date of the completion of follow-up for the last patient is 01-FEB-2027.

Section 2. Introduction.

2.1. What is the background and rationale for the study?

More than 70% of patients with metastatic cancer have pain that often requires treatment with opioids (morphine-like agents) (Teunissen 2007). Constipation occurs in 59% of patients treated with opioids (Davies 2021). Opioid-induced constipation (OIC) has a significant negative effect on the quality of life of patients, due to physical problems, psychological problems and social consequences (Bell 2009, Christensen 2017, Davies 2021, Dhingra 2013, Penning-van Beest 2010). It has consequences that range from daily discomfort with social insecurity and disability to intestinal obstruction. It leads to limitations in self-management, a reduced quality of life and a risk of need for more care, including hospital admission. Standard laxatives are recommended to prevent OIC, although there is little evidence to support this (Farmer 2019).
Macrogol/electrolytes has only been studied in patients with symptomatic OIC. Another standard laxative is magnesium hydroxide, which is registered as an antipeptic drug, but also used as a laxative (but not registered for this indication). In the past and in previous studies magnesium oxide was used. As magnesium oxide is transformed in the stomach tot magnesium hydroxide, these drugs are considered to be the same. Presently, only magnesium hydroxide is prescribed in The Netherlands. There have been no studies on magnesium (hydr)oxide in symptomatic OIC. There has been only one randomized study about prevention of OIC by a magnesium compound (Ozaki 2022). This recent study compared magnesium oxide with naldemedine (a peripheral μ-receptor antagonist) in preventing OIC. It showed that naldemedine resulted in significantly better constipation-related quality of life, measured with two different questionnaires, better stool consistency and less constipation based on Rome IV criteria, both after two weeks and three months of treatment.

Thus, macrogol/electrolytes has been studied in symptomatic OIC and has been registered for this indication. However, it has not been proven to be effective for prevention of OIC and is not explicitly registered for this indication. It is sometimes perceived by patients as unpleasant due to its taste. For magnesium oxide one RCT is available, where its efficacy was less than naldemedine. Although it is also recommended by the guideline, it has not been registered for the treatment or prevention of constipation. To support the advice of the guideline and to prove that a choice is possible, it is important to demonstrate that magnesium hydroxide is not inferior to macrogol/electrolytes and to compare its side-effects and tolerability.

2.2. What are the objectives of the study?

The primary objective is to show non-inferiority of magnesium hydroxide to macrogol/electrolytes in the prevention of OIC in patients with advanced cancer, starting with opioids for pain, based on the percentage of patients without constipation (BFI-score <30 after 14 days of treatment).

Secondary objectives are to compare magnesium hydroxide with macrogol/electrolytes with regard to the change of the BFI score between day 0 and day 14, BFI score on day 14, change of the percentage of patients without constipation based on the Rome IV criteria between day 0 and day 14, percentage of patients without constipation based on the Rome IV criteria on day 14, quality of life (as measured with EQ5D) on day 14, change in total score of EQ5D between day 0 and day 14, side effects and patient satisfaction with laxative, difference in pain score between day 0 and day 14 and total score on day 14 and cost-effectiveness. Lastly, a secondary objective is to predict non-responders by sex, age, BMI, site of cancer, metastases (yes/no), morphine equivalent dose and use of constipation-inducing medication (yes/no). For details see page 12 of the protocol.

Section 3. Study Methods.

3.1. What is the study design?

This study is a randomized, open label clinical trial with two parallel treatment groups. The study has two arms, these are "magnesium hydroxide" and "macrogol/electrolytes". Both medications are administered orally. For details see page 12-13 of the protocol.

3.2. Will randomization be performed in this study?

A total of 258 patients will be randomized in the ratio 1:1 to treatment with magnesium hydroxide or treatment with macrogol/electrolytes stratified for center (16 centers) and BFI at baseline (2 strata: BFI<30 and BFI ≥30). The randomization will be 1:1 using computerized block randomization with varying block sizes of 2 and 4 in random order in Castor EDC. Since magnesium hydroxide is administered in a tablet and macrogol/electrolytes is administered in a sachet and placebos are not used, it is an open label study.

