PEKANNUSS

Open-label, randomized, multicenter, phase IV trial comparing parenteral nutrition using Eurotubes® vs. traditional 2/3-chamber bags in subjects with metastatic or localized solid tumors requiring parenteral nutrition – The PEKANNUSS Trial

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I have read and checked the protocol diligently; I comply with the stated demands and requirements and agree to conduct the study according to the applicable guidelines of Good Clinical Practice (GCP) and the requirements of the responsible authorities in regard to reconciliation of original data and to audits/inspections.

I consent to the safety reporting obligations as indicated in the respective protocol section below.

_____ _____

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2 Relevant Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
ALT	Alanine transaminase
AST	Aspartate transaminase
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BMI	Body Mass Index
BSI	Bloodstream infections
CC	Cancer anorexia-cachexia
CLABSI	Central line-associated bloodstream infections
COM	Compounded bag
CRBSI	Catheter related bloodstream infection
CRP	C-reactive protein
CRI	Catheter Related Infection
CTC	Common toxicity criteria
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EOT	End of treatment
(e)CRF	(electronic) case report form
ESPEN	European Society of Parenteral and Enteral Nutrition
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamate-pyruvate transaminase
HPN	Home parenteral nutrition
HPN-PROQ	Home parenteral nutrition Patient-reported outcome Questionnaire
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IIT	Investigator-initiated trial
IRB	Institutional Review Board
ISF	Investigator site file
ITT	Intent-to-treat
IWRS	Interactive Web Response Systems
LDH	Lactate dehydrogenase
LKP	Leiter der Klinischen Prüfung/Lead Coordinating Investigator
MCB	Multi-chamber bags
mGPS	modified Glasgow Prognostic Score
MPG	Medizinproduktegesetz
NI	Nutritional intervention
NRS	Nutritional Risk Screening
OS	Overall survival
PN	Parenteral nutrition
PP	Per protocol
QoL	Quality of life
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SmPC	Summary of Product Characteristics
WHO	World Health Organization

To avoid misunderstandings, the following terms shall be clarified: In the context of this study, the term “standard PN” refers to the standard composition of the PN. The 2/3-chamber bags, that have been used in clinical routine for decades (industrially manufactured bags as well as pharmacy-compounded bags) will be referred to as “traditional” bags, that will be tested vs. Eurotubes®.

3 Background and rationale

3.1 The medical problem

Cancer is often characterized by extensive invasion, early metastases, and, in many cases, a rapidly occurring marked cachexia leading to a very limited prognosis especially in the metastatic situation.

Cachexia is a strong and independent predictor of mortality, poor therapeutic response, diminished functional capacity, and reduced quality of life (QoL). It is defined as the debilitating state of involuntary weight loss, often connected with anorexia, tissue wasting, malnutrition, and inability for natural nutrition intake. The combination of these symptoms, also characterized by systemic inflammation, is also named „cancer anorexia-cachexia syndrome" (CC) [Vanhoutte et al., 2016; Fearon et. al, 2011]. The most important phenotypic feature is muscle wasting and functional impairment as a result of increased protein degradation and reduced protein synthesis or both [Bossola et al., 2007]. The syndrome is life-threatening and debilitating for approximately 50% of all cancer subjects [Bossola et al., 2007].

As reported, the QoL is significantly impaired in CC subjects and there is evidence for increased morbidity and mortality of subjects with CC [Bossola et al., 2007]. Subjects suffering from CC commonly have derangements in basal metabolic rate as well as reduced appetite and food intake. Even moderate weight loss is associated with psychological stress and lower QoL. Furthermore, CC affects subject’s response to chemotherapy [Bossola et al., 2007].

Malnourished patients are more difficult to guide through chemotherapy experiencing more severe side effects resulting in progressive cachexia. The outcomes of subjects with CC receiving chemotherapy can be improved with nutritional intervention (NI) [Bauer and Capra, 2005]. Supplementation with parenteral nutrition (PN) improves the QoL in subjects with advanced CC. There is also data indicating that NI has a synergistic effect with anti-cancer

therapy and results in better clinical outcome [Ravasco et al., 2005a; Ravasco et al., 2005b; Bauer and Capra, 2005; Caccialanza R. et al., 2018].

The European Society of Parenteral and Enteral Nutrition (ESPEN) recommends PN only for malnourished subjects but does not reflect the situation in CC patients. Nevertheless, PN has become a standard of care in cancer patients who are not able to maintain their weight or who are at risk of suffering cachexia. PN is now widely accepted as an important component of cancer patients' treatment in the oncology community and is covered by the patients' insurances.

Despite recent advances in PN for cancer, several clinical problems are still unresolved:

1. Patients receiving PN are dependent on home nursing service, which represent a major limitation of their autonomy and quality of life.
2. Patients receiving PN are at high risk of developing blood stream infections.
3. The potential benefit of reduced glucose levels and in the consequence higher levels of fat is a long-lasting question that has not been evaluated yet.

3.2 Background and Rationale

Approximately 50% of all cancer subjects suffer from CC and its severe impact on QoL and response to chemotherapy [Bossola et al., 2007]. Especially in the advanced stages, it cannot be fully cured by increased food intake or oral supplements and requires supportive or total parenteral nutrition. If needed, patients can live on PN for an unlimited time, the mean administration period varies depending on the underlying disease and the patient's general condition. However, the change from oral food intake to PN is associated with many changes in the subject's everyday life that lead to restriction of autonomy and flexibility. CC patients are often unable to handle the connection and disconnection of the nutrition bags to their catheter correctly on their own, especially when supplements need to be added. Nursing services need to visit the subject daily to perform the PN administration. The infusion takes around 12 to 14 hours to finish and is typically administered in the evening to be infused overnight. The subjects' daily life is highly determined by the appointments of the nursing service, overnight stays away from home are nearly impossible and the dependency on outside assistance can diminish the patients' self-esteem and QoL. The extent to which these limitations to the subject's self-determination impact the QoL is currently poorly studied and needs further

investigation. Subsequently, it is of high interest to assess if the QoL shows to be higher in subjects performing the PN administration autonomously without nursing service assistance.