3.3. How was the sample size calculated?

The null hypothesis tested in this study is "Magnesium hydroxide is inferior to macrogol/electrolytes in the prevention of OIC". We calculated a sample size of 103 evaluable patients per arm, required to test whether this hypothesis can be rejected or not, based on the following: power set at 80%, to reduce to the possibility of a "false negative" result which is preferable in non-inferiority designs (Head 2012) and one-sided alpha set at 2.5% because of the one-sided testing in the noninferiority design (Head 2012). There is limited evidence on the effect of macrogol/electrolytes in our study population, as was also concluded in the current guidelines (https://www.pallialine.nl/pijn-bijpatienten-met-kanker). Two non-randomised studies (Ishihara 2012, Tokoro 2019) show that approximately 40% of patients, starting with opioids and not using laxatives, will not develop constipation after 14 days. Prophylaxis with laxatives can only be effective in (part of) the remaining 60%. Treatment with macrogol/elektrolytes is effective in 70% of patients with symptomatic constipation (Lyseng-Williamsen 2018, Taylor 2010). Based on these data, we estimated a response rate (percentage of patients without constipation) of macrogol/electrolytes in our study population of 82% (40% + 42% (70% of 60%)). The non-inferiority margin is set at 15%, based on a combination of statistical reasoning and clinical judgement, as advised by the EMA guidelines (https://www.ema.europa.eu/en/documents/scientific-guideline/guidelinechoice-non-inferioritymargin_en.pdf). The main considerations are that the margin should clearly be higher than the estimated 40% of patients without opioid induced constipation and the clinical judgement that more than 15% difference could not be translated in a conclusion that magnesium hydroxide is non inferior to macrogol/electrolytes. We will increase the inclusion with ~20% to anticipate potential loss to follow-up, to N=129 per arm.

3.4. What is the hypothesis testing framework for this study?

The OMAMA trial aims to show that magnesium hydroxide is non-inferior to macrogol/electrolytes for prevention of OIC. Hence, the primary outcome has a non-inferiority hypothesis testing framework using the non-inferiority margins specified in the sample size calculations. No formal testing will be performed for secondary outcomes.

3.5. Will interim analyses be performed in this study?
No interim analyses will be performed.
3.6. When will the final statistical analysis of the study data be performed?
The statistical analysis of the primary outcome (proportion of responders) and all secondary outcomes measured will be performed after the end of the study period of the last patient and after data cleaning for these outcomes has been completed. It is expected that this will occur within three months of the inclusion of the final patient in the study. As the current estimate is that the final patient will be included in the study in January 2027, we expect that the statistical analyses of these outcomes will be performed in February 2027.
3.7. At which time points are the outcomes measured and which "windows" are allowed?
Baseline measurements are made and patients are randomized on day 0. All primary and secondary outcomes are measured on day 0 and day 14. The measurements have a permitted window from day 13-15. Patients are included on Monday till Friday, so generally day 14 will fall within this window. In the event that Day 14 coincides with a national holiday, the measurement will be conducted on the preceding or following day.

Section 4. Statistical Principles.

4.1. Which level or levels of statistical significance will be used in the study?

The primary outcome is the proportion of responders, where a responder is defined as a patient with BFI<30 on day 14. The primary analysis will use the Newcombe-Wilson score method to estimate a one-sided 97.5% confidence interval for difference in the proportion of responders (proportion responders under magnesium hydroxide minus proportion responder under macrogol/electrolytes). We will reject the null hypothesis (H0: Magnesium hydroxide is inferior to macrogol/electrolytes in the prevention of OIC) and claim non-inferiority for magnesium hydroxide if the lower boundary of the 97.5% confidence interval is larger than the prespecified non-inferiority margin of -15%. This non-inferiority margin was based on a combination of statistical reasoning and clinical judgement, as advised by the EMA guidelines.

No formal testing will be performed for secondary endpoints. For these we will present effect sizes (absolute differences in proportions for dichotomous endpoints and absolute differences in means for continuous outcomes). For effect sizes on secondary endpoints, we will also calculate their two-sided 95% confidence intervals.