Furthermore, data has shown that PN is accompanied by an increased risk of blood stream infections (BSI) [Dissanaike et al., 2007] and is an independent risk factor for both catheter-related bloodstream infections (CRBSI) and central line-associated bloodstream infections (CLABSI) [Beghetto et al., 2005]. BSI represent 15% of all nosocomial infections and are associated with increased mortality and other serious medical conditions such as severe sepsis or septic shock [Pontes-Arruda et al., 2012]. In addition to the safety aspect, BSI lead to longer hospital stays and hence, additional costs [Turpin et al., 2011].

Although most PN related BSI are caused by the intravenous catheter, numerous manipulations on the infusion unit may multiply the hazard of extrinsic contaminations [Didier et al., 1998].

To reduce this well-known risk, the relevant phases of PN (production, adding of supplements, administration) are subject to highest standards of hygiene in order to minimize the contamination risk. Industrial PN is manufactured following the guidelines of Good Manufacturing Practice (GMP) and under clean room conditions which reduces the contamination hazard significantly. Data indicate advantages of industrially manufactured PN compared to pharmacy-compounded PN formulations in terms of safety, however the limited data do not allow a definite conclusion [Turpin et al., 2012].

Blood glucose levels and ketogenic diets are a contentious issue and subject of controversial discussion among oncologists. In the 1920s, Nobel laureate Otto Warburg observed that unlike healthy body cells, cancer cells strongly upregulate the glucose intake to produce energy preferably via glycolysis, instead of the much more efficient way of oxidative phosphorylation [Liberti and Locasane, 2016]. This phenomenon is known as the Warburg-Effect. Data prudently suggest that carbohydrate restriction and ketogenic diets possibly obstruct cancer growths [Klement and Kaemmerer, 2016], however, too few clinical data is available to come to a definite conclusion. Due to the low level of evidence, the ESPEN guidelines 2017 encourages further research on the effect of high fat diets on clinical outcome in patients with systemic inflammation and generally the effect of varying the fat [ESPEN guidelines, 2017, p. 21].

3.3 Parenteral nutrition

Parenteral nutrition is a sterile, liquid formula that is administered through an intravenous catheter directly into the bloodstream. It bypasses the normal digestion of the gastro-intestinal tract and may contain all necessary nutrients such as carbohydrate, protein, fat, electrolytes, (trace) minerals and vitamins. Various diseases and conditions that impair food intake or nutrient absorption may require the partial or complete substitution of oral or enteral nourishment. Patients who underwent acute surgery, suffer from short bowel syndrome or gastro-intestinal fistulas as well as critically ill patients including cancer patients at risk of CC may (temporarily) depend on PN. The specific composition needs to be customized to the individual needs of the patient depending on several factors as age, height, weight, nutritional requirements, underlying disease and the ability to intake enteral nutrition.

The most common product types used in parenteral nutrition are either industrially premixed multi-chamber (2/3-chamber) bags or pharmacy-compounded admixtures in a mono- or 2-chamber bags. The third, latest development are 7-, 8- or 9-chamber bags (Eurotubes®).

3.3.1 Traditional 2/3-chamber bags

Traditional 2/3-chamber bags are widely used in the PN landscape. Two or three separate compartments provide a combination of amino acids, lipids, glucose and electrolytes. Typically, most supplements cannot be added to the premixed 2/3-chamber bags due to stability reasons and incompatibilities. Also, the individual requirements vary significantly. To fully meet the patients' needs, additional substances and agents are injected via syringe into the infusion unit shortly before administration of the product. That causes extra steps within the preparation process and increases the risk of errors and contamination. In patients receiving PN at home, that final step is usually performed by the nursing service, a family member or the patient himself. It is critical to perform this procedure in an environment as sterile as possible to avoid contamination of the product.

The industrially premixed formulation can be stored at room temperature for several months and is available in different admixtures to meet various patients' needs. However, the addition of vitamins, drugs or other supplements shortly before administration is always necessary if the composition of the industrially manufactured bags do not meet the individual requirements, which is frequently the case.

3.3.2 Pharmacy-compounding

The on-demand compounding comprises another possibility to customize the PN formulations and provide the optimal composition of all needed supplements and medical agents. Pharmacies or commercial compounding services offer the PN customization on-demand and deliver the required infusion units. If there are no restrictions in compatibility, stability and/or storage then as many substances as possible can be combined. However, at least the addition of vitamins still needs to be performed and the problem of additional manipulations before administration remains.

3.3.3 Eurotubes®

Eurotubes® have been developed in 2013 to offer fully individualized PN compounding under GMP standard without the need for further line or bag manipulation outside the controlled GMP environment.

Depending on the patient's nutritional requirements the PN's composition may be considerably complex. Besides trace minerals, extra electrolytes and vitamins, additional medications may be necessary. The 7-,8- or 9-chamber bags provide six extra compartments to separately add further substances such as vitamins or pharmaceuticals in the needed quantity and without the risk of instability or incompatibilities. They are customized to the individual recipient and contain all prescribed nutrients or medical agents in a ready-to-use system. After mixing the individual compartments, the infusion unit is ready to be used without further preparation. The system can also be equipped with an integrated pump feeding set which is ventilated and does not require further manipulations. Depending on the patient's general condition, it is easily possible to self-administer the bags without the assistance of a nursing service or family member. The subjects' daily routine stays independent from the nursing service, which is presumed to increase personal independence and flexibility while decreasing the overall treatment costs.

3.4 Studies on parenteral nutrition and infection

To the present day, multiple studies have been conducted comparing industrially manufactured bags versus pharmacy-compounded bags to investigate the correlation of CRBSI and PN in subjects malnourished due to various reasons, including but not limited to cancer anorexia cachexia. It has been sufficiently demonstrated that PN is associated with an increased hazard of CRBSI, consequently with a prolonged hospital stay and thus, with higher costs.

Pontes-Arruda et al. [Pontes-Arruda et al., 2012] compared industrially pre-mixed PN products to individually compounded bags (COM-group, fabricated either by the hospital's pharmacy or a compounding service provider) in 403 patients in total. The subjects of the COM-group showed a higher incidence of BSI and CLABSI than the subjects receiving industrially pre-mixed PN (BSI: 22,5 % vs. 16,8 %, p = 0,03 and CLABSI: 13,2 % vs. 10,3 % per 1.000 catheter days, p < 0,0001). This suggests an advantage in terms of safety of PN products that are manufactured under GMP standards, however the study neglects to investigate the individual contamination risks in all occurring phases (production, compounding, injection of supplements, administration) and consequently cannot isolate the primary source of the infections.

Pounds et al. [Pounds et al., 2013] showed in a single center trial that subjects treated with pharmacy-compounded PN experienced more adverse drug reactions and metabolic abnormalities than subjects receiving premixed parenteral nutrition. 18% of the COM-group developed a severe sepsis vs. 12% in the comparator arm, however, the sample size of 50 patients per cohort limits the significance and requires further investigations.

The review of Turpin et al. [Turpin et al., 2014] evaluated the impact of parenteral nutrition preparation on BSI risk and costs in 1.995 patients in Germany and brings an interesting angle into the investigations: He evaluated the risk of BSI and the cost of PN by retrospectively reviewing data of patients receiving PN via either multi-chamber bags (MCB), single bottle or hospital compounded admixtures and correlated the type of PN to the hospital costs. In his research he also discovered that adding supplements to MCB on the ward almost doubles the BSI hazard (rate of BSI per 1.000 PN days in MCB without additions vs. with addition: 4,3 vs. 8,5). These data suggest that the quantity of manipulations and injections at the infusion unit correlates with the number of BSI and associated Adverse Events. However, further prospective, randomized trials will be needed to confirm this implication.

3.5 Rationale for PEKANNUSS trial

PN at home using traditional 2/3-chambers is associated with a significant limitation and burden to the patients, as they are dependent on home care and nursing for administering the PN and injection of the required nutrition compounds. PN is, therefore, associated with frequent manipulation at the peripheral or central intravenous device. Data indicate that less manipulation on the PN bags before actual application to the patient reduces the hazard of BSI, however, industrially premixed MCB are often unable to entirely meet the patients' needs and

require additional injections of supplements. Multiple line manipulations are required to substitute several nutrition compounds, leading to a high risk of catheter related complications, and limiting subjects' autonomy. Eurotubes® – as ready-to-use system – require less manipulations and are, therefore, expected to be associated with less complications. The Eurotubes® are already used in the clinical routine practice. However, there is no clear recommendation which type of bags should be used in cancer patients, as there are no clinical trials comparing Eurotubes® versus traditional bags with regards to safety, QoL and response to concomitant anti-cancer therapy. Therefore, further research with randomized controlled trials is urgently required.

3.6 The relevance of this study to current care and benefit-risk assessment

As elaborated above, the CC patients could benefit from a higher QoL by preserving the subjects' autonomy and ability to self-administer the PN infusions.

Furthermore, CRI represent a serious complication in patients receiving PN, weakens the already impaired subject, potentially delays chemotherapy and thereby diminishes therapeutic success. If the Eurotubes® prove to be efficient in preventing CRI, PN could become safer, more efficient and hospitalization time could be abbreviated.

The procedures used in this study (such as PN application, blood tests, use of a patient's study diary and QoL questionnaires) are in line with the current standard of care or minimal interventional, respectively. 2/3-chamber bags and Eurotubes® used for PN are market-approved infusion units with no experimental approach.

There is no evidence of a negative impact of glucose-reduced nutrition on CC subjects and can therefore be tested for its potential inhibitory effect on tumor growth.

Taken together, the risks emerging from participation in this clinical trial are acceptable, considering the anticipated direct benefits for a subset of patients and the impact of the study results on the future treatment of patients in the given indication.

4 Study design

This is an open-label, randomized, multicenter, investigator-initiated, phase IV trial. A total number of 216 patients will be enrolled (see chapter 7 for statistical calculations).

Patients with metastatic or localized solid tumors who fulfil the eligibility criteria and who have an indication for parenteral nutrition will be enrolled.

Patients will be stratified according to ECOG (0-1 vs. 2 vs. 3), the modified Glasgow Prognostic Score (mGPS) (0-1 vs. 2) and whether the patient receives concurrent systemic anti-cancer treatment (e.g. chemotherapy, targeted therapy, immunotherapy) or not.

In a first step, patients will be randomized in a 2:1 ratio to Arm A or Arm B:

Arm A: Standard Parenteral Nutrition using Eurotubes®.

or

Arm B: Standard Parenteral Nutrition using 2/3-chamber bags.

Patients randomized to Arm B will receive PN according to the routine used by the participating site.

Patients in Arm A will be stratified again by the same criteria as listed above and randomized in a 1:1 ratio to Arm A-1 or Arm A-2:

Arm A-1: Standard Low Glucose Parenteral Nutrition using Eurotubes®.

Patients randomized to Arm A and in a second randomization to treatment Arm A-1 receive PN reduced in glucose in Eurotubes®.

or

Arm A-2: Standard Parenteral Nutrition using Eurotubes®.

Patients randomized to Arm A and in a second randomization to treatment Arm A-2 will receive standard PN in Eurotubes®.

Patients will be recruited during regular consultation visits.

An overview of the study scheme is given in Figure 1.