4.2. Will the analysis adjust for multiplicity of statistical testing to ensure control of type I error rate?

There is only a single primary outcome. No multiplicity adjustment for statistical testing will be performed. All secondary endpoints will be considered exploratory, and for these no only nominal 95% confidence intervals will be presented.

4.3. Which confidence intervals will be reported?

In this non-inferiority study, we will present a one-sided 97.5% confidence interval for difference in proportion of responders (proportion of responders in the magnesium hydroxide minus the proportion of responders in the macrogol/electrolytes group). For secondary outcomes nominal two-sided 95% confidence intervals will be provided.

4.4. How is compliance defined and assessed?

Adherence is defined as the proportion of prescribed medication actually taken by each patient. The patients will keep a diary of their intake of the medication.
We define non-adherence if <80% of the prescribed medication is taken.

4.5. How will compliance be presented?

Adherence will be reported as the median and interquartile range of the proportion of prescribed medication actually taken by each patient for each arm of the study. In addition, the proportion of the participants that are non-adherent (<80% of prescribed intake) will be reported.

4.6. What are defined as protocol deviations in this study?
Protocol deviations are defined as any of the following: non-adherence to the eligibility criteria; use of rescue medication not in accordance with the study protocol; crossover to the alternative study drug.
4.7. How will protocol deviations be presented in the reporting of this study?
All protocol deviations will be line-listed according to treatment group. In addition, the number and percentage of patients in each treatment group experiencing one or more protocol deviations will be presented.
4.8. Which analysis populations will be defined?
Separate analyses for non-inferiority will be performed in subgroup of participants who adhered to their randomization assignment without protocol deviation (per protocol analysis), as well as the total population randomized (intention-to-treat analysis).

Section 5. Study populations.

5.1. Which data were collected from participants, who were screened for eligibility for inclusion in the study, and how will these data be presented in study reports?

Due to privacy concerns, no data are collected from patients who are screened for eligibility. However, the number of patients screened and the date on which they are screened will be recorded. We will present a flow diagram of the number of patients screened, the number of patients invited to participate and the number actually included in the study.

5.2. What are the inclusion and exclusion criteria for the study?

Patients of 18 years or older with advanced cancer who start with slow-release or transdermal opioids for pain and are able to complete a Dutch questionnaire are eligible for inclusion. Patients with cancer are considered advanced if they developed pain due to their cancer or due to their cancer treatment and that required treatment with around-the-clock opioids. Patients will be excluded if they: have contra-indications for laxatives, maintenance treatment with laxatives during the last two weeks, severely impaired renal function, an estimated life expectancy <1 month or diarrhea at the start of the study. Detailed inclusion and exclusion criteria are presented on pages 13 and 14 of the protocol.

5.3. Which information will be presented in the flow chart for this study?

The mock-up of the CONSORT flow diagram is presented in the appendix to this statistical analysis plan.

5.4. What is the expected level of, timing of and reasons for withdrawal from the intervention and/or from follow-up and how will this be presented in the study reports?

We expect that 20% of all patients will drop out of the study before assessment of the primary outcome is complete. We will report the number and percentage of patients in each study arm who: stop taking the allocated medication before the end of the treatment; or drop out before assessment of the primary outcome. We will also report the line listings of the reasons for withdrawal or loss to follow-up as defined in the EDC: patient refusal, adverse events, discontinuation of pain medication, hospital admission, death, or other.

5.5. Which baseline characteristics of participants will be presented?

** Age in completed years at randomization*
** Sex*
** WHO performance status*
** received systemic therapy or radiotherapy during study period*
** Location of primary tumor (lung, gastro-intestinal, urogenital, gynaecological, breast, head and neck, skin, brain, other*
** Metastases (yes/no)*
** Location of metastases (bone, liver, lymph nodes, brain, other)*

** Other comorbidities (cardiovascular disease, pulmonary disease, stroke/TIA, auto-immune, psychiatric disease, other, none*
** Height in cm*
** Weight in kg*
** Body mass index in kg/m^2*
** Prescribed long-acting opioid (oxycodone, fentanyl, morphine, buprenorphine, tramadol, other)*
** Prescribed short-acting opioid (oxycodone IR, morphine IR, fentanyl IR, hydromorfon, other, none*
** Starting dose of long-acting opioïd*
** Change of opioid dose between day 0 and day 14*
A mock-up of the baseline characteristics table is presented in the appendix to this statistical analysis plan.

5.6. How will the baseline characteristics be summarized?

Categorical baseline characteristics will be summarized by presenting the number and percentage in each category. Continuous, normally distributed variables will be summarized by presenting the mean and standard deviation. Continuous, non-normally distributed variables will be summarized by presenting the median and interquartile range (25th percentile, 75th percentile). As this is a randomized clinical trial, we will not statistically test for differences between treatment groups on baseline characteristics.

Section 6. Analysis.

6.1. How are the outcomes of this study defined?

The primary endpoint is the percentage of responders (no constipation), defined as the percentage of patients with a score of <30 of the Bowel Function Index, measured on day 14.

Secondary endpoints are:
- *Change of the Bowel Function Index Score between day 0 and day 14;*
- *Bowel Function Index score on day 14*
- *Change in total score of the EQ5D between day 0 and day 14*
- *Change in percentage of patients without constipation, based on the Rome IV criteria for opioid-induced constipation on day 14*
- *Percentage of patients without constipation, based on the Rome IV criteria for opioid-induced constipation on day 14;*
- *Change in cancer pain score between day 0 and day 14 and total score on day 14;*
- *Patient satisfaction with laxative;*
- *Side effects of laxatives;*
- *Cost-effectiveness of macrogol/electrolytes compared to magnesium hydroxide.*
- *Prediction of the response to macrogol/electrolytes and magnesium hydroxide in patients starting with opioids.*

6.2. Will any calculations or transformations be used to derive any outcome from the original data?

The following calculations will be performed:

BFI score	*Sum score subitems BFI : 3*
Change of the Bowel Function Index Score between day 0 and day 14	*BFI score day 14 - BFI score day 4*
Change in total score of EQ5D	*Total score EQ5D day 14 - Total score EQ5D day 0*
Change in pain score	*Pain score day 14 - pain score day 0*
Patient without constipation, based on Rome IV criteria	*Total score <2 for Rome IV criteria*
Starting dose of opioids	*All opioid doses will be converted into a morphine equivalent dose using a conversion table [1]*
Change of opioid dose	*Morphine equivalent dose day 14 - morphine equivalent dose day 0*
BMI	*Weight : ((height : 100)^2)*

[1] https://palliaweb.nl/richtlijnen-palliatieve-zorg/richtlijn/pijn-bij-patienten-met-kanker

6.3. What analysis method will be used and how will the treatment effects be presented?

The primary analysis will use the Newcombe-Wilson score method to estimate a one-sided 97.5% confidence interval for difference in proportion of responders (proportion responders under magnesium hydroxide minus proportion responder under macrogol/electrolytes). Primary analysis will not be corrected for stratification factors. A sensitivity analysis for the primary endpoint will be performed where a two-sided 95% confidence interval for the difference in proportion responders corrected for stratification factor constipation at the start of the study based on the BFI (BFI <30 versus BFI ≥30) is calculated using a generalized linear model with a binary outcome and an identity link. A correction for center as stratification factor will not be performed, due to the large number of participating centers.

The analysis of the secondary outcomes will only be performed in the intention-to-treat and the per-protocol population. For secondary outcomes that are dichotomous variables, Newcombe-Wilson score method will be used to calculate a two-sided 95% confidence interval for difference in proportions between the arms. Continuous secondary outcomes will be analyzed using linear regression with an adjustment for constipation at start of the study. Categorical outcomes with more than two categories will be analysed using multinomial logistic regression.