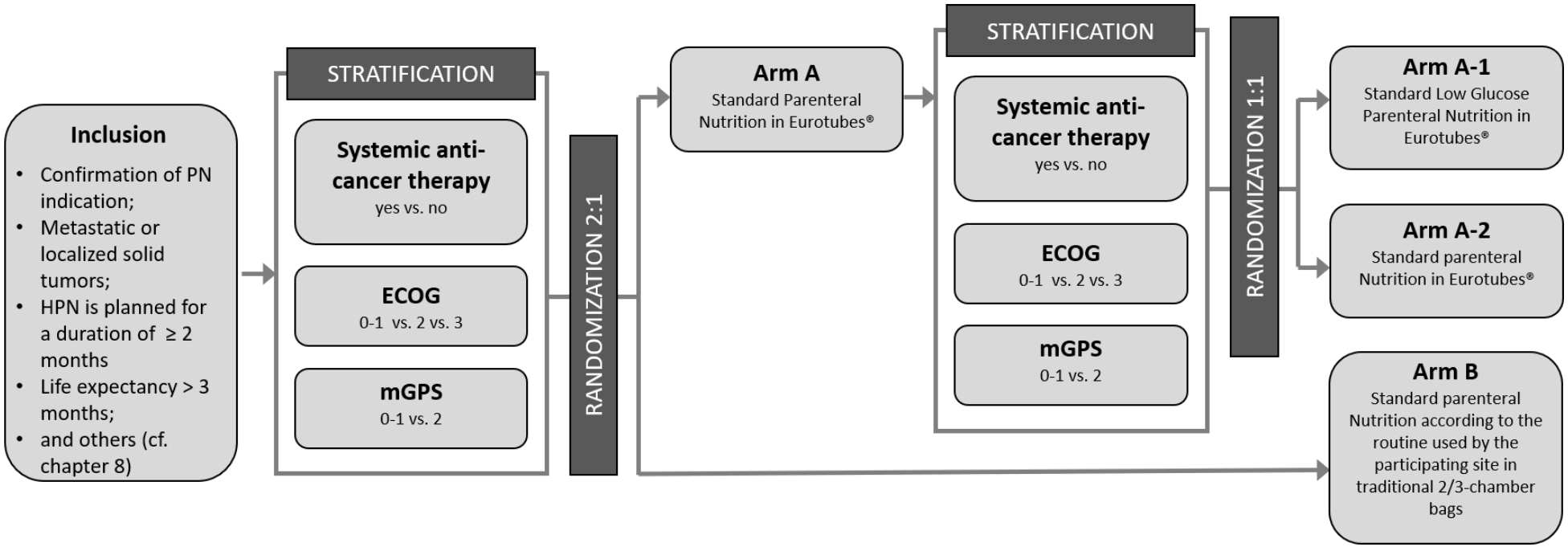

Figure 1: Study Scheme.

At screening and at all regular visits during the HPN treatment period (one visit per four-week interval after randomization for a maximum of 12 months) the ECOG performance status and body weight will be determined. Additionally, physical examinations and laboratory assessments including CRP, albumin and total protein levels will be performed. Laboratory assessments do not need to be repeated at screening if laboratory assessments were done prior to screening within clinical routine and results are not older than 2 weeks. The type of catheter used for parenteral nutrition will be documented (Port-a-Cath, Hickmann/Broviac catheter etc).

The HPN therapy and any modifications and adjustments to this plan during the course of HPN treatment will be recorded from visit 1 onwards.

Anti-cancer treatment at the time of screening and any changes during the course of the HPN treatment period (e.g. type of treatment) will be documented.

Monitoring of Adverse Events and medical device deficiencies will be performed at every visit. AEs will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

During the study the patient will maintain a study diary to document details of the administration of the HPN. A QoL questionnaire will be completed during regular study visits until EOT.

After completion of study treatment, patients will enter the follow-up period. During this period, they will be followed approximately every 3 months for survival which can be done by phone.

5 Objectives and Endpoints

5.1 Objectives

5.1.1 Primary objective

Patient autonomy

To compare the frequency of self-administered parenteral nutrition at home (HPN) (autonomy rate) in patients with metastatic or localized solid tumors receiving standard parenteral nutrition through Eurotubes® versus traditional 2/3-chamber bags in the intent to treat population (ITT).

5.1.2 Secondary Objectives

Secondary Objectives

- To compare the incidence of catheter related infections (CRI) between treatment Arms A and B in the per protocol population.
- To compare the efficacy of PN in terms of body weight, C-reactive protein (CRP) and albumin levels, and overall survival (OS)
- To compare the Quality of life (QoL) by use of the MODIFIED HPN-PROQ questionnaire
- To determine the frequency of PN-related visits by the nursing service
- To compare the safety in terms of the incidence of other catheter related complications, severe, common toxicity criteria (CTC) grade 3-5 infections, and PN-related Adverse Events (AEs)

Secondary Objectives (Arm A-1 vs. A-2)

- To compare the incidence of catheter related infections (CRI)
- To compare the efficacy of PN in terms of body weight, C-reactive protein (CRP) and albumin levels, and overall survival (OS)
- To compare the Quality of life (QoL) by use of the MODIFIED HPN-PROQ questionnaire
- To compare the safety in terms of the incidence of other catheter related complications, severe, common toxicity criteria (CTC) grade 3-5 infections, and PN-related Adverse Events (AEs)

5.2 Endpoints

5.2.1 Primary endpoint

Patients' autonomy

The rate of self-administered parenteral nutrition at home (autonomy rate), defined as administration without nursing service assistance, as documented within the patient's study diary and calculated as the number of patients with autonomy divided by the total number of patients in the respective arm. Autonomy – as relevant for the primary endpoint – is achieved if the patient self-administers 70% or more of her/his total administrations (Note: Help of family members or other personal caregivers accounts for self-administration).