For the cost-effectiveness analysis, we will compare the cost-effectiveness of macrogol/electrolyte and magnesium hydroxide in patients with advanced cancer starting with opioids for pain (258). The analyses will be performed from a healthcare perspective with a time horizon of two weeks. A decision tree will be developed including different branches for initial therapy and responders and non-responders. The costs and quality of life of the patients in the trial will be used as input for this decision tree. This requires data collection on healthcare procedures and quality of life in responders, non-responders and patients with side-effects of laxatives for the follow-up period of the study (2 weeks). These healthcare procedures will be extracted from the iMCQ questionnaire after 2 weeks. The iMCQ will be adjusted in such a way that resource use due to gastrointestinal complaints will only be measured in these patients with intensive healthcare resource use. All individual health care procedures will be linked to unit costs. Reimbursement prices issued by the Dutch Healthcare Authority (NZA) and national reference prices will be used for this assessment as outlined in current Dutch pharmaco-economic guidance. Quality of life will be measured using the EuroQol-5D-5L (EQ-5D-5L) at baseline and after 2 weeks. Missing data of the questionnaire will by imputed using multiple imputation. A scenario will be added to the analysis for the use of naloxegol and naldemedine as firstline treatment. Naloxegol and naldemedine are peripheral μ-receptor antagonists that have shown to be effective for the treatment of OIC (Rekatsine 2021). As no effect data of first-line treatment will be measured during the trial, this scenario analysis will be an early health-economic analysis. In this scenario analysis we will use effect data based on literature and expert opinion and will perform a threshold analyses to estimate the effect size needed to result in a cost-effective intervention. Bootstrapping will be performed to assess the uncertainty of costs and utility loss of (sub)groups, while deterministic (one-way) and probabilistic sensitivity analyses will be performed to assess the uncertainty of the analyses in the decision tree.

6.4. Will any assumptions for statistical methods be checked?

Normality of continuous baseline and outcome variables and residuals from linear regression analyses will be assessed by visual inspection of q-q plots. Kay Kistemaker will make the decision in consultation with Peter van de Ven. Continuous baseline variables judged to follow a non-normal distribution will additionally be summarized using medians and interquartile ranges.

6.5. Will sensitivity analyses be performed?

The primary analysis will be performed in both the ITT and PP population. In case of missing outcome data, sensitivity analyses as specified in section 6.7 will be performed to assess

robustness of conclusions. A supplementary analysis is planned targeting the effect under the hypothetical scenario that all participants would adhere to the treatment (see section 6.8).

6.6. Will subgroup analyses be performed?

Subgroup analyses will be performed to explore whether treatment response differs across clinically relevant patient groups. Prespecified subgroups include BFI on baseline (BFI<30 and BFI ≥30), sex (male/female), age (<65/≥65 years), type of opioid (oral vs. transdermal), and the presence of a gastrointestinal malignancy or ovarian malignancy (yes/no). In addition, we will explore predictors of response to either laxative in patients starting opioids using clinical variables measured at baseline, including sex (male/female), age, gastrointestinal malignancy or ovarian malignancy (yes/no), metastases (yes/no), morphine equivalent dose, opioid type and use of constipation-inducing medication (yes/no). Effect sizes will be calculated per subgroup with 95% confidence intervals and visualized in a forest plot. Subgroup analysis will be considered exploratory and no tests for interaction will be performed.

6.7. How will missing data be reported in the study reports and handled in the statistical analysis?

With regards to missing data, we do not plan imputation for the main outcome. If unexpectedly outcomes are missing, we will perform the primary analysis in the group for which the outcome is available. In sensitivity analyses, we will considering the most extremes scenarios: what if all participants with outcome missing in one arm experienced constipation and all participants with outcome missing in the other arm did not experience constipation. Multiple imputation may be considered if important confounders are missing or if missingness on the main outcome is higher than currently anticipated.

6.8. Will additional analyses on the primary or secondary outcomes be performed?

A supplementary analysis for the primary (responder) endpoint will be performed to estimate the treatment effect under the hypothetical scenario that all patients would fully adhere to the protocol. Inverse probability weighing (IPW) will be used to account for differences in adherence between the treatment arms. Logistic regression analysis will first be performed in the intention-to-treat population to estimate the probability of a subject being adherent (≥80% of prescribed intake) conditional on assigned treatment arm and the following covariates: age and WHO performance status. The estimated probabilities will then be used to calculate stabilized weights which will be used in a weighted generalized linear model analyses to calculate the risk difference and odds ratio between the treatments arms with confidence interval based on robust sandwich standard errors. These will be contrasted to effect sizes obtained from the unweighted logistic regression model in the intention-to-treat and per-protocol population.

Predictors of non-response will be assessed exploratively in logistic regression analyses. For candidate predictors of non-response we will perform separate logistic regression analyses with non-response as outcome and the candidate predictor and treatment arm as independent variables. The odds ratios for the candidate predictors will be reported together with their 95% CI. The following candidate predictors will be considered: sex (male/female), age, gastrointestinal malignancy or ovarian malignancy (yes/no), metastases (yes/no), morphine equivalent dose, opioid type (oral versus transdermal) and use of constipation-inducing medication (yes/no). Age and BMI will be included as continuous predictors.

6.9. How will harms be reported?

Safety outcomes will be presented using line listings. Adverse events will be reported by patients through a questionnaire, and the percentage of patients reporting each adverse event will be presented. Safety outcomes will be classified by the local primary investigators as expected complications of treatment with magnesium hydroxide or macrogol/electrolytes, suspected unexpected serious adverse drug reactions (SUSARs), or other serious adverse events, such as ED visit, hospital admission or death due to the failure of laxative treatments.
For each treatment arm, tabulations will be provided showing the number and percentage of events and the number and percentage of patients experiencing one or more events within each safety category. No formal statistical testing will be performed.

6.10. Which statistical software will be used to carry out the statistical analyses?

All statistical analysis will be performed in R [1].

[1] R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/

Section 7. References.

7.1. What is the title, date and version number of the current data management plan?
The current data management plan has the title "DMP_OMAMA", version number 8, is dated 04-03-2024 and is stored in the trial master file.
7.2. What is the title, date and version number of the current data validation and derivation plan?
The current data validation and derivation plan has the title "Datavalidation and derivation plan_OMAMA v1 dd 25-07-2022", version number 1, is dated 25-07-2022 and is stored in the trial master file.
7.3. Where is the study master file stored?
The trial master file is stored at the location Z:\RESEARCH\Palliatieve Zorg\OMAMA
7.4. Where are the syntax files for data extraction, manipulation and preparation and statistical analysis stored?
The syntax files for data extraction, manipulation and preparation and statistical analysis are stored at the location Z:\RESEARCH\Palliatieve Zorg\OMAMA\ISF\O. Datamanagement.
7.5. Which standard operating procedures will be adhered to when using and analysing data from this study?
When using and analysing data from the ABCD randomized clinical trial, researchers will adhere to the Amsterdam UMC standard operating procedure RDM001 Research data management.
7.6. Which reporting guidelines will be adhered to when reporting on this study?
When reporting the results of this non-inferiority randomized clinical trial, the researchers will adhere to the SAMPL and CONSORT reporting guidelines. In addition, they will adhere to the CONSORT extension for non-inferiority and equivalence trials.

Section 8. Appendix.

Additional Tables, Figures and Documents.

Illustrative examples

Figure 1. The flow chart of patients enrolled in the OMAMA trial.