5.2.2 Secondary endpoints

Efficacy endpoints

- Relative weight change determined at baseline and during study visits approx. every four weeks after enrolment;
- Relative change of albumin and CRP levels measured at baseline and during regular study visits;
- Overall survival (OS) defined as the time from randomization to death from any cause.

Quality of Life endpoints

- Quality of Life (QoL) through the MODIFIED HPN-PROQ questionnaire;
- To determine the frequency of PN-related visits by the nursing service

Safety endpoints

- Catheter related infections (CRI) defined as the presence of bacteraemia originating from the intravenous (port) catheter – Bacteraemia must be confirmed through a blood culture according to study site-specific routine, preferably through paired quantitative blood cultures or a culture of the catheter if the catheter is removed – OR any infections originating from the intravenous (port) catheter, requiring intravenous antibiotics OR infections in the intravenous (port) catheter, requiring intravenous antibiotics or antibiotics delivered to the catheter itself or catheter removal.
  For the diagnostic procedures to be done to confirm CRI, investigators are recommended to follow the DGHO guidelines.
- Catheter related complications such as line occlusions of catheter-related central venous thrombosis;

- Severe, NCI-CTC common toxicity criteria version 5.0 grade 3-5, infections including fever of unknown origin and other Adverse Events according to NCI-CTC common toxicity criteria version 5.0;
- PN-Related Adverse Events (AEs) and hospitalizations during therapy;

6 Statistical design

The present trial is designed as an open-label, randomized, multicenter, investigator-initiated phase IV trial comparing standard parenteral nutrition using Eurotubes® vs. traditional 2/3-chamber bags in subjects with metastatic or localized solid tumors requiring parenteral nutrition.

The primary endpoint is defined as the frequency of self-administered HPN (patients' autonomy).

6.1 Sample size calculation

For the primary endpoint statistical significance is assessed using a fisher's exact test at a two-sided alpha level of 0.05 for the objective patient autonomy.

The power calculation was carried out using the Power Procedure in SAS version 9.4 (method: Walters normal approximation for unbalanced groups): Considering the 2:1 randomization, 128 patients must be included in Arm A (Standard Parenteral Nutrition using Eurotubes®) and 64 patients in Arm B (Standard Parenteral Nutrition using 2/3-chamber bags), resulting in a sample size of 192 patients, to ensure 80% power to detect an improvement of the objective patient autonomy from 5% with traditional 2/3-chamber bags to 20% with Eurotubes®.

Assuming a dropout rate of about 10% it is planned to include 216patients.

6.2 Study Duration

Each patient will receive study-specific PN for a maximum of 12 months starting from the date of randomization. Physicians are free to continue PN after the end of this 12 months period if they believe that PN is in the best interest of the patients, but this is done outside the study and is captured in the eCRF as post-discontinuation therapy.

Recruitment is expected to occur over 3 years, followed by a maximum treatment duration of 12 months within the trial and a 6 months period for data cleaning and monitoring resulting in

an expected total study duration of approximately 4.5 years. The study will be conducted at up to 50 sites located in Germany.

6.3 Analysis

Prior to final analysis, data verification with respect to completeness and plausibility (data cleaning) will be performed. Inconsistencies and mistakes will be clarified with the study sites and will be removed. The data cleaning process starts soon after first patients are enrolled and monitored. Major protocol violations and special cases will be listed.

After enrolment of 100 patientsan interim analysis will be performed, non-including the primary endpoint.

The study analysis plan (SAP) and the handling of special cases and major violations will be defined and completed prior to study completion and prior to any conduct of analyses.

6.3.1 Study populations for the analysis

The following data sets for analysis are defined:

Intent-to-treat population (ITT)

The intent-to-treat (ITT) population includes all patients who were randomized. Treatment assignment is based on the randomized treatment (primary population).
The ITT population is the primary population for the description of the patient and treatment characteristics and is used for the primary efficacy analysis.

Per protocol (PP) population

This population will include all randomized patients who fulfill the inclusion and exclusion criteria and received at least two weeks of PN at home according to treatment arm. Treatment assignment is based on the treatment actually given. Sensitivity analyses of the primary endpoint will be performed on the per protocol analysis set.

Safety analysis set

The evaluation of safety parameters is carried out in the safety population, which is defined as all randomized patients who received at least one application of PN at home. Treatment assignment is based on the treatment actually given.

Several subgroup analyses will be performed including but not limited to NRS score, ECOG classification and whether the patient receives concomitant anti-cancer therapy or not. Further details will be specified in the SAP.

6.3.2 Statistical methods for the analysis

Patient Demographics/Other Baseline Characteristics

The following demographic and baseline characteristics will be summarized descriptively by treatment group:

- Gender and age;
- Patients' disease (e.g. colon cancer, breast cancer, gastric cancer);
- Tumor status (localized or metastatic solid tumors);
- Number and type of organs involved in metastatic disease (e.g. liver, lung, lymph nodes, bone);
- Patients history (concomitant disease, number and type of previous anti-cancer therapies);
- Type and start date of the current/concomitant anti-cancer therapy;
- ECOG performance status;
- mGPS
- Nutrition risk screening score;
- Baseline lab values and baseline QoL;
- Other characteristics.
- Type of central catheter used for parenteral nutrition

Primary Endpoint

The primary analysis will compare patients randomized to Arm A (Standard Parenteral Nutrition using Eurotubes®) with those randomized to Arm B (Standard Parenteral Nutrition using 2/3-chamber bags) regarding the objective patient autonomy and will be based on the ITT population. To test the hypothesis:

H_{01}: "The objective patient autonomy does not differ between the treatment Arms A and B ($P_{12} = P_{22}$)."

vs.

H_{11}: "The objective patient autonomy differs between the treatment Arms A and B ($P_{12} \neq P_{22}$)."

fisher's exact test is used with a type I error of 0.05.