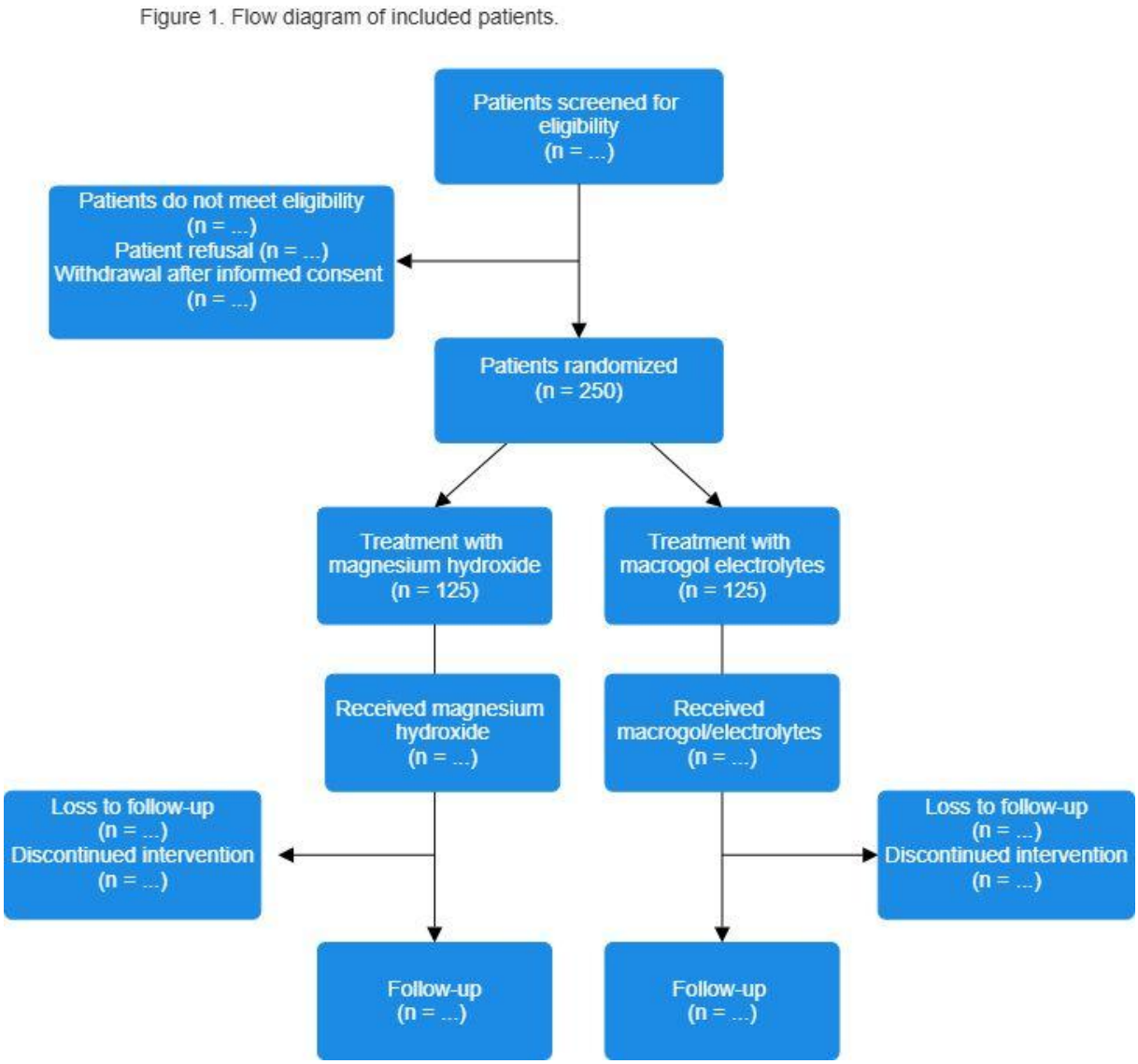


Table 1. The baseline characteristics of patients randomized in the OMAMA trial.

	Magnesium hydroxide (n = …)	Macrogol/electrolytes (n =…)
Age in years (mean ± SD)		
Sex (M:F)		
Weight in kg (mean ± SD)		
Length in cm (mean ± SD)		

BMI in kg/m^2 (mean ± SD)		
WHO performance status		
Location of primary tumor (n, %) - Lung - Gastro-intestinal - Urogenital - Gynaecological - Breast - Head and neck - Skin - Brain - Other		
Metastases (n, %) - Bone - Liver - Lymph nodes - Brain - Other		
Comorbidities - Cardiovascular disease - Pulmonary disease - Stroke/TIA - Auto-immune - Psychiatric disease - Other		
Treatment during study period (n, %) - I.v. chemotherapy - Oral chemotherapy - Immunotherapy - Radiotherapy		
Prescribed long acting opioid (n, %) - Oxycodone - Fentanyl - Morphine - Buprenorphine - Tramadol - Other		
Prescribed short-acting opioid (n, %) - oxycodone IR - Morphine IR - Fentanyl IR - Hydromorfon - Other - None		
Starting dose of long-acting opioid in morphine equivalents dose in mg (mean ± SD)		
Use of constipation-inducing comedication		
Pain score at start study		
BFI score at start study		