Secondary Endpoints

All secondary analyses, excluding safety endpoints analyses, which will be based on the safety population, and the CRI, which will be based on the per protocol population, will be based on the ITT population. Sensitivity analysis of the primary endpoint and other important endpoints will be performed in the per protocol population, also. The parameters will be evaluated in an explorative manner, providing means, medians, ranges, standard deviations and/or confidence intervals. Rates will be compared using fisher's exact test and continuous variables using t-test. For the time-to-event variable OS, the Kaplan-Meier method will be used, and treatment groups will be compared using a log rank test. All resulting p-values for secondary endpoints will be considered descriptive and will be presented explicitly without referring to hypotheses or a significance level. Usually, no p-value adjustment for multiple-testing will be performed. Thus, the p-values will reflect the comparison-wise error and not the experiment-wise error. All p-values will be two-sided if not stated otherwise. The statistical methods described in this section are suited for the data and distributions usually expected in this type of trials. The suitability will be checked and if necessary, the statistical method will be modified accordingly, with critical discussion of the original and modified results.

Further details of the planned procedures and specific analyses will be defined in the statistical analysis plan, latest prior to locking the database.

7 Patient Selection

7.1 Inclusion Criteria

Patients* must meet the following criteria to be eligible for the study:

1. Age ≥ 18 years
2. Histologically confirmed metastatic or localized solid tumor. Perioperative setting of HPN is allowed if HPN is planned for a duration of ≥ 2 months
3. ECOG performance status of 0, 1, 2 or 3
4. Indication for PN (the subject needs a PN independent of the trial)
5. PN planned for 3 or more days per week
6. Negative pregnancy test in women of childbearing potential
7. Willingness to perform double-barrier contraception during study for women of childbearing potential

8. Willingness to maintain a study diary
9. Life expectancy > 3 months
10. Written informed consent

*There are no data that indicate special gender distribution. Therefore, patients will be enrolled in the study gender-independently.

7.2 Exclusion Criteria

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

1. > 4 weeks of consecutive (3 ≥ days per week) parenteral nutrition in the last 3 months prior to study enrolment
2. Participation in another interventional clinical trial that could influence the endpoints of this trial or planned participation in such a study at the same time as this study is active (participation in other trials is possible in the follow up time for OS). The study is active, if the patients receive study treatment (PN), did not discontinue the trial for other reasons, and is still within the 12 months active study period
3. Current catheter related infection at baseline. In patients with a suspected/proven previous conservatively managed catheter-related infection, a negative pair of blood cultures drawn from the central catheter is required.
4. Pregnancy or breastfeeding
5. Known hypertriglyceridemia ≥ CTCAE grade 3
6. Unable or unwilling to provide written informed consent and to comply with the study protocol
7. Uncontrolled diabetes mellitus
8. Congestive heart failure NYHA ≥ 3
9. Renal insufficiency GFR < 30 ml/min
10. Uncontrolled infection
11. Liver insufficiency

8 Therapy scheme

The S3-Guideline of the German Society for Nutritional Medicine for Clinical Nutrition in Oncology should be used as guidance when setting-up the PN therapy plan [S3-Guideline of the German Society for Nutritional Medicine (DGEM) in Cooperation with the DGHO, the ASORS and the AKE, Clinical Nutrition in Oncology].

The following must always be considered before determining the patient's therapy scheme:

- For all treatment arms the composition of the nutrients can differ from the tables below due to site-specific routine or investigator's/medical decision.

- The frequency of PN is not pre-determined for any treatment arm and can change during the course of the study based on the evolving nutritional status of the patient.
- The recommended infusion duration is 12-14 hours. However, the duration can differ and the maximum infusion speed per macronutrient should always be considered.
- If the run-in phase was not conducted at the inpatient facility, then a low energy nutrition should be considered for the start of HPN to avoid a refeeding syndrome.
- For Arm A-1 and Arm A-2 some modifications to the initially considered therapy plan might become necessary based on to the randomization results. These modifications should only be done if medically acceptable.

Note: Any existent clinical contraindications must always be of overriding importance compared to the randomization results and therapy as randomized should only be administered if medically acceptable.

Arm A-1: Standard Low Glucose Parenteral Nutrition using Eurotubes®

Patients randomized to treatment Arm A-1 will receive PN reduced in glucose in Eurotubes® (Eurozyto).

The following displays a guidance for the PN composition administered in Arm A-1. The amounts listed are understood as daily dose. Underlying medical conditions, intolerance etc. must always be considered per individual patient.

Macronutrients:

For the macronutrients, body weight is understood as the ideal body weight for the patient according to a BMI of 19 – 24 for women and 20 – 25 for men.

Glucose:	1.0 – < 2.0 g per kg body weight
Amino acids:	1.2 – 1.5 g per kg body weight
Lipids:	0.5 – 2.0 g per kg body weight

Micronutrients:

Independent of the ideal body weight, should be added taken the actual serum levels into account.

Sodium:	60 – 150 mmol
Potassium:	40 – 100 mmol

Magnesium: 4 – 12 mmol

Calcium: 2.5 – 7.5 mmol

Phosphate: 10 – 30 mmol

Trace Elements and Vitamins:

Trace Elements and Vitamins are added according to the standard dietary reference intake.

Water:

The amount of water depends on the oral intake of water, volume tolerance and kidney function. As general guidance 30 – 40 ml per kg body weight should be considered.

TOTAL:

Total Volume: 30 – 40 ml per kg body weight

Total Calories: 25 – 30 kcal per kg body weight

guidance for calculating calories:

1 g glucose ~ 4 kcal

1 g amino acids ~ 4 kcal

1 g lipids ~ 10 kcal

The investigator should specify the PN composition according to the site-specific routine in consultation with a nutritional expert, if routinely involved in the PN at this site, considering the guidance above. At the investigator's discretion he/she can also consult the Care Management/Supply Management of LIGETIS for advice and fine-tuning the PN composition.

Arm A-2: Standard Parenteral Nutrition using Eurotubes®

Patients randomized to treatment Arm A-2 will receive standard PN in Eurotubes® (Eurozyto).

The following displays the specifications for the PN composition administered in Arm A-2. The amounts listed are understood as daily dose. Underlying medical conditions, intolerance etc. must always be considered per individual patient.

Macronutrients:

For the macronutrients, body weight is understood as the ideal body weight for the patient according to a BMI of 19 – 24 for women and 20 – 25 for men.

Glucose: ≥2.0 – 4.0 g per kg body weight

Amino acids: 1.2 – 1.5 g per kg body weight

Lipids: 0.5 – 2.0 g per kg body weight

Micronutrients:

Independent of the ideal body weight, should be added taken the actual serum levels into account.

Sodium: 60 – 150 mmol

Potassium: 40 – 100 mmol

Magnesium: 4 – 12 mmol

Calcium: 2.5 – 7.5 mmol

Phosphate: 10 – 30 mmol

Trace Elements and Vitamins:

Trace Elements and Vitamins are added according to the standard dietary reference intake.

Water:

The amount of water depends on the oral intake of water, volume tolerance and kidney function. As general guidance 30 – 40 ml per kg body weight should be considered.

TOTAL:

Total Volume: 30 – 40 ml per kg body weight

Total Calories: 25 – 30 kcal per kg body weight

guidance for calculating calories:

1 g glucose ~ 4 kcal

1 g amino acids ~ 4 kcal

1 g lipids ~ 10 kcal

The investigator should specify the PN composition according to the site-specific routine in consultation with a nutritional expert, if routinely involved in the PN at this site, considering the guidance above. At the investigator's discretion he/she can also consult the Care Management/Supply Management of LIGETIS for advice and fine-tuning the PN composition.

Arm B: Standard Parenteral Nutrition using 2/3-chamber bags

Patients randomized to Arm B will receive standard PN using 2/3-chamber bags (various manufactures) according to the routine used by the participating site.

The following displays a guidance for the PN composition administered in Arm B. The amounts listed are understood as daily dose. Underlying medical conditions, intolerance etc. must always be considered per individual patient.

Macronutrients:

For the macronutrients, body weight is understood as the ideal body weight for the patient according to a BMI of 19 – 24 for women and 20 – 25 for men.

Glucose:	≥2.0 – 4.0 g per kg body weight
Amino acids:	1.2 – 1.5 g per kg body weight
Lipids:	0.5 – 2.0 g per kg body weight

Micronutrients:

Independent of the ideal body weight, should be added taken the actual serum levels into account.

Sodium:	60 – 150 mmol
Potassium:	40 – 100 mmol
Magnesium:	4 – 12 mmol
Calcium:	2.5 – 7.5 mmol
Phosphate:	10 – 30 mmol

Trace Elements and Vitamins:

Trace Elements and Vitamins are added according to the standard dietary reference intake.

Water:

The amount of water depends on the oral intake of water, volume tolerance and kidney function. As general guidance 30 – 40 ml per kg body weight should be considered.

TOTAL:

Total Volume:	30 – 40 ml per kg body weight
Total Calories:	25 – 30 kcal per kg body weight
	guidance for calculating calories:
	1 g glucose ~ 4 kcal

1 g amino acids ~ 4 kcal

1 g lipids ~ 10 kcal

The investigator should specify the PN composition according to the site-specific routine in consultation with a nutritional expert, if routinely involved in the PN at this site, considering the guidance above. The investigator is free to use any manufacturer of traditional 2/3-chamber bags but should follow the site-specific routine. At the investigator's discretion he/she can also consult the Care Management/Supply Management of the respective manufacturer or of LIGETIS. Examples of manufactures providing 2/3-chamber bags are Braun (Nutriflex portfolio), Fresenius (SMOF Kabiven or Kabiven portfolio) or Baxter (Olimel portfolio).

9 Treatment schedule and schedule of assessments

The treatment schedule is displayed in Figure 4.

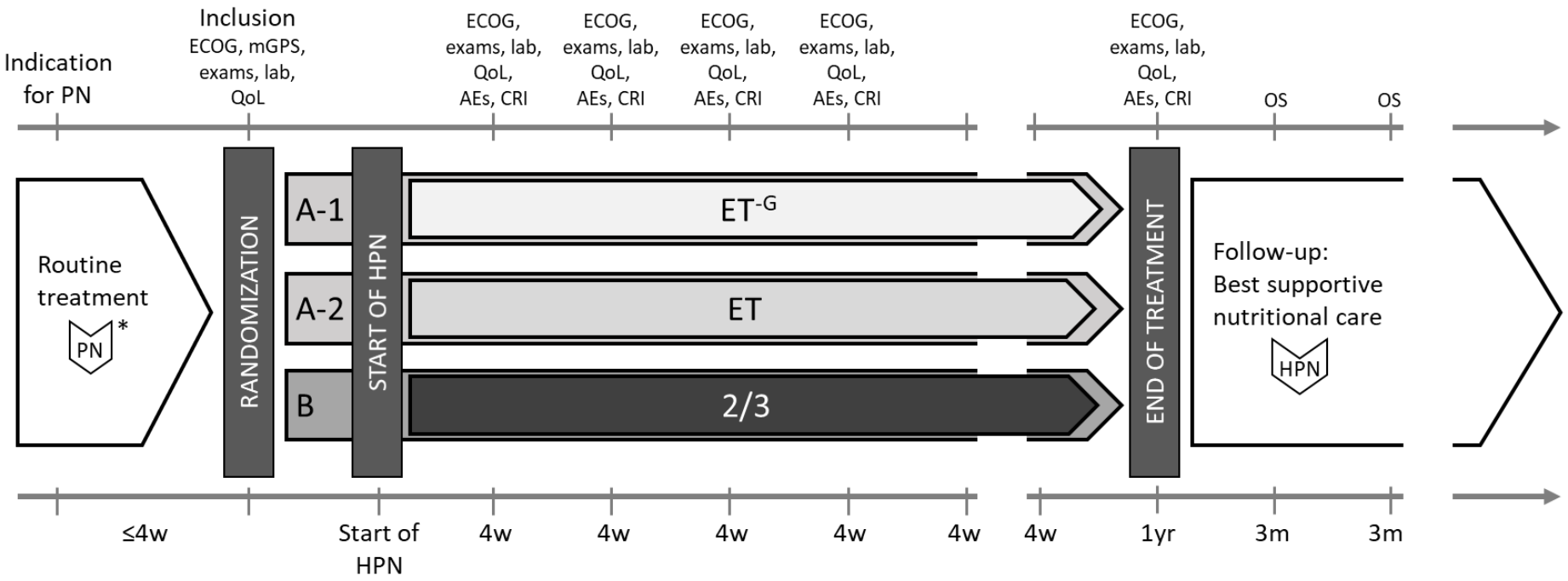

Figure 2: Treatment schedule and schedule of assessments.

* The indication for PN will usually come from a physician during routine treatment in a hospital inpatient or outpatient setting and should be given independent of the trial.. The patient might have started PN already during routine (inpatient) treatment. PN=Parenteral nutrition (here: potential run-in phase); ET^{-G}= standard low glucose HPN in Eurotubes®; ET= standard HPN in Eurotubes®; 2/3=standard HPN in 2/3-chamber bags; HPN=Home Parenteral nutrition in any PN bag; w=week; m=month, yr=year.

Please note: the protocol visits may be less frequent than the medically indicated visits. Please schedule visits as it is usual in your study site independent of the study but at least as frequent as indicated in this protocol. Reportable events occurring in other visits (scheduled or unscheduled) other than those required here should be reported in the eCRF with the documentation of the subsequent protocol visits.

9.1 Schedule of assessments

The schedule of assessments is displayed in Table 1. The assessments are the same irrespective of the treatment arm.

Table 1: Schedule of Assessments

Schedule of Assessments	Screening	Visit 1 – Visit 12[1]	EOT Visit	Follow-Up[2]
Informed consent[3]	X			
ECOG	X[4]	X	X[16]	
Modified Glasgow Prognostic Score (mGPS)	X[4]	X	X	
Nutritional Risk Screening	X[4]			
Physical Examination	X	X	X[16]	
Weight	X	X	X[16]	
Height	X			
Medical History	X			
Demographics, other baseline parameters	X			
Concomitant anti-cancer therapy (if any)	X[5]	X[6]	X[6]	
Laboratory[7]	X	X	X	
Pregnancy test[8]	X			
Catheter Related Infections (CRI)	X	X	X	
Any catheter related complications	X	X	X	
Adverse Events[9]	X	X	X	(X)
Medical device deficiencies[10]		X	X	
QoL questionnaire[11]	X	X	X[16]	
Patient's study diary	X[12]	X[13]	X[13]	
HPN therapy plan / administration/documentation		X[14]	X[14]	
Post discontinuation PN				X[15]
Overall survival		X	X	X

(1) A maximum of 12 visits should be documented within the study. The visit schedule itself is up to the clinical routine at the site and may occur approx. every four weeks. However, only the first visit within each four-week interval (starting from randomization) will be documented. If there is more than one visit within a four-week interval, only the first visit will be documented.
(2) Every 3 months (+/- 2 weeks) until death or end of the study for survival status.
(3) Mandatory prior to any study procedure.
(4) Should be (re-)determined by the study personnel even if known through the documentation received by the inpatient facility. Please note: ECOG PS of 0, 1, 2 and 3 are eligible for the trial.
(5) Any anti-cancer therapy (including surgery and radiation) should be documented.
(6) Changes in the anti-cancer therapy should be documented
(7) Routine peripheral blood lab usually done in patients receiving HPN including but not limited to: Complete blood count (German: kleines Blutbild), albumin, total protein level (German: Gesamteiweiß), CRP, GOT (AST), GPT (ALT), LDH, cholinesterase, creatinine, triglycerides, urea, glucose, electrolytes (sodium, potassium, magnesium, calcium, phosphate) should be

determined according to local lab routine. Laboratory assessments do not need to be repeated at screening if laboratory assessments were done prior to screening within clinical routine and results are not older than 2 weeks.

(8) In case of women of child-bearing potential. Serum pregnancy test at Screening.

(9) Adverse Events (related or not) are captured at any time throughout the study as soon as they become known to the study team, beginning after the patient has given written informed consent and up to 14 days after the last study treatment was administered.

(10) Medical device deficiencies are captured from randomization until last study specific HPN.

(11) The site staff instructs the patient of how to complete the QoL questionnaire. Questionnaire is completed during all documented study visit until EOT. Results of the completed QoL questionnaire(s) are transcribed to the eCRF by the site.

(12) The site staff instructs the patient how to complete the patient's study diary. Handing out of a diary covering enough days until the next planned visit. Patient should complete diary daily until EOT. **Please note: patients' diary is very important as it includes information on one of the study primary endpoint!**

(13) Results of the completed study diary are transcribed to the eCRF. Handing out of new diaries as needed.

(14) Adjustments of the PN therapy plan are possible throughout the study, independent from the planned study visits. The latest adjustment will be documented at the time of each visit. The PN is administered at home through the nursing service, a caregiver or the patient.

(15) After EOT, subsequent HPN/PN will be captured (only manufacturer).

(16) If results of examinations are available which are not older than 14 days no further examination will be necessary.

Important note: These assessments are required by the study protocol. All examinations are part of routine clinical practice. It is important to note that the study protocol does not limit the examinations to the points mentioned above. The investigator shall perform all other/additional routine or site-specific examinations relevant to the safety of the patient or for any other procedures done.

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